Nickel-Catalyzed anti-Selective Alkyne Functionalization Reactions

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Abstract Nickel-catalyzed anti-selective alkyne functionalization reactions are reviewed with an emphasis on the mechanisms that lead to their observed stereoselectivity. Since the isomerization of alkenynickel species plays a key role in a large number of these reactions, the potential mechanisms for these processes are also described in detail.

1 Introduction

Transition-metal-catalyzed alkyne hydro- and difunctionalization reactions are commonplace in modern synthetic chemistry. These reactions are popular because they produce synthetically relevant alkenes in a manner that is often regioselective and/or stereoselective. Because these reactions generally involve migratory insertion at the catalytic metal, syn selectivity is expected. A variety of different Ni-catalyzed alkyne functionalization reactions have, however, demonstrated anti stereoselectivity. These reactions are highlighted in this Short Review (Scheme 1), and their mechanisms are described whenever possible. The anti-selective reactions described in this review frequently (but not exclusively) rely on the isomerization of catalytic alkenynickel intermediates. The penultimate section of this review focuses on the different mechanisms that can lead to alkenynickel isomerization since these processes are a common unifying feature for many anti-selective alkyne functionalization reactions.

Dale Wilger (left) was born in 1984 in Buffalo, New York. He obtained his undergraduate degree in chemistry at Fredonia State. He pursued his graduate studies at the University of North Carolina at Chapel Hill within the lab of Professor Marcey Waters (2006–2011). After performing postdoctoral research with Professor David Nicewicz, he became a professor of chemistry at Samford University in Birmingham, Alabama (2015). Dr. Wilger’s research interests include the development of novel Ni-catalyzed cross-coupling reactions and mechanistic studies related to these important transformations.

Sydney Bottcher (middle) was born in 1999 in Ft. Benning, Georgia. In 2018, she began an undergraduate degree in chemistry and biochemistry at Samford University where she joined the group of Professor Dale Wilger. Her research focuses on anti-selective alkyne hydroarylation reactions and subsequent modifications to form triaryl alkenes.

Lauren Hutchinson (right) was born in 2000 in Orlando, Florida. After receiving her high school diploma from The Master’s Academy, she went on to study chemistry and biochemistry at Samford University. Lauren joined the research group of Professor Dale Wilger in 2019. Lauren’s research focuses on organometallic chemistry and the Ni-catalyzed synthesis of indenones.

Key words alkyne difunctionalization, Ni-catalyzed, cross-coupling, anti-selective, mechanistic studies, alkenynickel
2 anti-Selective Hydroarylation

Transition-metal-catalyzed alkyne hydroarylation is a well-established approach for the stereoselective synthesis of alkenes. Catalytic systems employing Cr, Mn, Fe, Co, Ni, Cu, Rh, and Pd have all been previously reported. Even though the mechanisms for these reactions vary, migratory insertion is often implicated as the key stereodefining step. Therefore, syn selectivity is commonly observed. However, notable exceptions do exist. Fujiwara has reported an anti-selective alkyne hydroarylation reaction that directly activates C–H bonds in aromatic compounds. The report by Fujiwara in 2000 was the first example of this reaction class to produce high anti stereoselectivity. More recently, several Au-catalyzed alkyne hydroarylation reactions have demonstrated comparable anti selectivity with similar substrates. This has helped to shed light on the mechanism of the Fujiwara hydroarylation, which likely proceeds through alkyne coordination and intermolecular nucleophilic attack by the arene (Wacker-type or Friedel–Crafts-type mechanisms).

Similar to Pd, Ni is well known for being able to provide syn-selective alkyne hydroarylations within a variety of substrate classes. Still, several different examples of anti-selective alkyne hydroarylations have been reported within the last decade. In 2011, Robbins and Hartwig reported two different sets of conditions for Ni-catalyzed alkyne hydroarylation, both of which provided moderate anti stereoselectivity with certain substrates. Both sets of conditions required Ni(cod)₂ as a precatalyst (cod = 1,5-cyclooctadiene). The first preparation employed aryloboronic acid derivatives 1 and diphenylacetylene 2 (Scheme 2). Triphenylphosphine was found to be the optimal supporting ligand under those conditions. Certain aryloboronic acid derivatives with electron-withdrawing substituents provided trisubstituted alkenes 3 in high yields and high anti stereoselectivity. Clear trends regarding the observed anti stereoselectivity are challenging to identify. For example, ester and ketone groups at the para position of 1 provided low anti selectivity (3b, 3c: ca. 3:1 Z/E), while an aldehyde and a nitrile group provided moderate and high anti selectivity, respectively (3f, 3g: 11.8:1 and >20:1 Z/E).

