ACS Catalysis

pubs.acs.org/acscatalysis

Perspective

Nickel-Catalyzed Dicarbofunctionalization of Alkenes

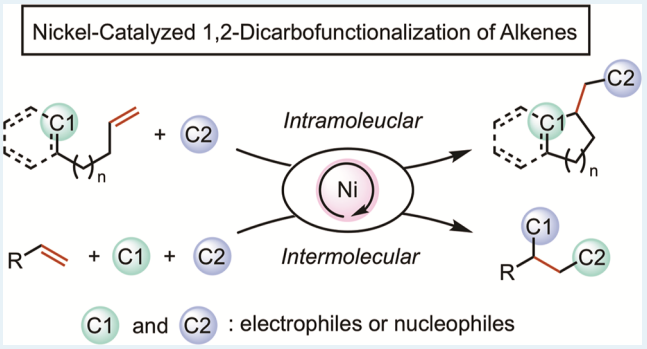
Xiaoxu Qi and Tianning Diao*

Cite This: *ACS Catal.* 2020, 10, 8542−8556

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: 1,2-Dicarbofunctionalization of alkenes has emerged as an efficient synthetic strategy for preparing substituted molecules by coupling readily available alkenes with electrophiles and/or nucleophiles. Nickel complexes serve as effective catalysts owing to their tendency to undergo facile oxidative addition and slow β-hydride elimination, and their capability to access both two-electron and radical pathways. Two-component alkene functionalization reactions have achieved high chemo-, regio-, and stereoselectivities by tethering one of the coupling partners to the alkene substrate. Three-component reactions, however, often incorporate directing groups to control the selectivity. Only a few examples of directing-group-free difunctionalizations of unactivated alkenes have been reported. Therefore, great opportunities exist for the development of three-component difunctionalization reactions with broad substrate scopes and tunable chemo-, regio-, and stereoselectivities.



KEYWORDS: *dicarbofunctionalization, nickel catalysis, alkenes, selectivity*

I. INTRODUCTION

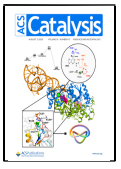
Alkenes represent one of the most useful building blocks for organic synthesis, owing to their abundance and versatile reactivity.[1] Carbofunctionalization of alkenes provides efficient access to substituted molecules from readily available alkenes by installing functional groups across their carbon−carbon double bonds.[1] The palladium-catalyzed Mizoroki−Heck reaction[2] and allylic alkylation reactions[3] have found widespread utilities in the synthesis of natural products and pharmaceuticals (Scheme 1). Representative examples include the use of the Heck reaction in the commercial synthesis of the HIV therapeutic rilpivirine,[4] and the application of the asymmetric allylic alkylation in the preparation of muscle relaxant flustramine derivatives.[5] Recently, hydrofunctionalization[6] and difunctionalization[7] of alkenes have emerged as useful methods with some enantioselective variants.[8] These new reactions have streamlined the preparation of the anti-inflammatory medicine naproxen[9] and a potential inhibitor for the 5-lipoxygenase activating protein (FLAP).[10]

1,2-Dicarbofunctionalization of alkenes can rapidly increase molecular complexity by coupling olefins with a range of simple, readily available electrophiles and nucleophiles (Scheme 2).[1,7] Typical electrophiles include organohalides and triflates, whereas various organometallic reagents can serve as the nucleophile. 1,2-Dicarbofunctionalization with an electrophile and a nucleophile is redox-neutral, which can usually provide good chemo- and regioselectivity due to the inherent difference in reactivities of the electrophile and the nucleophile (Scheme 2A).

1,2-Difunctionalization with two electrophiles requires reductants but prevents the use of air-sensitive, stoichiometric organometallic reagents, such as the Grignard and organozinc reagents (Scheme 2B). Chemo- and regioselectivity issues may arise when the reactivities of the two electrophiles are insufficiently distinct. Dicarbofunctionalizations with two organometallic reagents under oxidative conditions are rare (Scheme 2C). While several reactions have been reported with palladium catalysts, there is no example conducted with nickel catalysis.[11]

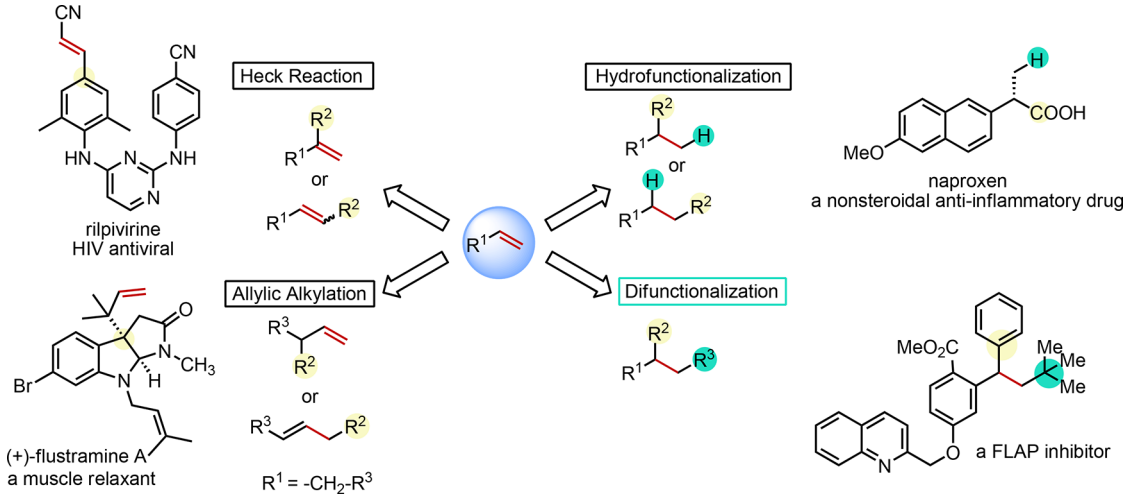
In this Perspective, we summarize recent progress in nickel-catalyzed 1,2-dicarbofunctionalization of alkenes. The review is organized by the polarity mode of the coupling partners: the first half details redox-neutral reactions with a nucleophile and an electrophile adding to the alkene, whereas the second half describes reductive reactions coupling the alkene with two electrophiles. In each section, intramolecular, two-component reactions are discussed prior to intermolecular, three-

Received: May 12, 2020
Revised: July 1, 2020
Published: July 2, 2020

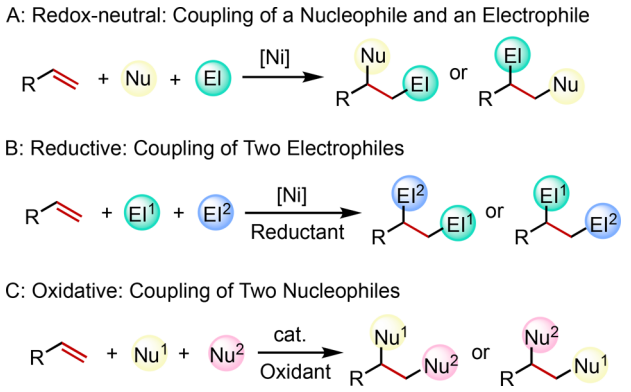


https://dx.doi.org/10.1021/acscatal.0c02115
ACS Catal. 2020, 10, 8542−8556

Scheme 1. Carbofunctionalization Reactions of Alkenes



Scheme 2. Overview of Nickel-Catalyzed 1,2-Dicarbofunctionalization and Mechanistic Considerations



component examples. In the end, we provide a short summary of the lingering challenges and an outlook for future directions.

A nickel-catalyzed alkene difunctionalization reaction can proceed by two types of pathways (Figure 1).[12] Reactions initiated by transmetalation of a nucleophile or oxidative addition of a C(sp^2) electrophile to the nickel catalyst typically enter a classic two-electron pathway (Figure 1A): The resulting organometallic nickel species undergoes migratory insertion with an alkene to afford a metal−alkyl intermediate. Palladium-catalyzed Heck reaction invokes β-H elimination of the metal−alkyl intermediate to restore the carbon−carbon double bond. In contrast to palladium nickel-alkyl intermediates tend to cross-couple with another electrophile or nucleophile, due to the intrinsically slower β-H elimination rate relative to that of palladium.[13]

In addition to the classic two-electron pathway, nickel catalysts can mediate the formation of radicals from C(sp^3) electrophiles and engage in radical mechanisms (Figure 1B).[14] Alkene functionalization via radical addition can result in different regioselectivity compared to that obtained from migratory insertion. The presence of radical intermediates has profound implications on stereoselectivities, as formation of radicals can scramble stereocenters.[15]

II. REDOX-NEUTRAL INTRAMOLECULAR DICARBOFUNCTIONALIZATION

The addition of two coupling partners across the carbon−carbon double bond raises chemo- and regioselectivity issues (Scheme 2). A common strategy to facilitate difunctionalization and control the selectivity involves linking one of the coupling partners to the alkene, which compensates for the activation entropy cost and eliminates the possibility of forming regioisomers.

In an early report on intramolecular 1,2-difunctionalization, an alkyl bromide tethered to an alkene is converted *in situ* to the corresponding alkylzinc compound upon treatment with $ZnEt_2$. Upon cyclization of the alkylzinc pendent to the alkene, the intermediate proceeds to couple with another electro-

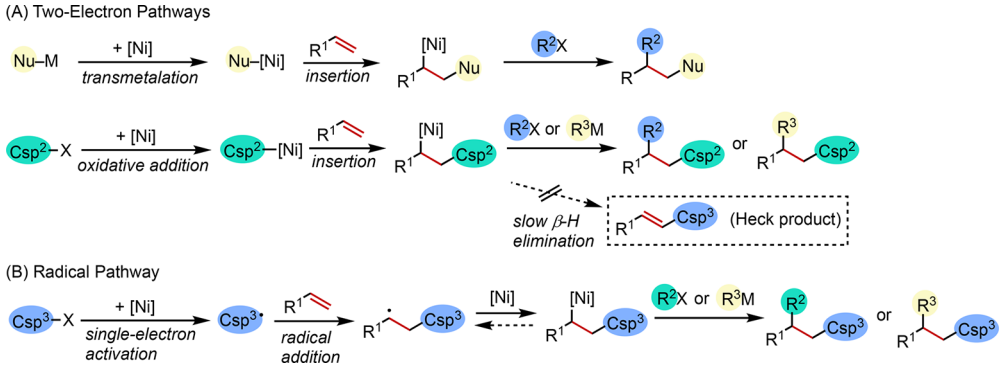
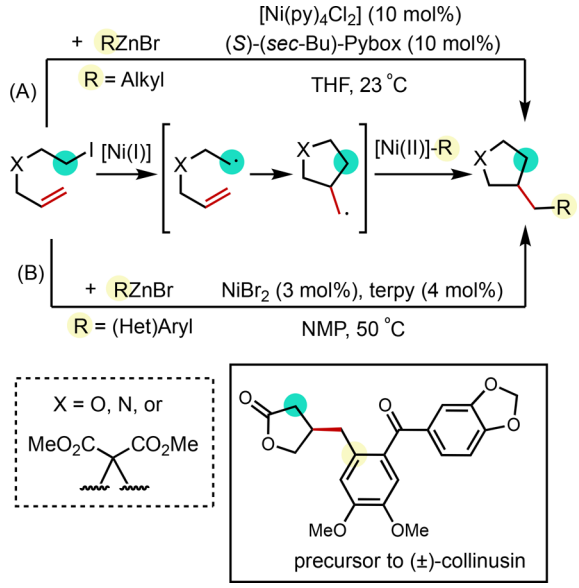


Figure 1. Representative pathways for nickel-catalyzed alkene difunctionalization.

https://dx.doi.org/10.1021/acscatal.0c02115
ACS Catal. 2020, 10, 8542−8556

phile.[16] The required $ZnEt_2$ limits the scope to substrates compatible with dialkylzinc reagents. Subsequent studies show that excellent functional group compatibility can be achieved by coupling the alkene with an organozinc halide reagent, thus preventing the use of more reactive dialkylzinc reagents (Scheme 3).

