CHEMICAL REVIEWS

Review

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Advances in Stereoconvergent Catalysis from 2005 to 2015: Transition-Metal-Mediated Stereoablative Reactions, Dynamic Kinetic Resolutions, and Dynamic Kinetic Asymmetric Transformations

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ABSTRACT: Stereoconvergent catalysis is an important subset of asymmetric synthesis that encompasses stereoablative transformations, dynamic kinetic resolutions, and dynamic kinetic asymmetric transformations. Initially, only enzymes were known to catalyze dynamic kinetic processes, but recently various synthetic catalysts have been developed. This Review summarizes major advances in nonenzymatic, transition-metal-promoted dynamic asymmetric transformations reported between 2005 and 2015.

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1. INTRODUCTION

One of the ultimate challenges in the field of organic synthesis is the development of methods for the construction of enantioenriched, carbon-based molecules. The vast majority of processes currently in existence toward this goal proceed through the selective construction of a stereocenter where one previously did not exist. An alternative strategy involves subjecting a racemic mixture of enantiomers to an enantioselective catalytic transformation, wherein the chiral catalyst undergoes preferential reaction with only one of the two enantiomers. This phenomenon is known as kinetic resolution, and while highly useful, kinetic resolutions suffer from a major practical limitation—they cannot produce enantioenriched products in >50% yield.[1−6]

If a mechanism for the rapid interconversion of enantiomers can be established in the presence of a chiral catalyst, however, the concept of kinetic resolution can lead to full conversion of a racemic mixture to a single, enantioenriched product, a concept known generally as stereoconvergence. It is the focus of this Review to highlight the developments of stereoconvergent transformations, with a particular emphasis on transition-metal-catalyzed processes. Within this realm there are three subclasses: stereoablative transformations, dynamic kinetic resolutions (DKRs), and dynamic kinetic asymmetric transformations (DyKATs). Each subclass contains its own section and is carefully defined in the corresponding section's introduction.

During the preparation of this Review, we happened upon a number of asymmetric transformations that were conceptually similar to DKR and DyKAT processes; however, the chiral information was contained on the substrate rather than the catalyst. Strictly speaking, these transformations do not involve asymmetric catalysis and therefore can be considered neither a DKR nor a DyKAT. While few in number, we found these transformations intellectually stimulating and included them in a final section under the title dynamic substrate-directed resolutions (DSDRs).

The final goal of this Review is to instruct readers as to the proper use of these terms. Because of the inherent similarity of these processes, particularly with respect to DKRs and DyKATs, some of the transformations described herein have been incorrectly classified by their authors. We have reclassified these examples into their proper categories according to the definitions presented in this Review. It is our hope that this Review will serve as a guide to the reader as to the proper use of these terms.

2. STEREOABLATIVE TRANSFORMATIONS

In the past decade the synthesis of enantiomerically enriched molecules via stereoablative processes has received much attention.[7] A stereoablative process is one in which a key reactive intermediate is formed via the irreversible destruction of a stereocenter; this prochiral species then interacts with a catalyst to form a new stereocenter selectively. As shown in Figure 1, both enantiomers of a starting material, (*R*)-**A** and (*S*)-**A**, undergo a reaction that irreversibly destroys a stereocenter—a process termed "stereoablation"—to produce prochiral intermediate **B**. Interaction of **B** with a chiral catalyst can lead preferentially to one enantiomer of product [(*R*)-**C** in this case]. Importantly, stereoablative enantioconvergent catalytic systems involve identical or nearly identical rates of stereoablation (i.e., $k_{racR} \approx k_{racS}$) but display substantially different rates of product formation (i.e., $k_R \gg k_S$). Stereoablative processes differ from traditional DKR or DyKAT processes in that there is no discernible dynamic or reversible nature to the process with respect to the organic stereogenicity.[8]

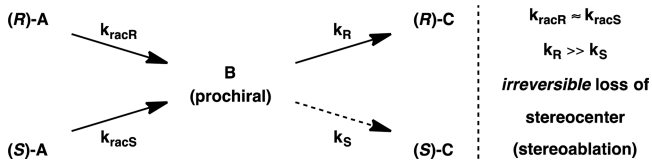


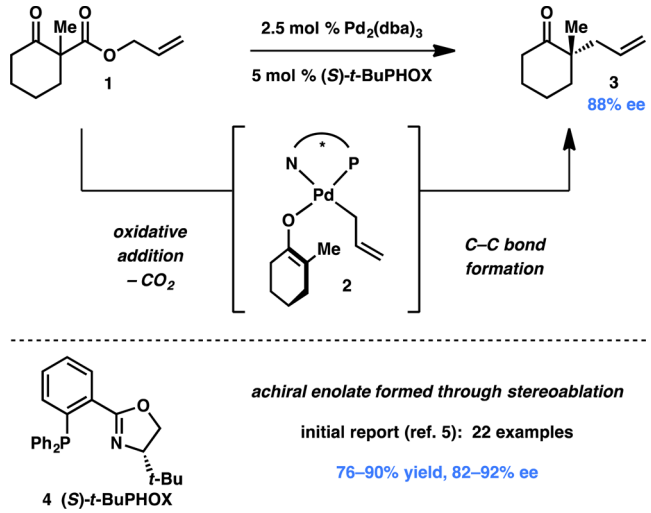
Figure 1. Stereoablative enantioconvergent catalysis.

While the remainder of this Review remains focused on transition-metal-catalyzed processes, because of the relative scarcity of truly stereoablative transformations, we chose to include transformations that operate through the use of chiral organic catalysts. We hope that this Review will inspire the development of novel stereoablative transformations catalyzed by chiral transition metal catalysts.

2.1. Decarboxylative Processes

2.1.1. Enantioselective Allylic Alkylation. Perhaps the most prevalent and commonly utilized stereoablative process is the enantioselective allylic alkylation[9] pioneered by Stoltz and co-workers (Scheme 1).[10] In 2004, the authors introduced a palladium/phosphinooxazoline (PHOX)-based catalytic system for the formation of α-ketone quaternary stereocenters from cyclohexanone-based allyl enol carbonates. One year later, they adapted this protocol for the use of chiral racemic α-quaternary β-ketoester substrates **1**.[11] This process represents a substantial advance in the construction of carbonyl α-quaternary stereocenters through a three-step process: carboxylation of a ketone enolate with allyl cyanoformate, alkylation of the resultant β-ketoester, and finally decarboxylative allylic alkylation to set the

Scheme 1. Stoltz's Stereoablative Allylic Alkylation



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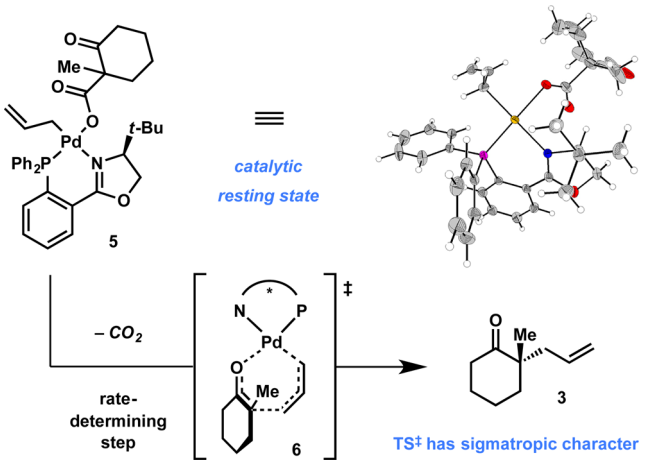
aforementioned fully substituted tertiary or all-carbon quaternary stereocenter.

Substantial effort has resulted in a detailed mechanistic understanding of this stereoablative process.[12−14] Preliminary studies (Scheme 2) suggested that an internal mechanism (i.e.,

Scheme 2. Mechanistic Investigation into Allylic Alkylations



reductive elimination) is a lower-energy pathway than the corresponding external mechanism involving attack of the enolate onto an η^3-allyl complex; it was later discovered that η^1-allylpalladium carboxylate **5** was found to be the resting state of the catalyst and that decarboxylation was likely rate-limiting.[15−17] The lowest-energy pathway for carbon−carbon bond formation occurs through a seven-membered, Claisen-like transition state (**6**) similar to that originally proposed by Echavarren and co-workers,[18] in which the chiral ligand imparts facial selectivity of the allylic alkylation. The sigmatropic character of the transition state likely accounts for the high efficiency with which these sterically hindered quaternary centers are formed, as sigmatropic rearrangements remain a preeminent method for their construction.[19] Crucially, these mechanistic studies found that palladium enolate **2** is the reactive intermediate that proceeds to the enantioenriched products. The chiral racemic allyl β-ketoester starting material is converted to this achiral intermediate through catalytic resting state **5**, and the catalyst-controlled allylic alkylation event provides the product in an enantioenriched fashion. Furthermore, an allyl β-ketoester, an allyl enol carbonate, or a combination of silyl enol ether and fluoride can be used as the enolate precursor to give almost identical yields and enantiomeric excesses (ee's), thus confirming the stereoablative nature of the transformation.[2,20]

Since their development of an enantioselective allylic alkylation, the Stoltz group has increased the scope of this transformation substantially to include 1,3-dioxan-5-one- (**9**),[21] β-thiocyclohexenone- (**10**),[22,23] 3-ketal- (**11**),[24] β-alkoxycycloheptenone- (**12**),[25,26] 5-alkyl- and 5-alkoxy- (**13**), β-aminocyclohexenone- (**14**), 1-alkoxypiperidine-2,6-dione- (**15**), dihydropyridin-4(1*H*)-one- (**16**),[27] cyclobutanone- (**17**),[28] valerolactam and 2-piperazinone- (**18**),[29] 2-aminomethylcyclohexanone- (**19**),[30] 4-oxazolidinone- (**20**), morpholin-3-one- (**21**), 1,2-oxazepan-3-one- (**22**),[31] and cyclopentanone-based (**23**)[32] allyl β-ketoesters (Figure 2). Notably, the use of oxygen- and nitrogen-based heterocycles allows for the facile synthesis of quaternary stereocenter-bearing polyketide and pharmaceutical-type fragments in a straightforward manner.

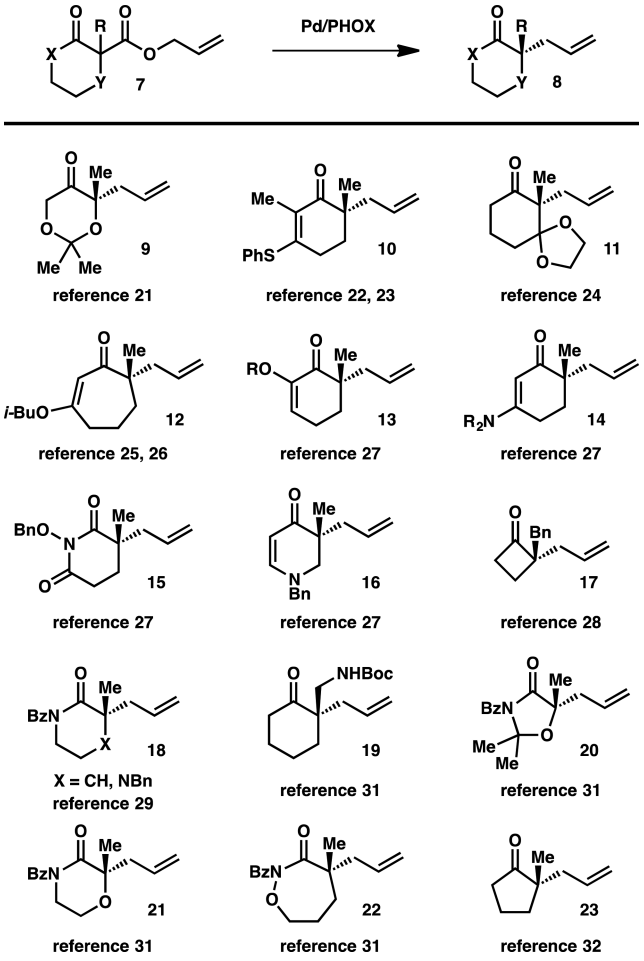
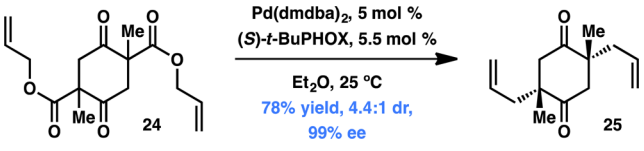


Figure 2. Substrate scope in Stoltz's allylic alkylation.

2.1.2. Enantioselective Allylic Alkylation in Total Synthesis. Given the value of ketones bearing enantioenriched α-quaternary stereocenters, it is not surprising that this chemistry has found substantial application to the total synthesis of biologically active natural products. Perhaps most notable is the total synthesis of cyanthiwigin F (**31**) by Enquist and Stoltz in 2008 (Scheme 3).[33,34] Bis-β-ketoester **24** was

Scheme 3. Double Allylic Alkylation Leads to Excellent ee



produced in two steps from diallyl succinate as a mixture of racemic and meso diastereomers (1:1). Treatment of **24** with the Pd/PHOX catalyst (vide supra) provided a 4.4:1 mixture of syn/meso diallylated products **25** with the major product produced in 99% ee. The stereoablative nature of this transformation simplifies the process of setting two quaternary stereocenters by the clever recognition of latent C_2 symmetry. As shown in Scheme 4, after a desymmetrizing vinyl triflate formation/alkyl Negishi coupling sequence to produce tetraene **26**, the synthesis is completed in four steps: tandem ring-

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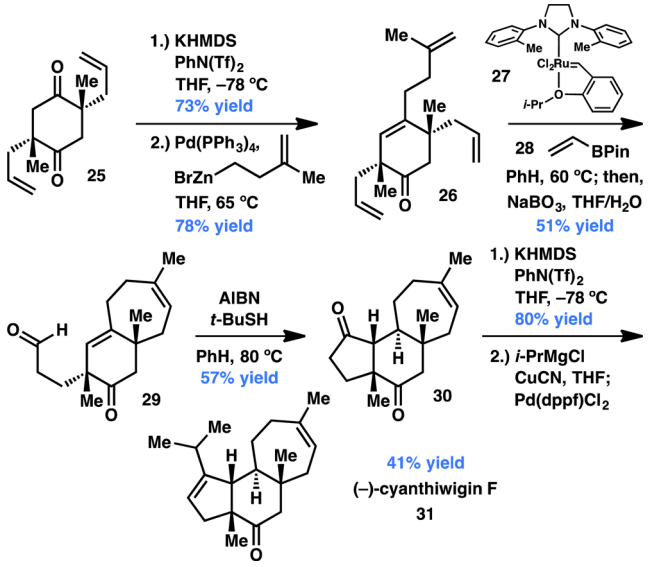
Scheme 4. Completion of the Synthesis of (−)-Cyanthiwigin F



closing/cross metathesis with vinyl boronate and its concomitant oxidation to aldehyde **29**, radical hydroacylation with a polarity reversal thiol catalyst to yield ketone **30**,[35,36] and a challenging vinyl triflate formation/alkyl Kumada coupling sequence. Overall, the total synthesis of cyanthiwigin F (**31**) was completed in just nine linear steps utilizing the enantioselective allylic alkylation.

More recently, the synthetic community has recognized the power of the allylic alkylation for setting such crucial stereocenters and as such has responded with a variety of total syntheses (Figure 3). In 2009, Stoltz applied the β-ketoester derived from α-methyl-β-phenylthiocyclohexenone to the total syntheses of (+)-carissone (**32**)[13] and (+)-cassiol (**33**),[13] utilizing the stereoablative allylation chemistry coupled with Stork−Danheiser-type cyclohexenone manipulations. Later, the Stoltz and Grubbs groups collaborated on an allylic alkylation/ring-closing metathesis strategy for a general synthesis of the chamigrene natural products including (+)-elatol (**35**).[37] In 2013, Gartshore and Lupton[38] and Shao and co-workers[39] reported the formal and total syntheses of (+)-kopsihainanine A (**38**), respectively, along with the total synthesis of (−)-aspidospermidine (**39**) by Shao and co-workers. More recently, in 2015 Zhu and co-workers reported the total synthesis of (−)-isoschizogamine (**41**) that utilized a stereoablative, enantioselective cyclopentanone allylic alkylation.[40] Given the power of this method for the construction of valuable all-carbon quaternary stereocenters, it is likely that we will continue to witness its use in natural product total synthesis for years to come.

2.2. Enantioselective Protonation

In 2006, Stoltz and co-workers applied this stereoablative concept to the enantioselective protonation of trisubstituted ketone enolates (Scheme 5, conditions A).[41] By employing an allyl β-ketoester with $Pd(OAc)_2$ and a chiral ligand, a similar palladium enolate as **2** (Scheme 1) was formed; however, instead of allylation, the authors reported that they could induce enantioselective protonation using formic acid and 4 Å molecular sieves. The authors noted that substantial optimization was required for each substrate; as a result, they also developed a fully homogeneous variant of this reaction shortly

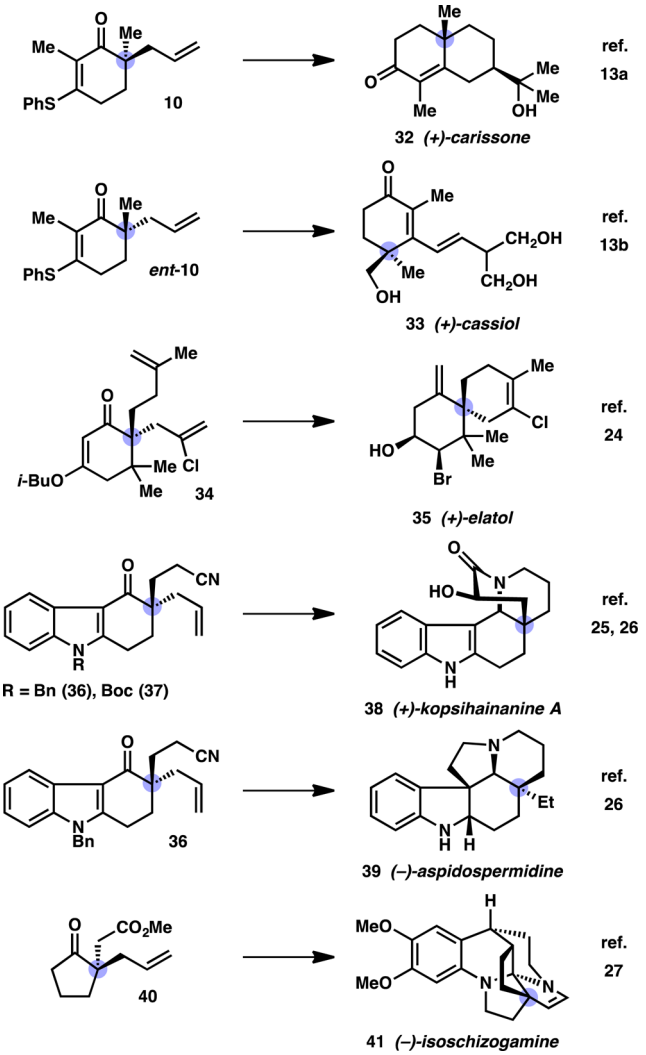
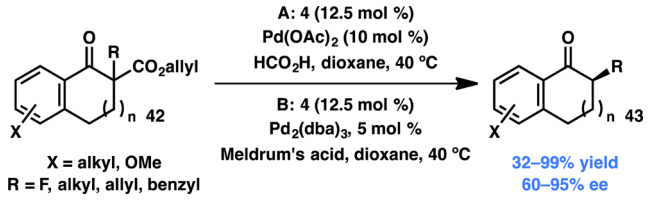


Figure 3. Total syntheses using allylic alkylation.

Scheme 5. Stoltz's Stereoablative Protonation Reaction



thereafter (Scheme 5, conditions B).[42] In this report, Meldrum's acid served a dual purpose as both the proton source and an allyl group scavenger. The latter conditions offered improved generality and scalability. Although only one antipode of the catalyst was used for these studies, the authors noted that the enolates were not always protonated from the same face. Despite the synthetic utility of this reaction, the mechanism of protonation remains unclear.

2.3. Cross-Coupling Reactions

2.3.1. Couplings with Organometallic Nucleophiles. In 2005 Fu and co-workers disclosed the use of a chiral nickel catalyst capable of performing enantioselective Negishi couplings of racemic alkyl halides (Figure 4).[43,44] These reports provide efficient procedures for constructing relatively remote tertiary stereocenters that possess three alkyl units.

