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Ni-Catalyzed stereoselective difunctionalization of alkynes

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Tri- and tetrasubstituted olefins are widely present in biologically active molecules and functional materials. However, the methods for the stereoselective construction of such moieties are still very limited and extremely challenging. The transition-metal-catalyzed difunctionalization of alkynes is one of the most straightforward and effective choices. In this review, we summarize the progress of the nickel-catalyzed alkyne difunctionalization reaction, with an emphasis on the strategy and control of stereochemistry.

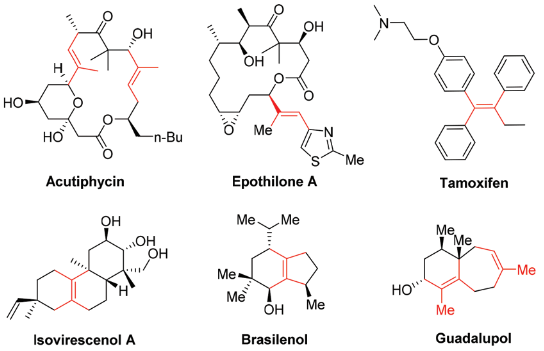
1. Introduction

Tri- and tetra-substituted alkenes are widely present in many biologically and pharmacologically active molecules, including acutiphycin, epothilone A, tamoxifen, isovirescenol A, brasilenol and guadalupol (Scheme 1).[1] However, the methods for the stereoselective construction of these unique motifs are still very limited and extremely challenging.[2]

Alkynes are readily available and inexpensive raw materials. Transition-metal-catalyzed difunctionalization of alkynes which is the *syn*- or *anti*-selective introduction of two functional groups across the triple bond represents one of the most straightforward and powerful approaches for assembling stereodefined tri- and tetrasubstituted alkenes. Traditionally used rare noble metal catalysts based on Rh, Ir and Pd have been widely used in alkyne difunctionalization reactions.[3] However, they are very expensive and their reserves are declining, thus limiting their applications in large-scale industrial processes. To develop more sustainable catalytic methods to produce chemicals, much attention has been directed to seek first row transition metals that are Earth-abundant and sustainable to replace these highly expensive and rare metals in alkyne difunctionalization reactions. In the past few decades, although tremendous progress has been made in the nickel-catalyzed difunctionalization of alkynes, there is still a lack of comprehensive discussion on stereoselectivity control.[4] In this review, we summarize the progress of the nickel-catalyzed alkyne difunctionalization reaction for the construction of multisubstituted alkenes, with an emphasis on the strategy and control of stereochemistry. Since the hydrofunctionalization of alkynes has been well reviewed, we will not discuss it in this paper.[5]

2. Ni-Catalyzed *syn*-difunctionalization of alkynes

The Ni-catalyzed *syn*-selective difunctionalization of alkynes has been well exploited, in which two functional groups are installed on the same side of the double bond in the products. As shown in Scheme 2, four effective strategies have been successfully developed. The most common strategy is to utilize the nature of *syn*-migratory insertion of an alkyne into organonickel species to form alkenyl-nickel intermediate **1**, which can undergo reductive elimination or further functionalization to provide a reliable route to multi-substituted alkenes (Scheme 2a). The migratory insertion of alkynes into a nickelacycle intermediate, followed by reductive elimination, is also a



Scheme 1 Representative biologically active compounds containing a tri- or tetrasubstituted alkene moiety.

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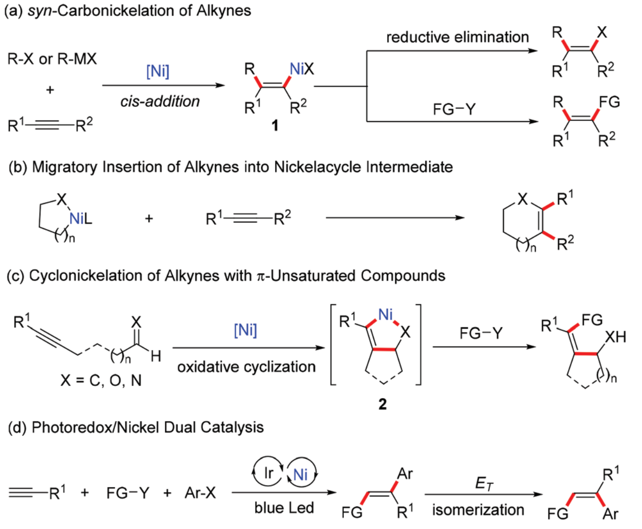


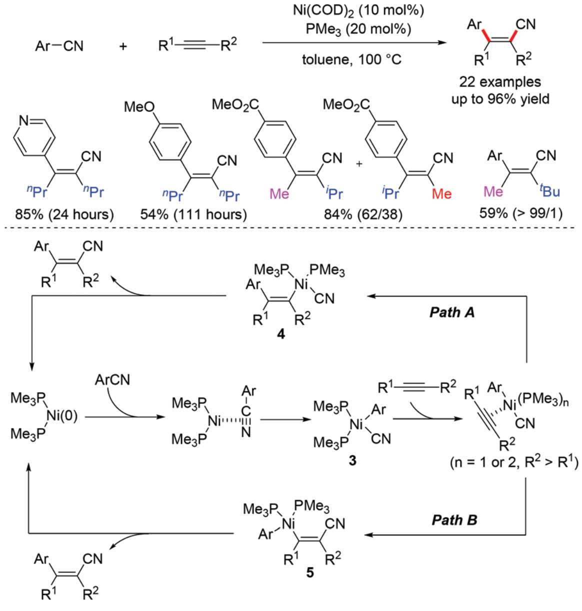
Scheme 2 Strategies for *syn*-selective difunctionalization of alkynes.

common method for the *syn*-selective difunctionalization of alkynes (Scheme 2b). Another powerful strategy is the coupling reaction of alkynes with π-unsaturated compounds, such as aldehydes, enones, and imines, which involves the formation of a five-membered nickelacycle intermediate **2** through oxidative cyclization (Scheme 2c). In addition, the merging of photoredox and nickel catalysis is emerging as an alternative strategy to access multi-substituted alkenes in a *syn*-selective manner (Scheme 2d).

2.1 *syn*-Carbonickelation of alkynes

The arylcyanation reaction of alkynes involves the direct cleavage and addition of strong aryl–CN bonds across the carbon–carbon triple bond, and represents a high atom-economic and efficient route for the preparation of alkenyl nitriles. In 2004, Hiyama and co-workers demonstrated the first example of the Ni-catalyzed arylcyanation of alkynes for the synthesis of β-aryl-substituted alkenyl nitriles (Scheme 3).[6] The electron-deficient benzonitriles can react efficiently to give alkenyl nitriles in excellent yields. However, the arylcyanation reaction of alkynes using electron-rich benzonitriles is generally sluggish.

Two possible mechanisms were considered for this transformation. The oxidative addition of Ar–CN to Ni(0) followed by the migratory insertion of alkynes into the resulting Ar–Ni(II)–CN species **3** at the Ar–Ni bond affords an alkenylnickel intermediate **4**, which undergoes reductive elimination to give the arylcyanation products and regenerate the active Ni(0) catalyst (path A). Alternatively, the possibility of migratory insertion of alkyne into the Ar–Ni(II)–CN species **3** at the CN–Ni bond to form alkenylnickel intermediate **5** cannot be ruled out (path B). Interestingly, when asymmetric alkynes were examined, the reaction preferably produced the arylcyanation product in which the aryl group is remote from the bulky isopropyl (62/38) or *tert*-butyl group (>99/1). These results indicate that the migratory insertion of alkynes into the Ni–Ar bond is



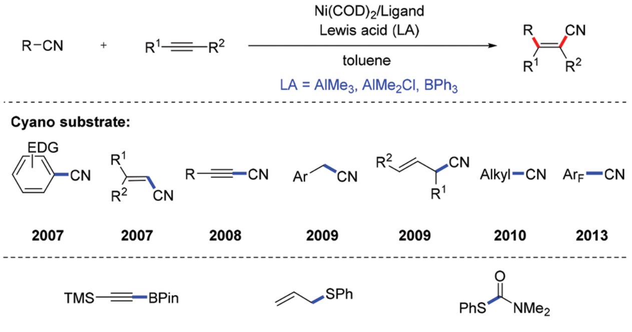
Scheme 3 Ni-Catalyzed arylcyanation of alkynes.

feasible, and the nickel center prefers to be far away from the bulky groups due to steric hindrance.