Scheme 3. Two-Component Coupling of Olefin-Tethered Alkyl Halides with Zinc Reagents

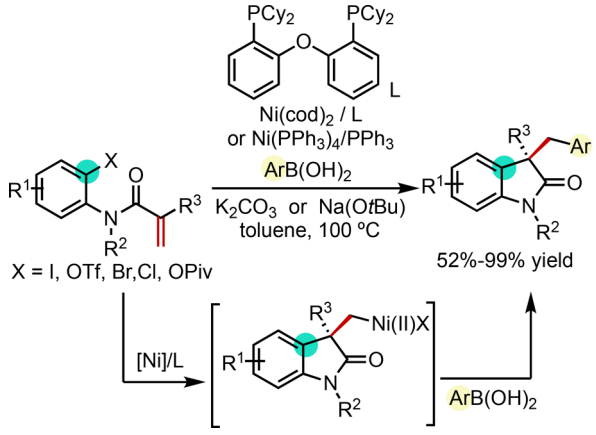


A reported two-component difunctionalization reaction couples alkyl iodides with alkylzinc reagents by applying a Ni(pybox) (pybox = 2,6-bis(4-*sec*-butyl-2-oxazolinyl)pyridine) catalyst to afford pyrrolidine and tetrahydrofuran derivatives (Scheme 3A).[17] Geminal-disubstituents on the carbon linkage proved essential to promote cyclization.[18] An analogous cyclization of alkyl iodides employs alkyl Grignard reagents as the nucleophile.[19] TMEDA (*N*,*N*,*N*′,*N*′-tetramethyl ethylenediamine) exhibits higher reactivity compared to bipyridine (bpy) and pyridine-bisoxazoline (pybox) ligands, possibly because the electron-rich (TMEDA)Ni(I) intermediate can rapidly activate $C(sp^3)$ electrophiles to form radicals.

A $(terpy)NiBr_2$ (terpy = 2,2′:6′,2″-terpyridine) catalyst has enabled a similar cyclization reaction that couples arylzinc reagents to the alkyl halide-tethered alkene (Scheme 3B).[20] The reaction tolerates a wide range of functional groups, including ketones, esters, halides, and nitriles. Base-sensitive stereocenters remain intact during the reaction. The gram-scale synthesis of a precursor to natural product (±)-collinusin has demonstrated the practical utility of this method. Radical clock experiments and analysis of the stereoselectivity, in combination with prior studies,[21] led the authors to propose a mechanism involving radical intermediates (Scheme 3). The transmetalation of organozinc reagents to the (terpy)Ni catalyst results in a Ni(I) intermediate, which activates the alkyl halide to form a radical. Upon cyclization, the resulting radical intermediate is trapped by a (terpy)Ni(II)(X)Ar species. The resulting Ni(III) intermediate undergoes reductive elimination to form the product. This mechanism appears to be general for alkene substrates tethered with $C(sp^3)$ electrophiles.[16] The involvement of radicals in the cyclization step imposes a challenge on controlling the enantioselectivity.

$C(sp^2)$ electrophiles have been shown to cyclize with tethered alkenes and couple to aryl boronic acids to afford 3,3-disubstituted oxindoles bearing all-carbon quaternary centers (Scheme 4).[22] The electrophile scope includes aryl iodides,

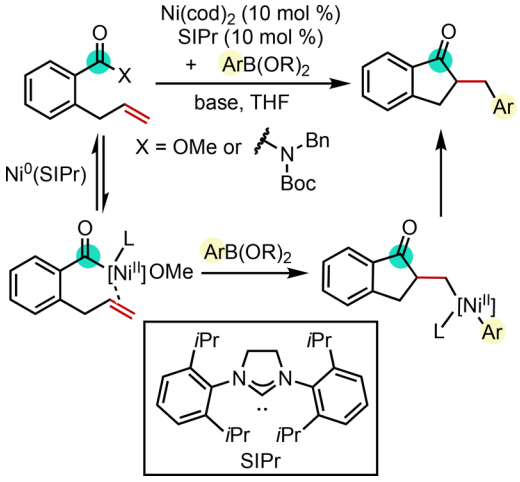
Scheme 4. Two-Component Coupling of Olefin-Tethered Aryl Halides with Boronic Acids



bromides, chlorides, triflates, and esters. Likely going through a Heck-type mechanism, this protocol provides a practical and sustainable alternative to the conventional palladium-catalyzed domino Heck cyclization.[2]

Allylarene-tethered amides[23] and esters[24] undergo cyclization in a similar fashion to afford indanone products (Scheme 5). These substrates are conventionally inert toward low-valent

Scheme 5. Two-Component Coupling of Allylarene-Tethered Esters and Amides with Boronic Acids

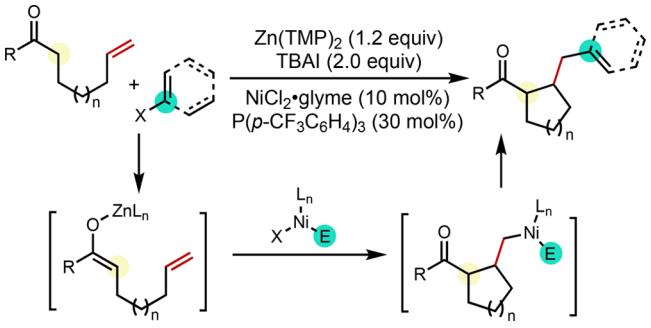


palladium-mediated oxidative addition. Nickel(0) complexes are electron-rich and more reactive in activating substrates via oxidative addition.[12] The strong σ-donor ligand, SIPr (SIPr = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidine), further increases the nucleophilicity and reduces the oxidation potential of the nickel center, which proved crucial for promoting the oxidative addition of amides and esters. The coupling partners include a variety of arylboronic acids and pinacol esters, and the alkene scope comprises substituted *o*-allylbenzamides and *o*-allylbenzoates.

https://dx.doi.org/10.1021/acscatal.0c02115
ACS Catal. 2020, 10, 8542−8556

In contrast to the numerous examples of reactions occurring to alkenes with a pendant electrophile, there are a few reports in which the alkene is tethered to a nucleophile. In a recent example, ketones have been shown to undergo cyclization with unactivated alkenes, followed by coupling to aryl and vinyl halides, and hydroxylamine derivatives (Scheme 6).[25] The

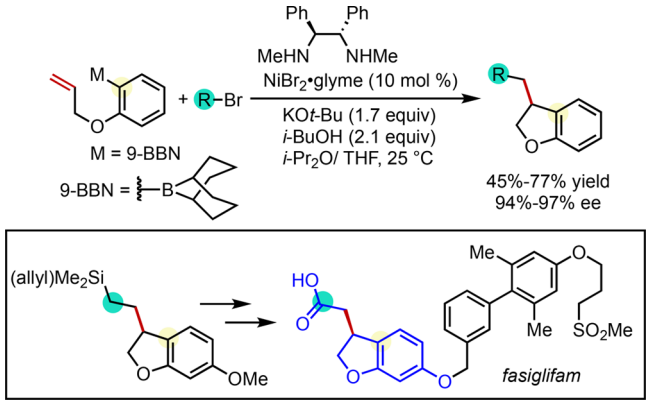
Scheme 6. Two-Component Coupling of Olefin-Tethered Ketones via Enolate Addition to the Alkene



reaction is initiated by enolization of the ketone in the presence of $Zn(TMP)_2$ (TMP = 2,2,6,6-tetramethylpiperidinyl). Notably, the electron-deficient phosphine ligand was essential, likely for promoting reductive elimination.

Despite their significant synthetic utility, enantioselective difunctionalization reactions remain rare. An early example of an enantioselective arylalkylation features the cyclization of an olefin-tethered aryl-9-BBN (9-borabicyclo[3.3.1]nonane), followed by coupling with an alkyl bromide (Scheme 7).[26] Using

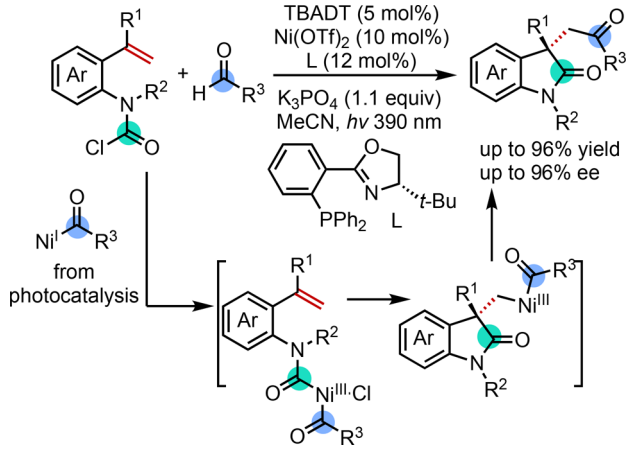
Scheme 7. Enantioselective Intramolecular Arylalkylation



C_2-symmetric 1,2-diamine as the chiral ligand, the reaction accomplished an efficient synthesis of the dihydrobenzofuran core of fasiglifam, investigated as an antidiabetic compound.

Photoredox-nickel dual catalysis has enabled the asymmetric keto-acylation of alkenes to afford a variety of oxindoles bearing a quaternary chiral center (Scheme 8).[27] The carbamoyl chloride substrate is linked to a vinylarene and can be coupled to aliphatic and aromatic aldehydes. The conditions apply a nickel-PHOX (PHOX = phosphinooxazoline) chiral catalyst in combination with tetrabutylammonium decatungstate (TBADT) as the photosensitizer. Upon photoexcitation, TBADT likely abstracts the hydrogen atom from the aldehyde to afford an acyl radical. Trapping the radical with Ni(0) forms a Ni(I)-acyl intermediate, which can undergo oxidative addition with the acyl chloride to afford a Ni(III)

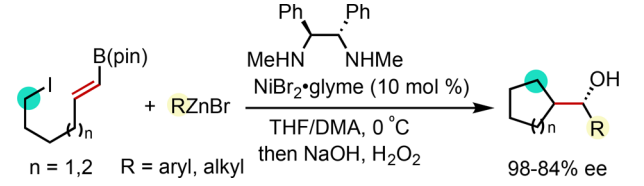
Scheme 8. Enantioselective Keto-Acylation via Photoredox-Ni Dual Catalysis



intermediate. Migratory insertion followed by reductive elimination delivers the oxindole product. Alkene insertion is speculated to be the enantio-determining step.

$C(sp^3)$ electrophiles usually form radicals under nickel catalytic conditions. Formation of the stereocenter via radical cyclization hampers control of stereoselectivity. A recent report utilizes an unsubstituted alkyl chain to link the alkyl iodide and olefin moieties (Scheme 9). Upon radical cyclization, the

Scheme 9. Enantioselective Intramolecular Dicarbofunctionalization of Vinyl Boronic Esters



newly formed tertiary carbon center is symmetric, preventing issues involving stereoselectivity. The resulting radical is stabilized by the adjacent boronic ester group and can be trapped by the nickel catalyst. Stereocontrol of the subsequent coupling with an organozinc reagent is dictated by the chiral diamine ligand.[28] Stereospecific oxidation of the boronic ester affords the corresponding chiral alcohols.

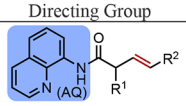
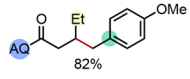
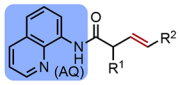
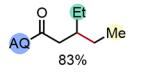
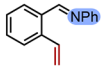
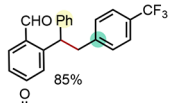
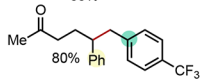
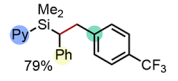
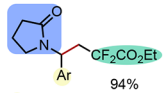
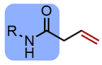
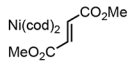
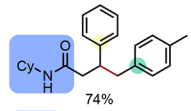
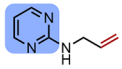
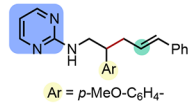
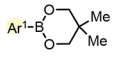
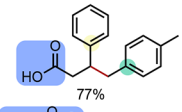
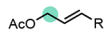
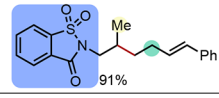
III. REDOX-NEUTRAL INTERMOLECULAR DICARBOFUNCTIONALIZATION

Intermolecular 1,2-dicarbofunctionalization reactions of alkenes have emerged as appealing ways to prepare functionalized molecules, since an early example of a 1,2-allylmethylation of unactivated alkenes using trimethylaluminum.[29] Control of the chemo- and regioselectivities in three-component coupling reactions remains a preeminent challenge. Moreover, β-H elimination of the intermediate from olefin insertion can afford an unsaturated side-product. The latter impediment could be ameliorated by the intrinsically slow β-H elimination of Ni-alkyl intermediates.[13] Directing groups proved useful in solving both issues by promoting olefin insertion, directing the regioselectivity, stabilizing the insertion intermediate, and preventing β-H elimination (Table 1).