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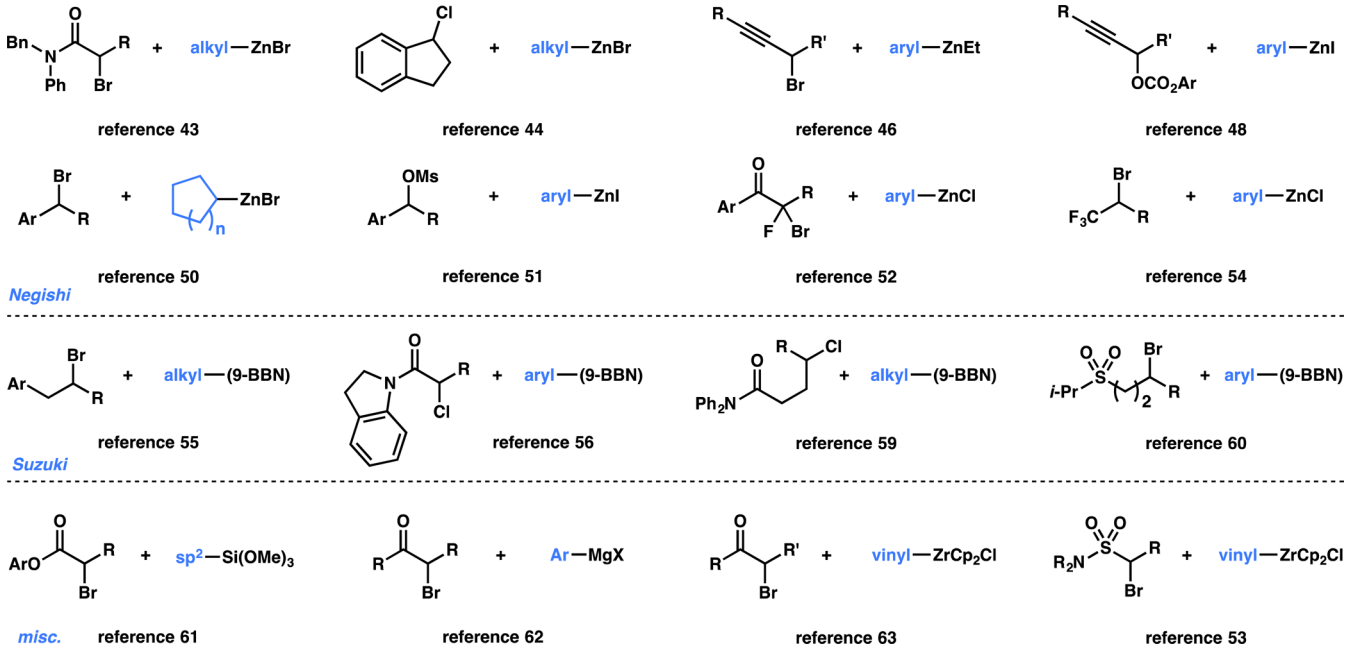
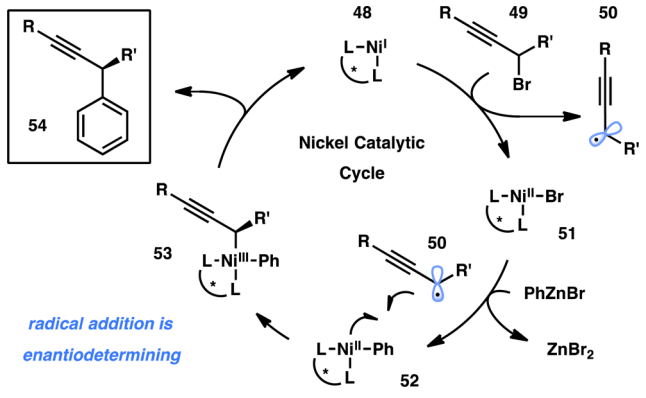


Figure 4. Selected scope of Fu's stereoablative couplings.

Following the initial disclosures the authors have demonstrated the exceptionally wide scope of the transformation, with efficient couplings of primary and secondary alkyl chlorides, bromides, iodides, carbonates, and sulfonates with alkyl-, vinyl-, and arylzinc nucleophiles (Figure 4).[45−54] Furthermore, the authors have also developed conditions for enantioselective Suzuki,[55−60] Hiyama,[61] Kumada,[62] and zirconium-Negishi[53,63] couplings with a variety of alkyl electrophiles.

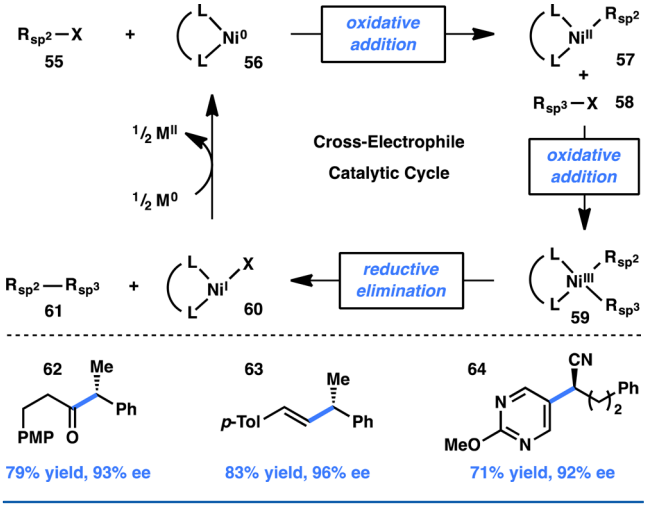
In each of the above reports, Fu and co-workers designed a catalyst that could overcome the inherent challenges associated with this type of coupling, most notably the use of alkyl electrophiles and nucleophiles without any competing β-hydride elimination or isomerization.[65−69] Furthermore, in all cases racemic alkyl electrophiles were employed, yet the products are produced in high enantiomeric excess. Recent mechanistic studies have elucidated the operating catalytic cycle (Scheme 6).[70] The cycle begins with a halide abstraction from **49** by in situ-generated nickel(I) species **48** to yield prochiral alkyl radical **50** and nickel(II) complex **51**. Transmetalation between **51** and an arylzinc reagent occurs, generating arylnickel(II) species **52**—the catalytic resting state. Radical addition to **52** is facile, and at this stage the chiral ligand controls facial selectivity of the prochiral radical addition to the metal, generating transient nickel(III) species **53**. Subsequent reductive elimination furnishes the enantio-enriched cross-coupled product **54**.

Scheme 6. Simplified Nickel Catalytic Cycle[64]



2.3.2. Cross-Electrophile Coupling. In recent years, there has been a great deal of interest in cross-electrophile coupling.[71−74] In particular, nickel catalysts have displayed exceptional reactivity and selectivity for cross-coupling processes, rather than simply providing statistical mixtures of products. Extensive mechanistic studies by Biswas and Weix have led to an understanding of the relevant catalytic cycles in these couplings (Scheme 7).[75] sp^2-Hybridized electrophiles **55** undergo oxidative addition selectively and rapidly in the presence of nickel(0) species such as **56**, thereby producing nickel(II) complex **57**. Bimetallic oxidative addition[76] of alkyl halide **58** leads to transient nickel(III) species **59**. Rapid reductive elimination then produces nickel(I) intermediate **60** and the C_{sp^3}–C_{sp^2} product **61**; **60** is then reduced to the active

Scheme 7. Reisman's Cross-Electrophile Coupling Reactions



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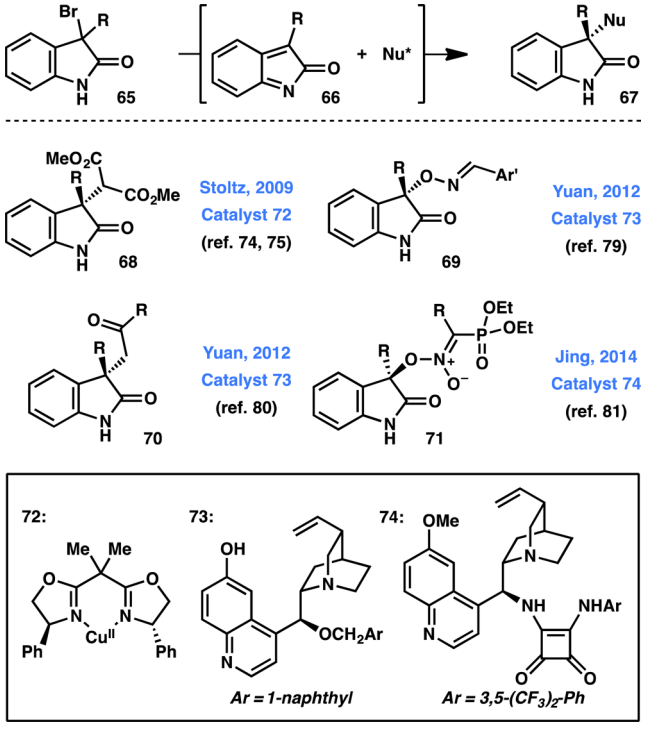
nickel(0) catalyst **56** by a low-valent metal reducing agent to complete the catalytic cycle.

In 2013, Reisman and co-workers reported an enantioselective cross-electrophile coupling of acyl chlorides and racemic benzyl chlorides (Scheme 7, product **62**).[77] The authors propose a mechanism similar to that proposed by Schley and Fu[70] wherein enantiodiscrimination occurs upon addition of a prochiral radical to nickel(II) species **57**. Since this original report, the authors have also disclosed the enantioselective coupling of vinyl halides with racemic benzyl chlorides (product **63**)[78] and that of heteroaryl halides with racemic α-chloronitriles (product **64**).[79]

2.4. Enantioselective Oxindole Functionalization

2.4.1. Copper Catalysis. 3,3-Disubstituted oxindoles are prominent pharmacophores and as such methods for their construction are in high demand. In 2009 Stoltz and co-workers introduced an enantioselective protocol for their construction from substituted 3-bromooxindoles using a copper bisoxazoline catalyst (Scheme 8).[80,81] In the presence of an amine base, the

Scheme 8. Catalytic Stereoablative Oxindole Synthesis



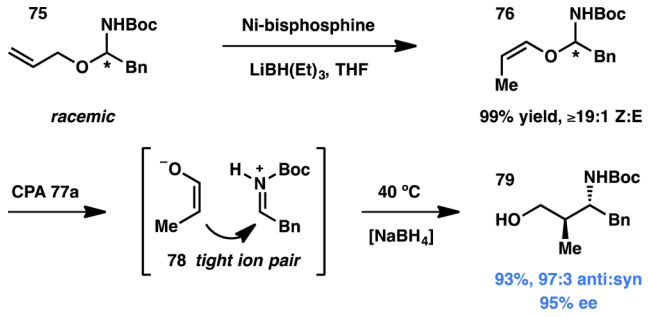
bromide-bearing stereocenter at the 3-position of **65** is ablated, generating *o*-azaxylylene **66**—an extended π-electrophile—that is attacked by the Lewis acid-bound enolate. Chirality is transferred from the ligand to generate a variety of enantioenriched 3,3-disubstituted oxindole motifs (**68**). The Stoltz group has utilized this strategy for the syntheses of communesin F[82] and perophoramidine.[83]

2.4.2. Brønsted Acid Catalysis. Since the initial report on the use of stereoablation as a handle for the efficient construction of 3,3-disubstituted oxindoles, a number of groups have disclosed similar strategies. Intriguingly, no other group has reported the use of copper bisoxazoline catalysts, opting instead to employ cinchona alkaloid-based hydrogen-bonding catalysts.[84] Yuan and co-workers reported in 2012 the use of cinchona alkaloid **73** for the *O*-alkylation of aldoximes with oxindole-based electrophiles (product **69**).[85] Their system was later modified to allow for the use of ketone enolates as π-nucleophiles (product **70**).[86] More recently, Jing and co-workers developed cinchona catalyst **74** that bears a squaramide hydrogen-bond donor for the *O*-alkylation of α-nitrophosphonates under similar conditions (product **71**).[87]

2.5. Miscellaneous Reactions

Terada and co-workers disclosed an enantioselective aza-Petasis–Ferrier reaction in 2009 (Scheme 9).[88] The authors

Scheme 9. Asymmetric aza-Petasis–Ferrier Rearrangement



found that treatment of racemic *O*-vinyl-*N*,*O*-acetals **76** with chiral phosphoric acid (CPA) **77** (Figure 5) promoted the

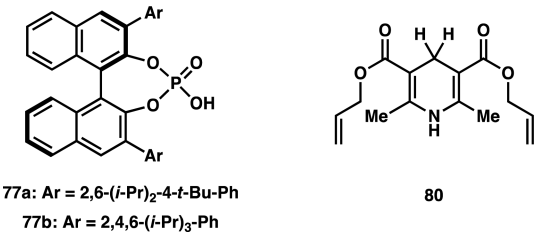


Figure 5. Catalyst and reagent from Schemes 9 and 10.

cleavage of these labile fragments to their corresponding enolate–iminium ion pair (**78**, Scheme 9), the collapse of which provided the corresponding Mannich adducts **79** after reductive workup. Not surprisingly, the authors noted a strong dependence of the enantioselectivity of the transformation on the geometry of the latent enolate (a product of the olefin geometry of the *O*-vinyl group). This observation led the authors to develop a set of novel, bulky bisphosphine-nickel complexes for the convenient preparation of the starting materials from the readily accessible *O*-allyl analogues **78**.

In contrast to many enantioselective catalysis protocols, the authors found that the enantioselectivity of the reaction increased with increasing temperature. The authors later disclosed a thorough mechanistic evaluation to further probe this reaction and account for the anomalous temperature effect.[89] They found that the CPA catalyst serves two purposes, acting both as a hydrogen-bond donor to the *N*-Boc-imine and a hydrogen-bond acceptor from the transient enol. This scaffolding bifunctionality is responsible for both the large degree of anti-selectivity as well as the high enantioselectivities the authors typically observed. Additionally, through an elegant crossover experiment, they elucidated the underlying cause of the temperature effect: at high temperatures the two ions produced from the fragmentation of the *N*,*O*-acetal dissociate fully and the catalyst-controlled addition of the enol to the protonated imine is the dominant mechanism, resulting in high

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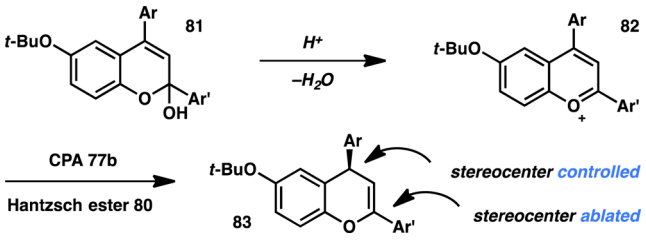
anti-selectivity and high enantioselectivity. At low temperature, however, dissociation of the two ions is incomplete and a noncatalyst-controlled pathway becomes competitive, thus leading to diminished enantioselectivity.

As a final example, in 2013 Terada et al. disclosed a CPA catalytic system coupled with Hantzsch ester hydride for the enantioselective 1,4-reduction of 1-benzopyrylium ions (Scheme 10).[90] In this case, racemic benzannulated lactols **81**

Scheme 10. CPA-Catalyzed Synthesis of 4*H*-Chromenes



are converted to achiral benzopyrylium ions **82** through the action of the CPA catalyst (**77**). This intermediate is then reduced in a 1,4-fashion with diallyl Hantzsch ester **80** to provide enantioenriched 4-aryl-4*H*-chromenes **83** with high yields and enantioselectivities. To our knowledge, this is the only report of a stereoablative process wherein the stereocenter created is not that which was originally destroyed.

2.6. Concluding Remarks—Stereoablative Transformations

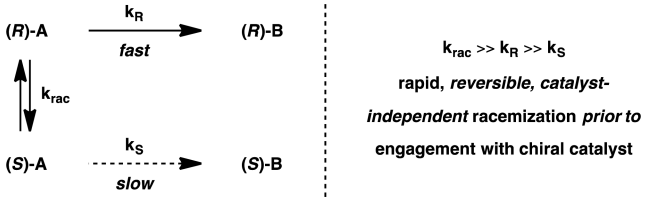
In conclusion, stereoablative enantioselective catalysis is a field that has burgeoned over the past decade, seeing advances in palladium, nickel, copper, and organic catalysis during that span. In contrast to DKR and DyKAT systems that often feature reversible racemization pathways, true stereoablative processes involve irreversible racemization and enantioselective reaction of the prochiral intermediate thereafter. Given the substantial amount of growth in this field over the past decade, we can expect to see even more in the years to come.

3. DYNAMIC KINETIC RESOLUTIONS

3.1. Introduction

In contrast to stereoablative transformations, dynamic kinetic resolutions involve *reversible* racemization prior to the selective reaction of one enantiomer with the chiral catalyst. The first requirement that must be fulfilled to achieve efficient and selective DKR is that the interconversion of enantiomers must be rapid and independent of the catalyst [the equilibration of (*R*)-**A** and (*S*)-**A** with a high k_{rac}, as shown in Scheme 11]. The second requirement is that the reaction of one enantiomer of substrate with the chiral catalyst must occur with a significantly higher rate than that of the other enantiomer (i.e., $k_R \gg k_S$) to provide the enantioenriched product [(*R*)-**B** in this case]. As one enantiomer of substrate **A** reacts with the catalyst, the

Scheme 11. Dynamic Kinetic Resolutions

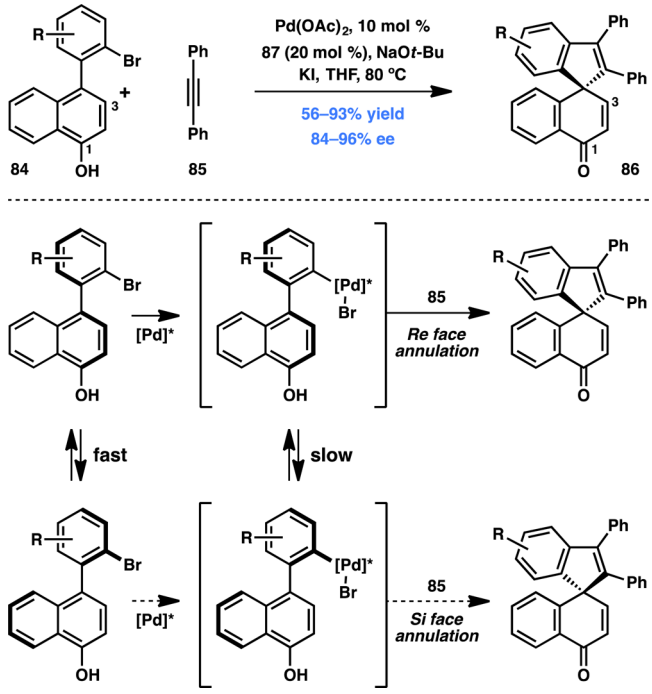


equilibrium between (*R*)-**A** and (*S*)-**A** shifts according to Le Châtelier's principle, such that all of the racemic starting material is eventually funneled through a single enantiomer by the chiral catalyst. As a result, the maximum theoretical yield for a DKR process is 100%.

3.2. Annulation Reactions

3.2.1. Asymmetric Spiroannulation. Luan and co-workers devised a novel approach to affect axial-to-central chirality transfer via Pd-catalyzed DKR (Scheme 12).[91] In the

Scheme 12. Luan's Dearomative Spirocyclization via DKR



event, racemic biaryl phenolic substrates (**84**) were efficiently converted to enantioenriched spirocyclic products (**86**) in good to excellent yields and enantioselectivities. It is proposed that the catalyst system comprising $Pd(OAc)_2$ and chiral NHC ligand **87** (Figure 6) complex can preferentially undergo

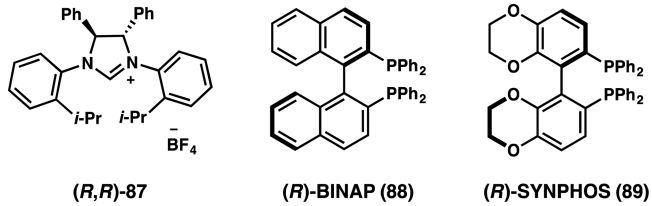


Figure 6. Chiral ligands from Schemes 12–14 and 45.

oxidative addition with one of the rapidly interconverting atropisomers of the brominated biaryl phenol substrate. The alkyne partner then intercepts the Pd-bound intermediate and, following a phenolic dearomatization event, the sprioannulated product is formed. The methodology is quite general, and a wide variety of substitutions are tolerated on the bromide-bearing (hetero)aromatic ring as well as on the alkyne unit. Interestingly, the positional isomer of substrate **84**, where the phenolic −OH group is at the 3-position, affords the expected product, albeit as a racemate. This observation can be explained by taking into account the detrimental effect of the −OH

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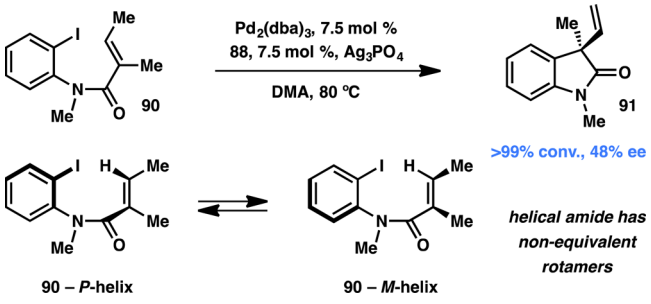
functionality on facile rotation along the biaryl bond. Although unsymmetrical alkynes react smoothly giving excellent yields, regioselectivities were modest (1.3:1−2:1), slightly favoring the product with the smaller substituent proximal to the quaternary spirocenter.