Further theoretical studies by DFT calculation also validate that path A is more favourable because it is much more difficult to achieve migratory insertion of alkyne into the Ni–CN bond than the Ni–Ar bond.[7]

The same group further developed the carbocyanation of alkynes with the aid of nickel–Lewis acid dual catalysis, in which the Lewis acid co-catalyst was thought to activate the electrophilic CN center. With this strategy, a wide array of nitriles not only electron-rich benzonitriles, but also alkenyl, alkynyl, benzyl, allyl, alkyl, as well as pentafluorobenzyl nitriles were demonstrated to be compatible with this alkyne carbocyanation reaction (Scheme 4).[8]

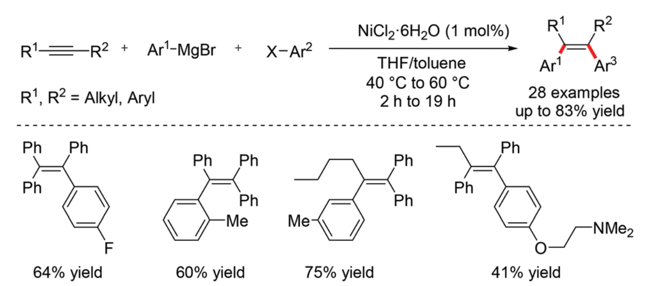
Ni-Catalyzed intermolecular alkynylboration,[9] thioallylation,[10] and thiocarbamoylation[11] of alkynes were also developed for the efficient synthesis of alkenylborons and alkenysulfides (Scheme 4), which are versatile synthetic intermediates in organic synthesis.



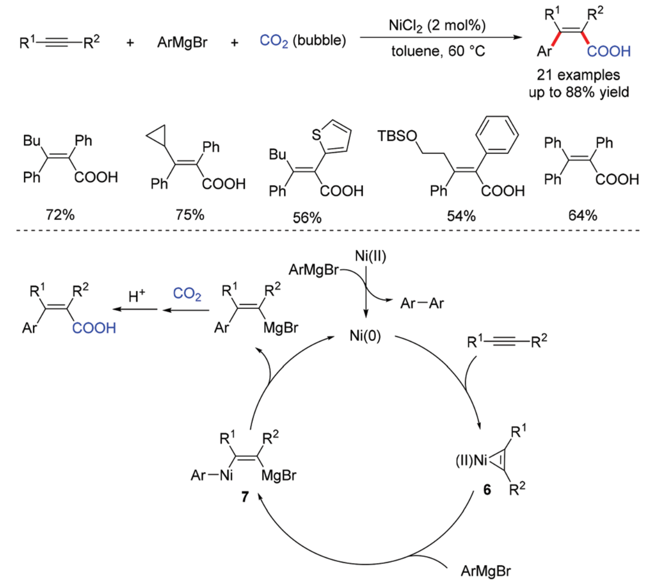
Scheme 4 Ni-Catalyzed carbocyanation, alkynylboration, thioallylation and thiocarbamoylation of alkynes.

The three-component redox neutral difunctionalization of alkynes is also a very effective method for constructing multisubstituted olefins by simultaneously introducing nucleophiles and electrophiles across the triple bonds. In 2015, Hayashi and co-workers reported a Ni-catalyzed cross coupling of alkynes with aryl Grignard reagents and aryl halides, providing an operationally simple method for synthesizing tetrasubstituted alkenes with high stereo- and regioselectivity (Scheme 5).[12]

Xi[13] and Cheng[14] independently reported the nickel-catalyzed regioselective arylcarboxylation of alkynes with arylmagnesium reagents and carbon dioxide (CO_2, 1 atm) for the synthesis of trisubstituted β-arylacrylic acids (Scheme 6). One possible mechanism is proposed in Scheme 6. The oxidative cycloaddition reaction of Ni(0) with alkyne affords the Ni(II) complex **6**, which undergoes transmetalation with the Grignard reagent to generate alkenyl-Ni(II) complex **7**. The reductive elimination of **7** followed by the addition of CO_2 and hydrolysis will deliver the desired β-arylacrylic acids.



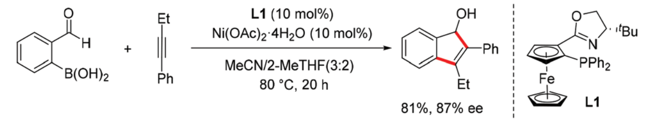
Scheme 5 Ni-Catalyzed three-component coupling of aryl Grignard reagents, alkynes and aryl halides.



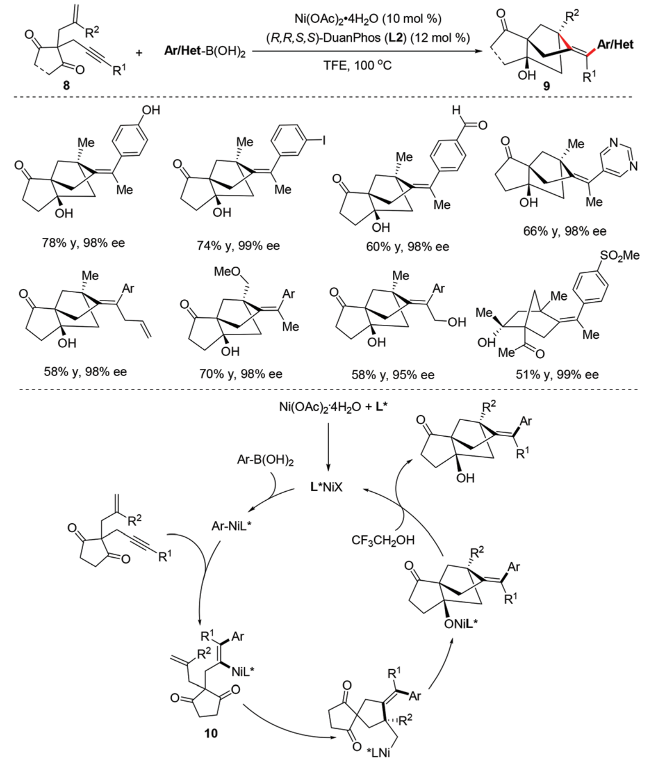
Scheme 6 Ni-Catalyzed arylcarboxylation of alkynes.

Following Hayashi[15] and Murakami's pioneering studies[16] on the Rh-catalyzed cyclization of *o*-formyl aryl boronic acids with alkynes, Lam reported the Ni-catalyzed cyclization reaction of 1-phenyl-1-butyne with 2-formylphenylboronic acid using (S,S_p)-^{t}Bu-phosferrox (**L1**) as the chiral ligand, giving the indenol product in 81% yield with 87% ee (Scheme 7).[17] The indene skeleton was constructed *via syn*-arylnickelation of the alkyne followed by nucleophilic addition of the resulting alkenylnickel species onto the aldehyde.

Our group reported a nickel-catalyzed cascade cyclization of enynones **8** for the modular synthesis of bridged tricyclo[5.2.1.0^{1,5}]decanes **9** with three quaternary stereocenters in good yields and excellent enantioselectivities (92–99% ee).[18] A possible catalytic cycle is proposed in Scheme 8. The *syn*-selective addition of arylnickel species to the triple bond formed the alkenylnickel intermediate **10**. Intramolecular migratory insertion of alkenylnickel **10** to the double bond followed by nucleophilic cyclization onto one of the ketone groups affords the tricyclo[5.2.1.0^{1,5}]decane product **9** upon hydrolysis (Scheme 8).



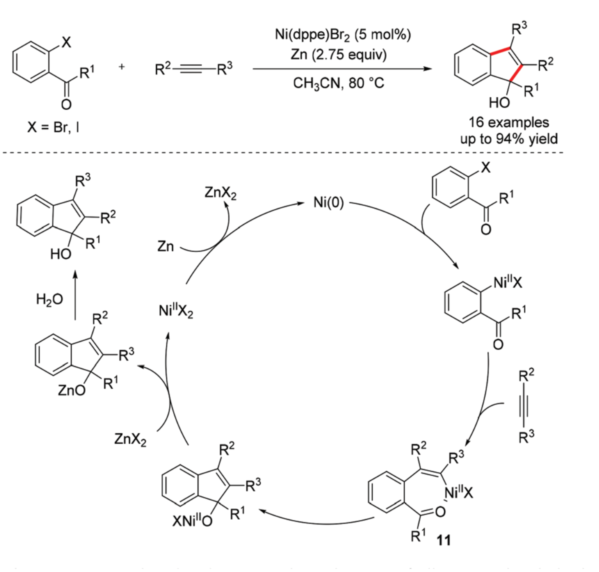
Scheme 7 Ni-Catalyzed cyclization of 2-formylphenylboronic acid with alkyne.



