Ni- and Pd-Catalyzed Enantioselective 1,2-Dicarbofunctionalization of Alkenes

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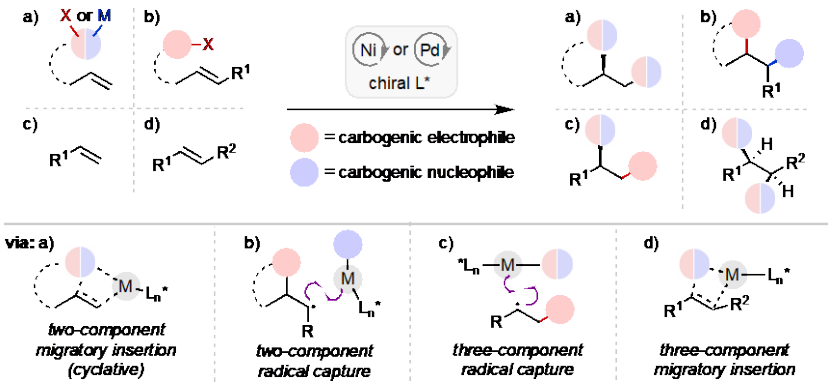

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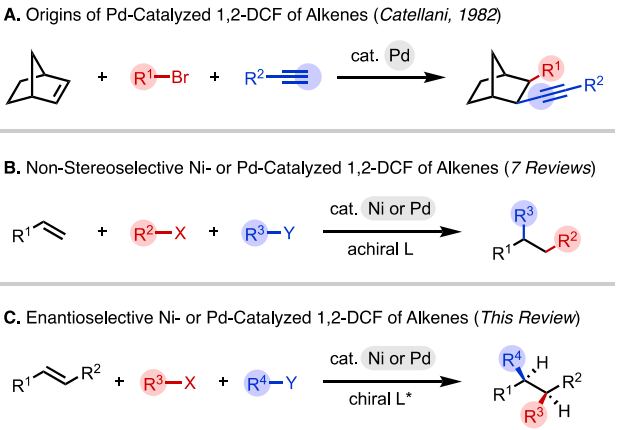
Abstract Catalytic enantioselective 1,2-dicarbofunctionalization (DCF) of alkenes is a powerful transformation of growing importance in organic synthesis for constructing chiral building blocks, bioactive molecules, and agrochemicals. Both in a two- and three-component context, this family of reactions generates densely functionalized, structurally complex products in a single step. Across several distinct mechanistic pathways at play in these transformations with nickel or palladium catalysts, stereocontrol can be through tailored chiral ligands. In this Review we discuss the various strategies, mechanisms, and catalysts that have been applied to achieve enantioinduction in alkene 1,2-DCF.

Key words alkenes, cross-coupling, dicarbofunctionalization, enantioselectivity, nickel, palladium

1. Introduction

Drug candidates in the pharmaceutical development pipeline have become increasingly structurally complex in recent years, bearing a higher number of stereocenters (among other features), which pose synthetic challenges. There is thus a pressing need for new methods in asymmetric synthesis that rapidly assemble complex substructures.[1] The apex goal of catalysis research is selectivity control, and obtaining both diastereo- and enantioselectivity enables precise sculpting of molecules with defined shapes and topologies to serve different functions.

Classical transition-metal catalyzed C–C cross-coupling reactions between organometallic nucleophiles and organohalide electrophiles are powerful tools in synthesis. Traditional C(sp^2)–C(sp^2) bond-forming methods offer limited opportunities for stereoselectivity control, with the notable exception of hindered couplings that generate atropisomers. With the rise of efficient C(sp^2)–C(sp^3) and C(sp^3)–C(sp^3) cross-couplings methods, there has been increase interest in enantioselective variants.[2]



Scheme 1. Background of Ni- and Pd-catalyzed 1,2-DCF of alkenes.

1,2-Dicarbofunctionalization (1,2-DCF) has recently emerged as a powerful family of transformation where a π-bond is integrated into a cross-coupling catalytic cycle as a third reaction component, furnishing two contiguous C(sp^3)–C centers in a single step.[3] Alkenes are the π-components most commonly used as conjunctive linkers in this transformation due to their widespread availability and distinct reactivity profile; thus, other conjunctive linkers such as alkynes, imines, and aldehydes will not be discussed herein. Both nickel and palladium catalysts have been used in this transformation with great success; comparing the two, nickel offers unique properties such as its ability to readily engage in single-electron transfer processes and its lower propensity towards β-hydride elimination relative to palladium.[4] Enantioselective 1,2-DCF offers a platform for forming multiple

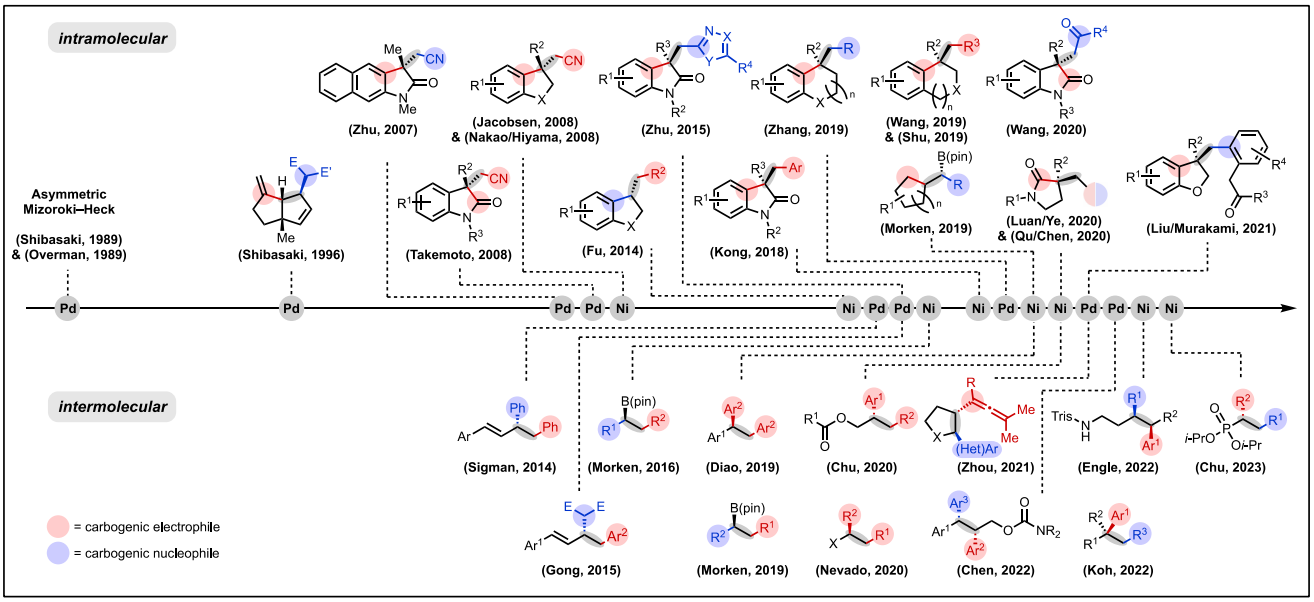
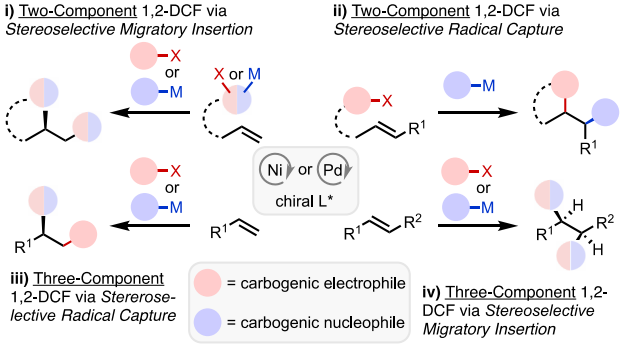


Figure 1. Timeline (1989–2023) of enantioselective Ni- and Pd-catalyzed 1,2-DCF of alkenes

C(sp^3)–C stereocenters in a single operation, but realizing the full preparative potential of this approach has proven challenging.

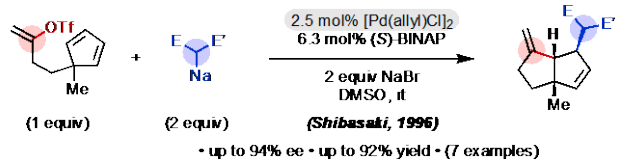
While a variety of metals and mechanisms have been pursued for 1,2-DCF,[5] most reports have concerned Cu, Ni, and Pd, with many cases leveraging shared mechanistic features. Because enantioselective Cu-catalyzed 1,2-DCF of alkenes via radical mechanisms has been recently comprehensively summarized,[5a] we have elected to focus this Review on progress in enantioselective Ni- and Pd-catalyzed 1,2-DCF of alkenes as these two metals constitute a significant fraction of the recently published literature and offer similarities and differences that are instructive to compare. For representative reports on closed-shell 1,2-DCF of alkenes with other metals, we direct the reader to seminal reports with Cu,[5b] Rh,[5c–e] and Co.[5f] The Review is organized by the number of reaction components, two-component (intramolecular) versus three-component (intermolecular) and by the mechanism of enantioinduction.