3.2.2. Asymmetric Heck Cyclizations. In 2006 the Stephenson group examined the mechanistic aspects of the asymmetric Heck reaction methodology previously laid out by Overman and co-workers.[92−95] The Overman group had found that intramolecular Heck cyclization of 2-iodoanilides produced either enantiomer of 3,3-disubstituted oxindoles using a single enantiomer of chiral bisphosphine ligand. In further studies by Stephenson and co-workers[96] over a range of temperatures, a distinct pattern took place (Scheme 13): reaction profiles at

Scheme 13. Asymmetric Heck Reaction of Helical Amide Rotamers



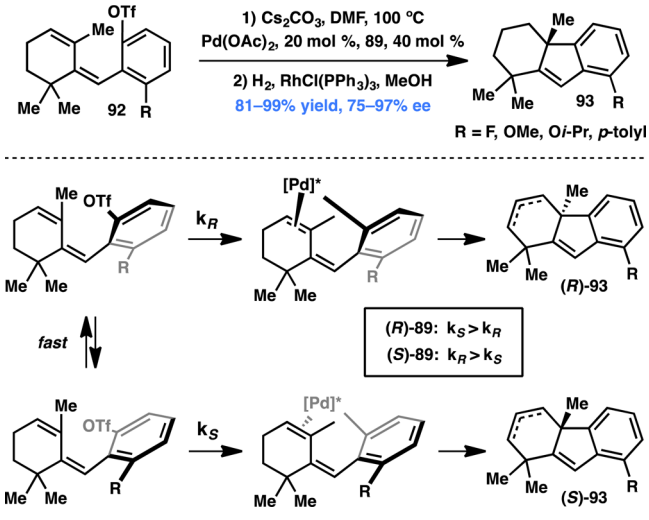
low conversions saw low ee's, while at high conversions high ee's were observed. This observation could not be explained simply by the interconversion of the rotameric forms of the starting material leading to DKR-induced enantioenriched formation of the product. Instead, the authors used a variety of X-ray crystal structures to propose a pathway between the Pd-bound oxidative addition complexes of the *P* and *M* helices opened in the presence of silver phosphate. Whereas the transformation from the *M* starting material to its corresponding Pd-bound complex is faster than that from the *P* starting material, the conversion of the (*M*)-Pd-bound complex to the (*P*)-Pd-bound complex is faster than the reverse, thereby leading to preferential access to the (*S*)-(−) form of the product, and provides a suitable explanation for the change in ee based on conversion.

Ozeki, Yamashita, and co-workers recently reported an interesting example of Pd-SYNPHOS-catalyzed asymmetric Heck reaction that proceeds via DKR (Scheme 14).[97] The hindered rotation about the aryl−alkenyl bond results in atropisomerism in triflate **92**, and at temperatures above 60 °C, equilibrium is attained between the atropisomers. Recognizing the potential of an intramolecular Heck reaction via DKR, the authors subjected triflate **92** to $Pd(OAc)_2$ and (*R*)-SYNPHOS (**89**, Figure 6) and obtained tricyclic product **93** with excellent yield and high enantioselectivity. The authors postulated that the chiral Pd complex readily differentiates between the two enantiotopic faces of the cyclohexenyl ring, so as to selectively produce the favored enantiomer. A detailed mechanistic discussion, including DFT calculations on the various possible transition states, can be found in the original reference.

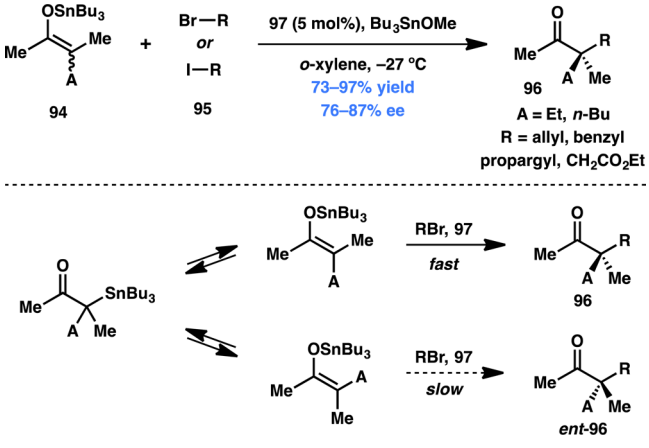
3.3. Enolate Alkylation

Jacobsen and co-workers reported a Cr(salen)-catalyzed method for enantioselective alkylation of acyclic α,α-disubstituted tin enolates (Scheme 15).[98] It is known that tin

Scheme 14. Asymmetric Heck Reaction Controlled by Restricted Rotation



Scheme 15. Jacobsen's Enantioselective Enolate Alkylation



enolates readily undergo tautomerization in solution,[99] leading to the dynamic interconversion of the *E* and *Z* isomers. The Cr(salen) complex **97** (Figure 7) is able to selectively react with one of the rapidly equilibrating geometric isomers and leads to the enantioselective construction of quaternary carbon stereocenters.[100,101]

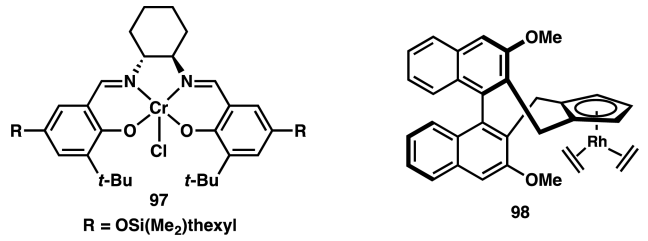


Figure 7. Catalysts from Schemes 15 and 16.

3.4. C−H Activation

In recent years, DKRs proceeding via C−H activation have attracted attention from researchers around the globe.[102−104] In one example, the You group described a dehydrogenative Heck coupling that occurred via the Rh-catalyzed C−H activation of biaryl substrates **99** to produce corresponding alkenylated

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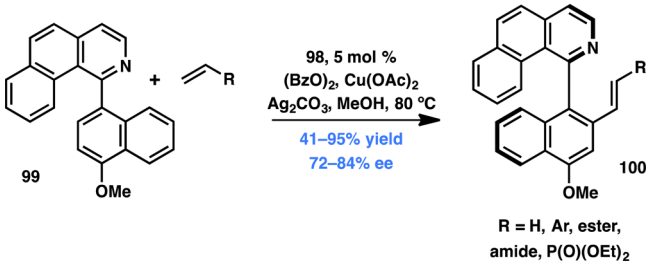
biaryls **100** with high efficiency and enantioselectivity (Scheme 16).[105] The atroposelectivity the authors observed is believed to

Scheme 16. You's Atroposelective C−H Activation Strategy

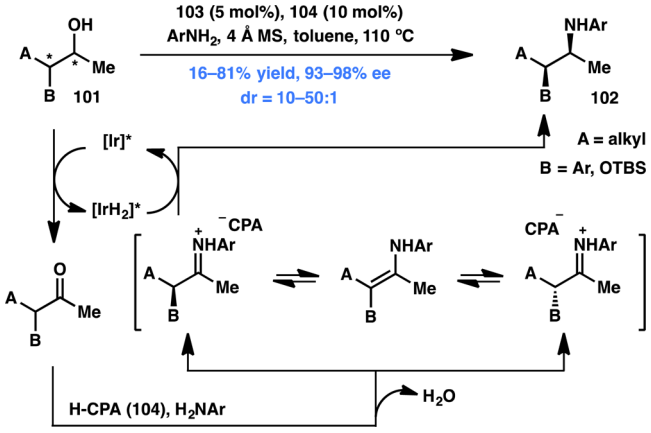


originate from the recognition by the chiral catalyst complex of only one atropisomer of either the substrate or the reactive intermediate. This methodology is the first instance in the literature where a chiral CpRh complex (**98**, Figure 7) is utilized in an oxidative coupling reaction. Although the substrate scope remains limited, this methodology is a promising lead that can spawn more general applications.

3.5. Amination

Zhao and co-workers recently disclosed a useful protocol for the conversion of racemic secondary alcohols to enantio- and diastereopure secondary amines (Scheme 17).[106] The trans-

Scheme 17. Zhao's Borrowing-Hydrogen DKR Strategy



formation utilizes cooperative catalysis involving chiral Ir complex **103** and CPA catalyst **104** (Figure 8). Impressively, a mixture of four isomers of alcohol **101** can be converted to predominantly a single diastereomer of acyclic amine **102** through a "borrowing hydrogen," redox-neutral pathway. The racemic alcohol substrate is first dehydrogenated to ketone by the Ir-catalyst (**103**), followed by CPA-promoted enantioselective protonation, resulting in the formation of an imine intermediate. This species is then reduced diastereoselectively by the [IrH_2] complex to afford the amine product in high enantio-and diastereopure fashion. In addition to providing facile access to chiral secondary amines, the Zhao group has also shown that chiral amino alcohols (B = OTBS) can be obtained using this methodology. As the racemization is not affected by the catalyst responsible for establishing the initial point of enantioselectivity, this example is classified as a DKR, rather than as a DyKAT (vide infra).

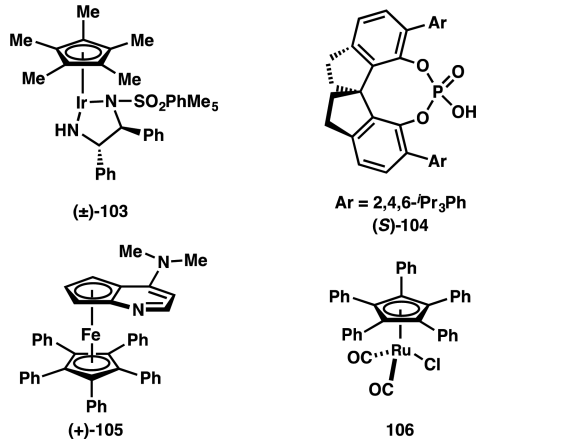
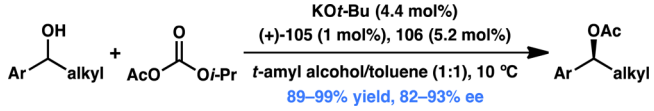


Figure 8. Catalysts from Schemes 17 and 18.

3.6. Acylation

In 2012, the Fu group reported the first example of a nonenzymatic DKR of aryl alkyl carbinols via enantioselective acylation (Scheme 18).[107] Previously, these authors had

Scheme 18. Fu's Nonenzymatic Acylation via DKR



established a classical kinetic resolution for the acetylation of secondary alcohols using planar-chiral DMAP derivative **105** (Figure 8).[108] Unfortunately, direct application of these conditions to a dynamic variant by simply adding a Ru-based racemization catalyst (**106**) did not prove fruitful.[109] It was observed that the Ru complex was being acylated by Ac_2O, thereby inhibiting the racemization catalyst. To circumvent this problem, less electrophilic acyl carbonates were explored as alternative acylation agents. Of the acyl carbonates examined, acetyl isopropyl carbonate gave the best yields and enantioselectivities. Using a mixture of toluene and *t*-amyl alcohol as solvent, the DKR of a variety of aryl alkyl carbinols was achieved in both high yield and enantioselectivity. Of note, this methodology applies to branched alkyl substrates, a current limitation of the analogous enzymatic methodologies. Substrates with electron-rich and electron-poor as well as ortho-, meta-, or para-substituted aromatic groups, extended π-systems, and allylic alcohols were well-tolerated. Mechanistic studies reveal the reversible nature of the *N*-acylation of the chiral DMAP catalyst (**105**) and the rate-determining step as the acyl transfer from **105** to the alcohol facilitated by carbonate anion.

3.7. Asymmetric Reduction

The Noyori group laid the foundations in the field of asymmetric hydrogenation with their pioneering research in the Ru-catalyzed asymmetric hydrogenation of β-ketoesters via DKR.[110] Since then, asymmetric hydrogenation and asymmetric transfer hydrogenation have become the most extensively studied and utilized class of transition-metal-catalyzed DKR transformations. The huge numbers of reports on this concept cover a broad substrate scope and are routinely used on milligram-scale in research laboratories to multikilogram-scale in industrial settings. Because of the large number of examples reported in the literature covering asymmetric

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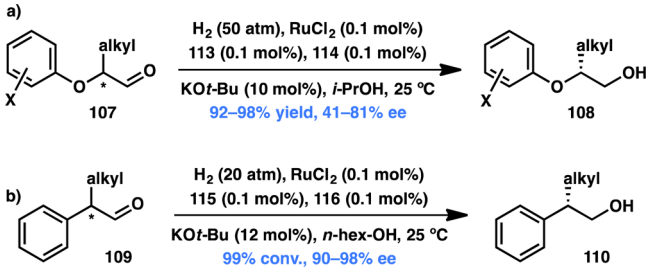
reduction via DKR, this Review will only cover a select few and the reader is directed to references for the rest.

3.7.1. Asymmetric Hydrogenation. In the present context, DKR−asymmetric hydrogenation processes have been a popular method to reduce aldehydes, ketones, and carbon−carbon double bonds. The typical catalyst system includes a transition-metal (usually Ru, Rh, Ir, Ni, Pd, or Pt) precatalyst, a chiral 1,2-diamine ligand, and in some cases a chiral bisphosphine ligand. The chiral catalyst reacts preferentially with one enantiomer of the substrate. For aldehydes, ketones, and other enolizable substrates, the reaction is performed in the presence of a base, which facilitates the substrate racemization via enolate formation, thus rendering the overall transformation a dynamic kinetic resolution.

Aldehydes. The Zhou and List groups independently reported the Ru(II)-catalyzed asymmetric reduction of racemic, α-branched aldehydes via DKR (Scheme 19). While the Zhou

Scheme 19. Zhou's and List's Aldehyde Reduction via DKR



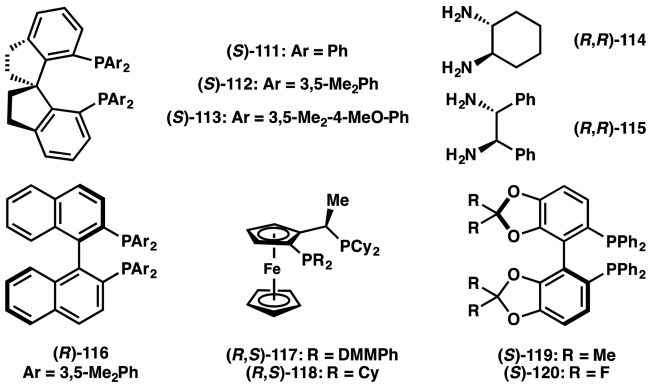
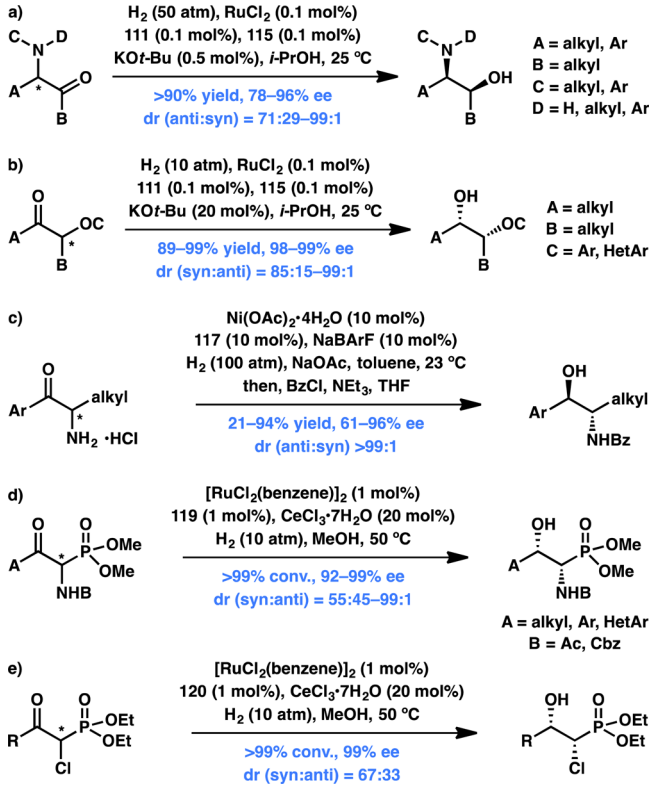


Figure 9. Chiral ligands used in Schemes 19, 20, and 32.

group enlisted SDP as the chiral ligand (**111**, Figure 9) to obtain moderate to good selectivity,[111,112] List and co-workers found that DM-BINAP (**116**, Figure 9) affords the alcohol product (**110**) with excellent enantioselectivity.[113] The List group has also reported reductive amination via DKR of the same substrate class.[114]

Ketones. Within the past few years, a number of groups have developed methods for the asymmetric hydrogenation of various α-functionalized ketones via DKR.[115−117] In 2009 the Zhou group developed a chiral $RuCl_2$−SDP/DPEN-catalyzed asymmetric hydrogenation of racemic α-amino aliphatic ketones to their corresponding chiral amino alcohols with two adjacent stereocenters of anti configuration (Scheme 20a).[118] Both alkyl and aryl substitution alpha to the ketone and on the nitrogen atom are tolerated, as are secondary

Scheme 20. Enantioselective Hydrogenative DKRs



amines. In 2010 these authors extended this methodology to α-aryloxydialkyl ketones (Scheme 20b).[119] Again using a chiral $RuCl_2$−SDP/DPEN catalyst, the substrates were converted to their corresponding chiral β-aryloxy alcohols with two adjacent stereocenters with anti configuration. The substrate scope could be extended to α-aryl substitution, as well as to α-heteroaryloxy substitution. In 2009 the Hamada group also employed a DKR process to access *anti*-amino alcohols (Scheme 20c).[120] In contrast to Zhou's approach, Hamada utilized nickel catalysis to effect the asymmetric hydrogenation of aromatic α-amino-ketone hydrochlorides to their corresponding β-aminoalcohols, again with anti stereochemistry. In 2013, the Zhang group utilized ruthenium catalysis to convert α-amido-β-ketophosphonates to their corresponding β-hydroxy-α-amido phosphonates with syn stereochemistry (Scheme 20d).[121] The scope of this transformation extends to alkyl, aryl, and heteroaryl ketones with secondary amines of acyl or Cbz protection. Similarly, in 2010 Ratovelomanana-Vidal, Genêt, and co-workers achieved the ruthenium-catalyzed asymmetric hydrogenation of α-chloro-β-ketophosphonates to their corresponding α-chloro-β-hydroxyphosphonates with syn stereochemistry (Scheme 20e).[122]

β-Ketoesters. In addition to ketones, several examples have also been reported on the asymmetric hydrogenation via DKR of racemic β-ketoesters,[123−125] especially with amino groups at the α-position.[126−130] A representative example on this topic described by the Hamada group is depicted in Scheme 21.[131] An Ir(I)−(*S*)-MeOBIPHEP (**123**, Figure 10) catalyst system is used in the hydrogenation of racemic α-amino-β-ketoester hydrochlorides **121** to obtain *anti*-β-hydroxy-α-amino acid derivatives **122** in high yield, high enantioselectivity, and with excellent diastereoselectivity.

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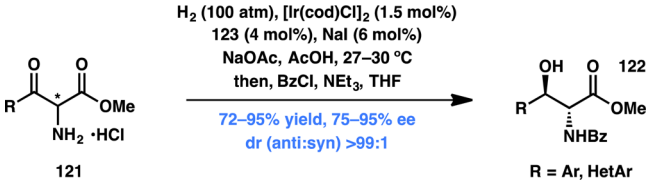
Scheme 21. Hamada's α-Amino-β-ketoester Hydrogenative DKR



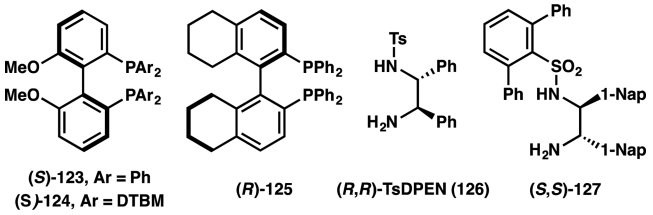
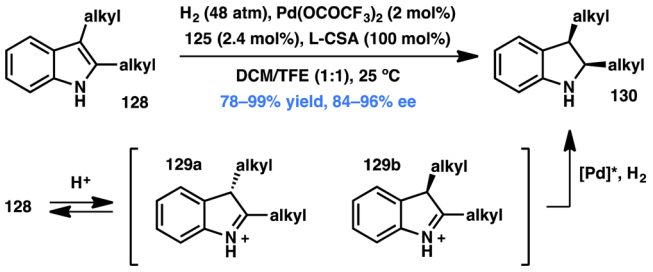


Figure 10. Chiral ligands used in Schemes 21–27, 29–31, 35, and 48.

Indoles. In 2010, Zhou and co-workers reported an asymmetric hydrogenation protocol of unprotected indoles that proceeds via DKR.[132−134] Both mono- and disubstituted indoles are readily reduced in the presence of a Brønsted acid promoter and Pd(II) and (*R*)-H8-BINAP (**125**, Figure 10) as the catalyst (Scheme 22). The reaction is believed to proceed

Scheme 22. Enantioselective Indole Protonation/Reduction

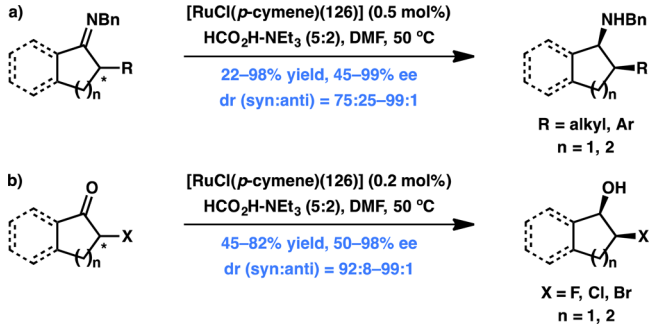


through the equilibrating iminium species **129a** and **129b**, which are generated through reversible, nonselective protonation of the indole 3-position. The iminium ions thus produced are then selectively reduced to afford the desired indoline (**130**) in high yield and enantioselectivity.

