The Spectacular Resurgence of Electrochemical Redox Reactions in Organic Synthesis

Carbon–Carbon π Bonds as Conjunctive Reagents in Cross-Coupling
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ABOUT OUR COVER

Ginevra de’ Benci (oil on panel, 38.1 × 37 cm, ca. 1474/1478) is one of Leonardo da Vinci’s (1452–1519) earliest works. Raised in an affluent family, he received a conventional education and apprenticed for several years as a painter and sculptor with Andrea del Verrocchio in Florence. Blessed with an extraordinary intellect and love of learning, Leonardo also immersed himself throughout his life in the study of what we call today anatomy, engineering, architecture, and mechanics, and left a legacy of important works in various fields of knowledge. As an artist, he worked for various wealthy, aristocratic, and royal patrons in Florence, Milan, Rome, and France. While da Vinci created only a small number of paintings, his compositions have strongly influenced later generations of artists, and a number of his paintings are now considered masterpieces of all time.

Ginevra de’ Benci is the obverse* side of a two-sided panel that was commissioned, as customary, on the occasion of the subject’s engagement or marriage. This portrait of the beautiful, but solemn and detached, 16-year-old is so flawlessly executed and lifelike that one is forgiven for believing one is in the presence of Ginevra herself. Leonardo’s strong interest in, and keen sense of observation of, the natural world as well as his break with tradition by placing Ginevra in a three-quarter pose in an outdoor, “natural”, setting is an early indication of how his realistic and expressive scenes would influence and change fine art in the Renaissance.

Purchased for the National Gallery of Art, Washington, DC, through the Ailsa Mellon Bruce Fund.

* So, what is on the reverse side of the Ginevra de’ Benci panel? To find out, visit SigmaAldrich.com/acta511

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Keywords. organic electrolysynthesis; radicals; anodic oxidation; cathodic reduction; paired electrosynthesis.

Abstract. Electrochemistry has had a profound impact on green chemistry and in applications such as energy conversion and storage, electroplating, water treatment, and environmental monitoring, and it has also been embraced by various industries. It is therefore quite surprising that electrochemistry has seldom been used by synthetic organic chemists. This could be partly attributed to the misconception that the electron as a reagent cannot be tamed easily. In recent years, the application of electrochemistry to the synthesis of fine chemicals has had a resurgence, and many elegant solutions based on electrochemistry have been devised to address synthetic challenges with easy-to-use experimental setups.

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1. Introduction
Chemistry is all about electrons. This general statement, though simple, is nonetheless true. In organic chemistry, many transformations are redox reactions, involving electrons being added to, or removed from, the molecule of interest. With this in mind, electrochemistry should be a natural choice for synthetic organic chemists. Indeed, what better reagent can there be for electron-transfer reactions than the electron itself? It is the cheapest possible reactant, its reducing power can easily be tuned by adjusting the potential at the electrode, and it does not generate any byproduct.

One of the best-known and useful organic electrosynthesis—the Kolbe reaction, in which a carboxylic acid is electrochemically decarboxylated and the resulting radical dimerizes—dates back to 1848. Since then, many industrial processes that use organic electrochemistry have been developed, and huge tonnages of commodity organic chemicals are produced electrochemically. In contrast and despite its success at the industrial scale, electrosynthesis has been more often than not one of the last options to use to perform a chemical transformation in the organic chemistry laboratory. Many reasons can be invoked to explain this reluctance, from lack of academic training, to wariness towards an almost magical reagent which cannot be weighed, to the reaction flask used. However, attitudes are rapidly evolving, and organic electrosynthesis is now back in the spotlight thanks to the “naturally green” electron, the easy interfacing with flow chemistry, and the direct scalability of electrochemical processes. This renewed interest is demonstrated by the number of recent review articles that have been published on the subject. This review is not a comprehensive treatment of the topic, and is intended only to highlight recent, salient, and accessible range due to degradative electrolysis of the solvent or electrolyte. Side reactions or electrode passivation, or is even beyond the potential required is too high in absolute value, giving rise to side reactions or electrode passivation, or is even beyond the accessible range due to degradative electrolysis of the solvent or electrolyte. Two strategies can then be envisioned to overcome these limitations. The first is to switch from direct electrolysis to indirect electrolysis using a mediator, which is a substance that is activated electrochemically at the electrode, giving a transient species that then reacts with the substrate in solution. The potential required for the activation of the mediator should be lower than that of the substrate. In some cases, the reaction between the activated species and the substrate regenerates the mediator, which can then be used in catalytic amounts. The second strategy is to use a substrate containing a functional group that can enable the desired electron transfer to take place at a lower potential and in a more selective fashion. Such a functional group is called electroauxiliary. Both approaches will be reported on in this article.

2. Basic Principles
2.1. The Electrochemical Cell and Cathode and Anode Reactions
In the basic electrochemical cell, electron transfer takes place at the surface of the electrodes, and an electrolyte is required to ensure conduction of the current from one electrode to the other; in other words, to close the circuit. Typically, the electrolyte is the reaction solvent to which a salt has been added. However, when ionic liquids are used, their reducing power can easily be tuned by adjusting the potential at the electrode, and it does not generate any byproduct.

In the simplest cases, the desired reaction can be directly realized by electron transfer between the electrode and the substrate. This is referred to as direct electrolysis. In most cases, however, the desired transformation cannot be achieved in this way, notably because the oxidation or reduction potential required is too high in absolute value, giving rise to side reactions or electrode passivation, or is even beyond the accessible range due to degradative electrolysis of the solvent or electrolyte. Two strategies can then be envisioned to overcome these limitations. The first is to switch from direct electrolysis to indirect electrolysis using a mediator, which is a substance that is activated electrochemically at the electrode, giving a transient species that then reacts with the substrate in solution. The potential required for the activation of the mediator should be lower than that of the substrate. In some cases, the reaction between the activated species and the substrate regenerates the mediator, which can then be used in catalytic amounts. The second strategy is to use a substrate containing a functional group that can enable the desired electron transfer to take place at a lower potential and in a more selective fashion. Such a functional group is called electroauxiliary. Both approaches will be reported on in this article.

2.2. Mediators and Electroauxiliaries
In the simplest cases, the desired reaction can be directly realized by electron transfer between the electrode and the substrate. This is referred to as direct electrolysis. In most cases, however, the desired transformation cannot be achieved in this way, notably because the oxidation or reduction potential required is too high in absolute value, giving rise to side reactions or electrode passivation, or is even beyond the accessible range due to degradative electrolysis of the solvent or electrolyte. Two strategies can then be envisioned to overcome these limitations. The first is to switch from direct electrolysis to indirect electrolysis using a mediator, which is a substance that is activated electrochemically at the electrode, giving a transient species that then reacts with the substrate in solution. The potential required for the activation of the mediator should be lower than that of the substrate. In some cases, the reaction between the activated species and the substrate regenerates the mediator, which can then be used in catalytic amounts. The second strategy is to use a substrate containing a functional group that can enable the desired electron transfer to take place at a lower potential and in a more selective fashion. Such a functional group is called electroauxiliary. Both approaches will be reported on in this article.
adoption is hampered by its inherent practical complexity. Moreover, electrochemical cells have been designed to intensify electrosynthesis processes, but the presentation of this technology is outside the scope of this review. An interesting electrochemical oxidation of N-isobutyl-(2F,6Z)-dodecadienamides, which showed that not all reactions benefit from electrochemistry. Although the comparison was primarily based on chemical yield, nevertheless it showed that electrochemical and classical tools can be complementary.

Badalyan and Stahl recently reported a cooperative electrocatalytic alcohol oxidation that employs tailor-designed, electron-proton-transfer mediators, and proceeds with faster rates and at lower overpotential than a similar process that uses only TEMPO. The use of (2,2'-bipyridine)Cu(II) and TEMPO paves the way for the discovery and development of non-precious-metal electrocatalysts. The authors emphasized the potential applications of this approach in the field of energy conversion.

As the usefulness of electrooxidation becomes more and more obvious, contemporary trends, proof-of-concept studies, and modern applications are being published. A recent report by Berlinguette’s group details the tandem reduction of CO₂ into CO along with the TEMPO-mediated oxidation of alcohols into the corresponding ketones at the anode. In some instances, electrochemical oxidation can mimic the enzymatic oxidation that occurs when molecules are metabolized by the liver. This feature was employed to replicate hepatic oxidation conditions in continuous-flow electrosynthesis, and the technology can help understand the fate of potential drug candidates prior to in vitro or in vivo testing.

3.2. C–Y Bond Formation

One of the great strengths of electrochemistry lies, not only in the possibility of turning existing C–C bonds into C=O bonds, but also in the possibility of creating C–C, C–N, C–O, and C–S bonds from C–H bonds, thus broadening the scope of this technology.

At present, the prevalence of (hetero)aromatic compounds in the pharmaceutical industry’s inventory of drugs is undisputable. Therefore, a plethora of methods for assembling such scaffolds have been developed, whereby industrial chemists routinely use the Suzuki, Heck, Negishi, or Kumada coupling. Despite the fact that these couplings are robust in terms of selectivity and efficiency, they often need a heavy metal catalyst and ligands that need to be carefully removed. Consequently, the associated processes end up being expensive. Electrochemistry can help pave the way to cleaner and more efficient variants.

3.2.1. C–C Bond

The C–C cross-coupling reaction is an essential tool for organic chemists. In this regard, a high-yield, selective, and metal- and reagent-free anodic cross-coupling of electron-rich aromatics (aniline derivatives) has been developed by Waldvogel and co-workers (Scheme 2, Part (a)). This electrochemical transformation does not require a leaving group to direct the nucleophilic attack from the aniline starting materials, and avoids the formation of homocoupling dimers, which is a typical side reaction. Similarly, anodic cross-coupling reactions of phenols have been reported by Waldvogel’s and other research teams.

Another type of interesting C–C cross-coupling is the intramolecular oxidative cyclization of substituted anilides to thermally unstable C-3-fluorinated oxindoles, which typically requires a stoichiometric amount of external oxidant such as a Cu(II) salt, hypervalent iodine reagent, NBS, or O₂. In contrast, the electrochemically induced variant does not require any of these reagents, and is therefore inherently safer and more efficient (Scheme 2, Part (b)). Similarly, indoles can be accessed easily and in good-to-excellent yields.
from the corresponding enamines through an electrocatalytic, intramolecular, and dehydrogenative annulation that is oxidant- and transition-metal-free. Interestingly, the anodic oxidation of unactivated cyclooctene leads to the formation of the [2 + 2] cycloaddition syn dimer in 70–80% yield. Markó and co-workers disclosed an efficient, safe, and environmentally benign conversion of ω-unsaturated aliphatic acids into carbocycles, tetrahydrofurans, and tetrahydropyrans in good yields and straightforward manner. The synthesis relies on a Kolbe decarboxylation followed by a radical cyclization and radical capture. The radical capture is made possible by the decarboxylation of a second, short-chain carboxylic acid (co-acid) that can trap and terminate the radical pathway. Different co-acids can be used, but acetic acid was shown to be the most efficient. The only ingredients needed for this transformation are 2 electrons and 1 molar equivalent of the co-acid, giving rise to the desired products along with carbon dioxide.