8-Aminoquinoline (AQ) proved effective in facilitating the difunctionalization of nonconjugated terminal and internal

https://dx.doi.org/10.1021/acscatal.0c02115
ACS Catal. 2020, 10, 8542−8556

Table 1. Dicarbofunctionalization of Alkenes Facilitated by Directing Groups

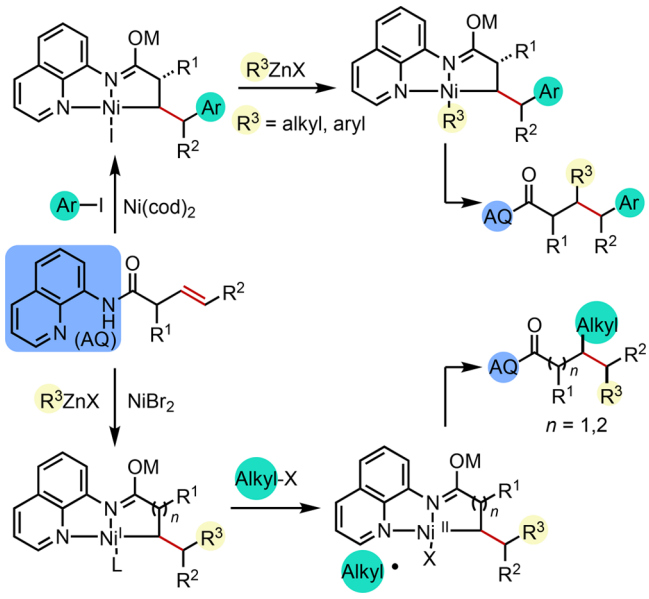
Entry	Alkene/ Directing Group	Nu	El	Catalyst	Representative Product	Ref
1		ZnR_2		$Ni(cod)_2$	 82%	30
2		ZnR_2 or RZnBr	Alkyl–X X = Br, I	$NiBr_2$	 83%	31
3		Ar^1ZnI	Ar^2X X = Br,I,OTf	$Ni(cod)_2$	 85%	32
4		Ar^1ZnI	Ar^2–I	$Ni(cod)_2$	 80%	33
5		Ar^1ZnI	Ar^2X X = Br,I	$NiBr_2$	 79%	34
6		$ArB(OH)_2$	RCF_2X X = Br,Cl	$NiCl_2$•glyme 4,4'-diMeO-bpy	 94% Ar = -*p*-Ph-C_6H_4-	35
7			Ar^2–I		 74%	36
8		$ArB(OH)_2$	RX X = I, Br R = aryl, alkenyl, alkynyl	$Ni(cod)_2$ dppm	 Ar = *p*-MeO-C_6H_4- 58% rr = 5.5:1	37
9			Ar^2–I	$Ni(cod)_2$	 77%	38
10		$ZnMe_2$		$NiBr_2$•glyme	 91%	39

alkenes, using alkylzinc reagents as the nucleophile and aryl or alkyl halides as the electrophile (Table 1, entries 1 and 2).[30,31] Excess loadings of the electrophile and the nucleophile are necessary for overcoming the competing two-component cross-coupling and homodimerization reactions. The regioselectivity and the mechanism are dependent on the nature of the electrophiles (Scheme 10). Reactions with $C(sp^2)$ electrophiles involve a two-electron mechanism,[30] whereas those involving $C(sp^3)$ electrophiles proceed through radical intermediates.[31] The $C(sp^2)$ electrophile first undergoes oxidative addition to the Ni catalyst; then, the resulting Ni intermediate inserts into the olefin, placing the electrophile to the position farther from AQ. In contrast, when a $C(sp^3)$ electrophile is used, transmetalation of the nucleophile occurs first, which places the nucleophile in the position farther from AQ.

Imines are effective directing groups for diarylation of vinylarenes and terminal aliphatic alkenes (Table 1, entries 3 and 4).[32,33] The latter reaction incorporates $AgBF_4$ or CuI as additives to *in situ* generate cationic Ni(II) catalysts in order to promote insertion (Table 1, entry 4).[33] After the reaction, imines can easily convert to ketones via hydrolysis.

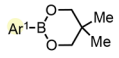
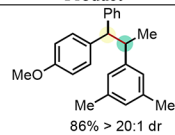
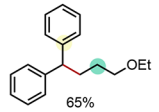
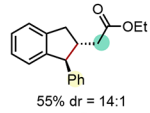
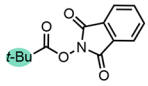
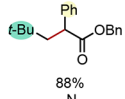
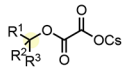
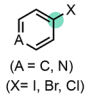
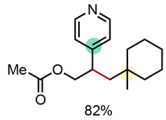
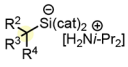
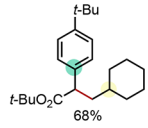
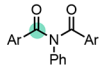
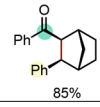
Other directing groups include pyridine (Table 1, entry 5)[34] and amides (Table 1, entries 6 and 7).[35,36] *β*-Difluoroalkylated

Scheme 10. Regioselective 1,2-Arylalkylation of Alkenes Directed by 8-Aminoquinoline (AQ)



https://dx.doi.org/10.1021/acscatal.0c02115
ACS Catal. 2020, 10, 8542−8556

Table 2. Redox-Neutral Intermolecular Dicarbofunctionalization of Alkenes

Entry	Alkene	Nu	El	Catalyst/ Ligand	Representative Product	Ref
1			Ar²Br	$NiCl_2$	 86% > 20:1 dr	40
2		ArZnI	Alk-X X = Br, I	$NiBr_2$ or $(Ph_3P)_2NiCl_2$	 65%	41
3		ArZnI	 X = Br, Cl	$Ni(cod)_2$	 55% dr = 14:1	42
4		PhZnCl•LiCl		$NiCl_2$•glyme dtbbpy	 88%	43
5			 (A = C, N) (X= I, Br, Cl)	[Ir]/$NiCl_2$•glyme dtbbpy	 82%	44
6			Ar—I	$Ru(bpy)_3Cl_2•6H_2O$ $NiCl_2•6H_2O$ dtbbpy	 68%	45
7		$NaBPh_4$		$Ni(cod)_2$	 85%	46

amines, formed from the difluoroalkylarylation of enamides, are important motifs in medicinal chemistry (Table 1, entry 6). Pyrimidine is a weakly coordinating group, which can direct the difunctionalization of allyl amines (Table 1, entry 8).[37] This reaction is selective for forming a 1,3-disubstitution pattern via a reversible β-H elimination and reinsertion, when aryl iodides are used as the electrophile. With alkenyl or alkynyl halides as the electrophile, the reaction forms 1,2-alkenylarylation or 2,1-alkynylarylation products.

Free carboxylic acids can serve as a directing group for the 1,2-diarylation of alkenes with aryl iodides and aryl boronates without the need of an ancillary ligand (Table 1, entry 9).[38] In addition, a 1,2-allylmethylation of alkenes is achieved by using an allyl electrophile and dimethylzinc as the nucleophile (Table 1, entry 10).[39] This reaction recruits a variety of weakly coordinating heterocycle directing groups, such as saccharin, phthalimide, pyridone, pyrazole, triazole, tetrazole, and benzoxazole. These conditions do not require ancillary ligands to the nickel catalyst.

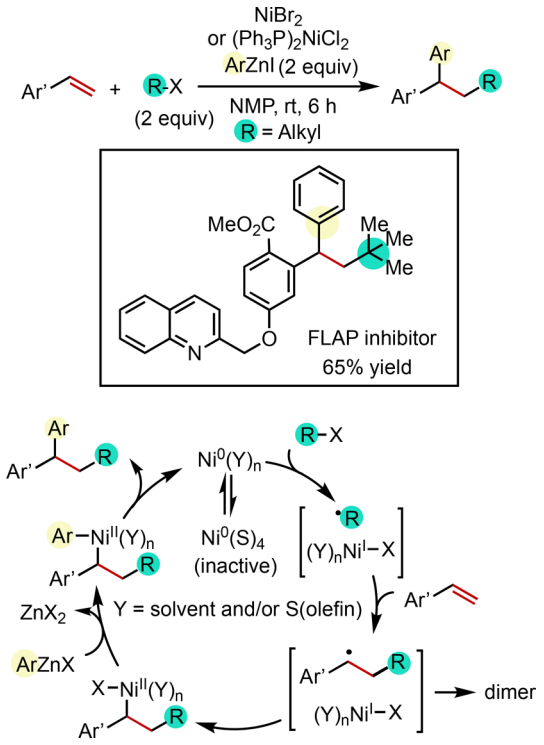
Recent efforts have endeavored to avoid directing groups as these moieties can mitigate the substrate scope and practical applications of difunctionalization reactions (Table 2). Diastereoselective diarylation of vinylarenes with aryl bromides and arylboron reagents affords triarylated products in high yields (Table 2, entry 1).[40] This reaction can be carried out on gram-scale. The mechanistic proposal invokes a Ni(0)/Ni(II) catalytic cycle. Notably, the use of 0.1 equiv of $(Bpin)_2$, in the presence of KOEt, is essential to reduce $NiCl_2$ to a Ni(0) species.

An alkylarylation of vinylarenes combines alkyl halides and arylzinc reagents to form 1,1-diarylalkane products (Table 2, entry 2).[41] This reaction has been applied as the final step to assemble a potential inhibitor for the 5-lipoxygenase activating protein (FLAP).[10] Recently, the scope of the electrophile has been extended to include α-halocarbonyl compounds (Table 2, entry 3).[42] Mechanistic studies reveal that the reaction is initiated by a Ni(0) species, stabilized by the solvent and the alkene, which activates the alkyl halide via SET to generate an alkyl radical as the turnover-limiting step. Addition of the alkyl radical to the olefin affords a benzylic radical, which combines with the Ni(I)-X intermediate. The resulting Ni(II)-X species undergoes transmetalation with ArZnX, followed by reductive elimination (Scheme 11).

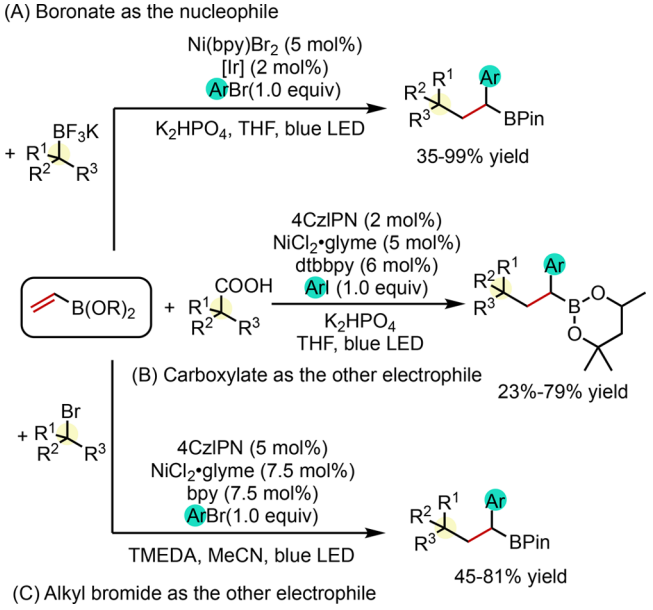
Radicals, frequently formed upon activation of alkyl halides, are key intermediates in Ni-catalyzed cross-coupling reactions. Novel methods to generate radicals have been applied toward 1,2-dicarbofunctionalization and to expand the substrate scope. Redox-active esters serve as the electrophile in the difunctionalization of α,β-unsaturated esters (Table 2, entry 4).[43] Alkyl oxalates have become common radical precursors under photoredox conditions, and the resulting organic radicals have shown to couple with vinyl and allylic esters (entry 5).[44] The reaction utilizes the common $[Ir\{dF(CF_3)_2\ ppy\}_2(bpy)]$-$PF_6$ photocatalyst with blue LED light irradiation in combination with $NiCl_2$·glyme and 4,4′-di-*tert*-butyl-2,2′-dipyridyl. A $Ru(bpy)_3Cl_2·6H_2O$/nickel dual catalytic condition has enabled the arylalkylation of vinyl esters with aryl iodide and alkyl silicates with blue light irradiation (Table 2, entry 6).[45] The relative stoichiometry of the substrates proved to be critical, as a slight excess of alkene and alkyl silicate prevents the direct cross-coupling of the aryl iodide.

https://dx.doi.org/10.1021/acscatal.0c02115
ACS Catal. 2020, 10, 8542−8556

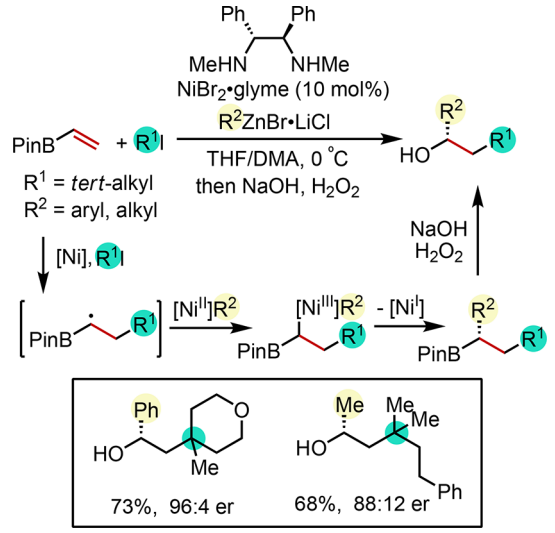
Scheme 11. Regioselective Alkylarylation of Vinylarenes



Scheme 12. Regioselective Alkylarylation of Vinyl Boronic Esters



Scheme 13. Asymmetric 1,2-Dicarbofunctionalization of Vinylboranes



An intermolecular carboacylation of norbornene uses acetylamides as the acyl source (Table 2, entry 7).[46] The reaction is initiated via oxidative addition of the amide C−N bond to Ni(0), followed by insertion to the alkene. Triarylboranes, generated *in situ* from the corresponding tetraarylborates, serve as the nucleophile.