3.7.2. Asymmetric Transfer Hydrogenation. In contrast to the examples discussed above where a number of transition-metal catalysts have been developed, Ru-based catalysts almost exclusively catalyze the corresponding asymmetric transfer hydrogenation (ATH) transformations. Additionally, the reducing agent is generated in situ using a number of recipes, most common being a 5:2 cocktail of formic acid and triethylamine. As was the case in the asymmetric hydrogenation reactions that proceed via DKR, the asymmetric transfer hydrogenations of enolizable substrates are also performed under conditions that are conducive to enolization.

Ketones. Fernández, Lassaletta, and co-workers have made significant contribution in the field of Ru-catalyzed hydrogenation of ketones and imines. For example, in 2005 they reported a highly enantio- and diastereoselective reduction protocol for α-substituted cyclic imines (Scheme 23a), with catalyst loadings as low as 0.2 mol %.[135] These authors also made another interesting breakthrough in the field by developing a method for the reduction of α-halo ketones to the corresponding vicinal halohydrins (Scheme 23b)[136] without

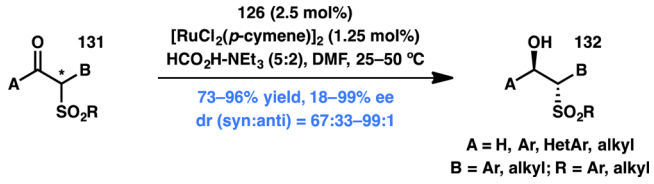
Scheme 23. ATH-Based DKR on 5-Membered Ring Ketones and Ketimines



the concomitant reduction of the alkyl halide, a common problem with this type of substrate.

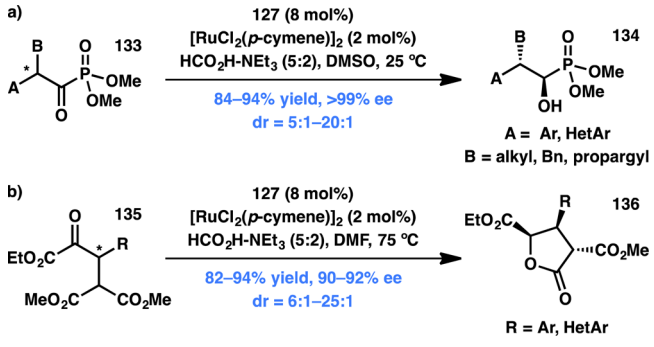
Through the endeavors of a number of research groups all over the world, a wide range of functionalities is now tolerated at the α-position of carbonyl compounds.[137−142] In 2009, Zhang and co-workers disclosed the asymmetric transfer hydrogenation DKR strategy for the reduction of cyclic and acyclic β-ketosulfones under mild conditions with a broad substrate scope (Scheme 24).[143] Along similar lines, β-formylsulfones can also be reduced efficiently to the corresponding primary alcohols.[144]

Scheme 24. ATH-Based DKR on β-Ketosulfones



A substantial impact in the ATH-based DKR arena can be attributed to the Johnson group. They have developed a robust methodology for the reduction of α-acyl phosphonates (**133**) that provides access to α-hydroxyalkylphosphonates (**134**) in excellent yield along with very high enantio- and diastereocontrol (Scheme 25a).[145] Another noteworthy accomplishment

Scheme 25. Johnson's ATH-Based DKR Strategies



from Johnson and co-workers is the reduction of β-aryl α-ketoesters via DKR followed by cyclization onto a pendent malonate to form lactone products (Scheme 25b).[146] This methodology provides access to highly functionalized γ-butyrolactones (**136**) that possess three contiguous stereocenters and, not surprisingly, has found applications in natural

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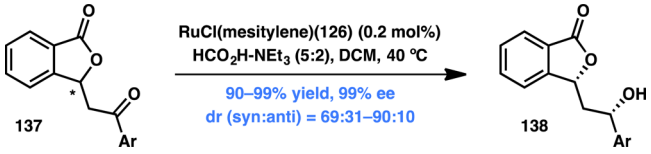
product synthesis and is discussed in section 3.7.4 of this Review.

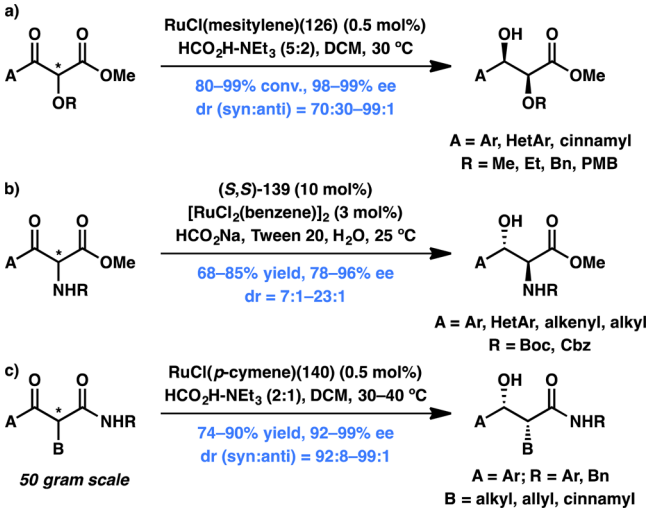
Liu and co-workers have demostrated that this technology can also be used to control diastereoselectivity in a 1,3-fashion in the reduction of β-ketophthalides (**137**) to obtain β-hydroxyisobenzofuranones (**138**) (Scheme 26).[147] The reaction only requires very low catalyst loading and affords desired product in excellent yield and enantioselectivity albeit with modest to good diastereoselecitvity.

Scheme 26. ATH-Based DKR on β-Ketophthalides



β-Ketoesters and β-Ketoamides. Transfer hydrogenation-based DKR has been extended to β-ketoesters and β-ketoamides, including those with heteroatom substitution at the α-position (Scheme 27). The products thus obtained are

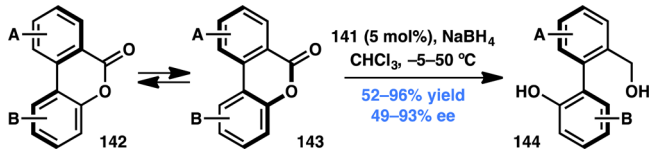
Scheme 27. ATH-Based DKR on β-Ketoesters and -amides



valuable chiral building blocks. For example, the Ratovelomanana-Vidal group has developed a protocol that delivers monodifferentiated *syn*-1,2-diols with high enantio- and diastereocontrol via the reduction of racemic α-alkoxy-β-ketoesters (Scheme 27a).[148,149] Seashore-Ludlow, Saint-Dizier, and Somfai employed a similar catalyst system to effectively reduce racemic α-NHBoc-β-ketoesters to *anti*-β-hydroxy-α-amino acid derivatives in aqueous media (Scheme 27b).[150] A team of researchers from Merck led by Limanto and Krska has found α-alkyl β-ketoamides to be excellent substrates for Ru-catalyzed ATH-DKR that afford *syn*-α-alkyl β-hydroxyamides with high enantio- and diastereoselectivity (Scheme 27c).[151]

3.7.3. Reduction with Hydride. In 2008 Yamada and co-workers extended Bringmann's DKR-based synthesis[152] of axially chiral biaryl compounds via the reduction of biaryl lactones (Scheme 28).[153] With the β-ketoiminatocobalt(II) catalyst ((*S*,*S*)-**141**, Figure 11) various substituted optically active biaryl compounds were synthesized in good yields and high ee's. Biaryl lactones required an increase in temperature to 50 °C for facile racemization of atropisomers. These new

Scheme 28. Cobalt-Based ATH for Chiral Biaryl Synthesis



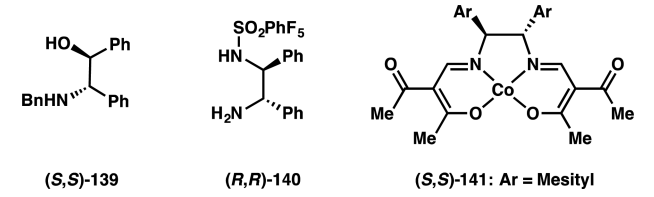
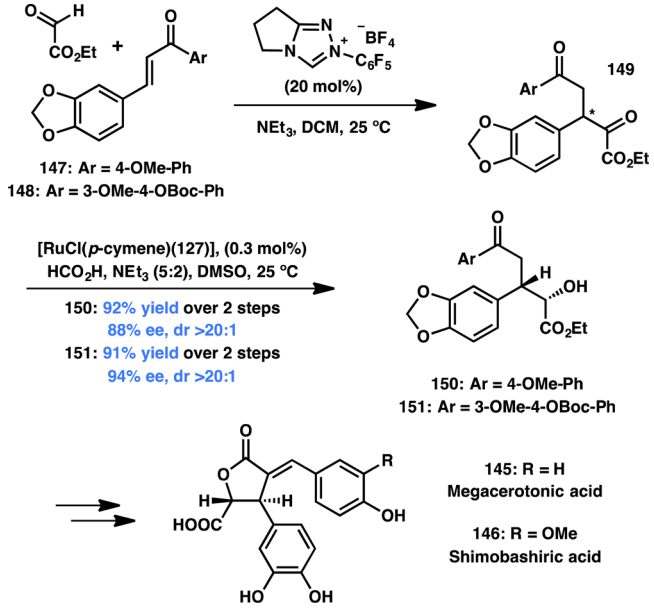


Figure 11. Chiral ligands used in Schemes 27 and 28.

conditions allowed for the synthesis of chiral biaryls in high yields and enantioselectivity.

3.7.4. Application of Asymmetric Reduction in Complex Molecule Synthesis. *Asymmetric Transfer Hydrogenation. Megacerotonic Acid and Shimobashiric Acid.* The Johnson group recently reported the first asymmetric total synthesis of megacerotonic acid (**145**) and shimobashiric acid (**146**) that utilizes their group's methodology for the asymmetric construction of γ-butyrolactones using a Ru-catalyzed, ATH-based DKR strategy (Scheme 29).[154] The

Scheme 29. Johnson's Total Syntheses of Megacerotonic Acid and Shimobashiric Acid



racemic substrates were prepared in one step via an NHC-catalyzed Stetter reaction of β-aryl enones **147** and **148** with ethyl glyoxylate. The crude product was subjected to the key ATH-based DKR with Ru-monosulfonamide **127** (Figure 10) as the catalyst. The requisite alcohol products **150** and **151** were obtained with over 90% yield with high enantio- and diastereoselectivity. With an efficient route to these key intermediates, the asymmetric synthesis of megacerotonic acid (**145**) and shimobashiric acid (**146**) was accomplished in 9 and 11 steps, respectively.

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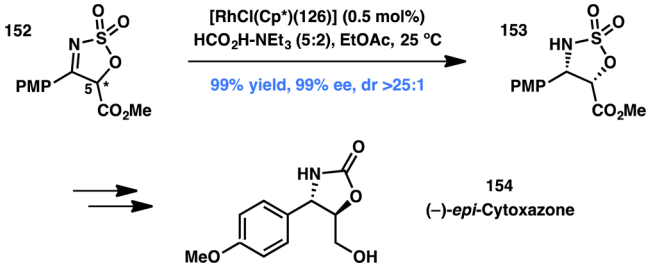
(−)-epi-Cytooxazone. A useful addition to the scope of ATH via DKR methodology is the asymmetric reduction of prochiral cyclic sulfamate imines that was pioneered by Lee and workers (Scheme 30).[155−157] The methodology provides an

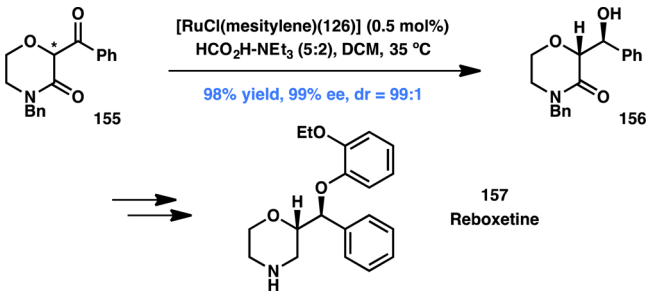
Scheme 30. Lee's Total Synthesis of (−)-*epi*-Cytoxazone



enantioselective technique to synthesize cyclic sulfamates that can be valuable chiral building blocks for the synthesis of complex molecules. In their initial efforts, substrates bearing aryl and alkyl groups at the 4-position were studied and enantioenriched products were obtained, however, only with a maximum of 75% ee, while substrates bearing alkyl groups at the 5-position afforded products in 98% ee. To improve the results, the authors hypothesized that, by increasing the acidity of the hydrogen at the 5-position, rapid racemization would be facilitated and improve the stereoselectivity of the transformation. Excellent results were obtained with electron-withdrawing groups at the 5-position. In a representative example, sulfonyl imine **152** was treated with a chiral rhodium catalyst to obtain sulfamate **153** in near perfect yield and enantio- and diastereoselectivity, and it was used to synthesize (−)-*epi*-cytoxazone (**154**).[156]

Reboxetine. Another interesting application of DKR-based ATH from the Lee laboratory describes the construction of two contiguous stereocenters in one step to obtain various 2-substituted morpholine analogues (Scheme 31).[158] In the

Scheme 31. Lee's ATH-Based Synthesis of Reboxetine



event, subjecting racemic morpholin-3-one **155** to ATH conditions cleanly affords the reduction product **156** with 98% yield and 99% ee. The method provides access to the pharmaceutically relevant 2-substituted morpholine benzyl alcohols in enantioenriched form. Alcohol **156** was transformed to the known antidepressant (*S*,*S*)-reboxetine (**157**) in a few straightforward steps.

Other noteworthy examples of ATH-based DKRs in complex molecules syntheses that are not discussed in this Review are depicted in Figure 12.[159−162]

Asymmetric Hydrogenation. (+)-γ-Lycorane. In a series of publications, Xie and Zhou have disclosed their group's efforts on the application of Ru-catalyzed asymmetric hydrogenation

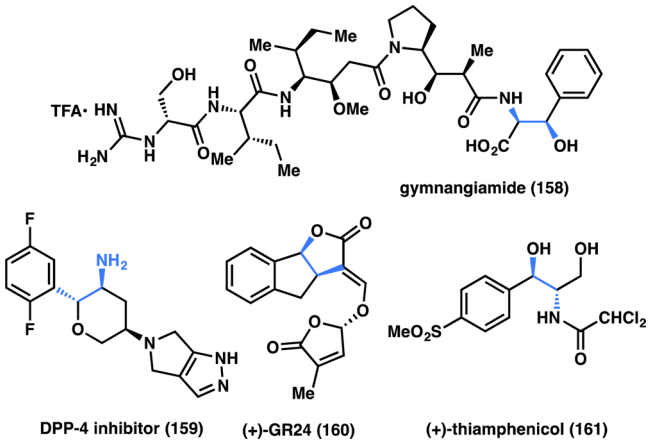
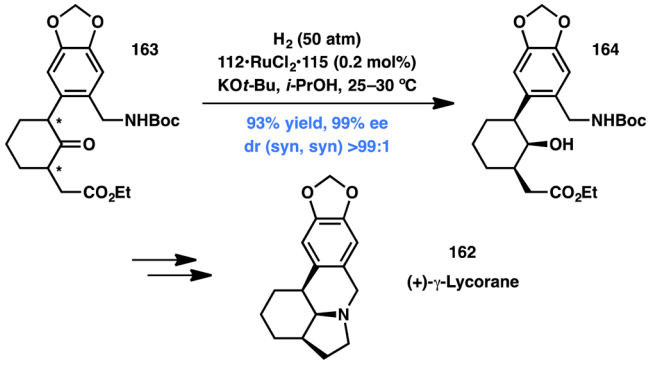


Figure 12. Other total syntheses involving ATH-based DKR.

involving DKR for the total synthesis of a number of natural products.[163−166] Racemic α-substituted cyclic ketone substrates were processed via this technology to establish two or three contiguous stereocenters. This approach has several advantages: the reaction is carried out on readily accessible substrates, tolerates a number of functional groups, and works well with sterically hindered substrates. The most impressive application of this methodology is showcased in the total synthesis of (+)-γ-lycorane (**162**).[155] α,α′-Disubstituted ketone **163** was subjected to asymmetric hydrogenation to afford alcohol **164**, thus creating three stereocenters via DKR in a single step (Scheme 32). With facile access to enantiopure **164**, Xie, Zhou, and co-workers completed the asymmetric synthesis of **162** in three additional steps.

Scheme 32. Xie and Zhou's Total Synthesis of (+)-γ-Lycorane



PF-00951966. Lall and co-workers reported the use of β-ketopyrrolidinone **165** as the substrate for asymmetric hydrogenation-based DKR (Scheme 33).[167] In a reaction performed on a multigram scale, **165** was reduced via a ruthenium-catalyzed process that afforded β-hydroxylactam **166** in good yield and excellent selectivity. Alcohol **166** was then transformed to furnish fluoroquinolone antibiotic **167** (PF-00951966) in 10 steps.

Glucagon Receptor Antagonist. A tour de force application of asymmetric hydrogenation−DKR transformation was developed at Merck, with the key reaction performed on an impressive 110 kg scale en route to the synthesis of **172**, a glucagon receptor antagonist (GRA) (Scheme 34), which has been recognized as a potential candidate in the treatment of

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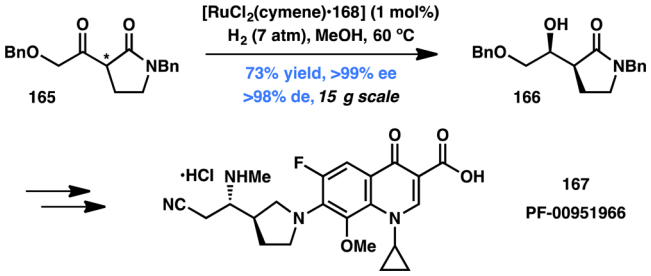
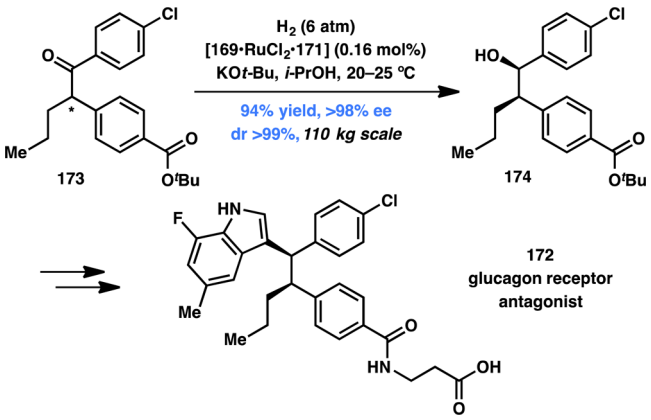
Scheme 33. Pfizer's DKR-Based Synthesis of PF-00951966



Scheme 34. Merck Process' Synthesis of GRA 172



type-2 diabetes.[168] In the event, ketone **173** was reduced in the presence of Ru-SEGPHOS (**168**, Figure 13) catalyst to afford alcohol **174** in 94% and >98% ee and dr, respectively. In five subsequent steps, alcohol **174** was processed to the target molecule.

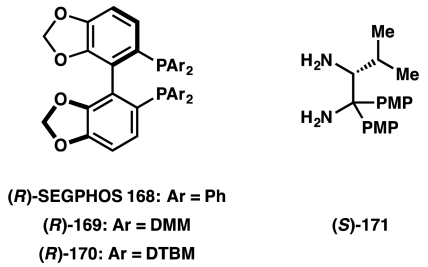
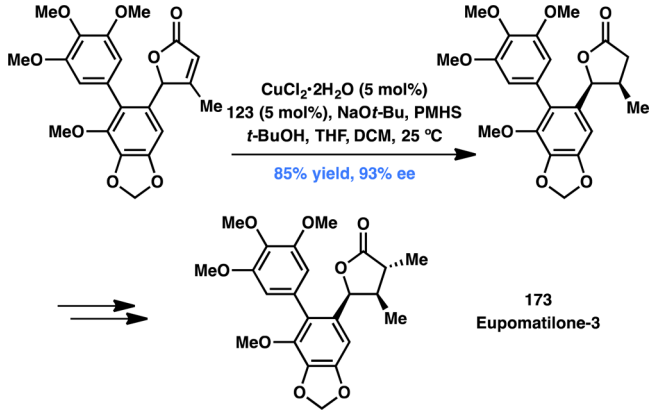


Figure 13. Chiral ligands used in Schemes 33–34, 41, and 51.