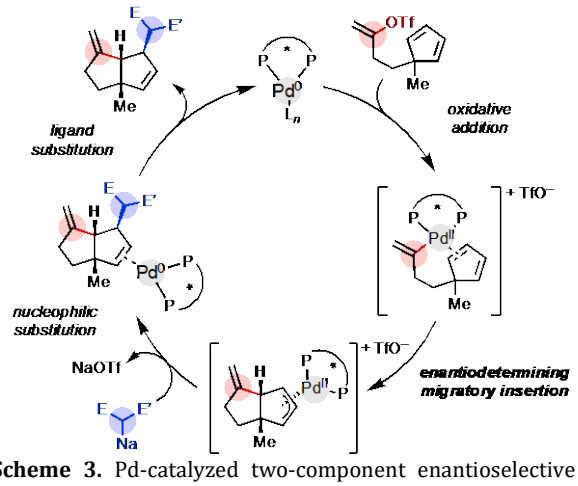
The origins of this field can be traced back to pioneering work by Catellani and colleagues.[6] A seminal report from her group reported the 1,2-dicarbofunctionalization of norbornene with aryl bromides and terminal alkynes under palladium catalysis (Scheme 1). Mechanistically the authors propose the reaction to proceed through sequential



Scheme 2. Mechanisms of enantioinduction in Ni- and Pd-catalyzed 1,2-DCF of alkenes.

carbopalladation steps across the alkene and then the alkyne, with β-hydride elimination as the last step. In this case, the initially generated alkylpalladium intermediate is recalcitrant towards β-hydride elimination due to the conformationally constrained nature of the substrate, illustrating an important principle of achieving high pathway selectivity in multicomponent 1,2-DCF systems. Most of the work in the following decades focused on expanding the scope of alkene substrates and coupling partners in 1,2-DCF, controlling regioselectivity, and devising strategies for pathway selectivity control (Figure 1).[3] In this context, advances during the past five years in nickel catalysis have opened new vistas in reactivity beyond what could historically be achieved with palladium.





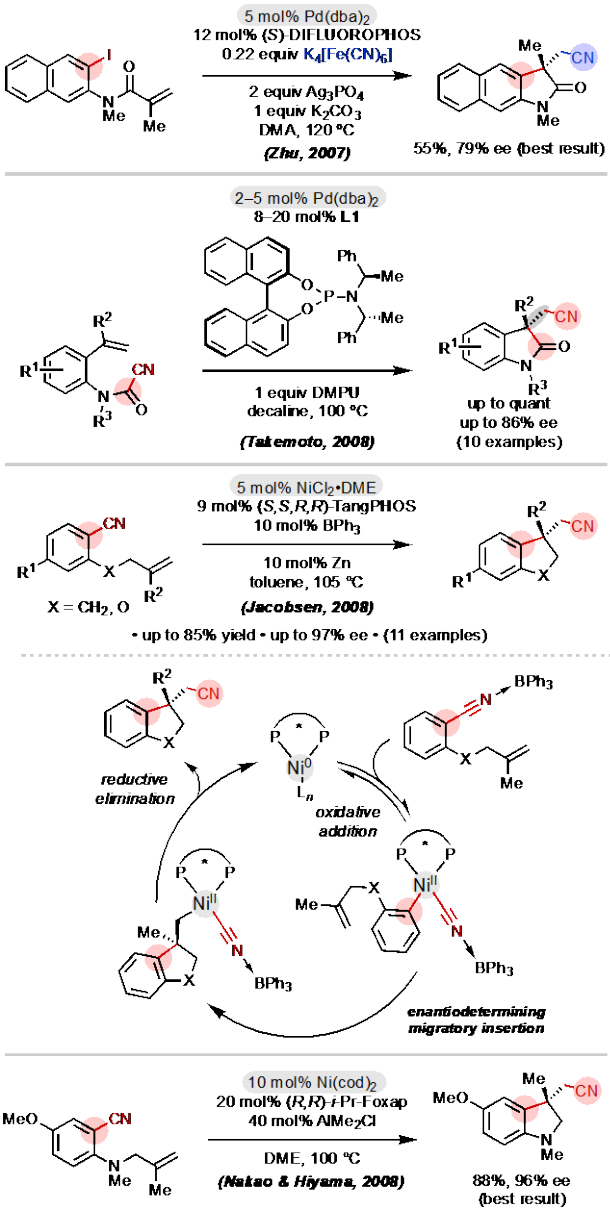
Scheme 3. Pd-catalyzed two-component enantioselective 1,2-DCF of cyclopentadiene-tethered alkenyl triflate with a carbanion nucleophile.

In the 2010s, enantioselective 1,2-DCF gained significant momentum. The majority of research focused on two-component approaches, mainly because enantioinduction in the C–C bond-forming migratory insertion step benefits from proceeding through a cyclic transition state (5- or 6-membered) that is conformationally constrained (Scheme 2). Development of complementary three-component couplings has proven elusive until recently. Since 2019, a handful of three-component methodologies based on radical mechanisms have been reported, whereby enantioinduction takes place via radical capture and subsequent reductive elimination. In 2022, asymmetric three-component 1,2-DCF of alkenes via arylnickel/palladium migratory insertion was demonstrated for the first time.

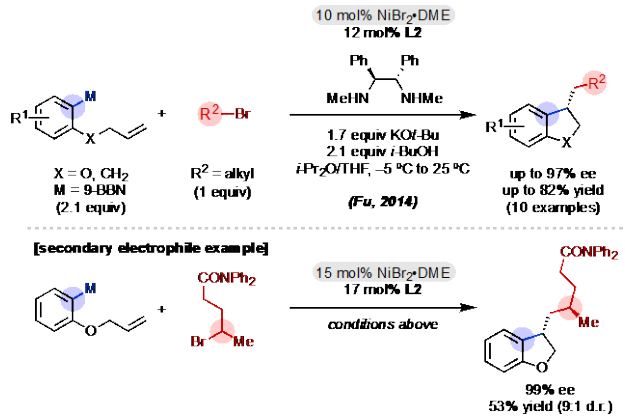
2. Two-Component Enantioselective 1,2-DCF via Migratory Insertion

The two-component enantioselective 1,2-DCF of alkenes originates from enantioselective Mizoroki–Heck arylation, which utilizes migratory insertion as a key step in enantioinduction.[7] The earliest example of enantioselective 1,2-DCF was demonstrated in 1996 by the Shibasaki group, who leveraged a cyclic diene substrate tethered to an alkenyl triflate to favor cyclative asymmetric migratory insertion and nucleophilic substitution (Scheme 3).[8] Under the action of Pd/(*S*)-BINAP catalysis, cyclopentadiene-tethered alkenyl triflate oxidatively adds into the Pd^0 catalyst, and the resulting alkenyl–Pd intermediate undergoes enantioselective migratory insertion into the cyclopentadiene motif, forming a π-allyl–Pd intermediate. This intermediate is then captured by an enolate nucleophile to give the desired 1,2-DCF product in a regio-, and stereoselective manner.

Since this initial precedent, several alkene functionalization reactions, including hydroarylations, have been developed that employ enantioselective intramolecular migratory insertion of arylmetal species into tethered alkenes.[9] In addition, four reports of intramolecular enantioselective 1,2-carbocyanation were disclosed. The first two were conducted under Pd catalysis, and the next two under Ni/Lewis acid cooperative catalysis (Scheme 4).[10] In 2007, the Zhu group reported the 1,2-carboarylation of acrylamides containing an aryl-iodide tethered to the nitrogen atom under Pd/(*S*)-DIFLUOROPHOS catalysis with $K_4[Fe(CN)_6]$ as cyanating reagent.[10a] Under the optimal reaction conditions, 3-substituted-3-cyanomethyl-2-oxindoles could be furnished in moderate yields and good enantioselectivity. The following year, the Takemoto group demonstrated enantioselective 1,2-cyanoamidation of styrenes tethered to cyanoformamide under Pd/chiral phosphoramidite ligand.[10b] Both the Jacobsen and Nakao/Hiyama groups reported 1,2-carbocyanation of alkenes tethered to benzonitriles with $NiCl_2$•DME/BPh_3/(*S*,*S*,*R*,*R*)-TangPHOS and $Ni(cod)_2$/$AlMe_2Cl$/(*R*,*R*)-*i*-Pr-Foxap or (*R*,*R*)-ChiralPhos catalytst, respectively.[10c, 10d] Though these examples are technical single-component couplings, they are discussed here together with related intramolecular examples for organizational purposes, high yields and enantioselectivities of the 1,2-carbocyanated products could be obtained through cooperativity of the Ni/chiral phosphine and Lewis acid catalysts in the enantiodetermining cyclative migratory insertion step.