Core structures of many biologically active natural products consist of polycyclic systems containing six-membered rings. The intramolecular anodic coupling of alkenes involving radical cations from enol ethers has been effectively used as a key step for the construction of a six-membered ring that is part of the ring skeleton of arteannuins, a class of natural products with a monocycle syn dimer in 70–80% yield. Of interest also is the direct functionalization of a C(sp 2)–H bond in azaaromatics, which has been successfully carried out under mild electrochemical oxidative conditions to produce unsymmetrical (hetero)biarylks in 63–99% yields. This step-and atom-economical S2H reaction offers the clear advantage of not requiring the use of metal catalysts, stoichiometric quantities of chemical oxidants, or haloaromatics as reactants.

Yoshida and co-workers have recently developed a stabilized-cation-pool method for the metal-free and oxidant-free cross-coupling of benzylc and aromatic C–H bonds. 4-Methoxytoluene was initially used as the substrate for screening of the stabilizing groups, which led to identifying diphenylsulfilimine (Ph2S=NTs) as the best precursor of a stabilized benzyl cation. This approach was successfully applied to a streamlined, formal total synthesis of TP27, a protein tyrosine phosphatase (PTPase) inhibitor (Scheme 4).

A straightforward method for late-stage functionalization of pharmacophors has very recently been proposed by Zeng’s group. This catalytic electrochemical method is a variant of the traditional Minisci reaction, and involves the selective monoacylation of electron-deficient azaaromatics (mostly pyrazines) at the 2 position with α-keto acids in the presence of NH4I as a redox catalyst. The reaction exhibits high functional-group tolerance and a wide substrate scope, generating the monoacylated products in 18–65% yields. In contrast, under the traditional Minisci conditions, the first acylation often activates the arene towards further acylation. In the electrochemical transformation, the carboxylate anion—generated by protonation of the heteroarene with the α-keto acid—is oxidized in the presence of a catalytic amount of ammonium iodide to the corresponding carboxylate hypoiodite [RC(O)CO2I]. The latter undergoes decarboxylation to generate the acyl radical [RC(O)•], which adds to the 2 position of the protonated heteroarene in a regioselective manner. The ensuing radical cation is further oxidized and deprotonated to give the monoacylated heteroarene. Hexafluoroisopropanol was found to be a key additive, and the reaction tolerates alkyl and aryl α-keto acids.

### 3.2.2. C–N Bond

An efficient, practical, and gram-scale electrochemical method for the α-amination of ketones using simple conditions has been reported by Liang et al. The protocol involves a metal- and additive-free cross-dehydrogenative coupling of ketones with secondary amines, and provides the desired products in up to 75% yields. The reaction exhibits a broad substrate scope, but requires the use of aromatic ketones to ensure high yields.

An earlier contribution from Yoshida’s group described the chemoselective and metal-free C–N coupling of adequately protected imidazoles and electron-rich aromatic or benzylc compounds. The authors reported that unprotected imidazole
was not a suitable coupling partner, because the initial imidazolium product easily undergoes overoxidation, and that mesylate and tosylate protection prevented the overoxidation. The final N-substituted imidazole product is obtained after non-oxidative deprotection. A robustness screen according to the protocol described by Collins and Gloriuss was also performed by Yoshida’s group and showed the coupling conditions to be compatible with a wide variety of frequently encountered functional groups.

A conceptually similar strategy was employed by the same group to design an electrochemically mediated coupling of functionalized alkylamines with aromatic compounds. For similar reasons, the reaction could not be run using unprotected alkylamines, so this was circumvented through transformation of the nucleophiles into transient heterocycles. The latter are electrochemically coupled to aromatic compounds, and the alkylamine is obtained upon treatment with aqueous NaHCO₃. This work demonstrates, once again, the complementarity of chemical and electrochemical approaches. The scope of this chemoselective and metal- and chemical-oxidant-free route to N-alkylaniline derivatives bearing either oxygen or nitrogen in the alkyl group is quite broad, and offers synthetic platforms for further elaboration. The value of this methodology was demonstrated in the selective functionalization of aniracetam, a modulator of AMPA receptors (Scheme 5).

Very recently, Waldvogel and co-workers developed a very efficient, sustainable, and direct anodic C–H amination of phenoxy acetates, leading to 1,4-benzoxazin-3-one scaffolds, which are important structural features in biologically active molecules and natural products such as DIBOA and DIMBOA. The reaction sequence includes anodic oxidation of the aromatic substrate via pyridine-enabled amination. The resulting pyridinium intermediate (Zincke-type salt) is then treated with a secondary amine such as piperidine to release the desired primary aniline, which immediately undergoes ring-closing condensation with the ester functional group to access the valuable scaffolds (Scheme 6).

Amidinyl radical formation through anodic N–H cleavage has been employed by Xu’s group as a sustainable, atom-economic, scalable, and metal- and reagent-free method for C–H bond functionalization in (hetero)aromatics (Scheme 7). This approach generates polycyclic benzimidazoles and pyridoimidazoles highly chemoselectively. The sequence proceeds through anodic oxidation of the N–H bond of the amidine group in the substrate to give rise to an amidinyl radical that reacts in a selective intramolecular fashion to produce the desired polycyclic benzimidazole or pyridoimidazole in very good yield. Similar high-yielding reactions were developed to produce heterocyclic benzoxazoles and benzothiazoles, anilines, cyclic carbamates, and (aza)indoles.

Xu and co-workers have recently developed an amidyl radical cyclization cascade of urea-tethered diynes for the efficient electrochemical synthesis of polycyclic N-heteroaromatics by using ferrocene as catalyst (Scheme 8). A distinct advantage of this method is the circumvention of the use of stoichiometric amounts of toxic metal hydrides such as (n-Bu)₃SnH.

![Scheme 5](image1.png)

**Scheme 5.** The Heterocyclization-Enabled Electrooxidative Coupling of Functional Primary Alkylamines with Aromatics as Applied to the Functionalization of Aniracetam. (Ref. 47)

![Scheme 6](image2.png)

**Scheme 6.** Efficient, Sustainable, and Direct Anodic C–H Amination Leading to 1,4-Benzoxazin-3-Ones. (Ref. 48,49)

![Scheme 7](image3.png)

**Scheme 7.** C–H Bond Functionalization in (Hetero)aromatics through Anodic N–H Cleavage and Amidinyl Radical Formation. (Ref. 50)
In 2017, Lin’s group reported an approach to synthesize vicinal diamines through a Mn(II)-catalyzed electrochemical diazidation of alkenes. Following voltammetric and spectrophotometric studies, the authors proposed a mechanism in which a radical adduct (RHC–CH2N3) is generated after transfer of an azidyl group from the active metal azidyl [Mn(III)–N3] to the less substituted end of the alkene. A second C–N bond is then formed selectively using another Mn-assisted azidyl transfer to the more-substituted carbon of the alkene to form the desired diazide product (RHCN3–CH2N3). This method offers the benefits of being environmentally friendly and operationally simple. It also takes place under mild conditions, is compatible with a large number of substrate types and functional groups, and generates 1,2-diazide products (62–98% yields) that can be easily reduced to the corresponding vicinal diamines.

3.2.3. C–O Bond
A very recent paper reported the first example of a Pd(II)-catalyzed electrochemical activation and oxygenation with oxyanions of C(sp3)–H bonds contained in oxime derivatives. This method, which is environmentally benign and avoids the use of strong chemical oxidants, exhibited broad substrate and oxygenated nucleophile scopes (Scheme 9). The proposed mechanism involves coordination of Pd(OAc)2 to the nitrogen atom of the oxime followed by activation of a proximal C–H. The resulting palladacycle is oxidized at the anode to a Pd(IV) complex, which undergoes reductive elimination to yield, after ligand exchange, the oxygenated product and the catalyst. The authors rigorously compared the results of the electrochemical synthesis with those obtained following the aerobic C(sp3)–H oxygenation method developed by Sanford and which employs NaN3 as catalyst.

Baran’s group, in collaboration with researchers from Bristol-Myers Squibb published a breakthrough paper in 2016 detailing the development of an electrochemical allylic oxidation method. While this transformation was already known in the literature, Baran’s team set out to better understand the underlying properties of the system and introduced several innovative modifications such as the use of (i) a reticulated vitreous carbon electrode, (ii) tert-butylhydroperoxide (t-BuOOH) instead of molecular oxygen as a co-oxidant, and tetrachloro-N-hydroxyphthalimide (Cl4NHPI, a cheap and readily available flame retardant) as the mediator. Their optimized procedure, with its easy setup, is far more efficient and environmentally acceptable than the standard, metal-based stoichiometric allylic oxidations. The proposed mechanism involves the electrochemical oxidation of the anion of the mediator (likely formed through an acid–base reaction with a nitrogen base such as pyridine). The resulting oxygen-centered radical abstracts a hydrogen atom from the allylic position to form a carbon-centered allylic radical. Subsequent reaction with t-BuOOH, followed by a second oxidation and cleavage of the resulting allylic peroxide affords the α,β-unsaturated ketone product. The reaction conditions were easily scalable, and several oxidations were performed on a 100 gram scale with no special setup. This paper, along with other applications of electrochemistry, was the focus of a recent short review from the same group.

In keeping with previous reports, the Baran laboratory, along with Asymchem Life Science and Pfizer’s Global R&D, recently reported a quinuclidine-mediated electrochemical oxidation of unreactive methylene and methine motifs. These moieties
often exhibit a high oxidation potential, making their mediator-free electrochemical functionalization elusive. Initial screening revealed that tertiary amines were superior mediators to the more frequently encountered TEMPO or hydroxypthalimide derivatives. The reaction conditions were optimized and scaled up (50 g scale) for sclareolide (Scheme 10), an exceedingly useful platform for further chemical modification such as the synthesis of (+)-2-oxo-yahazunone. HFIP is a key additive, while oxygen likely serves as the terminal oxidant. This newly developed methodology compares well with the more classical approaches such as the Gif-type chemistry developed by Barton or the methyl(trifluoromethyl)dioxirane (TFDO) based oxidation. The proposed mechanism involves oxidation of quinuclidine into a highly reactive radical cation that is capable of abstracting the more accessible hydrogen from the substrate. The ensuing radical is quenched with oxygen to yield the corresponding ketone (from secondary C-H’s) or tertiary alcohol (from methine C-H’s) after peroxide decomposition.