Reduction with Hydride. Eupomatilone-3. In 2005 Buchwald and co-workers completed the first asymmetric total synthesis of eupomatilone-3 (**173**, Scheme 35).[169] All members of the family possess a highly oxygenated biaryl moiety appended to a cis-4,5-disubstituted butyrolactone that, for eupomatilone-3, was accessed via the asymmetric conjugate reduction via DKR of the intermediate 3-methyl-4-aryl butenolide. Using MeO-BIPHEP (**123**, Figure 10) as the chiral ligand, PMHS as the hydride source, and an excess of base at room temperature, the corresponding cis-4,5-disubstituted lactone was obtained as a single diastereomer in 85% yield and 93% ee. The scope of this DKR was successfully extended to other 3-methyl-4-aryl butenolides; however, the extension of these conditions to γ-alkyl lactones proved unsuccessful. Nonetheless, this work represents the first copper-catalyzed

Scheme 35. Buchwald's Total Synthesis of Eupomatilone-3



DKR of an unsaturated lactone, enabling the asymmetric total synthesis of eupomatilone-3 in six steps and 48% overall yield.

The examples discussed above were chosen to give the reader an idea of the versatility of the asymmetric hydrogenation–DKR strategy in complex molecules synthesis. Other examples that were not covered are depicted in Figure 14.[170−176]

3.8. Concluding Remarks—Dynamic Kinetic Resolutions

DKRs have become a vital piece in the organic chemist's toolkit, particularly with respect to asymmetric hydrogenation

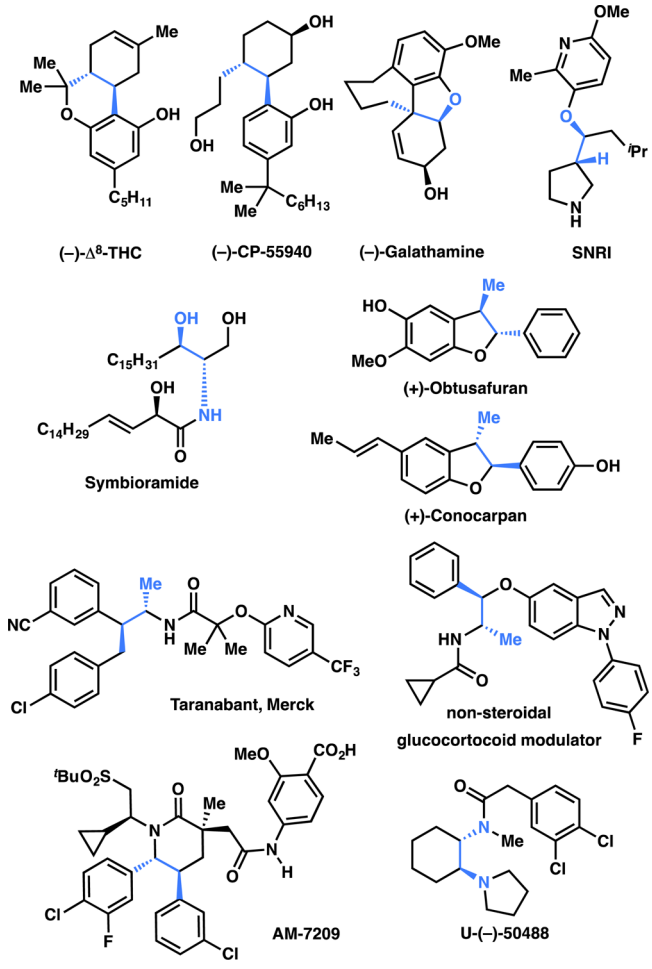


Figure 14. Other natural products and pharmaceuticals synthesized via DKR.

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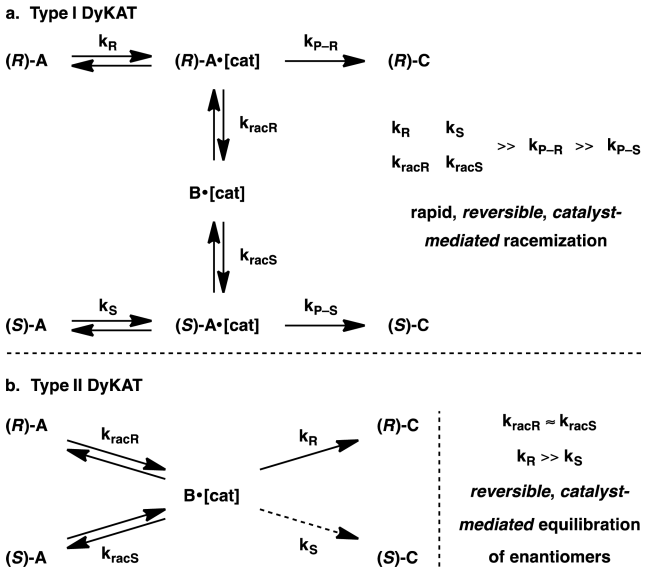
and transfer hydrogenation. The possibility of funneling all material through a single enantiomer brings incredible value to DKRs, especially when compared to classical kinetic resolution. It is our hope that this important research area will continue to grow in the coming years.

4. DYNAMIC KINETIC ASYMMETRIC TRANSFORMATIONS

The third section in this Review belongs to dynamic kinetic asymmetric transformations, or DyKATs.[177] Similar to DKRs, DyKATs also involve an equilibration of substrate enantiomers; however, they differ in that a chiral catalyst is responsible for this equilibration. Furthermore, DyKATs can be divided into two types. Type I DyKATs involve the binding of both enantiomers of the substrate to the catalyst to provide a mixture of diastereomeric substrate−catalyst pairs {cf. (*R*)-A·[cat] vs (*S*)-A·[cat], Scheme 36a}. These pairs are then rapidly equilibrated, often through a prochiral intermediate B (B·[cat]), with one of the two reacting to form the product [(*R*)-C in this case] with a much higher rate than the other (i.e., $k_{P\text{-}R} \gg k_{P\text{-}S}$, Scheme 36a). Type I DyKATs resemble DKRs in that the rate of enantiomeric equilibration k_{rac} must be faster than the rate of product formation $k_{P\text{-}R}$, with the notable difference that the interconversion of enantiomers is catalyst-mediated. In contrast, Type II DyKATs involve the loss of the substrate's chiral center during its interaction with the chiral catalyst to form a prochiral substrate B bound to the chiral catalyst. Selectivity in the overall transformation is achieved when one enantiomer of the product [(*R*)-C in this case] is produced with a significantly higher rate than the other (i.e., $k_{P\text{-}R} \gg k_{P\text{-}S}$, Scheme 36b). Type II DyKATs bear similarity to stereoablative transformations in that the rate of racemization of each enantiomer must be similar, and that both must be faster than the rate of product formation [i.e., $k_{racR} \approx k_{racS} \gg k_{P\text{-}R}$ (or $k_{P\text{-}S}$)]. Crucially, the loss of chirality in Type II DyKATs is both reversible and catalyst-mediated, distinguishing them from stereoablative transformations (Section 2).

Scheme 36. Schematic Representation of Type I and Type II DyKATs



4.1. Carbon−Carbon Bond-Forming Reactions

4.1.1. Asymmetric Allylic Alkylation. Recognized as one of the most general and reliable transformations, the asymmetric allylic alkylation (AAA) reactions come in many flavors including DyKAT. This particular subset has found numerous applications and has been reviewed periodically.[178−181] As such, a limited number of examples are presented here for illustration, and the reader is advised to consult previous reviews dedicated to this topic for more information.

In 2009 Trost and co-workers disclosed the allylic alkylation of benzylic nucleophiles generated from the deprotonation of BF_3-bound 2-alkylpyridine units (Scheme 37).[182] A mixture of BF_3·OEt_2, LiHMDS, and *n*-BuLi was needed to affect this challenging deprotonation, while a Pd-ANDEN (**173**, Figure 15) catalyst system was used to activate the racemic cyclic-pivalate electrophile. This combination makes for a highly efficient and selective method for the construction of vicinal tertiary stereocenters, a stereodyad whose construction is certainly not trivial.

Scheme 37. Trost's AAA Reaction (Type I DyKAT) on 2-Alkylpyridine Systems

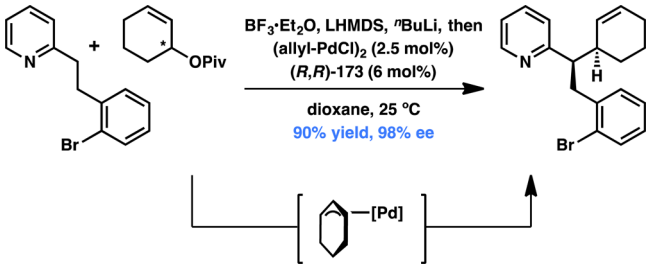


Figure 15. Chiral ligands used in Schemes 37−39.

The Fletcher group disclosed an important breakthrough in this area of nonstabilized AAA reactions with their report on the copper-catalyzed AAA between alkyl zirconium reagents and racemic allylic chloride substrates (Scheme 38).[183,184] The organozirconium species can be conveniently generated in situ from alkenes and Schwartz's reagent (Cp_2ZrHCl). Interestingly, neither Pd- nor Ir-based catalysts delivered the desired product. While it is not entirely clear as to how the chiral catalyst system interacts with the substrate and the alkylzirconium species to afford the product, the authors believe a rapid, copper catalyst-promoted suprafacial S_N2' mechanism to be the reason behind the observed dynamic behavior. The most practical aspect of this transformation is that readily available terminal alkenes can be added to allylic halides to obtain products in good to excellent yield and enantioselectivity. A minor drawback of this strategy, however, is that the presence of Schwartz reagent in

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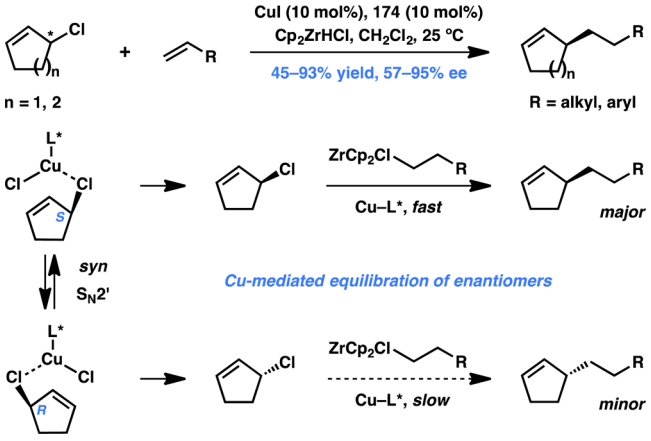
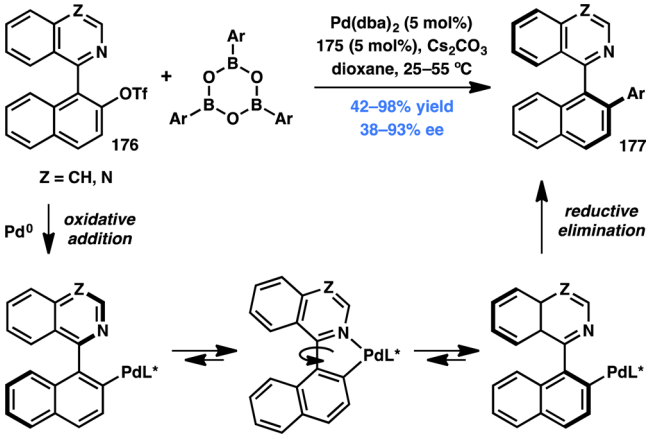
Scheme 38. Fletcher's Copper-Catalyzed AAA Reaction (Type II DyKAT)



the reaction may limit the overall functional group tolerance of the transformation. Thus, there is room for expanding the substrate scope for this methodology.

4.1.2. Cross–Coupling Reactions. *Suzuki–Miyaura Cross-Coupling.* Fernández, Lassaletta, and co-workers demonstrated that the DyKAT strategy could be applied to generate axial chirality via C–C bond construction in racemic biaryl substrates (Scheme 39).[185] Using Pd(0) and TADDOL-derived

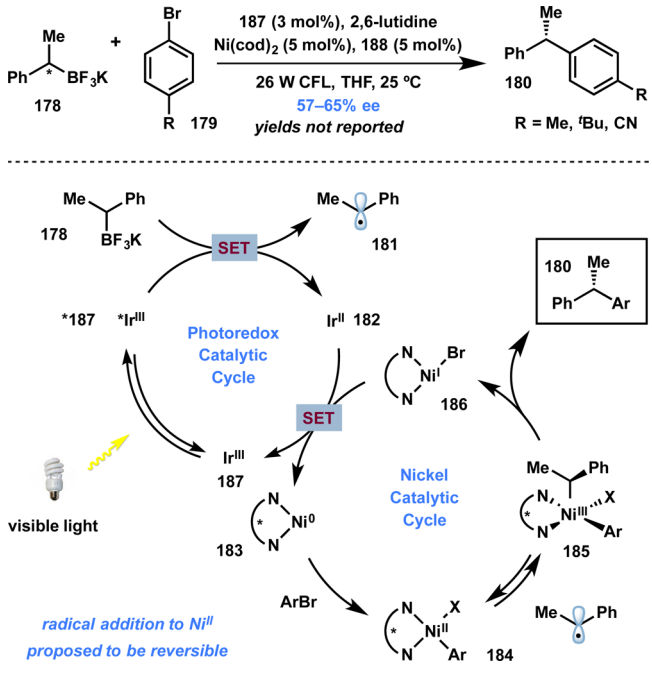
Scheme 39. Fernández and Lassaletta's Asymmetric Biaryl Synthesis



phosphoramidite ligand **175** (Figure 15) as the catalyst system, a Suzuki–Miyaura coupling between racemic 1-aryl-2-triflyloxynaphthalenes and triaryl boroxines effected the asymmetric synthesis of atropisomeric heterocycles.[186−191] It is postulated that the palladium intermediate generated upon the oxidative addition of a racemic 1-aryl-2-triflyloxynaphthalenese **176** to Pd(0) can rotate freely around the biaryl bond, allowing for the facile interconversion of enantiomers. There are two possible mechanisms for enantiodiscrimination: enrichment of one of the two possible oxidative addition products prior to reductive elimination (Type I DyKAT) or a relatively equal ratio of the two in solution with different rates of reductive elimination leading to enantioenriched products (Type II DyKAT). The authors demonstrated that this strategy was effective when a number of 2-substituted pyridines and isoquinolines as well as 4-substituted quinazolines were utilized, obtaining the corresponding products with good to high yield and enantioselectivity.

Nickel-Catalyzed Cross-Couplings. In 2015, Molander, Kozlowski, and co-workers disclosed mechanistic insights into the asymmetric cross-coupling reactions between a racemic secondary alkyltrifluoroborate (**178**) and three aryl bromides (**179**) (Scheme 40).[192] The catalyst system for the trans-

Scheme 40. Molander's SET-Based Coupling (Type II DyKAT)



formation comprises an Ir(III) photoredox catalyst (**187**), $Ni(COD)_2$, and biox ligand **188** (Figure 16). The iridium(III)

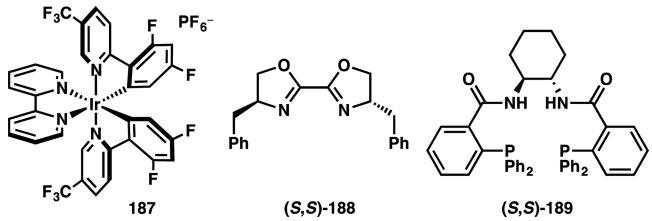


Figure 16. Catalyst and chiral ligands used in Schemes 40 and 42.

photocatalyst **187** plays a dual role in the overall transformation, generating carbon-centered radicals from the alkyltrifluoroborate via single electron transfer (SET) and by reducing Ni(I) species **186** to regenerate the Ni(0) catalyst. DFT calculations suggest that enantioselectivity arises via reversible association and dissociation of the stabilized radical to the Ni(II) intermediate. The authors propose that the diastereomeric Ni(III) complexes display different rates of reductive elimination, providing modestly enantioneriched products through a Type II DyKAT process. The authors did not report the yields of these coupling reactions.

4.1.3. Cycloadditions. *[3 + 2] Cycloadditions.* In 2013, the Davies group reported the first example of DyKAT in carbenoid chemistry in the formation of cyclopentene derivatives from the gold(I)-catalyzed formal [3 + 2] cycloaddition of enol ethers **190** and vinyldiazoacetates **191**

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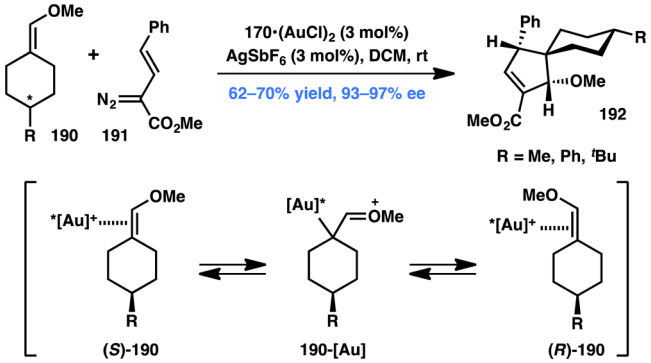
(Scheme 41).[193] This reaction delivered highly functionalized spirocyclic cyclopentene products in high yield and in >90% ee.

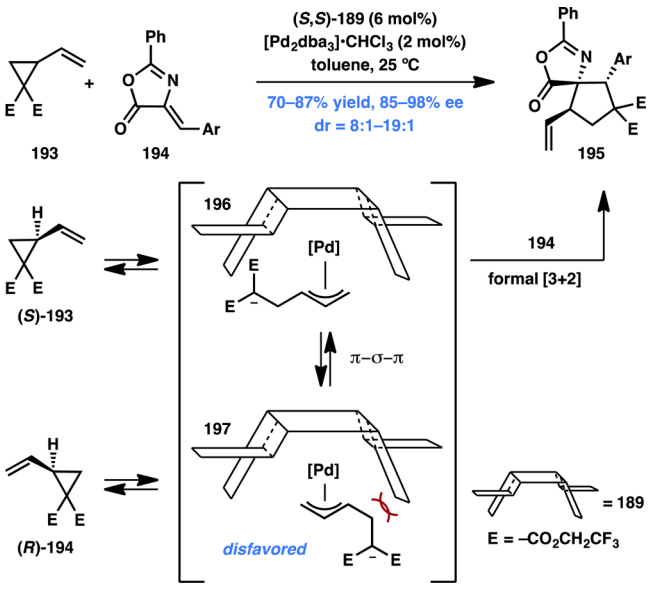
Scheme 41. Gold-Catalyzed [3 + 2] Cycloaddition Featuring a Gold-Mediated Interconversion of Enantiomers (Type II DyKAT)



The reaction generates three contiguous stereocenters in a single step, and remarkably, the products are formed as a single diastereomer. It is proposed that both enantiomers of the product are accessed via rapid, gold-promoted equilibration of *E*- and *Z*-enol isomers via the diastereomeric complex **190**-[**Au**]. Intriguingly, the chiral center itself is inert to the transformation, but this equilibration of enol isomers results in scrambling of its *R* and *S* identity. Subsequent to this equilibration, only the enantiomer that is matched for the reaction at the *Re* face of the DTBM-SegPhos [(*R*)-**170**, Figure 13] gold−vinylcarbene undergoes cycloaddition via initial attack at the vinylogous position of the vinylcarbene intermediate.

Reactions involving donor−acceptor cyclopropanes (DACs) have recently found widespread use.[194−199] The Trost group reported a Pd-catalyzed formal [3 + 2] cycloaddition between racemic vinyl cyclopropane **193** and alkylidene azalactones **194** via a DyKAT process to afford spirocyclic cycloadduct **195** (Scheme 42).[200] Impressively, the reaction produces mainly

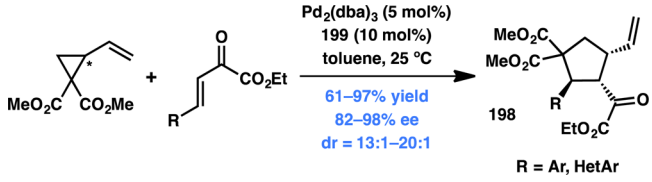
Scheme 42. Trost's Formal [3 + 2] Cycloaddition (Type I DyKAT)



one of the four possible diastereomers as the major product in good yield and excellent enantioselectivity. Mechanistically, the reaction initiates through the nonselective ionization of the vinyl cyclopropane to generate intermediates **196** and **197**. The unique "wall and flap" steric environment created by ligand **189** is able to funnel the equilibrating mixture to thermodynamically favored intermediate **196**. The malonate anion in **196** attacks the azalactone in a 1,4-fashion, and the resulting azalactone enolate traps the π-allylpalladium moiety to produce the desired product. The methodology can be applied to a broad substrate scope and provides access to highly functionalized products.

Xu, Shi, and co-workers developed a Pd-catalyzed formal [3 + 2] cycloaddition reaction of vinyl cyclopropanes with β,γ-unsaturated α-ketoesters to obtain highly functionalized cyclopentane derivatives **198** bearing three contiguous stereocenters (Scheme 43).[201] The reaction tolerates a variety of

Scheme 43. Xu's and Shi's Formal [3 + 2] Cycloaddition (Type I DyKAT)



substitutions on the enone substrate and delivers products with excellent yields and high enantio- and diastereoselectivities.[202] The mechanistic rationale for the observed selectivity is expected to be similar to that observed in Trost's methodology (Scheme 42).