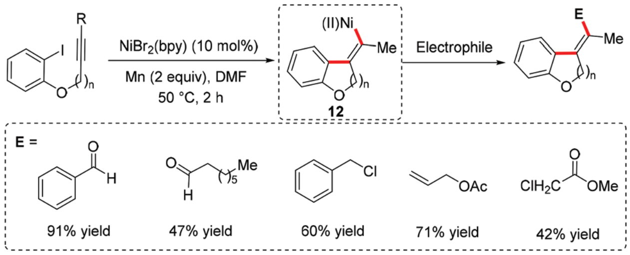
Scheme 8 Ni-Catalyzed enantioselective cyclization of enynones.

The reductive difunctionalization of alkynes has also been developed, which involves the simultaneous incorporation of two electrophiles to both sides of the triple bond without the use of preformed organometallic reagents. In 2002, Cheng *et al.* disclosed a Ni-catalyzed intermolecular reductive carbonickelation of *o*-halophenyl ketones with alkynes using Zn powder as a reducing agent, providing an efficient route to functionalized indenol derivatives (Scheme 9).[19] The oxidative addition of aryl halides to nickel(0) species, followed by the migratory insertion of alkynes into the Ni–Ar bond affords alkenylnickel intermediate **11.** Intramolecular nucleophilic addition of alkenylnickel **11** to the carbonyl, followed by transmetalation with zinc halide, delivers the indenol product upon hydrolysis. In addition, the same strategy has also been applied to the preparation of substituted quinolines[20] and (iso)quinolines.[21]

Maddaluno and co-workers described a Ni-catalyzed reductive arylfunctionalization of alkynes (Scheme 10).[22] Remarkably, the nucleophilic alkenylnickel species **12** resulting from the intramolecular arylnickelation of the triple bond could be trapped by a variety of electrophiles, such as benzaldehyde, nonanal, benzyl chloride, allyl acetate, and α-chloroesters, providing a convenient method for the synthesis of substituted benzofurans and chromanes.



Scheme 9 Ni-Catalyzed reductive carbocyclization of alkynes with *o*-halophenyl ketones.

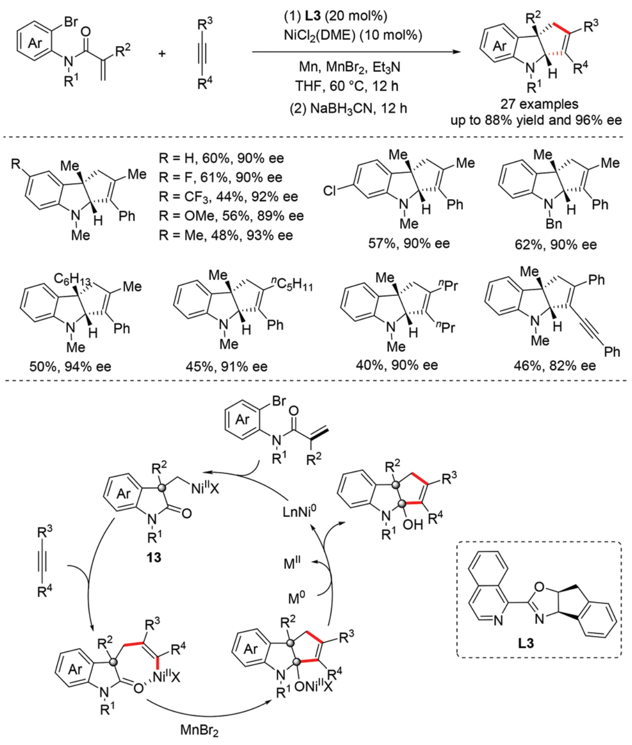


Scheme 10 Ni-Catalyzed reductive arylfunctionalization of alkynes.

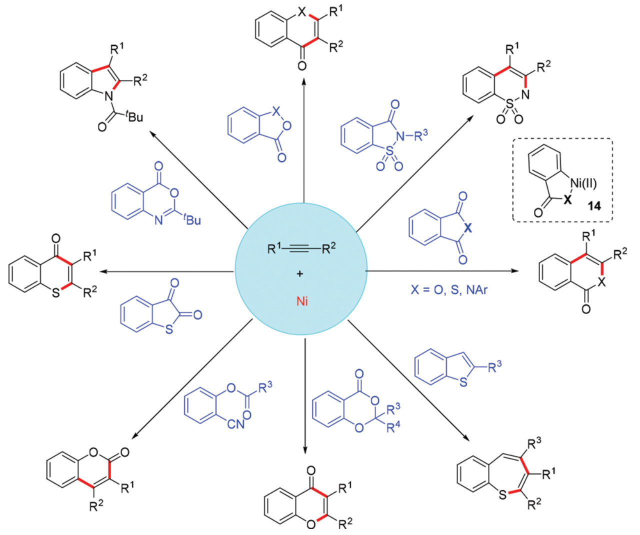
Recently, our group had also reported a Ni-catalyzed highly regio- and enantioselective reductive cyclization reaction of acrylamides with asymmetric internal alkynes.[23] This transformation takes place under mild conditions with high efficiency, providing rapid access to structurally diverse cyclopentannulated indolines in good yields with high regioselectivity (>20/1) and enantioselectivities (27 examples, 82–96% ee) (Scheme 11). A mechanistic study showed that the cyclopentannulated indolines are afforded through a highly regioselective migratory insertion of asymmetric internal alkynes into the σ-alkyl-Ni(II) species **13**, followed by nucleophilic addition of the resulting alkenyl nickel to unactivated amides.

2.2 Migratory insertion of alkynes into the nickelacycle intermediate

Another method for the *syn*-difunctionalization of alkynes is to replace a part of the cyclic compounds with low-valent nickel while eliminating small molecules such as CO or CO_2 to form the nickelacycle intermediate **14** followed by migratory insertion of alkynes. Matsubara and co-workers initiated the study of Ni-catalyzed decarbonylative cycloaddition of anhydrides to alkynes for the synthesis of isocoumarins (Scheme 12).[24] As shown in Scheme 12, a series of heterocycles could be effectively constructed by this strategy.[25]



Scheme 11 Ni-Catalyzed enantioselective reductive cyclization of alkynes with arylbromide-tethered acrylamides.



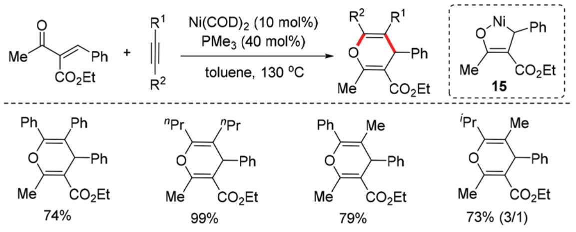
Scheme 12 Ni-Catalyzed cycloaddition reaction of unsaturated compounds with alkynes.

Matsubara and co-workers reported a Ni-catalyzed cycloaddition between α,β-unsaturated carbonyl compounds with alkynes.[26] Mechanistic studies have shown that the reaction proceeded through the oxidative cyclization of Ni(0) and enone to form an oxa-nickelacycle intermediate **15**, followed by migratory insertion of alkyne (Scheme 13).