Vinylboronates are appealing and useful substrates. The capability of boryl groups stabilizing adjacent radicals can exert excellent control of regioselectivity.[47] The boryl products are useful cross-coupling partners and can be readily oxidized to give alcohols. Alkylarylation reactions of vinylboronates exploit photoredox-nickel dual catalysis (Scheme 12).[48−50] These reactions proceed through a common mechanism: the photocatalyst activates the alkyl substrate to generate a radical intermediate, which may then add to vinylboranates. The high regioselectivity is dictated by the formation of an α-boryl radical. Trapping the radical with a nickel catalyst sets the stage for subsequent coupling with an aryl halide. Alkyl radical precursors include alkyltrifluoroborates,[48] carboxylic acids,[49] and alkyl halides,[50] which are activated by photocatalysts, $[Ir\{dF(CF_3)_2\ ppy\}_2(bpy)]PF_6$,[48] and 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN).[49,50] The use of alkyl halides as the other coupling partner necessitates a reductant, tetramethylethylenediamine (TMEDA) (see further in Section V).[50]

The enantioselectivity of the intermolecular dicarbofunctionalization reaction is particularly difficult to control with only few examples having been reported.[51] The 1,2-dialkylation and 1,2-arylalkylation of alkenyl boronic acid pinacol esters (BPin) take advantage of α-boryl radical stabilization (Scheme 13).[28] In the presence of $NiBr_2$·glyme and a chiral diamine ligand, alkyl zinc halides and tertiary alkyl halides are added across a vinyl boron reagent in good yield and enantioselectivity. Following oxidation of pinacol borane easily generates chiral secondary alcohol products with a retention of the stereochemistry

IV. REDUCTIVE INTRAMOLECULAR DICARBOFUNCTIONALIZATION WITH ELECTROPHILES

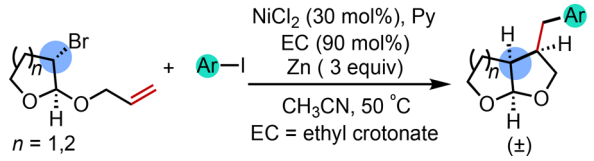
The use of stoichiometric organometallic reagents has limitations in cost, sustainability, and reagent availability. Additionally, organometallic reagents, such as Grignard or organozinc reagents, tend to interfere with acidic or electrophilic functional groups.[52] Reductive alkene 1,2-dicarbofunctionalization reactions with electrophiles have emerged, which avoid the need for organometallic nucleophiles. A major challenge of this strategy is to achieve chemo- and regioselectivity, as the two electrophiles can exhibit indistinguishable reactivity. Two-component coupling by tethering

https://dx.doi.org/10.1021/acscatal.0c02115
ACS Catal. 2020, 10, 8542−8556

one of the electrophiles to the olefin has been applied as a perfunctory solution to this issue.

An early example of two-component reductive difunctionalization incorporates an alkene substrate tethered to an alkyl bromide and couples it with an aryl iodide. The reaction requires a [Ni^0·2EC·Py] (EC = ethyl crotonate, Py = pyridine) catalyst, generated by mixing $NiCl_2$ with Zn, pyridine, and EC (Scheme 14).[53] The diastereoselectivity is consistent with the

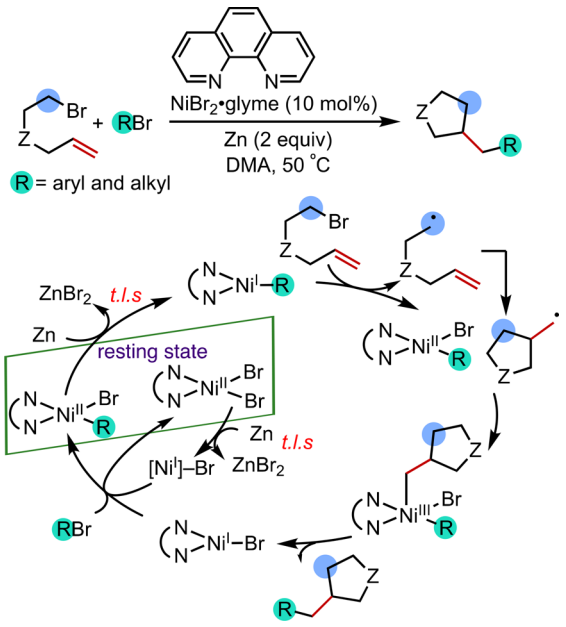
Scheme 14. Two-Component Reductive Dicarbofunctionalization



prediction of the Beckwith−Houk model.[54] This reaction can be applied to prepare diverse spiroketals,[55] *trans*-tetrahydronaphtho[2,3-β]furans,[56] and a podophyllum lignan core.[57] An analogous arylalkylation occurs with alkenes, to which aryl bromides are tethered.[58] In addition, redox active *N*-hydroxyphthalimide esters can be used as an alkyl source in place of alkyl bromides.[59]

A relevant intramolecular reductive dicarbofunctionalization of alkenes with pendant alkyl bromide electrophiles employs the common precatalyst $NiBr_2$·glyme and the ligand 1,10-phenanthroline (phen) (Scheme 15).[60] These mild conditions

Scheme 15. Mechanism of Two-Component Reductive Dicarbofunctionalization of Alkenes



are compatible with a wide range of bromo-alkene substrates and aryl, heteroaryl, and alkyl bromide electrophiles to afford substituted carbo- and heterocycles. A mechanistic study on this system rules out the "radical chain" mechanism[61] but favors a "sequential reduction" pathway.[62] The reduction of (phen)Ni(II) intermediates to Ni(I) species by Zn is determined to be the turnover-limiting step. The sequence and mechanism of electrophile activation control the chemoselectivity for cross-coupling over homocoupling of each electrophile. The $C(sp^2)$ and the $C(sp^3)$ electrophiles are activated by different Ni intermediates via different pathways. The sterically accessible (phen)Ni(I)−Br selectively activates aryl bromides via two-electron oxidative addition, whereas alkyl bromides are activated by the more electron-rich (phen)Ni(I)−Ar to afford radicals.

Several examples of asymmetric arylalkylation,[63] arylalkenylation,[64] and diarylation[65] have been reported to form indanes, indolines, and dihydrobenzofurans bearing quaternary carbon centers (Table 3). A common feature of the substrate is a $C(sp^2)$ electrophile tethered to an alkene. The other suitable coupling partners include alkyl bromides[63a] (entry 1), benzyl chlorides (entry 2),[63b] vinyl triflates (entry 3),[64a] vinyl bromides (entry 4),[64b] gem-difluoroalkenes (entry 5),[64c] and aryl bromides (entry 6),[65] and the alkene scope includes both activated and unactivated alkenes. Effective chiral ligands include bioxazolines (biOx), pyridine-oxazolines (pyrOx), and phosphinooxazolines (PHOX).

The mechanism of the diarylation of enamides (Table 3, entry 6) has been investigated.[65] Control experiments ruled out the participation of arylzinc intermediates. The reaction is proposed to be initiated by the oxidative addition of the aryl bromide to a Ni(0) species to afford an aryl-Ni intermediate (Scheme 16). The subsequent *5-exo* cyclization is irreversible and likely determines the stereoselectivity. The Ni(II) alkyl intermediate is further reduced, followed by oxidative addition of the aryl bromide substrate and reductive elimination.

Enantioselective carboacylation has been developed by tethering aryl carbamoyl chlorides to styrenes, which are coupled to primary and secondary alkyl iodides or benzyl chlorides (Scheme 17).[66] This cascade cyclization/cross-coupling reaction enables the construction of diverse oxindoles bearing a quaternary stereocenter. Mechanistic investigations suggest that the Ni(II)-mediated intramolecular migratory insertion serves as the enantio-determining step.

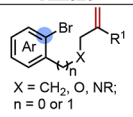
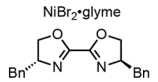
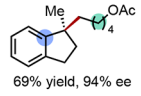
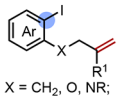
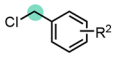
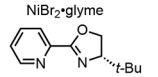
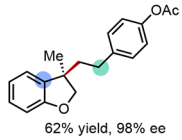
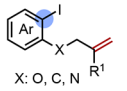
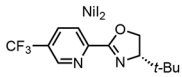
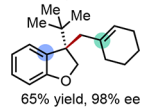
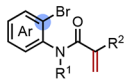
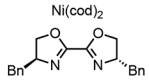
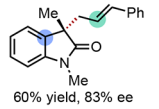
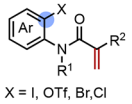
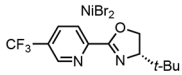
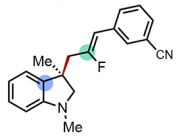
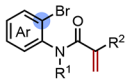
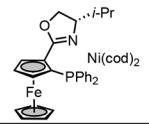
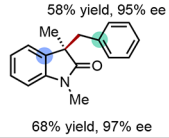
Existing enantioselective dicarbofunctionalization reactions are initiated by oxidative addition of the olefin-tethered $C(sp^2)$ electrophile and involves the insertion of the aryl-Ni intermediate into the alkene as a common enantio-determining step. $C(sp^3)$ electrophiles usually form radicals upon activation by Ni catalysts. Therefore, there have been no examples of asymmetric alkylarylation for an alkene with a pendent $C(sp^3)$ electrophile, likely due to the difficulty of controlling the stereoselectivity of radical cyclization.

V. REDUCTIVE INTERMOLECULAR 1,2-DICARBOFUNCTIONALIZATION

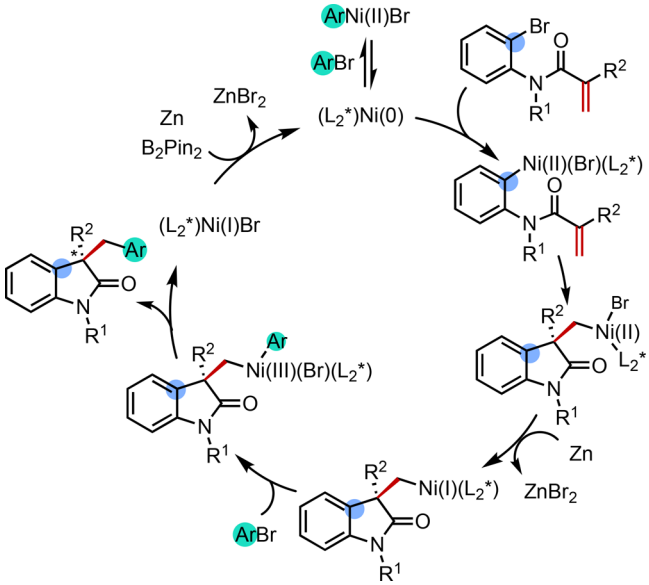
Intermolecular reductive 1,2-dicarbofunctionalization reactions are underdeveloped owing to the challenge of controlling chemo- and regioselectivity for two electrophiles with similar reactivity. Directing groups have been used to overcome this issue. The first example of reductive arylalkylation was developed with allylic acetates, amines, and nitriles (Scheme 18).[67] The alkene scope was later expanded to simple olefins, 1,4- and 1,5-dienes, and enynes, which undergo cascade cyclization and coupling.[68] While the reaction is compatible with a variety of aryl iodides, the alkyl coupling partner is limited to tertiary alkyl iodides. Control experiments and computational studies reveal that oxidative addition of the aryl iodide to the low-valent Ni catalyst is followed by reduction of the Ni(III)-aryl species by TDAE (TDAE = tetrakis(dimethylamino)ethylene) to afford a Ni(I)-aryl intermediate.

https://dx.doi.org/10.1021/acscatal.0c02115
ACS Catal. 2020, 10, 8542−8556

Table 3. Asymmetric Two-Component Dicarbofunctionalization of Alkenes

Entry	Tethered Alkene	El	Catalyst/ Ligand	Representative Product	Ref
1	 X = CH_2, O, NR; n = 0 or 1	 R^2 = Alkyl	 $NiBr_2$•glyme	 69% yield, 94% ee	63a
2	 X = CH_2, O, NR;		 $NiBr_2$•glyme	 62% yield, 98% ee	63b
3	 X: O, C, N		 NiI_2	 65% yield, 98% ee	64a
4			 $Ni(cod)_2$	 60% yield, 83% ee	64b
5	 X = I, OTf, Br,Cl		 $NiBr_2$	 58% yield, 95% ee	64c
6		ArBr		 68% yield, 97% ee	65