Tang and co-workers have reported a DyKAT involving [3 + 2] annulation of cyclic silyl enol ethers and racemic DACs catalyzed by a copper(II)/**200** system (Scheme 44a).[203] More recently, Waser and co-workers reported [3 + 2] cycloaddition via DKR that utilizes amino-DACs and aldehydes or enol ethers as annulation partners to afford the tetrahydrofuran or cyclopentane products, respectively, in good to excellent yields and enantio- and diastereoselectivity (Scheme 44b).[204] Readily available copper/*t*-Bu-Box (**201**, Figure 17) complex was used as the chiral catalyst. The authors propose that the facial selectivity of the formal [3 + 2] cyclization event is dictated by the catalyst system and that the dynamic process proceeds via reversible cyclopropane ring opening/closing, which may also be mediated by the copper catalyst.

[3 + 2] Annulation of Racemic Allenes with Aryl Ketimines. Cramer and co-workers reported a useful method for the selective construction of substituted indanylamine building blocks (Scheme 45).[205] The Rh(I)-BINAP (**88**, Figure 6) catalyzed transformation can tolerate a broad substrate scope using readily available precursors. Importantly, the authors obtained good to excellent chemical yield and enantio- and diastereoselectivity make this technology a particularly attractive route to access complex scaffolds. The reaction is believed to proceed through a rhodium-catalyzed, ketimine-directed C−H activation and is followed by coordination and insertion of the allenic moiety. A dynamic system is established as a result of isomerization of the diastereomeric allyl rhodium intermediates (**206**), as shown in Scheme 45. The isomerization occurs faster than the ultimate addition across the imine fragment. It was observed that the reaction stereochemistry is

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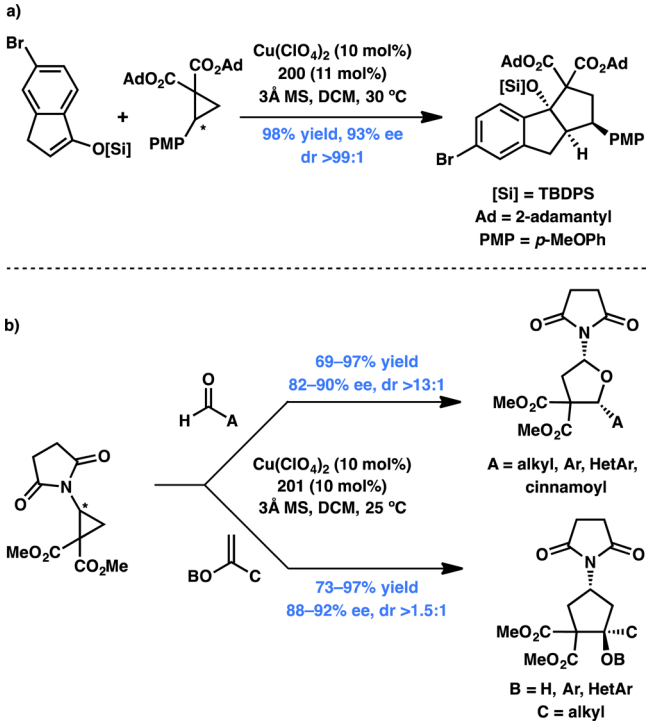
Scheme 44. Copper-Catalyzed Formal [3 + 2] Cycloadditions from Tang and Waser (Type II DyKAT)



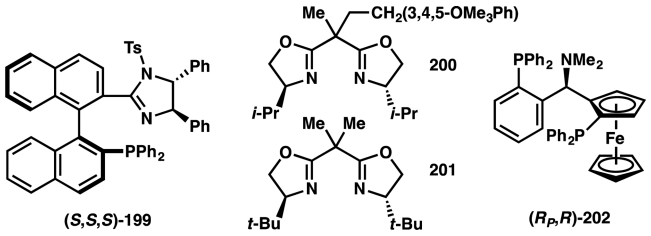
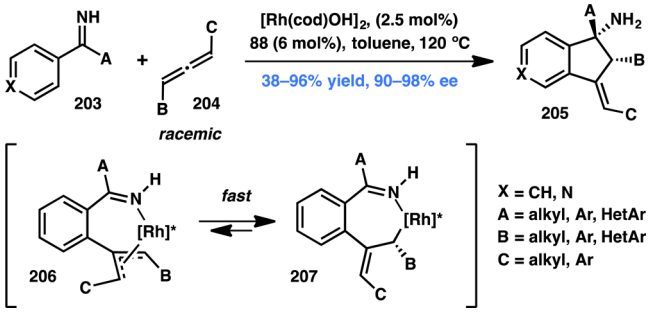


Figure 17. Chiral ligands used in Schemes 43, 44, and 46.

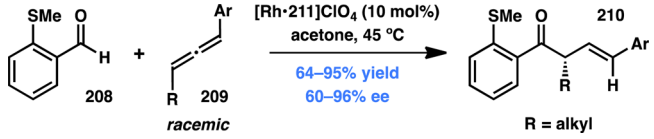
Scheme 45. Cramer's C−H Activation via Type II DyKAT



controlled entirely by the chiral catalyst system and the axial chirality of the allene component has no effect on the product stereochemistry. Moreover, submitting enantioenriched allene to the rhodium complex in the absence of imine led to complete racemization, providing further evidence for a catalyst-mediated interconversion of enantiomers.

4.1.4. Hydroacylation. Willis and co-workers have used allenes as substrates in rhodium-catalyzed dynamic kinetic asymmetric hydroacylation reactions (Scheme 46).[206] Preliminary reports focused on the use of aliphatic and aromatic aldehydes bearing a thiomethyl moiety at the β-position,

Scheme 46. Willis' Rhodium-Catalyzed Allene Hydroacylation



presumably to facilitate metal coordination and subsequent insertion in the aldehyde C−H bond. Under Rh(I)/Me-DuPhos catalysis (**211**, Figure 18), various 1,3-disubstituted

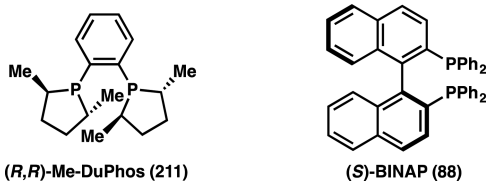


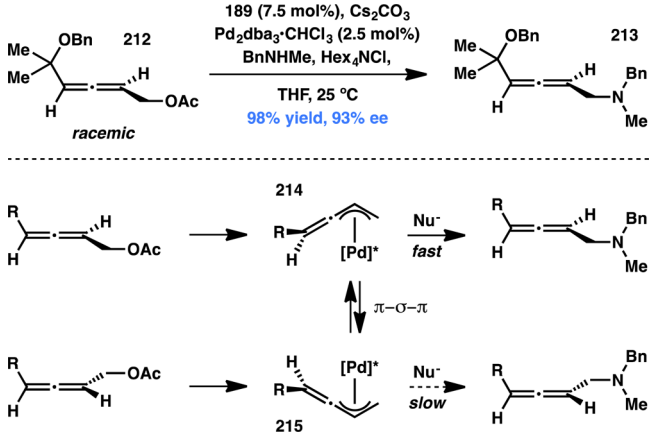
Figure 18. Chiral ligands used in Schemes 46 and 49.

allenes smoothly reacted with aldehydes to afford the corresponding β,γ-enone products in good to excellent yields and enantioselectivities. The authors also carried out mechanistic studies that support a DyKAT mechanism responsible for the observed selectivities. Catalyst control was observed when an enantiomerically enriched allene was employed in the reaction. Moreover, the ee of the recovered allene was found to be significantly reduced, strengthening the proposal of a DyKAT mechanism.

4.2. Carbon−Heteroatom Bond-Forming Reactions

4.2.1. Carbon−Nitrogen Bond-Forming Reactions. *Amination.* In 2005, Trost and co-workers reported the Pd-catalyzed dynamic kinetic asymmetric addition of secondary amines to racemic allenyl acetates (Scheme 47).[207] The

Scheme 47. Trost's C−N Bond-Forming Type I DyKAT on Allenyl Acetates



reaction efficiently produced allenamine **213** via the rapid interconversion of vinyl-Pd(II) intermediates **214** and **215**. In addition to secondary amines, this methodology also tolerates malonate nucleophiles.[208]

The Widenhoefer group reported a gold-catalyzed enantioselective intramolecular hydroamination[209−211] of γ-amino allenes **216** to form 2-vinyl pyrrolidine products **217** (Scheme 48).[212] The cationic gold complex participates in the

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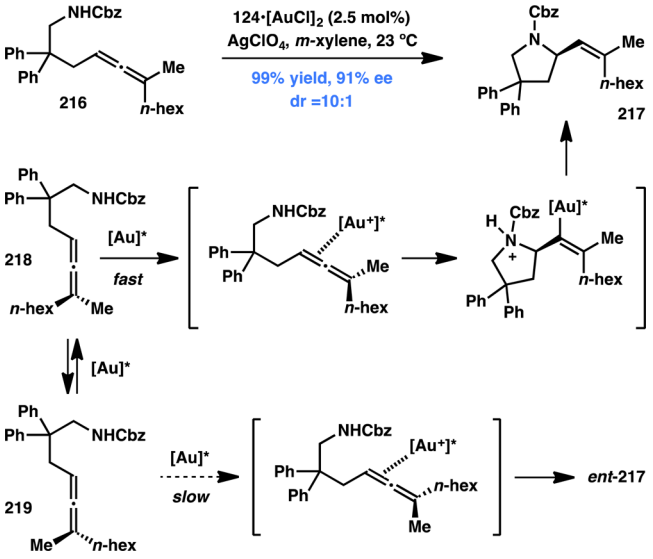
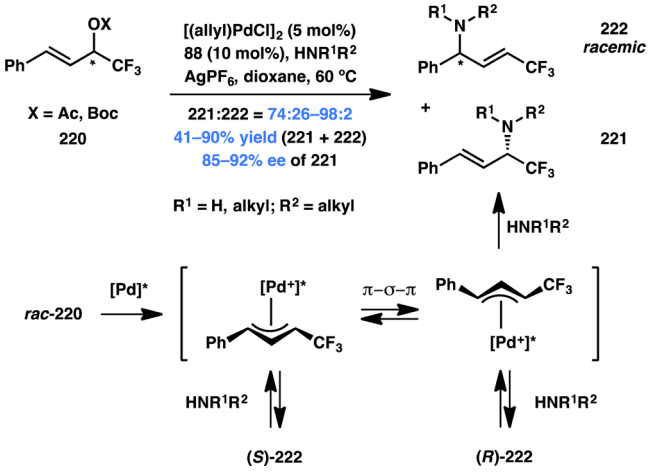
Scheme 48. Widenhoefer's Vinylative Pyrrolidine Formation via Type I DyKAT



racemization of enantiomers **218** and **219** and selectively reacts with one enantiomer of the substrate, thus qualifying as a Type I DyKAT system.[213] Under these conditions, disubstituted allenes deliver the corresponding product *ent*-**217** with poor enantioselectivity.[214]

Kawatsura, Itoh, and co-workers developed an interesting approach for accessing acyclic, chiral CF_3-bearing amines from unsymmetrical 1,3-disubstituted allylic acetates and carbonates via a Pd-catalyzed DyKAT (Scheme 49). The desired α-product

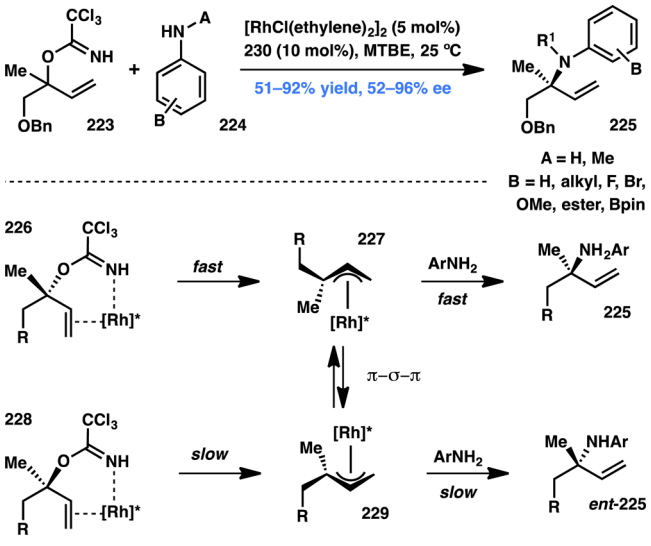
Scheme 49. Reversible Addition of Amine to Benzylic Site Leads to Efficient Type I DyKAT



(**221**) was obtained with good to excellent enantioselectivity along with minor amounts of nearly racemic γ-product (**222**). It was found that the presence of silver additive was critical in achieving the observed enantioselectivity in this dynamic process.

In 2012 the Nguyen group developed a rhodium-catalyzed regio- and enantioselective amination via DyKAT of racemic tertiary allylic trichloroacetimidates with anilines (Scheme 50).[215] Prior research in their group on racemic allylic amination[216] had indicated that the oxidative addition of trichloroimidates **226** and **228** occurred with different rates,

Scheme 50. Nguyen's Type I DyKAT-Based Synthesis of Allylic Amines



suggesting a kinetic resolution was at play. The authors also noted, however, that isomerization of the diastereomeric π-allylrhodium intermediates appeared to be facile, which could be taken advantage of in a DyKAT. The authors hypothesized that the use of an appropriate ligand that would slow the rate of aniline addition could allow more time for a $\pi-\sigma-\pi$ interconversion of the diastereomeric π-allylrhodium intermediates. If this ligand was chiral, such a DyKAT could be realized. A broad ligand evaluation showed that diarylbicyclo[2.2.2]octadiene **230** (Figure 19) provided the

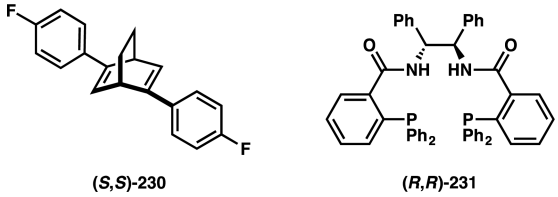


Figure 19. Chiral ligands used in Schemes 50 and 52.

desired product in both high yield and enantioselectivity. Consistent with the authors' observations, electron-rich anilines formed adducts with lower enantioselectivity than their electron-deficient counterparts. This trend likely stems from the correspondingly higher rates of addition of these more nucleophilic coupling partners.

These authors have also developed a closely related Ir-catalyzed dynamic kinetic asymmetric fluorination of racemic, secondary allylic trichloroacetimidates with $Et_3N{\cdot}3HF$ as the fluoride source.[217]

Kitagawa and co-workers reported the use of a DyKAT process for the synthesis of axially chiral 1,2-biaryl indoles via a Pd-catalyzed C–N bond-forming 5-endo-dig amination (Scheme 51).[218,219] The authors recognized that the 2-*t*-butylphenylindole products have a high rotational barrier and can be accessed via an atroposelective, intramolecular cyclization starting from ethynylaryl anilines **232**. Of the numerous chiral ligands screened, (*R*)-SEGPHOS **168** (Figure 13) was found to affect the cyclization with highest enantioselectivity. Best results were obtained with substrates in which the alkyne moiety was capped with 2-substituted

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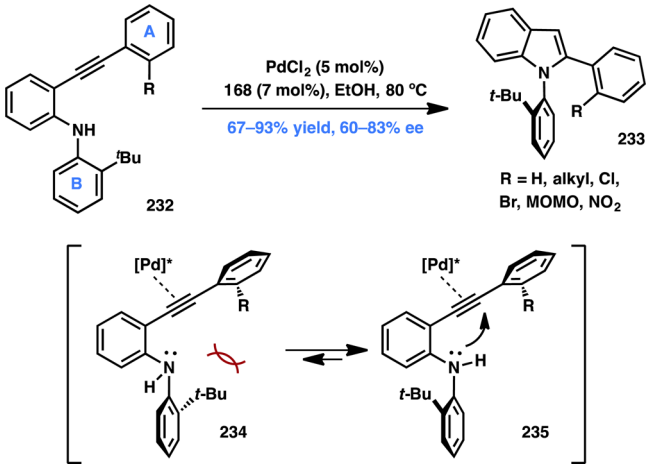
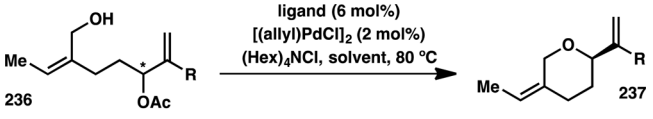
Scheme 51. Kitagawa's Type II DyKAT Method for Atroposelective Indole Synthesis



phenyl groups (ring A). It is believed that, in the enantiodetermining step, axial chirality is generated due to the presence of a substituent at the 2-position of ring A. As a result, the conformation with minimum steric clash between the R group on ring A, the *t*-butyl moiety on ring B, and the chiral ligand on the catalyst is favored. Thus, for R = H, the indole product was obtained in 60% ee, whereas for R = Br, the ee was determined to be 83%, correlating agreeably with the hypothesis. Replacing the *tert*-butyl group on ring B with the smaller isopropyl or phenyl groups was detrimental to the observed enantioselectivities.[220−222]

4.2.2. Carbon−Oxygen Bond-Forming Reactions. Trost and co-workers reported a Pd-catalyzed AAA−DyKAT approach for the synthesis of tetrahydropyran (THP) moieties from racemic Baylis−Hillman-type adducts bearing a tethered alcohol as the nucleophile (Scheme 52).[223] High yield and

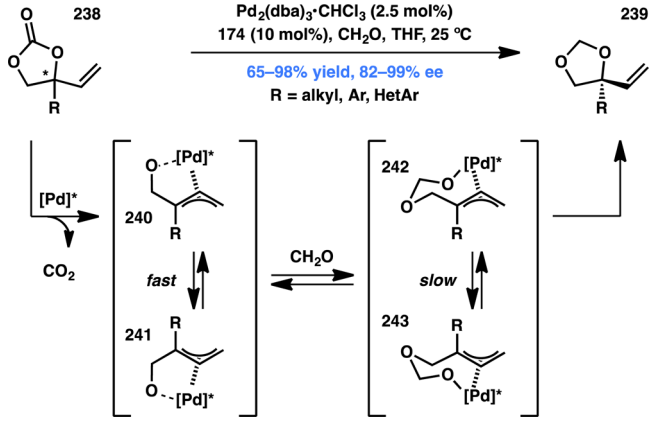
Scheme 52. Trost's Type I DyKAT-Based Method for THP Synthesis



enantioselectivity was observed for both ester and nitrile substrates, although the two required slightly different conditions to achieve the highest levels of efficiency and enantioselectivity. The dynamic system is set up through π-allyl equilibration and enantioselectivity is achieved when this process is faster than the attack by the pendant alcohol. Interestingly, a highly selective kinetic resolution process is observed when the reaction is carried out at 23 °C, indicating that higher temperature is required for the π-allyl equilibration. Kitamura and co-workers disclosed a similar transformation utilizing allylic alcohols, rather than acetates, and showed that one of their substrates provides enantioselective products through a Type I DyKAT.[224]

Zhang and co-workers have reported an interesting extension to the Pd-catalyzed allylic substitution by *O*-nucleophiles (Scheme 53).[225] Their approach utilizes racemic vinyl-substituted ethylene carbonates as substrates that undergo

Scheme 53. Zhang's Decarboxylative Type I DyKAT for Chiral Dioxolane Synthesis



CO_2 extrusion upon exposure to catalytic $Pd_2(dba)_3{\cdot}CHCl_3$ and (*S*,*S*,*S*)-phosphoramidite **174** (Figure 20), leading to a

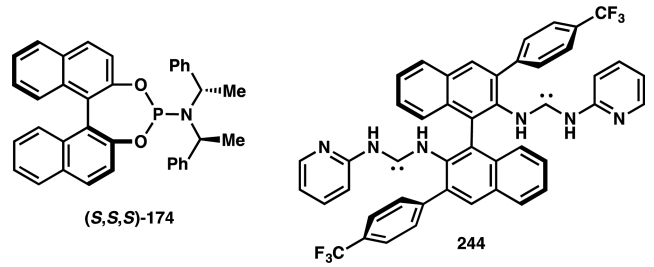
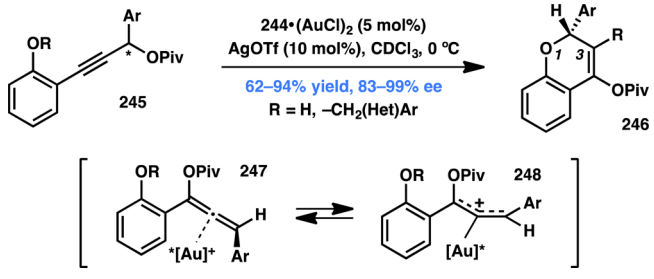


Figure 20. Chiral ligands from Schemes 53 and 54.

rapidly interconverting dynamic system comprising diastereomeric π-allylpalladium intermediates. Formaldehyde then reversibly captures the Pd-alkoxide intermediate, generating a new pair of diastereomeric Pd-allyl complexes, which is much slower to equilibrate. The DyKAT is realized upon reductive elimination, affording methylene acetal-protected tertiary vinylglycols in excellent yield and enantioselectivity.