The second synthetic procedure reported by Robbins and Hartwig engaged aryl bromides 4 and required triethylsilane as an added reductant (Scheme 2). The optimal ligand in that preparation was tributylphosphine. The scope for this procedure was less extensive, but low to moderate anti stereoselectivity was observed when aryl bromides with ortho substituents were examined (3j, k). The primary focus of this report by Robbins and Hartwig was a new method for the high-throughput discovery of transition-metal-catalyzed reactions. A Cu-catalyzed oxidative (Chan–Lam) coupling reaction and a Cu-catalyzed alkyne hydroamination reaction were also reported. No potential mechanism for the hydroamination reactions was discussed.

In 2017, Reddy et al. reported a Ni-catalyzed hydroarylation procedure for propargyl and homopropargyl alcohols (Scheme 3). Aryloboronic acids served as the aryl donors. When terminal alkenes 5 were employed, hydroarylation products 6, with linear regioselectivity and syn stereoselectivity, were obtained. When otherwise similar internal alkenes 7 were examined, hydroarylation products 8 were...
isolated with the opposite regioselectivity and stereoselectivity. Reddy proposed a hydroarylation mechanism that operated entirely within the Ni(I) oxidation state. This proposed mechanism was based on findings previously reported by Liu (see below).\(^\text{17}\)

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\text{Scheme 4} \quad \text{Hydroarylation mechanism proposed by Reddy et al.}\(^\text{16}\)
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The mechanism described by Reddy et al. involved transmetalation, syn-selective migratory insertion to give 9, and protodenickelation to give 8 (Scheme 4). Interestingly, the change in regioselectivity observed for internal alkynes suggested that the orientation for migratory insertion depended on steric factors and not on directing group coordination, or at least that steric factors could override the stabilization provided by directing group coordination. Reddy proposed that isomerization of the alkenylnickel intermediate syn-9 allowed for the formation of the anti hydroarylation product. Coordination of the directing group to the metal center would stabilize anti-9 and provide the thermodynamic driving force for the observed stereoselectivity. This same rationale was provided by Cheng et al. to explain the anti stereoselectivity observed when propargylic substrates were employed in a Co-catalyzed alkyne hydroarylation procedure.\(^\text{18}\) In that report, Cheng et al. observed syn selectivity with nearly all other alkyl substrates. Both Cheng et al. and Reddy et al. reported no stereoselectivity (1:1 \(Z/E\)) when alkynes lacking coordinating directing groups were examined.\(^\text{16,18}\)

In 2019, Wilger et al. reported a Ni-catalyzed alkyne hydroarylation procedure that required only air-stable precatalysts, reagents, and substrates (Scheme 5; phen = 1,10-phenanthroline).\(^\text{19}\) This reaction supplied trisubstituted alkynes 3 under operationally simple and inherently scalable conditions. Aryl bromides 4 served as aryl donors under reductive conditions with Zn and water. Certain aryl bromides provided moderate \textit{anti} stereoselectivity, similar to previous reports, although numerous substrates behaved differently. Aryl bromides with \textit{ortho} substituents provided adequate \textit{anti} stereoselectivity (3i–p). Aryl bromides with \textit{meta} substituents provided low \textit{anti} stereoselectivity (3q,r). Aryl bromides with a \textit{para} substituent provided good yields, but no measurable stereoselectivity (1:1 \(Z/E\)). This stood in stark contrast to the report by Hartwig and Robins, which recorded high \textit{anti} stereoselectivity with several different \textit{para}-substituted arylboronic acids.\(^\text{15}\)

Wilger et al. performed deuterium-labeling experiments with \(D_2O\), \(d_7\)-DMF, and \(d_8\)-toluene in order to better define the mechanism for Ni-catalyzed alkyne hydro-
arylation (Scheme 6). These experiments indicated that the vinyl hydrogen atom in 3 was primarily derived from added water. Small quantities (<20%) of 3 were likely created via Ni–C bond homolysis and hydrogen-atom transfer, especially under anhydrous conditions. The hydrogen atom donor was not the solvent under any of the conditions examined. Hydrogen atom abstraction most likely occurred from benzylic groups in 3 or 4 since added d₈-toluene could contribute to product deuteration.