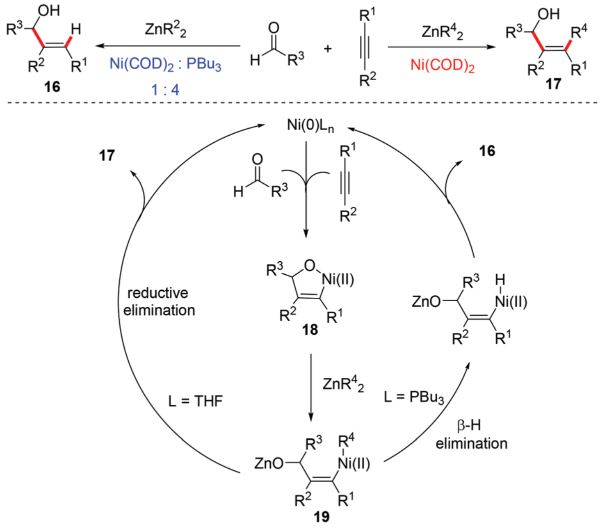
2.3 Cyclonickelation of alkynes with π-unsaturated compounds

Ni-Catalyzed reductive coupling of alkynes and aldehydes, pioneered by the group of Sato,[27] Montgomery,[28] and Jamison,[29] is an attractive and general approach for the synthesis of stereodefined allylic alcohols bearing tri- and tetrasubstituted alkenes.[2d,30]

The Montgomery group demonstrated the first example of Ni-catalyzed cyclization/alkylation of alkynals with organozinc reagents to form cyclic allylic alcohols and the three-component coupling of aldehydes, organozincs and alkynes to synthesize acyclic allylic alcohols with complete control of alkene stereochemistry (Scheme 14).[31] The oxidative cyclization of Ni(0) with aldehydes and alkynes affords a common oxa-nickelacycle intermediate **18.** Transmetalation of species **18** with an organozinc reagent gives the alkenylnickel species **19**, followed by reductive elimination to deliver the alkylated product **17.** Alternatively, in the presence of a catalytic PPh$_3$ ligand, β-hydride elimination occurs prior to reductive elimination, therefore resulting in the reductive product **16.**



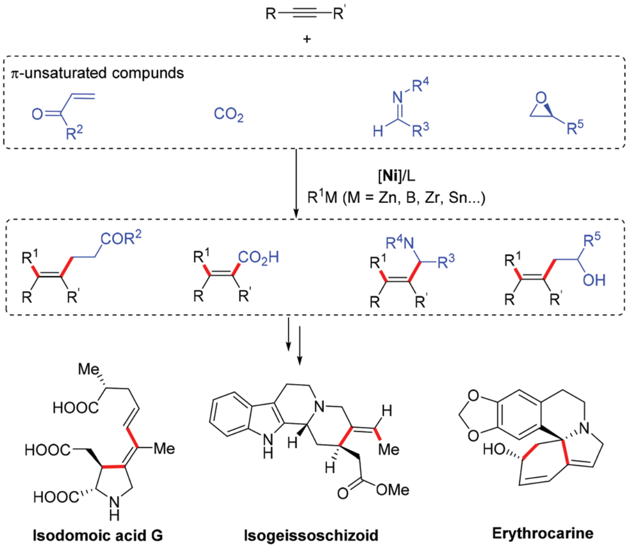
Scheme 13 Nickel-catalyzed cycloaddition of enone with alkynes.



Scheme 14 Ni-Catalyzed reductive coupling of alkynes and aldehydes.

The reductive coupling reaction of alkynes with other unsaturated carbonyl compounds, such as enones,[28a,32] carbon dioxide,[33] imines,[29c] and epoxides,[34] have also been successfully developed for the synthesis of various functionalized tetrasubstituted alkenes (Scheme 15). This Ni-catalyzed multicomponent coupling of alkynes has been applied to the total synthesis of many biologically active natural products, such as isodomoic acid G,[35] isogeissoschizoid,[36] and erythrocarine[37] (Scheme 15).

Asymmetric versions of the multi-component coupling of alkynes have been exploited. The Jamison group realized the

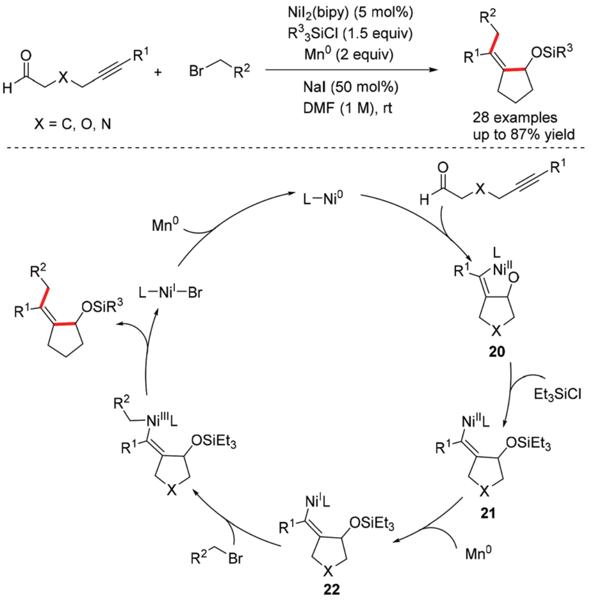


Scheme 15 Ni-Catalyzed reductive coupling of alkynes and various π-unsaturated compounds and synthetic applications.

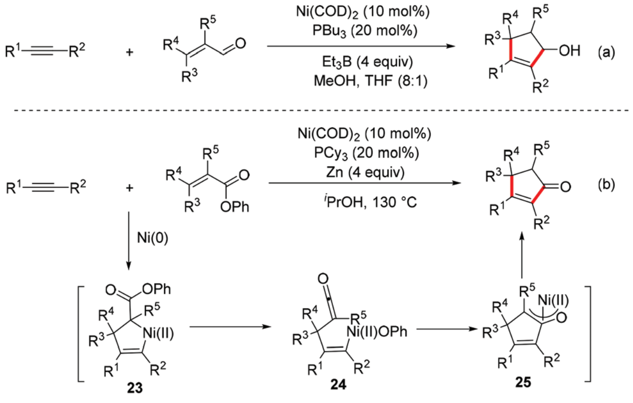
asymmetric three-component reductive coupling of alkynes, Et_3B and imines using a P-chiral ferrocenyl phosphane ligand **L4**, providing an efficient way to enantiomerically enriched tetrasubstituted allylic amines (Scheme 16a).[38] Zhou and coworkers developed an Ni-catalyzed asymmetric alkylative coupling reaction of alkynes, aldehydes and $ZnMe_2$ using a spiro phosphoramidite ligand **L5** (Scheme 16b).[39] In addition, Tang's group used their own independently developed P-chiral phosphorus ligand **L6** to further explore this reaction (Scheme 16c).[40] The asymmetric transformation provides an efficient way to prepare chiral allylic alcohols bearing tetrasubstituted olefin functionality.

Recently, Montgomery *et al.* combined the Ni-catalyzed oxidative cyclization of alkynals and reductive cross-electrophile coupling together as a new approach for the synthesis of tetrasubstituted alkenes (Scheme 17).[41] The reaction employed alkyl halide as an alkylating reagent and obviated the requirement for preformed organometallic reagents, greatly improving the functional group compatibility compared to the classic coupling method. The oxidative cyclization of nickel(0) with alkynals affords the nickelacycle intermediate **20**. The nickel–oxygen bond is cleaved by Et_3SiCl to form the silyl protected alkenyl nickel(II) intermediate **21**, which is reduced by Mn(0) to generate the alkenyl Ni(I) species **22**. The oxidative addition of alkyl halide followed by reductive elimination delivers the desired products along with Ni(I) species, which undergoes further Mn-mediated reduction to regenerate the active Ni(0) catalyst (Scheme 17).

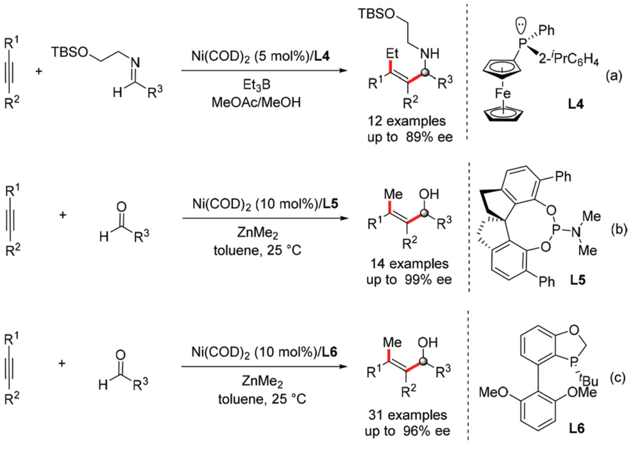
The same group further developed a Ni-catalyzed [3 + 2] reductive cycloaddition of alkynes with enals using $Ni(COD)_2/PBu_3$ as the catalyst and Et_3B as the reductant. This method provides a novel strategy for the assembly of five-membered carbocyclic rings. Both inter- and intramolecular variants of the process could proceed smoothly to provide an array of cyclopentenol derivatives (Scheme 18a).[42]



Scheme 17 Ni-Catalyzed reductive coupling of alkynals with alkyl halides.



Scheme 18 Ni-Catalyzed reductive [3 + 2] cycloaddition of alkynes with α,β-unsaturated carbonyl compounds.