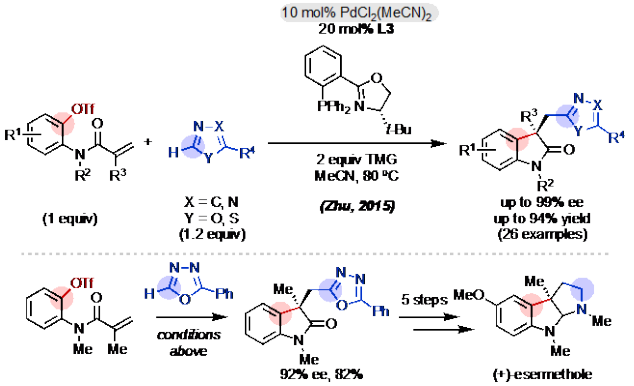
Scheme 4. Ni-catalyzed two-component enantioselective 1,2-carbocyanation of alkenes.



Scheme 5. Ni-catalyzed two-component enantioselective 1,2-DCF of alkene tethered arylborane and alkylbromide.

Major progress was then achieved by the Fu group in 2014 (Scheme 5),[11] who showed that alkene-tethered arylborane

nucleophiles undergo transmetalation and enantioselective intramolecular cyclization, followed by oxidative addition of alkyl bromide and reductive elimination under Ni/chiral diamine (**L2**) catalysis to provide the 1,2-dicarbofunctionalized products. The key to success of this reaction is that the relative rate of the intramolecular migratory insertion step is faster than that of the direct Suzuki–Miyaura coupling between the arylborane and alkyl bromide. It is also noteworthy that this single chiral catalyst system accomplishes both enantioselective migratory insertion

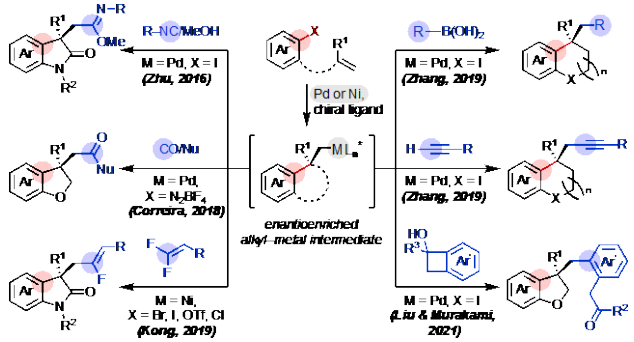


Scheme 6. Pd-catalyzed two-component enantioselective 1,2-DCF of acrylamides containing a tethered aryltriflate with heteroarenes.

and stereoconvergent cross-coupling to generate two distinct stereocenters when a racemic secondary alkyl bromide is used.

In 2015, the Zhu group reported enantioselective 1,2-DCF of an acrylamide containing an aryl triflate tethered through the nitrogen atom under Pd catalysis (Scheme 6).[12] High enantioselectivity in the intramolecular migratory insertion step was enabled by a Pd/phosphinooxazoline (PHOS, **L3**) catalyst. Following enantiodetermining migratory insertion, the resulting alkyl–Pd^{II} intermediate is captured by the heteroarene, (e.g., a oxadiazole or benzoxazole), via C–H functionalization with the aid of tetramethylguanidine (TMG) base. Through this transformation, various oxindoles bearing all-carbon quaternary stereocenters were prepared. The authors further highlighted the utility of this reaction by applying this method as the key step in the total synthesis of (+)-esermethole.

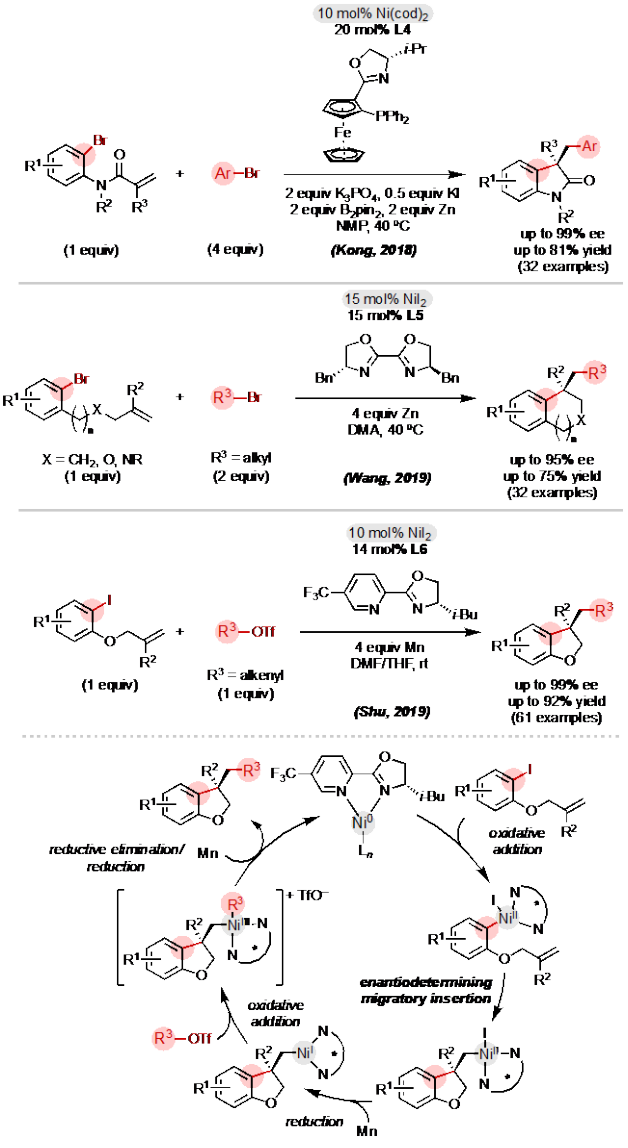
Based on the early examples mentioned above, various two-component 1,2-DCFs have been developed using different combinations of coupling partners and chiral ligands under Pd or Ni catalysis. These reactions generally involve a shared sequence of oxidative addition and enantiodetermining migratory



Scheme 7. Redox-neutral two-component enantioselective 1,2-DCFs of aryl-(pseudo)halide-tethered alkenes.

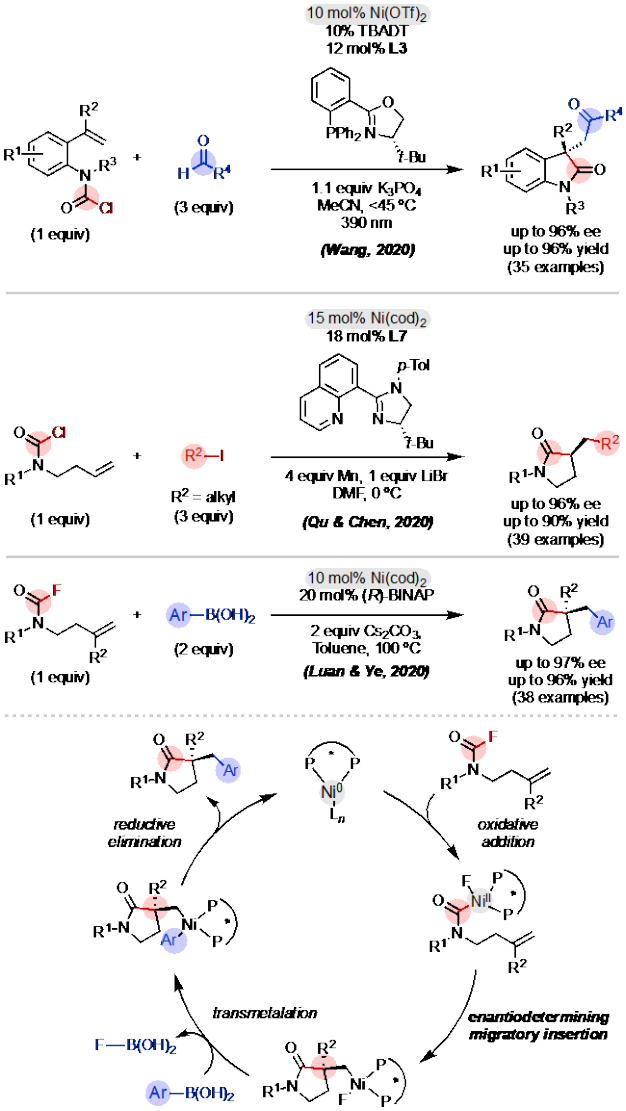
insertion of alkene-tethered aryl(pseudo)halide electrophiles. Diversification of the resultant alkylmetal species is then achieved by employing different nucleophilic trapping reagents (Scheme 7). For example, isocyanates,[13] carbon monoxide,[14] alkenes,[15] aryl/alkylboronic acids,[16] and alkynes[17] have been reported as coupling partners for these 1,2-DCF reactions, each involving different mechanisms. Flexibility in this alkylmetal trapping step arises from the versatility of the alkyl–Pd/Ni intermediate. In addition, several enantioselective 1,2-DCF reactions using unusual carbon nucleophiles, such as cyclobutenols (via β-carbon elimination)[18] or internal arenes (via C–H activation), have been described.[19]