Wilger et al. also performed mechanistic experiments with a Ni(II) aryl bromide complex, Ni(‘BuBpy) ‘o-tol)Br 10 (Scheme 7; ‘BuBpy = 4,4‘di-tert-butyl-2,2‘dipyridyl). The complex 10 was competent as a precatalyst when compared to Ni(‘BuBpy)Cl₂ 11, indicating that a Ni(II) aryl halide complex is a likely catalytic intermediate. Stoichiometric experiments with 2, 4I, and 10 indicated that Zn was required for adequate chemical yield. This suggested that at least one of the relevant catalytic intermediates exists in the Ni(I) oxidation state. Additional mechanistic experiments indicated that an arylnickel intermediate was not likely. Other protic donors (such as MeOH, EtOH, ‘PrOH, and ‘BuOH) gave similar Z/E ratios, indicating that the diastereoselectivity of these reactions was not affected by the rate of protodenickelation.

The substrate scope for this reaction suggested that the thermodynamic driving force for isomerization was steric repulsion within the allenynickel intermediates syn-14 and anti-14. Aryl groups with ortho substituents are more sterically demanding, and equilibration through reversible isomerization would therefore tend to position these groups further away from the Ni center. This explains why ortho substituents on the aryl donors led to higher diastereoselectivity, while meta substituents led to low levels of selectivity, and para substituents led to no measurable selectivity. If the hydroarylation reaction reported by Hartwig and Robbins operates with a similar mechanism, then para-substituted aryl donors may have provided better selectivity.

Wilger et al. proposed the mechanism shown below for Ni-catalyzed alkyne hydroarylation (Scheme 8). Off cycle, the Ni(II) precatalyst is reduced to an active Ni(0) species 12 by Zn. Oxidative addition into the C–Br bond of 4 would produce an intermediate analogous to 10. Subsequent reduction with Zn and alkyl coordination would give a Ni(0) complex 13. Migratory insertion would produce syn-14. Isomerization of the allenynickel intermediate syn-14 to anti-14 and protodenickelation would provide 3, and the net effect of an anti-selective hydroarylation. Reduction of 15 by Zn would facilitate catalytic turnover. It has been shown that Zn is capable of reducing Ni(II) aryl halide complexes to Ni(0) aryl complexes. Therefore, Wilger et al. proposed that single-electron reduction occurs with 10 before migratory insertion and other subsequent steps. Since the complex 10 can produce non-negligible quantities of 3 without reductant, it may be possible that the requisite alkenforming steps can occur from both the Ni(I) and Ni(II) oxidation states, but that product formation is faster from the Ni(I) oxidation state.
because phosphine ligands were used. Bipyridyl ligands are planar and possibly capable of rotating away from the substituted aryl group. Phosphine ligands are trigonal pyramidal and therefore present a greater three-dimensional steric profile. The observation that the more sterically hindered Bubpy ligand provided higher anti stereoselectivity compared to phenanthroline is consistent with this hypothesis. Steric repulsion is often implicated as the driving force for alkenylnickel isomerization in other catalytic reactions (see below).

3 anti-Selective Carboborylation

Organoboron compounds are viewed as some of the most versatile cross-coupling partners available to synthet-ic chemists. Aryl- and vinylboron reagents can be employed in a vast array of C–C bond-forming reactions. This has led to an interest in synthesizing organoboron reagents with increasing functionalization. In 2005, Suginome et al. reported an anti-selective Ni-catalyzed alkynylation reaction (Scheme 9).22 This cross-coupling was developed based on observations from a previously reported syn-selective cyanoboration reaction.23 Chloroboryl homopropargylic ethers 16 and alkynylstannanes 17 underwent clean 5-exo cyclization and carboboration across the alkyne triple bond, forming substituted alkene derivatives 18. The precatalyst used for this transformation was Ni(cod)2. Triphenylphosphine was found to be the optimal supporting ligand for catalytic reactions. The products 18 were moisture sensitive and were therefore converted into pinacolborane derivatives 19 before silica gel chromatography.