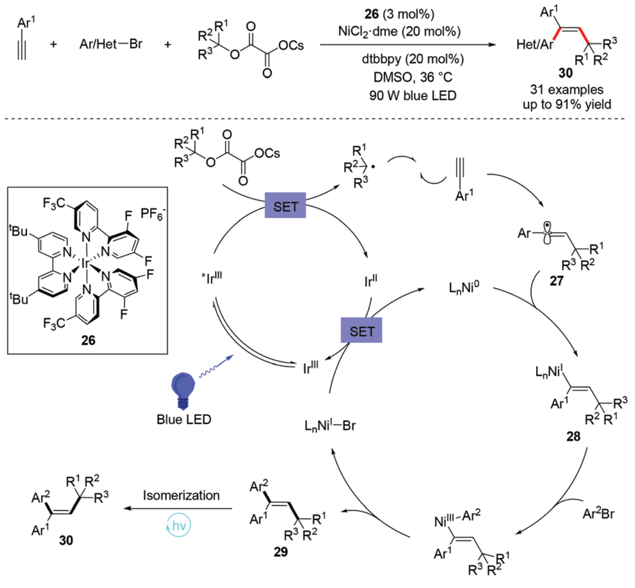


Scheme 16 Ni-Catalyzed asymmetric coupling of alkynes with imines or aldehydes.

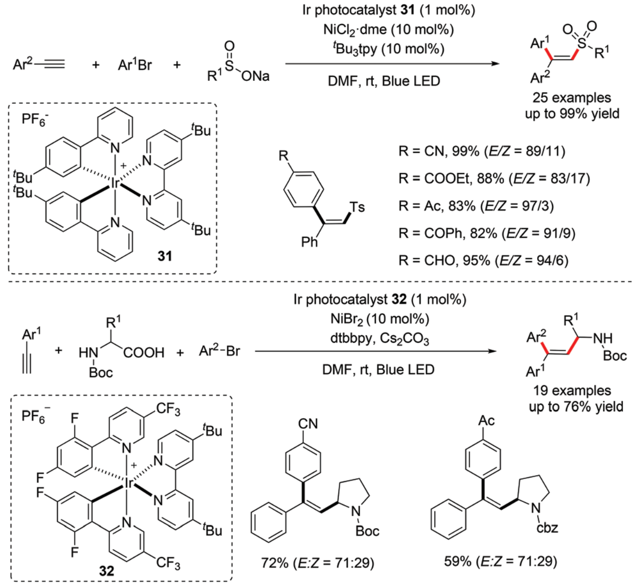
In addition, a Ni-catalyzed [3 + 2] cycloaddition reaction of α,β-unsaturated phenyl esters with alkyne in ^{i}PrOH using Zn powder as the reductant was also demonstrated by Ohashi and co-workers (Scheme 18b).[43] A possible mechanism involving C–O bond activation was proposed. The nickelacyclopentene intermediate **23** was formed through the oxidative cyclization of α,β-unsaturated phenyl ester with alkyne and nickel(0). β-Phenoxy elimination followed by insertion of the resulting ketene intermediate **24** into the C–Ni bond provides η^3-oxaallylnickel species **25**, which undergoes alcoholysis to deliver the cyclopentenone product.

2.4 Ni/photoredox dual catalysis

Photoredox catalysis has been studied and can be used to promote the contra-thermodynamic *E*/*Z* isomerization of olefins through energy-transfer. Chu *et al.* reported an intermolecular *syn*-selective alkylarylation of terminal alkynes with



Scheme 19 Ni/photoredox dual catalyzed *syn*-selective alkylarylation of terminal alkynes.



Scheme 20 Ni/photoredox dual-catalyzed arylsulfonylation and arylalkylation of alkynes.

tertiary alkyl oxalates and aryl bromides *via* photoredox-nickel dual catalysis.[44] Scheme 19 explains the mechanism of *syn*-selectivity. Single-electron transfer between photoexcited Ir(III) and tertiary alkyl oxalate is expected to generate the tertiary alkyl radical and Ir(II). Addition of the resulting alkyl radical to terminal alkyne gives alkenyl radical **27**. An *anti*-addition of alkenyl radical **27** to Ni(0) leads to the (*E*)-alkenyl-Ni(I) species **28**. The oxidative addition with aryl bromide, followed by reductive elimination gives *E*-substituted alkenes **29**. Finally, a photochemical *E*/*Z* isomerization of the resulting *E*-alkenes through the energy transfer process will deliver the desired *Z*-alkene **30**.

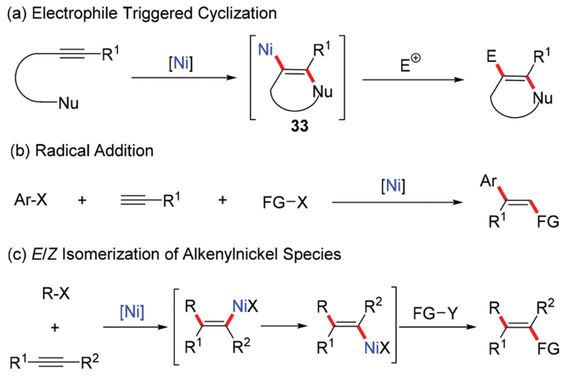
Very recently, Rueping *et al.* further developed a three-component cross-coupling reaction of alkynes, aryl halides and sodium sulfinates *via* a photoredox/nickel dual catalysis, enabling one-pot access to alkenyl sulfoxides under mild reaction conditions (Scheme 20, top).[45] In addition, a similar arylalkylation of alkynes was also reported.[46] The protocols possess a broad substrate scope and good functional-group tolerance, albeit with moderate stereoselectivity (*syn*-addition manner) (Scheme 20, bottom). Both these transformations proceed *via* a mechanism involving a single-electron transfer with a subsequent energy-transfer activation pathway.

3. Ni-Catalyzed *anti*-difunctionalization of alkynes

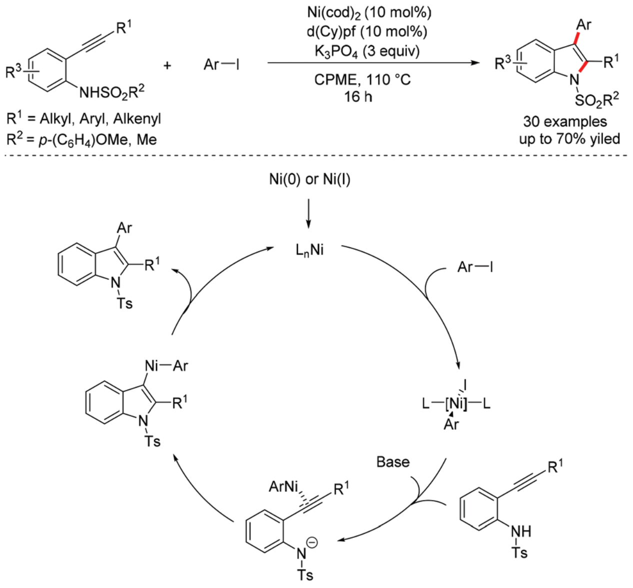
Compared with the well-developed *syn*-selective difunctionalization of alkynes, the Ni-catalyzed *anti*-selective alkyne difunctionalization reaction is still uncommon. One effective strategy to obtain formal *anti*-difunctionalized products is electrophile triggered cyclization, which employs alkyne substrates bearing a heteroatom-containing substituent at the adjacent position. After activation of the triple bond by nickel coordination, an intramolecular nucleophilic addition to the alkyne forms the *trans*-alkenylnickel species **33** (Scheme 21a). Alternatively, Ni-catalyzed radical addition/coupling reaction of terminal alkynes is another important method to provide *anti*-difunctionalized products (Scheme 21b). In addition, although the carbonickelation of alkynes usually undergoes in a *syn*-selective manner, in some cases, due to the steric hindrance of the substrates or driven by the formation of more stable and chelated alkenyl-nickel species, *E*/*Z* isomerization of the resulting alkenyl-nickel species may take place (Scheme 21c).

3.1 Electrophile triggered cyclization

Although palladium-catalyzed electrophile triggered cyclization of alkynes bearing a hetero nucleophile has been well developed for the synthesis of a wide variety of heterocycles,[47] the nickel catalyst was less employed as a catalytic precursor within this



Scheme 21 Strategies for *anti*-selective difunctionalization of alkynes.