3.2.4. C–S Bond
Fewer C–S bond-forming reactions are known as compared to reactions that generate C–C and C–N bonds. This could be due to the fact that sulfur-containing molecules can be good metal scavengers. Electrochemical synthesis could pave the way to developing C–S cross-coupling reactions mainly because heavy-metal catalysts, such as palladium, are not needed for reaction. In this regard, synthesis of (E)-vinyl sulfones has been developed via an electron-mediated, oxidative N–S bond cleavage of aromatic sulfonimidylhydrazides (Ar$^+$SNNH$_2$). This robust method works well for a broad range of halogenated and heterocyclic substrates. Mechanistically, the oxidative cleavage of Ar$^+$SNNH$_2$ at the anode releases N$_2$ and a sulfonyl radical (Ar$^+$SO$_2$). The latter reacts with an $\alpha,\beta$-unsaturated carboxylate [(E)-Ar$^+$CH=CHCO$_2$] to generate an $\alpha$-sulfonyl carboxylate [Ar$^+$CH=CH(Ar$^+$SO$_2$)CO$_2$] that can easily undergo decarboxylation to selectively access the (E)-unsaturated sulfone [(E)-Ar$^+$CH=CH(Ar$^+$SO$_2$)] in good yield.

Another type of C–S cross-coupling has been achieved in generally good yields (24–99%) by Lei’s group by reacting $N$-methylindoles with thiophenols in an electrochemical cell. A broad range of aryl and heteroaryl thiols, as well as electron-rich amines, served as good substrates for this electrocatalytic and environmentally benign reaction (Scheme 11, Part (a)).$^{66}$ The electron-mediated and oxidant-free cross-coupling is carried out under simple reaction conditions, and can be run on a gram scale. After extensive mechanistic studies, the authors found that formation of an aryl radical cation by anodic oxidation of the indole or electron-rich arene was the key step in the transformation. Coupling of this radical cation with the aryl sulfoxide radical (ArS$^+$), followed by rearomatization, leads to the observed cross-coupling product.

An intramolecular variant, leading to a broad range of benzothiazoles and thiazolopyridines from $N$-(hetero)-arylthioamides, was recently reported by Qian et al. (Scheme 11, Part (b)).$^{67}$ Electron-rich and electron-poor (hetero)aromatics were suitable substrates, and a catalytic amount (5 mol %) of TEMPO was necessary to produce the active thioamidyl radical species, which undergoes radical cyclization and subsequent rearomatization to produce the desired products. This methodology proved useful in a formal total synthesis of CL075, a toll-like receptor 8 (TLR8) agonist. N-Arylthioamides can be generated in situ directly from the reaction of isothiocyanates with secondary amines such as morpholine or diethylamine under electrolytic conditions [(n-Bu)4NBF$_4$ (6 equiv), MeCN–H$_2$O (9:1), 70 °C, 4 h]. The N-arylthioamides thus formed undergo, in a similar fashion, intramolecular dehydrogenative C–S cross-coupling to yield 2-aminobenzothiazoles in up to 99% yield. As with the other C–S cross-coupling variants, this transformation is also external-oxidant-free, metal-free, and be carried out on a gram scale.$^{68}$

3.2.5. C–Cl Bond
An elegant electrochemical Mn(II)-catalyzed dichlorination of alkenes with MgCl$_2$ as a nucleophilic chlorine source has been reported by Lin and co-workers. One important advantage of this sustainable, operationally simple, chemoselective, and scalable protocol is its compatibility with oxidatively labile groups on the alkene such as amines, alcohols, sulfides, and aldehydes (eq 1).$^{69}$

![Scheme 10. Efficient and Scalable Electrochemical Functionalization of Unactivated C(sp$^3$)–H Bonds. (Ref. 62)](image)

![Scheme 11. The Electrochemical C–S Cross-Coupling Reaction. (Ref. 66–68)](image)
3.3. N–Y Bond Formation

3.3.1. N–N Bond

A novel, electrochemical N–N coupling induced by anodic oxidation has been developed as a favorable and sustainable alternative to conventional methods for the synthesis of pyrazolidin-3,5-diones, which are important motifs in medicinal and veterinary drugs (eq 2).70 This approach relies on the oxidative N–N cyclization of malonic dianilides through the intermediacy of an amidyl radical. It avoids the use of toxic N,N'-diarylhydrazines as starting materials, tolerates a broad substitution pattern, is applicable to unsymmetrical substrates, and forms the desired pyrazolidin-3,5-diones in moderate-to-good yields.

3.3.2. N–S Bond

Zeng, Little, and co-workers have reported an efficient method for the synthesis of sulfonamides through the oxidative amination of sodium sulfinates (eq 3).71 Ammonium iodide is employed both as a substoichiometric redox catalyst and a supporting electrolyte, thus eliminating the need for additional conducting salt and simplifying reaction workup and product isolation. Moreover, the anode serves as co-oxidant, obviating the need for a terminal chemical oxidant.

3.4. Shono Oxidation

Since the first reports by Shono,14,72 this type of oxidation has been extensively studied and thoroughly reviewed.73–75 Alkyl amides [RCONCH₂R’R’’] or carbamates [R’OCONCH₂R’’R’’] can easily undergo anodic oxidation to the corresponding N-centered radical cations [R’CON+•CH₂R’’R’’], which then lead to the N-acyliminium intermediate [R’CON+(=CHR’’R’’)]. This iminium ion is instantaneously trapped by a nucleophile (classically by alcohols used as solvents) to yield a hemiaminal [R’CON(CH(OMe)R’’R’’)]. Under the action of a Lewis acid, this hemiaminal can revert back to the iminium ion and then be trapped by another nucleophile. A variety of nucleophiles such as heteroaromatic primary amines76 and chiral enamines77 have been employed in this transformation to build C–N and C–C bonds, respectively.

To broaden the scope of this anodic oxidation, the concept of the cation pool method was developed by Yoshida.78–80 Taking advantage of the cation pool method and flow chemistry, Ley and co-workers accomplished a rapid (two-step) synthesis of nazlinine, a biologically active indole alkaloid, as well as a small library of its unnatural relatives (Scheme 12).81

Silicon-, sulfur-, and tin-based electroauxiliaries can facilitate electron transfer by lowering the oxidation potential of the substrate resulting in better control of the regioselectivity of the Shono oxidation. For example, introduction of a phenylthio group in the α position of methyl 1-pyrrolidinecarboxylate lowers the oxidation potential from 1.9 V to 1.2 V (vs Ag/AgCl), enabling the oxidative C–S bond cleavage in the presence of electron-rich olefins such as allyltrimethylsilane.82 Several applications of the cation pool and the Shono reaction strategies are described in this reference.

3.5. Miscellaneous Reactions

3.5.1. [3 + 2] Annulation

A scalable, green, and efficient electrochemical oxidative [3 + 2] annulation between C-2 or C-3 substituted N-acetylinolines and phenols was reported from Levi’s laboratory. This external-oxidant-free and metal-free reaction produces benzofuroindolines (important structural motifs in bioactive natural products such as phalarine, diazomamines, and azonazines) in good-to-excellent yields (up to 99%) under atmospheric conditions. Depending on the position of the substituent in the N-acetylinoline starting material, the reaction leads to either benzofuro[3,2-b]indolines (C-3 substitution) or benzofuro[2,3-b]indolines (C-2 substitution) (Scheme 13).83

### Scheme 12. Flow Electrochemistry as an Enabling Methodology for the Synthesis of a Small Library of Indole Alkaloids. (Ref. 81)
3.5.2. Fluorination

The electrochemical fluorination of C–H bonds with HF or fluoride, the Simons process, is of paramount importance in the preparation of perfluorinated compounds. Although it is very much substrate-dependent and not well-suited for the introduction of a single fluorine atom due to competitive polyfluorination, this method remains an essential fluorination protocol when compared to more conventional ones. Fuchigami’s group has studied extensively the partial electrochemical fluorination of organic compounds, and these studies have shown that sulfides are privileged reaction partners.

3.5.3. Other Reactions

Fuchigami’s group has also studied the electrochemical properties of sulfur-containing organoboranes and organotrifluoroborates. The reduction of electrochemical potential between a boronic acid (or ester) and its ate-complex can be used to introduce various nucleophiles including fluorides. In Pd-catalyzed C–H functionalizations, replacing strong chemical oxidants with electron-transfer mediators. It readily takes place at room temperature in [EMIM][NTf₂]–DMSO in the absence of metal catalysts or bases, and provides the cross-coupling products (ortho-arylated pyrroles) in moderate-to-good isolated yields.

One of the classical C–C bond forming reactions is the Michael addition. Shono and co-workers noted as early as 1980 that electroreduction of α,β-unsaturated esters or α,β-unsaturated nitriles in the presence of aldehydes or ketones and TMSCl leads directly to γ-lactones or γ-hydroxynitriles in 51–86% yields (Scheme 15). A similar approach reported by Kise’s group employed aromatic ketones with 1,3-dimethyluracils or coumarins as the activated olefins.

Only recently has the transition-metal catalyzed C(sp³)–C(sp³) coupling been explored in the context of electrochemistry. In 2017, Lai and Huang reported the palladium-catalyzed Barbier–Negishi-type alkylation of alkyl or benzyl halides in air and in aqueous medium by using a Zn cathode. This novel, ligand-free cross-coupling takes place through the intermediacy of an in situ electron-transfer mediator.

4. Cathodic Reduction
4.1. C–Y Bond Formation

4.1.1. C–C Bond

The reductive electrochemical pinacol coupling of ketones and aldehydes has been successfully carried out in an 80% mixture of a room-temperature ionic liquid (RTIL) and water ([BMIM][BF₄])–H₂O). This scalable process obviates the need for a catalyst–cocatalyst system, avoids the generation of metallic and salt byproducts, and simplifies the product separation and purification steps. Moreover, the electrolyte was recycled and reused up to five times without loss of activity. The 1,2-diol products were obtained in high yields and moderate diastereoselectivities (Scheme 14). A more recent example of an electroreductive C–H functionalization is the direct arylation of pyrroles with various aromatic halides. This novel C–C bond-forming reaction employs a sacrificial zinc anode and 10 mol% of perylene-3,4,9,10-tetracarboxylic acid dimides (PDIs) as electron-transfer mediators. It readily takes place at room temperature in [EMIM][NTf₂]–DMSO in the absence of metal catalysts or bases, and provides the cross-coupling products (ortho-arylated pyrroles) in moderate-to-good isolated yields.