Suginome et al. proposed a mechanism that began with oxidative addition into the B–Cl bond to give 20. Migratory insertion of the alkyne into the Ni–B bond would give syn-21. Isomerization would produce anti-21, then transmetalation would produce 22, and reductive elimination would produce 18. Steric repulsion between the dipropylamino group and the phosphine-ligated Ni center in syn-21 was proposed to drive the isomerization process. This hypothetical mechanism was strongly bolstered by the isolation and characterization of anti-21d, which was synthesized via a stoichiometric reaction between 16d, Ni(cod)2, and the ligand PMe3 (Scheme 10). X-ray analysis of anti-21d clearly showed the trans configuration of the C–B and C–Ni bonds.

Scheme 10 Ni-catalyzed alkynylation mechanism22

4 anti-Selective Dicarbobfunctionalization

4.1 Carbocyanative Cyclization

In 2013, Arai et al. reported a Ni-catalyzed cyclative carbocyanation for enynes (Scheme 11).24 This procedure used Ni(P(OPh)3)4 as a precatalyst and acetone cyanohydrin as a HCN source. The enynes 23 underwent carbocyanative 5-exo-cyclization to produce 24. In certain cases, stoichiometric quantities of the P(OPh)3 ligand were found to be beneficial. When less sterically congested enynes were examined, 24 was obtained with low syn selectivity (3–5:1 Z/E). More sterically congested enynes gave 24 with very high anti selectivity (>20:1 E/Z). The substrate scope for this transformation was somewhat limited, but importantly, this study...
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provided the first example of an *anti*-selective carbocyanation.

Arai et al. proposed a mechanism beginning with oxidative addition of HCN or the cyanohydrin (Scheme 12). Migratory insertion of the alkene group in 23 would produce 25 and subsequent alkyne carbometalation would produce *syn*-26. Isomerization of the alkenynickel intermediate *syn*-26 is likely driven by steric repulsion between the bulky silyl group and α-substituents on the enyne scaffold. Reductive elimination of *anti*-26 would provide the product 24. Some evidence for migratory insertion of the alkene with the opposite regioselectivity (6-*exo* cyclization products) was observed during optimization. In addition to influencing alkenynickel isomerization, bulky silyl groups were also necessary to discourage an initial migratory insertion of the more reactive C–C triple bond, a reaction that did not result in cyclization.

4.2 Cyclization with Aryl Donors

In 2016, Liu et al. reported a Ni-catalyzed cyclization of alkynyl nitriles 27 to produce 1-naphthylamines 28 (Scheme 13). This transformation was necessarily facilitated by the isomerization of an alkenynickel intermediate. Arylboronic acids 1 served as the aryl donors. Yields for the reaction were good when a wide variety of different arylboronic acids 1 and substituted alkynyl nitriles 27 were used. Arylboronic acids with either electron-donating or electron-withdrawing substituents were tolerated, as were sensitive functional groups such as ketones, esters, nitriles, and halides. A similarly wide scope was observed for substituents on 27, although alkyl substituents on the alkyne moiety resulted in substantially lower yields.

Liu et al. performed several mechanistic experiments and found the Ni precatalyst Ni(acac)₂, arylboronic acid 1, KOtBu, and the ligand IPr produced a Ni(I) species IPrNi(acac)₂ (Scheme 14; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene). The Ni(I) complex 29 was characterized by X-ray analysis. The complex 29 was found to be catalytically competent (yield = 53%) when compared to mixtures of Ni(acac)₂ and the IPr ligand (yield = 64%). This suggested that a Ni(I) complex analogous to 29 is a catalytic intermediate in the cyclization reaction.

Liu et al. proposed a catalytic mechanism that began with transmetalation to form a Ni(I) aryl species. Migratory insertion with the C–C triple bond would produce *syn*-30. Isomerization to the alkenynickel isomer *anti*-30 must occur before cyclization with the nitrile C–N triple bond.
Protonolysis of 31 and tautomerization would produce 28. The regioselectivity of the alkyne migratory insertion step is critical to the transformation. Substrates lacking the OTBS group provided very low yields (ca. 10%), implying that the substituent might play a role in directing the regioselectivity of alkyne migratory insertion. To our knowledge, this report by Liu was the first example of a catalytic reaction in which equilibrating alkenylzinc species are trapped via a cyclization event that is specific to the anti stereoisomer. Several other examples described below share this mechanistic feature.