Reductive 1,2-DCF reactions using a nickel catalyst and a terminal reductant are another important class of enantioselective 1,2-DCFs. In contrast to the classical redox-neutral reactions that require one electrophile and one nucleophile to complete the catalytic cycle, these reactions allow two different electrophilic reactants to be coupled. Compared to Pd, Ni is more easily able to maneuver among various oxidation states, such as Ni(I) and Ni(III), via single-electron transfer



Scheme 8. Reductive Ni-catalyzed two-component enantioselective 1,2-DCFs.

events in the catalytic cycle.[20] As such, single-electron reductants, such as Zn and Mn metals are commonly used in reductive 1,2-DCF catalyzed by nickel.



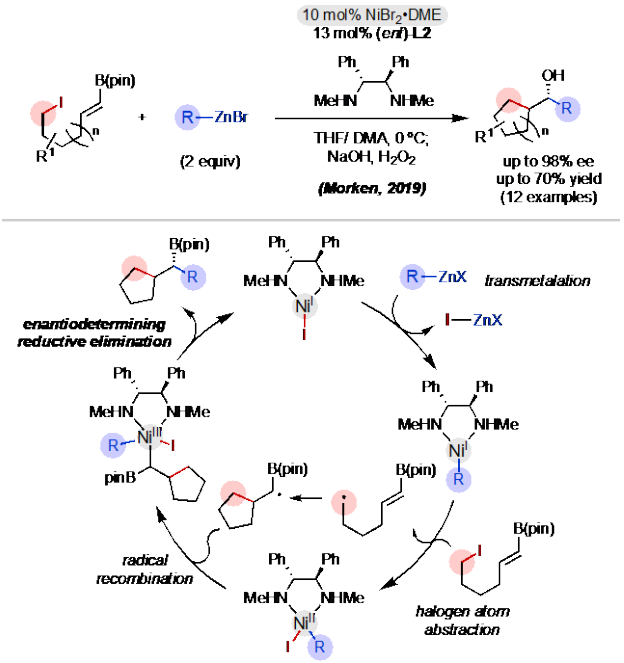
Scheme 9. Ni-catalyzed two-component enantioselective 1,2-DCFs using carbamoyl halide tethered alkenes.

Indeed, various Ni-catalyzed enantioselective reductive 1,2-DCFs of aryl-halide-tethered alkenes using aryl bromides,[21] alkyl bromides,[22] alkenyl triflates,[23] alkenyl bromides,[24] or benzyl chlorides[25] as the corresponding electrophilic coupling partner have been demonstrated by different research groups (Scheme 8). In 2023, a ball milling approach for this enantioselective reductive platform was reported by Morrill and Browne but with modest enantioselectivity.[26] Although detailed mechanistic studies have not been conducted in most cases, a mechanism involving sequential single-electron reduction by Mn or Zn as reductants is generally proposed for these reductive 1,2-DCFs.

Although most enantioselective two-component 1,2-DCF reactions utilize alkene-tethered aryl (pseudo)halides as substrates that undergo oxidative addition and subsequent enantioselective migratory insertion, recent developments in the field have employed alkene-tethered carbamoyl halides as starting materials under Ni catalysis (Scheme 9). For instance, the Wang group demonstrated that carbamoyl chlorides containing a pendant styrene undergo oxidative addition and enantioselective migratory insertion to generate analogous alkyl–Ni intermediates that can be captured by photogenerated acyl radicals.[27] Furthermore, both reductive 1,2-DCF and redox-neutral 1,2-DCF of carbamoyl-halide-tethered alkenes were demonstrated, providing chiral γ-lactam products, by the Qu and Chen groups,[28] and the Ye groups,[29] respectively.[30]

3. Two-Component Enantioselective 1,2-DCF via Radical Capture/Reductive Elimination

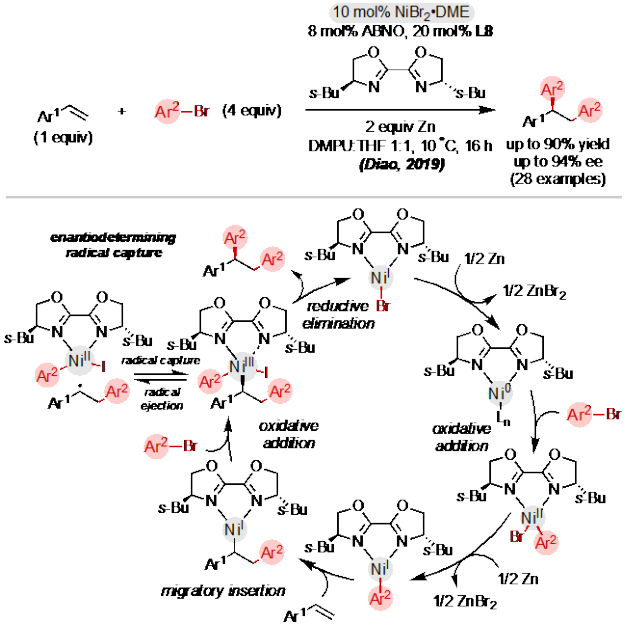
Radical-based two-component enantioselective 1,2-DCF is rare, and only one example has been reported by the Morken group in 2019, employing substrates containing both



Scheme 10. Ni-catalyzed two-component enantioselective 1,2-DCFs via radical capture/reductive elimination.

alkenylboronic ester and alkyl iodide motifs (Scheme 10).[31] Under nickel catalysis with a chiral 1,2-diamine ligand, the alkyl iodide generates an alkyl radical via halide abstraction. This alkyl radical undergoes exo-selective intramolecular cyclization onto the alkene and forms a five or six-membered ring bearing a stable α-boryl radical. Recombination with the aryl/alkyl–Ni species, generated via transmetallation from the corresponding organozinc reagent, followed by reductive elimination, provides the product in this stereoselective cross-coupling. The authors showed that the chiral ligand is not involved in the radical cyclization step and does not affect its diastereoselectivity but nevertheless controls enantioselectivity during the radical recombination step between the α-boryl radical and the chiral Ni/ligand catalyst.

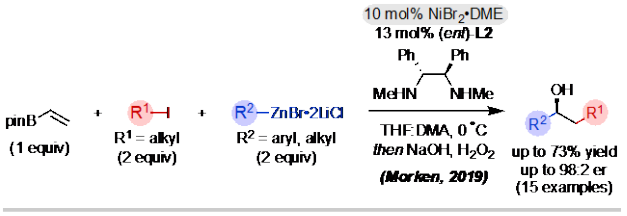
4. Three-Component Enantioselective 1,2-DCF via Radical Capture/Reductive Elimination

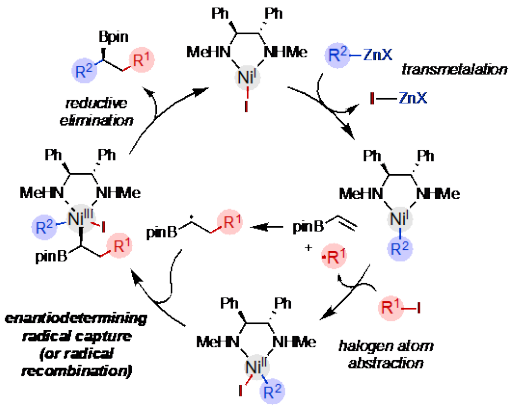


Scheme 11. Enantioselective homodiarylation of styrenes via enantiodetermining radical capture.