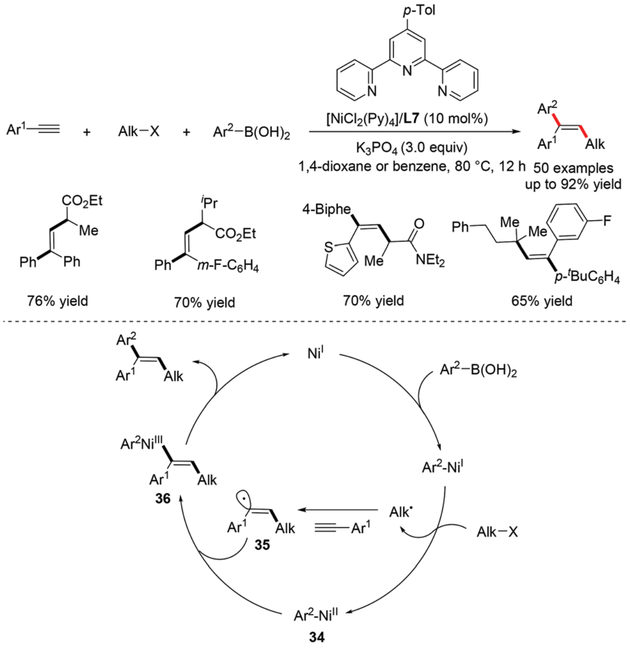
Scheme 22 Ni-Catalyzed *anti*-selective arylamination of 2-alkynyl-*N*-sulfonylanilides.

reactivity pattern. Recently, Dake *et al.* reported a nickel-catalyzed *anti*-arylamination of 2-alkynyl-*N*-sulfonylanilides to form 2,3-difunctionalized *N*-arylsulfonylindoles.[48] A possible mechanism involving oxidative addition, alkyne amination and reductive elimination was proposed (Scheme 22).

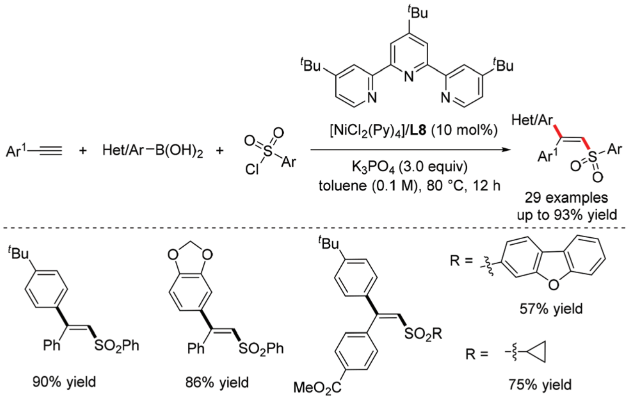
3.2 Radical addition/coupling with terminal alkynes

In 2016, Nevado and co-workers disclosed a Ni-catalyzed three-component coupling reaction of terminal alkynes, alkyl halides and boronic acids for the stereoselective synthesis of trisubstituted alkenes (Scheme 23).[49] The protocol, involving the simultaneous incorporation of both aryl and alkyl groups across the triple bond in a radical-mediated process, provided access to trisubstituted alkenes in a highly regio- and stereocontrolled manner. Significantly, both activated and unactivated alkyl halides were well tolerated under the optimized reaction conditions. The proposed mechanism starts with the generation of active Ni(I) species *in situ* and reacts with organoboron reagents through transmetalation. The resulting Ar–Ni(I) species is responsible for the activation of alkyl halides to produce an alkyl radical along with the Ar–Ni(II) intermediate **34**. The alkyl radical then undergoes highly selective addition to the terminal alkyne to deliver vinyl radical intermediate **35**. The subsequent recombination of the vinyl radical intermediate **35** with Ar–Ni(II) **34** will afford the key Ni(III) intermediate **36**, which undergoes reductive elimination to furnish the desired products while regenerating the active Ni(I) catalyst (Scheme 23).

The same group further reported a similar stereoselective carbosulfonylation of terminal alkynes by utilizing sulfonyl chlorides as radical precursors, enabling the rapid synthesis of β,β-disubstituted vinyl sulfones with broad functional group compatibility (Scheme 24).[50]



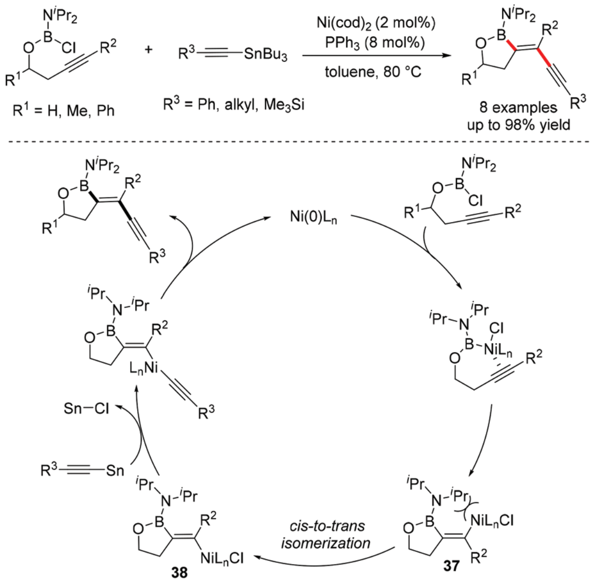
Scheme 23 Ni-Catalyzed *anti*-selective arylalkylation of terminal alkynes.



Scheme 24 Ni-Catalyzed *anti*-selective carbosulfonylation of terminal alkynes.

3.3 *E*/*Z* isomerization of alkenylnickel species

3.3.1 *E*/*Z* isomerization driven by steric hindrance of substrates. In 2005, Suginome's group reported a nickel-catalyzed *trans*-carboboration of chloroboryl homopropargylic ethers with organotin regents, which provided a new way for the stereoselective synthesis of highly functionalized organoboron compounds (Scheme 25).[51] A possible mechanism was put forward to elucidate the observed *trans*-addition mode. The oxidative addition of the B–Cl bond to nickel, followed by intramolecular *cis*-migratory insertion of alkyne into the B–Ni bond resulted in *cis*-alkenylnickel intermediate **37**. It was speculated that the considerable steric repulsion caused by the diisopropylamino group and the chlorobis-(triphenylphosphine)nickel moiety forced the



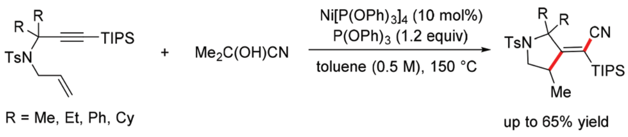
Scheme 25 Ni-Catalyzed *anti*-carboboration of alkynes.

isomerization of *cis*-alkenylnickel to *trans*-alkenylnickel **38**. Delivery of the alkynyl group from the organotin reagent *via* the transmetalation step and the subsequent reductive elimination would afford *trans*-alkynylboration products (Scheme 25).

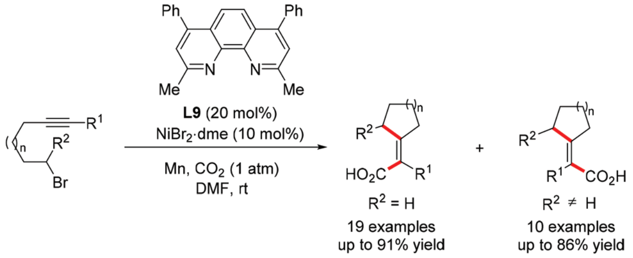
Inspired by the dramatic impact of steric factors on promoting the isomerization of alkenyl nickel species, an unprecedented *anti*-carbocyanation of 1,6-enynes under nickel catalysis was realized by the Arai group (Scheme 26).[52] The catalytic protocol was triggered by hydronickelation of alkenes followed by carbonickelation of alkynes. Mechanism studies have shown that bulky substituents such as TIPS or TMS are essential for causing steric repulsion after enyne cyclization, and this effect would control the geometry of the C–C double bond through a key nickel–carbene intermediate.

Martin and co-workers reported a Ni-catalyzed reductive cyclization/carbonylation of unactivated alkyl halides with carbon dioxide (Scheme 27).[53] This robust protocol fused the CO_2 fixation with a cascade reductive process, resulting in carbonylated carbocyclic products with a divergent *syn*/*anti* selectivity pattern modulated by substrates. Specifically, the *cis*-selective cyclization/carboxylation products were exclusively produced as preliminary alkyl halides were used, however, the *trans*-selectivity was favoured with bulk substituents at the α-position of alkyl bromides.