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Scheme 14. Electroreductive Pinacol Coupling of Aldehydes and Ketones. (Ref. 89)

Scheme 15. Electroreductive Coupling of Activated Olefins with Carbonyl Compounds Leading to γ-Lactones or γ-Hydroxynitriles. (Ref. 91)
generated alkylzinc reagent, and it complements the traditional reaction employing air-sensitive organometallic reagents and requiring protection–deprotection of acidic hydrogens in the substrates (Scheme 16). 94

The same year, Hansen and co-workers from Pfizer’s R&D reported the nickel-catalyzed C(sp^2)–C(sp^3) cross-coupling of electrophilic aryl bromides with electrophilic alkyl bromides using a sacrificial Zn anode and a reticulated vitreous carbon (RVC) cathode. This protocol gave the cross-coupling products in 51% to 86% yields, offered access to a broader substrate scope, and resulted in selectivities that are comparable to, or higher than, those achieved with activated metal powder reductants such as zinc powder.95

4.1.2. C–B Bond

While organoboron compounds such as boronic esters and acids are versatile reactants, as evidenced by their extensive use in industry,96,97 their industrial-scale preparation remains a challenge. Indeed, classical approaches to aryloboron compounds require low temperatures (for the metalation step) or expensive catalysts and reagents (in the case of the Miyaura borylation reaction). To overcome these drawbacks, Duñach and co-workers98 reported an electrochemical alternative for synthesizing aryl-, heteroaryl-,99,100 allyl-,101 and benzylboronic102 acids and esters (Scheme 17). The reactions were performed at room temperature in a single-compartment cell using a consumable magnesium or aluminum anode. Pinacolborane (or trialkylborate) was the electrophilic boron source of choice. The scope ranges from aromatics bearing electron-withdrawing or electron-donating groups to polyhalogenated aryl derivatives. 103 The role of the electrochemical cell is to cause a polarity inversion (umpolung) of the electrophile Ar–X into nucleophile Ar– and the generation of Mg^2+ from the sacrificial anode. This combination produces a formal Grignard reagent “ArMgX”, which reacts with the electrophilic boron (HBPin) to form an ate-complex and generate the targeted boronic acids after hydrolysis.

4.1.3. C–O Bond

The transformation of a C–B bond into a C–O bond can also be achieved by electrochemical means. Indeed, cathodic hydroxylation of organoboron compounds under an O_2 atmosphere leads to the corresponding phenols with high chemoselectivity (eq 4).104 The method could be used in the presence of easily oxidizable functional groups such as a thioether group, and is superior to classical methods that employ H_2O_2 under basic conditions, since, in the latter case, unselective oxidation of both the thioether and the C–B bond takes place. Mechanistically, oxygen undergoes a one-electron reduction at the cathode to generate the superoxide radical anion (O_2•^–), which reacts rapidly with the neutral boron atom to form a peroxy radical [ArB(OH)O–O•]. Reduction of the peroxy radical at the cathode or by O_2•^– leads to a three-membered ring intermediate in which the aryl group migrates from boron to oxygen to produce the phenol precursor ArOB(OH)O^–. Hydrolysis of this last species under acidic conditions generates the desired phenol.

(a) Br

(b) Br

(c) Br

Scheme 17. Electrochemical Synthesis of Aryl-, Allyl-, and Benzylboronic Esters.
4.2. Markó-Lam Reduction
Replacement of a hydroxyl group with hydrogen is an exceedingly useful transformation in organic synthesis. In addition to the Barton–McCombie reaction and to more recent alternatives,105 Lam and Markó reported a novel and elegant electrochemical method for the deoxygenation of the alcohol moiety in toluate esters.106 The protocol tolerates the presence of a broad range of functional groups, and eliminates the need for metals, toxic co-solvents, and unstable xanthates all of which are employed in traditional alcohol deoxygenations. This efficient and economical method provided the corresponding deoxygenated products in good yields in the case of secondary and tertiary toluates and moderate yields in the case of primary ones. In the proposed mechanism, the reaction is initiated by reduction of the ester starting material to the corresponding radical anion [ArCO•––OR], which decomposes to give a benzoate anion (ArCO2–) and an alkyl radical (R•). The alkyl radical is then rapidly captured to give the corresponding alkanes.107 The authors also reported that addition of a protic source to the reaction mixture quenches the radical anion [ArCO•––OR] and generates a hemiketal [ArCHOH–OR] that leads to alcohols ArCH2OH and ROH. These observations demonstrated that toluate esters can be useful protecting groups for alcohols and that their electrochemical deprotection is highly chemoselective and efficient. 108

Further, the authors described a new, scalable, and one-pot process for the direct conversion of primary alcohols into the corresponding alkanes without prior esterification by using an excess of methyl toluate. The significant advantage of this protocol is that it leads to uniformly high yields, tolerates a wide variety of functional and protecting groups, and is a greener and less expensive alternative to classical deoxygenation methods (Scheme 18).109 The same authors have also reported that diphenylphosphinates can be used as alternatives to toluate esters in this electrochemical transformation.110

4.3. Dehalogenation
In 2015, Waldvogel’s group, in collaboration with a team from Novartis, described a cathodic debromination of 1,1-dibromocyclopropane under batch and flow conditions.111,112 This type of reaction provides efficient access to the cyclopropane ring of a key intermediate for the synthesis of the NS5A inhibitor ledipasvir (used in the treatment of hepatitis C infection). The authors highlighted the crucial role of the solvent used in the electrolyte in the formation of monodebrominated or didebrominated compound. Indeed, switching from MeCN to DMF and decreasing the proton concentration afforded the didebrominated cyclopropane in 93% yield (eq 5). Compared to classical, purely chemical methods, the electrochemical dehalogenation is sustainable and exhibits higher selectivity and better yields. The application of this method on a gram scale both in batch-type electrochemical cell and in a continuous-flow gap cell clearly demonstrates the promising potential of organic electrochemistry in the synthesis of key pharmaceutical intermediates.

4.4. Cyclopropane Synthesis
The cyclopropane moiety is an essential building block in medicinal chemistry,113,114 and, consequently, efforts have been undertaken to explore further the electrosynthesis of cyclopropanes. Although, there are few examples of anodic cyclopropane synthesis, there are many examples of cathodic cyclopropane formation.115 Several of the reports on the direct electrochemical synthesis of cyclopropanes can be classified into four types of reaction (Scheme 19): (i) Cyclization of 1,3-dihalogens or 1,3-dimethanesulfonates,116 (ii) [2 + 1] cycloadDITION with electrogenerated carbene (electrochemical version of the Simmons–Smith reaction),117 (iii) Michael addition of halogenobenzylphosphonate anion to an alkene followed by ring closure,118 and (iv) the electrochemical version of the Perkin reaction.119 The cyclopropane can also be formed indirectly by electrogeneration of the conjugate base of a C–H acid at the cathode and electrogeneration of I2 from a catalytic amount of KI at the anode. Reaction of the base with I2 leads to an α-iodoketone intermediate, which undergoes deprotonation and intramolecular S_N2 reaction to yield the cyclopropanated compound under very mild conditions.120

Scheme 18. Lam and Markó’s New, Scalable, and One-Pot Process for the Direct Conversion of Primary Alcohols into the Corresponding Alkanes without Prior Esterification. (Ref. 109)

Scheme 19. Various electrochemical processes for the synthesis of cyclopropanes.

eq 5 (Ref. 112)
4.5. Electrogend Bases

4.5.1. β-Lactam Synthesis

As mentioned previously, it is possible to generate a base by electrolysis of compounds containing an acidic proton. Such an electrogend base can engage in a number of reactions. In 2005, Feroci’s group disclosed a high-yield, electrochemical synthesis of β-lactams from bromoamides through C–N bond formation. A year later, the same laboratory extended this approach to substrates bearing an acidic proton such as amido esters to access β-lactams by C–C bond formation instead of C–N bond formation (Scheme 20). Of the solvents tested, MeCN proved to be the solvent of choice for the generation of a solvent-derived strong base that is capable of deprotonating the C–H bond of the substrate and thus initiating the first step of the overall process.

4.5.2. C–N Bond Formation

Building on the results with the electrochemically generated acetonitrile anion discussed in Section 4.5.1, Feroci and co-workers developed a similar protocol for the alkylation of N-alkylated 4-aminopyridines. A mixture of the substrate, electrolyte, and acetonitrile was electrolyzed and then treated with various alkyl and benzyl halides. Again, the acetonitrile anion was sufficiently strong to abstract the N–H proton of the 4-aminopyridine. Some of the resulting N-alkylated 4-aminopyridines exhibited antifungal and antiprotozoal activity.

4.5.3. C–C Bond Formation

Arcadi’s group has reported another application of the electrochemically generated cyanomethide ion. In this versatile and mild protocol, alkynes containing proximate malonyl functional groups undergo intramolecular cyclization to afford functionalized butenolides, quinolones, and 3-pyrrolin-2-ones in good-to-excellent yields, obviating the need for transition-metal catalysts and bases.

It is worth mentioning in this context that, when the product of an electrochemical C–C bond-forming reaction bears another acidic proton, it could engage in further bond-forming reactions, which would open the door to electrochemically induced tandem and sequential reactions. For instance, Massa, Palombi, and co-workers have shown that addition of malonate or malonitrile anions to cyanobenzaldehydes leads to isoidolinones, which could be functionalized further by Michael reaction with acrylates (Scheme 22). By now, it is quite apparent that MeCN is a versatile precursor of strong base under electrolysis conditions. Nevertheless, EtOH, MeOH, and NHCs derived from ionic liquids can also serve as valuable precursors of bases, as has been demonstrated by various research groups.

5. Paired Electrosynthesis

In many electrochemical syntheses, the expected product is generated at one electrode, while the reaction at the other...
electrode ensures electroneutrality. Paired electrosynthesis takes advantage of the two simultaneous reactions to generate a product. It can be classified into four types of reaction mode: (i) parallel, (ii) convergent, (iii) linear, and (iv) divergent.\textsuperscript{129} In terms of sustainability, the pairing of electrode processes is the best way to reduce energy consumption.