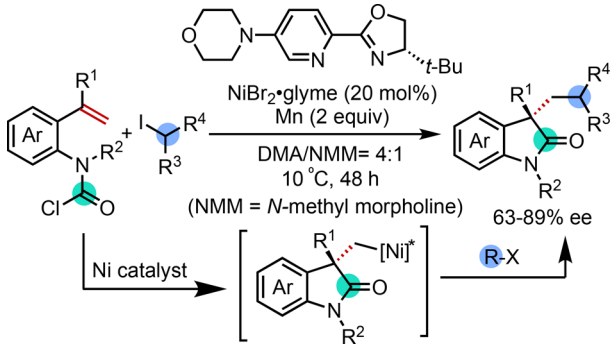
Scheme 16. Proposed Mechanism of Intramolecular Enantioselective Diarylation of Enamides



The Ni(I)-aryl species subsequently activates the alkyl iodide to form a radical. Radical addition to the alkene at the terminal position forms a secondary radical intermediate. Trapping of the intermediate by the Ni(II)-aryl species generates a Ni(III) intermediate that can undergo reductive elimination. This sequence of electrophile activation is consistent with the experimental study on a two-component reductive difunctionalization reaction.[62]

The directing group strategy has been used to develop a 1,2-acyl-fluoroalkylation and an arylalkylation of alkenes. The

Scheme 17. Enantioselective Reductive Carboacylation of Alkenes

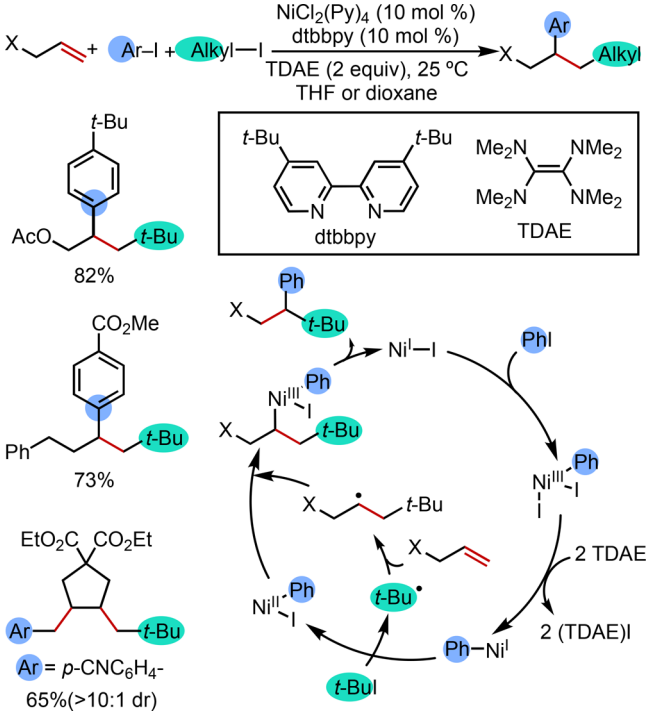


former reaction is effective for alkenes tethered to chelating groups including esters, carbonates, sulfonates, and phosphates (Scheme 19A).[69] The alkyl radical, generated from alkyl iodides, adds to the alkene, which then coordinates to Ni and proceeds to couple with the acyl chloride. The pendent, weak chelating group plays a vital role in facilitating the capture of the alkyl radical intermediate by the nickel species, thereby controlling the chemo- and regioselectivity. Primary and secondary alkyl electrophiles are ineffective substrates, and reactions are limited to terminal olefins. By using the 8-aminoquinoline directing group, the scope of difunctionalization has been expanded to aryl-alkylation, alkenyl-alkylation, and dialkylation of internal alkenes (Scheme 19B).[70]

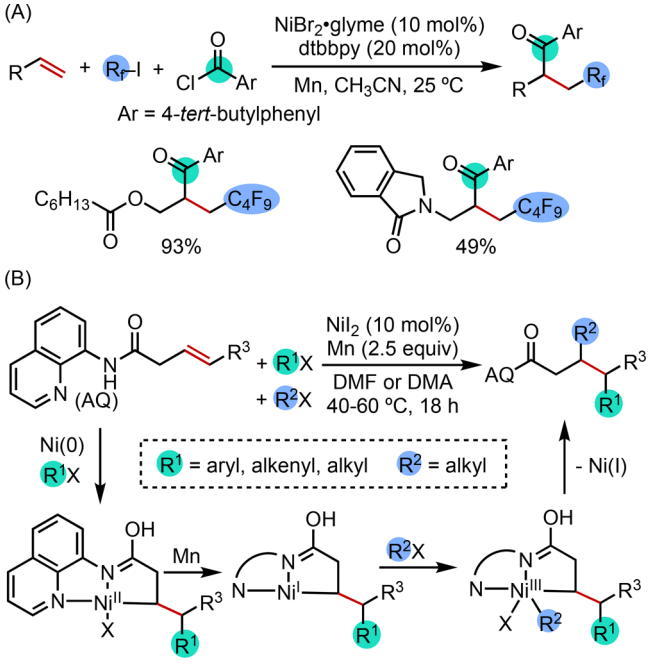
Three-component, intermolecular asymmetric alkene difunctionalization is rare and challenging. The first example of asymmetric 1,2-diarylation couples vinylarenes with bromoarenes to afford α,α,β-triarylated ethane scaffolds, which are prominent in biologically active molecules (Scheme 20).[71] The

https://dx.doi.org/10.1021/acscatal.0c02115
ACS Catal. 2020, 10, 8542−8556

Scheme 18. Intermolecular Reductive Alkylarylation of Alkenes and the Mechanistic Proposal

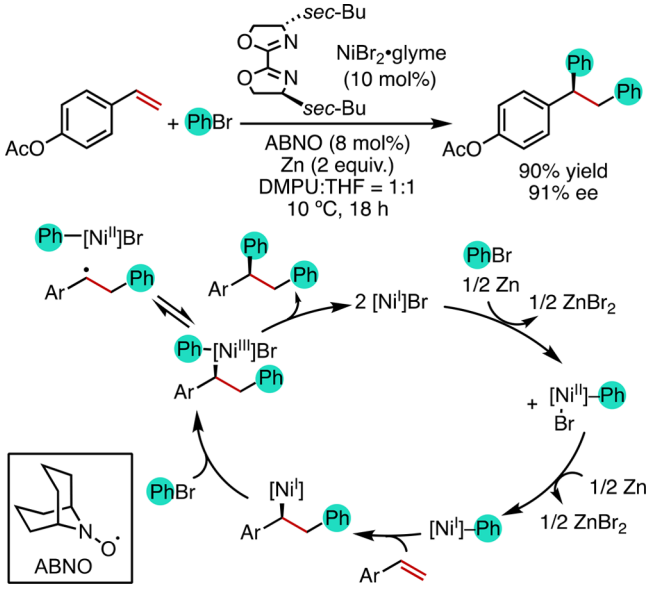


Scheme 19. Intermolecular Reductive Dicarbofunctionalization by Using Directing Group



reaction utilizes $NiBr_2$·glyme as the precatalyst, (S,S)-*sec*-Bu-biOx as the chiral ligand, and Zn as the reductant. An *N*-oxyl radical additive, ABNO (9-azabicyclo[3.3.1]nonane *N*-oxyl), substantially improves the enantioselectivity. Preliminary data suggests that ABNO may serve as a ligand to Ni. Several observations serve as evidence for the formation of a radical intermediate at the benzylic position, which reversibly binds to the Ni catalyst. It is conceivable that the reductive elimination is the enantio-determining step. This reaction, however, is

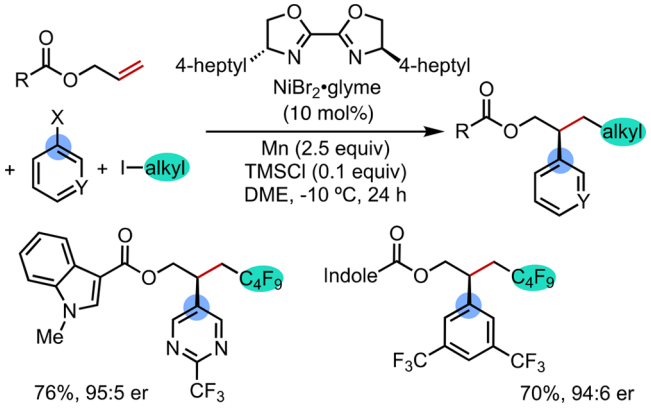
Scheme 20. Asymmetric Reductive Diarylation of Vinylarenes



limited to the addition of two identical aryl groups across the double bond, and the alkene scope is limited to vinylarenes.

The first example of an asymmetric three-component difunctionalization using two different electrophiles was recently reported (Scheme 21).[72] Allyl esters undergo 1,2-

Scheme 21. Asymmetric Reductive 1,2-Fluoroalkylarylation of Allyl Esters

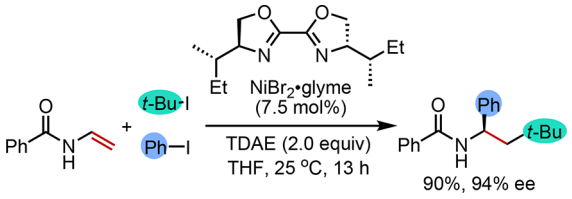


fluoroalkylarylation, coupling with aryl and heteroaryl halides and perfluoroalkyl iodides. The enantioselectivity is induced by chiral biOx ligands, and the indole 3-carboxylate ester plays a crucial role in achieving high yields and the enantioselectivity. Control experiments reveal that the reaction is likely initiated by the addition of the perfluoroalkyl radical to the allyl ester, followed by cross-coupling with the aryl halide. The use of electron-deficient arenes appears to improve the enantioselectivity.

An analogous asymmetric three-component coupling adds tertiary iodides and aryl iodides or bromides across the carbon−carbon double bond of vinyl amides, boronic esters, and phosphates (Scheme 22).[73] The reaction proceeds at room temperature in the presence of an organic reductant, TDAE. An alkyl Ni(III) intermediate ligated with (L)-isoleucine derived biOx is proposed based on DFT calculations. This

https://dx.doi.org/10.1021/acscatal.0c02115
ACS Catal. 2020, 10, 8542−8556

Scheme 22. Asymmetric Reductive Dicarbofunctionalization of Alkenes



intermediate is stabilized by the coordination of amides or other coordinating groups on the alkene, which contribute to defining the stereochemical outcome.

CONCLUSION AND OUTLOOK

Nickel-catalyzed 1,2-dicarbofunctionalization of alkenes has emerged as an efficient strategy to build substituted structural motifs. Common reaction conditions employ commercially available nickel precursors and nitrogen-containing ligands. The conditions are generally mild and do not require high temperatures. Maintaining an inert atmosphere for the reactions, however, is necessary for those involving air-sensitive organometallic nucleophiles and radical intermediates. Reactions involving nucleophiles and C(sp^2) electrophiles often proceed by two-electron pathways, whereas C(sp^3) electrophiles likely invoke radical intermediates.

Intramolecular, two-component difunctionalization reactions have achieved notable success with a broad substrate scope. By tethering a coupling partner to the alkene, intramolecular reactions limit the number of possible regioisomers and hence improve the selectivity. As a result, intramolecular, two-component dicarbofunctionalization reactions have found applications in the synthesis of a series of biologically active molecules. Significant challenges remain in intermolecular, three-component coupling reactions in achieving chemo-, regio-, and stereoselectivities with a broad scope of substrates, due to the multiple numbers of possible products. Consequently, rarely does organic synthesis leverage these reactions as intermediate steps.

Regioselectivity issues have limited most intermolecular reactions to electronically biased alkenes or ones with directing groups. Directing groups have been used to promote functionalization of unactivated alkenes and have permitted the control of regioselectivity, but the removal of directing groups is not always straightforward and could cause limitations in its application. Only a few numbers of difunctionalization reactions have been discovered for unactivated alkenes without directing groups, and their synthetic applications are yet to be explored. Chemo- and regioselectivities remain challenging for reductive dicarbofunctionalization with two electrophiles, due to their inherent similar reactivity. Recent mechanistic studies reveal that C(sp^2) and C(sp^3) electrophiles can be activated by different nickel species via two-electron and radical pathways, respectively.[62] This finding provides a basis for distinguishing the reactivity of different electrophiles and achieving chemoselectivity, and has already been practiced in reaction methodology.

Enantioselectivity has been achieved for intramolecular difunctionalization of alkenes tethered to C(sp^2) nucleophiles and electrophiles. Migratory insertion of the C(sp^2) moiety into the alkene is commonly proposed to be the enantio-determining step. In contrast, when the alkene substrate is tethered to a C(sp^3) coupling partner, enantioselectivity becomes difficult, due to the formation of radical intermediates that undergo cyclization, which does not involve a chiral catalyst.