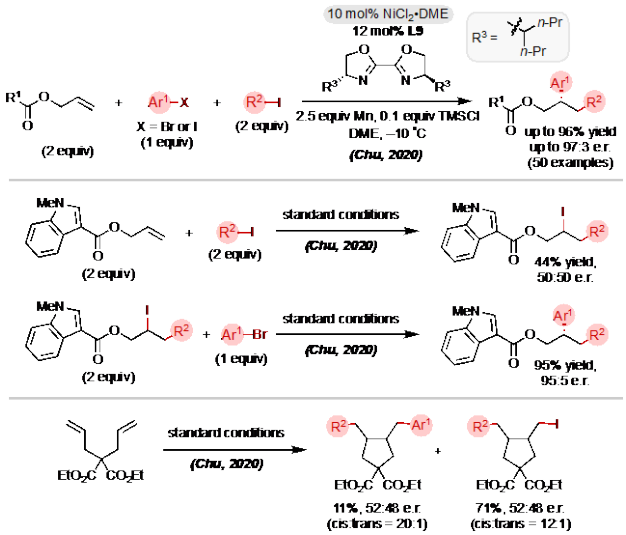
While impressive strides have been made in intramolecular 1,2-DCF with Pd and Ni catalysts, progress on analogous fully intermolecular (i.e., three-component) couplings has been stymied by poor stereocontrol, generation of many side products, and lack of reactivity of certain alkene classes, such as internal alkenes. Without the benefits of having one the Ni/Pd–alkyl or carbogenic radical species tethered intramolecularly, bringing about an enantioselective migratory insertion step or an enantioselective radical capture step is more challenging.

The early reports in Ni-catalyzed three-component enantioselective 1,2-DCF of alkenes in the late 2010s mainly

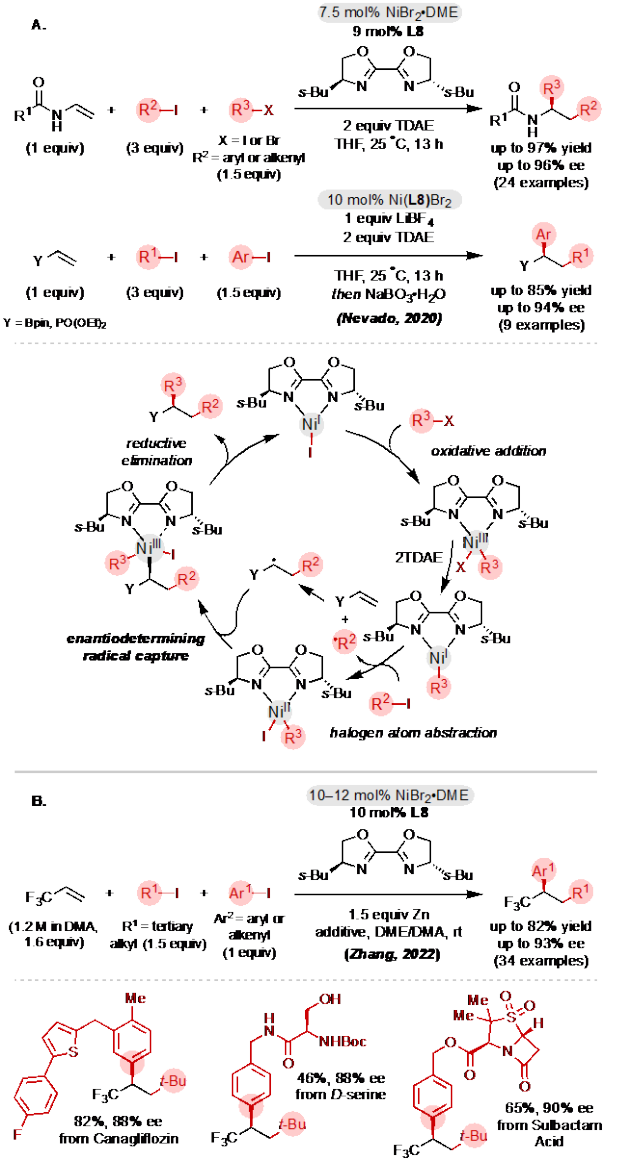




Scheme 12. Enantioselective 1,2-DCF of vinylboronic esters via enantiodetermining radical capture.

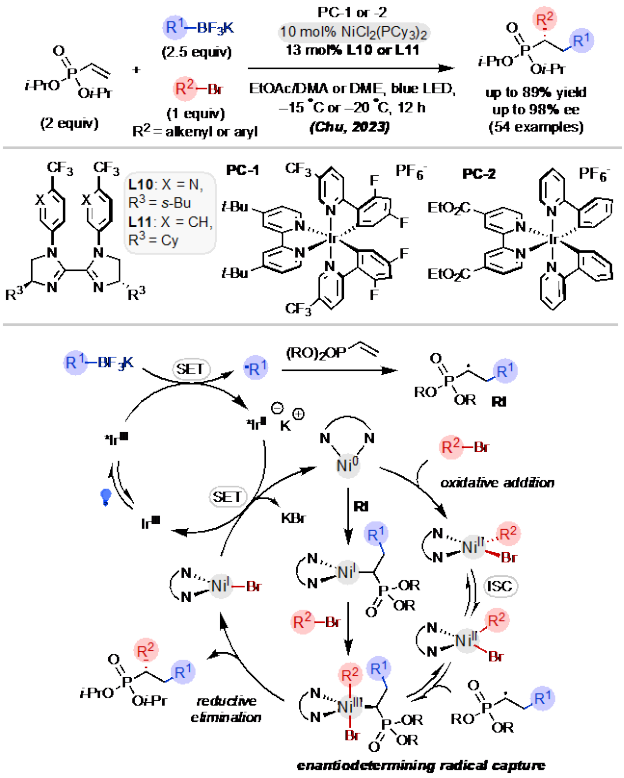


Scheme 13. Enantioselective 1,2-DCF of allylic esters via enantiodetermining radical capture.



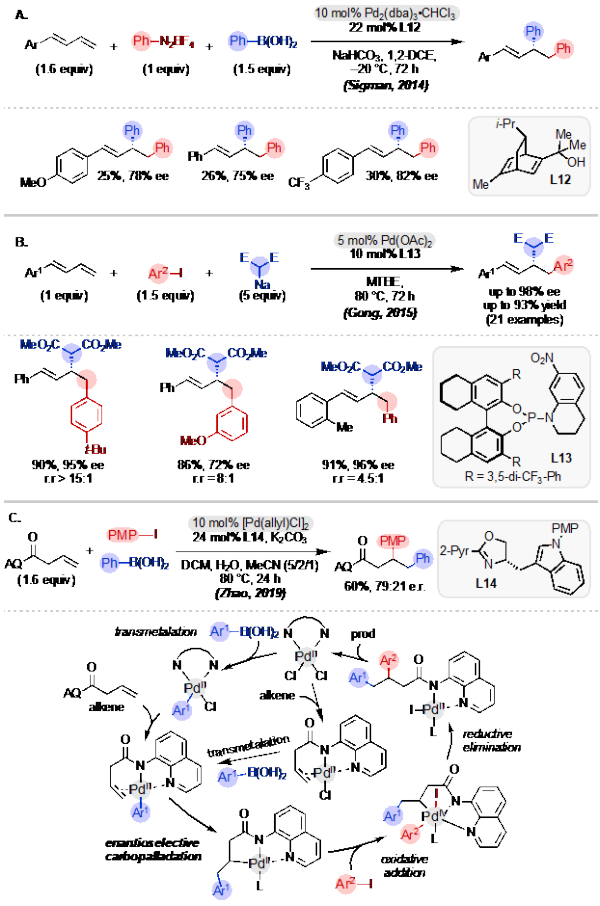
Scheme 14. A) Enantioselective reductive 1,2-DCF of vinyl amide, boranes, and phosphonates. B) Enantioselective reductive 1,2-DCF of 3,3,3-trifluoropropene.

focused on methods involving an enantioselective radical capture strategy. This strategy arises from research on nonstereoselective radical 1,2-DCF reactions, involving carbon radical addition into the alkene followed by radical capture with Ni catalyst. By adding a chiral ligand under similar reaction conditions, the key radical capture process can occur in an enantioselective manner, resulting in a single stereocenter. In an initial proof-of-concept study in 2016, the Zhang group demonstrated a single example of enantioselective 1,2-DCF via enantiodetermining radical capture, observing 18% ee when chiral diamine ligand was used in the 1,2-difluoroalkylation-arylation reaction that had been optimized to prepare racemic products.[32] It is also important to note that methods involving enantioselective radical capture have thus far been most successful with nickel owing to nickel's unique accessibility of various oxidation states compared to palladium.

