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The Spectacular Resurgence of Electrochemical Redox Reactions in Organic Synthesis

Carbon–Carbon π Bonds as Conjunctive Reagents in Cross-Coupling

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CEO, MilliporeSigma

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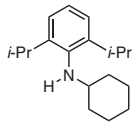
Chen, Y.; Turlik, A.; Newhouse, T. R. *J. Am. Chem. Soc.* **2016**, *138*, 1166.



809527

InChI Key: **YDWZEQMCJKBGTO-UHFFFAOYSA-N**

809527	*N*-Cyclohexyl-2,6-bis(1-methylethyl)benzenamine (CyanH)	1 g

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Udit Batra, Ph.D.
CEO, MilliporeSigma

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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.

Detail from ***Ginevra de' Benci***. Photo courtesy National Gallery of Art, Washington, DC.

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***

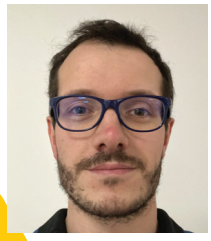
The Spectacular Resurgence of Electrochemical Redox Reactions in Organic Synthesis

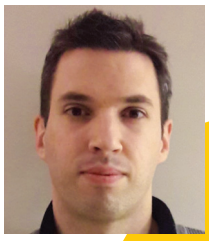

Dr. P.-G. Echeverria


Mr. D. Delbrayelle


Dr. A. Letort


Ms. F. Nomertin


Dr. M. Perez


Dr. L. Petit

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Dedicated to the memory of Prof. Dr. István E. Markó

Keywords. organic electrosynthesis; 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.

Outline

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 electrosyntheses—the Kolbe reaction, in which a carboxylic acid is electrochemically decarboxylated and the resulting radical dimerizes—dates back to 1848.[1] Since then, many industrial processes that use organic electrochemistry have been developed, and huge tonnages of commodity organic chemicals are produced electrochemically.[2] 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.[3-12] This review is not a comprehensive treatment of the topic, and is intended only to highlight recent, salient, and representative applications of electrochemical redox reactions in organic synthesis, with possible industrial development in mind.

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, they act both as solvent and electrolyte.[13] The cell can also be divided into separate anodic and cathodic compartments to avoid recombination of the products in the bulk. In that case, a membrane, diaphragm, or electrochemical junction is required. Finally, a reference electrode can be employed in addition to the anode and cathode, to better measure and control the potential.

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,[14,15] 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.[16] Both approaches will be reported on in this article.

3. Anodic Oxidation

3.1. Alcohol Oxidation

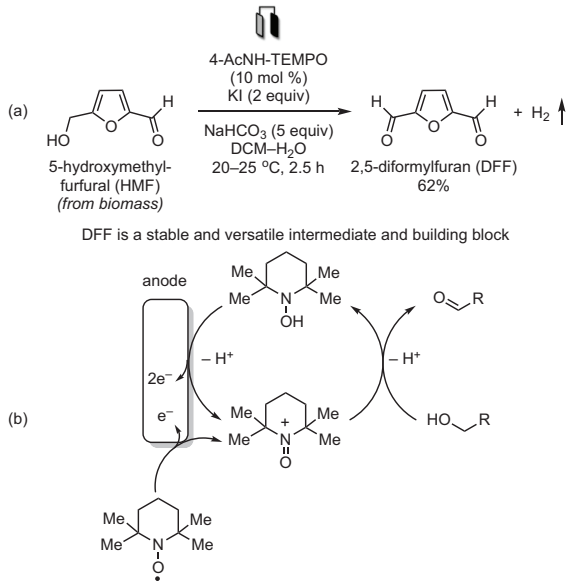
While a plethora of alcohol oxidation methods have been developed, the number of such reactions that are used on a large scale is quite small. This can be attributed to safety concerns over the fact that the three ingredients needed for combustion (oxidant, fuel, and energy) can be present in the reactor at the same time.[17] Proper design of reaction conditions and careful process safety studies can help mitigate the risks associated with large-scale oxidations. In practice, many API syntheses invoke such a transformation and the Anelli oxidation is often employed.[18] The advent of TEMPO-mediated electrochemical alcohol oxidation has spurred interest in many research groups, and has been met with considerable success, leading to the development of general electrochemical methods to oxidize alcohols with TEMPO-like radicals.[19] Previous electrochemical oxidation methods using in situ generated iodine have been replaced with more general variants.[20] The TEMPO-mediated alcohol oxidation has now become an enabling method, and is expected to be widely adopted in total synthesis and methodology development. This approach has found application in the context of innovative production of biosourced materials such as the formation of 2,5-diformylfuran (DFF) from the parent primary alcohol, 5-hydroxymethylfurfural (HMF) (**Scheme 1**, Part (a)).[21] Mechanistic studies were conducted using cyclic voltammetry to better understand the reactivity of various alcohols towards TEMPO and NHPI (Scheme 1, Part (b)),[22] and mechanistic studies of NHPI-mediated alcohol oxidation using rotating disc electrode voltammetry have also been published.[23]

When contemplating electrochemistry for synthesis, one should study the effect of a given electrode material on the reaction of interest, as well as the fact that electrodes can also be grafted with active chemical species. In some cases, this can result in increased TON for classical oxidations.[24] This intrinsically waste-free variant of the well-established TEMPO-mediated oxidation is conceptually appealing, but its wide

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.[25] An interesting comparative approach was described during the synthesis of *N*-isobutyl-(2*E*,6*Z*)-dodecadienamides, which showed that not all reactions benefit from electrochemistry.[26] 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.[27] 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 CO_2 into CO along with the TEMPO-mediated oxidation of alcohols into the corresponding ketones at the anode.[28] 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.[29]



Scheme 1. (a) The 4-AcNH-TEMPO-Mediated Electrochemical Oxidation of Alcohols and (b) Proposed Mechanism for the TEMPO-Mediated Variant. *(Ref. 21,22)*

3.2. C–Y Bond Formation

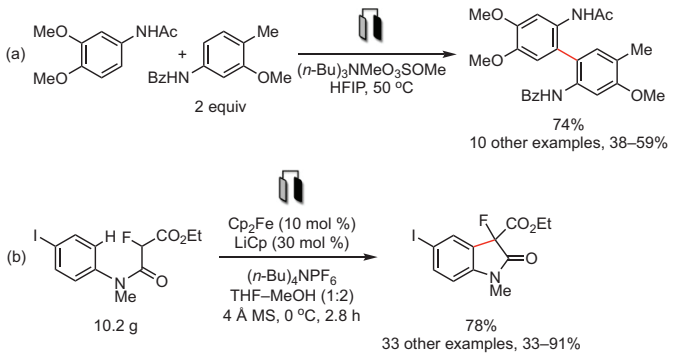
One of the great strengths of electrochemistry lies, not only in the possibility of turning existing C–O bonds into C=O bonds, but also in the possibility of creating C–C, C–N, C–O, and C–S bonds from C–H bonds, thus broadening the scope of this technology.

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)).[30] This electrochemical transformation does not require a leaving group to direct the nucleophilic attack from the anilide 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.[31–35]

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 O_2. 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)).[36] Similarly, indoles can be accessed easily and in good-to-excellent yields



Scheme 2. Electrochemical C–C Inter- and Intramolecular Cross-Couplings. *(Ref. 30,36)*

from the corresponding enamines through an electrocatalytic, intramolecular, and dehydrogenative annulation that is oxidant- and transition-metal-free.[37] Interestingly, the anodic oxidation of unactivated cyclooctene leads to the formation of the [2 + 2] cycloaddition syn dimer in 70–80% yield.[38]

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.[39] 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 potential antimalarial and antitumor activities (**Scheme 3**).[40] 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)biaryls in 63–99% yields.[41] This step- and atom-economical S_NH reaction offers the clear advantage of not requiring the use of metal catalysts, stoichiometric quantities of chemical oxidants, or haloaromatics as reactants.

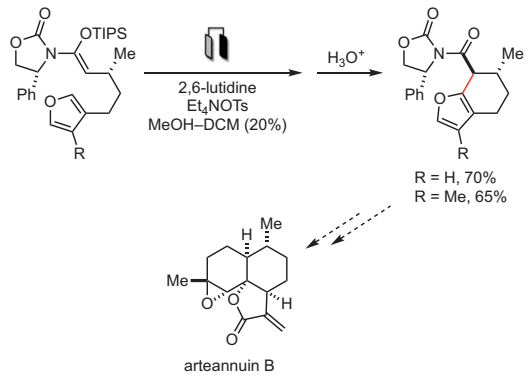
Yoshida and co-workers have recently developed a stabilized-cation-pool method for the metal-free and oxidant-free cross-coupling of benzylic and aromatic C–H bonds.[42] 4-Methoxytoluene was initially used as the substrate for screening of the stabilizing groups, which led to identifying diphenylsulfilimine (Ph_2S=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**).[42]

A straightforward method for late-stage functionalization of pharmacophores has very recently been proposed by Zeng's group.[43] 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 NH_4I 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 [$RC(O)CO_2I$]. 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.

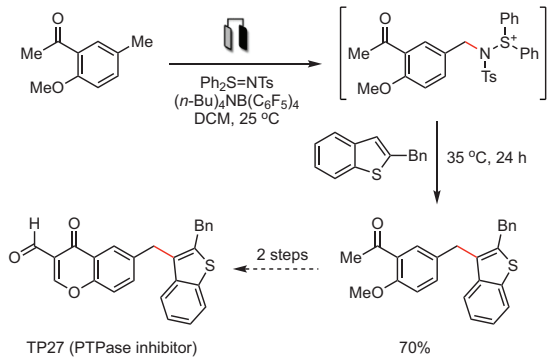
3.2.2. C–N Bond

An efficient, practical, and gram-scale electrochemical method for the α-amination of ketones using simple conditions has been reported by Liang et al.[44] 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 benzylic compounds.[45] The authors reported that unprotected imidazole



Scheme 3. Intramolecular Anodic Coupling of Alkenes Involving Radical Cations from Enol Ethers. *(Ref. 40)*

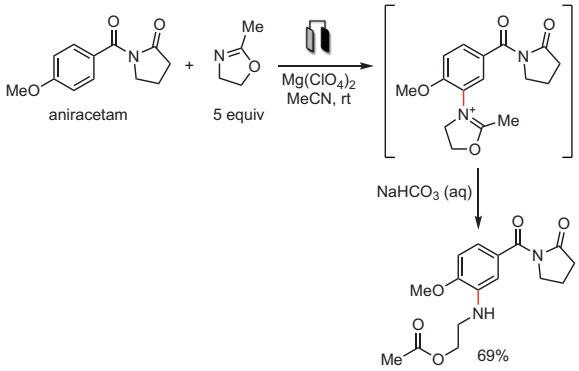


Scheme 4. Benzylic C–H/Aromatic C–H Cross-Coupling via the Stabilized-Cation-Pool Method. *(Ref. 42)*

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 Glorius[46] 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.[47] 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 $NaHCO_3$. 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**).[47]

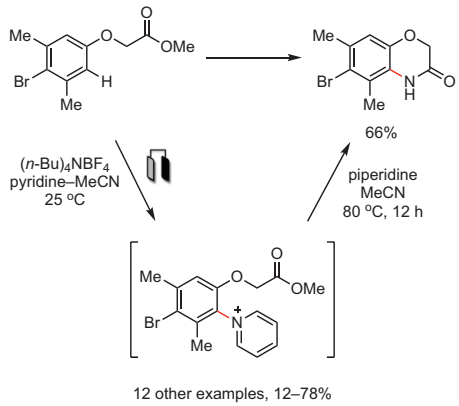
Very recently, Waldvogel and co-workers developed a very efficient, sustainable, and direct anodic C–H amination of phenoxy acetates, leading to 1,4-benzoxazin-3-one scaffolds, which are important structural features in biologically active molecules and natural products such as DIBOA and DIMBOA.[48] 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**).[49]



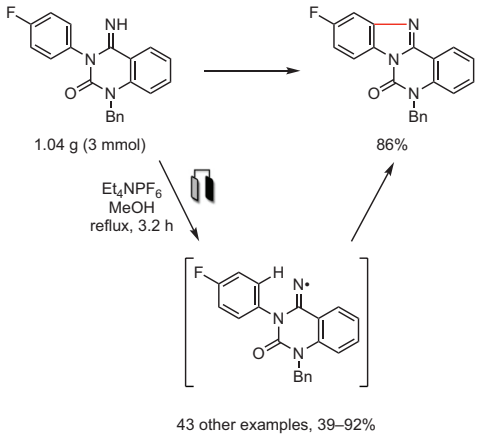
Scheme 5. The Heterocyclization-Enabled Electrooxidative Coupling of Functional Primary Alkylamines with Aromatics as Applied to the Functionalization of Aniracetam. *(Ref. 47)*

Amidinyl radical formation through anodic N–H cleavage has been employed by Xu's group as a sustainable, atom-economical, scalable, and metal- and reagent-free method for C–H bond functionalization in (hetero)aromatics (**Scheme 7**).[50] 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,[51] anilines,[52] cyclic carbamates,[53,54] and (aza)indoles.[55]

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**).[55,56] A distinct advantage of this method is the circumvention of the use of stoichiometric amounts of toxic metal hydrides such as $(n\text{-Bu})_3SnH$.



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



Scheme 7. C–H Bond Functionalization in (Hetero)aromatics through Anodic N–H Cleavage and Amidinyl Radical Formation. *(Ref. 50)*

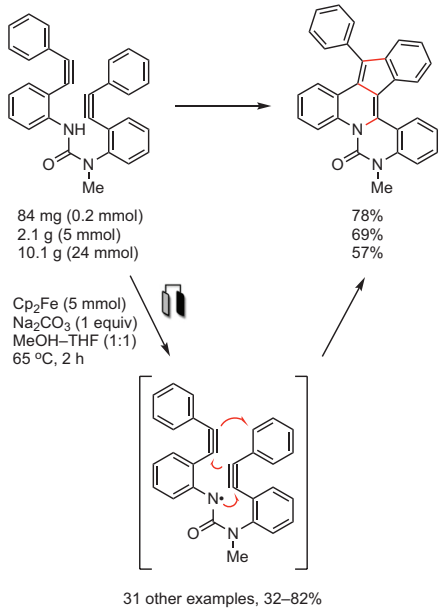
In 2017, Lin's group reported an approach to synthesize vicinal diamines through a Mn(II)-catalyzed electrochemical diazidation of alkenes.[57] Following voltammetric and spectrophotometric studies, the authors proposed a mechanism in which a radical adduct ($RHC^{\bullet}$–CH_2N_3) is generated after transfer of an azidyl group from the active metal azidyl [Mn(III)–N_3] 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 ($RHCN_3$–CH_2N_3). 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

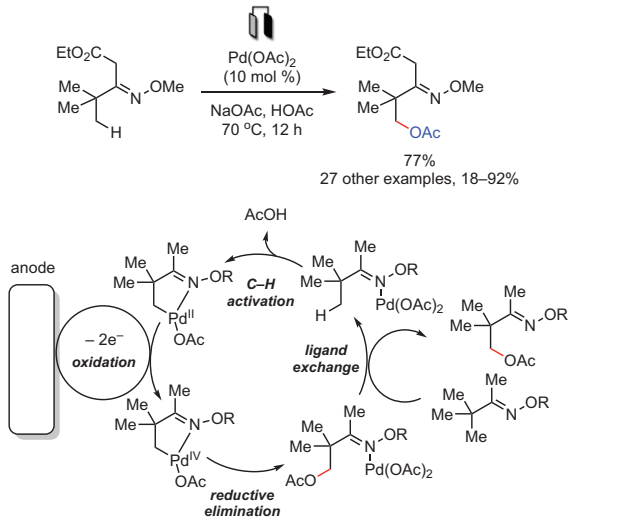
A very recent paper reported the first example of a Pd(II)-catalyzed electrochemical activation and oxygenation with oxyanions of C(sp^3)–H bonds contained in oxime derivatives.[58] This method, which is environmentally benign and avoids the use of strong chemical oxidants, exhibited broad substrate 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(sp^3)–H oxygenation method developed by Sanford and which employs $NaNO_3$ as catalyst.[59]

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.[60] 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 (Cl_4NHPI, 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.[61]

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.[62,63] These moieties



Scheme 8. Amidyl Radical Cyclization Cascade of Urea-Tethered Diynes for the Efficient Electrochemical Synthesis of Polycyclic N-Heteroaromatics. *(Ref. 56)*



Scheme 9. Environmentally Benign Pd(II)-Catalyzed Electrochemical Activation and Oxygenation of C(sp^3)–H Bonds in Oxime Derivatives. *(Ref. 58)*

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 hydroxyphthalimide derivatives. The reaction conditions were optimized and scaled up (50 g scale) for sclareolide (**Scheme 10**),[62] 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 carbon-based 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

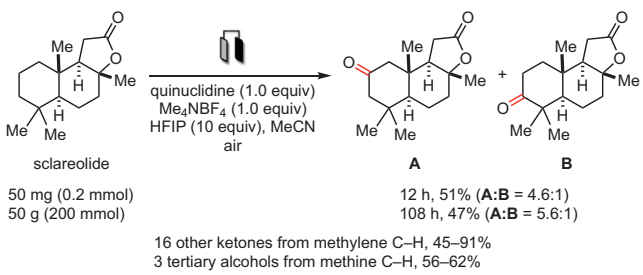
Fewer C–S bond-forming reactions are known as compared to reactions that generate C–C and C–N bonds. This could be due to the fact that sulfur-containing molecules can be good metal scavengers. Electrochemical synthesis could pave the way to developing C–S cross-coupling reactions mainly because heavy-metal 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 sulfonylhydrazides (Ar^1SNHNH_2). This robust method works well for a broad range of halogenated and heterocyclic substrates. Mechanistically, the oxidative cleavage of Ar^1SNHNH_2 at the anode releases N_2 and a sulfonyl radical ($Ar^1SO_2^{\bullet}$). The latter reacts with an α,β-unsaturated carboxylate [(*E*)-$Ar^2CH{=}CHCO_2^-$] to generate an α-sulfonyl carboxylate [$Ar^2CH^{\bullet}$–$CH(Ar^1SO_2)CO_2^-$] that can easily undergo decarboxylation to selectively access the (*E*)-unsaturated sulfone [(*E*)-$Ar^2CH{=}CH(Ar^1SO_2)$] in good yield.[64,65]

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 arenes, 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 sulfide radical (ArS•), followed by rearomatization, leads to the observed cross-coupling product.

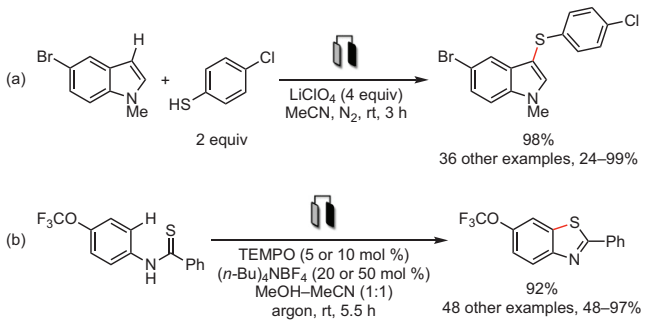
An intramolecular variant, leading to a broad range of benzothiazoles and thiazolopyridines from *N*-(hetero)-arylthioamides, was recently reported by Qian et al. (Scheme 11, Part (b))[67] Electron-rich and electron-poor (hetero)aromatics were suitable substrates, and a catalytic amount (5 mol %) of 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*-Arylthioureas can be generated in situ directly from the reaction of isothiocyanates with secondary amines such as morpholine or dialkylamine under electrolytic conditions [(n-Bu)$_4$NBF$_4$ (6 equiv), MeCN–H_2O (9:1), 70 °C, 4 h]. The *N*-arylthioureas 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)*



Scheme 11. The Electrochemical C–S Cross-Coupling Reaction. *(Ref. 66–68)*

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 [$R^1CONCH_2R^2R^3$] or carbamates [$R^1OCONCH_2R^2R^3$] can easily undergo anodic oxidation to the corresponding N-centered radical cations [$R^1CON^{+\bullet}CH_2R^2R^3$], which then lead to the *N*-acyliminium intermediate [$R^1CON^+(=CHR^2)R^3$]. This iminium ion is instantaneously trapped by a nucleophile (classically by alcohols used as solvents) to yield a hemiaminal [$R^1CON(CH(OMe)R^2)R^3$]. 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 amines[76] and chiral enamines[77] have been employed in this transformation to build C–N and C–C bonds, respectively.

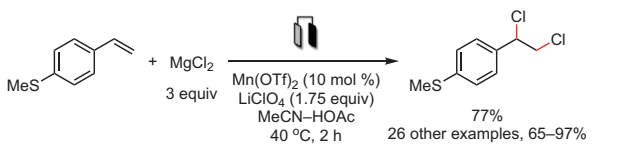
To broaden the scope of this anodic oxidation, the concept of the cation pool method was developed by Yoshida.[78–80] Taking advantage of the cation pool method and flow chemistry, Ley and co-workers accomplished a rapid (two-step) synthesis of nazlinine, a biologically active indole alkaloid, as well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

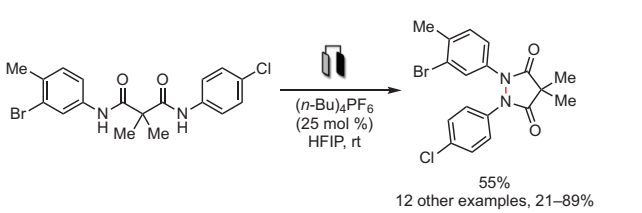
3.5. Miscellaneous Reactions

3.5.1. [3 + 2] Annulation

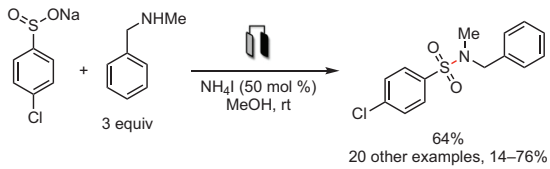
A scalable, green, and efficient electrochemical oxidative [3 + 2] annulation between C-2 or C-3 substituted *N*-acetylindoles and phenols was reported from Lei's laboratory. This external-oxidant-free and metal-free reaction produces benzofuroindolines (important structural motifs in bioactive natural products such as phalarine, diazonamides, and azonazines) in good-to-excellent yields (up to 99%) under atmospheric conditions. Depending on the position of the substituent in the *N*-acetylindole 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]



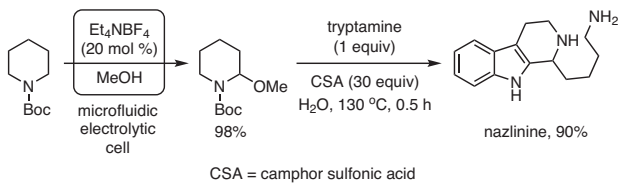
eq 1 *(Ref. 69)*



eq 2 *(Ref. 70)*



eq 3 *(Ref. 71)*



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.[84] 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.[85] Fuchigami's group has studied extensively the partial electrochemical fluorination of organic compounds, and these studies have shown that sulfides are privileged reaction partners.[86]

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.[87] In Pd-catalyzed C–H functionalizations, replacing strong chemical oxidants with electrochemical oxidation has enormous potential in streamlining chemical syntheses of complex molecules and, at the same time, provides an opportunity to develop efficient processes. This has been recently reviewed by Mei's group at the Shanghai Institute of Organic Chemistry.[88]