In 2016, nearly concurrently with Liu’s seminal example, Lam et al. reported a highly enantioselective catalytic cyclization reaction that was also facilitated by an alkenylzinc isomerization process (Scheme 15). Alkynyl 1,3-diketones 32 underwent enantioselective cyclization with arylboronic acids 1 as aryl donors. The chiral bicyclic β-hydroxyketone products 34 were obtained with excellent yields and enantioselectivities when the phosphinooxazoline ligand 33 was used in conjunction with a Ni(OAc)₂·4H₂O precatalyst. Lam et al. proposed a mechanism that began with transmetalation and alkyne migratory insertion to produce syn-35. The isomerization of syn-35 is driven by the removal of anti-35 from the reaction mixture via cyclization with the pendant carbonyl group. Protonation of the Ni alkoxide intermediate 36 provides the product 34 and catalyst turnover. Additionally, cyclohexane-1,3-diones 37 and cyclohexa-1,3-dienones 39 provided the cyclic products 38 and 40, respectively, with high yields and enantioselectivities.

The Lam group has reported several other enantioselective cyclization reactions that operate with similar mechanistic principles (Scheme 16). In 2017, Lam et al. reported a Ni-catalyzed cyclization with amine-tethered 1,6-enynes 41 and arylboronic acid donors 1. In this case, Ni(OAc)₂·4H₂O and the NeoPHOX ligand 42 provided cyclic amine products 43 with high yields and enantioselectivities. The Z-configuration of the alkene moiety in 41 was found to be critical for cyclization to occur. In 2018, Lam et al. reported a Ni-catalyzed desymmetrization of propargyl-
substituted malonate esters 44 to produce cyclic products 45. The ligand 33 once again provided high yields and enantioselectivities. The substrate scope for the aryloboronic acids and aryl alkynes was extensive in this report. This procedure allowed for gram-scale enantioselective syntheses. In 2018, Lam et al. reported a Ni-catalyzed cyclization reaction for propargyl-substituted amides 46. The pyrrole products 47 in this report were achiral, but yields were high and a wide variety of different aryl groups could be incorporated. All three reactions shown in Scheme 16 are proposed to occur through a similar mechanism involving transmetalation (from Ni(I)), regioselective and syn-selective alkyne migratory insertion, alkenyl nickel isomerization, and cyclization of the anti alkenyl nickel stereoisomer. In 2018, Reddy et al. reported a Ni-catalyzed cyclization reaction for alkynyl azides that synthesized diarylquinolines in a closely related manner.16b

Scheme 16 Ni-Catalyzed cyclization of bifunctional substrates

4.3 Cyclization with CO₂

In 2015, Martin et al. reported a cyclative carboxylation for unactivated primary and secondary alkyl halides with CO₂ (Scheme 17).25c As a C1 synthon, CO₂ is ideal in terms of its cost, availability, and environmental impact. Martin et al. found that the precatalyst NiBr₂·diglyme was effective in combination with bipyridyl ligands such as bathophenan. 45

Scheme 17 Ni-Catalyzed cyclization and carboxylation with CO₂

4.4 Intermolecular Dicarbofunctionalization

The Nevado group has reported several intermolecular alkyne difunctionalization reactions that provide anti stereoselectivity through mechanisms that are distinct from those described above.27 In 2016, Martin et al. reported that terminal alkynes 50, aryloboronic acids 1, and alkyl halides 51 could serve as carbon-based building blocks for stereoselective alke ne synthesis (Scheme 18).28 The chemical yields for alkenes 52 were good and the anti stereoselectivities were excellent (>99:1 in most cases). Moreover, the substrate scope for this cross-coupling was extensive. Even tertiary halides such as tert-butyl iodide could be used as alkyl donors within this procedure. Control experiments indicated that free radical inhibitors such as TEMPO or BHT...
halted reactivity. Reactions with both Ni(0) and Ni(II) precursors failed to provide vinyl halides without halted reactivity. Reactions with both Ni(0) and Ni(II) proposed that transmetalation with 1 would produce a Ni(I) aryl species 53 capable of intercepting 51. This reaction would generate a Ni(II) aryl halide species 54 and a carbon-centered radical. The carbon-centered radical would add to the terminal alkyne 50 in an intermolecular fashion and produce a freely interconverting vinyl radical 55. Selective radical recombination of 55 with 54 would provide the Ni(III) complex 56 and explain the observed diastereoselectivity. Reductive elimination from 56 would furnish the product 52 and regenerate the Ni(I) catalyst.