In 2016, Kubiak, Moeller, and co-workers reported an elegant parallel paired electrosynthesis in a divided cell that could serve as a model for the sustainable production of fine chemicals in a closed system that does not use sacrificial redox reagents (Scheme 23).\textsuperscript{130} Production of a “privileged” benzimidazole building block took place in the anode compartment by oxidative condensation of syringaldehyde (derived from the lignin in sawdust) with 1,2-diaminobenzene mediated by ceric ammonium nitrate \([\text{Ce(NH}_4\text{)}_2(\text{NO}_3)_6]\). The paired half-reaction in the cathode compartment consisted of the reduction of \(\text{CO}_2\) to \(\text{CO}\) (which is a valuable starting material) facilitated by \(\text{Re(bipy} \text{Bu})_3(\text{CO})\text{Cl}\).

Senboku’s group has described the carboxylation of benzylic halides by using a convergent paired electrosynthesis (Scheme 24).\textsuperscript{131} It is the first report of this type of reaction that does not employ a sacrificial electrode. Reduction of the \(\text{C(sp}^3)\text{–Br}\) bond at the cathode generates a benzylic anion which is trapped by \(\text{CO}_2\) to form the corresponding carboxylate anion. At the anode, DMF is oxidized in the presence of (\(\text{i-Pr}\))\(_2\text{NEt}\) to an \(\text{N}\)-acyliminium ion, which reacts with the carboxylate anion to form the final product.

In 2015, Hartmer and Waldvogel reported a linear, paired electrosynthesis for the dehydration of aldoximes into the corresponding nitriles under mild conditions without the need for halogens. Anode oxidation of the aldoxime leads to a nitrile oxide intermediate, which then deoxygenates at the cathode to produce the nitrile final product.\textsuperscript{132} It is noteworthy that the efficiency of this step is highly dependent on the nature of the electrode employed.

An example of “double” linear paired electrolysis was reported by Baran’s group and collaborators from Pfizer’s Global R&D and Asymchem Labs.\textsuperscript{133} The authors described a nickel(II)-catalyzed, base-free electrochemical amination of aryl halides with alkyl amines. This reaction takes advantage of the ability of nickel to react with less reactive electrophiles and the fact that different oxidation states of the nickel can be accessed by electrochemical means. In particular, high-valent nickel is prone

\begin{align*}
\text{Scheme 22.} & \quad \text{Electrochemically Initiated, One-Pot Sequential Reactions Leading to Functionalized Isoindolinones. (Ref. 125)} \\
\text{Scheme 23.} & \quad \text{Parallel, Paired Electrosynthesis Produces a “Privileged” Benzimidazole Derivative at the Anode and Reduces CO}_2\text{ to the More Valuable CO at the Cathode. (Ref. 130)} \\
\text{Scheme 24.} & \quad \text{Three-Component-Coupling Products of Benzyl Halides, CO}_2\text{, and DMF via a Convergent Paired Electrosynthesis. (Ref. 131)} \\
\text{Scheme 25.} & \quad \text{Divergent, Paired Electrosynthesis of \(\alpha,\beta\)-Unsaturated Diacids and Protected Allylic Diols. (Ref. 134)}
\end{align*}
to reductive elimination. The reaction scope included a large number of aryl donors (Ar–X; X = Cl, Br, I, OTf) and amines (primary and secondary).

A novel and divergent paired electrosynthesis of α,β-unsaturated di(trifluoroacetate esters) (as diol precursors) and dicarboxylate salts has been reported by De Vos and coworkers (Scheme 25).134 The synthesis starts with conjugated dienes, which react with CO₂ at the cathode to generate the dicarboxylate salt. Simultaneously, the dienes react at the anode with tetraethylammonium trifluoroacetate to form the trifluoroacetate-protected allylic 1,4-diols. Good-to-excellent yields are obtained, and the use of an inert and stable non-sacrificial graphite anode makes this process a promising one for implementation in continuous-flow systems. However, a high substrate dependence—both with respect to alkyl substitution and molecular configuration—was found, which makes it difficult to extend this approach to other conjugated dienes.

6. Conclusion and Outlook

The field of electrochemistry is experiencing such a spectacular revival that it is on the verge of being used by non-specialists, whether in academia or in industry. Electrochemistry is developing new variations of old reactions and, more importantly, is creating new reactivity pathways. Perhaps more exciting is the fact that much remains to be discovered in this field. In the twentieth century, the complexity of reaction setups and lack of universal tools and methodologies slowed down considerably the development of electrochemistry as an enabling technique. Such tools and methodologies are currently being developed by some of the best scientists around the globe, and it is our hope that others will invest in these efforts to ultimately invent better chemistry. As Maslow put it, “I suppose it is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail.”135 electrochemistry has the potential of becoming a key asset of the chemist tool box. It is our sincere hope that the examples showcased in this review do provide the reader with a glimpse of the practical applications of this vibrant field of research.

7. Acknowledgment

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8. References

The Spectacular Resurgence of Electrochemical Redox Reactions in Organic Synthesis

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Dominique Delbrayelle graduated in 1995 from L’École Supérieure de Physique et de Chimie Industrielles de la Ville de Paris (ESPCI Paris), with an Engineer degree and an M.Sc. degree in analytical chemistry. He joined Minakem (then SEAC) in 1997 as analytical R&D manager. Since then, he has occupied various positions in the R&D organization, including process development, continuous process improvement, laboratory supervision, and project management. He has been the Scientific Director of Minakem Recherche since 2014.

Aurélien Letort obtained his Ph.D. degree in 2015 under the supervision of Dr. Joëlle Prunet at the University of Glasgow (U.K.), for studies aimed at a formal synthesis of paclitaxel using a ring-closing metathesis cascade. He then took a position as a postdoctoral fellow in the group of Prof. Alois Fürstner at the Max-Planck-Institut für Kohlenforschung, where he worked on the total synthesis of a structurally challenging natural product and the ruthenium-catalyzed trans-hydroelementation of conjugated diynes. In 2017, he joined Minakem as a process R&D chemist working on the custom synthesis of intermediates and APIs.

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**Bench-Stable Nickel(II) Precatalysts**

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Keywords. conjunctive cross-coupling; transition-metal catalysis; carbon–carbon π bonds; three-component coupling.

Abstract. Transition-metal-catalyzed cross-couplings comprise a group of two-component C–C bond-forming reactions between organohalide electrophiles and organometallic nucleophiles. These transformations have been applied for the construction of C–C bonds across numerous subdisciplines of chemistry. Recently, this reactivity paradigm has been expanded to incorporate a third component, or a conjunctive reagent, for the rapid assembly of molecular complexity. In the past decade, significant effort has focused on utilizing carbon–carbon π bonds as conjunctive reagents in three-component cross-coupling reactions. This review covers advances made in this area, including different strategies that have been employed, limitations of current methods, and the outlook for future developments in the field.

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1. Introduction
Transition-metal-catalyzed cross-coupling reactions constitute an indispensable toolkit for C–C bond formation in complex-molecule synthesis. In only a matter of decades from the discovery of the first cross-coupling reaction, seminal contributions from Heck, Kumada, Stille, Negishi, Suzuki, and others have garnered widespread interest and adoption. The idea of linking an electrophilic and nucleophilic component together by non-traditional means greatly expanded available synthetic routes to diverse target compounds. The development of complementary methodology for carbon–heteroatom bond formation soon followed. Advances in ligand design have made such processes remarkably facile, practical, and versatile. While two-component cross-coupling reactions continue to serve as powerful methods for connecting chemical fragments, recent forays in three-component cross-coupling reactions add another dimension of synthetic utility. In such processes, the conjunctive reagent serves as a synthetic linchpin to connect two coupling partners. In the context of this review, the term “conjunctive reagent” refers to a chemical entity that is ultimately difunctionalized with nucleophiles and/or electrophiles that would otherwise be expected to react with one another in a two-component fashion under the reaction
Carbon–Carbon π Bonds as Conjunctive Reagents in Cross-Coupling
Joseph Derosa, Van T. Tran, Vincent A. van der Puyl, and Keary M. Engle*

2. Carbon–Carbon π Bonds in Conjunctive Cross-Coupling
The ability to harness the power of a two-component cross-coupling in a modular fashion by using a conjunctive reagent as a linker allows for rapid buildup of complexity in a single step. In the context of carbon–carbon π bonds, the site-selective incorporation of two separate chemical components at defined carbon atoms has the potential for simplifying chemical synthesis, especially in the realm of drug discovery and development. Vicinal substitution patterns are among the most prevalent motifs in pharmaceuticals, rendering methods for modular difunctionalization of π systems highly attractive. Moreover, implementing cross-coupling with inexpensive and abundant alkenes and alkynes as conjunctive reagents would turn them into masked retrons for vicinal alkyl or aryl substituents. Although methodologies exist for transforming carbon–carbon π systems into 1,2-difunctionalized products, many functional group combinations are still a major challenge for practical synthesis. As a result, several research groups have focused on developing strategies for conjunctive cross-coupling reactions that utilize carbon–carbon π bonds with the goal of realizing the untapped potential of this reactivity mode.

2.1. Traditional Challenges in Three-Component Conjunctive Cross-Coupling Using Carbon–Carbon π Bonds
Despite the attractiveness of such an approach, achieving the desired reactivity is no simple task. The robustness of traditional two-component cross-coupling reactions often serves as an obstacle itself, necessitating careful tuning of the conjunctive cross-coupling reaction parameters to favor insertion into the conjunctive reagent before the catalyst can interact with the second cross-coupling partner. In the event that the rate of insertion is indeed faster than the two-component coupling, the resulting highly reactive organometallic intermediate must then be intercepted by the desired electrophile or nucleophile prior to succumbing to β-hydride elimination, oligomerization, or other undesirable pathways.

To illustrate the inherent difficulty of choreographing this sequence, consider the case of an unconjugated alkene (1) (Scheme 1). In the first step, the catalyst oxidatively adds to the organohalide electrophile. The organometallic intermediate must then react with alkene 1 through a 1,2-migratory addition to deliver an alkylmetal intermediate (2). This step competes with a traditional two-component cross-coupling reaction, which directly forms a C–C bond between the electrophilic and nucleophilic components. Intermediate 2 must then be intercepted with the organometallic nucleophile (R2-M) before succumbing to other reaction pathways. In particular, β-hydride elimination is often rapid with many alkylmetal species. This can lead to Heck-type products, such as 3, and result in the formation of a high-energy metal hydride (H-[M]-X) that is prone to insert into the new alkene and erode the regio- and chemoselectivity of the desired 1,2-difunctionalization reaction. The rapid

![Scheme 1. General Catalytic Cycle for the Conjunctive Cross-Coupling of Alkenes and Potential Obstacles.](image-url)
nature of this reinsertion can result in 1,1-difunctionalization being the predominant pathway, leading to alkane product 4. Provided these undesirable pathways can be avoided, the desired transmetalation with the organometallic nucleophile (R²−M) results in an alkylmetal intermediate possessing a second organic fragment (5). C–C reductive elimination from 5 then yields the desired 1,2-difunctionalized product (6).