4. Cathodic Reduction

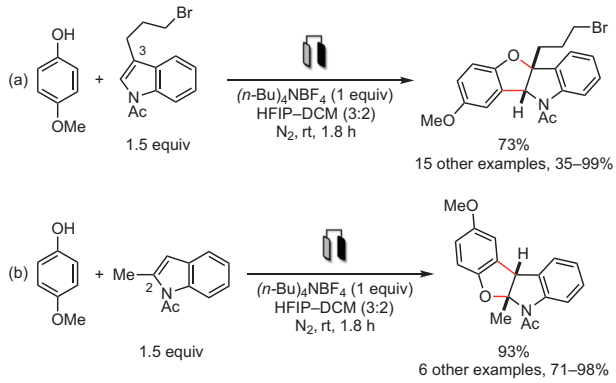
4.1. C–Y Bond Formation

4.1.1. C–C Bond

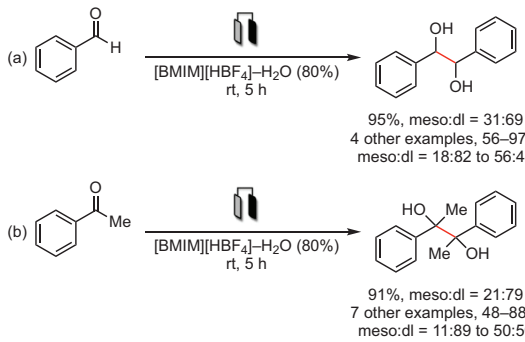
The reductive electrochemical pinacol coupling of ketones and aldehydes has been successfully carried out in an 80% mixture of a room-temperature ionic liquid (RTIL) and water {[BMIM][BF_4]–H_2O}. This scalable process obviates the need for a catalyst–cocatalyst system, avoids the generation of metallic 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**).[89] A more recent example of an electroreductive C–H functionalization is the direct arylation of pyrroles with various aromatic halides.[90] This novel C–C bond-forming reaction employs a sacrificial zinc anode and 10 mol % of perylene-3,4,9,10-tetracarboxylic acid diimides (PDIs) as electron-transfer mediators. It readily takes place at room temperature in [EMIM][NTf_2]–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**).[91] A similar approach reported by Kise's group employed aromatic ketones with 1,3-dimethyluracils or coumarins as the activated olefins.[92,93]

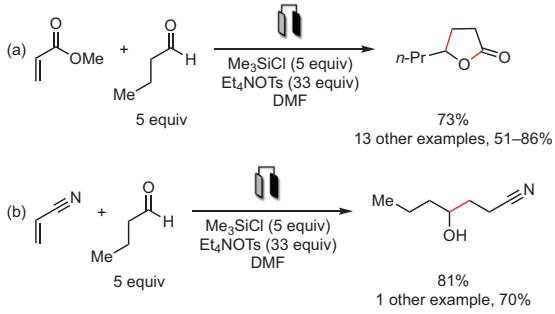
Only recently has the transition-metal catalyzed C(sp^3)–C(sp^3) coupling been explored in the context of electrochemistry. In 2017, Lai and Huang reported the palladium-catalyzed Barbier–Negishi-type allylation of alkyl or benzyl halides in air and in aqueous medium by using a Zn cathode. This novel, ligand-free cross-coupling takes place through the intermediacy of an in situ



Scheme 13. Regioselective, Intermolecular, Electrooxidative [3 + 2] Annulation Leading to Benzofuro[2,3-*b*]indolines and Benzofuro[3,2-*b*]indolines. *(Ref. 83)*



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



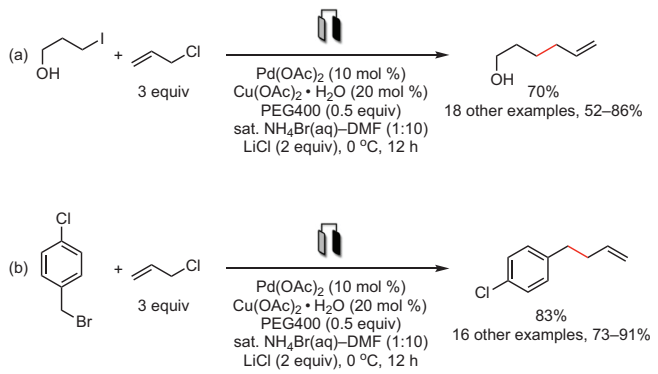
Scheme 15. Electroreductive Coupling of Activated Olefins with Carbonyl Compounds Leading to γ-Lactones or γ-Hydroxynitriles. *(Ref. 91)*

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

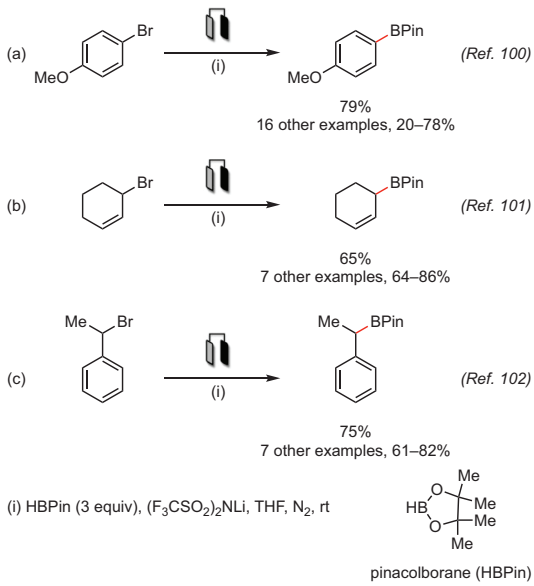
While organoboron compounds such as boronic esters and acids are versatile reactants, as evidenced by their extensive use in industry,[96,97] their industrial-scale preparation remains a challenge. Indeed, classical approaches to arylboron compounds require low temperatures (for the metalation step) or expensive catalysts and reagents (in the case of the Miyaura borylation reaction). To overcome these drawbacks, Duñach and co-workers[98] reported an electrochemical alternative for synthesizing aryl-, heteroaryl-,[99,100] allyl-,[101] and benzylboronic[102] 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.



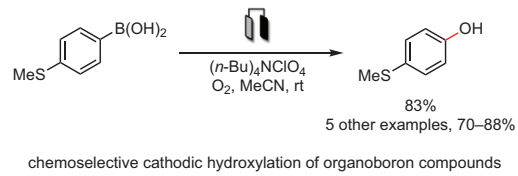
Scheme 16. Palladium-Catalyzed Electrochemical Allylic Alkylation in Air and in Aqueous Medium. *(Ref. 94)*

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.



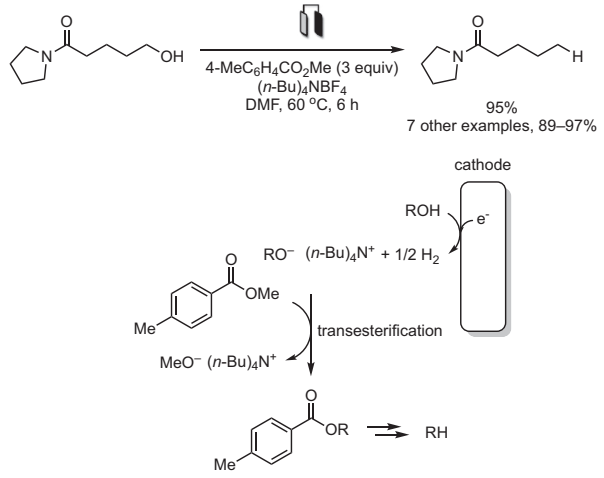
Scheme 17. Electrochemical Synthesis of Aryl-, Allyl-, and Benzylboronic Esters.



eq 4 *(Ref. 104)*

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 [$ArCO^{\bullet -}$–OR], which decomposes to give a benzoate anion ($ArCO_2^-$) and an alkyl radical ($R^{\bullet}$). 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 [$ArCO^{\bullet -}$–OR] and generates a hemiketal [ArCHOH–OR] that leads to alcohols $ArCH_2OH$ 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] Furthermore, 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]



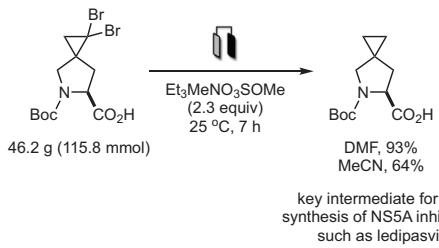
Scheme 18. Lam and Markó's New, Scalable, and One-Pot Process for the Direct Conversion of Primary Alcohols into the Corresponding Alkanes without Prior Esterification. *(Ref. 109)*

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 I_2 from a catalytic amount of KI at the anode. Reaction of the base with I_2 leads to an α-iodoketone intermediate, which undergoes deprotonation and intramolecular S_N2 reaction to yield the cyclopropanated compound under very mild conditions.[120]



eq 5 *(Ref. 112)*

4.5. Electrogenerated 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 electrogenerated 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.[121] 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.[122]

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*-Boc-protected 4-aminopyridines. A mixture of the substrate, electrolyte, and acetonitrile was electrolyzed and then treated with various alkyl and benzyl halides (**Scheme 21**). 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.[123]

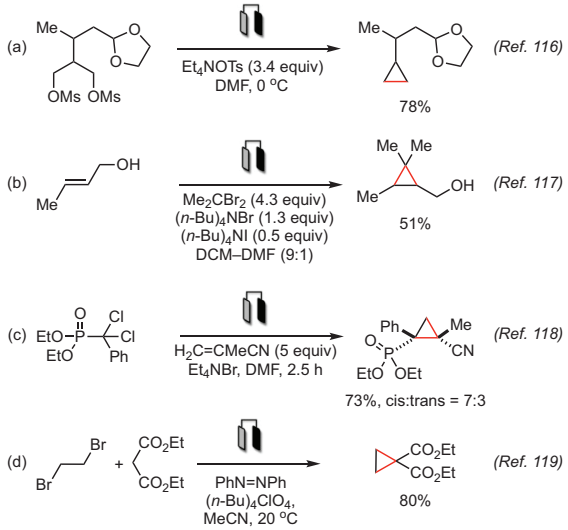
4.5.3. C–C Bond Formation

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.[124]

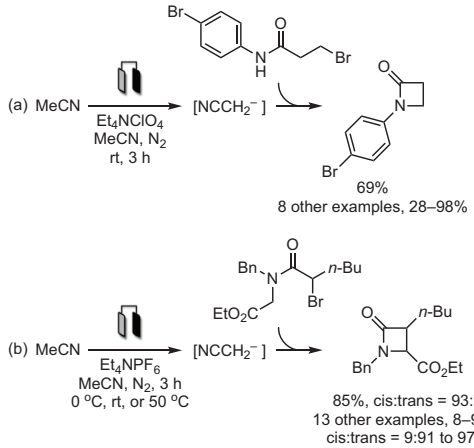
It is worth mentioning in this context that, when the product of an electrochemical C–C bond-forming reaction bears another acidic proton, it could engage in further bond-forming reactions, which would open the door to electrochemically induced tandem and sequential reactions. For instance, Massa, Palombi, and co-workers have shown that addition of malonate or malonitrile anions to cyanobenzaldehydes leads to isoindolinones,[125] 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.[120,126–128]

5. Paired Electrosynthesis

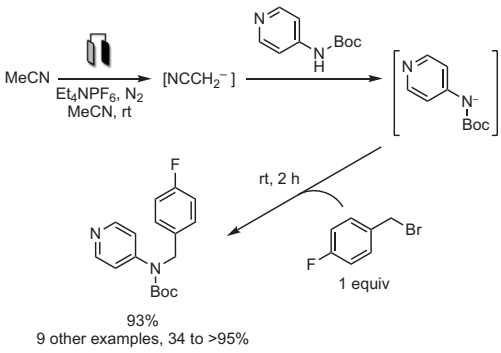
In many electrochemical syntheses, the expected product is generated at one electrode, while the reaction at the other



Scheme 19. Examples of Cathodic Cyclopropane Synthesis.



Scheme 20. Synthesis of β-Lactams by C–N or C–C Bond Formation through a Process Initiated by an Electrogenerated Strong Base [$NCCH_2^-$]. *(Ref. 121,122)*



Scheme 21. Application of the Electrogenerated Strong Base Protocol to the Alkylation of *N*-Boc-protected 4-Aminopyridines. *(Ref. 123)*

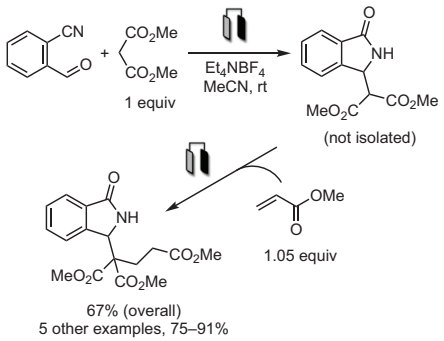
electrode ensures electroneutrality. Paired electrosynthesis takes advantage of the two simultaneous reactions to generate a product. It can be classified into four types of reaction mode: (i) parallel, (ii) convergent, (iii) linear, and (iv) divergent.[129] In terms of sustainability, the pairing of 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**).[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 [$Ce(NH_4)_2(NO_3)_6$]. The paired half-reaction in the cathode compartment consisted of the reduction of CO_2 to CO (which is a valuable starting material) facilitated by $Re(bipytBu)(CO)_3Cl$.

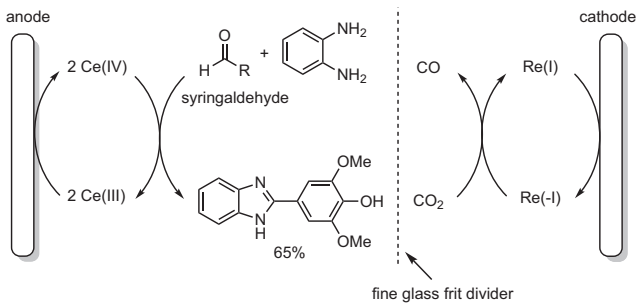
Senboku's group has described the carboxylation of benzylic halides by using a convergent paired electrosynthesis (**Scheme 24**).[131] It is the first report of this type of reaction that does not employ a sacrificial electrode. Reduction of the $C(sp^3)$–Br bond at the cathode generates a benzylic anion which is trapped by CO_2 to form the corresponding carboxylate anion. At the anode, DMF is oxidized in the presence of $(i\text{-Pr})_2NEt$ to an *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.[132] It is noteworthy that the efficiency of this step is highly dependent on the nature of the electrode employed.

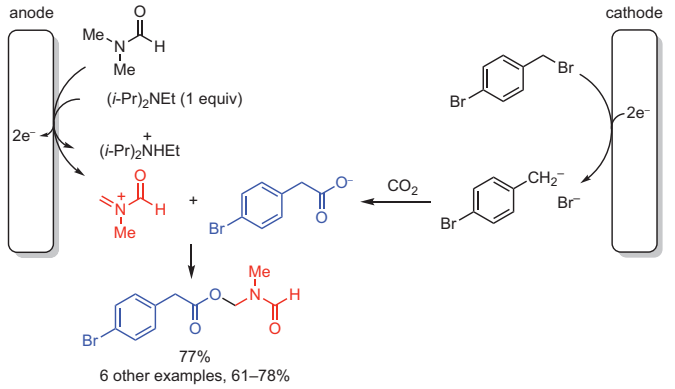
An example of "double" linear paired electrolysis was reported by Baran's group and collaborators from Pfizer's Global R&D and Asymchem Labs.[133] The authors described a nickel(II)-catalyzed, base-free electrochemical amination of aryl halides with alkyl amines. This reaction takes advantage of the 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



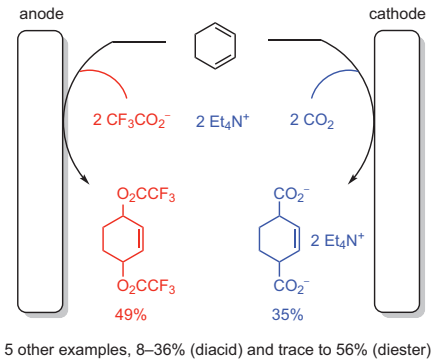
Scheme 22. Electrochemically Initiated, One-Pot Sequential Reactions Leading to Functionalized Isoindolinones. *(Ref. 125)*



Scheme 23. Parallel, Paired Electrosynthesis Produces a "Privileged" Benzimidazole Derivative at the Anode and Reduces CO_2 to the More Valuable CO at the Cathode. *(Ref. 130)*



Scheme 24. Three-Component-Coupling Products of Benzyl Halides, CO_2, and DMF via a Convergent Paired Electrosynthesis. *(Ref. 131)*



Scheme 25. Divergent, Paired Electrosynthesis of α,β-Unsaturated Diacids and Protected Allylic Diols. *(Ref. 134)*

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 co-workers (**Scheme 25**).[134] The synthesis starts with conjugated dienes, which react with CO_2 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

(1) Kolbe, H. *Ann. Chemie Pharm.* **1848**, *64*, 339.
(2) Sequeira, C. A. C.; Santos, D. M. F. *J. Braz. Chem. Soc.* **2009**, *20*, 387.
(3) Frontana-Uribe, B. A.; Little, R. D.; Ibanez, J. G.; Palma, A.; Vasquez-Medrano, R. *Green Chem.* **2010**, *12*, 2099.
(4) Gütz, C.; Klöckner, B.; Waldvogel, S. R. *Org. Process Res. Dev.* **2016**, *20*, 26.
(5) Cardoso, D. S. P.; Šljukić, B.; Santos, D. M. F.; Sequeira, C. A. C. *Org. Process Res. Dev.* **2017**, *21*, 1213.
(6) Atobe, M. *Curr. Opin. Electrochem.* **2017**, *2*, 1.
(7) Chiba, K.; Okada, Y. *Curr. Opin. Electrochem.* **2017**, *2*, 53.
(8) Ritter, S. K. *Chem. Eng. News* **2017**, *95* (11), March 13th, pp 23–25.
(9) Yan, M.; Kawamata, Y.; Baran, P. S. *Chem. Rev.* **2017**, *117*, 13230.
(10) Jiang, Y.; Xu, K.; Zeng, C. *Chem. Rev.* **2017** (DOI: 10.1021/acs.chemrev.7b00271).
(11) Yoshida, J.; Shimizu, A.; Hayashi, R. *Chem. Rev.* **2017** (DOI:10.1021/acs.chemrev.7b00475).
(12) Yan, M.; Kawamata, Y.; Baran, P. S. *Angew. Chem., Int. Ed.* **2017** (DOI: 10.1002/anie.201707584).
(13) Kathiresan, M.; Velayutham, D. *Chem. Commun.* **2015**, *51*, 17499.
(14) Shono, T. *Tetrahedron* **1984**, *40*, 811.
(15) Ogibin, Y. N.; Elinson, M. N.; Nikishin, G. I. *Russ. Chem. Rev. (Engl. Transl.)* **2009**, *78*, 89.
(16) Yoshida, J.; Nishiwaki, K. *J. Chem. Soc., Dalton Trans.* **1998**, 2589.
(17) Caron, S.; Dugger, R. W.; Ruggeri, S. G.; Ragan, J. A.; Brown Ripin, D. H. *Chem. Rev.* **2006**, *106*, 2943.
(18) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52,* 2559.
(19) Ciriminna, R.; Ghahremani, M.; Karimi, B.; Pagliaro, M. *ChemistryOpen* **2017**, *6*, 5.
(20) Kagan, E. S.; Kashparova, V. P.; Zhukova, I. Y.; Kashparov, I. I. *Russ. J. Appl. Chem. (Engl. Transl.)* **2010**, *83*, 745.
(21) Kashparova, V. P.; Klushin, V. A.; Leontyeva, D. V.; Smirnova, N. V.; Chernyshev V. M.; Ananikov, V. P. *Chem.—Asian. J.* **2016**, *11*, 2578.
(22) Rafiee, M.; Karimi, B.; Alizadeh, S. *ChemElectroChem* **2014**, *1*, 455.
(23) Kishioka, S.; Yamada, A. *J. Electroanal. Chem.* **2005**, *578*, 71.
(24) Ciriminna, R.; Palmisano, G.; Pagliaro, M. *ChemCatChem* **2015**, *7*, 552.
(25) Attour, A.; Dirrenberger, P.; Rode, S.; Ziogas, A.; Matlosz, M.; Lapicque, F. *Chem. Eng. Sci.* **2011**, *66*, 480.
(26) Palma, A.; Cárdenas, J.; Frontana-Uribe, B. A. *Green Chem.* **2009**, *11*, 283.
(27) Badalyan, A.; Stahl, S. S. *Nature* **2016**, *535*, 406.
(28) Li, T.; Cao, Y.; He, J.; Berlinguette, C. P. *ACS Cent. Sci.* **2017**, *3*, 778.
(29) Stalder, R.; Roth, G. P. *ACS Med. Chem. Lett.* **2013**, *4*, 1119.
(30) Schulz, L.; Enders, M.; Elsler, B.; Schollmeyer, D.; Dyballa, K. M.; Franke, R.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2017**, *56*, 4877.
(31) Schäfer, H. J. *Angew. Chem., Int. Ed.* **2017**, *56*, 15502.
(32) Elsler, B.; Schollmeyer, D.; Dyballa, K. M.; Franke, R.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 5210.
(33) Wiebe, A.; Schollmeyer, D.; Dyballa, K. M.; Franke, R.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2016**, *55*, 11801.
(34) Riehl, B.; Dyballa, K. M.; Franke, R.; Waldvogel, S. R. *Synthesis* **2017**, *49*, 252.
(35) Elsler, B.; Wiebe, A.; Schollmeyer, D.; Dyballa, K. M.; Franke, R.; Waldvogel, S. R. *Chem.—Eur. J.* **2015**, *21*, 12321.