In 2017, Nevado et al. reported a Ni-catalyzed anti-selective alkyne carbosulfonylation reaction (Scheme 19). Terminal alkynes 50, arylboronic acids 1, and sulfonyl chlorides 57 combined to produce highly substituted vinyl sulfones 58 in high yields and high anti stereoselectivities. In this case, a preformed catalyst with a unique ligand 59 was optimal (59 = 4,4’,4”-tri-tert-butyl-2,2’:6’,2”-terpyridine). The substrate scope for this reaction was broad. Nevado et al. proposed a mechanism very similar to the previously reported Ni-catalyzed dicarbofunctionalization reaction shown above (Scheme 18). A Ni(I) aryl complex was hypothesized to react with 57 to produce sulfonyl radicals. These sulfonyl radicals would add to 50 to generate freely interconverting vinyl radicals in much the same way. Selective recombination of these carbon-centered radicals with a Ni(II) aryl halide complex and reductive elimination would explain product formation and the observed diastereoselectivity. These alkyne difunctionalization mechanisms are unique compared to the other examples covered in this review. These reports have so far been limited to terminal alkynes, but the anti stereoselectivities have been exceptional. Similar approaches will likely be used to develop future anti-selective alkyne functionalization reactions.

6 Alkenylnickel Isomerization

Many of the anti-selective alkyne functionalization reactions described above rely on the isomerization of key alkenylnickel intermediates to provide adequate stereoselection. Numerous thermodynamic and kinetic factors influence the relative abundance of these alkenylnickel isomers, including steric repulsion, directing group coordination, and/or subsequent irreversible reactions. While these relationships that dictate the relative differences between alkenylnickel stereoisomers are often easily inferred, the kinetic factors that render one alkenylnickel species configurationally stable, and another configurationally labile, are more challenging to determine. It should be emphasized that C=C double-bond isomerization is not inherent to all alkenylnickel species. Numerous syn-selective alkyne functionalizations and other cross-coupling reactions require alkenylnickel species that are configurationally stable. Understanding how alkenylnickel complexes undergo isomerization is highly important since it may allow further reaction development. Furthermore, in some cases the isomerization of alkenylnickel intermediates has led to the loss of stereochemical integrity. Therefore, there are compelling arguments for being able to both selectively facilitate and prevent alkenylnickel isomerization. It should also be emphasized that C=C double-bond isomerization is not entirely unique to Ni. Alkenylcobalt,18 alkenylruthenium,19 alkenylrhodium,20 alkenylpalladium,21 and alkenylosmium22
complexes are also known to undergo isomerization processes that can help inform the discussion regarding alkenynickel intermediates. In 1979, Huggins and Bergman demonstrated that the rapid isomerization of alkenynickel species can explain the observation of kinetic products with apparent anti stereoselectivity (Scheme 20). The authors elegantly showed that Ni(acac)(PPh₃)Me and Ni(acac)(PPh₃)Ph add to diphenylethylene 2 and 1-phenylpropyne 60, respectively, to give the same kinetic product 61. Moreover, Huggins and Bergman went on to show that reactions with isotopically labelled components (60 and d₆-60) undergo an initial addition reaction with measurable syn selectivity and then equilibrate to form a statistical mixture of isomers (d₆-61). This report by Huggins and Bergman was the first to experimentally determine that anti-selective alkyne functionalization reactions could be explained by the isomerization of alkenynickel species.

The report by Huggins and Bergman was also innovative because they carefully investigated the mechanism for alkenynickel isomerization. The authors noted that direct unimolecular rotation about the alkenynickel C=C double bond was the most straightforward explanation conceptually, but ultimately discredited this mechanism based on experimental evidence (see below). A wide variety of mechanisms could explain the isomerization of alkenynickel species. Several of these possible mechanisms are illustrated in Scheme 21. We suggest that mechanisms involving: (a) direct unimolecular rotation, (b) reversible nucleophilic attack, (c) reversible protonation, and (d) reversible bond homolysis are the most relevant for consideration here. This is not meant to be an exhaustive list of all possible isomerization mechanisms. Since direct unimolecular rotation about an alkenynickel double bond is arguably the simplest mechanism for isomerization, it is discussed first.