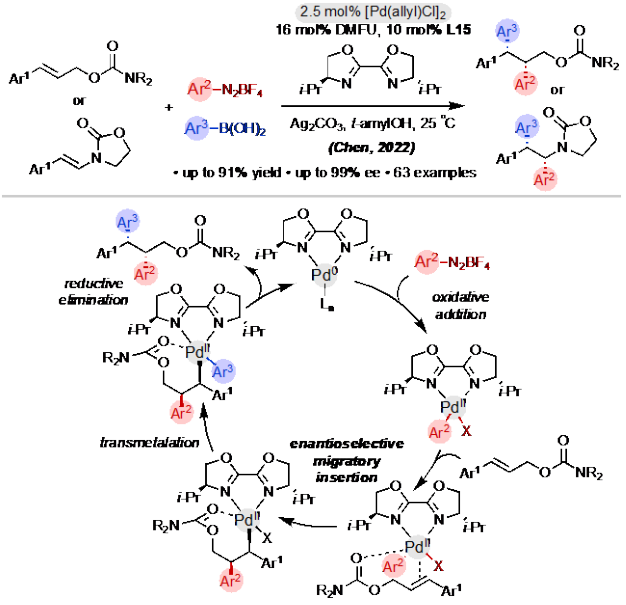


Scheme 15. Enantioselective, metallaphotoredox catalyzed 1,2-DCF of vinyl phosphonates via enantiodetermining radical capture.

The first report of fully intermolecular and highly enantioselective 1,2-DCF without intramolecular tethering was disclosed by Diao and coworkers in 2019. The authors demonstrated an enantioselective 1,2-homodiarylation of styrenes with aryl bromides with $NiBr_2$•DME/(*S*)-*sec*-butyl-biOx (*s*-Bu-biOx) as the catalyst (Scheme 11).[33a] Yields up to 78% and enantioselectivity up to 94% ee were obtained. The authors proposed that the mechanism likely starts with a low-valent (*s*-Bu-biOx)Ni^{I}–Br active catalyst that is reduced by zinc to a (*s*-Bu-biOx)Ni^{0}–L_n species. Then oxidative addition into the aryl bromide occurs to generate a (*s*-Bu-biOx)(aryl)Ni^{II}–Br organometallic species. Another single-electron reduction by Zn, followed by a non-stereoselective migratory insertion step, furnishes the putative (*s*-Bu-biOx)(alkyl)Ni^{I} species. A second oxidative addition step then yields the key (*s*-Bu-biOx)(aryl)(alkyl)Ni^{III}–Br species, which undergoes radical ejection, with subsequent radical capture preferentially taking



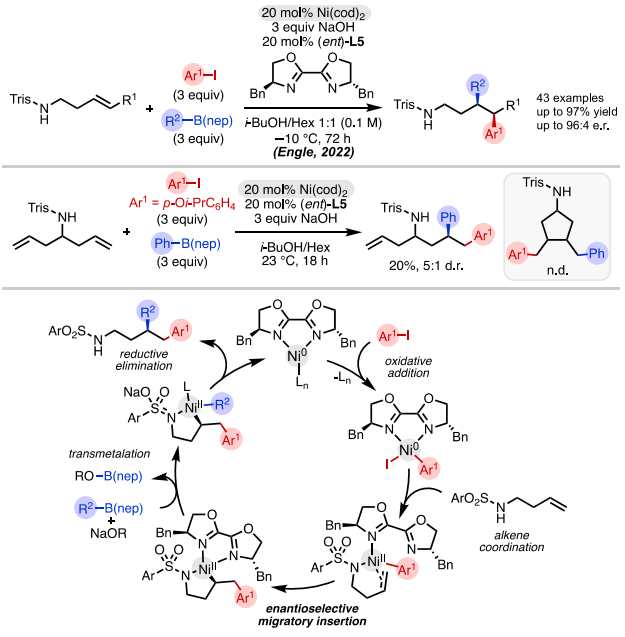
Scheme 16. A) Enantioselective Pd-catalyzed 1,2-diarylation of 1,3-dienes by the Sigman group. B) Enantioselective Pd-catalyzed 1,2-diarylation of 1,3-dienes by the Gong group. C) Enantioselective Pd-catalyzed 1,2-diarylation of unactivated alkenes with AQ directing group.



Scheme 17. Enantioselective Pd-catalyzed 1,2-DCF of activated alkenes via enantiodetermining migratory insertion.

place at the less hindered face. Finally, reductive elimination forges the enantioenriched 1,2-homodiarylated product and turns over the catalytic cycle. The authors did not propose which step is enantiodetermining, but recent mechanistic studies point towards the radical capture step being enantiodetermining.[33b] The presence of a benzylic radical was inferred based on several pieces of empirical data: (i) inhibition of the reaction with excess 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO) ligand, (ii) observation of benzyl radical dimerization products, and (iii) the *anti*-selectivity of addition to indene.

The same year, the Morken group reported a 1,2-DCF of vinylboronic acid pinacol ester with alkyl iodides and alkyl/aryl zinc reagents using a $NiBr_2$ chiral diamine (**L2**) catalytic system (Scheme 12).[31] Enantioenriched secondary alcohols could be obtained in yields up to 73% yield and enantioselectivity up to 98:2 e.r. following oxidative workup. The catalytic cycle was proposed to begin with (diamine)Ni^{I}–I complex undergoing transmetalation with the alkyl/arylzinc reagent to produce the (diamine)(alkyl/aryl)Ni^{I} complex. Halogen atom abstraction of the alkyl iodide by the Ni^{I} catalyst gives rise to an alkyl radical species. Addition of the alkyl radical into the vinylboronic ester substrate furnishes an α-boryl radical intermediate. Capture of this radical intermediate with the Ni^{II} catalyst forms the key (diamine)(alkyl/aryl)(alkyl)Ni^{III}–I species, which undergoes facile reductive elimination to forge the enantioenriched 1,2-dicarbofunctionalized alcohol products after oxidative workup. The authors did not comment on the enantiodetermining step, but it may be radical capture. When the reaction was treated with TEMPO, complete inhibition of the reaction was observed indicating the possible presence of radical species. This was further probed by using a substrate that tethers the vinylboronic ester to a pendant alkyl iodide. Subjection of this substrate to the reaction conditions formed the desired cyclic product as a 1:1 diastereomeric mixture; thus, indicating a radical addition process instead of a stereoselective migratory insertion step.



Scheme 18. Enantioselective Ni-catalyzed 1,2-DCF of unactivated alkenes via enantiodetermining migratory insertion.

The first three-component 1,2-DCF of unactivated alkenes was described by Chu and coworkers in 2020. The method couples allylic esters, aryl halides, and alkyl iodides using $NiCl_2$•DME/(*R*)-4-heptyl-biOx catalyst (Scheme 13).[34] Yields up to 96% and enantioselectivity up to 97:3 e.r. were obtained. In the mechanistic discussion, the authors propose that under the reductive conditions employed, an alkyl radical intermediate is generated that is then captured by a (4-heptyl-biOx)nickel complex forming the key (4-heptyl-biOx)(aryl)(alkyl)Ni^{III}–X species. Then, reductive elimination occurs to form the enantioenriched 1,2-dicarbofunctionalized product. The Chu lab performed several experiments to provide evidence of a radical intermediate. An allylic ester substrate was subjected to the reaction conditions without the aryl halide present, and in this experiment a racemic 1,2-iodoalkylated compound was formed in moderate yield. Subjection of the 1,2-iodoalkylated adduct to the standard reaction conditions without the alkyl iodide afforded the desired 1,2-arylalkylated product in high yield with excellent enantioselectivity. In addition, cyclic 1,2-iodoalkylated and 1,2-arylalkylated products were observed in a radical clock experiment, indicating the presence of a radical intermediate. Both mechanistic experiments indicate that the radical capture is the enantiodetermining step. The Nevado group reported a similar reductive approach for the enantioselective 1,2-DCF of alkenes under $NiBr_2$•DME/*s*-Bu-biOx catalysis but using tetrakis(dimethylamino)ethylene (TDAE) organic reductant (Scheme 14).[35a] Excellent yields up to 97% and excellent enantioselectivity up to 96% ee could be obtained with the optimized method. DFT calculations at the UB3LYP/6-31G(d) level supported radical capture as the enantiodetermining step. Although the authors do not propose a detailed mechanism in this study, by analogy to their previous work, it[35b] could be envisioned that the catalytic cycle starts with (*s*-Bu-biOx)Ni^{I}–I undergoing oxidative addition of the aryl halide followed by reduction by TDAE to the corresponding Ni^{I} complex. A halogen atom abstraction of the alkyl iodide occurs forming alkyl radical and the (*s*-Bu-biOx)(aryl)Ni^{II}–I species. This sets up the stage for an enantioselective radical capture step providing the key (*s*-Bu-biOx)(aryl)(alkyl)Ni^{III}–I intermediate. Finally, reductive elimination forms the enantioenriched 1,2-arylalkylated product and turns over the catalytic cycle. In addition to these reports, Zhang group also demonstrated reductive enantioselective 1,2-DCF of 3,3,3-trifluoropropene with a similar catalyst system.[36]