(36) Wu, Z.-J.; Xu, H.-C. *Angew. Chem., Int. Ed.* **2017**, *56*, 4734.
(37) Tang, S.; Gao, X.; Lei, A. *Chem. Commun.* **2017**, *53*, 3354.
(38) Chong, D.; Stewart, M.; Geiger, W. E. *J. Am. Chem. Soc.* **2009**, *131*, 7968.
(39) Lebreux, F.; Buzzo, F.; Markó, I. E. *Synlett* **2008**, 2815.
(40) Wu, H.; Moeller, K. D. *Org. Lett.* **2007**, *9*, 4599.
(41) Chupakhin, O. N.; Shchepochkin, A. V.; Charushin, V. N. *Green Chem*. **2017**, *19*, 2931.
(42) Hayashi, R.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2016**, *138*, 8400.
(43) Wang, Q.-Q.; Xu, K.; Jiang, Y.-Y.; Liu, Y.-G.; Sun, B.-G.; Zeng, C.-C. *Org. Lett.* **2017**, *19*, 5517.
(44) Liang, S.; Zeng, C.-C.; Tian, H.-Y.; Sun, B.-G.; Luo, X.-G.; Ren, F.-z. *J. Org. Chem.* **2016**, *81*, 11565.
(45) Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2014**, *136*, 4496.
(46) Collins, K. D.; Glorius, F. *Nat. Chem.* **2013**, *5*, 597.
(47) Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2015**, *137*, 9816.
(48) Wesenberg, L. J.; Herold, S.; Shimizu, A.; Yoshida, J.; Waldvogel, S. R. *Chem.—Eur. J.* **2017**, *23*, 12096.
(49) Waldvogel, S. R.; Möhle, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 6398.
(50) Zhao, H.-B.; Hou, Z.-W.; Liu, Z.-J.; Zhou, Z.-F.; Song, J.; Xu, H.-C. *Angew. Chem., Int. Ed.* **2017**, *56*, 587.
(51) Morofuji, T.; Shimizu, A.; Yoshida, J. *Chem.—Eur. J*. **2015**, *21*, 3211.
(52) Möhle, S.; Herold, S.; Richter, F.; Nefzger, H.; Waldvogel, S. R. *ChemElectroChem* **2017**, *4*, 2196.
(53) Zhu, L.; Xiong, P.; Mao, Z.-Y.; Wang, Y.-H.; Yan, X.; Lu, X.; Xu, H.-C. *Angew. Chem., Int. Ed.* **2016**, *55*, 2226.
(54) Xiong, P.; Xu, H.-H.; Xu, H.-C. *J. Am. Chem. Soc.* **2017**, *139*, 2956.
(55) Hou, Z.-W.; Mao, Z.-Y.; Zhao, H.-B.; Melcamu, Y. Y.; Lu, X.; Song, J.; Xu, H.-C. *Angew. Chem., Int. Ed.* **2016**, *55*, 9168.
(56) Hou, Z.-W.; Mao, Z.-Y.; Song, J.; Xu, H.-C. *ACS Catal*. **2017**, *7*, 5810.
(57) Fu, N.; Sauer, G. S.; Saha, A.; Loo, A.; Lin, S. *Science* **2017**, *357*, 575.
(58) Yang, Q.-L.; Li, Y.-Q.; Ma, C.; Fang, P.; Zhang X.-J.; Mei, T.-S. *J. Am. Chem. Soc.* **2017**, *139*, 3293.
(59) Stowers, K. J.; Kubota, A.; Sanford, M. S. *Chem. Sci.* **2012**, *3*, 3192.
(60) Horn, E. J.; Rosen, B. R.; Chen, Y.; Tang, J.; Chen, K.; Eastgate, M. D.; Baran, P. S. *Nature* **2016**, *533*, 77.
(61) Horn, E. J.; Rosen, B. R.; Baran, P. S. *ACS Cent. Sci*. **2016**, *2*, 302.
(62) Kawamata, Y.; Yan, M.; Liu, Z.; Bao, D.-H.; Chen, J.; Starr, J. T.; Baran, P. S. *J. Am. Chem. Soc.* **2017**, *139*, 7448.
(63) Sambiagio, C.; Sterckx, H.; Maes, B. U. W. *ACS Cent. Sci.* **2017**, *3*, 686.
(64) Qian, P.; Bi, M.; Su, J.; Zha, Z.; Wang, Z. *J. Org. Chem.* **2016**, *81*, 4876.
(65) Zhao, Y.; Lai, Y.-L.; Du, K.-S.; Lin, D.-Z.; Huang, J.-M. *J. Org. Chem.* **2017**, *82*, 9655.
(66) Wang, P.; Tang, S.; Huang, P.; Lei, A. *Angew. Chem., Int. Ed.* **2017**, *56*, 3009.
(67) Qian, X.-Y.; Li, S.-Q.; Song, J.; Xu, H.-C. *ACS Catal.* **2017**, *7*, 2730.
(68) Wang, P.; Tang, S.; Lei, A. *Green Chem.* **2017**, *19*, 2092.
(69) Fu, N.; Sauer, G. S.; Lin, S. *J. Am. Chem. Soc.* **2017**, *139*, 15548.
(70) Gieshoff, T.; Schollmeyer, D.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2016**, *55*, 9437.
(71) Jiang, Y.-y.; Wang, Q.-Q.; Liang, S.; Hu, L.-M.; Little, R. D.; Zeng, C.-C. *J. Org. Chem.* **2016**, *81*, 4713.
(72) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172.
(73) Onomura, O. *Heterocycles* **2012**, *85*, 2111.
(74) Jones, A. M.; Banks, C. E. *Beilstein J. Org. Chem.* **2014**, *10*, 3056.
(75) Alfonso-Súarez, P.; Kolliopoulos, A. V.; Smith, J. P.; Banks, C. E.; Jones, A. M. *Tetrahedron Lett.* **2015**, *56*, 6863.
(76) Gong, M.; Huang, J.-M. *Chem.—Eur. J.* **2016**, *22*, 14293.
(77) Fu, N.; Li, L.; Yang, Q.; Luo, S. *Org. Lett.* **2017**, *19*, 2122.
(78) Yoshida, J. *Chem. Commun.* **2005**, 4509.
(79) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265.
(80) Yoshida, J.; Saito, K.; Nokami, T.; Nagaki, A. *Synlett* **2011**, 1189.
(81) Kabeshov, M. A.; Musio, B.; Murray, P. R. D.; Browne, D. L.; Ley, S. V. *Org. Lett.* **2014**, *16*, 4618.
(82) Kim, S.; Hayashi, K.; Kitano, Y.; Tada, M.; Chiba, K. *Org. Lett.* **2002**, *4*, 3735.
(83) Lui, K.; Tang, S.; Huang, P.; Lei, A. *Nat. Commun.* **2017**, *8* (775) (DOI: 10.1038/s41467-017-00873-1).
(84) Conte, L.; Gambaretto, G. *J. Fluorine Chem*. **2004**, *125*, 139.
(85) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.* **2015**, *115*, 9073.
(86) Takahashi, K.; Inagi, S.; Fuchigami, T. *J. Electrochem. Soc.* **2013**, *160*, G3046 and references therein.
(87) Tanigawa, M.; Kuriyama, Y.; Inagi, S.; Fuchigami, T. *Electrochim. Acta*. **2016**, *199*, 314.
(88) Jiao, K.-J.; Zhao, C.-Q.; Fang, P.; Mei, T.-S. *Tetrahedron Lett.* **2017**, *58*, 797.
(89) Kronenwetter, H.; Husek, J.; Etz, B.; Jones, A.; Manchanayakage, R. *Green Chem.* **2014**, *16*, 1489.
(90) Sun, G.; Ren, S.; Zhu, X.; Huang, M.; Wan, Y. *Org. Lett.* **2016**, *18*, 544.
(91) Shono, T.; Ohmizu, H.; Kawakami, S.; Sugiyama, H. *Tetrahedron Lett.* **1980**, *21*, 5029.
(92) Kise, N.; Miyamoto, H.; Hamada, Y.; Sakurai, T. *Tetrahedron Lett.* **2015**, *56*, 4599.
(93) Kise, N.; Hamada, Y.; Sakurai, T. *J. Org. Chem.* **2016**, *81*, 11043.
(94) Lai, Y.-L.; Huang, J.-M. *Org. Lett.* **2017**, *19*, 2022.
(95) Perkins, R. J.; Pedro, D. J.; Hansen, E. C. *Org. Lett.* **2017**, *19*, 3755.
(96) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599.

(97) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564.
(98) Olivero, S.; Duñach, E. *Curr. Opin. Electrochem.* **2017**, *2*, 38.
(99) Laza, C.; Duñach, E.; Serein-Spirau, F.; Moreau, J. J. E.; Vellutini, L. *New J. Chem.* **2002**, *26*, 373.
(100) Laza, C.; Duñach, E. *Adv. Synth. Catal.* **2003**, *345*, 580.
(101) Godeau, J.; Pintaric, C.; Olivero, S.; Duñach, E. *Electrochim. Acta* **2009**, *54*, 5116.
(102) Pintaric, C.; Laza, C.; Olivero, S.; Duñach, E. *Tetrahedron Lett.* **2004**, *45*, 8031.
(103) Laza, C.; Pintaric, C.; Olivero, S.; Duñach, E. *Electrochim. Acta* **2005**, *50*, 4897.
(104) Hosoi, K.; Kuriyama, Y.; Inagi, S.; Fuchigami, T. *Chem. Commun.* **2010**, *46*, 1284.
(105) Dai, X.-J.; Li, C.-J. *J. Am. Chem. Soc.* **2016**, *138*, 5433.
(106) Lam, K.; Markó, I. E. *Chem. Commun.* **2009**, 95.
(107) Lam, K.; Markó, I. E. *Tetrahedron* **2009**, *65*, 10930.
(108) Lam, K.; Markó, I. E. *Org. Lett.* **2009**, *11*, 2752.
(109) Lam, K.; Markó, I. E. *Synlett* **2012**, *23*, 1235.
(110) Lam, K.; Markó, I. E. *Org. Lett.* **2011**, *13*, 406.
(111) Gütz, C.; Selt, M.; Bänziger, M.; Bucher, C.; Römelt, C.; Hecken, N.; Gallou, F.; Galvão, T. R.; Waldvogel, S. R. *Chem.—Eur. J.* **2015**, *21*, 13878.
(112) Gütz, C.; Bänziger, M.; Bucher, C.; Galvão, T. R.; Waldvogel, S. R. *Org. Process Res. Dev.* **2015**, *19*, 1428.
(113) Talele, T. T. *J. Med. Chem.* **2016**, *59*, 8712.
(114) Ebner, C.; Carreira, E. M. *Chem. Rev.* **2017**, *117*, 11651.
(115) Elinson, M. N.; Dorofeeva, E. O.; Vereshchagin, A. N.; Nikishin, G. I. *Russ. Chem. Rev. (Engl. Transl.)* **2015**, *84*, 485.
(116) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y. *J. Org. Chem.* **1982**, *47*, 3090.
(117) Durandetti, S.; Sibille, S.; Périchon, J. *J. Org. Chem.* **1991**, *56*, 3255.
(118) Duquenne, C.; Goumain, S.; Jubault, P.; Feasson, C.; Quirion, J.-C. *Org. Lett.* **2000**, *2*, 453.
(119) Petrosyan, V. A.; Vasil'ev, A. A.; Tatarinova, V. I. *Russ. Chem. Bull. (Engl. Transl.)* **1994**, *43*, 84.
(120) Okimito, M.; Takahashi, Y.; Kakuchi, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 207.
(121) Feroci, M.; Orsini, M.; Palombi, L.; Rossi, L.; Inesi, A. *Electrochim. Acta* **2005**, *50*, 2029.
(122) Feroci, M.; Orsini, M.; Rossi, L.; Sotgiu, G.; Inesi, A. *Electrochim. Acta* **2006**, *51*, 5540.
(123) Feroci, M.; Chiarotto, I.; Forte, G.; Simonetti, G.; D'Auria, F. D.; Maes, L.; De Vita, D.; Scipione, L.; Friggeri, L.; Di Santo, R.; Tortorella, S. *ISRN Org. Chem.* **2014**, 1.
(124) Arcadi, A.; Inesi, A.; Marinelli, F.; Rossi, L.; Verdecchia, M. *Eur. J. Org. Chem.* **2007**, 2430.
(125) Antico, P.; Capaccio, V.; Di Mola, A.; Massa, A.; Palombi, L. *Adv. Synth. Catal.* **2012**, *354*, 1717.
(126) Elinson, M. N.; Gorbunov, S. V.; Vereshchagin, A. N.; Nasybullin, R. F.; Goloveshkin, A. S.; Bushmarinov, I. S.; Egorov, M. P. *Tetrahedron* **2014**, *70*, 8559.
(127) Upadhyay, A.; Sharma, L. K.; Singh, V. K.; Dubey, R.; Kumar, N.; Singh, R. K. P. *Tetrahedron Lett.* **2017**, *58*, 1245.
(128) Feroci, M.; Elinson, M. N.; Rossi, L.; Inesi, A. *Electrochim. Commun.* **2009**, *11*, 1523.
(129) Paddon, C. A.; Atobe, M.; Fuchigami, T.; He, P.; Watts, P.; Haswell, S. J.; Pritchard, G. J.; Bull, S. D.; Marken, F. *J. Appl. Electrochem.* **2006**, *36*, 617.
(130) Llorente, M. J.; Nguyen, B. H.; Kubiak, C. P.; Moeller, K. D. *J. Am. Chem. Soc.* **2016**, *138*, 15110.
(131) Senboku, H.; Nagakura, K.; Fukuhara, T.; Hara, S. *Tetrahedron* **2015**, *71*, 3850.
(132) Hartmer, M. F.; Waldvogel, S. R. *Chem. Commun.* **2015**, *51*, 16346.
(133) Li, C.; Kawamata, Y.; Nakamura, H.; Vantourout, J. C.; Liu, Z.; Hou, Q.; Bao, D.; Starr, J. T.; Chen, J.; Yan, M.; Baran, P. S. *Angew. Chem., Int. Ed.* **2017**, *56*, 13088.
(134) Matthessen, R.; Fransaer, J.; Binnemans, K.; De Vos, D. E. *ChemElectroChem* **2015**, *2*, 73.
(135) Maslow, A. H. *The Psychology of Science: A Reconnaissance*; Maurice Bassett Publishing, 1966.

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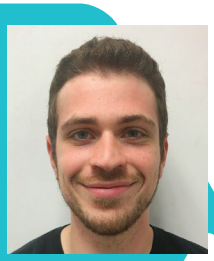
Carbon–Carbon π Bonds as Conjunctive Reagents in Cross-Coupling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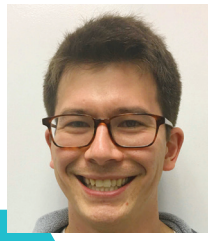
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Keywords. conjunctive cross-coupling; transition-metal catalysis; carbon–carbon π bonds; three-component coupling.

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.

Outline

1. Introduction

Transition-metal-catalyzed cross-coupling reactions constitute an indispensable toolkit for C–C bond formation in complex-molecule synthesis.[1] 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.[2] 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

conditions. Prominent examples of conjunctive reagents include carbon monoxide,[3] carbenes,[4] 1,1-diboron species,[5] and carbon–carbon π bonds (**Figure 1**). This review highlights carbon–carbon π bonds as ambiphilic conjunctive reagents in cross-coupling reactions. It is focused primarily on reactions involving: (i) two C–C bond forming events, (ii) a 1,2-addition mode, and (iii) organometallic nucleophiles and organohalide electrophiles. Exceptions to these general organization principles are utilized to illustrate important points.

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.[6] 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 insertion 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 (R^2–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 reinsert into the new alkene and erode the regio- and chemoselectivity of the desired 1,2-difunctionalization reaction. The rapid

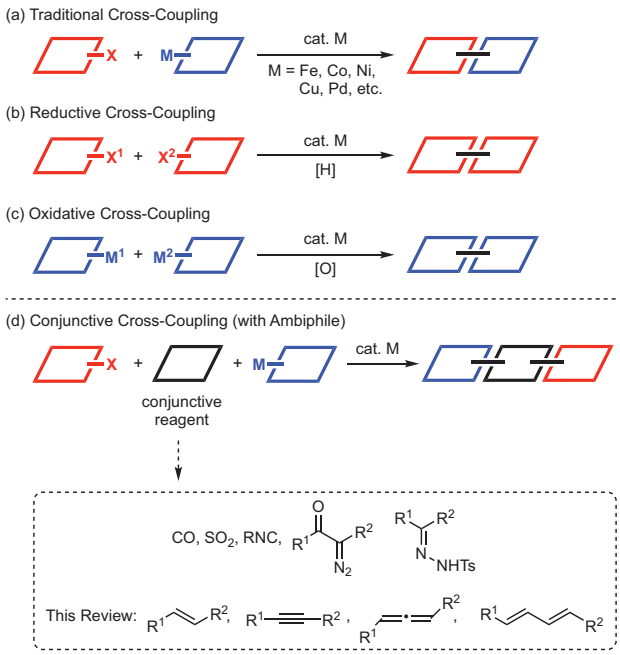
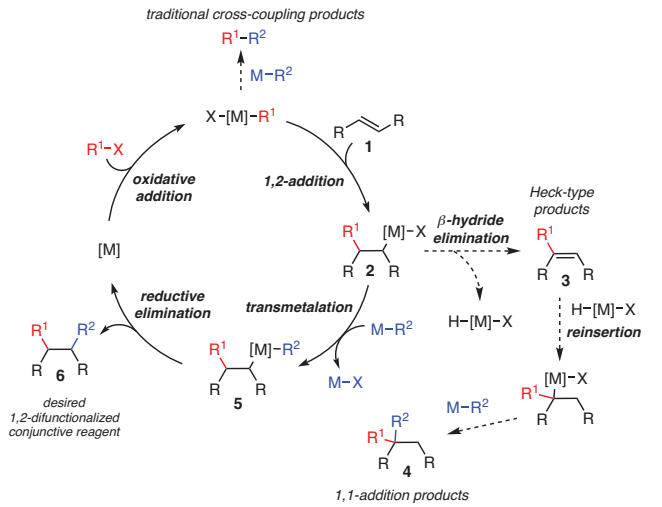


Figure 1. General Depiction of Traditional Two-Component Cross-Couplings and the Three-Component Conjunctive Cross-Coupling Utilizing C–C π Bonds. *(Ref. 1–5)*



Scheme 1. General Catalytic Cycle for the Conjunctive Cross-Coupling of Alkenes and Potential Obstacles.

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 (R^2–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**).

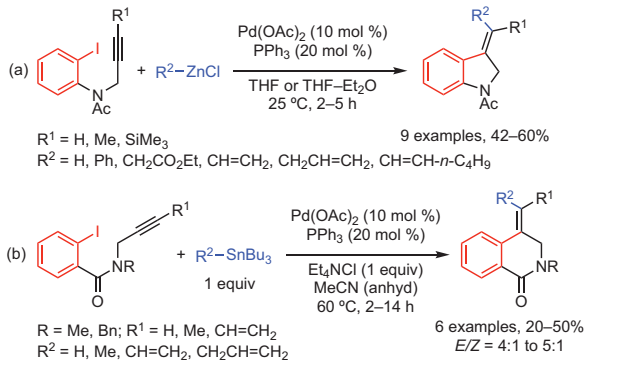
For the reasons articulated above, the reaction with unconjugated alkenes, depicted in Scheme 1, remains a formidable challenge to date. However, various strategies have been developed to circumvent some of the problematic steps in this general catalytic cycle. One such strategy involves covalently tethering 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

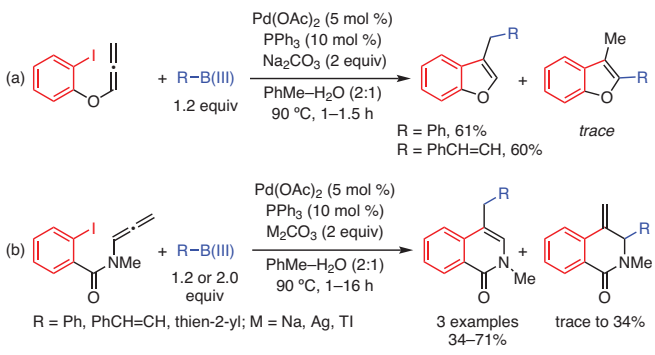
2.2.1. Tethered Alkynes and Allenes

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.[7,8] 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)).[7,8] 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)).[8] 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.[9] Additionally, Cook utilized palladium catalysis to extend the reactivity to arylboronic acids.[10]

Grigg and colleagues applied the same concept to allenes under similar conditions using boronic acids as the nucleophilic component (**Scheme 3**).[11,12] 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(sp^2)-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.



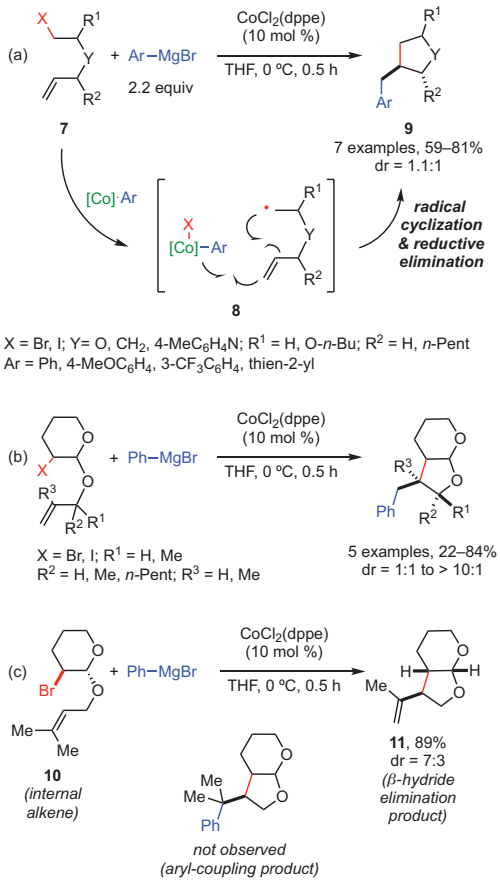
Scheme 2. Conjunctive Cross-Coupling of Tethered Alkynes under Palladium Catalysis. *(Ref. 7,8)*



Scheme 3. Conjunctive Cross-Coupling of Tethered Allenes under Palladium Catalysis. *(Ref. 11)*

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 β-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, intramolecularity allows for rapid insertion, and the resulting cyclization limits the number of accessible β-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 C(sp^3)–X bond of tethered alkene **7**, leading to a 5-hexen-1-yl radical, **8**, a commonly encountered intermediate in radical clock experiments, which undergoes rapid *5-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** in high yield. This cascade was successfully applied toward the synthesis of polysubstituted tetrahydrofuran cores along with bicyclic oxygen-containing heterocycles (Scheme 4, Parts (b) and (c)). The corresponding acetal products can be subjected to Jones oxidation to provide a wide range of lactone derivatives. Although this approach was successful when terminal alkene starting materials were employed, the authors noted that internal alkene substrates did not give the anticipated products. For example, trisubstituted alkene **10** produced the radical-cyclization product **11** without any observed incorporation of the aryl coupling partner. This result indicates that the rapid nature of β-hydride elimination remained challenging to overcome in this cobalt-catalyzed reaction. In 2005, Fu and colleagues observed a similar radical cyclization–cross-coupling cascade when they used mono-organotin reagents and a nickel(II) catalyst. Here, too, the substrate scope was imited to terminal alkenes bearing pendant alkyl bromides.[14] In a series of reports by Peng, a reductive 1,2-arylalkylation was achieved under nickel catalysis by using aryl iodides and pendant alkyl bromides in a similar fashion.[15–17]



Scheme 4. Conjunctive Cross-Coupling of Tethered Alkenes by a Radical Cyclization–Cross-Coupling Cascade. *(Ref. 13)*

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,[13] the facile nature of the competing β-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 coordinatively saturate the nickel center in the catalyst.[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.[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**).[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 fasiglifam (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 aryl iodides and tethered arylboronic acids.[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.[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.

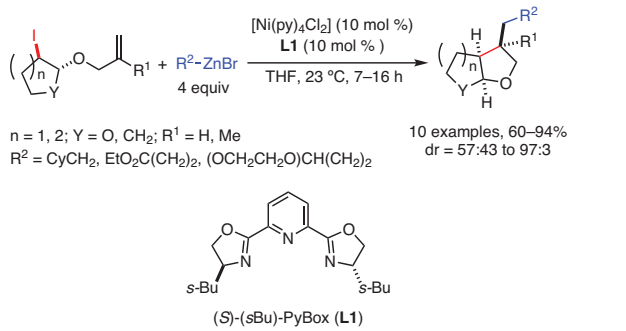
3. Approaches toward Three-Component Conjunctive Cross-Coupling Using Alkynes and Allenes

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

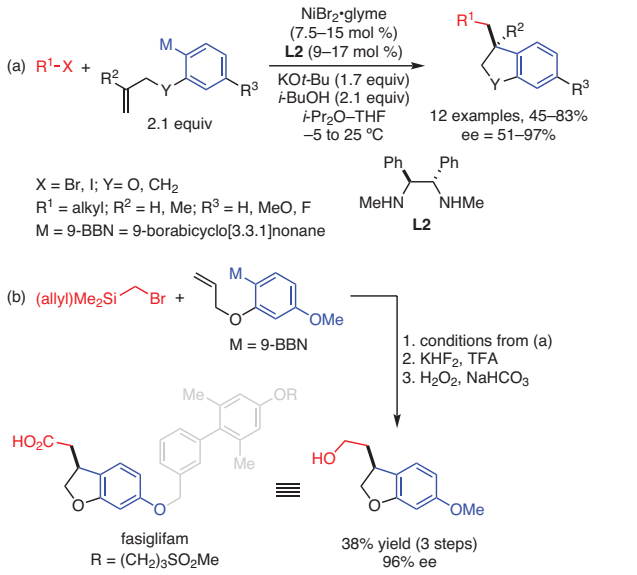
In 2003 and 2005, Larock and co-workers reported a palladium-catalyzed, three-component coupling between internal alkynes, aryl iodides, and arylboronic acids.[23,24] Through a reaction sequence similar to the tethered variant described above, an initial oxidative addition results in an arylpalladium(II) 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

Alkyl–Alkyl Conjunctive Cross-Coupling Utilizing Electrophile-Tethered Terminal Alkenes



(*S*)-(*s*Bu)-PyBox (**L1**)

eq 1 *(Ref. 18)*

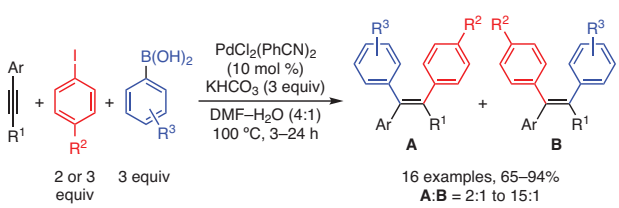


Scheme 5. Conjunctive Cross-Coupling Using Aryl Boron Reagents Possessing Tethered Alkenes and Its Application in a Short Synthesis of the 2,3-Dihydrobenzofuran Core of Fasiglifam, a Potent and Selective GPR40 Agonist. *(Ref. 20)*

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**).[23] For non-symmetric substrates, the regiochemical outcome was dependent on both electronic and steric factors. The authors comment that the arylboronic 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 regioisomeric ratio of products formed from 1-(4-nitrophenyl) propyne is 15:1, a dramatic increase compared to that of the standard 1-phenylpropyne (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.[25] The authors observed the same regio- and stereochemical trend, suggesting that the reaction involves an analogous mechanism. In related work by Duan, Wu, and colleagues, potassium ferrocyanide {$K_4[Fe(CN)_6]$} was used in place of arylboronic acids to effect 1,2-arylcyanation under palladium catalysis.[26] In 2015, Nevado and co-workers reported a palladium-catalyzed carboperfluoroalkylation of terminal alkynes using perfluoroalkyl iodides and arylboronic acids.[27] A plausible catalytic cycle for this transformation involves radical-based oxidative addition and migratory insertion to yield a vinylpalladium(II) species that can undergo a 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 arylacetylenes with alkylzinc or alkylmagnesium reagents and secondary or tertiary alkyl electrophiles (**eq 3**).[28] 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(I) 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 intermolecular dialkylation of alkynes via conjunctive cross-coupling. In related work by Nevado in 2016, a radical-based anti addition to terminal alkynes was reported using a nickel catalyst with arylboronic acids and unactivated alkyl halides under the same catalytic manifold.[29] 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**).[29] 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.