The Toste group has demonstrated the use of a chiral cationic Au(I)−carbene complex as catalyst for the asymmetric synthesis of highly substituted chromene analogues from suitably functionalized propargylic esters (Scheme 54).[226] A variety of chiral phosphines and NHC ligands were evaluated, and ligand **244** (Figure 20) was identified to be the optimum candidate that delivered the desired product in high yield and selectivity. Both free phenol and benzyl aryl ethers may be used as substrates. The reaction initiates with Au-catalyzed formal [3,3] sigmatropic rearrangement of propargylic ester substrate

Scheme 54. Toste's Type II DyKAT-Based Strategy for Asymmetric Chromene Synthesis



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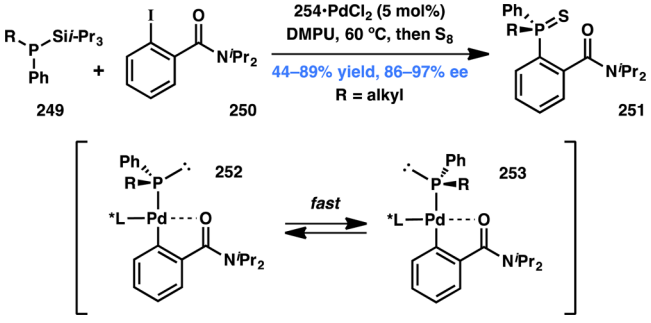
to generate a gold-bound allene. The allene−gold interaction results in scrambling of axial chirality, and stereoselectivity is achieved via a 6-endo-trig attack of the phenolic oxygen to construct the chromene skeleton, followed by either proton or benzyl group transfer to the insipient cation. Mechanistic studies indicate that one of the enantiomers of the substrate reacts faster while the unreacted isomer undergoes racemization via the aforementioned gold−allene pathway.

4.2.3. Carbon−Phosphorus Bond-Forming Reactions.

Glueck and co-workers pioneered Pd-catalyzed C−P cross-couplings involving DKR to obtain chiral phosphines.[227,228] Since then, this field has evolved substantially and reviewed in the recent literature.[229,230] As such, only a couple of representative examples will be discussed here.

In 2007 Chan, Bergman, and Toste designed a Pd-catalyzed arylation of tertiary racemic silylphosphines as a means to synthesize *P*-stereogenic phosphines (Scheme 55).[231] After

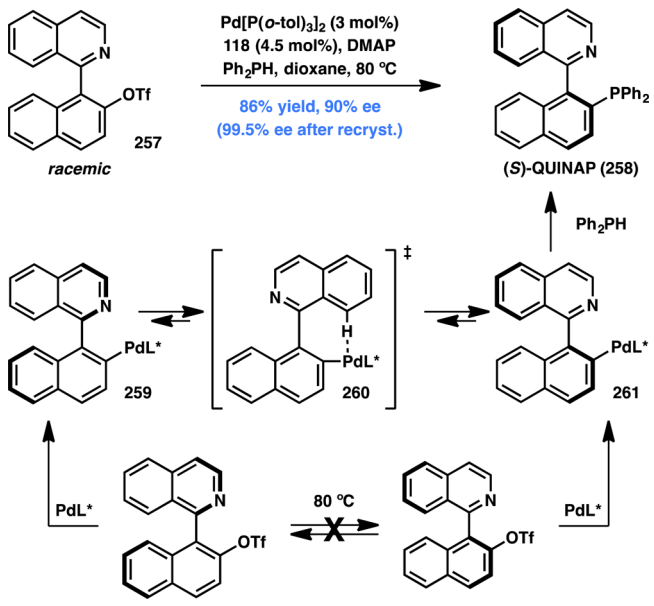
Scheme 55. Bergman and Toste's Type I Synthesis of Enantioenriched *P*-Stereogenic Phosphines



extensive screening it was discovered that *ortho*-benzamide substituents improved the enantioselectivity of the C−P coupling. The authors found that the one-carbon arylacetamide homologues provided decreased ee's, implying that a five-membered palladacycle was crucial for obtaining the highest enantioselectivity. The source of DyKAT stems from the low barrier to epimerization of Pd(II)-phosphide intermediates (due to the facile pyramidal inversion of metal phosphido complexes), which occurs faster than the reductive elimination. Exploration of substrate scope around iodobenzamides revealed that changes in electronics para- to the iodide or to the amide have very little effect on the ee. Electron-rich iodides required longer reaction times but also show excellent enantioselectivities. Other competent variations include substrates with extended conjugation, electron-rich heteroarenes, thiophenyl substrates, and sterically congested amides. Exploration of substrate scope around phosphines revealed that electron-poor substrates decrease ee. Tolerated phosphine variations include less sterically congested alkyl groups as well as oxygenated alkyl groups.

Stoltz, Virgil, and co-workers reported a palladium-catalyzed, atroposelective DyKAT for the asymmetric synthesis of the chiral ligand QUINAP (**258**, Scheme 56).[232] Using a Pd(0)/Josiphos (**118**, Figure 9) catalyst system, racemic triflate precursor **257** was phosphinated to afford QUINAP **258** in good yield and enantioselectivity. It is believed that the diastereomeric arylpalladium intermediates **259** and **261**, produced after a nonselective oxidative addition event, undergo racemization to preferentially form one atropisomer that upon phosphination yields QUINAP with high selectivity. Interest-

Scheme 56. Pd-Mediated Type I DyKAT for the Synthesis of QUINAP

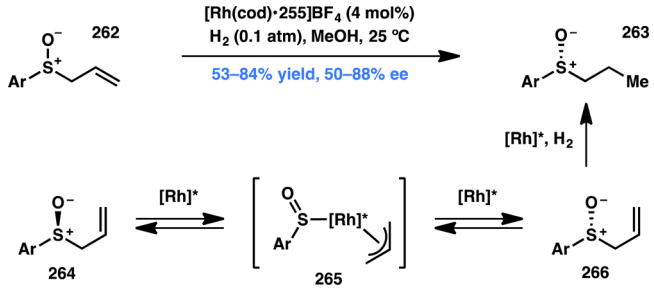


ingly, replacing triflate with bromide on the substrate results in a kinetic resolution process that provides both QUINAP and the unreacted bromide in high yield and enantioselectivity.

4.3. Asymmetric Reduction

Dong and co-workers have developed a Rh-catalyzed asymmetric hydrogenation proceeding through a DyKAT process on allylic sulfoxides, an entirely different substrate class than those discussed above.[233,234] This interesting transformation provides a complementary route to chiral sulfoxide products (Scheme 57), which are usually accessed

Scheme 57. Dong's Reductive Chiral Sulfoxide Synthesis via a Rhodium-Catalyzed Type II DyKAT



via the oxidation of sulfides. Racemic allylic sulfoxides of the type **262** were transformed into enantioenriched sulfoxides **263** under a hydrogen atmosphere with Rh(cod)BF_4-(*S*,*S*)-Ph-BPE (**255**, Figure 21) as the catalyst. The authors postulate a

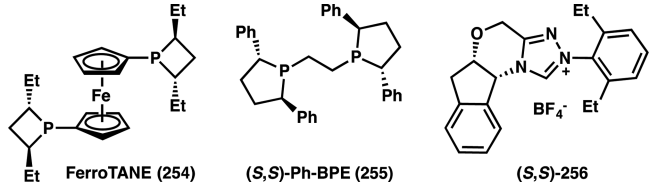


Figure 21. Chiral ligands used in Schemes 55, 57, and 58.

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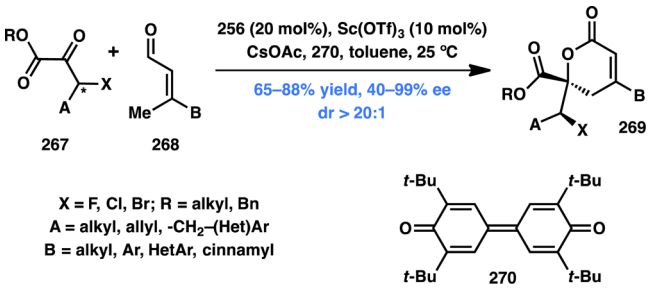
pathway wherein the Rh-catalyst is involved in the racemization of the allylic sulfoxide via reversible C−S bond cleavage−recombination, in addition to the selective hydrogenation of one of the resulting substrate enantiomers, to deliver the desired product in moderate to good yield and enantioselectivity. The reaction optimization process revealed several noteworthy aspects: a relatively low hydrogen pressure (0.1 atm) ensures that the rate of hydrogenation is slow compared to the rate of racemization, and the use of polar solvents, such as methanol, favors the intermediacy of polar intermediates during racemization.

4.4. Miscellaneous Reactions

Wang and co-workers recently disclosed the first example of an intermolecular DKR of α-ketoesters through the synergistic combination of NHC and Lewis acid catalysis (Scheme 58).[235]

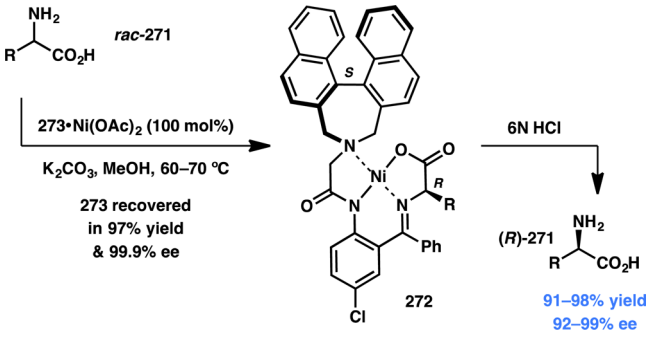
Scheme 58. Wang's Type I DyKAT for the Synthesis of Unsaturated Lactones



The reaction between α-ketoesters (**267**) and β-methylenals (**268**) occurred to produce δ-lactone products (**269**) in good to excellent chemical and stereochemical efficiency. The methodology tolerates a wide substrate scope and furnishes products that have numerous functional group handles for further manipulations. The exact role of the Lewis acidic $Sc(OTf)_3$ cocatalyst is not fully understood at this time; however, it was required to achieve high enantioselectivity in addition to high yield in the transformation.

Moriwaki, Liu, Soloshonok, and co-workers recently reported a Ni-promoted DKR of unprotected α-amino acids (**271**, Scheme 59).[236] It was postulated that, when the enantiomers in the racemic sample were subjected to the reaction conditions, chiral ligand **273** (Figure 22) reacts faster with the *R* enantiomer of the substrate to make the (*S*,*R*) diastereomer (**272**) as the kinetically favored product. The other (*S*,*S*) diastereomer (not shown) forms slowly and converts to the

Scheme 59. Type I DyKAT-Based Method for Enantioconvergence of Racemic α-Amino Acids



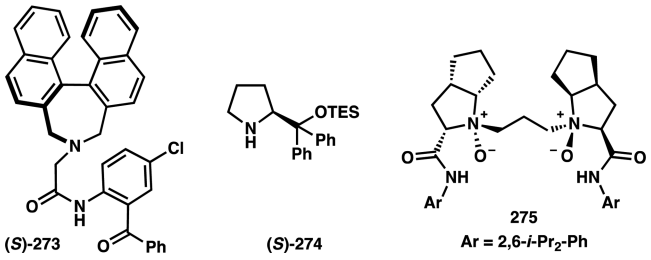
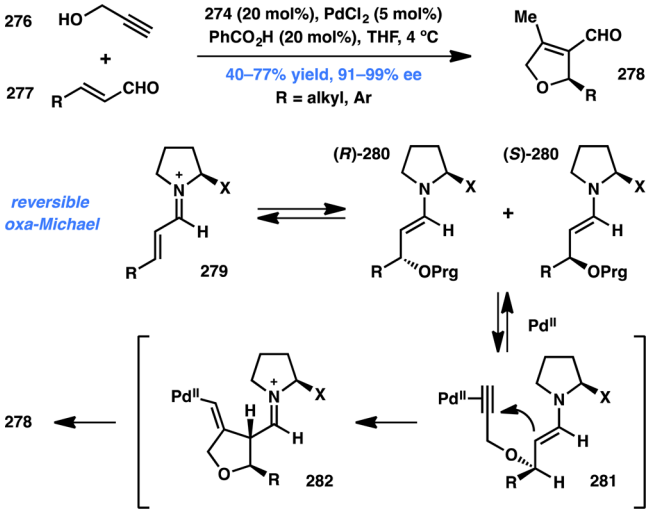


Figure 22. Chiral ligands and catalysts used in Schemes 59−61.

(*S*,*R*) diastereomer via a base-catalyzed enolate equilibration. Access to the enantiopure amino acid products can be readily realized via treatment of intermediate **272** with 6 N HCl. This also allows for the recovery and recycling of the chiral ligand. Furthermore, similar efficiency of this DKR to the *S*/*R* interconversion of α-amino acids was also demonstrated. Structural analyses show that (*S*)-ligand **273** creates *S*-helical chirality of the chelate rings, which gives rise to the *R*-absolute configuration of the α-amino acid. The substrate scope of this resolution encompasses aliphatic, aromatic, and ω-functionalized amino acids with high yields and diastereoselectivity.

Córdova and co-workers have developed a fascinating one-pot oxa-Michael/cyclization cascade between propargyl alcohols **276** and enals **277** to produce highly substituted dihydrofurans (DHFs) **278** that proceeds under a synergistic combination of chiral amine **274** (Figure 22) and $PdCl_2$ (Scheme 60).[237] The authors reasoned that, while the addition

Scheme 60. Córdova's Type II DyKAT for Enantioselective DHFSynthesis



of propargyl alcohol (PrgOH) to the iminium intermediate was expected to be reversible and nonselective, the participation of palladium via its interaction with the triple bond would force the reaction forward. Irreversible asymmetric induction takes place at this stage of the reaction, as only the sterically favored diastereomeric Pd-alkyne complex **281** can entertain a nucleophilic attack to forge oxacyclopentane **282** that contains an exocyclic olefin at this stage. Thermodynamic equilibration to the fully substituted and conjugated olefin eventually yields **278** as the overall product. However, the authors were not able to rule out the possibility of Pd(II) acting as a Lewis acid that activates the triple bond toward an enantioselective, and

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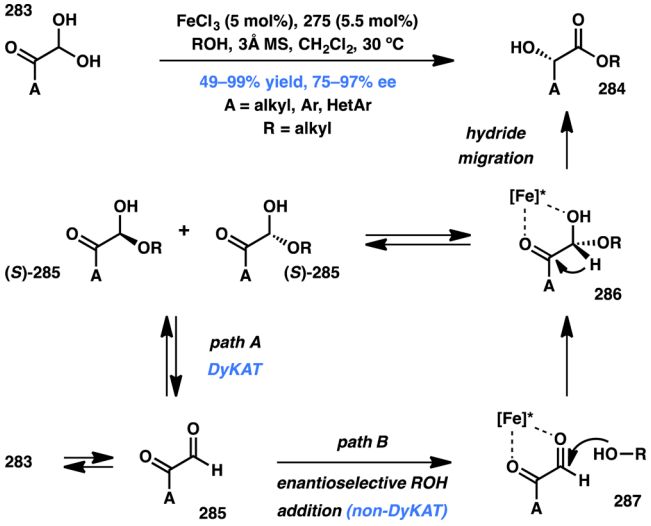
therefore a non-DyKAT, attack by the enamine onto the Pd-alkyne prior to oxa-Michael addition. The Córdova group has since expanded this technology to obtain a variety of useful structural motifs.[238,239]

Feng and co-workers recently disclosed an iron-catalyzed asymmetric Cannizzaro reaction (Scheme 61).[240] A variety of

Scheme 61. Feng's Asymmetric Cannizzaro Reaction via a Type II DyKAT Process



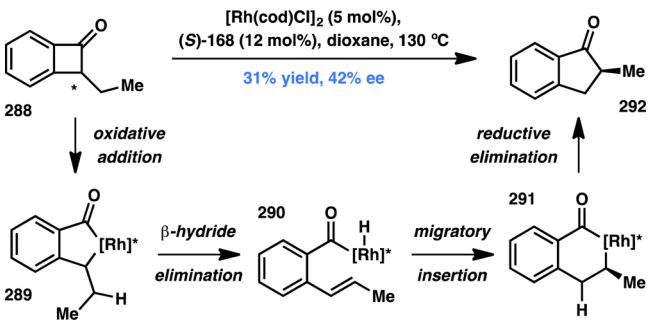
aryl and alkyl glyoxal hydrates reacted smoothly with alcohols to produce α-hydroxyesters with excellent ee. The mechanism for stereoinduction in asymmetric Cannizzaro reactions is subject to an ongoing debate, and where one proposal qualifies as a DyKAT (path A)[241,242] another favors an enantioselective addition route (path B).[243] It is postulated that, under the reaction conditions, substrate **283** dehydrates to form glyoxal **285** that can reversibly form racemic hemiacetals **285**. The chiral iron-*N*,*N*′-dioxide (**275**, Figure 22) complex then selectively binds and promotes the suprafacial hydride migration to afford α-hydroxyester product **284**. As shown in path B, one can imagine the iron catalyst chelating to the glyoxal (**287**) and inducing enantioselective alcohol addition. In the present case the authors, based on experimental evidence, believe that both DyKAT (path A) and enantioselective addition of alcohol to glyoxal (path B) are in synergy and deliver the products in excellent yield and enantioselectivity. Considering that these conditions promote the reverse of the alcohol addition (rendering path B reversible), we feel that path A is likely predominant and, thus, classify this transformation as a DyKAT.

The Dong group reported their initial investigations on the rhodium-catalyzed ring-expansion methodology to obtain indanone **292** from benzocyclobutanone **288** (Scheme 62).[244] The proposed C−C bond-cleavage approach was broadly effective for racemic reactions; however, limited success was achieved in an asymmetric variant catalyzed by Rh(I)/(*S*)-SEGPHOS (**168**, Figure 23) with product **292** obtained in a modest 42% ee (Scheme 62). The reaction is believed to be an example of DyKAT and at the moment requires careful optimization for achieving useful levels of yield and selectivity.

4.5. DyKATs in Complex Molecule Synthesis

Muscone. In 2005 Ikariya and co-workers completed the asymmetric synthesis of muscone (**297**), establishing the lone

Scheme 62. Dong's Type II DyKAT for Benzocyclobutanone Expansion



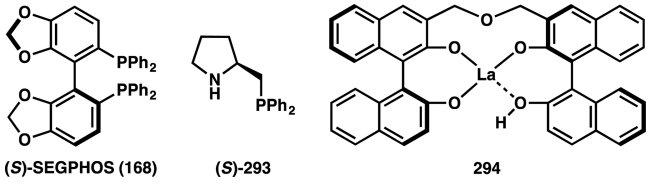
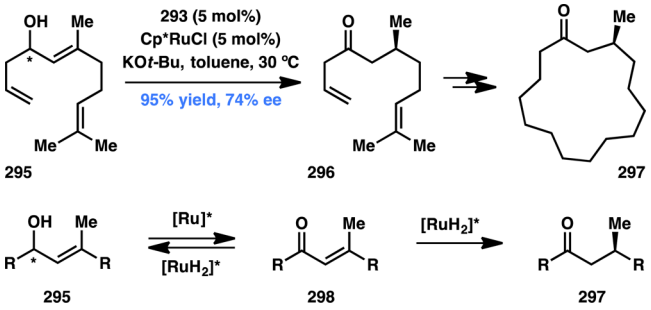


Figure 23. Chiral ligands and catalysts used in Schemes 62−64.

stereocenter with a ruthenium-catalyzed asymmetric double-bond isomerization of an allylic alcohol precursor (**295**, Scheme 63).[245] When using a chiral catalyst comprising Ru(I) and L-

Scheme 63. Ikariya's Total Synthesis of Muscone Utilizing a Type I DyKAT



proline-derived ligand **293** (Figure 23), the (±)-(*E*)-allylic alcohol precursor **295** afforded the (*S*)-ketone **296** in 74% ee. The authors speculate that the allylic alcohol is reversibly oxidized to enone **298**, providing the active hydrogenation catalyst and electronically activating the now-conjugated olefin. Enantioselective reduction delivers ketone **297** via a selective 1,4-addition event.

M58163 and M58169. Saitoh, Mikami, and co-workers completed the asymmetric total syntheses of M58163 (**303**) and M58169 (**304**), both of which display antithrombotic activity (Scheme 64). Access to their imidazopyrazinone core (**301**) was achieved using a lanthanum-catalyzed asymmetric cascade cyclization proceeding through racemic aminal **302**.[246,247] Mechanistic studies revealed that the aminal is formed reversibly, with enantioselection occurring during the La-catalyzed amide bond-forming step. A survey of various lanthanide metal complexes revealed that the La-linked BINOL complex **294** (Figure 23) gave the best yield and selectivity. Despite the modest enantioselectivity, the authors note that this marks the first catalytic enantioselective aminal synthesis.