For the reasons articulated above, the reaction with unconjugated alkenes, depicted in Scheme 1, remains a formidable challenge to date. However, various strategies have been developed to circumvent some of the problematic steps in this general catalytic cycle. One such strategy involves covalently tethering one reaction partner to the C–C π system to enhance the rate of the 1,2-migratory insertion step. Using this approach, various research groups have reported that the resulting alkyl- or vinylmetal species can then be intercepted for subsequent functionalization, which is the subject of the next section.

2.2. Intramolecular Conjunctive Cross-Coupling Using Tethered Components

2.2.1. Tethered Alkynes and Alkenes

In a series of publications by Grigg and co-workers, regioselective alkyne 1,2-difunctionalization was achieved using tethered aryl and vinyl halides under palladium catalysis. Under this reaction manifold, tethered internal alkynes were found to react with organozinc, organotin, and organoboron reagents via a 5-exo-dig or 6-exo-dig cyclization. The reaction mechanism involves initial oxidative addition of palladium(0) to the C–X bond to anchor the catalyst in the vicinity of the C–C π bond. This, in turn, facilitates intramolecular 1,2-migratory insertion. The regiochemical outcome is governed by Baldwin’s rules, allowing for reliable formation of the cyclic core that is kinetically favored. This step forges a new vinylpalladium(II) intermediate that then reacts with the corresponding vinyl/aryl organometallic nucleophile via transmetalation and C–C reductive elimination to deliver the product. Notably, indolene derivatives could be synthesized in moderate yields under relatively mild conditions using a wide range of organometallic nucleophiles with high stereoselectivity for the E isomer (Scheme 2, Part (a)).

In attempts to extend this methodology to the synthesis of other nitrogen-containing heterocycles through a 6-exo-dig cascade, various isoquinoline derivatives were synthesized using organostannanes. Interestingly, when this method was then tested using amide-containing substrates, both the product yield and stereoselectivity were diminished (Scheme 2, Part (b)). Though the nature of this decrease in selectivity was not investigated further, the authors noted that the high reactivity of organostannanes may lead to background reactions with the resulting alkene. This mode of reactivity was also reported by Knochel to also include alkynes tethered to alkyl iodides, in which arylzinc reagents were employed under nickel catalysis in a similar carbocyclization cascade. Additionally, Cook utilized palladium catalysis to extend the reactivity to arylboronic acids.

Grigg and colleagues applied the same concept to allenes under similar conditions using boronic acids as the nucleophilic component (Scheme 3). At the outset, the authors predicted that the regioselectivity would be controlled by the proclivity for transmetalation at the less hindered (exocyclic) carbon atom of the π-allyl palladium species that is formed upon migratory insertion. This hypothesis was put to the test in benzofuran synthesis using allene precursors with aryl- and vinylboronic acids. Of the examples reported, only trace amounts of the opposite regioisomers were detected. In the case of amide-containing substrates, arylboronic acids yielded the anticipated products; however, the undesired regioisomer was also formed in variable yield, depending on the carbonate base utilized. Interestingly, the authors observed that organostannanes gave a mixture of regioisomers in a 1:1 ratio that could be improved in the presence of silver salts. Overall, the application of this strategy to alkynes and allenes demonstrated the potential for a transition-metal-catalyzed 1,2-difunctionalization in which a carbometalated intermediate can be diversified after an insertion event. Although the developed methodology remained limited to the formation of five- and six-membered rings, C(sp²)-hybridized coupling partners, and a relatively small scope of alkynes and allenes, this alkyne- and allene-tethering strategy served as an important foundation for the cross-coupling with alkenes as conjunctive reagents.
2.2.2. Tethered Alkenes

Transitioning from alkynes or allenes to alkenes in 1,2-difunctionalization is fraught with challenges. In general, the initial insertion step is less favorable, and subsequent \( \beta \)-hydride elimination from the resulting alkylmetal species is facile. Utilizing a tethering strategy, these two shortcomings can be circumvented. Similar to the aforementioned cascade processes for tethered alkynes and allenes, intramolecularly allows for rapid insertion, and the resulting cyclization limits the number of accessible \( \beta \)-hydrogens. In 2001, Oshima reported a cobalt-catalyzed radical cyclization and cross-coupling cascade involving alkyl halides tethered to unconjugated alkenes.\(^{13}\) In the proposed mechanism, an initial single-electron transfer allows for homolytic cleavage of the \( \text{C(sp}^3\text{)}-\text{X} \) bond of tethered alkene, leading to a 5-hexen-1-yl radical, a commonly encountered intermediate in radical clock experiments, which undergoes rapid \( 5\text{-exo-trig} \) cyclization (Scheme 4, Part (a)), and the cobalt(I) species transmetalates with the aryl Grignard reagent. The cyclopentyl methyl radical, which would typically recombine with the corresponding halide radical, reacts instead with the catalyst to form an arylalkylcobalt(II) species capable of undergoing reductive elimination to deliver the desired product \(^9\).

Building on this pioneering work, other transition-metal catalysts that are capable of single-electron transfer were then investigated in order to broaden the scope of tethered alkene substrates and coupling partners in cyclization-cross-coupling cascades. Prior to contributions by Cardenas in 2007,\(^{18}\) the terminating step in the cascade was limited to coupling with an aryl organometallic reagent. As observed by Oshima,\(^\text{13}\) the facile nature of the competing \( \beta \)-hydride elimination precluded the formation of multiple alkyl-alkyl bonds in a single catalytic cycle. Inspired by concurrent advances in two-component alkyl–alkyl cross-coupling reactions, Cardenas and co-workers utilized tridentate ligand scaffolds to coordinately saturate the nickel center in the catalyst.\(^\text{18}\) Specifically, pyridine bisoxazoline (PyBox) and terpyridine ligands were initially studied, but eventually a di-sec-butyl PyBox ligand was shown to be superior under the optimized conditions. By employing alkylzinc reagents in this cascade, a wide range of bicyclic cis-fused, furan-based products were obtained in high yields and with high diastereomeric ratios. The reaction was also found to exhibit broad functional group tolerance (eq 1).\(^{18}\) In a series of experimental and computational mechanistic studies,\(^{18}\) the authors concluded that a radical-based intermediate is likely involved in this process, lending credence to the proposed mechanism by Oshima and co-workers.\(^{13}\)

Recently, Giri and colleagues reported a new method for the dicarbofunctionalization of similar scaffolds by using copper catalysis in conjunction with alkyl- and arylzinc reagents.\(^{19}\)

Generally speaking, achieving asymmetric induction in radical-based, three-component cross-coupling reactions is very challenging. In the studies presented above, an alkyl halide containing a tethered alkene initiates a radical cyclization cascade. Even in the presence of chiral ligands, racemic products were obtained, likely due to the rapid nature of the key radical cyclization step. Following those studies, similar structural motifs were prepared in an asymmetric fashion by attenuating the reactivity of the intermediates. In seminal work,
Cong and Fu disclosed a complementary cyclization–cross-coupling cascade involving an arylboron nucleophile possessing an appended alkene.\textsuperscript{20} Using a catalyst system consisting of a nickel precatalyst and a chiral diamine ligand, they found that a transmetalation–migratory insertion sequence takes place and is followed by coupling with alkyl electrophiles (Scheme 5).\textsuperscript{20} Both alkyl bromides and iodides reacted to deliver the desired dihydrobenzofuran products in high enantiomeric excess (ee). This methodology was elegantly applied in the three-step synthesis of the dihydrobenzofuran core of fasigilfam (38% overall yield, 96% ee). The optimized reaction was further extended to racemic secondary alkyl bromides, allowing two chiral centers to be set in 99% ee and with a 9:1 dr. This result establishes the synthetic viability of enantioselective conjunctive cross-coupling reactions. Concurrent with these studies, You and Brown reported a diastereoselective, copper-catalyzed diarylation reaction using alkyl iodosides and tethered arylboronic acids.\textsuperscript{21} In this work, a competing two-component cross-coupling predominated when a monodentate tricyclohexylphosphine-copper(I) chloride catalyst was employed. Bidentate ligands, on the other hand, provided the desired conjunctive cross-coupling product. Expanding on this work, the reaction was later applied to 1,1-disubstituted aryl iodides and tethered arylboronic acids.\textsuperscript{23} This methodology was elegantly applied in the three-step synthesis of dihydrobenzofuran core of fasigilfam (38% overall yield, 96% ee). The optimized reaction was further extended to racemic secondary alkyl bromides, allowing two chiral centers to be set in 99% ee and with a 9:1 dr. This result establishes the synthetic viability of enantioselective conjunctive cross-coupling reactions. Concurrent with these studies, You and Brown reported a diastereoselective, copper-catalyzed diarylation reaction using alkyl iodosides and tethered arylboronic acids.\textsuperscript{21} In this work, a competing two-component cross-coupling predominated when a monodentate tricyclohexylphosphine-copper(I) chloride catalyst was employed. Bidentate ligands, on the other hand, provided the desired conjunctive cross-coupling product. Expanding on this work, the reaction was later applied to 1,1-disubstituted tethered alkenes and was rendered enantioselective by utilizing chiral bisphosphine ligands.\textsuperscript{22}

Conjunctive cross-coupling reactions using electrophiles or nucleophiles that are tethered to the reactive carbon–carbon π bond have been invaluable in illuminating the mechanism of this type of reaction. Moreover, they are powerful synthetic tools in their own right, providing access to a unique subset of bioactive heterocycles. However, this methodology also has limitations. For instance, it is typically not possible to form larger than 6-membered ring systems, as the regioselectivity is often unpredictable with such substrates.