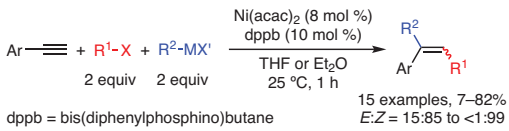
Three-Component Cross-Coupling Utilizing Internal Alkynes as Conjunctive Reagents



Ar = Ph, 4-$CF_3C_6H_4$, 3,5-pyrimidinyl, 4-$O_2NC_6H_4$; R^1 = Ph, Me, Et, COMe, CO_2Et
R^2 = H, Me, MeO, Cl; R^3 = H, 4-Me, 4-MeO, 3,5-F_2

eq 2 *(Ref. 23)*

Dialkylation of Terminal Alkynes through a Nickel-Catalyzed Conjunctive Cross-Coupling

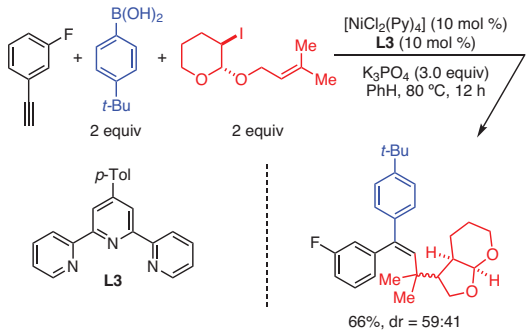


dppb = bis(diphenylphosphino)butane

Ar = YC_6H_4 (Y = H, 3-Me, 3-NC, 3-MeO_2C, 3-Ac, 4-MeO, 4-CF_3), 2-Np, thien-2-yl
R^1 = *n*-Bu, *s*-Bu, *t*-Bu; R^2 = Me, Bn, Ph, 4-$EtO_2CC_6H_4$
X = I, Br; MX' = MgBr, MgCl, ZnPh, $ZnCH_2SiMe_3$

eq 3 *(Ref. 28)*

Nickel-Catalyzed, Cyclization-Initiated Three-Component Conjunctive Cross-Coupling

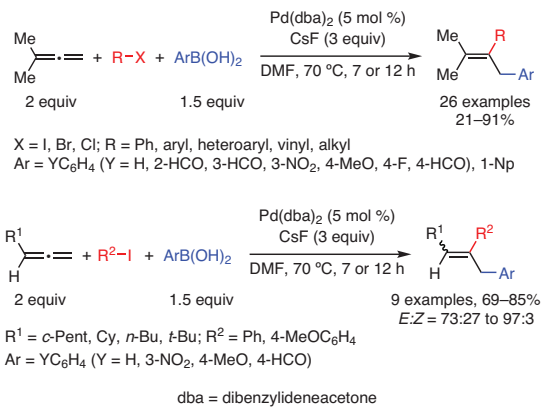


eq 4 *(Ref. 29)*

In 2015, Xue et al. developed a nickel-catalyzed, three-component conjunctive coupling of symmetrical diarylacetylenes and alkylarylacetylenes using aryl Grignard reagents and aryl halides.[30] 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,[23–25] 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 internal alkynes using a conjunctive cross-coupling in which a vinyl copper species was the active transmetalating agent.[31] Additionally, Brown and co-workers have disclosed a copper-catalyzed carboboration of internal alkynes and allenes using B_2Pin_2 and aryl iodides.[32]

3.2. Three-Component Conjunctive Cross-Couplings of Allenes

Contemporaneous with the development of efficient three-component conjunctive cross-couplings of alkynes, 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.[33] 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)*

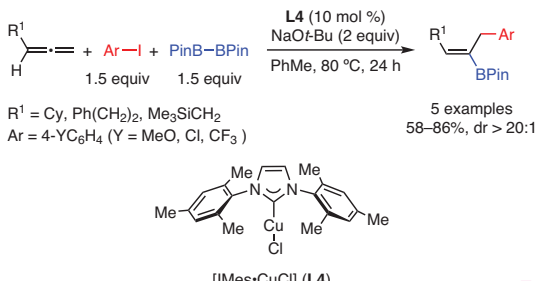
In the case of monosubstituted allenes, the stereoselectivity was governed by the steric bulk of the substituent. For example, *tert*-butyl-substituted allenes gave stereoselectivities as high as 97:3 (*E*:*Z*). A stereomodel proposed by the authors suggests that the palladium catalyst coordinates preferentially 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 brief 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.[34] 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**).[32] 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-

Copper-Catalyzed Conjunctive Cross-Coupling
Using Allenes as Conjunctive Reagents



eq 5 *(Ref. 32)*

coupling reaction can become more problematic. As described in earlier sections, rapid β-hydride elimination after insertion into the alkene can lead to a complex mixture of undesired products. In spite of these challenges, recent reports have illustrated several effective strategies toward using alkenes in conjunctive cross-coupling.

4.1. Electronically Activated or Conjugated Alkenes

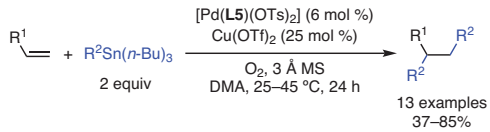
In order to achieve efficient and selective 1,2-difunctionalization of alkenes via conjunctive cross-coupling, the intervening alkylmetal species must be sufficiently stable. Alkene substrates bearing functional groups in conjugation with the alkene π system often result in alkylmetal species that are 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 arylstannane 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 arylnickel species. A subsequent reductive elimination step yields the desired products and regenerates the nickel catalyst.

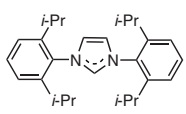
4.2. Simple, Unconjugated Alkenes

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.

Palladium-Catalyzed 1,2-Diarylation of Conjugated Alkenes with Organostannanes



R^1 = YC_6H_4 (Y = 2-Me, 2-MeO, 4-Me, 4-MeO), PhCH=CH, 4,4-Me_2cyclohexenyl
R^2 = YC_6H_4 (Y = H, 4-MeO, 4-F, 4-CF_3), 3,3-$(MeO)_2C_6H_3$, dihydropyren-2-yl



I*i*Pr (**L5**)

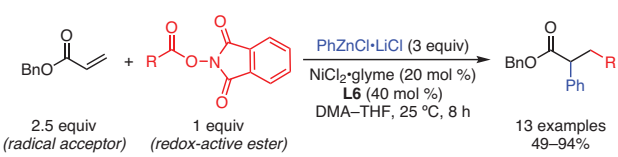
eq 6 *(Ref. 35)*

1,2-Difunctionalization of 1,3-Dienes through a Three-Component Conjunctive Cross-Coupling under Palladium Catalysis

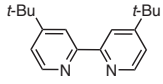
R^1, R^2 = alkyl, cycloalkyl; Ar^1 = Ph, 4-$MeOC_6H_4$, 4-FC_6H_4
Ar^2 = YC_6H_4 (Y = H, 2-Me, 4-MeO, 4-CF_3, 4-Ac, 4-H_2NCO, 4-AcNH), 3,3-$(MeO)_2C_6H_3$, dibenzofuran-4-yl

eq 7 *(Ref. 36)*

Three-Component Conjunctive Cross-Coupling Using Redox-Active Esters with Acrylates under Nickel Catalysis



R = secondary or tertiary alkyl

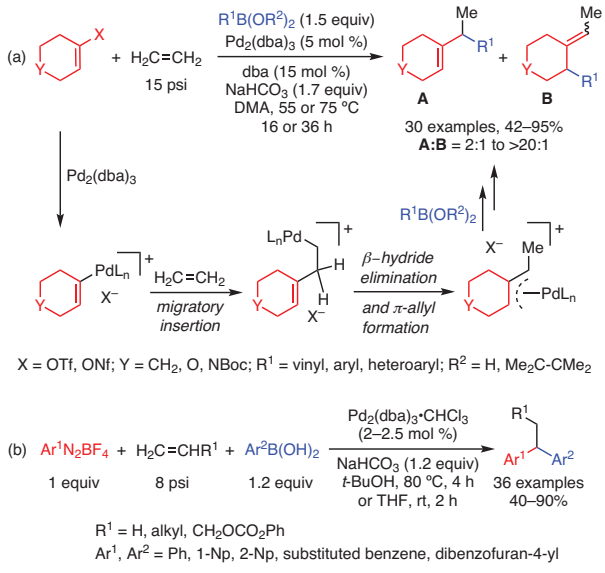


L6

eq 8 *(Ref. 37)*

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.

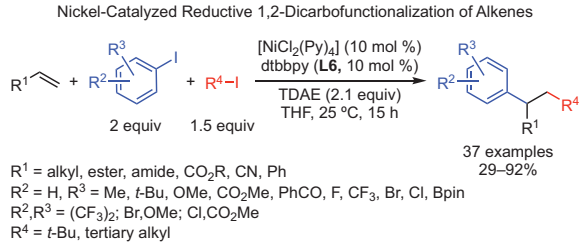
In the context of "simple" alkene substrates, ethylene is an example of an unconjugated conjunctive reagent that is not electronically activated. In 2012, Saini and Sigman reported a 1,1-difunctionalization of ethylene with a palladium catalyst using vinyl triflates and vinyl- or arylboronic acids.[38] 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**).[38] In subsequent studies, Sigman's team reported that regiocontrol could be improved by employing aryldiazonium salts as electrophiles in place of vinyl triflates.[39] 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.[40] In this elegant work, a wide range of alkenes including acrylates, acrylonitriles, allylic acetates, and styrenes were competent conjunctive reagents for 1,2-arylalkylation by way of a radical-based mechanism (**eq 9**).[40] Impressively, internal alkenes were also effective substrates, delivering the desired products with high regio- and diastereocontrol. Notably, steric factors have an unfavorable effect on the efficiency of the reaction, as ortho-substituted aryl iodides lead to diminished yields.



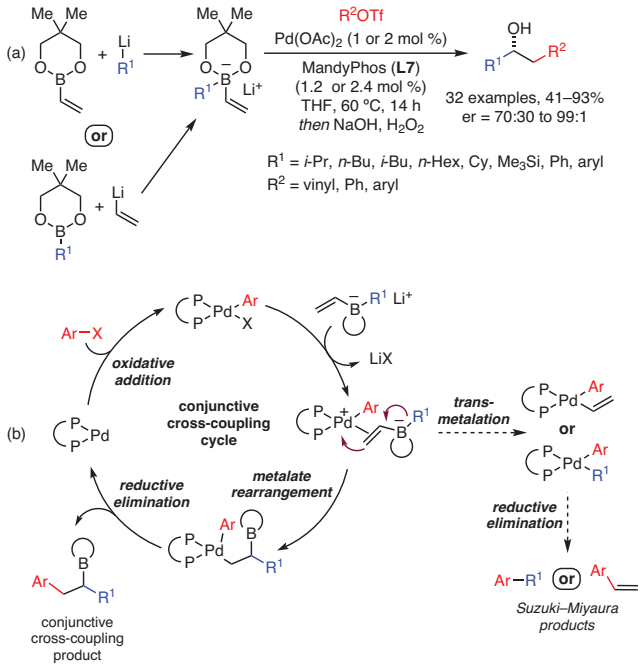
Scheme 7. 1,1-Difunctionalization of Simple Alkenes via Conjunctive Cross-Coupling. *(Ref. 38,39)*

4.3. Conjunctive Cross-Coupling of Alkenes via Metalate Rearrangements

In 2016, Morken demonstrated a powerful tool for the enantioselective 1,2-difunctionalization of vinyl boronates.[41] In this conjunctive cross-coupling, two organometallic nucleophiles merge to generate an ate-complex that can undergo a metal-induced metalate 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**).[41] 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



eq 9 *(Ref. 40)*



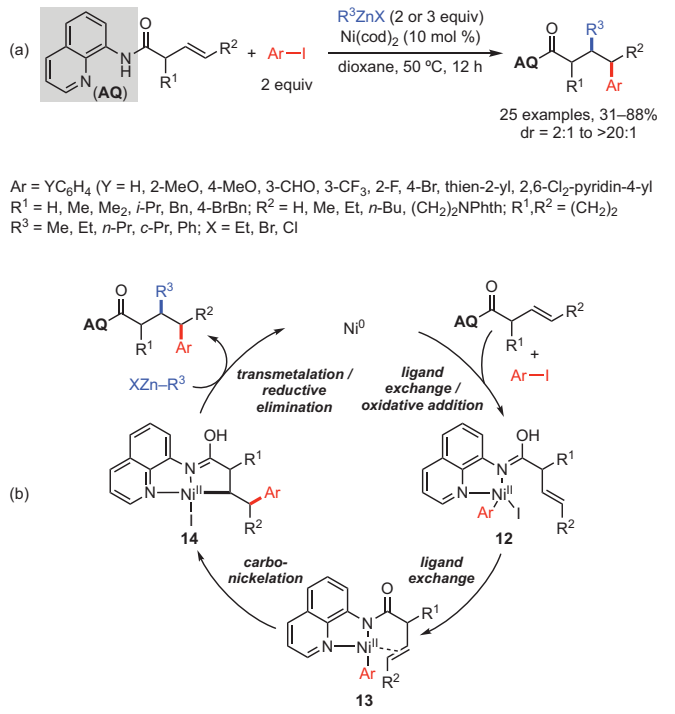
Scheme 8. Conjunctive Cross-Coupling via Metal-Induced Metalate Rearrangement. *(Ref. 41)*

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 enantioselectivity 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 metalate rearrangement mechanism, which requires nucleophilic attack of the alkene to generate the key alkylpalladium(II) intermediate.

Morken's team expanded the utility of this metalate rearrangement approach by substituting the organolithium species with Grignard reagents activated by NaOTf, resulting in a protocol that exhibited increased functional group tolerance.[42] 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.[43] Additionally, this strategy was recently adapted to operate under nickel catalysis, enabling the conjunctive cross-coupling of 9-BBN borates with aryl electrophiles by using simple chiral diamine ligands to achieve enantioinduction.[44]

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 alkene 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,[45–46] its application in the context of 1,2-dicarbofunctionalization of unconjugated alkenes has been comparatively unexplored.[47]



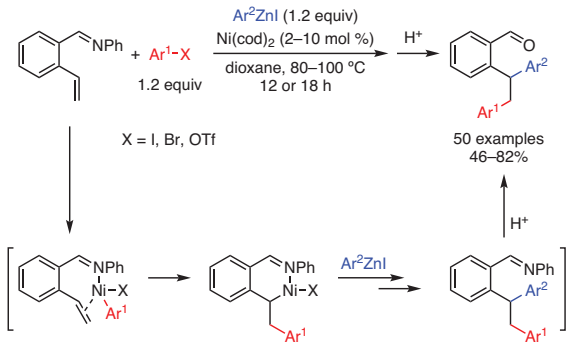
Scheme 9. Conjunctive Cross-Coupling of Unconjugated Alkenes Using a Directed Approach. *(Ref. 49)*

Our group has recently published a collection of directed alkene functionalization reactions.[48] 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 metallacycle 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**).[49] 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 nickelacycle **14** is formed via 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-arylalkylation 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.

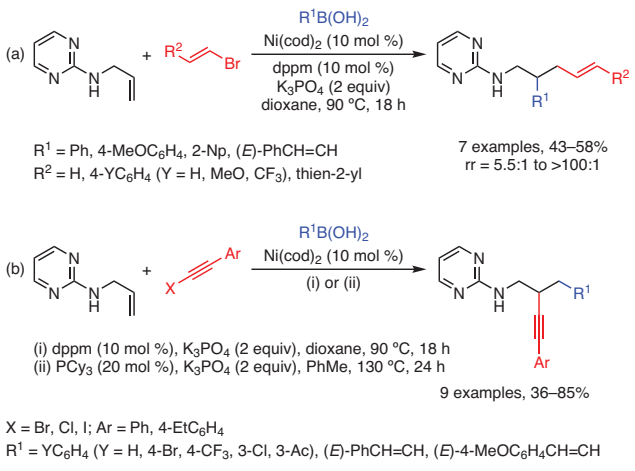
In 2017, Giri and co-workers employed a directing group approach for the nickel-catalyzed diarylation of 2-vinylbenzaldimines, which contain a styrenyl alkene (**Scheme 10**).[50] Arylzinc reagents and aryl halides were incorporated regioselectively via an intervening imine-bound metallacycle. A plausible catalytic cycle is reported in which an initial oxidative addition with nickel(0) provides an imine-coordinated arylnickel 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**).[51] The regioselectivity

was determined by the choice of electrophile, whereby vinyl bromides led to incorporation of the electrophile at the terminal position and alkynyl 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 alkylnickel 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 alkynyl halide electrophiles, 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.



Scheme 10. 1,2-Diarylation via Conjunctive Cross-Coupling Involving Transient Directing Groups. *(Ref. 50)*



Scheme 11. 1,2-Alkenylcarbonation and 1,2-Arylalkynylation via Conjunctive Cross-Coupling Using a 2-Aminopyrimidine Directing Group. *(Ref. 51)*

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, allenes, 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

(1) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062.
(2) Hartwig, J. F. *Nature* **2008**, *455*, 314.
(3) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1.
(4) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704.
(5) Potter, B.; Szymaniak, A. A.; Edelstein, E. K.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 17918.
(6) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752.
(7) Burns, B.; Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron Lett.* **1989**, *30*, 1135.
(8) Fretwell, P.; Grigg, R.; Sansano, J. M.; Sridharan, V.; Sukirthalingam, S.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7525.
(9) Stüdemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 93.
(10) Monks, B. M.; Cook, S. P. *J. Am. Chem. Soc.* **2012**, *134*, 15297.
(11) Grigg, R.; Sansano, J. M.; Santhakumar, V.; Sridharan, V.; Thangavelanthum, R.; Thornton-Pett, M.; Wilson, D. *Tetrahedron* **1997**, *53*, 11803.
(12) Aftab, T.; Grigg, R.; Ladlow, M.; Sridharan, V.; Thornton-Pett, M. *Chem. Commun.* **2002**, 1754.
(13) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374.
(14) Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510.
(15) Peng, Y.; Xiao, J.; Xu, X.-B.; Duan, S.-M.; Ren, L.; Shao, Y.-L.; Wang, Y.-W. *Org. Lett.* **2016**, *18*, 5170.
(16) Peng, Y.; Xu, X.-B.; Xiao, J.; Wang, Y.-W. *Chem. Commun.* **2014**, *50*, 472.
(17) Yan, C.-S.; Peng, Y.; Xu, X.-B.; Wang, Y.-W. *Chem.—Eur. J.* **2012**, *18*, 6039.
(18) Phapale, V. B.; Buñuel, E.; García-Iglesias, M.; Cardenas, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8790.
(19) Thapa, S.; Basnet, P.; Giri, R. *J. Am. Chem. Soc.* **2017**, *139*, 5700.
(20) Cong, H.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 3788.
(21) You, W.; Brown, M. K. *J. Am. Chem. Soc.* **2014**, *136*, 14730.

(22) You, W.; Brown, M. K. *J. Am. Chem. Soc.* **2015**, *137*, 14578.
(23) Zhou, C.; Emrich, D. E.; Larock, R. C. *Org. Lett.* **2003**, *5*, 1579.
(24) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765.
(25) Zhang, X.; Larock, R. C. *Org. Lett.* **2003**, *5*, 2993.
(26) Cheng, Y.; Duan, Z.; Yu, L.; Li, Z.; Zhu, Y.; Wu, Y. *Org. Lett.* **2008**, *10*, 901.
(27) Li, Z.; García-Domínguez, A.; Nevado, C. *J. Am. Chem. Soc.* **2015**, *137*, 11610.
(28) Terao, J.; Bando, F.; Kambe, N. *Chem. Commun.* **2009**, 7336.
(29) Li, Z.; García-Domínguez, A.; Nevado, C. *Angew. Chem., Int. Ed.* **2016**, *55*, 6938.
(30) Xue, F.; Zhao, J.; Hor, T. S. A.; Hayashi, T. *J. Am. Chem. Soc.* **2015**, *137*, 3189.
(31) Shintani, R.; Kurata, H.; Nozaki, K. *J. Org. Chem.* **2016**, *81*, 3065.
(32) Zhou, Y.; You, W.; Smith, K. B.; Brown, M. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 3475.
(33) Huang, T.-H.; Chang, H.-M.; Wu, M.-Y.; Cheng, C.-H. *J. Org. Chem.* **2002**, *67*, 99.
(34) Wu, M.-S.; Rayabarapu, D. K.; Cheng, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 12426.
(35) Urkalan, K. B.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 3146.
(36) Liao, L.; Jana, R.; Urkalan, K. B.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 5784.
(37) Qin, T.; Cornella, J.; Li, C.; Malins, L. R.; Edwards, J. T.; Kawamura, S.; Maxwell, B. D.; Eastgate, M. D.; Baran, P. S. *Science* **2016**, *352*, 801.
(38) Saini, V.; Sigman, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 11372.
(39) Saini, V.; Liao, L.; Wang, Q.; Jana, R.; Sigman, M. S. *Org. Lett.* **2013**, *15*, 5008.
(40) García-Domínguez, A.; Li, Z.; Nevado, C. *J. Am. Chem. Soc.* **2017**, *139*, 6835.
(41) Zhang, L.; Lovinger, G. J.; Edelstein, E. K.; Szymaniak, A. A.; Chierchia, M. P.; Morken, J. P. *Science* **2016**, *351*, 70.
(42) Lovinger, G. J.; Aparece, M. D.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 3153.
(43) Edelstein, E. K.; Namirembe, S.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 5027.
(44) Chierchia, M.; Law, C.; Morken, J. P. *Angew. Chem., Int. Ed.* **2017**, *56*, 11870.
(45) Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 11270.
(46) Stadler, A.; von Schenck, H.; Vallin, K. S. A.; Larhed, M.; Hallberg, A. *Adv. Synth. Catal.* **2004**, *346*, 1773.
(47) Trejos, A.; Fardost, A.; Yahiaoui, S.; Larhed, M. *Chem. Commun.* **2009**, 7587.
(48) (a) Liu, Z.; Zeng, T.; Yang, K. S.; Engle, K. M. *J. Am. Chem. Soc*. **2016**, *138*, 15122. (b) Gurak, J. A., Jr.; Engle, K. M. *Synlett* **2017**, *28*, 2057. (c) Liu, Z.; Ni, H.-Q.; Zeng, T.; Engle, K. M. *J. Am. Chem. Soc*. **2018**, *140*, 3223.
(49) Derosa, J.; Tran, V. T.; Boulous, M. N.; Chen, J. S.; Engle, K. M. *J. Am. Chem. Soc.* **2017**, *139*, 10657.
(50) Shrestha, B.; Basnet, P.; Dhungana, R. K.; Kc, S.; Thapa, S.; Sears, J. M.; Giri, R. *J. Am. Chem. Soc.* **2017**, *139*, 10653.
(51) Li, W.; Boon, J. K.; Zhao, Y. *Chem. Sci.* **2018**, *9*, 600.