It was only until recently that asymmetric intermolecular difunctionalization reactions have been discovered. They all invoke open-shell nickel intermediates and a radical pathway. Radical intermediates, formed from C(sp^3) electrophiles, present both challenges and opportunities for controlling stereoselectivity via new stereocontrol mechanisms. The coordination of a radical intermediate to the nickel center could serve as the enantio-determining step. With stabilized radicals, it has been proposed that the trapping of radical by the nickel center could be reversible.[71] This process can scramble the stereocenter, making the stereoselectivity of prior steps inconsequential. In this scenario, the enantio-determining step could thus be deferred to the following reductive elimination.

Challenges also remain in the scope of alkenes. Most difunctionalization reactions are performed on terminal alkenes. The reactivity of internal alkenes is intuitively lower, if alkene coordination to the metal center is required prior to insertion. This limitation could be overcome by invoking the addition of radicals to the alkene. Furthermore, the difficulty to control the regio- and stereo-selectivity may have also hampered the development of difunctionalization reactions of internal alkenes.

AUTHOR INFORMATION

Corresponding Author

Tianning Diao − *Department of Chemistry, New York University, New York, New York 10003, United States;* orcid.org/0000-0003-3916-8372; Email: diao@nyu.edu

Author

Xiaoxu Qi − *Department of Chemistry, New York University, New York, New York 10003, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.0c02115

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Support was provided by the National Institutes of Health, National Institute of General Medical Sciences (GM-127778) and the National Science Foundation (CHE-1654483). T.D. thanks the Alfred P. Sloan Foundation (FG-2018-10354) and the Camille and Henry Dreyfus Foundation (TC-19-019) for providing fellowships to partially support this work.

REFERENCES

(1) For selected reviews, see: (a) Jensen, K. H.; Sigman, M. S. Mechanistic Approaches to Palladium-Catalyzed Alkene Difunctionalization Reactions. *Org. Biomol. Chem.* **2008**, *6*, 4083−4088. (b) McDonald, R. I.; Liu, G.; Stahl, S. S. Palladium (II)-Catalyzed Alkene Functionalization via Nucleopalladation: Stereochemical Pathways and Enantioselective Catalytic Applications. *Chem. Rev.* **2011**, *111*, 2981−3019. (c) Egami, H.; Sodeoka, M. Trifluoromethylation of Alkenes with Concomitant Introduction of Additional Functional Groups. *Angew. Chem., Int. Ed.* **2014**, *53*, 8294−8308. (d) Merino, E.; Nevado, C. Addition of CF_3 Across Unsaturated Moieties: A Powerful Functionalization Tool. *Chem. Soc. Rev.* **2014**, *43*, 6598−6608. (e) Yin, G.; Mu, X.; Liu, G. Palladium (II)-Catalyzed

Oxidative Difunctionalization of Alkenes: Bond Forming at a High-Valent Palladium Center. *Acc. Chem. Res.* **2016**, *49*, 2413−2423. (f) Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefins. *Chem. Rev.* **2016**, *116*, 8912−9000. (g) Lan, X.-W.; Wang, N.-X.; Xing, Y. Recent Advances in Radical Difunctionalization of Simple Alkenes. *Eur. J. Org. Chem.* **2017**, *2017*, 5821−5851. (h) Dhungana, R. K.; KC, S.; Basnet, P.; Giri, R. Transition Metal-Catalyzed Dicarbofunctionalization of Unactivated Olefins. *Chem. Rec.* **2018**, *18*, 1314−1340. (i) KC, S.; Giri, R. Strategies toward Dicarbofunctionalization of Unactivated Olefins by Combined Heck Carbometalation and Cross-Coupling. *J. Org. Chem.* **2018**, *83*, 3013−3022. (j) Zhang, J.-S.; Liu, L.; Chen, T.; Han, L. B. Transition-Metal-Catalyzed Three-Component Difunctionalizations of Alkenes. *Chem. - Asian J.* **2018**, *13*, 2277−2291. (k) Lin, J.; Song, R.-J.; Hu, M.; Li, J.-H. Recent Advances in the Intermolecular Oxidative Difunctionalization of Alkenes. *Chem. Rec.* **2019**, *19*, 440−451. (l) Jiang, H.; Studer, A. Intermolecular Radical Carboamination of Alkenes. *Chem. Soc. Rev.* **2020**, *49*, 1790−1811. (m) Li, Y.; Wu, D.; Cheng, H.; Yin, G. Difunctionalization of Alkenes Involving Metal Migration. *Angew. Chem., Int. Ed.* **2020**, *59*, 7990−8003.

(2) (a) Beletskaya, I. P.; Cheprakov, A. V. The Heck Reaction as a Sharpening Stone of Palladium Catalysis. *Chem. Rev.* **2000**, *100* (8), 3009−3066. (b) Dounay, A. B.; Overman, L. E. The Asymmetric Intramolecular Heck Reaction in Natural Product Total Synthesis. *Chem. Rev.* **2003**, *103*, 2945−2963. (c) Mc Cartney, D.; Guiry, P. J. The Asymmetric Heck and Related Reactions. *Chem. Soc. Rev.* **2011**, *40*, 5122−5150.

(3) (a) Trost, B. M.; Van Vranken, D. L. Asymmetric Transition Metal-Catalyzed Allylic Alkylations. *Chem. Rev.* **1996**, *96*, 395−422. (b) Trost, B. M. Designing a Receptor for Molecular Recognition in a Catalytic Synthetic Reaction: Allylic Alkylation. *Acc. Chem. Res.* **1996**, *29*, 355−364. (c) Helmchen, G. Enantioselective Palladium-Catalyzed Allylic substitutions with Asymmetric chiral ligands. *J. Organomet. Chem.* **1999**, *576*, 203−214. (d) Trost, B. M.; Crawley, M. L. Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis. *Chem. Rev.* **2003**, *103*, 2921−2944. (e) Trost, B. M.; Machacek, M. R.; Aponick, A. Predicting the Stereochemistry of Diphenylphosphino Benzoic Acid (DPPBA)-Based Palladium-Catalyzed Asymmetric Allylic Alkylation Reactions: A Working Model. *Acc. Chem. Res.* **2006**, *39*, 747−760. (f) Lu, Z.; Ma, S. Metal-Catalyzed Enantioselective Allylation in Asymmetric Synthesis. *Angew. Chem., Int. Ed.* **2008**, *47*, 258−297. (g) Trost, B. M. Pd- and Mo-Catalyzed Asymmetric Allylic Alkylation. *Org. Process Res. Dev.* **2012**, *16*, 185−194.

(4) (a) Schils, D.; Stappers, F.; Solberghe, G.; van Heck, R.; Coppens, M.; Van den Heuvel, D.; Van der Donck, P.; Callewaert, T.; Meeussen, F.; De Bie, E.; Eersels, K.; Schouteden, E. Ligandless Heck Coupling between a Halogenated Aniline and Acrylonitrile Catalyzed by Pd/C: Development and Optimization of an Industrial-Scale Heck Process for the Production of a Pharmaceutical Intermediate. *Org. Process Res. Dev.* **2008**, *12*, 530−536. (b) *Applications of Transition Metal Catalysis in Drug Discovery and Development: An Industrial Perspective*; Crawley, M. L., Trost, B. M., Eds.; Wiley: Hoboken, NJ, 2012.

(5) Trost, B. M.; Malhotra, S.; Chan, W. Exercising Regiocontrol in Palladium-Catalyzed Asymmetric Prenylations and Geranylation: Unifying Strategy toward Flustramines A and B. *J. Am. Chem. Soc.* **2011**, *133*, 7328−7331.

(6) For selected examples: (a) Green, S. A.; Matos, J. L. M.; Yagi, A.; Shenvi, R. A. Branch-Selective Hydroarylation: Iodoarene Olefin Cross-Coupling. *J. Am. Chem. Soc.* **2016**, *138*, 12779−12782. (b) He, Y.; Cai, Y.; Zhu, S. Mild and Regioselective Benzylic C-H Functionalization: Ni-Catalyzed Reductive Arylation of Remote and Proximal Olefins. *J. Am. Chem. Soc.* **2017**, *139*, 1061−1064. (c) Chen, F.; Chen, K.; Zhang, Y.; He, Y.; Wang, Y.-M.; Zhu, S. Remote Migratory Cross-Electrophile Coupling and Olefin Hydroarylation Reactions Enabled by in Situ Generation of Ni H. *J. Am. Chem. Soc.* **2017**, *139*, 13929−13935. (d) Xiao, L.-J.; Chen, L.; Feng, W.-M.; Li, M.-L.; Xie, J.-H.; Zhou, Q.-L. Nickel (0)-catalyzed Hydroarylation of Styrenes and 1,3-Dienes with Organoboron Compounds. *Angew. Chem., Int. Ed.* **2018**, *57*, 461−464. (e) Lv, H.; Xiao, L.-J.; Zhao, D.; Zhou, Q.-L. Nickel (0)-Catalyzed Linear-Selective Hydroarylation of Unactivated Alkenes and Styrenes with Aryl Boronic Acids. *Chem. Sci.* **2018**, *9*, 6839−6843. (f) Shevick, S. L.; Obradors, C.; Shenvi, R. A. Mechanistic Interrogation of Co/Ni-Dual Catalyzed Hydroarylation. *J. Am. Chem. Soc.* **2018**, *140*, 12056−12068. (g) Green, S. A.; Vásquez-Céspedes, S.; Shenvi, R. A. Iron-Nickel Dual-Catalysis: A New Engine for Olefin Functionalization and the Formation of Quaternary Centers. *J. Am. Chem. Soc.* **2018**, *140*, 11317−11324. (h) Wang, Z.-Y.; Wan, J.-H.; Wang, G.-Y.; Wang, R.; Jin, R.-X.; Lan, Q.; Wang, X.-S. Terminal C(sp^3)-H alkylation of internal alkenes via Ni/H-catalyzed isomerization. *Tetrahedron Lett.* **2018**, *59*, 2302−2305. (i) Wang, Z.; Yin, H.; Fu, G. C. Catalytic Enantioconvergent Coupling of Secondary and Tertiary Electrophiles with Olefins. *Nature* **2018**, *563*, 379−383. (j) Chen, Y.-G.; Shuai, B.; Xu, X.-T.; Li, Y.-Q.; Yang, Q.-L.; Qiu, H.; Zhang, K.; Fang, P.; Mei, T.-S. Nickel-catalyzed Enantioselective Hydroarylation and Hydroalkenylation of Styrenes. *J. Am. Chem. Soc.* **2019**, *141*, 3395−3399. (k) Nguyen, J.; Chong, A.; Lalic, G. Nickel-catalyzed anti-Markovnikov Hydroarylation of Alkenes. *Chem. Sci.* **2019**, *10*, 3231−3236. (l) Bera, S.; Hu, X. Nickel-Catalyzed Regioselective Hydroalkylation and Hydroarylation of Alkenyl Boronic Esters. *Angew. Chem., Int. Ed.* **2019**, *58*, 13854−13859. (m) Zhang, Y.; Han, B.; Zhu, S. Rapid Access to Highly Functionalized Alkyl Boronates by NiH-Catalyzed Remote Hydroarylation of Boron-Containing Alkenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 13860−13864. (n) Green, S. A.; Huffman, T. R.; McCourt, R.; Puyl, V.; Shenvi, R. A. Hydroalkylation of Olefins to Form Quaternary Carbons. *J. Am. Chem. Soc.* **2019**, *141*, 7709−7714. (o) Sun, S.-Z.; Romano, C.; Martin, R. Site-Selective Catalytic Deaminative Alkylation of Unactivated Olefins. *J. Am. Chem. Soc.* **2019**, *141*, 16197−16201. (p) Diccianni, J. B.; Chin, M.; Diao, T. Synthesis of Lactate Derivatives via Reductive Radical Addition to α-Oxyacrylates. *Tetrahedron* **2019**, *75*, 4180−4185. (q) He, S.-J.; Wang, J.-W.; Li, Y.; Xu, Z.-Y.; Wang, X.-X.; Lu, X.; Fu, Y. Nickel-Catalyzed Enantioconvergent Reductive Hydroalkylation of Olefins with α-Heteroatom Phosphorus or Sulfur Alkyl Electrophiles. *J. Am. Chem. Soc.* **2020**, *142*, 214−221. (r) Saper, N. I.; Ohgi, A.; Small, D.; Semba, K.; Nakao, Y.; Hartwig, J. F. Nickel-Catalysed anti-Markovnikov Hydroarylation of Unactivated Alkenes with Unactivated Arenes Facilitated by Non-covalent Interactions. *Nat. Chem.* **2020**, *12*, 276−283.