### 3. Approaches toward Three-Component Conjunctive Cross-Coupling Using Alkynes and Allenes

Compared to the reactions described in the previous section, eliminating the need for covalent tethering of the C–C π bond to one of the reaction partners would greatly expand the breadth of possible coupling partners. Several challenges exist in three-component conjunctive cross-coupling. First, controlling the regiochemical course of the reaction is difficult in the absence of steric or electronic bias within the substrate. Second, the migratory insertion step is less facile, compared to the cases above, which are driven by a favorable cyclization step after the transition metal is brought into the vicinity of the carbon–carbon π bond. Third, such reaction systems are susceptible to isomerization via chain-walking processes (particularly with alkenes as conjunctive reagents). In spite of these challenges, the attractive aspects of three-component conjunctive cross-coupling for rapidly assembling molecular complexity have motivated several research groups to pursue the development of such reaction systems.

#### 3.1. Three-Component Conjunctive Cross-Couplings of Alkynes

In 2003 and 2005, Larock and co-workers reported a palladium-catalyzed, three-component coupling between internal alkynes, aryl iodides, and arylboronic acids.\textsuperscript{23,24} Through a reaction sequence similar to the tethered variant described above, an initial oxidative addition results in an arylpalladium(II) species that undergoes migratory insertion with the alkyne conjunctive reagent. Transmetalation between the resulting vinylpalladium(II) species and an arylboronic acid, followed by C–C reductive elimination, yields the desired tetrasubstituted alkene. Upon reacting 1-phenylpropyne with 4-iodotoluene, phenylboronic acid, and 5 mol % PdCl$_2$(PhCN)$_2$, a 6.5:1 mixture of regioisomers was obtained in 36% isolated yield. The remaining

![Scheme 5](image-url)
mass balance is believed to be oligomerization byproducts. It was determined by $^1$H NMR that the two aryl groups are cis to one another, supporting a syn-insertion mechanism. Surprisingly, byproducts resulting from two-component Suzuki coupling were only detected in low yields. These results illustrate that the reaction conditions can be tuned to favor incorporation of the conjunctive π bond in preference to traditional two-component cross-coupling. Under optimized conditions, a wide range of aryl electrophiles and nucleophiles containing various functional groups were well tolerated with diarylacetylene substrates (eq 2). For non-symmetric substrates, the regiochemical outcome was dependent on both electronic and steric factors. The authors comment that the aryloboronic acids are preferentially incorporated at the more hindered and more electropositive carbon atom. Electronic polarization of the alkyne was an effective means of controlling the regioselectivity. For example, the regiosomeric ratio of products formed from 1-(4-nitrophenyl) propane is 15:1, a dramatic increase compared to that of the standard 1-phenylpropane (6.5:1). In a subsequent study, Zhang and Larock established that vinyl iodides and vinylboronic acids are also competent coupling partners in this conjunctive cross-coupling, reliably delivering an assortment of conjugated dienes. The authors comment that the arylboronic acids are preferentially used in place of aryloboronic acids to effect 1,2-arylcyanation under palladium catalysis. In 2015, Nevada and co-workers reported a palladium-catalyzed carboperfluoroalkylation of terminal alkynes using perfluoroalkyl iodides and aryloboronic acids. A plausible catalytic cycle for this transformation involves radical-based oxidative addition and migratory insertion to yield a vinylpalladium(II) species that can undergo transmetalation and reductive elimination cascade.

Over the ensuing decade following Larock’s work, a more diverse array of electrophiles and organometallic nucleophiles were employed toward the synthesis of tetrasubstituted alkenes via conjunctive cross-coupling catalyzed by palladium and other metals. In 2009, Terao et al. developed a nickel-catalyzed conjunctive cross-coupling of terminal allicylenes with alkylzinc or alkylmagnesium reagents and secondary or tertiary alkyl electrophiles (eq 3). Interestingly, the reaction proceeded with nearly complete stereoselectivity for the Z-alkene product, corresponding to addition of the electrophilic and nucleophilic components in an anti fashion across the alkyne. This result was rationalized by invoking an initial radical addition to the terminal end of the acetylene substrate catalyzed by a nickel(II) species. Subsequently, the resulting vinyl radical can recombine with the catalyst to form a vinylnickel(II) species that undergoes transmetalation and reductive elimination. This seminal work represents the first, non-tethered intramolecular dialkylation of alkynes via conjunctive cross-coupling. In related work by Nevada in 2016, a radical-based anti addition to terminal alkynes was reported using a nickel catalyst with aryloboronic acids and unactivated alkyl halides under the same catalytic manifold. With boronic acids as nucleophiles, broad functional group tolerance was observed (>50 examples). It was also discovered that alkyl iodides containing tethered alkenes could be employed; in this case, the nickel-mediated cyclization generates a radical intermediate that can then engage the alkyne. This allows for the generation of complex heterocyclic scaffolds in a single step (eq 4). Control experiments ruled out the possibility that vinyl halides were formed in situ—as these compounds were not reactive coupling partners under the reaction conditions—which is consistent with a conjunctive cross-coupling mechanism.
In 2015, Xue et al. developed a nickel-catalyzed, three-component conjunctive coupling of symmetrical diallylacetylenes and alkylarylacetylenes using aryl Grignard reagents and aryl halides. The authors proposed an initial carbomagnesiation to generate a vinylmagnesium species that can undergo a Kumada-type cross-coupling with an arylnickel component, yielding a range of diarylated tetrasubstituted alkenes. Although this reaction is conceptually related to the earlier examples from Larock, the reaction mechanism is distinct and can be thought of as a nickel-catalyzed two-component coupling where one of the coupling partners is generated in situ in a process that does not involve nickel. The resulting alkenyl Grignard reagent was shown to react faster than the progenitor aryl Grignard reagent, and detailed kinetic studies revealed that arylmagnesiation of the alkyne is rapid under the reaction conditions. Along the same lines, Shintani et al. reported a cooperative palladium–copper catalysis for the arylsilylation of allenes. The authors concluded that transmetalation was active in these processes that do not involve nickel. The resulting alkenyl Grignard reagent was shown to react faster than the progenitor aryl Grignard reagent, and detailed kinetic studies revealed that arylmagnesiation of the alkyne is rapid under the reaction conditions. Along the same lines, Shintani et al. reported a cooperative palladium–copper catalysis for the arylsilylation of allenes. The authors concluded that transmetalation was active in these processes that do not involve nickel.

Additionally, Brown and co-workers have disclosed a copper-catalyzed carboboration of internal alkenes and allenes using B2Pin2 and aryl iodides.

3.2. Three-Component Conjunctive Cross-Couplings of Allenes

Contemporaneous with the development of efficient three-component conjunctive cross-couplings of alkenes, extension of this methodology to allenes was also actively pursued. In the context of cross-coupling reactions, allenes serve as precursors for π-allyl species, which are relatively stable and resilient toward β-hydride elimination. In their pioneering work, Cheng and co-workers reported in 2002 a palladium-catalyzed, chemo-, regio-, and stereoselective conjunctive cross-coupling of allenes, arylboronic acids, and organohalides. The optimized process tolerated aryl, vinyl, and α-halo ester electrophiles, as well as electron-rich and electron-poor arylboronic acids (Scheme 6).

![Scheme 6. Palladium-Catalyzed Conjunctive Cross-Coupling Using Allenes as Conjunctive Reagents. (Ref. 33)](image)

In the case of monosubstituted allenes, the stereoselectivity was governed by the steric bulk of the substituent. For example, tert-butyl-substituted allenes gave stereoselectivities as high as 97:3 (E:Z). A stereomodel proposed by the authors suggests that the palladium catalyst coordinates preferentially to the less sterically congested face of the allene, and that migratory insertion then happens from this face. To probe the effect of additional steric bulk at the metal center, a survey of phosphine ligands was undertaken, which revealed that higher selectivities could be obtained by tuning the ligand structure. In a separate report, Cheng’s group utilized a nickel catalyst with alkenylzirconium reagents and aryl and vinyl halides to achieve a highly E-selective synthesis of 1,4-dienes. Though the same mechanism was invoked as in the previously described studies, attempts to promote this reaction with a palladium catalyst only yielded the two-component cross-coupling products. The authors attributed this result to the faster rate of arylnickel(II) insertion compared to that of its palladium counterpart.

In addition to the palladium- and nickel-catalyzed conjunctive cross-couplings of allenes, several groups have employed copper catalysis in analogous processes. Notably, Brown and colleagues found that [IMes•CuCl] catalyzed the carboboration of monosubstituted allenes, leading to the desired products in >98:2 regioisomeric ratios (eq 5). Interestingly, the regiochemical outcome of this copper-catalyzed reaction is the opposite of that of the palladium- and nickel-catalyzed counterparts. The authors concluded that transmetalation occurs first and results in the generation of the least-substituted allylcopper species, which can undergo an oxidative addition–reductive elimination sequence to yield the desired products.

4. Strategies for Conjunctive Cross-Coupling Using Alkenes as Conjunctive Reagents

Despite the many advances described above in which alkynes and allenes serve as π-bond conjunctive reagents, the translation of these strategies to alkenes (particularly those that are unconjugated) remains an ongoing challenge. The affinity of transition metals for alkenes is significantly diminished in comparison to their affinities for alkynes and allenes, which lowers the rate of the initial migratory insertion event. For this reason, the competitive, undesired two-component cross-
Carbon–Carbon π Bonds as Conjunctive Reagents in Cross-Coupling
Joseph Derosa, Van T. Tran, Vincent A. van der Puyl, and Keary M. Engle*

4.1. Electronically Activated or Conjugated Alkenes
In order to achieve efficient and selective 1,2-difunctionalization of alkenes via conjunctive cross-coupling, the intervening alkylmetal species must be sufficiently stable. Alkene substrates bearing functional groups in conjugation with the alkene π system often result in alkylmetal species that are more stable (e.g., π-allyl metal, π-benzyl metal, or metal enolate). In 2009, Urkalan and Sigman reported a 1,2-diarylation reaction of conjugated terminal alkenes with 2 equivalents of an aryllstannane through the formation of a stabilized palladium(II) π-benzyl or allyl intermediate (eq 6).35

Though not formally a three-component conjunctive cross-coupling reaction, 1,2-difunctionalization is achieved despite the high driving force for β-hydride elimination to re-establish the conjugated system. The authors note that oxidative Heck and hydroarylation byproducts were observed during optimization. Although the formation of these byproducts was never completely suppressed, the desired 1,2-diarylation product was formed in 78% yield under the optimal conditions of DMA as solvent, copper(II) as co-catalyst, and molecular oxygen as terminal oxidant. Through exploration of the substrate scope, it was discovered that the electronic properties of the styrene substrate play a substantial role in controlling selectivity for 1,2-diarylation over 1,1-diarylation. According to the reported trend, electron-withdrawing groups on the styrene promoted the formation of 1,1-diarylation products. Notably, unconjugated terminal alkenes gave exclusively the 1,1-diarylation products due to favorable formation of a stabilized π-benzyl species after incorporation of the first aryl equivalent via β-hydride elimination–reinsertion. In a further development by Sigman’s group, two distinct coupling partners could be introduced across 1,3-dienes using a similar π-allyl stabilization strategy. In this report, styrenyl 1,3-dienes were reacted with vinyl triflates and arylboronic acids under palladium catalysis to generate 1,2-difunctionalized products (eq 7).36 When a deuterated starting material was subjected to the reaction conditions, >95% deuterium retention was observed in the product, further emphasizing the power of such a stabilization strategy. Similar to their previous observations, the authors found that 1,1-dicarbofunctionalization was favored in the absence of conjugation.