About the Authors

Joseph Derosa earned his B.S. degree in 2015 from The City College of New York, where he conducted research with Prof. Mark R. Biscoe in the field of transition-metal catalysis. Later that year, he joined the graduate program at The Scripps Research Institute and received an NSF Graduate Research Fellowship (2016). He is currently carrying out his graduate studies under the guidance of Prof. Keary M. Engle, and is working on developing new catalysis-driven methodology.

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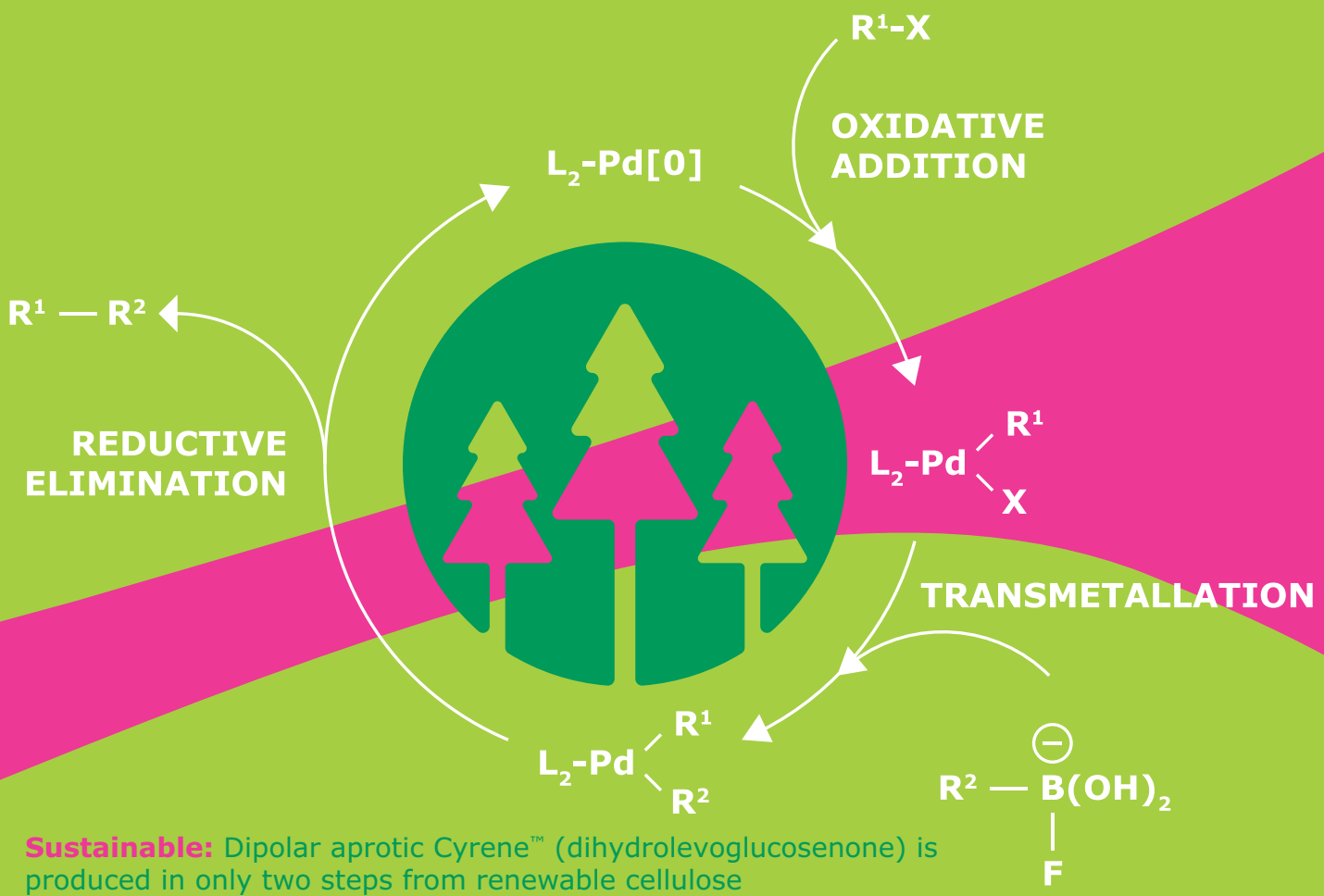

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(1) Wilson et al. *Beilstein J. Org. Chem.* **2016**, *12*, 2005 (DOI:10.3762/bjoc.12.187). (2) Sherwood et al. *Chem. Commun.* **2014**, *50*, 9650 (DOI: 10.1039/C4CC04133J). (3) Salavagione et al. *Green Chem.* **2017**, *19*, 2550 (DOI: 10.1039/C7GC00112F). (4) Mistry et al. *Green Chem.* **2017**, *19*, 2123 (DOI: 10.1039/C7GC00908A).

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Continuous-Flow Macrocyclization

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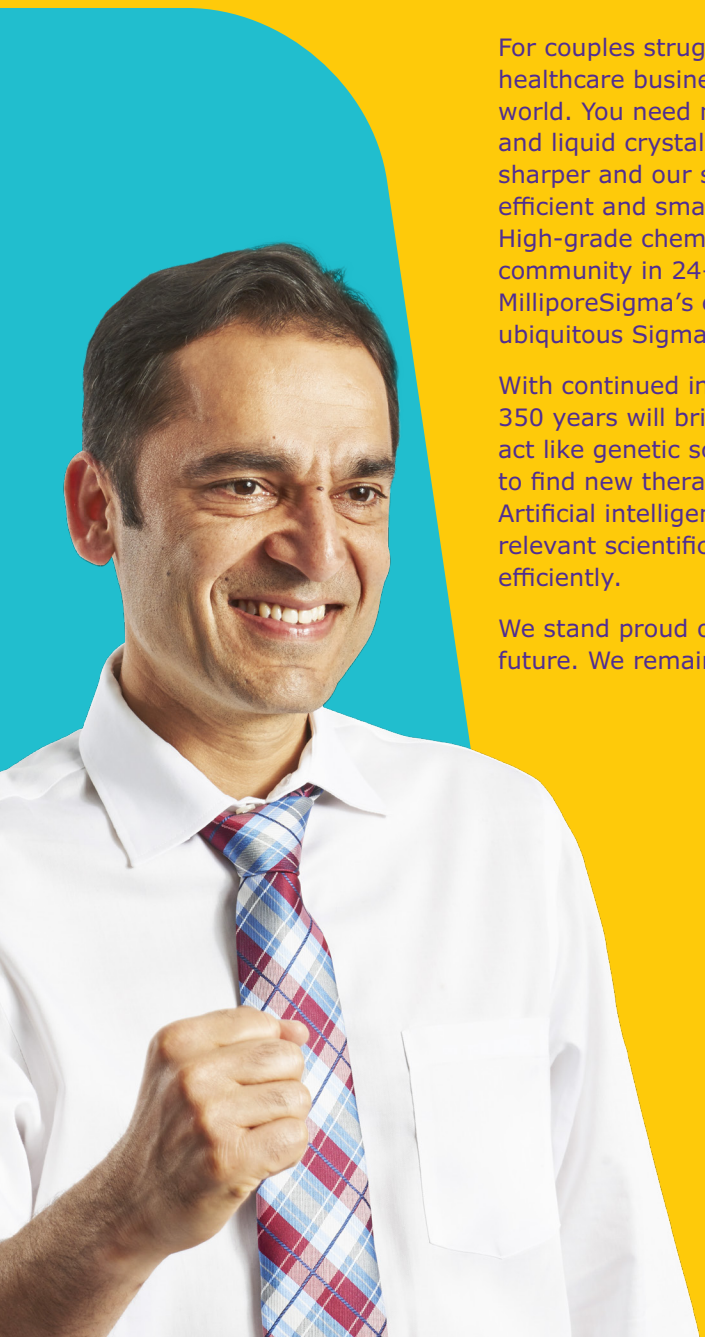

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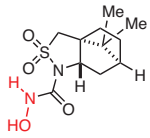

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ABOUT OUR COVER

"Velvet" Brueghel, as Jan Brueghel the Elder (1568–1625) was nicknamed, painted this charming little riverscape (oil on copper, 20.7 × 32.1 cm, 1607). Born into a family of artists, he learned to draw and paint first from his maternal grandmother and then from resident artists in Brussels and Antwerp. He honed his painting skills further during a three-year stay in Italy. Brueghel was prolific, versatile,* and highly regarded, and his works were much sought-after by aristocratic and royal families, as well as collectors. He collaborated extensively with other artists, notably with his lifelong friend Peter Paul Rubens. He worked mainly in Antwerp, and his style and works strongly influenced later Flemish and Dutch landscape artists among them his son, Jan Brueghel the Younger, and the famed flower painter Daniel Seghers.

Detail from ***River Landscape***. Photo courtesy National Gallery of Art, Washington, DC.

Brueghel's elaborate and refined landscapes, of which ***River Landscape*** is a beautiful example, are noted for their exquisite and rich details of the settings and the people in them, as well as for Brueghel's delicate brushstrokes. They depict carefully composed tranquil scenes of townsfolk conducting their daily lives in harmony with each other and with nature. Brueghel often included familiar motifs, such as fishermen and dead or live fish, a winding road leading to a church, the outline of a big city in the distance, and sunlight illuminating a motif of particular interest. The masterful and nuanced use of color in his lively scenes not only helps with depth perception, but also sets off parts of the scenes as writers would acts in a theatrical play or story boards in an illustrated short story.

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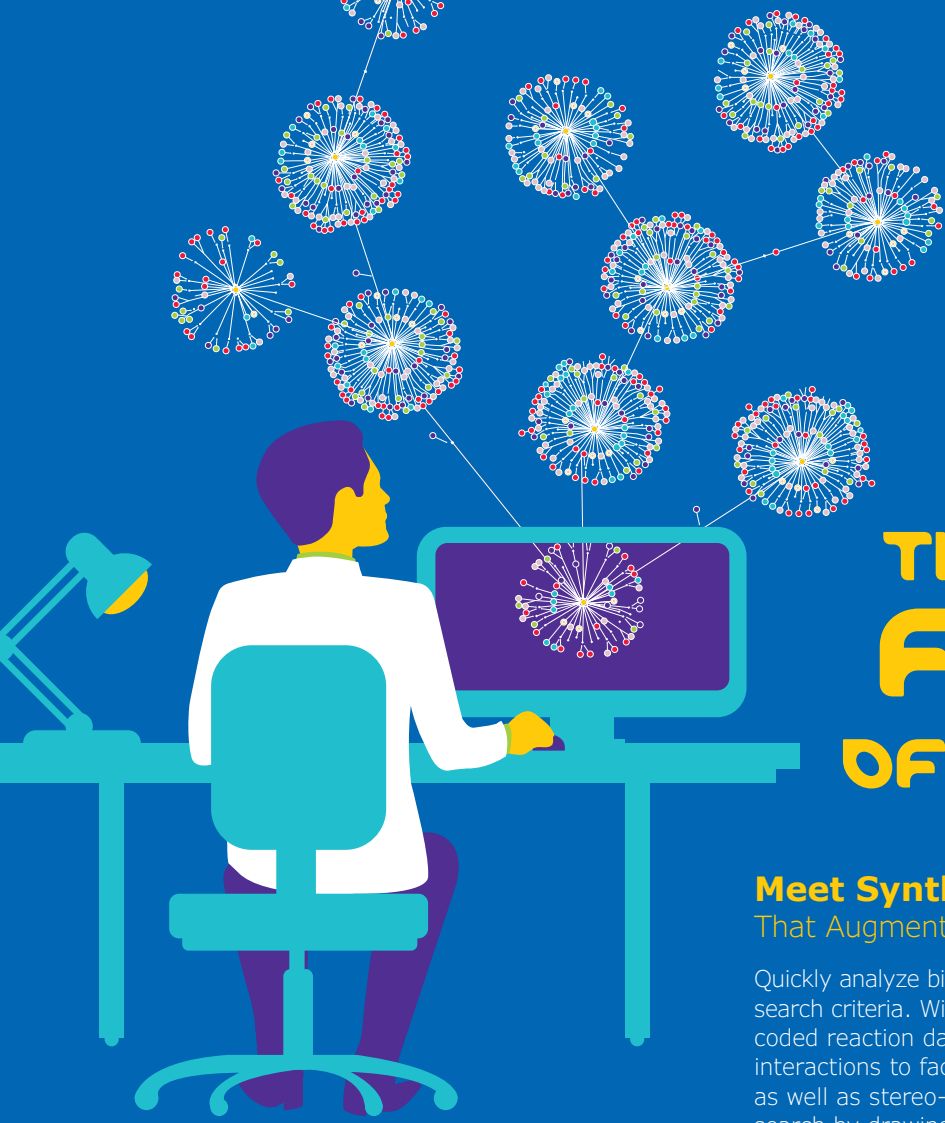
** Jan Brueghel the Elder had an amazing range of artistic interests and skills. To find out more, visit* ***SigmaAldrich.com/Acta***



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Continuous-Flow Macrocyclization


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Éric Godin, Émilie Morin, and Shawn K. Collins*

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Keywords. macrocyclization; continuous flow; olefin metathesis; Glaser–Hay coupling; CuAAC reactions; ring expansion; photochemical reactions.

Abstract. Traditional macrocyclization reactions often use batch reactors and/or apparatus for slow-addition protocols. However, a more advantageous alternative has now emerged whereby these reactions are carried out in a continuous-flow process. Continuous processing can offer several advantages, including higher yields and shorter reaction times owing to improved mass and energy transfers. To date, continuous-flow macrocyclization has had a significant impact on well-known reactions, such as olefin metathesis, the Glaser–Hay coupling, and CuAAC reactions; has been applied to ring expansions; and has opened the door to exploring new photochemical macrocyclizations.

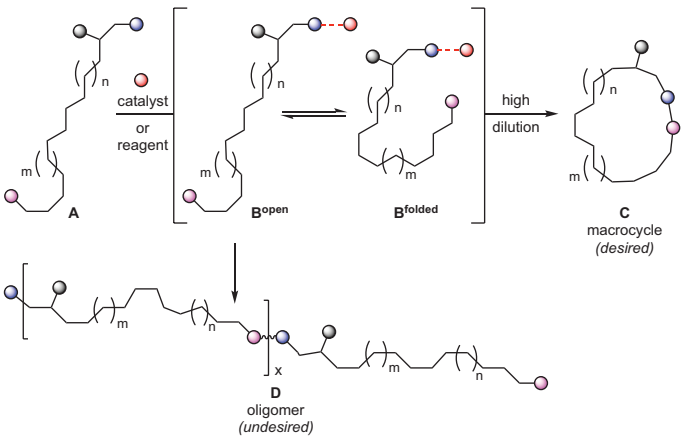
Outline

1. Introduction

Macrocyclization is a unique reaction manifold in synthesis.[1] As a reaction type, it is an intramolecular reaction that does not actually benefit from the kinetics of its intramolecularity. Due to the distance between the relevant functional groups in the acyclic precursor (**A**, Scheme 1), the intramolecular reaction rate is often comparable to that of the corresponding intermolecular reaction between two of the acyclic precursors. Consequently, there is competition between the undesired oligomerization to form **D** and the desired ring-closing reaction to generate macrocycle **C**. Typically in an intermolecular reaction, the reaction yield can be improved by increasing the concentrations of the reactants. Despite macrocyclizations having slow reaction rates similar to intermolecular reactions, increasing the reactant concentration in the former case only serves to favor the undesired oligomerization pathway. Over a century ago, an important guideline for successful macrocyclization was established: The ring-closing reaction can be favored over oligomerization by working under low concentrations.[2]

Further evolution of the concept led to pseudo-high-dilution strategies, where the acyclic precursor, **A**, is added slowly (often by syringe pump) over time to a solution containing the reagent or catalyst. However, under the dilute reaction conditions, the overall rate of macrocyclization suffers, as the first step is an intermolecular reaction between one of the functionalities in **A** and the catalyst or reagent, and the first step is slowed down by the high dilution. As a consequence, macrocyclization reactions are typically heated to high temperatures to improve the rate of formation of the substrate–reagent (or catalyst) adduct, **B**. An additional benefit of higher temperatures is achieving conformations in **B** that are conducive to ring closure. Acyclic precursors may not necessarily adopt conformations in which the reactive functionalities are in close proximity ($\mathbf{B}^{open}$). The extra energy provided can allow molecules the flexibility to adopt conformations such as $\mathbf{B}^{folded}$, which may be unfavored at the lower temperatures. Despite the concentration limitations, chemists have now devised a number of macrocyclization processes that can be exploited within the context of aroma chemicals and pharmaceuticals and in materials science. Reaction types such as macrolactonization,[3] macrocyclic olefin metathesis,[4]

Pd-catalyzed macrocyclic cross-coupling,[5] and the copper-catalyzed macrocyclic azide–alkyne cycloaddition (CuAAC)[6] have become go-to methods for practitioners to prepare large-ring compounds. However, just as the syringe pump made macrocyclization more practical, it could be argued that we are on the verge of another technological leap toward improving macrocyclization processes. Continuous-flow technology has impacted a host of different chemical reaction types. Synthetic photochemistry is now viewed as practical because of the possible use of flow chemistry to control light penetration and scalability.[7] A host of previously believed "unstable" reagents and intermediates can now be harnessed in a safe and controllable manner via flow technology, providing access to new or streamlined synthetic routes to important targets.[8] It could be argued that macrocylization can also benefit from advances in continuous-flow technology. For example, the formation of adduct **B** (Scheme 1) could be accelerated or augmented through the improved mixing observed in flow. Alternatively, the catalyst or reagent could be immobilized and packed into a cartridge. Thus, when the solution of the acyclic precursor, **A**, enters the reactor, the relative concentration of reagent is high, accelerating the formation of **B**. The rate of ring-closing ($B^{open} \rightarrow B^{folded}$ or $B^{folded} \rightarrow C$) could similarly be improved through better heat transfer between the tubing and the reaction solution. The use of continuously stirred reactors has also been demonstrated, rendering the transfer of slow-addition processes to continuous flow more viable. Despite the advantages, the development of flow protocols for macrocyclization is still in its infancy. The remainder of this article will shed light on the emerging field of continuous-flow macrocyclization in different reaction types.



Scheme 1. Schematic Representation of a Macrocyclization Reaction and the Competing Oligomerization.

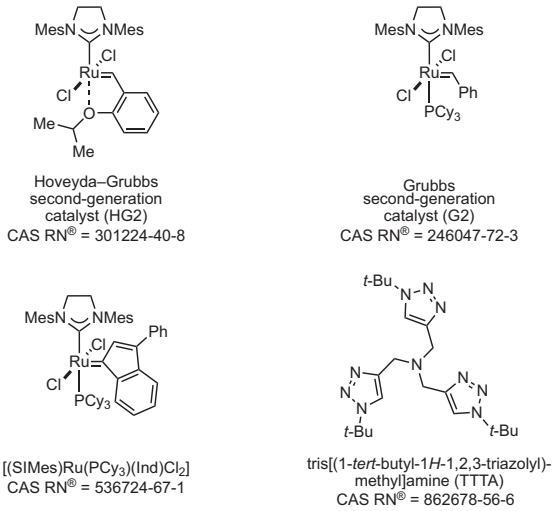


Figure 1. Some of the Catalysts and Ligands Featured in the Review.

2. Ring-Closing Olefin Metathesis

Olefin metathesis is one of the most widely used reactions for carbon–carbon bond formation. The commercial availability of catalysts possessing high activities and good functional group tolerance has led to numerous applications in total synthesis, particularly for macrocyclization.[4] Continuous-flow techniques can improve the mass and/or heat transfer, thus improving yields, selectivities, and reaction times, but can also have a negative impact on catalyst lifetime, loading, and removal.[9] Thus, despite its promise, few examples exist of the application of continuous flow to macrocyclic olefin metathesis.

Limbach and co-workers have explored a ring-opening/ring-closing (RO–RCM) tandem process in continuous flow by evaluating the performance of new heterogeneous metathesis catalysts supported on silica in the cyclodimerization of cyclooctene (COE).[10] One of their best results was obtained with the second-generation Hoveyda–Grubbs Catalyst™ (HG2) (**Figure 1**), giving a selectivity of 19% and a TON of 4350. They further explored the linker-free supports by testing different silica-based microporous, mesoporous, and macroporous materials.[11] The mesoporous material MCM-41, with a pore size of 180 Å, gave the best selectivity for small cyclic oligomers without any polymerization side-product. The authors observed that no significant leaching of ruthenium occurred, which is important for the recycling of the catalyst and the purification of the reaction mixture. Some process parameters were also optimized such as residence time, temperature, and concentration. The optimal continuous-flow process was the injection of a 25 mM cyclohexane solution of COE into a steel reactor loaded with heterogeneous metathesis catalyst HG2@MCM-41 and heated at 60 °C for a residence time of 5 minutes (**eq 1**).[11]

Unlike the RO–RCM described above, simple RCM reactions can be problematic in continuous flow. Indeed, in many cases where the starting material possesses a terminal olefin group, the reaction cannot be transposed easily from batch to continuous flow because of the release of ethylene gas as a byproduct. Grubbs has reported that, in the presence of ethylene, catalyst deactivation can occur through formation of unstable ruthenium methylidene species.[12] In such cases, continuous-flow methods would have to permit somehow the evolution of ethylene gas. Roberge, Fogg, and

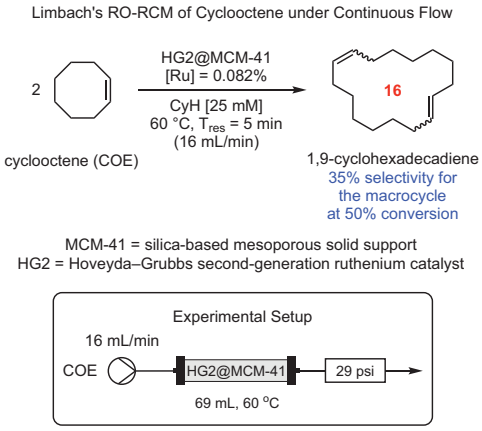
co-workers have studied the influence of reactor configuration on the RCM of diene ester **1** (**Scheme 2**).[9] The batch reactor (BR) setup consisted of a round-bottom flask containing all the reagents and catalyst (Scheme 2, Part (a)), while the continuous-flow (PFR) setup had the substrate and the catalyst injected from two separate syringes and mixed in a micromixer before passing through the coil (Scheme 2, Part (b)). To insure that the reaction ends upon exit of the solution from the tubing, the solution was eluted into a flask containing potassium tris(1-pyrazolyl)borate (KTp) to quench the catalyst. The authors observed that the yields and reaction rates were always higher in the batch reactor, even after optimization of the continuous-flow process by adjusting the temperature, the residence time, the concentration, and the catalyst loading. For example, at 80 °C with 1 mol % of catalyst G2 at a concentration of 5 mM, the yield obtained after 10 minutes in the batch reactor was 82%, while only 70% was reached after an 11-minute residence time in the continuous-flow process.

The authors then suggested that the ethylene byproduct trapped in the tubing was detrimental, and moved toward a continuous stirred-tank reactor (CSTR) which allows the ethylene to escape the reaction mixture (Scheme 2, Part (c)). The substrate and catalyst were injected in the same manner as in Part (b), but were eluted into a round-bottom flask containing toluene and a magnetic stir bar. A constant volume was maintained in the flask with an output pumping at a fast rate of 40 mL/min. To ensure that ethylene exited the reactor, a stream of argon was constantly applied in the headspace. The setup achieved a better yield of **2** (>99%, 20 min residence time) than in the BR and the PFR processes. The CSTR process showed the least catalyst deactivation with a maximum turnover frequency (TOF_{max}) of 15.2 min^{-1}, as compared to 8.2 min^{-1} for the BR and 6.4 min^{-1} for the PFR processes.

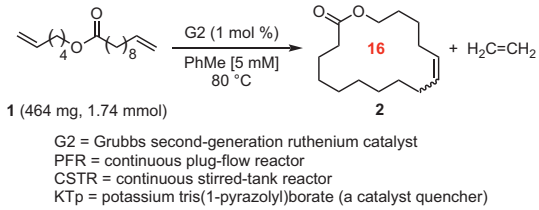
Skowerski and co-workers later published an alternative to the CSTR process that would also permit the removal of ethylene and would be applicable to both homogeneous and heterogeneous catalyses.[13] They proposed the use of a tube-in-tube reactor made with an outer tube of Teflon® and an inner tube made of semipermeable Teflon® AF2400.[14] In pumping the reaction mixture through the outer tubing and connecting a vacuum pump to the inner tubing, removal of ethylene was possible through the pressure difference (0.05–0.07 mbar). The reactor was also applied to a 5-membered-ring RCM under heterogeneous catalysis by loading a silica gel immobilized catalyst between the inner and outer tubing, but was not tested in a macrocyclization reaction.