(7) (a) Ping, Y.; Kong, W. Ni-Catalyzed Reductive Difunctionalization of Alkenes. *Synthesis* **2020**, *52*, 979−992. (b) Tu, H.-Y.; Zhu, S.; Qing, F.-L.; Chu, L. Recent Advances in Nickel-Catalyzed Three-Component Difunctionalization of Unactivated Alkenes. *Synthesis* **2020**, *52*, 1346−1356. (c) Derosa, J.; Apolinar, O.; Kang, T.; Tran, V.; Engle, K. Recent Developments in Nickel-Catalyzed Intermolecular Dicarbofunctionalization of Alkenes. *Chem. Sci.* **2020**, *11*, 4287−4296.

(8) (a) Coombs, J. R.; Morken, J. P. Catalytic Enantioselective Functionalization of Unactivated Terminal Alkenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 2636−2649. (b) Chen, J.; Lu, Z. Asymmetric Hydrofunctionalization of Minimally Functionalized Alkenes via Earth Abundant Transition Metal Catalysis. *Org. Chem. Front.* **2018**, *5*, 260−272. (c) Wang, Z.-X.; Bai, X.-Y.; Li, B.-J. Metal-Catalyzed Substrate-Directed Enantioselective Functionalization of Unactivated Alkenes. *Chin. J. Chem.* **2019**, *37*, 1174−1180. (e) Wang, F.; Chen, P.; Liu, G. Copper-Catalyzed Radical Relay for Asymmetric Radical Transformations. *Acc. Chem. Res.* **2018**, *51*, 2036−2046. (f) Li, Z.-L.; Fang, G.-C.; Gu, Q.-S.; Liu, X.-Y. Recent Advances in Copper-Catalysed Radical-involved Asymmetric 1,2-difunctionalization of Alkenes. *Chem. Soc. Rev.* **2020**, *49*, 32−48.

(9) Gaydou, M.; Moragas, T.; Julia-Hernandez, F.; Martin, R. Site-Selective Catalytic Carboxylation of Unsaturated Hydrocarbons with CO2 and Water. *J. Am. Chem. Soc.* **2017**, *139*, 12161−12164.

(10) KC, S.; Dhungana, R. K.; Aryal, V.; Giri, R. Concise Synthesis of a Potential 5-Lipoxygenase Activating (FLAP) Inhibitor and its

https://dx.doi.org/10.1021/acscatal.0c02115
ACS Catal. 2020, 10, 8542−8556

Analogs Through Late-Stage Dicarbofunctionalization. *Org. Process Res. Dev.* **2019**, *23*, 1686−1694.
(11) (a) Urkalan, K. B.; Sigman, M. S. Palladium-Catalyzed Oxidative Intermolecular Difunctionalization of Terminal Alkenes with Organostannanes and Molecular Oxygen. *Angew. Chem., Int. Ed.* **2009**, *48*, 3146−3149. (b) Trejos, A.; Fardost, A.; Yahiaoui, S.; Larhed, M. Palladium(II)-Catalyzed Coupling Reactions with a Chelating Vinyl Ether and Arylboronic Acids: a New Heck/Suzuki Domino Diarylation Reaction. *Chem. Commun.* **2009**, 7587−7589. (c) Yahiaoui, S.; Fardost, A.; Trejos, A.; Larhed, M. Chelation-Mediated Palladium (II)-Catalyzed Domino Heck-Mizoroki/Suzuki-Miyaura Reactions Using Arylboronic Acids: Increasing Scope and Mechanistic Understanding. *J. Org. Chem.* **2011**, *76*, 2433−2438. (d) Kusunuru, A. K.; Jaladanki, C. K.; Tatina, M. B.; Bharatam, P. V.; Mukherjee, D. TEMPO-Promoted Domino Heck-Suzuki Arylation: Diastereoselective *Cis*-Diarylation of Glycals and Pseudoglycals. *Org. Lett.* **2015**, *17*, 3742−3745.
(12) (a) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. Recent Advances in Homogeneous Nickel Catalysis. *Nature* **2014**, *509*, 299−309. (b) Fu, G. C. Transition-Metal Catalysis of Nucleophilic Substitution Reactions: A Radical Alternative to S_N1 and S_N2 Processes. *ACS Cent. Sci.* **2017**, *3*, 692−700. (c) Diccianni, J.; Diao, T. Mechanisms of Nickel-Catalyzed Cross Coupling Reactions. *Trends Chem.* **2019**, *1*, 830−844. (d) Diccianni, J.; Lin, Q.; Diao, T. Mechanisms of Nickel-Catalyzed Coupling Reactions and Applications in Alkene Functionalization. *Acc. Chem. Res.* **2020**, *53*, 906−919.
(13) (a) Leatherman, M. D.; Svejda, S. A.; Johnson, L. K.; Brookhart, M. Mechanistic Studies of Nickel(II) Alkyl Agostic Cations and Alkyl Ethylene Complexes: Investigations of Chain Propagation and Isomerization in (α-diimine)Ni(II)-Catalyzed Ethylene Polymerization. *J. Am. Chem. Soc.* **2003**, *125*, 3068−3081. (b) Xu, H.; White, P. B.; Hu, C.; Diao, T. Structure and Isotope Effects of the β-H Agostic (α-Diimine)Nickel Cation as a Polymerization Intermediate. *Angew. Chem., Int. Ed.* **2017**, *56*, 1535−1538. (c) Xu, H.; Hu, C. T.; Wang, X.; Diao, T. Structural Characterization of β-Agostic Bonds in Pd-Catalyzed Polymerization. *Organometallics* **2017**, *36*, 4099−4102.
(14) (a) Tsou, T. T.; Kochi, J. K. Mechanism of Oxidative Addition. Reaction of Nickel (0) Complexes with Aromatic Halides. *J. Am. Chem. Soc.* **1979**, *101*, 6319−6332. (b) Diccianni, J. B.; Katigbak, J.; Hu, C.; Diao, T. Mechanistic Characterization of (Xantphos)Ni(I)-Mediated Alkyl Bromide Activation: Oxidative Addition, Electron Transfer, or Halogen-Atom Abstraction. *J. Am. Chem. Soc.* **2019**, *141*, 1788−1796.
(15) Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. Nickel-Catalyzed Cross-Coupling of Photoredox-Generated Radicals: Uncovering a General Manifold for Stereoconvergence in Nickel-Catalyzed Cross-Couplings. *J. Am. Chem. Soc.* **2015**, *137*, 4896−4899.
(16) Vaupel, A.; Knochel, P. Stereoselective Synthesis of Heterocyclic Zinc Reagents via a Nickel-Catalyzed Radical Cyclization. *J. Org. Chem.* **1996**, *61*, 5743−5753.
(17) Phapale, V. B.; Buñuel, E.; García-Iglesias, M.; Cárdenas, D. J. Ni-catalyzed Cascade Formation of $C(sp^3)$-$C(sp^3)$ Bonds by Cyclization and Cross-coupling Reactions of Iodoalkanes with Alkyl Zinc Halides. *Angew. Chem., Int. Ed.* **2007**, *46*, 8790−8795.
(18) Jung, M. E.; Piizi, G. *gem*-Disubstituent Effect: Theoretical Basis and Synthetic Applications. *Chem. Rev.* **2005**, *105*, 1735−1766.
(19) Guisán-Ceinos, M.; Soler-Yanes, R.; Collado-Sanz, D.; Phapale, V. B.; Buñuel, E.; Cárdenas, D. J. Ni-Catalyzed Cascade Cyclization-Kumada Alkyl-Alkyl Cross-Coupling. *Chem. - Eur. J.* **2013**, *19*, 8405−8410.
(20) Kc, S.; Basnet, P.; Thapa, S.; Shrestha, B.; Giri, R. Ni-Catalyzed Regioselective Dicarbofunctionalization of Unactivated Olefins by Tandem Cyclization/Cross-Coupling and Application to the Concise Synthesis of Lignan Natural Products. *J. Org. Chem.* **2018**, *83*, 2920−2936.
(21) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R.; Konovalova, J. T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. Ligand Redox Effects in the Synthesis, Electronic Structure, and Reactivity of an Alkyl-Alkyl Cross-Coupling Catalyst. *J. Am. Chem. Soc.* **2006**, *128*, 13175−13183.
(22) Li, Y.; Wang, K.; Ping, Y.; Wang, Y.; Kong, W. Nickel-Catalyzed Domino Heck Cyclization/Suzuki Coupling for the Synthesis of 3,3-Disubstituted Oxindoles. *Org. Lett.* **2018**, *20*, 921−924.
(23) Walker, J. A., Jr.; Vickerman, K. L.; Humke, J. N.; Stanley, L. M. Ni-Catalyzed Alkene Carboacylation via Amide C-N Bond Activation. *J. Am. Chem. Soc.* **2017**, *139*, 10228−10231.
(24) Zheng, Y.-L.; Newman, S. Nickel-Catalyzed Domino Heck-Type Reactions Using Methyl Esters as Cross-Coupling Electrophiles. *Angew. Chem., Int. Ed.* **2019**, *58*, 18159−18164.
(25) Huang, D.; Olivieri, D.; Sun, Y.; Zhang, P.; Newhouse, T. Nickel-Catalyzed Difunctionalization of Unactivated Alkenes Initiated by Unstabilized Enolates. *J. Am. Chem. Soc.* **2019**, *141*, 16249−16254.
(26) Cong, H.; Fu, G. C. Catalytic Enantioselective Cyclization/cross-coupling with Alkyl Electrophiles. *J. Am. Chem. Soc.* **2014**, *136*, 3788−3791.
(27) Fan, P.; Lan, Y.; Zhang, C.; Wang, C. Nickel/Photo-Cocatalyzed Asymmetric Acyl-Carbamoylation of Alkenes. *J. Am. Chem. Soc.* **2020**, *142*, 2180−2186.
(28) Chierchia, M.; Xu, P.; Lovinger, G. J.; Morken, J. P. Enantioselective Radical Addition/Cross-Coupling of Organozinc Reagents, Alkyl Iodides, and Alkenyl Boron Reagents. *Angew. Chem., Int. Ed.* **2019**, *58*, 14245−14249.
(29) Early example, see: Taniguchi, T.; Ogasawara, K. Nickel-catalyzed generation of 2-methylhex-5-enyl ethers from allyl ethers with trimethylaluminium. *Chem. Commun.* **1998**, 1531−1532.
(30) Derosa, J.; Tran, V. T.; Boulous, M. N.; Chen, J. S.; Engle, K. M. Nickel-Catalyzed β,γ-Dicarbofunctionalization of Alkenyl Carbonyl Compounds via Conjunctive Cross-Coupling. *J. Am. Chem. Soc.* **2017**, *139*, 10657−10660.
(31) Derosa, J.; van der Puyl, V. A.; Tran, V. T.; Liu, M.; Engle, K. Directed Nickel-Catalyzed 1,2-Dialkylation of Alkenyl Carbonyl Compounds. *Chem. Sci.* **2018**, *9*, 5278−5283.
(32) Shrestha, B.; Basnet, P.; Dhungana, R. K.; Kc, S.; Thapa, S.; Sears, J. M.; Giri, R. Ni-Catalyzed Regioselective 1,2-Dicarbofunctionalization of Olefins by Intercepting Heck Intermediates as Imine-Stabilized Transient Metallacycles. *J. Am. Chem. Soc.* **2017**, *139*, 10653−10656. (b) Niroula, D.; Sapkota, R.; Dhungana, R. K.; Shrestha, B.; Giri, R. An Expedient Route to 9-Arylmethylanthracene Derivatives via Tandem Ni-Catalyzed Alkene Dicarbofunctionalization and Acid-Promoted Cyclization-Aromatization. *Isr. J. Chem.* **2020**, *60*, 424−428.
(33) Basnet, P.; Kc, S.; Dhungana, R. K.; Shrestha, B.; Boyle, T. J.; Giri, R. Synergistic Bimetallic Ni/Ag and Ni/Cu Catalysis for Regioselective γ, δ -Diarylation of Alkenyl Ketimines: Addressing β-H Elimination by in Situ Generation of Cationic Ni(II) Catalysts. *J. Am. Chem. Soc.* **2018**, *140*, 15586−15590.
(34) Thapa, S.; Dhungana, R. K.; Magar, R. T.; Shrestha, B.; KC, S.; Giri, R. Ni-Catalysed Regioselective 1,2-Diarylation of Unactivated Olefins by Stabilizing Heck Intermediates as Pyridylsilyl-Coordinated Transient Metallacycles. *Chem. Sci.* **2018**, *9*, 904−909.
(35) (a) Gu, J.-W.; Min, Q.-Q.; Yu, L.-C.; Zhang, X. Tandem Difluoroalkylation-Arylation of Enamides Catalyzed by Nickel. *Angew. Chem., Int. Ed.* **2016**, *55*, 12270−12274. (b) Xu, C.; Yang, Z.-F.; An, L.; Zhang, X. Nickel-Catalyzed Difluoroalkylation-Alkylation of Enamides. *ACS Catal.* **2019**, *9*, 8224−8229.
(36) Derosa, J.; Kleinmans, R.; Tran, V. T.; Karunananda, M. K.; Wisniewski, S. R.; Eastgate, M. D.; Engle, K. M. Nickel-Catalyzed 1,2-Diarylation of Simple Alkenyl Amides. *J. Am. Chem. Soc.* **2018**, *140*, 17878−17883.
(37) Li, W.; Boon, J. K.; Zhao, Y. Nickel-catalyzed Difunctionalization of Allyl Moieties Using Organoboronic Acids and Halides with Divergent Regioselectivities. *Chem. Sci.* **2018**, *9*, 600−607.
(38) Derosa, J.; Kang, T.; Tran, V. T.; Wisniewski, S. R.; Karunananda, M. K.; Jankins, T. C.; Xu, K. L.; Engle, K. M. Nickel-Catalyzed 1,2-Diarylation of Alkenyl Carboxylates: A Gateway to