Similar effects have been demonstrated in Montgomery's work on three-component reaction of aldehydes, alkynes, and alkyl halides, in which the *Z* isomer of alkylative cyclization products predominated when secondary alkyl bromides were employed (Scheme 28).[41] The result of this *Z*/*E* isomerization may be driven by the crowded steric environment of the vinylnickel intermediate. Significantly, the reaction concentration also has an extraordinary effect on the *E*/*Z* selectivity, where the proportion of the *Z* isomer of the product increases as the reaction concentration decreases.



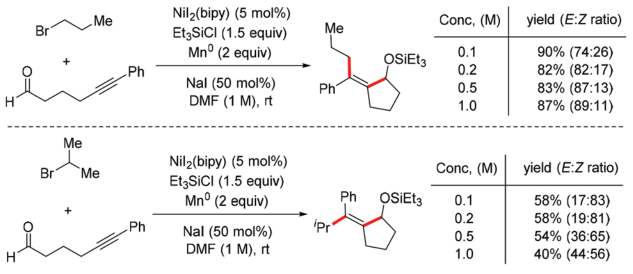
Scheme 26 Ni-Catalyzed *anti*-carbocyanation of 1,6-enynes.



Scheme 27 Ni-Catalyzed divergent cyclization/carboxylation of unactivated alkyl bromides with CO_2.

3.3.2 ***E*/*Z* isomerization driven by the formation of chelated alkenyl-nickel species.** In 2016, Liu *et al.* disclosed a nickel-catalyzed addition/cyclization of alkyne-nitriles with organoboronic acids, enabling the construction of highly functionalized 1-naphthylamines (Scheme 29).[54] Remarkably, aryl boronic acids bearing a wide range of diverse substitutes underwent the cyclization smoothly to afford the desired 1-naphthylamines in moderate to high yields. On the basis of mechanistic studies, the author proposed a catalytic cycle triggered by Ni(I) species, which was generated by the disproportionation reaction of Ni(0) and Ni(II). Transmetalation of Ni(I) species with arylboronic acid leading to an arylnickel(I) complex, followed by migratory insertion of the carbon–carbon triple bond into Ar–Ni(I) species affords an alkenylnickel(I) intermediate **39**. The tethered cyano group may play a role in facilitating the *cis*–*trans* isomerization by stabilizing the alkenylnickel(I) species. An intramolecular nucleophilic addition of the alkenylnickel(I) **39** to the cyano group, followed by protonation and tautomerization, will furnish 1-naphthylamines and regenerate the active Ni(I) catalyst (Scheme 29).

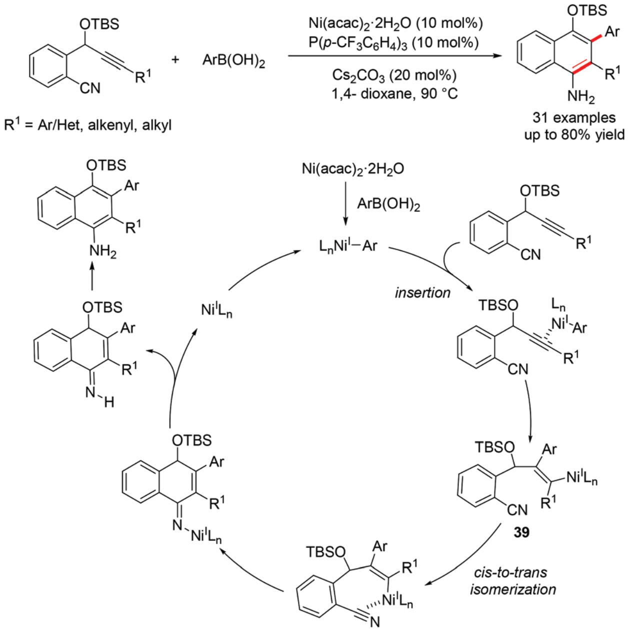
Lam and co-workers independently reported a Ni-catalyzed enantioselective *anti*-arylative cyclization of alkynones and



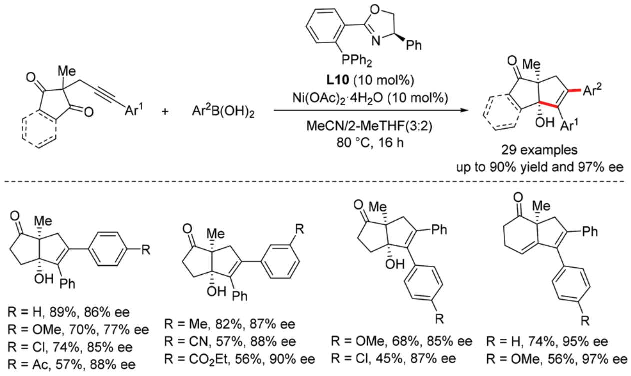
Conc, (M)	yield (*E*:*Z* ratio)
0.1	90% (74:26)
0.2	82% (82:17)
0.5	83% (87:13)
1.0	87% (89:11)

Conc, (M)	yield (*E*:*Z* ratio)
0.1	58% (17:83)
0.2	58% (19:81)
0.5	54% (36:65)
1.0	40% (44:56)

Scheme 28 Ni-Catalyzed oxidative cyclization and reductive cross electrophile coupling of aldehydes, alkynes, and alkyl halides.



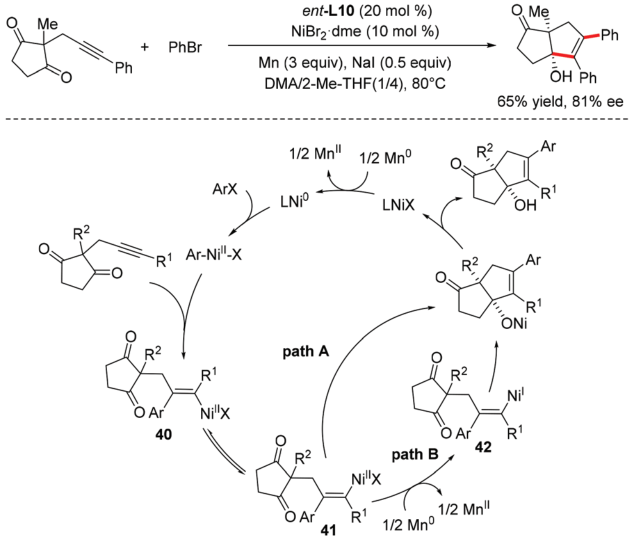
Scheme 29 Ni-Catalyzed *anti*-addition/cyclization of alkyne-nitriles with organoboronic acids.



Scheme 30 Ni-Catalyzed enantioselective *anti*-arylative cyclization of alkynyl electrophiles with organoboronic acids.

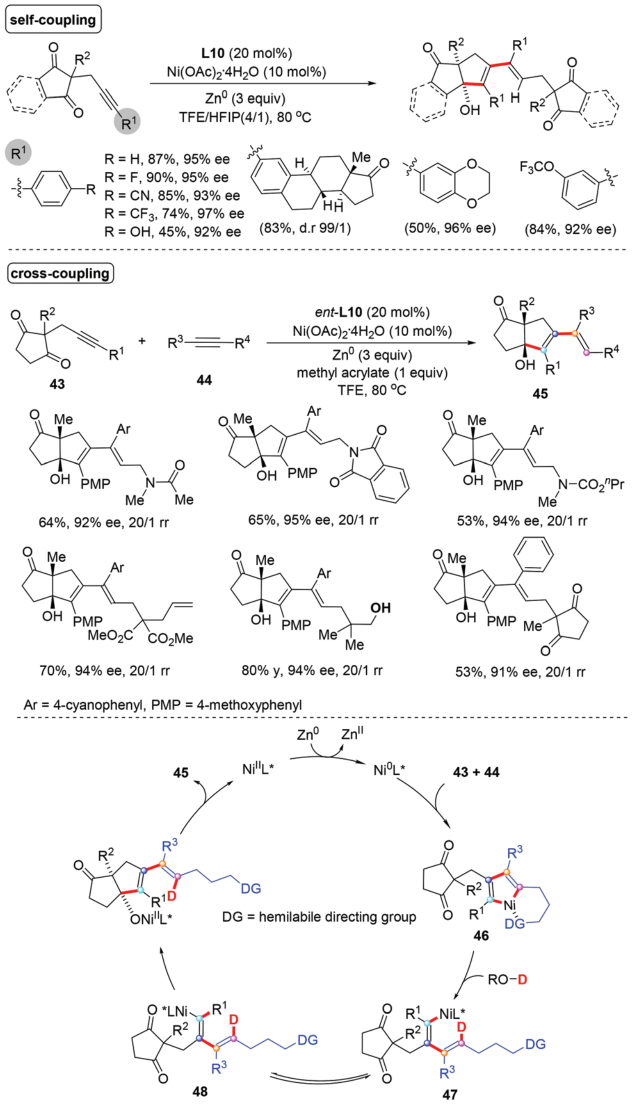
organoboronic acids (Scheme 30).[17] By using the (*R*)-Ph-Phox as a ligand, a wide variety of alkynones or cyclohexa-1,3-dienones are compatible with this transformation and exhibit excellent enantioselectivities.