Huggins and Bergman proposed that charge-separated resonance contributors might lower the barrier for unimolecular rotation about the alkenynickel C=C double bond since they would impart more single-bond character to these species (Scheme 21a). Often referred to using different terms (dipolar, 30b bipolar, 31a zwitterionic 31b and/or carbene 31c), similar resonance structures have been proposed to contribute to the isomerization of other alkenylnickel species. Huggins and Bergman proposed a resonance structure in which the metal center has significant π-acidity and accepts electron density from the alkenyl ligand. This is consistent with the final conclusion of Huggins and Bergman regarding the isomerization mechanism (see below).

Resonance structures proposed for alkenylrhodium and alkenylpalladium species are more typically represented with significant π-basicity and back-donation from the metal center to the alkenyl ligand. These representations are consistent with the established π-donating abilities of these metals. There are several instances in which the extent of isomerization can be directly correlated with the electron density present at the metal center. For example, alkenylrhodium complexes with substituted triphenyl-
phosphine ligands \( (P(C_6H_4X)\text{)}_3 \) undergo isomerization with rates reflecting the relative electron-donating ability of the phosphine ligand \( (X = F < H < OCH_3) \). In other instances, isomerization can be directly linked to the \( \pi \)-accepting ability of the alkenyl ligand. Alkynes with conjugated carbonyl substituents will often undergo isomerization, while alkynes lacking these substituents are configurationally stable under identical conditions.

Catalytic intermediates in the Ni(I) oxidation state may facilitate isomerization in several of the difunctionalization reactions described above. A Ni(I) complex would possess greater electron density compared to a Ni(II) complex, and that would presumably facilitate back-donation consistent with the examples above. The isomerization process observed by Huggins and Bergman occurred within the Ni(II) oxidation state, but the ancillary ligand was anionic (acac = acetylacetone). That isomerization reaction was also found to be phosphine-catalyzed (see below). Importantly, a catalytic intermediate that is formally a Ni(I) complex may be more accurately described as a Ni(II) complex with a reduced (radical-anion) ligand. That electronic structure would resemble the Ni complexes studied by Huggins and Bergman more closely. It should be noted that Liu, Wilger, and Martin have all independently reported alkenylnickel isomerization and each of these reports implicated Ni(I) species as key catalytic intermediates. Because Ni(I) species are odd-electron intermediates it may be prudent to consider resonance contributors that distribute spin density throughout the alkenyl ligand.