https://dx.doi.org/10.1021/acscatal.0c02115
ACS Catal. 2020, 10, 8542−8556

1,2,3-Trifunctionalized Building Blocks. *Angew. Chem., Int. Ed.* **2020**, *59*, 1201−1205.
(39) Tran, V. T.; Li, Z.; Gallagher, T. J.; Derosa, J.; Liu, P.; Engle, K. M. Integrating Allyl Electrophiles into Nickel-Catalyzed Conjunctive Cross-Coupling. *Angew. Chem., Int. Ed.* **2020**, *59*, 7029−7034.
(40) Gao, P.; Chen, L. A.; Brown, M. K. Nickel-Catalyzed Stereoselective Diarylation of Alkenylarenes. *J. Am. Chem. Soc.* **2018**, *140*, 10653−10657.
(41) KC, S.; Dhungana, R. K.; Shrestha, B.; Thapa, S.; Khanal, N.; Basnet, P.; Lebrun, R. W.; Giri, R. Ni-Catalyzed Regioselective Alkylarylation of Vinylarenes via C(sp3)-C(sp3)/C(sp3)-C(sp2) Bond Formation and Mechanistic Studies. *J. Am. Chem. Soc.* **2018**, *140*, 9801−9805.
(42) KC, S.; Dhungana, R. K.; Khanal, N.; Giri, R. Nickel-Catalyzed a-Carbonylalkylarylation of Vinylarenes: Expedient Access to γ,γ-Diarylcarbonyl and Aryltetralone Derivatives. *Angew. Chem., Int. Ed.* **2020**, *59*, 8047−8051.
(43) Qin, T.; Cornella, J.; Li, C.; Malins, L. R.; Edwards, J. T.; Kawamura, S.; Maxwell, B. D.; Eastgate, M. D.; Baran, P. S. A General Alkyl-Alkyl Cross-Coupling Enabled by Redox-active Esters and Alkylzinc Reagents. *Science* **2016**, *352*, 801−805.
(44) Guo, L.; Tu, H. Y.; Zhu, S.; Chu, L. Selective, Intermolecular Alkylarylation of Alkenes via Photoredox/Nickel Dual Catalysis. *Org. Lett.* **2019**, *21*, 4771−4776.
(45) García-Domínguez, A.; Mondal, R.; Nevado, C. Dual Photoredox/Nickel-Catalyzed Three-Component Carbofunctionalization of Alkenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 12286−12290.
(46) Kadam, A. A.; Metz, T. L.; Qian, Y.; Stanley, L. M. Ni-Catalyzed Three-Component Alkene Carboacylation Initiated by Amide C−N Bond Activation. *ACS Catal.* **2019**, *9*, 5651−5656.
(47) Lovinger, G. J.; Morken, J. P. Recent Advances in Radical Addition to Alkenylboron Compounds. *Eur. J. Org. Chem.* **2020**, *2020*, 2362−2368.
(48) Campbell, M. W.; Compton, J. S.; Kelly, C. B.; Molander, G. A. Three-Component Olefin Dicarbofunctionalization Enabled by Nickel/Photoredox Dual Catalysis. *J. Am. Chem. Soc.* **2019**, *141*, 20069−20078.
(49) Mega, R. S.; Duong, V. K.; Noble, A.; Aggarwal, V. K. Decarboxylative Conjunctive Cross-coupling of Vinyl Boronic Esters using Metallaphotoredox Catalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 4375−4379.
(50) Sun, S.-Z.; Duan, Y.; Mega, R.; Somerville, R.; Martin, R. Site-Selective 1,2-Dicarbofunctionalization of Vinyl Boronates through Dual Catalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 4370−4374.
(51) In ref 35a, Zhang and co-workers describe a preliminary result of 1,2-difunctionalization of a vinylamide to give 18% ee using a chiral-diamine ligand.
(52) (a) Knappke, C. E. I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; Jacobi von Wangelin, A. Reductive Cross-Coupling Reactions between Two Electrophiles. *Chem. - Eur. J.* **2014**, *20*, 6828−6842. (b) Everson, D. A.; Weix, D. J. Cross-Electrophile Coupling: Principles of Reactivity and Selectivity. *J. Org. Chem.* **2014**, *79*, 4793−4798. (c) Weix, D. J. Methods and Mechanisms for Cross-Electrophile Coupling of $C(sp^2)$ Halides with Alkyl Electrophiles. *Acc. Chem. Res.* **2015**, *48*, 1767−1775. (d) Gu, J.; Wang, X.; Xue, W.; Gong, H. Nickel-Catalyzed Reductive Coupling of Alkyl Halides with Other Eelectrophiles: Concept and Mechanistic Considerations. *Org. Chem. Front.* **2015**, *2*, 1411−1421. (e) Wang, X.; Dai, Y.; Gong, H. *Nickel-Catalyzed Reductive Couplings. In Ni- and Fe-Based Cross-Coupling Reactions*; Correa, A., Ed.; Topics in Current Chemistry Collections; Springer International Publishing: Cham, Switzerland, 2017; pp 61−89.
(53) Yan, C.-S.; Peng, Y.; Xu, X.-B.; Wang, Y.-W. Nickel-Mediated Inter- and Intramolecular Reductive Cross-Coupling of Unactivated Alkyl bromides and Aryl iodides at Room Temperature. *Chem. - Eur. J.* **2012**, *18*, 6039−6048.
(54) (a) Beckwith, A. L. J.; Schiesser, C. H. Regio-and Stereo-Selectivity of Alkenyl Radical Ring Closure: A Theoretical Study. *Tetrahedron* **1985**, *41*, 3925−3941. (b) Spellmeyer, D. C.; Houk, K. N. Force-Field Model for Intramolecular Radical Additions. *J. Org. Chem.* **1987**, *52*, 959−974.
(55) Peng, Y.; Xu, X.-B.; Xiao, J.; Wang, Y.-W. Nickel-Mediated Stereocontrolled Synthesis of Spiroketals *via* Tandem Cyclization-Coupling of β-Bromo Ketals and Aryl Iodides. *Chem. Commun.* **2014**, *50*, 472−474.
(56) Peng, Y.; Xiao, J.; Xu, X. B.; Duan, S. M.; Ren, L.; Shao, Y. L.; Wang, Y. W. Stereospecific Synthesis of Tetrahydronaphtho[2,3-b]furans Enabled by a Nickel-Promoted Tandem Reductive Cyclization. *Org. Lett.* **2016**, *18*, 5170−5173.
(57) (a) Xiao, J.; Cong, X.-W.; Yang, G. Z.; Wang, Y.-W.; Peng, Y. Stereoselective Synthesis of a Podophyllum Lignan Core by Intramolecular Reductive Nickel-Catalysis. *Chem. Commun.* **2018**, *54*, 2040−2043. (b) Xiao, J.; Cong, X.-W.; Yang, G. Z.; Wang, Y.-W.; Peng, Y. Divergent Asymmetric Syntheses of Podophyllotoxin and Related Family Members via Stereoselective Reductive Ni-Catalysis. *Org. Lett.* **2018**, *20*, 1651−1654.
(58) Jin, Y.; Wang, C. Ni-Catalysed Reductive Arylalkylation of Unactivated Alkenes. *Chem. Sci.* **2019**, *10*, 1780−1785.
(59) Jin, Y.; Yang, H.; Wang, C. Nickel-Catalyzed Reductive Arylalkylation via a Migratory Insertion/Decarboxylative Cross-Coupling Cascade. *Org. Lett.* **2019**, *21*, 7602−7608.
(60) Kuang, Y.; Wang, X.; Anthony, D.; Diao, T. Ni-Catalyzed Two-Component Reductive Dicarbofunctionalization of Alkenes via Radical Cyclization. *Chem. Commun.* **2018**, *54*, 2558−2561.
(61) Biswas, S.; Weix, D. J. Mechanism and Selectivity in Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2013**, *135*, 16192−16197.
(62) Lin, Q.; Diao, T. Mechanism of Ni-Catalyzed Reductive 1,2-Dicarbofunctionalization of Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 17937−17948.
(63) (a) Jin, Y.; Wang, C. Ni-Catalyzed Asymmetric Reductive Arylalkylation of Unactivated Alkenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 6722−6726. (b) Jin, Y.; Yang, H.; Wang, C. Ni-Catalyzed Asymmetric Reductive Arylbenzylation of Unactivated Alkenes. *Org. Lett.* **2020**, *22*, 2724−2729.
(64) (a) Tian, Z.-X.; Qiao, J.-B.; Xu, G.-L.; Pang, X.; Qi, L.; Ma, W.-Y.; Zhao, Z.-Z.; Duan, J.; Du, Y.-F.; Su, P.; Liu, X.-Y.; Shu, X.-Z. Highly Enantioselective Cross-Electrophile Aryl-Alkenylation of Unactivated Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 7637−7643. (b) Li, Y.; Ding, Z.; Lei, A.; Kong, W. Ni-Catalyzed Enantioselective Reductive Aryl-Alkenylation of Alkenes: Application to the Synthesis of (+)-Physovenine and (+)-Physostigmine. *Org. Chem. Front.* **2019**, *6*, 3305−3309. (c) Ma, T.; Chen, Y.; Li, Y.; Ping, Y.; Kong, W. Nickel-Catalyzed Enantioselective Reductive Aryl Fluoroalkenylation of Alkenes. *ACS Catal.* **2019**, *9*, 9127−9133.
(65) Wang, K.; Ding, Z.; Zhou, Z.; Kong, W. Ni-Catalyzed Enantioselective Reductive Diarylation of Activated Alkenes by Domino Cyclization/Cross-Coupling. *J. Am. Chem. Soc.* **2018**, *140*, 12364−12368.
(66) Lan, Y.; Wang, C. Nickel-Catalyzed Enantioselective Reductive Carbo-Acylation of Alkenes. *Commun. Chem.* **2020**, *3*, 45.
(67) Garcia-Dominguez, A.; Li, Z.; Nevado, C. Nickel-Catalyzed Reductive Dicarbofunctionalization of Alkenes. *J. Am. Chem. Soc.* **2017**, *139*, 6835−6838.
(68) Shu, W.; García-Domínguez, A.; Quirós, M. T.; Mondal, R.; Cárdenas, D. H. J.; Nevado, C. Ni-Catalyzed Reductive Dicarbofunctionalization of Nonactivated Alkenes: Scope and Mechanistic Insights. *J. Am. Chem. Soc.* **2019**, *141*, 13812−13821.
(69) Zhao, X.; Tu, H. Y.; Guo, L.; Zhu, S.; Qing, F.-L.; Chu, L. Intermolecular Selective Carboacylation of Alkenes via Nickel-Catalyzed Reductive Radical Relay. *Nat. Commun.* **2018**, *9*, 3488.
(70) Yang, T.; Chen, X.; Rao, W.; Koh, M. Broadly Applicable Directed Catalytic Reductive Difunctionalization of Alkenyl Carbonyl Compounds. *Chem.* **2020**, *6*, 738−751.
(71) Anthony, D.; Lin, Q.; Baudet, J.; Diao, T. Nickel-Catalyzed Asymmetric Reductive Diarylation of Vinylarenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 3198−3202.

https://dx.doi.org/10.1021/acscatal.0c02115
ACS Catal. 2020, 10, 8542−8556

(72) Tu, H.-Y.; Wang, F.; Huo, L.; Li, Y.; Zhu, S.; Zhao, X.; Li, H.; Qing, F.-L.; Chu, L. Enantioselective Three-Component Fluoroalkylarylation of Unactivated Olefins through Nickel- Catalyzed Cross-Electrophile Coupling. *J. Am. Chem. Soc.* **2020**, *142* (21), 9604−9611.
(73) Wei, X.; Shu, W.; García-Domínguez, A.; Merino, E.; Nevado, C. *J. Am. Chem. Soc.* **2020**, in press. DOI: 10.1021/jacs.0c05254.

https://dx.doi.org/10.1021/acscatal.0c02115
ACS Catal. 2020, 10, 8542−8556