When a homogeneous reaction was performed, the authors observed that the impact of the vacuum pump was greater when the concentration of the reaction was low, which made it applicable to the macrocyclization reactions of diene **1** (**eq 2**).[13] Macrocyclization was performed using 0.5 mol % of ruthenium catalyst pumped at the same rate as the substrate to achieve a total concentration of 5 mM after the T-mixer. The reaction solution was then passed through the tube-in-tube reactor placed in an oil bath heated at 70 °C and finally quenched with ethyl vinyl ether ($EtOCH{=}CH_2$). As observed previously and under the same reaction conditions, the closed, continuous-flow process (PFR) gave a moderate yield of 57% of macrocycle **2**, the batch reactor (BR) a better yield of 84%, but the tube-in-tube reactor connected to the vacuum pump (PFR-V) afforded the best yield, 90%.

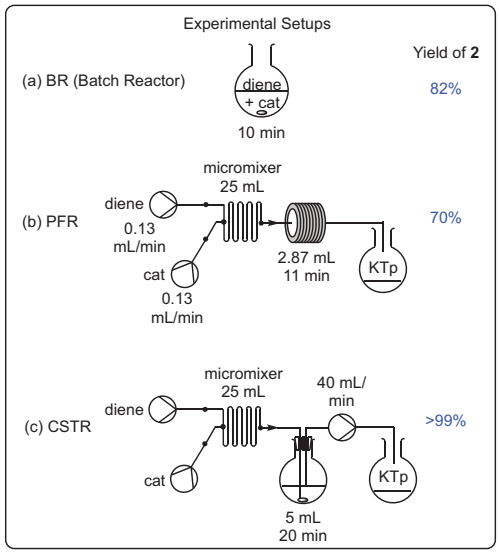
In 2017, our research group published the total synthesis of neomarchantin A, a macrocyclic bisbibenzyl natural product,[15] with an interesting and rigid three-dimensional shape due to the



eq 1 *(Ref. 11)*

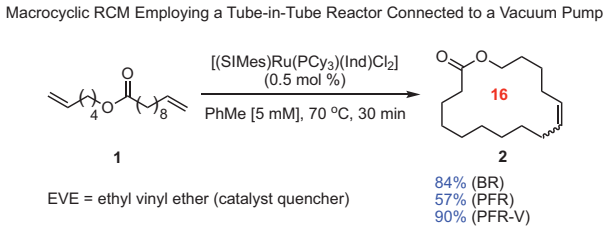


G2 = Grubbs second-generation ruthenium catalyst
PFR = continuous plug-flow reactor
CSTR = continuous stirred-tank reactor
KTp = potassium tris(1-pyrazolyl)borate (a catalyst quencher)

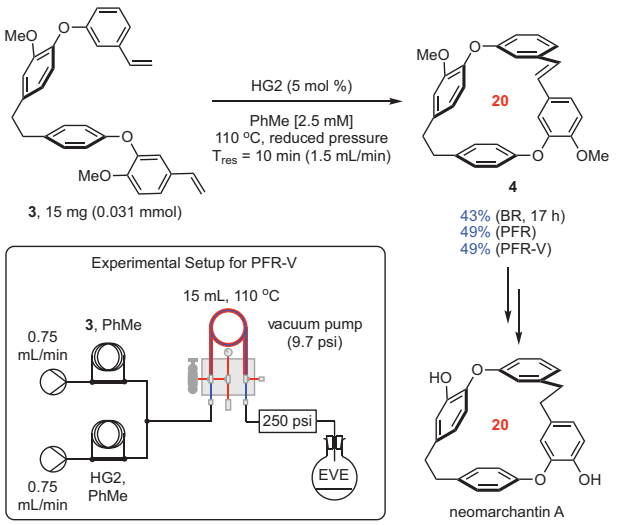


Scheme 2. Ring-Closing Metathesis Reaction (RCM) and Experimental Setups for (a) Batch, (b) Continuous-Flow, and (c) Continuous Stirred-Tank Reactor (CSTR) Processes. *(Ref. 9)*

connectivity of the four aromatic rings in the macrocycle (two rings through para and two rings through meta substitutions). Three different continuous-flow processes were developed for the key steps of the synthesis, including the macrocyclization step (**Scheme 3**),[15] which was the first catalytic macrocyclization reported for a bisbibenzyl natural product. The substrate, **3**, and catalyst (HG2) were injected separately from two sample loops and were mixed via a T-mixer before passing through a 15 mL tube-in-tube reactor heated at 110 °C. After 10 minutes of residence time, the reaction mixture was eluted into a flask containing ethyl vinyl ether to quench residual catalyst. Several tests with and without a vacuum pump connected to the reactor gave similar yields (49%) of macrocycle **4**. For comparison, the reaction in batch required 17 h to achieve full conversion and resulted in a similar yield of intermediate **4** (43%). However, the continuous-flow process (PFR) afforded a "cleaner" reaction, as there were no oligomers generated and only unreacted starting material made up the mass balance.



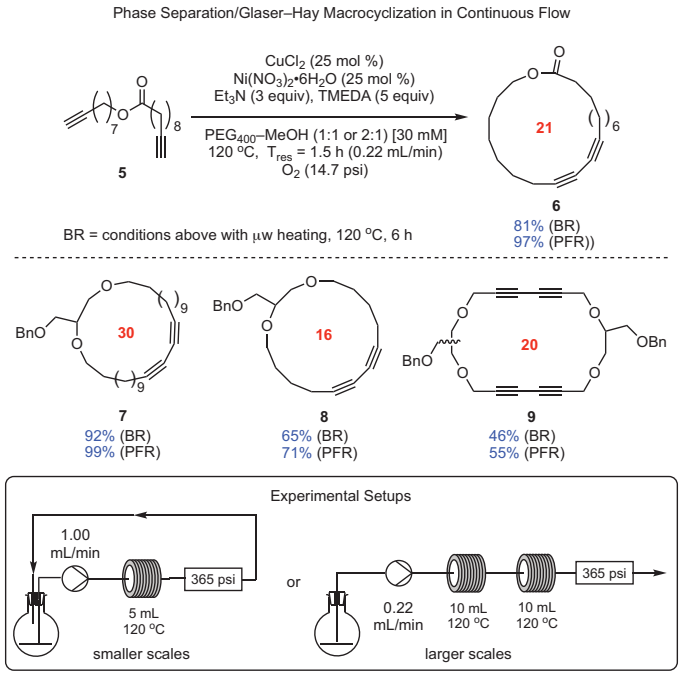
eq 2 *(Ref. 13)*



Scheme 3. Application of RCM, Enabled by a Continuous-Flow Process (PFR), to the Total Synthesis of Neomarchantin A. *(Ref. 15)*

3. Glaser–Hay Coupling

The Glaser–Hay coupling is one of the most straightforward strategies to construct the 1,3-butadiyne moiety,[16] with applications in the synthesis of natural products.[17] In 2013, our laboratory employed the Glaser–Hay coupling in a new macrocyclization strategy called "phase separation" that exploits the aggregation properties of different poly(ethylene glycol) (PEG) co-solvents in methanol (MeOH).[18] The slow diffusion of the acyclic organic precursor from a PEG aggregate toward the MeOH phase mimics common slow addition and high dilution protocols, making possible macrocyclization reactions at relatively high concentrations without the need for cumbersome syringe pumps or addition funnels. The phase separation strategy was first developed in batch[19] and then transposed to continuous flow.[20] It was believed that the improved mass transfer would help accelerate diffusion of the acyclic precursors, and the enhanced heat transfer would shorten reaction times and increase yields. In the batch process, the acyclic precursor **5** underwent cyclization to the 21-membered-ring macrocycle **6** in 81% yield, whereas in flow macrocycle **6** was obtained in 97% yield (**eq 3**).[20] Depending on reaction scale, two continuous-flow setups were utilized: For smaller scales, the reactor consisted of a 5 mL stainless-steel coil heated at 120 °C, the solution was pumped at a flow rate of 1 mL/min, and the 10 mL reaction mixture was cycled for a total residence time of



eq 3 *(Ref. 20)*

1.5 h. For larger scales, the reaction mixture was pumped through two sequential 10 mL stainless steel coils heated at 120 °C at a flow rate of 0.22 mL/min for an identical residence time of 1.5 h. The phase separation strategy in continuous flow was employed on up to a multigram scale (~4 mmol) to the preparation, in moderate-to-high yields, of a variety of macrocycles, **7**–**9**, that act as mimics of archaeal membrane lipids.

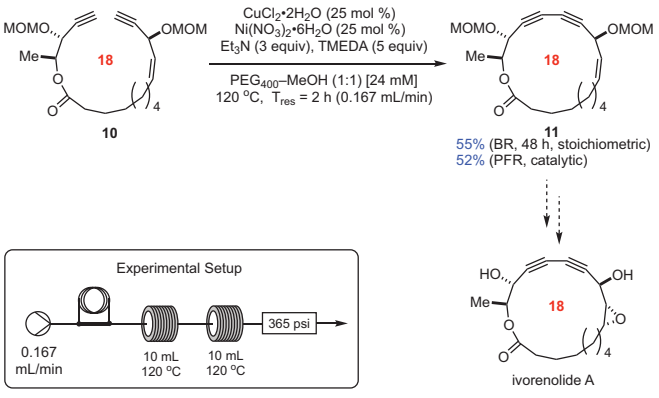
The same strategy was also applied to the formal total synthesis of ivorenolide A,[21] an 18-membered-ring macrolide containing the first known naturally occurring cyclic 1,3-butadiyne moiety (**Scheme 4**).[22] Yadav and co-workers completed the first total synthesis of ivorenolide A in 2015 by employing Shiina's MNBA macrolactonization as the key macrocyclization step.[23] Our group exploited the presence of the 1,3-butadiyne moiety and applied the Glaser–Hay oxidative macrocyclization for the key ring-closing step. The experimental setup consisted of two 10 mL stainless-steel coils heated at 120 °C, and the reaction solution was pumped at a flow rate of 0.167 mL/min for a total residence time of 2 h. Using the protocol, the macrocyclic core, **11**, of ivorenolide A was synthesized in 52% yield by utilizing a one-pot *catalytic* reaction at concentrations about 120 times higher than those employed in the slow-addition protocol. A similar yield (55%) was obtained in a batch mode after 48 h, but it required much lower concentrations (0.2 mM) and the use of slow-addition techniques as well as superstoichiometric amounts of copper salt and ligand.

Recently, our group also achieved the synthesis of the macrocyclic core, **13**, of vaniprevir (MK-7009), an NS3/4a protease inhibitor of hepatitis C virus, developed by Merck & Co. (Kenilworth, NJ) (**Scheme 5**).[24] The oxidative Glaser–Hay macrocyclization/phase separation protocol was once again used for the ring-closing step. In addition, the utility of a dendritic PEG co-solvent, StarPEG$_{1014}$, for the phase-separation strategy was demonstrated in control experiments, whereby the modified PEG allowed for macrocyclization to form the 21-membered ring **6** at up to 200 mM, while maintaining a yield greater than 60%. In this way, the vaniprevir macrocyclic core, **13**, was formed in 64% yield at 24 mM, 120 °C, and a total residence time of 4 h using a tube-in-tube reactor and a stainless steel coil reactor. A traditional batch macrocyclization to afford the same yield required a lower concentration (0.2 mM), longer reaction times (48 h) using slow addition (over 24 h), and superstoichiometric amounts of copper salt and ligand.

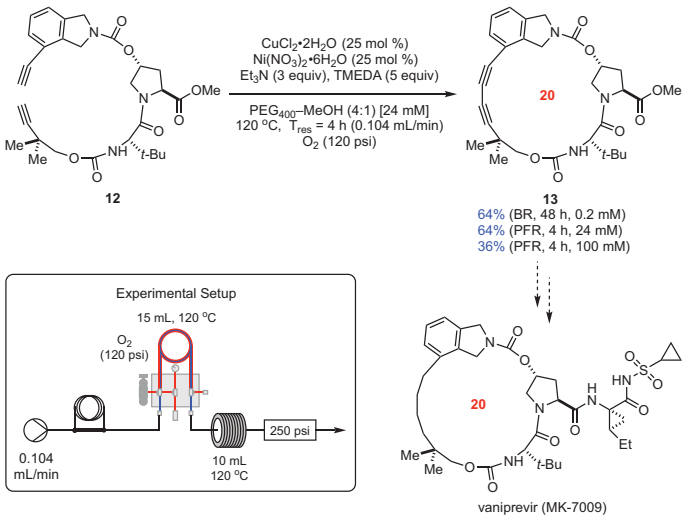
Macrocyclization via Glaser-type alkyne–alkyne coupling has also been employed by Doonan and co-workers in the synthesis of carbon-based molecular cages, which possess photophysical properties and permanent porosities that are of interest to materials scientists.[25,26] The synthetic approach relied on the dimerization of two half-cages by utilizing a Breslow-modified Glaser–Eglinton coupling. In the batch process [using high dilution (2.22 mM) to avoid oligomerization and employing superstoichiometric amounts of CuCl (65 equiv) and Cu(OAc)$_2$•H$_2$O (25 equiv) in pyridine at 65 °C for 8 h under inert atmosphere], a 20% yield of the desired macrocyclic cage, **15**, was produced. In a more recent report, Doonan's laboratory performed the coupling in a continuous-flow process, whereby reduced quantities of CuCl (32 equiv) and Cu(OAc)$_2$•H$_2$O (21 equiv) were used, and only a 33.3 min residence time was necessary to obtain a similar 21% yield of **15** (**eq 4**).[26]

4. Alkylation

Alkylation reactions are some of the most direct methods to obtain heteroatom-C$_{sp^3}$ bonds. The Williamson etherification, developed in 1850, consists of the substitution of the halogen in an alkyl halide by alkoxide ion in a S$_N$2-type mechanism.[27] Due to the nature of the mechanism, such intermolecular alkylation reactions are often performed at very high concentrations, but can be slowed by the highly diluted reaction media often required in macrocyclization reactions. Huszthy and co-workers have employed an alkylation approach to synthesize chiral pyridine-18-crown-6 ethers,[28] which are useful for the chromatographic separation of

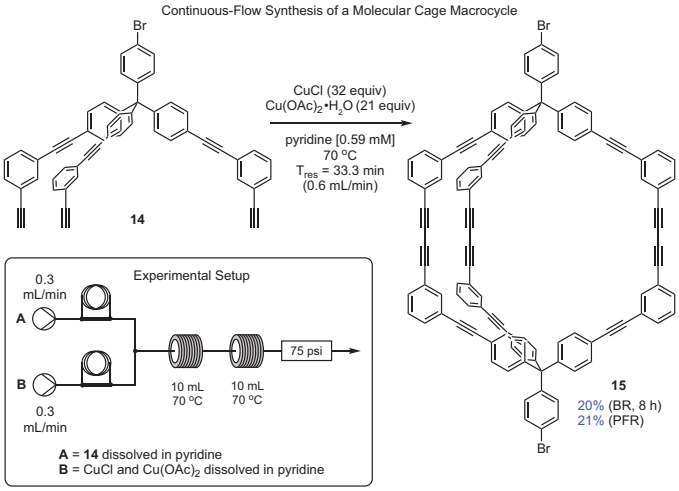


Scheme 4. Synthesis of the Macrocyclic Core of Ivorenolide A by Employing a Phase Separation/Continuous Flow Strategy in the Key Glaser–Hay Macrocyclization Step. *(Ref. 21)*

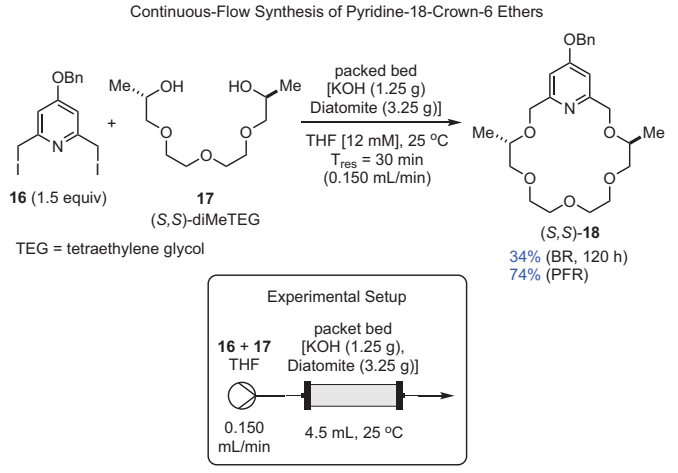


Scheme 5. Phase Separation/Continuous Flow Synthesis of the Vaniprevir (MK-7009) Macrocyclic Core. *(Ref. 24)*

protonated amines and amino acid derivatives.[29] Originally, the synthesis utilized an excess of strong base (NaH, 3.16 equiv) and tosylate (OTs) as the leaving group for 120 h at 12 mM to afford only moderate yields of pyridine-18-crown-6 ethers (e.g., 34% of **18**). Subsequently, the authors used a continuous-flow process to improve the synthesis of the pyridine-18-crown-6 ethers (**eq 5**).[28b] It is important to note that the authors needed to change the leaving group from OTs to iodide to avoid coil clogging due to the insolubility of the tosylate salt formed. This new protocol allowed for the synthesis of chiral pyridine-18-crown-6-ethers in shorter reaction times (30 min), with a safer and weaker base (KOH) packed in a reusable column, while providing higher yields (e.g., 74% of **18**) than the original batch method.



eq 4 *(Ref. 25,26)*



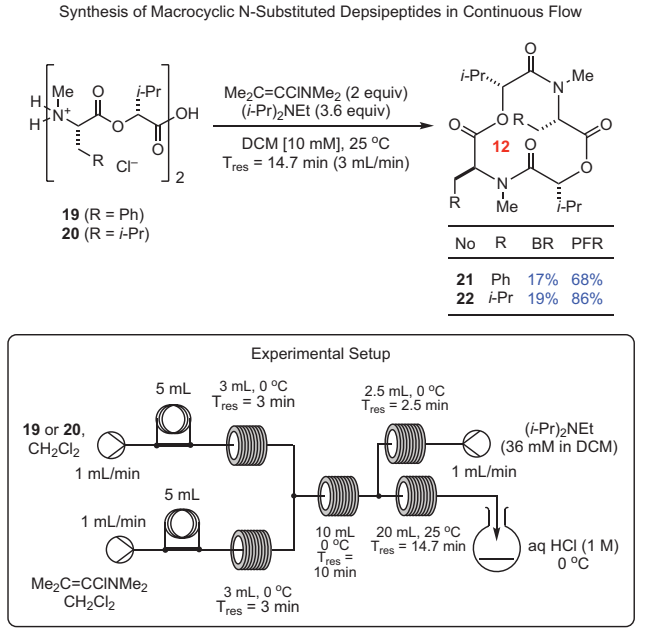
eq 5 *(Ref. 28b)*

5. Amide-Bond-Forming Reactions

Amide-bond synthesis remains a significant challenge in complex-peptide synthesis.[30,31] In 2016, Wilson, Ley, and co-workers tackled the synthesis of complex macrocyclic depsipeptides—a class of peptides where some amide bonds are replaced by ester bonds—by utilizing a continuous-flow protocol to prepare 12-, 18-, and 24-membered cyclooligomeric depsipeptides, including the natural products beauvericin, bassianolide, and enniatin C (**eq 6**).[32] The synthesis of the linear precursors was performed using both batch and flow methods. When the linear amino acids **19** and **20** were cyclized in batch at 4 mM using Ghosez' reagent ($Me_2C{=}CClNMe_2$) as the coupling agent, only low yields of the cyclic monomers (17% and 19%, respectively) were obtained along with higher yields of the undesired cyclic dimers (41% and 45%, respectively). After optimizing the residence time and temperature, the same reaction at 10 mM in continuous flow afforded the desired 12-membered depsipeptides **21** and **22** as the sole products in 68% and 86% yield, respectively. The authors also synthesized a small library of cyclic N-substituted depsipeptides, while improving the average yield of the reactions from 41% (batch) to 81% (flow).

6. Azide–Alkyne Cycloaddition Reactions

With over 50 years of development[33] the Cu-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC) reaction has found numerous applications in organic synthesis, most notably in medicinal chemistry.[34] The first report of CuAAC reactions in flow, by Bogdan and Sach in 2009, described the use of copper tubing as a flow reactor for the synthesis of 1,4-disubstituted-1,2,3-triazoles.[35] In 2010, Bogdan and James adapted the same copper tubing flow



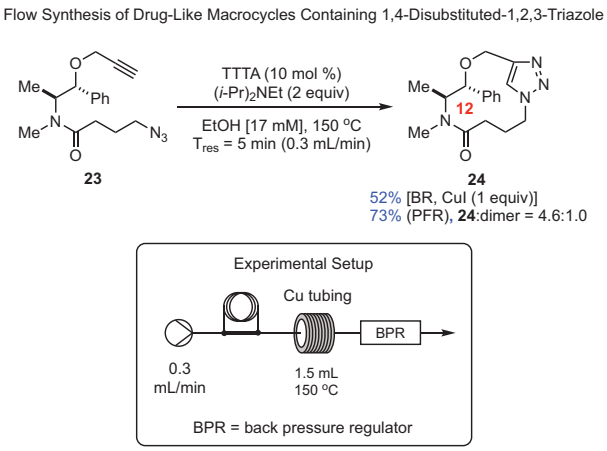
eq 6 *(Ref. 32)*

reactor for the synthesis of a library of drug-like 12- to 22-membered macrocycles in generally high yields (28–90%) (**eq 7**).[36] The reaction was carried out in the presence of a catalytic amount (10 mol %) of tris[(1-*tert*-butyl-1*H*-1,2,3-triazolyl)methyl]amine (TTTA) (10 mol %) as ligand and 2 equivalents of *N,N*-diisopropylethylamine (DIPEA) as base in ethanol. For example, the linear precursor **23**, bearing a pendant azide and a terminal alkyne, was transformed into its corresponding 12-membered macrocycle **24** in 73% yield (**24**:dimer = 4.6:1.0) in only 5 min. Interestingly, the macrocyclization reaction could be performed at relatively high concentration (17 mM). The authors rationalized the observation by suggesting that the reaction occurred at the surface of the copper tubing, creating a "pseudo-dilution" effect. Indeed, elemental analysis of the resulting reaction mixture indicated the presence of low levels of copper (<5 ppm), and running the reaction in batch mode [CuI (1 equiv), 150 °C, 5 min) afforded a 52% yield of **24** with a lower product:dimer ratio.

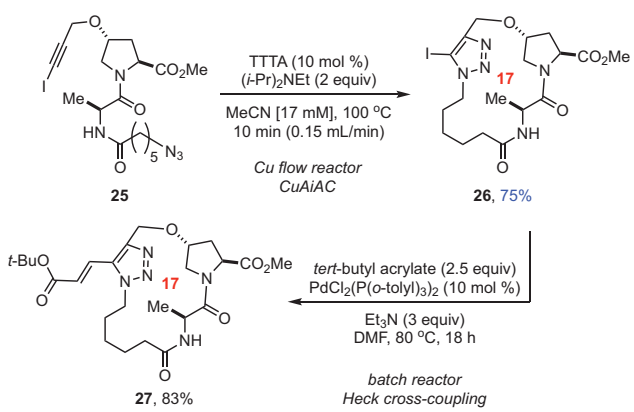
This process is tolerant of a number of functional groups, and allowed for the synthesis of a large variety of strained macrocycles, highlighted by the first 11-membered cyclophane macrocycle bearing a triazole ring.[37]

James's laboratory employed the same methodology, with only minor modifications of the reaction conditions, for a Cu-catalyzed azide–iodoalkyne cycloaddition (CuAiAC) that resulted in the first efficient and regiocontrolled synthesis of macrocycles incorporating a 5-iodo-1,2,3-triazole moiety (**Scheme 6**).[38] In this way, azidoiodoalkyne **25** afforded macrocycle **26** in 75% yield at 17 mM, along with several other structurally diverse 12- to 31-membered macrocycles (21–83% yield). The authors demonstrated the ability to diversify the iodotriazole in the macrocycle by using palladium-catalyzed Suzuki, Heck, and Sonogashira cross-couplings. For example, when **26** was subjected to the Heck cross-coupling conditions (in batch) in the presence of *tert*-butyl acrylate, the modified macrocycle **27** was obtained in 83% yield.