Hydroxypyrrolidine Natural Products. Trost and co-workers reported a versatile application of the Pd-catalyzed

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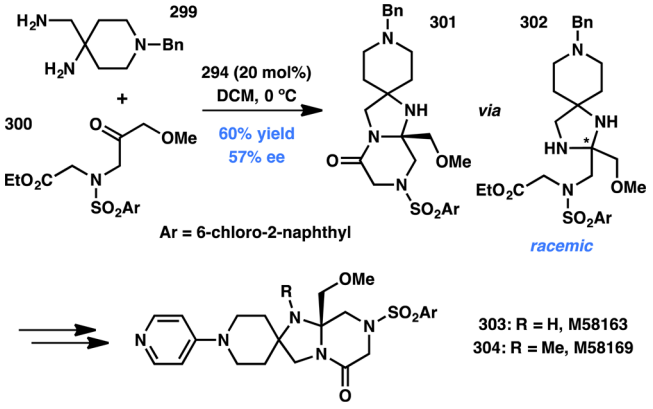
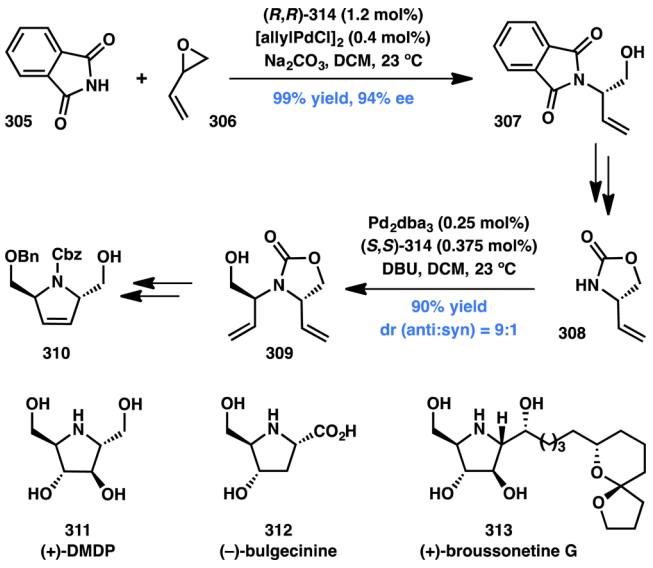
Scheme 64. Saitoh's and Mikami's Synthesis of Antithrombotic Agents 303 and 304 Utilizing a Type II DyKAT



AAA in the total synthesis of (+)-broussonetine G (**313**) and other structurally related pyrrolidine-containing alkaloids like (+)-dihydroxymethyldihydroxypyrrolidine (DMDP) (**311**) and (−)-bulgecinine (**312**, Scheme 65).[248] In the event, racemic

Scheme 65. Trost's Syntheses of Some Hydroxypyrrolidine Natural Products Utilizing a Type I DyKAT



butadiene monoxide undergoes a Pd-catalyzed DyKAT with phthalimide to afford homoallylic alcohol **307** with excellent yield and enantioselectivity (Scheme 65). **307** was then transformed into oxazolidinone **308**, which was used for a second Pd-catalyzed DyKAT with butadiene monoxide to produce alcohol **309**, once again with high yield and selectivity. Pyrrolidine scaffold **310** is forged using ring-closing olefin metathesis (RCM) technology. Thus, sequential application of AAA transforms readily available feedstock material into a flexible intermediate **309** that was further elaborated to accomplish the total synthesis of (+)-broussonetinine G (**313**), (+)-DMDP (**311**), and (−)-bulgecinine (**312**).

Elbasavir. Researchers from Process Chemistry at Merck have recently disclosed a Pd-catalyzed Buchwald−Hartwig C−N coupling to synthesize chiral indoles **317** (Scheme 66).[249] By using a high-throughput experimentation approach, palladium(II) acetate, bisphosphine ligand **315** (Figure 24), and K_3PO_4

Scheme 66. Merck's Type I DyKAT-Based Synthesis of Elbasavir

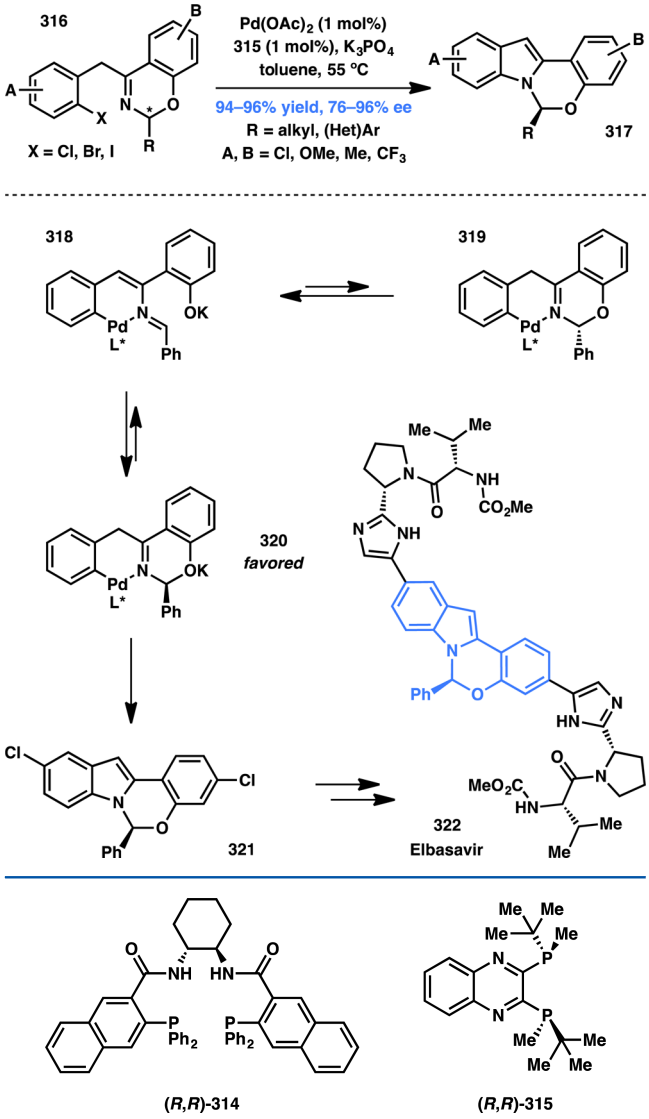


Figure 24. Chiral ligands used in Schemes 65 and 66.

in toluene were identified as the optimum conditions to transform racemic hemiaminals **316** to chiral benzoxazino indoles in excellent yield and high enantioselectivity. While the exact mechanistic pathway has yet to be confirmed, the authors postulate a base-promoted epimerization to be key in the isomerization of the substrate via its ring-open form (**318**). The "matched" hemiaminal-Pd complex (**320**) selectively undergoes reductive amination to forge the C−N bond. The methodology was used as the key step in the efficient synthesis of elbasavir (**322**), a drug candidate for treating HCV infections.

4.6. Concluding Remarks—Dynamic Kinetic Asymmetric Transformations

While DyKAT systems have the added complexity of a catalyst-mediated racemization event, they also offer the possibility of stereoconvergence to substrates that are not typically prone to epimerization. As such they form a fine complement to DKR processes, and as newer and more sophisticated catalytic systems are introduced, we can expect this field to continue its pattern of rapid growth.

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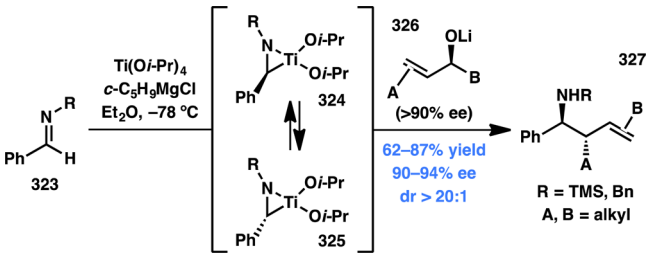
5. DYNAMIC SUBSTRATE-DIRECTED RESOLUTIONS

As mentioned in the Introduction section, during the preparation of this Review we came across a few systems that displayed dynamic behavior yet were not controlled by a chiral catalyst. While these do not fall under one of the traditional categories of stereoconvergence, we were intrigued by the concept of a dynamic substrate-directed resolution and thus opted for their inclusion with the hope of inspiring future work in this area.

5.1. Azatitanacyclopropane Reductive Cross-Coupling

In 2013, Micalizio and co-workers observed the epimerization of azatitanacyclopropanes under reductive cross-coupling conditions (Scheme 67).[250−254] Application of this phenomenon to the stereoconvergent reductive cross−coupling of achiral aromatic imines **323** with chiral allylic alcohols **326** provided homoallylic amines **327** in good yields and high enantioselectivity. Treatment of the achiral aromatic imines with $Ti(O^iPr)_4$ and *c*-C_5H_9MgCl gives a rapidly interconverting mixture of enantiomeric azatitanacyclopropanes, which upon treatment with 1.3−2.0 equiv of chiral allylic alcohol provides the stereodefined amine product (**327**). Both TMS- and Bn-substituted aromatic imines can be employed. The methodology has also been applied to cyclic and acyclic allylic alcohols, with di- or trisubstituted alkene functionality, and is tolerant of vinyl bromides.

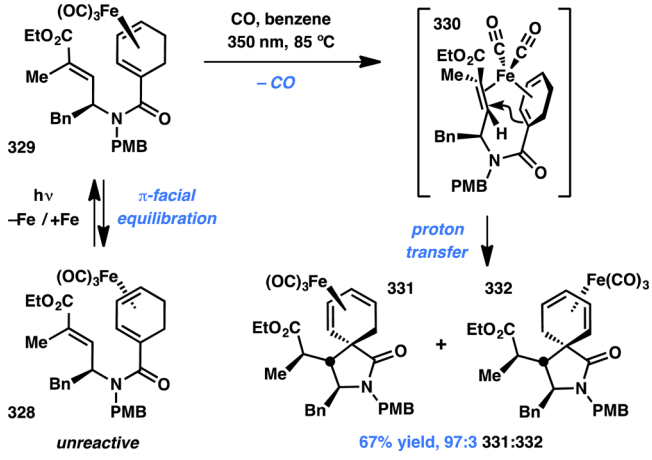
Scheme 67. Micalizio's Use of Chiral Alcohols for the Synthesis of Enantiopure Amines



5.2. Intramolecular Ring-Closing Ene Reaction

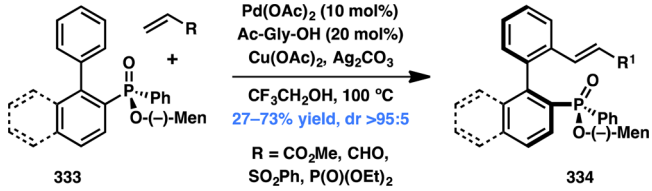
In 2005, the Pearson group reported a novel intramolecular ene-type reaction between a diene−$Fe(CO)_3$ complex and an alkene, resulting in the stereospecific generation of the corresponding spirolactam (Scheme 68).[255] The precursor can be easily synthesized from the corresponding chiral amino ester and the racemic carboxylic acid as a diastereomeric mixture of **328** and **329**. Under photolytic conditions, the iron-center loses coordination to the diene, eventually establishing an equilibrium between the two π-faces that allows for the dynamic interconversion of **328** and **329**. The two diastereomers can be separated, and when individually subjected to the [6 + 2] ene-type reaction conditions, one generated the spirolactam and the other converted to the reactive diastereomer and then underwent the cyclization. The authors propose that interconversion of diastereomeric precursors **328** and **329** occurs faster than the formation of the putative reactive intermediate **330**. Initially, one product is formed but thermal rearrangement gives access to olefin isomers (not shown); however, all isomers converge to a single product after demetalation and hydrogenation. In this process the chiral amide substituent directs the stereospecific formation of a single enantiomer, setting multiple stereocenters in a single step.

Scheme 68. Pearson's Use of an Iron-Bound Diene for Enantioselective Lactam Synthesis



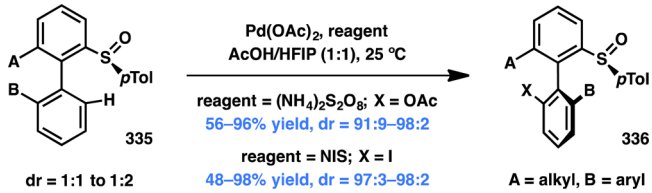
5.2.1. Atroposelective Biaryl Vinylation. Soon afterward, Yang and co-workers[256] reported the C−H alkenylation of biaryls bearing a chiral phosphinate (Scheme 69).[257] Using $Pd(OAc)_2$ and *N*-acyl glycine as the catalyst system, a wide variety of alkenes were coupled in good yield and diastereoselectivity. The methodology can also be extended to acylation, hydroxylation, acetoxylation, and iodination on the same substrates, albeit through kinetic resolution.

Scheme 69. Yang's Enantioselective Biaryl Vinylation



5.2.2. Carbon−Oxygen Bond Formation via C−H Activation. A highly diastereoselective Pd-catalyzed acetoxylation of biaryls **335** that contain a chiral sulfoxide auxiliary was disclosed by Wencel-Delord, Colobert, and co-workers (Scheme 70).[258,259] The C−O coupling was realized using ammonium persulfate in a 1:1 mixture of acetic acid and hexafluoroisopropanol (HFIP) as the solvent. The reaction was performed at ambient temperature and was found to be tolerant to air and moisture, implying that Pd(II), rather than Pd(0), was the key catalytic intermediate in the transformation. Moreover, replacing the persulfate reagent with *N*-iodosuccinimide affords the corresponding iodinated product with good to excellent yield and diastereoselectivity.

Scheme 70. Colobert's Atroposelective C−H Acetoxylation/Iodination



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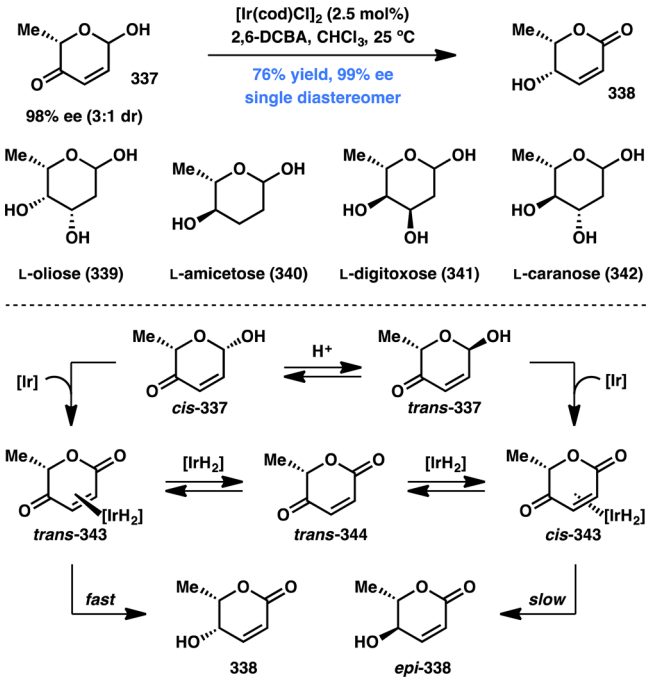
5.2.3. Application of DSDR in Total Synthesis. *Carbohydrates.* Guo, Tang, and co-workers recently reported an impressive application of the Achmatowicz rearrangement[260,261] for the formal synthesis of several deoxysugars that progresses via an iridium-catalyzed dynamic kinetic internal transfer hydrogenation (Scheme 71).[262] Alcohol **337** can be

Scheme 71. Guo and Tang's Synthesis of Deoxysugars



accessed as an enantiopure, 3:1 mixture of diastereomers in two steps via the asymmetric reduction of acetylfuran followed by an Achmatowicz rearrangement. In the key step, subjecting the diastereomeric mixture of **337** to catalytic $[Ir(cod)Cl]_2$ and 2,6-dichlorobenzoic acid (2,6-DCBA) results in a stereoselective internal transfer hydrogenation to generate lactone **338** in 99% ee with complete diastereocontrol. Mechanistically, the reaction is believed to proceed through a rapid acid-catalyzed epimerization of the hemiacetal, followed by stereoselective Ir-catalyzed internal transfer hydrogenation via a dynamic system. Lactone **338** can be processed to a number of deoxysugars by utilizing previously established protocols.[263]

6. CONCLUSION

Stereoconvergent methods for the construction of enantioenriched organic molecules remain among the most valuable for the construction of chiral, nonracemic organic molecules. In particular, the ablative or dynamic aspect of these processes is a significant advantage, allowing for the full conversion of racemic starting materials to products of a single enantiomer. We hope that this Review has served as an educational tool to not only summarize work in this field but also instruct readers as to the proper use of these terminologies.

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Notes

The authors declare no competing financial interest.

Biographies

Vikram Bhat was born in Ajmer, India. He obtained his undergraduate degree at the Indian Institute of Technology, Bombay. He then attended the University of Chicago for graduate studies in natural product synthesis with Professor Viresh Rawal. His dissertation topic was the total synthesis of welwitindolinone alkaloids, which possess a dauntingly complex molecular architecture and interesting biological properties. His work was recognized through the 2011 Reaxys Ph.D. Prize. Upon completion of his doctorate in chemistry, he took a postdoctoral position at the Center for Catalysis and Chemical Synthesis at the California Institute of Technology. There, he developed a novel methodology for the asymmetric synthesis of QUINAP and related P,N ligands. He is currently a Senior Scientist at AbbVie Inc.

Eric R. Welin was born in Columbus, Ohio, in 1987. He obtained his B.S. degree in Chemistry in 2010 from the Ohio State University, where he conducted undergraduate research in the laboratory of Professor James P. Stambuli. In the same year, he began his graduate studies at Princeton University under the supervision of Professor David W. C. MacMillan. At Princeton his research focused on developing new methods utilizing photoredox catalysis. He earned his Ph.D. in 2015, and later that year he joined the laboratory of Professor Brian M. Stoltz as an American Cancer Society postdoctoral fellow. His current research focuses on the total synthesis of bioactive natural products.

Xuelei Guo received her B.S. in Chemistry from the University of California at Berkeley in 2009. As an undergraduate researcher she worked in the lab of Professor Ahamindra Jain, focusing on the synthesis of menthol derivatives, and in the lab of Professor Richmond Sarpong, focusing on the synthesis of the icetexane and cortistatin families of natural products. Upon graduation, Xuelei worked at the National Institutes of Health under the direction of Dr. Victor Pike on the synthesis of radioactive PET ligands. In 2011 Xuelei received her M.S. in Chemistry from the University of Chicago, where she conducted research toward the total synthesis of (+)-catharanthine under the direction of Professor Viresh Rawal. Currently, she is an Associate Scientist at AbbVie Inc.

Brian M. Stoltz was born in Philadelphia, PA, in 1970 and obtained his B.S. degree from the Indiana University of Pennsylvania in Indiana, PA. After graduate work at Yale University in the laboratories of John L. Wood and an NIH postdoctoral fellowship at Harvard with E. J. Corey, he took a position at the California Institute of Technology. A member of the Caltech faculty since 2000, he is currently Professor of Chemistry. His research interests lie in the development of new methodology for general applications in synthetic chemistry.

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ABBREVIATIONS

9-BBN	9-borabicyclo[3.3.1]nonane
AAA	asymmetric allylic alkylation

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acac	acetylacetonate
Ar	aryl
ATH	asymmetric transfer hydrogenation
BArF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Boc	*tert*-butoxycarbonyl
BPE	1,2-di(phospholan-1-yl)ethane
BPin	(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)-2-yl
Bz	benzoyl
cat	catalyst
Cbz	carboxybenzyl
CFL	compact fluorescent lamp
cod	1,5-cyclooctadiene
conv	conversion
CPA	chiral phosphoric acid
CPME	cyclopentyl methyl ether
CSA	camphor sulfonic acid
DAC	donor−acceptor cyclopropane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCBA	dichlorobenzoic acid
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCM	dichloromethane
DFT	density functional theory
DHF	dihydrofuran
DIBAL-H	diisobutylaluminum hydride
DKR	dynamic kinetic resolution
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMMPh	3,5-dimethyl-4-methoxyphenyl
DMPU	*N*,*N*′-dimethylpropyleneurea
DMSO	dimethyl sulfoxide
DPEN	diphenylethylenediamine
dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1′-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
DTBM	3,5-di-*tert*-butyl-4-methoxyphenyl
DyKAT	dynamic kinetic asymmetric transformation
ee	enantiomeric excess
EtOAc	ethyl acetate
Gly	glycine
HetAr	heteroaryl
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMPA	hexamethylphosphoramide
Men(−)	(−)-menthyl
MOM	methoxymethyl
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
Nap	naphthyl
nbd	norbornadiene
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosuccinimide
phen	1,10-phenanthroline
Pin	pinacol; 2,3-dimethyl-2,3-butanediol
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
Prg	propargyl, 1-propynyl
SDP	7,7′-bis(diphenylphosphino)-1,1′-spirobiindane
TADDOL	α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TFE	2,2,2-trifluoroethanol
thexyl	2,3-dimethyl-2-butyl
THF	tetrahydrofuran
THP	tetrahydropyran
Tf	triflyl, trifluoromethanesulfonyl
Tol	tolyl, 4-methylphenyl
Ts	tosyl, *p*-toluenesulfonyl

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