Conjugated alkenes offer other advantages in the context of conjunctive cross-coupling. For instance, the electronic polarization can be used to control regioselectivity and stabilize radical intermediates. In a seminal study, Baran and colleagues described a nickel-catalyzed approach to 1,2-difunctionalization using alkenes (eq 8).37 This radical-based process employs a collection of versatile redox-active esters and organozinc reagents with acrylate substrates. The mechanism of this reaction takes advantage of acrylates as effective radical acceptors and of the stability of the resulting metal enolates. An alkyl radical attacks the terminal end of the alkene, generating a stabilized α-radical that recombines with an aryllnickel species. A subsequent reductive elimination step yields the desired products and regenerates the nickel catalyst.

4.2. Simple, Unconjugated Alkenes
In the absence of functional groups in conjugation with the alkene, 1,2-difunctionalization of alkenes via conjunctive cross-coupling is plagued by rapid β-hydride elimination, making it difficult to selectively incorporate two differentiated reaction partners in a 1,2-fashion. After migratory insertion, there are several possible fates for the resulting alkylmetal intermediate.
β-Hydride elimination, followed by dissociation of the metal hydride and HX reductive elimination lead to formation of the undesired Heck product. In some cases (particularly when β-hydride elimination generates styrene), the metal hydride can reinsert to generate a π-benzyl species that can be further functionalized to give 1,1-difunctionalization.

In the context of "simple" alkene substrates, ethylene is an example of an unconjugated conjunctive reagent that is not electronically activated. In 2012, Saini and Sigman reported a 1,1-difunctionalization of ethylene with a palladium catalyst using vinyl triflates and vinyl- or arylboronic acids. After initial formation of a 1,3-diene–bound palladium hydride intermediate via a Heck-type pathway, reinsertion of the metal hydride leads to a stabilized π-allyl palladium species that can intercept an arylboronic acid for 1,1-difunctionalization. A limitation of this strategy is that the C–C reductive elimination can occur on either side of the π-allyl species, leading to a mixture of regioisomers (Scheme 7). In subsequent studies, Sigman’s team reported that regiocontrol could be improved by employing aryldiazonium salts as electrophiles in place of vinyl triflates. In a seminal study published in 2017, Nevado’s group reported a nickel-catalyzed reductive dicarbofunctionalization of alkenes using tertiary alkyl iodides and aryl iodides. In this elegant work, a wide range of alkenes including acrylates, acrylonitriles, allylic acetates, and styrenes were competent conjunctive reagents for 1,2-arylation by way of a radical-based mechanism (eq 9). Impressively, internal alkenes were also effective substrates, delivering the desired products with high regio- and diastereoregular control. Notably, steric factors have an unfavorable effect on the efficiency of the reaction, as ortho-substituted aryl iodides lead to diminished yields.

4.3. Conjunctive Cross-Coupling of Alkenes via Metallate Rearrangements

In 2016, Morken demonstrated a powerful tool for the enantioselective 1,2-difunctionalization of vinyl boronates. In this conjunctive cross-coupling, two organometallic nucleophiles merge to generate an ate-complex that can undergo a metal-induced metallate rearrangement. In the net transformation, two carbogenic fragments are added across the alkenyl portion of the conjunctive vinyl boronate reagent, leaving the C–B bond unperturbed. Initially, a palladium catalyst with a chiral ferrocene-based ligand was employed with organoboronic esters, organolithium species, and aryl/alkenyl triflates to generate enantioenriched 1,2-difunctionalized organoboron products that are typically oxidized to provide the corresponding alcohols (Scheme 8). During reaction optimization, the authors screened a set of chiral ligands in an effort to favor reductive elimination over β-hydride elimination of the putative π-allyl species. In the context of this study, a few examples are provided below.

**Scheme 7.** 1,1-Difunctionalization of Simple Alkenes via Conjunctive Cross-Coupling. (Ref. 36, 39)

**Scheme 8.** Conjunctive Cross-Coupling via Metal-Induced Metallate Rearrangement. (Ref. 41)
alkyl palladium intermediate. To initiate these studies, bidentate ligands with large bite angles were first examined, such as JosiPhos and MandyPhos (L7), which provided very high enantiomeric purity and yield. Though tolerating an impressive range of electrophiles and nucleophiles, electron-poor nucleophilic components did not react well under the optimal conditions. The authors concluded that this reactivity trend is consistent with a metatation rearrangement mechanism, which requires nucleophilic attack of the alkene to generate the key alkylpalladium(II) intermediate.

Morken’s team expanded the utility of this metatation rearrangement approach by substituting the organolithium species with Grignard reagents activated by NaOTf, resulting in a protocol that exhibited increased functional group tolerance. Moreover, the newly developed conditions allowed aryl halide electrophiles to be compatible with the reaction. The scope of migrating nucleophilic groups was later expanded to include alkenyl groups, providing access to enantiopure allylic boronates. Additionally, this strategy was recently adapted to operate under nickel catalysis, enabling the conjunctive cross-coupling of 9-BBN boranes with aryl electrophiles by using simple chiral diamine ligands to achieve enantioinduction.

4.4. Substrate Directivity Approach toward Conjunctive Cross-Coupling of Alkenes

In each of the examples presented thus far, the major challenge has been to avoid β-hydride elimination while still promoting insertion of the transition metal catalyst into an alkene substrate. In the absence of electronically activating substituents (as in Section 4.1) or a vacant p-orbital (as in Section 4.3) adjacent to the alkene, it remains fundamentally challenging to develop conjunctive cross-coupling reactions using unconjugated alkenes (particularly internal alkenes). In the broad field of alkeno functionalization, proximal Lewis basic groups that chelate transition metals have been used successfully as part of a strategy for promoting reactivity and controlling selectivity. Substrate directivity has been utilized in venerable reactions such as the Sharpless asymmetric epoxidation of allylic alcohols and the Noyori asymmetric hydrogenation of acrylic acid derivatives. Although substrate directivity also has a rich history in Heck-type cross-coupling reactions, its application in the context of 1,2-dicarbofunctionalization of unconjugated alkenes has been comparatively unexplored.

Our group has recently published a collection of directed alkene functionalization reactions. Utilizing bidentate coordinating groups, such as Daugulis’s removable 8-aminoquinoline (AQ) auxiliary, we have demonstrated that such directing groups can enable unique modes of bond construction in alkene functionalization through stabilization of the metalacycle intermediates that are formed upon nucleometalation. In 2017, we developed a nickel-catalyzed conjunctive cross-coupling using aryl iodides and alkyl- or arylzinc reagents to enable the regioselective synthesis of β,γ-dicarbofunctionalized products (Scheme 9). Strategic use of the AQ directing group serves to simultaneously control the regioselectivity and prevent rapid β-hydride elimination. In the proposed reaction mechanism, stabilized nickelacyclic 14 is formed via a 1,2-migratory insertion, and is intercepted with an organozinc species in a transmetalation/C–C reductive elimination sequence. Internal alkenes were also found to be competent in this reaction, providing the desired 1,2-arylation products as a result of a syn-insertion pathway. Importantly, the steric environment of the nickelacycle can be tuned to influence the diastereoselectivity of the reaction. After the conjunctive cross-coupling has been completed, these auxiliaries can be hydrolyzed to unmask synthetically useful carboxylic acid functional groups.

In 2017, Giri and co-workers employed a directing group approach for the nickel-catalyzed diarylation of 2-vinylbenzaldimines, which contain a styrenyl alkene (Scheme 10). Arylzinc reagents and aryl halides were incorporated regioselectively via an intervening imine-bound metallacycle. A plausible catalytic cycle is reported in which an initial oxidative addition with nickel(0) provides an imine-coordinated arynickel species that inserts into the proximal alkene. It is noteworthy that 2-vinylbenzaldimines can be replaced with imines derived from 2-vinylanilines, thereby expanding the utility of the method.

Following these discoveries, Zhao’s group disclosed a series of 1,2-dicarbofunctionalization reactions of N-allyl-2-aminopyrimidines by using a directed conjunctive cross-coupling approach and aryl- and styrenylboronic acids as the nucleophilic component (Scheme 11). The regioselectivity...
was determined by the choice of electrophile, whereby vinyl bromides led to incorporation of the electrophile at the terminal position and alkenyl halides led to incorporation of the electrophile at the internal position. Based on the correlation of higher regioselectivity with increasing electron density on the styrenyl boronic acid, the authors proposed that coordination of the nickel center to the styrenyl alkene in the intermediate alkynickel species facilitates 1,2-incorporation rather than 1,3-incorporation via chain-walking, as observed when methyl or aryl iodides are used. In the case of alkenyl halides, observation of a Suzuki–Miyaura side product suggested an intermediate nickel species with two carbanion ligands resulting from oxidative addition and subsequent transmetalation. The authors hypothesized that a stronger nickel–C(sp) bond enables preferential 1,2-migratory insertion of the aryl or alkenyl component, leading to the observed reversed regioselectivity. With the 1,2-arylalkynylation variant of the reaction, an N-allylbenzamide was also a viable substrate.

5. Conclusion and Outlook
In recent years, significant effort has been put forward to develop general methodology for 1,2-dicarbofunctionalization of carbon–carbon π bonds. From the perspective of complex-molecule synthesis, the conjunctive cross-coupling methodology would be highly enabling. Alkynes, alkenes, and alkenes have been actively explored as conjunctive reagents that can serve as linchpins to bring together two additional reaction partners. The strategies and approaches discussed in this review and their subsequent applications illustrate the exciting potential for this area of research and also highlight existing challenges. By overcoming present limitations, such as suppressing the rapid rate of β-hydride elimination through ligand design, we anticipate that conjunctive cross-coupling will emerge as an even more powerful synthetic strategy in the years to come.

6. References
Carbon–Carbon π Bonds as Conjunctive Reagents in Cross-Coupling

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