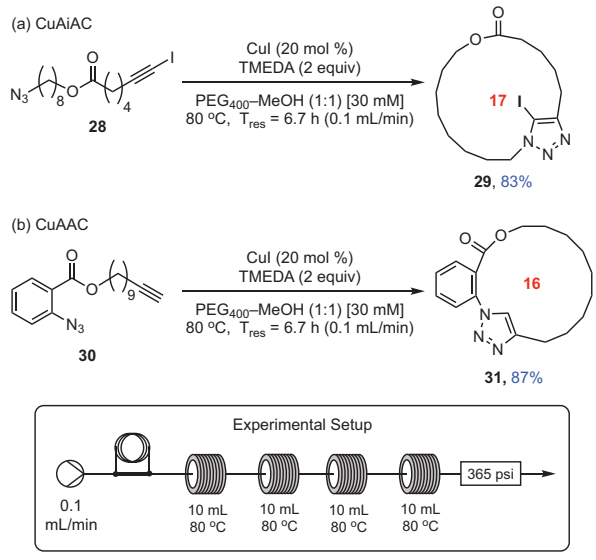
In 2015, our group applied the "phase separation" strategy in CuAiAC and CuAAC reactions aimed at synthesizing a variety of triazole-containing macrocycles in moderate-to-high yields (65–90%) at relatively high concentrations (30–50 mM) using continuous flow (**Scheme 7**).[39] Although the reaction was originally developed in a batch process,[40] a change in ligand was necessary to prevent decomposition of the catalyst at the higher temperatures in flow. When the conformationally unbiased azidoiodoalkyne **28** was subjected to the optimized conditions, triazole-containing macrocycle **29** was obtained in 83% yield at 30 mM. A small library of 17- to 24-membered 5-iodotriazole-containing macrocycles incorporating amino acids and phenolic ethers in their core structures was then synthesized. The same methodology was also applied to the CuAAC macrocyclization to form 11- to 26-membered macrocycles (e.g., **31**) derived from either aryl azides or aryl alkynes.



eq 7 *(Ref. 36)*



Scheme 6. Copper Tubing Flow Reactor for the CuAiAC Synthesis of Drug-Like Macrocycles Incorporating a 5-Iodo-1,2,3-triazole Moiety and Elaboration of the Latter with Palladium-Catalyzed Cross-Coupling. *(Ref. 38)*



Scheme 7. Phase-Separation Strategy in Continuous-Flow CuAiAC and CuAAC Macrocyclizations. *(Ref. 39)*

Concurrently in 2015, Kappe and co-workers developed a multistep sequence for the synthesis and macrocyclization of linear peptoids [poly(N-substituted glycines)] via Ugi 4-component (U-4CR) and CuAAC reactions (**eq 8**).[41] Traditionally, peptoids had been prepared by using sub-monomer solid-phase synthesis,[42] but recent work[43] has shown that U-4CR to be a versatile and efficient way to access this class of molecules. In both U-4CR and CuAAC reactions, toxicity (isocyanide) and stability/reactivity (azide) of the building blocks can lead to safety concerns, which can be mitigated by continuous-flow technologies. As such, the authors developed a reaction sequence in continuous flow where the building blocks needed in the Ugi and CuAAC reactions are synthesized from safer starting materials. As an example, after the generation and purification of the linear azidoalkyne peptidomimetic **32**, the CuAAC reaction was performed in dilute media (2 mM) using a copper tubing flow reactor to afford the peptoid macrocycle **33** in 83% yield. The authors observed better conversions when the reaction was performed without ligand (TTTA) and base (DIPEA), in contrast to previous work.[38] Depending on the resulting ring strain in the macrocycle, either the macrocycle or a macrocyclic dimer could be formed. The experimental setup used consisted of a 20 mL copper coil heated at 140 °C in a GC oven. The solution was pumped at a flow rate of 0.8 mL/min using a syringe pump for a total residence time of 25 min.

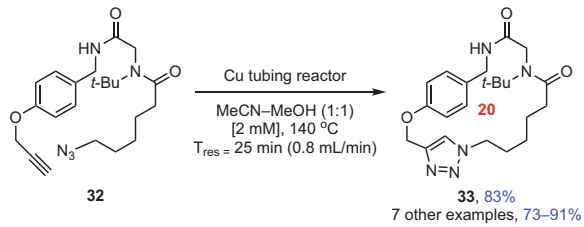
7. Photochemical Reactions

In the past decade, interest in new synthetic photochemical reactions has been growing because of the possibility of accessing new mechanistic pathways and of the promise of using light as a renewable and traceless reagent. Unfortunately, photochemistry is inherently limited in batch processes, where limited light penetration becomes increasingly problematic with reaction scale. In macrocyclizations requiring low concentrations, the problem of light penetration is even significantly worse. It is possible that in a continuous-flow process, the high surface-to-volume ratio and homogeneous irradiation could enhance photochemical macrocyclizations, allowing for shorter reaction times, better reproducibility, higher yields and selectivities, and more facile scale-up.[7]

In 2016, Zhang and co-workers[44] published a scalable synthesis of cyclic polymers using continuous flow via a photoenol reaction[45] mediated by UV irradiation at 310 nm. When performed in batch on a small scale of 4.3 mg, the reaction was complete in 30 minutes and afforded a 93% yield. In flow, the macrocyclization only required a 2 minute residence time for a similar yield (90%) (**eq 9**).[44] For a 1 g scale-up in continuous flow, the solution was pumped through a homemade coiled glass reactor (200 mL) wrapped around the light source at a flow rate of 100 mL/min for a residence time of 2 minutes and a process time of only 3 h to achieve similar yields as the small-scale reactions.

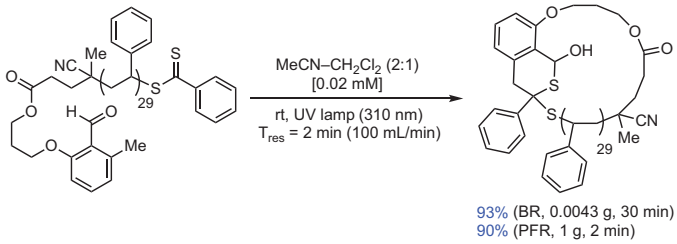
An alternative process for the formation of cyclic polymers via the same photoenol macrocyclization was reported in 2017 by Barner-Kowollik, Junkers, and co-workers (**eq 10**).[46] Use of a looped flow process allowed this research team to reduce the amount of solvent required (compared to Zhang's process) by a factor of 43. A relatively concentrated solution of substrate (5 g/L) was injected with a syringe pump at a very slow flow rate (0.01 mL/min) while the loop pump was pumping solvent at a faster rate (2 mL/min) to mimic slow addition in a batch process. The residence time was only 30 seconds, which corresponds to the time spent in the 1 mL tubing exposed to the UV lamp (312 nm), while no reaction took place in the reservoir of 10 mL. When performed on a 50 mg scale, the

CuAAC Macrocyclization of a Triazole-Containing Peptoid in Continuous Flow



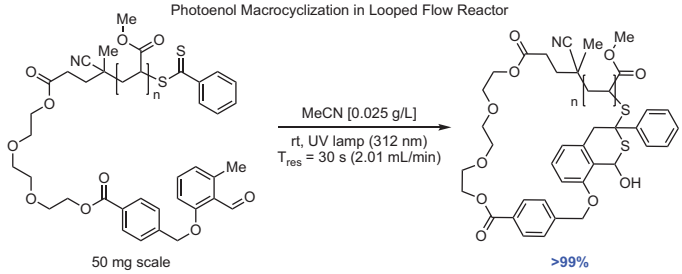
eq 8 *(Ref. 41)*

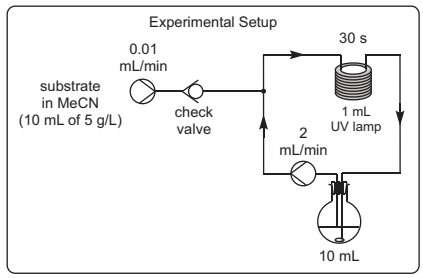
Gram-Scale Photoenol Macrocyclization in Continuous-Flow Glass Reactor



eq 9 *(Ref. 44)*

Photoenol Macrocyclization in Looped Flow Reactor





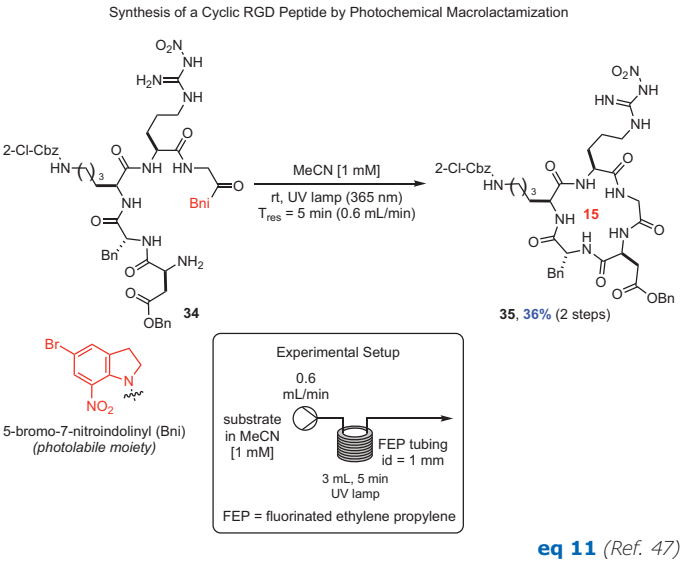
eq 10 *(Ref. 46)*

reaction yielded >99% of the macrocyclization product after 16.6 h of process time due to the small size of the reactor.

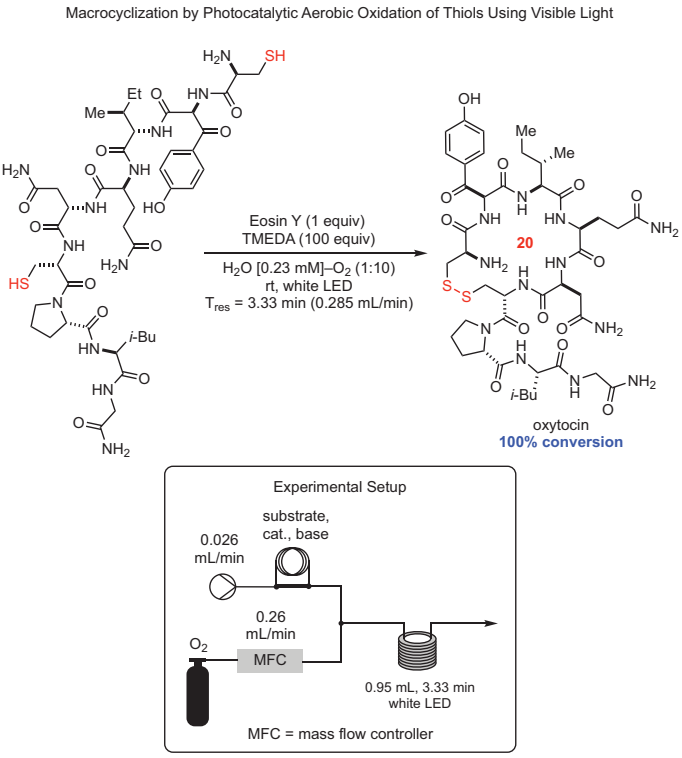
In 2016, Fuse and co-workers prepared a cyclic arginine-glycine-aspartate (RGD) peptide by photochemical macrolactamization (**eq 11**).[47] Following preparation of the linear peptide also using a flow technique,[48] the authors employed a photolabile moiety—previously reported by Nicolaou and co-workers[49] for photoactivation of the carboxyl group—that helped promote the macrolactamization. Usually, the photochemical transformation requires long reaction times (6 to 12 h); however, in flow, the cyclization of peptide **34** required only a five-minute residence time to afford a 36% yield of macrocycle **35** over two steps.

Photochemical macrocyclizations are not limited to UV light mediated processes; visible-light-mediated reactions are becoming increasingly common. Noël and co-workers utilized white LEDs in combination with Eosin Y to promote the oxidation of thiols in the presence of oxygen.[50] They first developed the intermolecular reaction in batch, and observed that the mixing efficiency greatly influenced the reaction rate, due to the importance of solvation of oxygen in the liquid phase. The use of continuous-flow techniques permits better mixing and mass transfer, especially in gas–liquid mixtures under slug flow regimes. To achieve a steady slug flow, the flow rate of oxygen was controlled by a Bronkhorst® mass-flow controller (MFC) for a gas:liquid ratio of 2:1. In combination with irradiation under flow conditions, shorter reaction times of 20 minutes, versus 16 hours in batch, were possible. However, to avoid peptide dimerization and clogging, concentrations in flow had to be lower (250 mM) than in the batch (1000 mM) process. The authors demonstrated their protocol by applying it to the synthesis of oxytocin using disulfide formation for the macrocyclization step (**eq 12**).[50] The macrocyclization was performed in water with a residence time of only 3.3 min (0.23 mM).

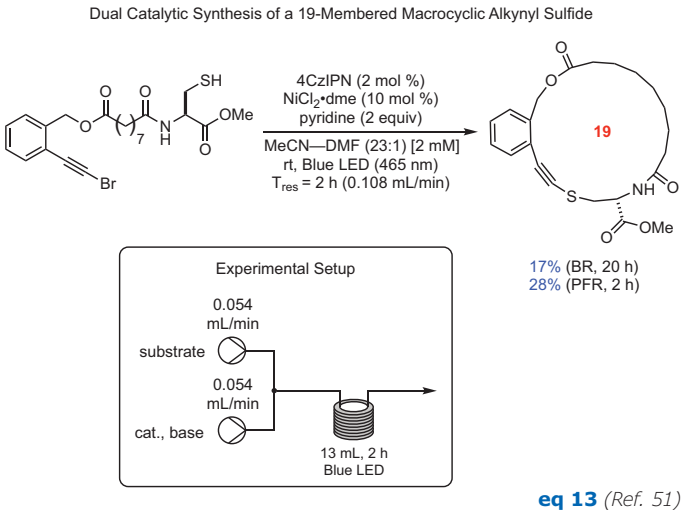
In 2017, our group reported another visible-light-mediated macrocyclization reaction that relies on a photochemical dual-catalytic cross-coupling between a bromoalkyne and a thiol to form alkynylsulfides.[51] The inexpensive, organic carbazole-based photosensitizer 4CzIPN[52] proved to be the best catalyst. The methodology was first developed for an intermolecular reaction, but was later applied to the formation of a 19-membered ring, which represents the first application of photoredox–nickel dual catalysis toward macrocyclization (**eq 13**).[51] The substrate and reagents were placed in separate syringes to obtain a 28% yield of the macrocycle (2 h residence time) (batch process: 17% yield, 20 h).



eq 11 *(Ref. 47)*



eq 12 *(Ref. 50)*



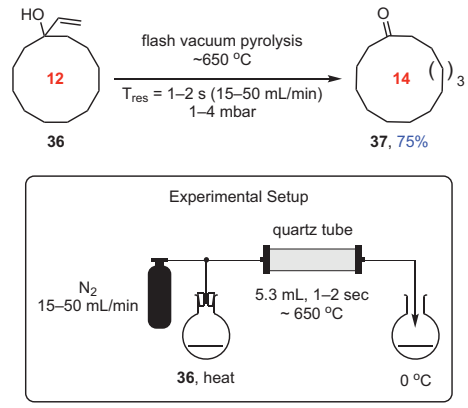
eq 13 *(Ref. 51)*

8. Ring-Expansion Reactions

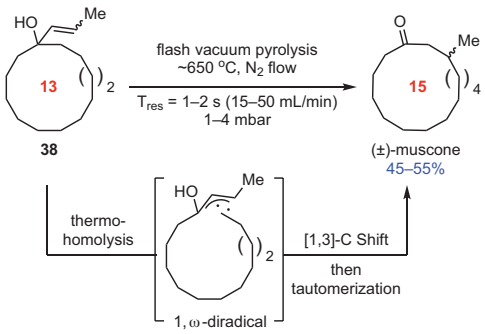
Ring-expansion reactions have been known for over a century and are still of great interest.[53] There are two major classes of ring expansions: (i) migration-expulsion of an exocyclic side-chain leaving group,[54] and (ii) fragmentation or ring opening of a bicycle.[55] However, many ring expansions often require tedious synthesis of the precursor, or result in adding a single carbon atom to a ring, which is not helpful when large macrocycles are desired. In 2002, Nagel and co-workers serendipitously discovered a gas-phase, two-carbon ring-expansion reaction which leads to the synthesis of macrocyclic ketones (**eq 14**).[56] They found that dynamic flash vacuum pyrolysis of 1-vinylcycloalkanol **36** (synthesized from the corresponding cycloalkanone and vinylmagnesium bromide) at 600–650 °C afforded the thermo-isomerized cycloalkanone **37** in about 75% yield. Interestingly, they observed that using a static thermolysis at 420 °C leads to no reaction or only to degradation products. Using this methodology, the authors reported the synthesis of a variety of macrocyclic ketones in 15–80% yields.[56b,c] They also demonstrated that the strategy could be employed iteratively to produce larger macrocycles from commercially available smaller ones. The experimental setup consisted of a horizontal quartz tube reactor (40 cm length, 22 or 40 mm id) heated by a tube furnace at 600–650 °C. The starting material, placed in a Büchi® Kugelrohr oven, was slowly distilled under reduced pressure (1–4 mbar) and carried through the heated zone by a flow of inert gas (N_2 or Ar, 15–50 mL/min) for an estimated contact time of 1–2 s. Following elution, the desired macrocycles could be collected in a cooling trap at 0 °C.

The authors also found that, when using more substituted alkenyl precursors, the corresponding alkyl-substituted cycloalkanones were obtained. For example, the two-carbon ring-expansion protocol was used to synthesize the 15-membered-ring macrocyclic musk odorant (±)-muscone from 1-propenylcycloalkanol **38** (**Scheme 8**).[56b,c] The reaction mechanism is believed to proceed through thermo-homolysis of the starting material to form the 1,ω-diradical intermediate. Intramolecular recombination of the diradical affords the expanded cyclic enol product, which tautomerizes to the corresponding macrocyclic ketone.

Two-Carbon Ring Expansion through Dynamic Flash Vacuum Pyrolysis



eq 14 *(Ref. 56a)*



Scheme 8. Efficient Synthesis of (±)-Muscone via Two-Carbon Ring Expansion in Continuous Flow. *(Ref. 56b,c)*

9. Conclusion

Conducting macrocyclizations in continuous flow can offer several advantages, including higher yields and shorter reaction times due to improved mass and energy transfers. To date, continuous flow has impacted well-known reactions for macrocyclization, such as the Glaser–Hay coupling, olefin metathesis, and CuAAC reactions. It has also demonstrated applications in ring-expansion reactions to access large-ring compounds, and it has opened the door to exploring new photochemical macrocyclizations and, arguably, to rendering them practical for the first time. However, the field is truly only in its infancy, and a number of areas remain underexplored. Technologies such as continuously stirred tank reactors, new reactors for supported or heterogeneous catalysis, and designs for recycling solvents have only been sparingly evaluated for macrocyclization in flow. Surprisingly, a number of important synthetic tools already well-established in batch have yet to be applied in flow. For example, macrolactonization and macrolactamization, processes so important in the field of cyclic peptides and pharmaceuticals, have rarely been explored in flow. Strategies involving biocatalysis or Pd-catalyzed cross-couplings for macrocyclization have yet to be reported. Given the number of advantages offered by continuous-flow technology, it is easy to envision an even greater impact on macrocyclization in the future.

10. References

(1) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.
(2) Ruggli, P. *Liebigs Ann. Chem*. **1912**, *392*, 92.
(3) Parenty, A.; Moreau, X.; Niel, G.; Campagne, J.-M. *Chem. Rev*. **2013**, *113*, PR1.
(4) (a) Gradillas, A.; Perez-Castells, J. Synthesis of Natural Products Containing Macrocycles by Alkene Ring-Closing Metathesis. In *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts;* Cossy, J., Arseniyadis, S., Meyer, C., Eds.; Wiley-VCH: Weinheim, Germany, 2010; Chapter 5, pp 149–182. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed*. **2005**, *44*, 4490.