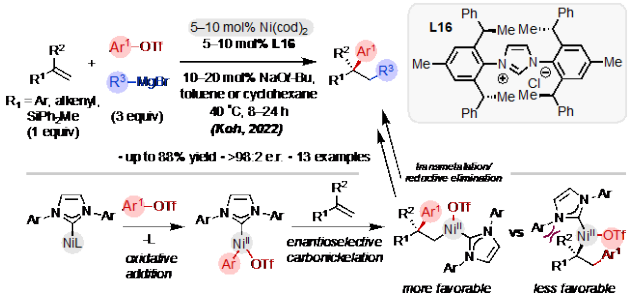
Recently, the Chu and Gutierrez groups reported an enantioselective 1,2-DCF of vinyl phosphonates with alkyl trifluoroborates and aryl/alkenyl bromides under metallaphotoredox catalysis (Scheme 15).[37] The combination of iridium photocatalyst and biimidazoline (biIm)-ligated nickel catalyst (**PC-1** with **L10** or **PC-2** with **L11**) produce 1,2-alkenylalkylated products. Either *cis*- or *trans*-products can be attained in high yields and enantioselectivity. Radical inhibition and radical clock studies both indicate radical intermediates. In-depth DFT studies shed light on the operative mechanism of the reaction and suggest the enantiodetermining step to be radical capture. The authors propose that the photocatalytic cycle begins with generation of an alkyl radical the alkyl trifluoroborate via single-electron transfer (SET) to the $*Ir^{III}$ photocatalyst. The alkyl radical then adds into the vinyl phosphonate forming an α-phosphonate radical intermediate (**RI**). The catalytic cycle for nickel begins with (biIm)Ni^{0} undergoing oxidative addition into

the C–Br bond of the alkenyl/aryl bromide to afford a square-planar (biIm)(alkenyl/aryl)Ni^{II}–Br complex. This then isomerizes to the tetrahedral triplet spin-state (biIm)(alkenyl/aryl)Ni^{II}–Br species via intersystem crossing (ISC). Subsequently, enantiodetermining radical capture of **RI** with (biIm)(alkenyl/aryl)(alkyl)Ni^{III}–Br followed by reductive elimination yields the product. An alternative route would be radical addition of **RI** to (biIm)Ni^{0} forming (biIm)(alkyl)Ni^{I} followed by oxidative addition to furnish the key (biIm)(alkenyl/aryl)(alkyl)Ni^{III}–Br, which may undergo a radical ejection and enantioselective radical capture sequence prior to reductive elimination. The newly formed (biIm)Ni^{I}–Br complex undergoes an SET event with the anionic Ir^{II} photocatalyst, thereby turning over the nickel catalytic cycle and regenerating Ir^{III}, which is then photoexcited to initiate a new cycle.

5. Three-Component Enantioselective 1,2-DCF via Migratory Insertion

As discussed in the previous section, three-component Ni- and Pd-catalyzed 1,2-DCF of alkenes involving enantioselective migratory insertion is challenging. In this mechanistic regime, both the absolute and relative stereochemistry of the arylmetal addition must be controlled. While closed shell migratory insertion is *syn*-stereospecific, the diastereoselectivity can nevertheless be eroded due to secondary processes.[38] One advantage of migratory-insertion-based methods is the ability to form two contiguous carbon centers in one step. Most of the early work has been dominated by Pd catalysis; only recently, in late 2022 and early 2023, did the first Ni-catalyzed protocols emerge.

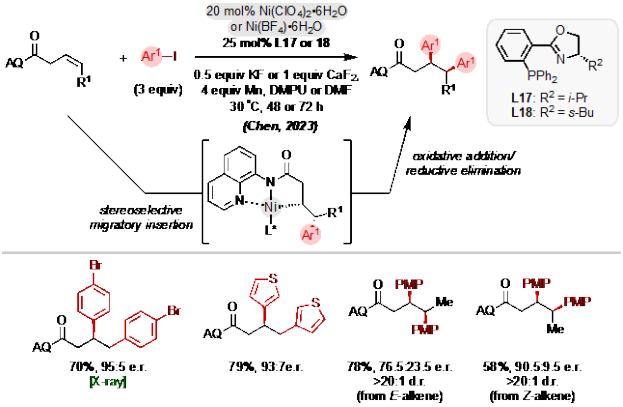
In 2014, the Sigman lab reported a Pd-catalyzed 1,2-diarylation of 1,3-dienes with aryldiazonium tetrafluoroborates and aryl boronic acids (Scheme 16a).[39] In this work, the authors employed a (*R*)-(−)-α-phellandrene-derived chiral ligand to afford 1,2-diarylated products with moderate enantioselectivity and low yields. The following year, the Gong group reported on



Scheme 19. Enantioselective Ni-catalyzed 1,2-diarylation of activated alkenes via enantiodetermining migratory insertion.

an enantioselective 1,2-DCF of the same 1,3-diene substrates using Pd/chiral phosphoramidite ligand with aryl iodides and enolates (Scheme 16b).[40] In both reactions, oxidative addition of electrophiles and migratory insertion of Pd(II)–aryl species into the 1,3-diene substrates are followed by nucleophilic trapping. A mechanism for enantioinduction step is still unclear, but one reasonable explanation would be that migratory insertion step is enantiodetermining, although enantioselective trapping of (chiral ligand)–Pd–π-allyl species cannot be ruled out. It is also notable that both reactions exhibit excellent 1,2-products selectivity over 1,4-products, and the Gong group further showed that the regioselectivity is affected by the substitution patterns of 1,3-diene substrates and electrophiles.

Several years later the Zhao group developed a Pd-catalyzed 1,2-diarylation of aryl iodides and aryl boronic acids with unactivated alkenes bearing an 8-aminoquinoline (AQ) directing auxiliary (Scheme 16c).[41] The authors reported a single enantioselective example with the use of a chiral PyrOx ligand (**L13**), where 1,2-diarylated product was obtained in moderate yield and enantiomeric excess. The authors proposed that the mechanism starts with (PyrOx)Pd^{II}Cl$_2$ undergoing transmetalation with the aryl boronic acid. Enantiodetermining carbopalladation step then affords the putative (AQ)(alkyl)Pd^{II}L intermediate. Subsequent oxidative addition of the aryl iodide forms a (AQ)(aryl)(alkyl)(L)Pd^{IV}–I species that undergoes reductive elimination and finally dissociation of the enantioenriched 1,2-diarylated product.



Scheme 20. Enantioselective Ni-catalyzed reductive 1,2-diarylation of unactivated alkenes.

Seminal work by Chen and coworkers in 2022 showcased an enantioselective 1,2-diarylation of internal styrenyl substrates with aryldiazonium trifluoroborates and aryl boronic acids with a [Pd(allyl)Cl]$_2$/isopropyl-biOx (*i*-Pr-biOx) catalyst system (Scheme 17).[42] Excellent yields of the 1,2-diarylated product (up to 91%) and excellent enantioselectivity (up to 99% ee) could be obtained under the optimized reaction conditions. The authors proposed the catalytic cycle to begin with (*i*-Pr-biOx)Pd^{0}L$_n$ undergoing oxidative addition into the aryldiazonium trifluoroborates forming a (*i*-Pr-biOx)(aryl)Pd^{II}–X complex. This then coordinates to the alkene starting material allowing for an enantioselective migratory insertion to occur affording a (*i*-Pr-biOx)(alkyl)Pd^{II}–X species. A subsequent transmetalation and reductive elimination sequence furnishes the desired enantioenriched 1,2-diarylated product. The authors observe excellent *syn*-diastereoselectivity, which indicates that the mechanism consists of enantioselective *syn*-carbopalladation followed by stereoretentive transmetallation and reductive elimination steps.