Huggins and Bergmans’ study of alkenylnickel isomerization provided compelling evidence that the process was catalyzed by free phosphine ligand (Scheme 22). Reversible phosphine exchange was evident by NMR analysis of the Ni reactants \( 62 \). The rate of addition to alkynes was inversely proportional to the concentration of added phosphine. The structure of the phosphine ligand in the Ni species also affected the rate of addition. Those observations implied that ligand substitution to form \( 63 \) was at least partially rate-limiting in the carbonickelation process. Huggins and Bergman suggested an associative mechanism for alkynephos- phine exchange. Since the observed products were formed by phosphine coordination to \( 64 \) after carbonickelation, it would be expected that the concentration of the ligand should have substantially influenced the observed stereoselectivity. However, the diastereomeric ratios observed for kinetic product mixtures displayed minimal dependence on the concentration of added phosphine. For example, the rates for addition reactions with added phosphine ligand displayed a linear dependence on \( 1/[PPh_3] \), but changing the added phosphine concentration one order of magnitude changed the diastereomeric ratio approximately 10%. These observations were consistent with a mechanism in which free phosphine catalyzed the isomerization of the alkenylnickel species \( \text{syn-64 to anti-64} \). In other words, if the alkenylnickel intermediate were capable of undergoing isomerization by a direct unimolecular pathway, then higher phosphine concentrations would be expected to favor the trapping of \( \text{syn-64} \) (and the observed \( \text{syn-65/anti-65 ratio} \)). Huggins and Bergman envisioned a mechanism in which free phosphine could reversibly attack the alkenyl carbon atom \( \beta \) to the metal center in \( 64 \), and thereby allow rotation around the \( C\_3-C\_7 \) bond. A phosphine-catalyzed isomerization mechanism could be operating in many of the Ni-catalyzed reactions reported above. In catalytic procedures that do not require added phosphines, it may be possible that another nucleophilic species such as dissociated pyridyl ligand, halide anion, or base could participate in this manner.
Acid-catalyzed processes may also contribute to the isomerization of alkenylnickel species (Scheme 21c). Several of the Ni-catalyzed reactions reported above require protodenickelation as a product-forming step. Tanke and Crabtree hypothesized that acidic species could catalyze the isomerization of alkenyliridium intermediates within a hydrosilylation reaction. Control experiments that included exogenous base disproved this hypothesis. Since protonolysis is often a productive step in the reported anti-selective alkyne functionalization reactions catalyzed by Ni, the effects of exogenous base would be challenging to interpret. Tanke and Crabtree eventually supported an isomerization mechanism that involved direct unimolecular rotation of an alkenyliridium intermediate. Nelson and Gagné later demonstrated that rapid proton transfer steps can interconvert alkenylplatinum regioisomers and in an enyne cycloisomerization reaction (Scheme 23). One could envision a similar sequence of proton transfer steps leading to the stereochemical isomerization of an alkenylnickel species. In the example reported by Nelson and Gagné, deuterated acids left a residual isotopic label in the product. This type of deuterium-labeling experiment would be challenging to perform or uninformative in many of the Ni-catalyzed alkyne functionalization reactions described above.

Martin et al. proposed that reversible Ni–C bond homolysis could explain the isomerization of alkenylnickel species in the carboxylation reaction described in Section 4.3 (Scheme 24). Martin et al. proposed that after oxidative addition and alkyne migratory insertion, an alkenylnickel species such as syn-68 may undergo bond homolysis to create a vinyl radical. The carbon-centered radical would isomerize to anti-69, and then radical recombination with the Ni(I) center would produce anti-68 (and then eventually anti-49). Perhaps most interesting, the isomerization process appeared to be strongly dependent upon the choice of supporting ligand (neocuproine versus bathocuproine). Martin et al. suggested that re- dox-noninnocent ligand behavior may be partially responsible for this observation. The mechanistic studies reported by Wilger et al. indicated that irreversible Ni–C bond homolysis did occur under catalytic alkyne hydroarylation conditions. However, the extent of reversible bond homolysis could not be assessed. Direct unimolecular bond rotation and reversible Ni–C bond homolysis are perhaps the most challenging isomerization processes to differentiate. Detailed mechanistic studies, including crossover experiments with well-defined alkenylnickel complexes, should
help to differentiate direct unimolecular rotation and reversible bond homolysis in the future.

7 Conclusions

A large sampling of recently reported Ni-catalyzed anti-selective alkyne functionalization reactions has been summarized. In many instances, the proposed mechanisms for these transformations have suggested alkenylnickel isomerization as the cause for their unusual stereoselectivity. Key outliers include the anti-selective intermolecular alkyne di-functionalization reactions reported by Nevado et al. Both of these mechanistic umbrellas hold promise for future reaction development. Because the isomerization of alkenylnickel species facilitates stereoselectivity in many of the examples described above, this topic was briefly reviewed as well (Section 6). Several possible mechanisms for alkenyl nickel isomerization were described in the context of reported catalytic reactions. Further understanding these isomerization processes will lead to improvements in Ni-catalyzed cross-coupling procedures and to the creation of new alkyne functionalization reactions.

Given the broad range of possible mechanisms that could explain alkenynickel isomerization, we believe that further experimentation will greatly elucidate this field of study. As noted above, several of the isomerization mechanisms are very difficult to differentiate between. Numerous questions regarding the oxidation state of configurationally unstable species (Ni(I) versus Ni(II)) remain. Other questions relate to the role that nucleophilic and acidic species might play in catalyzing isomerization. Although challenging, the synthesis and characterization of discrete alkenynickel complexes should be pursued. Catalytic and stoichiometric control experiments with these complexes should help to fully define the relevant mechanisms. We hope this Short Review inspires further investigations in this area.

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