Our group recently developed a new catalyst system for the *anti*-arylative cyclization of alkynones and aryl halides through a reductive cross-coupling strategy.[55] The transformation proceeds smoothly in the absence of organometallic reagents and features high functional group tolerance, providing an effective platform to access a wide variety of synthetically useful *endo*-cyclic tetrasubstituted allylic alcohols in a stereoselective manner (Scheme 31). A possible reaction mechanism for the reductive arylative cyclization of alkynone was proposed. The oxidative addition of ArX into Ni(0) followed by migratory insertion of alkyne into the resulting arylnickel(II) species affords an alkenyl-Ni(II) intermediate **40**. A reversible *E*/*Z* isomerization process takes place to produce a new alkenyl-Ni(II) intermediate **41**, which could be reduced by Mn^0 to give more nucleophilic alkenyl-Ni(I) species **42.** Nucleophilic addition of alkenyl-Ni(I) **42** to the ketone followed by protonolysis produced the *endo*-cyclic tetrasubstituted allylic alcohols. The catalytically active Ni(0) species was then regenerated upon Mn^0 reduction (path B, Scheme 31). The direct cyclization of the alkenyl-Ni(II) intermediate **41** to the ketone carbonyl cannot be excluded (path A, Scheme 31).



Scheme 31 Ni-Catalyzed enantioselective *anti*-arylative cyclization of alkynones with aryl halides.

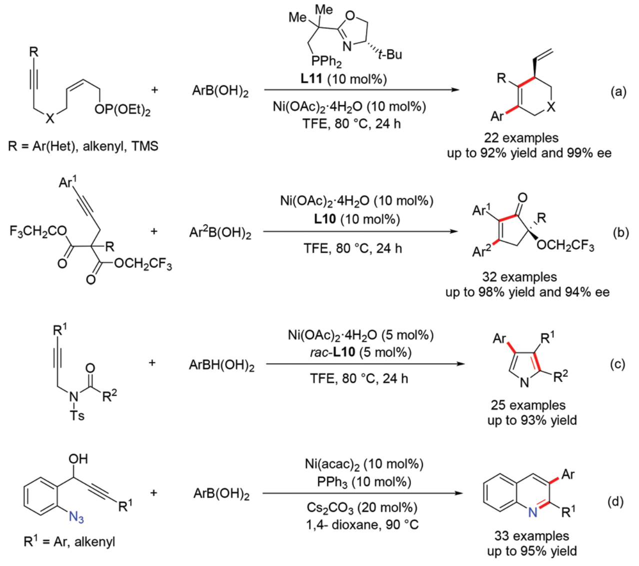
Our group further demonstrated the Ni-catalyzed reductive coupling of unsymmetrical internal alkynes, which is still a significant challenge in organic synthesis (Scheme 32).[56] Both self-coupling and cross-coupling versions of reductive coupling of two unsymmetrical internal alkynes were achieved using a hemilabile directing group strategy, enabling rapidly access to a series of synthetically challenging pentasubstituted 1,3-dienes with diverse functional groups in good yields with high regio- and enantioselectivity (mostly >20/1 rr, >90% ee). Compared to traditional cross-coupling reactions, the reaction features high atom- and step-economy, without requiring the use of prepared stereodefined coupling partners such as vinyl halides or vinyl organometallics. A rationalized mechanism for this transformation was proposed based on the mechanistic studies. Initially, a catalytically active Ni(0) species was formed upon the reduction of the Ni(II) precatalyst by Zn dust. Oxidative cyclization of alkynone **43** with another unsymmetrical internal alkyne **44** gave a nickelacycle **46**, in which the tethered carbonyl or hydroxyl group serves as a hemilabile directing group to control the regioselectivity. Then, selective protonation of **46** by alcohol would afford the conjugated dienylnickel species **47**, which could undergo a reversible *cis*–*trans* isomerization to produce a new dienylnickel intermediate **48.** Finally, the target pentasubstituted 1,3-diene **45** was



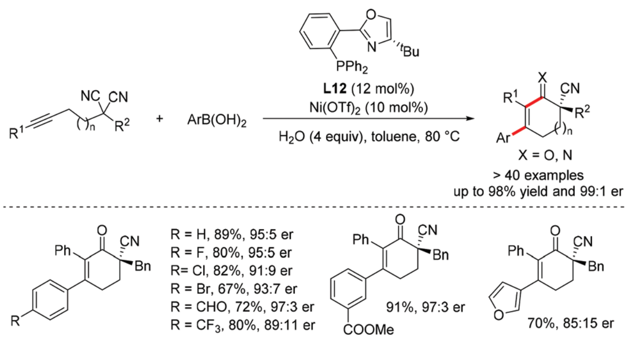
Scheme 32 Ni-Catalyzed reductive coupling of unsymmetrical internal alkynes.

formed through intramolecular nucleophilic attack of the dienylnickel **48** to carbonyls and the subsequent protonation.

Several other types of electrophiles were demonstrated to be suitable for this nickel-catalyzed *anti*-carbonickelation cyclization reaction. In 2017, the Lam group developed highly enantioselective allylic alkenylations of *Z*-allylic phosphate tethered alkynes which provide a range of chiral 1,4-diene-containing carbo- and heterocycles (Scheme 33a).[57] In 2018, the same group further developed a nickel-catalyzed desymmetrization of malonate esters for the enantioselective synthesis of highly functionalized cyclopent-2-enones, and the cyclization is enabled by the reversible *E*/*Z* isomerization of alkenylnickel species (Scheme 33b).[58] Later, the less electrophilic *N*-Ts-amides were proved to effectively capture the alkenylnickel species to obtain multisubstituted pyrroles (Scheme 33c).[59] Trapping the alkenylnickel intermediate by an azide group, a non-carbon center electrophile has also been developed for the efficient synthesis of 2,3-diarylquinolines (Scheme 33d).[60]



Scheme 33 Ni-Catalyzed cyclization of alkynyl electrophiles with organoboronic acids involving *anti*-carbonickelation of alkynes.



Scheme 34 Ni-Catalyzed enantioselective *anti*-arylative cyclization of alkyne-tethered malononitriles.

Ni-Catalyzed desymmetrization of alkyne-tethered malononitriles with aryl boronic acids was developed by Liu group (Scheme 34).[61] This protocol involves the *cis*-addition of aryl boronic acids to alkynes, followed by *E*/*Z* isomerization of alkenylnickel species and selective nitrile insertion, providing unprecedented access to 5–7-membered skeletons bearing a nitrile-containing quaternary stereocenter in good yields with excellent enantioselectivities.

4. Conclusions

In this review, we summarize the recent advances in the nickel-catalyzed stereoselective alkyne difunctionalization reaction. Different strategies for controlling stereoselectivity towards the synthesis of stereodefined tri- and tetrasubstituted alkenes have been highlighted. Although considerable progress has been made in this rapidly evolving field in the past few decades, many intriguing challenges still lie ahead to extend the use of these methodologies.

Firstly, most of these methods require the use of stoichiometric organometallic regents, which impose limitations in their synthetic applicability. The stereoselective difunctionalization of alkynes *via* the reductive cross-coupling strategy would be more advantageous, but there are very minimal successful examples in this area.

Secondly, the stereoselective difunctionalization of alkynes is still tailored for a specific substrate class. In particular, the *anti*-difunctionalization of alkynes by the radical-mediated process is restricted to terminal alkynes.

Thirdly, the detailed reaction mechanism for controlling stereoselectivity is still indistinct in many transformations. Thus more effort needs to be focused on the detailed mechanistic studies, as it will be conducive for designing and developing innovative catalytic systems.

Conflicts of interest

There are no conflicts to declare.

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