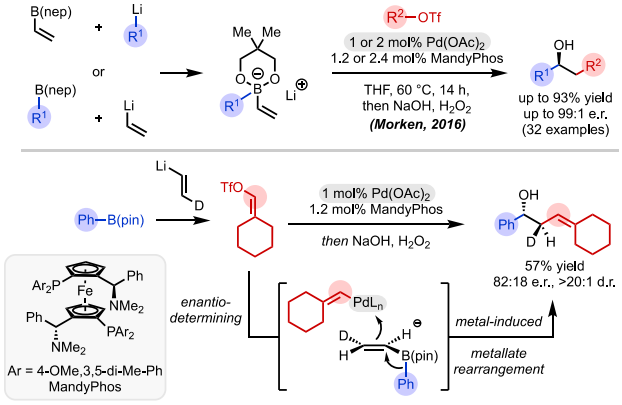
After this report, the first three-component Ni-catalyzed 1,2-DCF of unactivated alkenes via enantioselective arylnickel migratory insertion was reported by the Engle and Liu groups (Scheme 18).[43] In this report, aryl iodides and aryl/alkenylboronic esters were successfully coupled to alkenyl sulfonamides under Ni(cod)$_2$/Bn-biOx catalysis. The

combination of a bulky sulfonamide directing group and Bn-biOx ligand furnished 1,2-diarylated products in high yields and enantioselectivity. The authors performed a radical clock experiment where a *N*-trisyl dienamine was subjected to the optimized reaction conditions resulting in the formation of 1,2-diarylated product in low yield; meanwhile, the potential radical cyclization byproduct was not observed. Based on these experiments and DFT studies, the authors proposed that the mechanistic pathway starts with the (Bn-biOx)$Ni^{0}L_{n}$ undergoing oxidative addition into the aryl iodide forming a (Bn-biOx)(aryl)Ni^{II}–I complex. The alkene substrate then coordinates to the nickel center to afford the key (Bn-biOx)(aryl)(alkenylsulfonamido)Ni^{II} species which upon enantiodetermining migratory insertion furnishes the putative (Bn-biOx)(alkyl)(sulfonamido)Ni^{II} organometallic complex. Subsequent transmetalation and reductive elimination afford the enantioenriched 1,2-dicarbofunctionalized product. Hammett studies and DFT calculations both support the notion that migratory insertion is the enantiodetermining step. Moreover, computational data indicates that favorable C–H/π interactions between the benzyl group of Bn-biOx and the alkene as well as diminished steric repulsion between the other benzyl group and the trisyl group allow for high enantioselectivity to be achieved.

The Shi and Koh group published a three-component Ni-catalyzed 1,2-DCF of activated alkenes via enantioselective arylnickel migratory insertion without a directing group (Scheme 19).[44] In this work, aryl triflates and carbogenic Grignard reagents were successfully installed across various activated alkenes under $Ni(cod)_2$/chiral NHC catalysis. Excellent enantioselectivity and products yield were obtained using the optimized methodology. The authors postulated that high enantioselectivity arises by having favorable insertion of the (NHC)(aryl)Ni^{II} species into the alkene where there is attenuated steric clashing between the NHC ligand and the substituents on the alkene starting material.

Recently, a reductive 1,2-homodiarylation of unactivated alkenes facilitated by an AQ directing group was reported by Chen and coworkers (Scheme 20).[45] This was achieved by using aryl iodides and alkenyl amides under $Ni(ClO_4)_2$•$6H_2O$/ *i*-Pr-PHOX or $Ni(BF_4)_2$•$6H_2O$/*s*-Bu-PHOX catalysis. The authors did not propose a catalytic cycle, however, high *syn*-diastereoselectivity and enantioselectivity are observed with internal alkene substrates, indicating that the migratory insertion is the enantioselective step. The exquisite *syn*-diastereoselectivity of this reaction is noteworthy—especially considering the potential for generation of an alkyl–Ni^{III} intermediate that could undergo C–Ni homolysis and erode the diastereoselectivity—and is likely aided by the strongly coordinating bidentate AQ auxiliary and the structural rigidity that it imposes withing the resulting nickelacycle.[38]

6. Miscellaneous Mechanisms

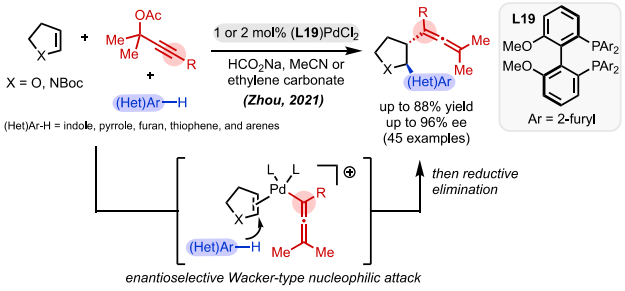


Scheme 21. Enantioselective Pd-catalyzed 1,2-DCF of vinylboronic esters via enantiodetermining metallate rearrangement.

Although this review mainly highlights mechanisms for enantioinduction such as radical capture and migratory insertion, other less common mechanisms, such as enantioselective metallate rearrangement and Wacker-type 1,2-DCF have been demonstrated.

In 2016, Morken and coworkers reported an enantioselective 1,2-DCF of lithium vinylboronate esters with aryl/alkenyl triflates under $Pd(OAc)_2$/MandyPhos catalysis (Scheme 21).[46] The organoboronates was made *in situ* either by using vinylboronic esters with alkenyl/aryl lithiums or alkenyl/arylboronic esters with vinyl lithium. Enantioenriched dicarbofunctionalized secondary alcohols could then be obtained in excellent yields and enantioselectivity upon treatment with NaOH and H_2O_2. The authors conducted a mechanistic experiment where a deuterated vinyl lithium species was used in the optimized reaction conditions resulting in the formation of desired 1,2-dicarbofunctionalized product in moderate yield and enantioselectivity but with excellent diastereoselectivity. The product had the two carbogenic components exclusively *trans* to each other likely due to the proposed anti-addition of the nucleophile from the ate complex upon enantiodetermining metal-induced metallate rearrangement.

In 2021, the Zhou group demonstrated an enantioselective Wacker-type 1,2-DCF of cyclic alkenes with heteroaryl nucleophiles and propargylic electrophiles under (**L19**)$PdCl_2$ catalysis (Scheme 22).[47] The enantioenriched



Scheme 22. Enantioselective Pd-catalyzed 1,2-DCF of cyclic alkenes via enantiodetermining Wacker-type nucleophilic attack.

products contain contiguous C(sp^3)–heteroaryl and C(sp^3)–allenyl bonds that are solely *trans* to each other as confirmed by single-crystal X-ray diffraction which indicates that enantiodetermining Wacker-type *anti*-carbopalladation is likely to be operative.

7. Conclusion

In summary, this review discusses the current state of the art of enantioselective 1,2-DCF of alkenes under nickel and palladium catalysis. The majority of the published work has focused on the two-component 1,2-DCF approach since enantiocontrol is more feasible in a cyclative migratory insertion step. The key alkyl–Pd/Ni intermediate in this approach has been leveraged to couple a wide array of carbogenic nuclophiles and electrophiles. The generated (hetero)cyclic 1,2-dicarbofunctionalized enantioenriched products structurally pose an attractive value to the synthetic community at large. The more challenging three-component 1,2-DCF of alkenes is the current focus of the field since stereocontrol in intermolecular organo-Ni/Pd migratory insertion has been historically difficult to achieve. While early efforts of Pd catalyzed three-component 1,2-DCF of alkenes has given products with moderate enantioselectivity, Ni-catalyzed approaches have dominated the chemical literature. In this context, a radical capture step was invoked to achieve high enantioselectivity, however, this approach restricts the methodology to the formation of enantioenriched products containing only one stereocenter. Fortunately, a series of recent Pd- and Ni-catalyzed three-component 1,2-DCF of various alkene classes including internal alkenes via non-cyclative enantioselective migratory insertion has come to fruition. The exciting advances that have appeared in the literature during the past two years illustrating the promising trajectory of this field.

We foresee further research focusing on three-component enantioselective couplings that employ commonly encountered, native directing groups. Mechanistic analysis of the reaction kinetics or isolation of organometallic intermediates would complement recent computational studies and may inform future ligand design. Furthermore, advances in chiral ligand design may lead to the development of non-directed methods with unactivated alkenes. Taken together these advances would establish a toolkit for universal Pd/Ni-catalyzed 1,2-DCF of diverse alkenes, giving rise to diverse product structures required for different synthetic applications. Finally, expanding the repertoire of enantioselective Ni-catalyzed 1,2-difunctionaliztion from DCF to a broad range of analogous two- and three-component enantioselective Ni-catalyzed 1,2-heterocarbofunctionalization (HCF) would be an impactful development for the field as well.

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Conflict of Interest

The authors declare no conflict of interest.

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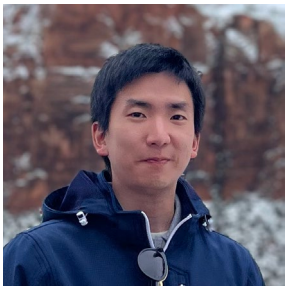
Biosketches



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