(5) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed*. **2005**, *44*, 4442.
(6) (a) Pehere, A. D.; Zhang, X.; Abell, A. D. *Aust. J. Chem*. **2017**, *70*, 138. (b) Pasini, D. *Molecules* **2013**, *18*, 9512.
(7) Cambié, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. *Chem. Rev.* **2016**, *116*, 10276.
(8) (a) Gutmann, B.; Cantillo, D.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2015**, *54,* 6688. (b) Dallinger, D.; Kappe, C. O. *Aldrichimica Acta* **2016**, *49*, 57.
(9) Monfette, S.; Eyholzer, M.; Roberge, D. R.; Fogg, D. E. *Chem.—Eur. J.* **2010**, *16*, 11720.
(10) Cabrera, J.; Padilla, R.; Bru, M.; Lindner, R.; Kageyama, T.; Wilckens, K.; Balof, S. L.; Schanz, H.-J.; Dehn, R.; Teles, J. H.; Deuerlein, S.; Miller, K.; Rominger, F.; Limbach, M. *Chem.—Eur. J.* **2012**, *18*, 14717.
(11) Bru, M.; Dehn, R.; Teles, J. H.; Deuerlein, S.; Danz, M.; Müller, I. B.; Limbach, M. *Chem.—Eur. J.* **2013**, *19*, 11661.
(12) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961.
(13) Skowerski, K.; Czarnocki, S. J.; Knapkiewicz, P. *ChemSusChem* **2014**, *7*, 536.
(14) (a) Polyzos, A.; O'Brien, M.; Petersen, T. P.; Baxendale, I. R.; Ley, S. V. *Angew. Chem., Int. Ed.* **2011**, *50*, 1190. (b) Brzozowski, M.; O'Brien, M.; Ley, S. V.; Polyzos, A. *Acc. Chem. Res.* **2015**, *48*, 349.
(15) Morin, É.; Raymond, M.; Dubart, A.; Collins, S. K. *Org. Lett.* **2017**, *19*, 2889.
(16) (a) Glaser, C. *Annal. Chem. Pharm.* **1870**, *154*, 137. (b) Hay, A. S. *J. Org. Chem*. **1962**, *27*, 3320.
(17) Sindhu, K. S.; Anilkumar, G. *RSC Adv*. **2014**, *4*, 27867.
(18) (a) Bédard, A.-C.; Collins, S. K. *Chem.—Eur. J.* **2013**, *19*, 2108. (b) Bédard, A.-C.; Collins, S. K. *ACS Catal.* **2013***, 3,* 773.
(19) (a) Bédard, A.-C.; Collins, S. K. *J. Am. Chem. Soc.* **2011***, 133,* 19976. (b) Bédard, A.-C.; Collins, S. K. *Chem. Commun.* **2012***, 48,* 6420.
(20) Bédard, A.-C.; Régnier, S.; Collins, S. K. *Green Chem.* **2013***, 15,* 1962.
(21) De Léséleuc, M.; Godin, É.; Parisien-Collette, S.; Lévesque, A.; Collins, S. K. *J. Org. Chem.* **2016**, *81*, 6750.
(22) Zhang, B.; Wang, Y.; Yang, S.-P.; Zhou, Y.; Wu, W.-B.; Tang, W.; Zuo, J.-P.; Li, Y.; Yue, J.-M. *J. Am. Chem. Soc.* **2012**, *134*, 20605.
(23) Mohapatra, D. K.; Umamaheshwar, G.; Rao, R. N.; Rao, T. S.; Kumar R, S.; Yadav, J. S. *Org. Lett.* **2015**, *17*, 979.
(24) Godin, É.; Bédard, A.-C.; Raymond, M.; Collins, S. K. *J. Org. Chem.* **2017**, *82*, 7576.
(25) Avellaneda, A.; Valente, P.; Burgun, A.; Evans, J. D.; Markwell-Heys, A. W.; Rankine, D.; Nielsen, D. J.; Hill, M. R.; Sumby, C. J.; Doonan, C. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 3746.
(26) Kitchin, M.; Konstas, K.; Sumby, C. J.; Czyz, M. L.; Valente, P.; Hill, M. R.; Polyzos, A.; Doonan, C. J. *Chem. Commun.* **2015**, *51*, 14231.
(27) Williamson, A. *Philos. Mag.* **1850**, *37*, 350.
(28) (a) Horváth, G.; Huszthy, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4573. (b) Fődi, T.; Kupai, J.; Túrós, G.; Németh, T.; Rojik, E.; Riethmüller, E.; Balogh, G. T.; Huszthy, P. *J. Flow Chem.* **2016**, *6*, 297.
(29) (a) Kupai, J.; Lévai, S.; Antal, K.; Balogh, G. T.; Tóth, T.; Huszthy, P. *Tetrahedron: Asymmetry* **2012**, *23*, 415. (b) Lévai, S.; Németh, T.; Födi, T.; Kupai, J.; Tóth, T.; Huszthy, P.; Balogh, G. T. *J. Pharm. Biomed. Anal.* **2015**, *115*, 192.
(30) El-Faham, A.; Albericio, F. *Chem. Rev*. **2011**, *111*, 6557.
(31) Albericio, F.; Burger, K.; Ruíz-Rodríguez, J.; Spengler, J. *Org. Lett.* **2005**, *7*, 597.
(32) Lücke, D.; Dalton, T.; Ley, S. V.; Wilson, Z. E. *Chem.—Eur. J.* **2016**, *22*, 4206.
(33) Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*, 565.
(34) (a) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51. (b) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128. (c) Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev.* **2009**, *109*, 4207.
(35) Bogdan, A. R.; Sach, N. W. *Adv. Synth. Catal.* **2009**, *351*, 849.
(36) Bogdan, A. R.; James, K. *Chem.—Eur. J.* **2010**, *16*, 14506.
(37) Bogdan, A. R.; Jerome, S. V.; Houk, K. N.; James, K. *J. Am. Chem. Soc.* **2012**, *134*, 2127.
(38) Bogdan, A. R.; James, K. *Org. Lett.* **2011**, *13*, 4060.
(39) Bédard, A.-C.; Santandrea, J.; Collins, S. K. *J. Flow Chem.* **2015**, *5*, 142.
(40) Bédard, A.-C.; Collins, S. K. *Org. Lett.* **2014**, *16*, 5286.
(41) Salvador, C. E. M.; Pieber, B.; Neu, P. M.; Torvisco, A.; Andrade, C. K. Z.; Kappe, C. O. *J. Org. Chem.* **2015**, *80*, 4590.
(42) Culf, A. S.; Ouellette, R. J. *Molecules* **2010**, *15*, 5282.
(43) (a) Brauer, M. C. N.; Neves Filho, R. A. W.; Westermann, B.; Heinke, R.; Wessjohann, L. A. *Beilstein J. Org. Chem*. **2015**, *11*, 25. (b) De Fátima S. Barreto, A.; Vercillo, O. E.; Birkett, M. A.; Caulfield, J. C.; Wessjohann, L. A.; Andrade, C. K. Z. *Org. Biomol. Chem.* **2011**, *9*, 5024.
(44) Sun, P.; Liu, J.; Zhang, Z.; Zhang, K. *Polym. Chem.* **2016**, *7*, 2239.
(45) Oehlenschlaeger, K. K.; Mueller, J. O.; Heine, N. B.; Glassner, M.; Guimard, N. K.; Delaittre, G.; Schmidt, F. G.; Barner-Kowollik, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 762.
(46) Baeten, E.; Rubens, M.; Wuest, K. N. R.; Barner-Kowollik, C.; Junkers, T. *React. Chem. Eng.* **2017**, *2*, 826.
(47) Mifune, Y.; Nakamura, H.; Fuse, S. *Org. Biomol. Chem.* **2016**, *14*, 11244.
(48) (a) Fuse, S.; Tanabe, N.; Takahashi, T. *Chem. Commun.* **2011**, *47*, 12661. (b) Fuse, S.; Mifune, Y.; Takahashi, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 851. (c) Fuse, S.; Mifune, Y.; Tanabe, N.; Takahashi, T. *Synlett* **2014**, 2087.
(49) Nicolaou, K. C.; Safina, B. S.; Winssinger, N. *Synlett* **2001**, *12*, 900.
(50) Talla, A.; Driessen, B.; Straathof, N. J. W.; Milroy, L.-G.; Brunsveld, L.; Hessel, V.; Noël, T. *Adv. Synth. Catal.* **2015**, *357,* 2180.
(51) Santandrea, J.; Minozzi, C.; Cruché, C.; Collins, S. K. *Angew. Chem., Int. Ed.* **2017**, *56*, 12255.
(52) Luo, J.; Zhang, J. *ACS Catal.* **2016**, *6*, 873.
(53) Donald, J. R.; Unsworth, W. P. *Chem.—Eur. J.* **2017**, *23*, 8780.
(54) Tiffeneau, M.; Weill, P.; Tchoubar, B. *C. R. Hebd. Seances Acad. Sci.* **1937***, 205*, 54.
(55) Zhang, Y.; Wang, J. *Chem. Commun.* **2009**, 5350.

(56) (a) Nagel, M.; Hansen, H.-J.; Fráter, G. *Synlett* **2002**, *13*, 275.
(b) Nagel, M.; Hansen, H.-J.; Fráter, G. *Synlett* **2002**, *13*, 280.
(c) Nagel, M.; Fráter, G.; Hansen, H.-J. *Chimia* **2003**, *57*, 196.

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Fluoroenolate-Enabled Monofluorinations and Difluoromethylations


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Abstract. A common approach for the synthesis of organic molecules containing a difluoromethyl unit is the use of a difluoroenolate, which can be produced by the Reformatsky reaction, copper-mediated processes, decarboxylations, and by the release of trifluoroacetate ($F_3CCO_2^-$). This article will survey the generation of these reactive difluoroenolate intermediates and their significant applications in the synthesis of difluorinated organic compounds.

Outline:

1. Introduction

The incorporation of fluorine in organic molecules is a powerful and common approach during pharmaceutical development. The structures of many top-selling pharmaceuticals—such as Emtriva®, Flonase®, Sovaldi®, Januvia®, and Crestor®—incorporate fluorinated atoms (**Figure 1**).[1] Moreover, fluorine has other significant applications in medical imaging,[2] materials science,[3] and agrochemicals.[4] Molecules containing a single fluorine atom or a trifluoromethyl group have found widespread use, because synthetic methods leading to them are readily available. In contrast, compounds containing a difluoromethyl group are not as prevalent because substantially fewer synthetic methods to assemble them exist. Despite this deficiency, several drugs on the market today—such as ledipasvir (part of Harvoni®), tafluprost (Zioptan®), pantoprazole (Protonix®), gemcitabine (Gemzar®), and maraviroc (Selzentry®)—incorporate a *gem*-difluorinated carbon (**Figure 2**).[1]

1.1. Fluorination Reagents and Fluorinated Building Blocks

The synthesis of fluorinated compounds is typically accomplished through fluorination or the use of fluorinated building blocks as starting materials. These reagents and building blocks, along with new synthetic methodologies for fluorination, have contributed significantly to the discovery of new pharmaceuticals. Fluorinating reagents are classified as nucleophilic or electrophilic sources of fluorine (**Figure 3**, Parts (a) and (b)). Nucleophilic fluorinating reagents, such as DAST,[5] Deoxo-Fluor®,[6] and Fluolead®[7] are sulfur trifluorides that deoxyfluorinate carbonyl and hydroxyl groups or dethiofluorinate thiocarbonyl and sulfide groups. Electrophilic fluorinating reagents, such as Selectfluor®[8] and NFSI,[9] are N–fluoro compounds that fluorinate nucleophiles such as enolates, enol ethers, and electron-rich aromatic rings. Selectfluor® II is a newer reagent with enhanced aqueous solubility. The most

common trifluoromethylating reagent is the Ruppert–Prakash reagent,[10] which introduces a CF_3 group through cleavage of the attached trimethylsilyl group. A CF_2H analogue of this reagent is also available for the incorporation of the CF_2H group. The difluoromethyl phenyl sulfone reagent is also widely used for introducing a difluoromethyl group. The Colby reagent was introduced in 2013 to release fluoroform gas (CHF_3) into organic solvents.[11] Fluoroform gas is another commonly used reagent for the synthesis of trifluoromethylated compounds. As compared to fluorine gas and HF, these newer reagents are more compatible with many organic functional groups.

The synthesis of fluorinated organic molecules can also be accomplished by utilizing fluorinated building blocks (**Figure 4**). This approach eliminates the concerns of over- and under-fluorination, and enhances functional-group tolerance. In addition, fluorinated building blocks are typically cheaper alternatives to the more expensive fluorination reagents. Common examples are 2,4,6-trifluorobenzenesulfonyl chloride, ethyl α,α-bromodifluoroacetate, and 3,3,3-trifluoroalanine.

1.2. Fluoroenolates

Installing a difluoromethyl subunit is more challenging than monofluorination or trifluoromethylation. The most common approach to accomplish that is to use difluoroenolates, resulting in α,α-difluorinated ketones. α,α-Difluorinated ketones are valuable synthetic intermediates and can also serve as inhibitors of pharmaceutically relevant enzymes and other biological targets.[12–18] The starting fluoroenolates are highly versatile, since their reactivity can be controlled through conversion into difluoroenoxysilanes and into fluoroenol ethers, phosphates, and sulfonates. Another reason for the widespread use of difluoroenolates is that they readily undergo aldol reactions, which are familiar to many synthetic chemists. Difluoroenolates can be generated in situ (typically through metalation) and immediately used or trapped and isolated. A comprehensive review of fluorinated enol ethers was published by Leclerc in 2015.[19] The present review will cover recent developments in the generation and reactivity of fluoroenolates, as well as key applications in the construction of fluorinated organic molecules.

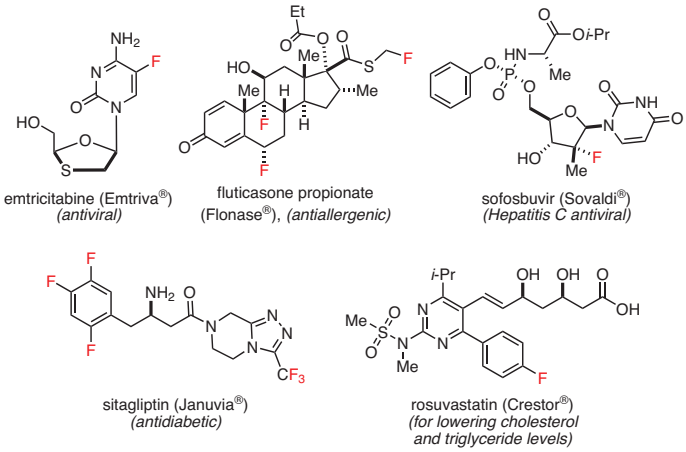


Figure 1. Some of the Popular Pharmaceuticals on the Market Today Incorporating One or Three Fluorines. *(Ref. 1)*

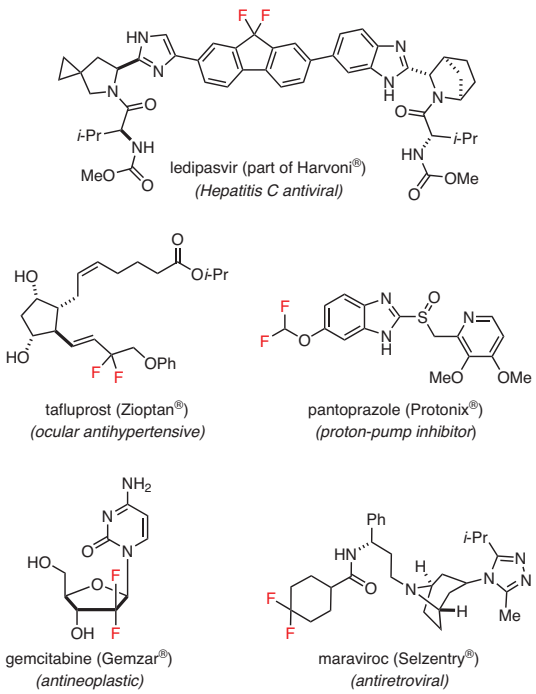


Figure 2. Some of the Popular Pharmaceuticals on the Market Today Incorporating a Difluoromethyl Group. *(Ref. 1)*

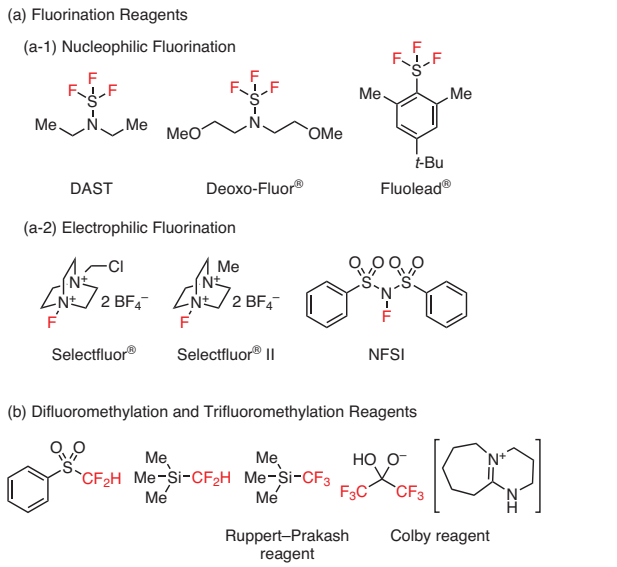


Figure 3. Popular Reagents for (a) Nucleophilic and Electrophilic Fluorinations, and (b) Difluoromethylation and Trifluoromethylation. *(Ref. 5–11)*

Fluoroenolates are readily produced via a number of reaction types: Reformatsky, copper-mediated Michael addition, coupling with aryl halides, decarboxylation, or trifluoroacetate-releasing reactions.

2. *gem*-Difluorinated Nucleosides, β-Lactams, and Peptidomimetics by Reformatsky-type Reactions

The Reformatsky reaction is one of the most popular methodologies for the formation of α-fluorinated carbonyl compounds, particularly from zinc and bromodifluoroacetates. No base or acid is required for the generation of the fluoroenolate, which enhances the versatility of the reaction, and, accordingly, a variety of electrophiles are tolerated and reagent cost is usually quite low.[20] Nonetheless, the Reformatsky reaction is disadvantaged by its relatively low yields when compared to the aldol reaction,[20] and by the difficulty of implementing stereoselective variants of the reaction.[21]

McBee and co-workers were the first to apply the Reformatsky reaction to ethyl bromofluoroacetate using zinc dust under reflux.[22] This report prompted a series of developments in the assembly of fluorinated organic compounds, and, in 1984, Hallinan and Fried applied this reaction to ethyl bromodifluoroacetate using conditions similar to those in the McBee report.[23] A few years later, Kuroboshi and Ishihara demonstrated that bromodifluoromethyl ketones react with aldehydes in the presence of zinc and copper(I) chloride and with ketones using zinc and silver acetate.[24] Many variations of the reaction have been reported, such as using indium as the initiator,[25–28] or using water as the solvent.[29] The Reformatsky reaction also allows the addition of difluoroacetate to iminium cations derived from benzotriazoles.[30–34]

The *gem*-difluorinated carbonyl compounds generated by the Reformatsky reaction have been employed as starting materials for many types of complex organic molecules, such as difluorinated dihydropyranones,[35] methylenedihydrofuranones,[36] dihydropyranoquinoxalinones,[37] and dihydropyrandiones. A key report from Gouverneur and co-workers describes the Reformatsky reaction of chlorodifluoromethylynones and aldehydes, and the subsequent application of a gold-catalyzed cyclization of the *gem*-difluorinated β-hydroxy-ynones to the synthesis of difluorodihydropyranones in good yields. Notably, the difluorodihydropyranone intermediate can be trapped with bromine or chlorine in addition to direct protonation. The *gem*-difluorinated β-hydroxy-ynones can be cyclized upon addition of 1,3-bis(diphenylphosphino)propane (dppp) to produce difluorinated methylenedihydrofuranones.[36] Shibata and co-workers reported the Reformatsky reaction of 4-amino-3-chlorodifluoroacetyl-2-methoxyquinoline with aldehydes, followed by intramolecular cyclization to generate difluorinated dihydropyranoquinoxalinones in moderate yields.[37] Similarly, the Reformatsky reaction can be employed to synthesize difluoromethyl lactones, and variants include the production of difluorinated 2-(triphenylphosphoranylidene)-δ-lactones.[38]

2.1. *gem*-Difluorinated Carbocyclic Nucleosides

The Reformatsky reaction has been employed extensively in the synthesis of biologically relevant molecules, chemical probes,[39] receptor modulators,[40] and enzyme inhibitors.[34,41-46] An example is a report by Qing and co-workers in which *gem*-difluorinated carbocyclic nucleosides are synthesized as potential chemotherapeutic agents.[47-48] The key step in the synthesis is a diastereoselective Reformatsky–Claisen rearrangement of allylic chlorodifluoroacetate **1** to **2**, which provides access to the difluorinated carbocyclic nucleosides **3**–**5** (**Scheme 1**, Part (a)).[48] Similarly, Kumamoto and co-workers utilized the Reformatsky reaction to convert aldehyde **6** into the difluorohydroxy ester **7** on the way to the *gem*-difluorocyclobutane analogue, **8**, of oxetanocin T, a nucleoside antibiotic (**Scheme 1**, Part (b)).[49]

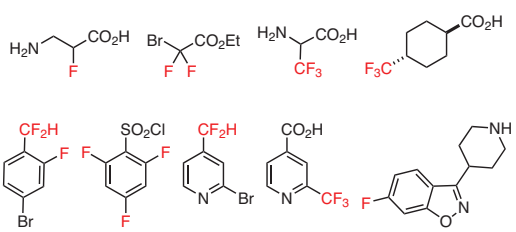
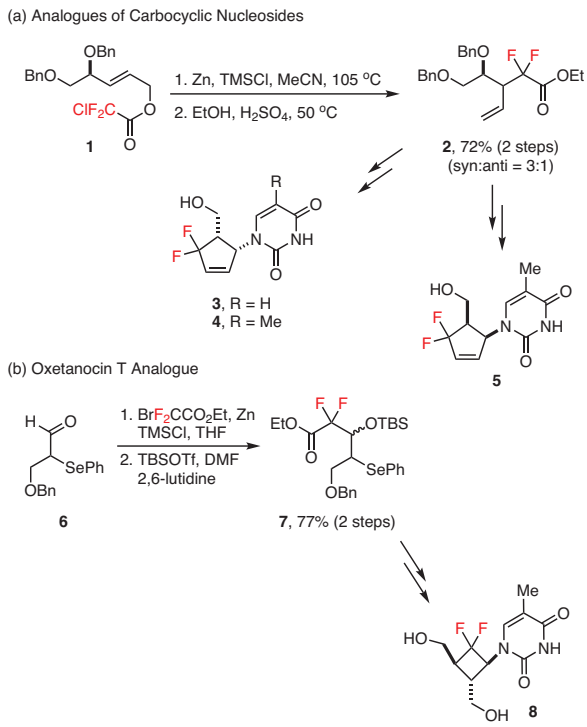


Figure 4. Popular Fluorinated Building Blocks.



Scheme 1. *gem*-Difluorinated Carbocyclic Nucleosides by Diastereoselective Reformatsky Reaction as Key Step. *(Ref. 48,49)*

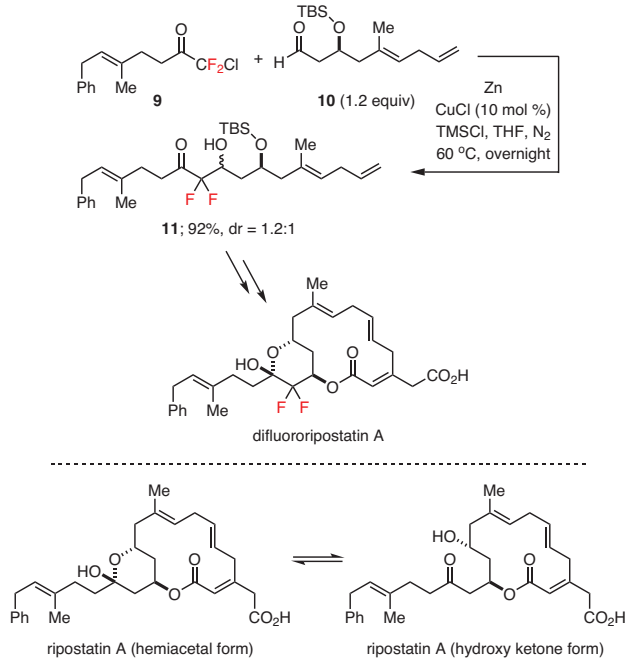
2.2. *gem*-Difluororipostatin A

Ripostatin A, a bacterial RNA-polymerase inhibitor, exists as a mixture of the hemiacetal and δ-hydroxy ketone forms, and it has been hypothesized that introducing two fluorine atoms adjacent to the keto group would favor the cyclic hemiacetal. A difluorinated analogue of ripostatin A has been synthesized starting with a Reformatsky reaction of chlorodifluoromethyl ketone **9** with aldehyde **10** and proceeding through the difluorinated intermediate **11** (**Scheme 2**).[39] This difluorinated hemiacetal analogue was two orders of magnitude less active than ripostatin A, suggesting that the δ-hydroxy ketone form is the primary active form.[39]

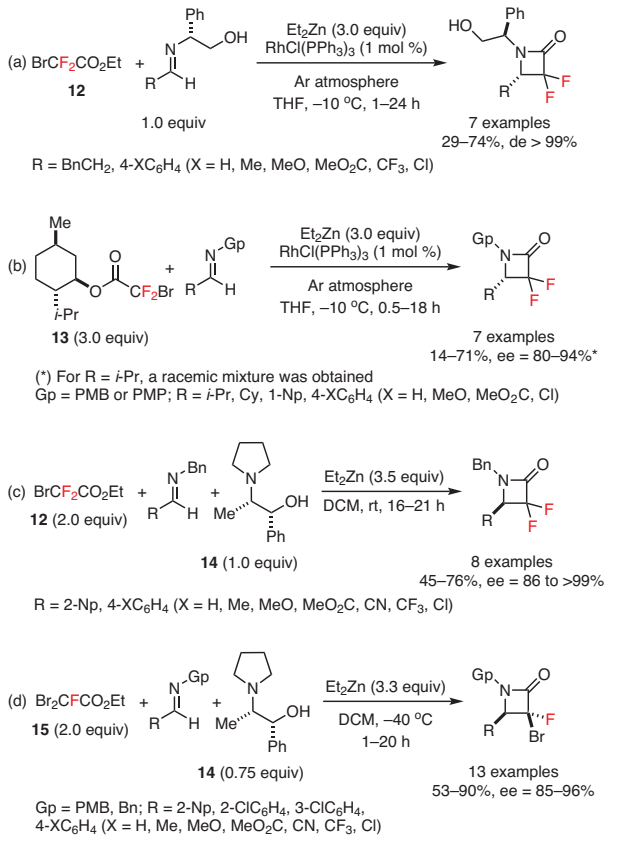
2.3. Optically Active Fluoro-β-lactams and Fluoropeptidomimetics

The Honda modification of the Reformatsky reaction uses Wilkinson's catalyst, $RhCl(PPh_3)_3$, and Et_2Zn as a homogeneous zinc source.[50] The reaction can be stereoselective in the presence of chiral auxiliaries or chiral ligands. Honda applied this approach to the one-pot, three-component synthesis of chiral β-amino esters using (*R*)-phenylglycinol as auxiliary.[51] Similarly, this method was employed in the diastereoselective synthesis of *gem*-difluorinated β-lactams (**Scheme 3,** Part (a)).[52] In this report, bromodifluoroacetate **12** reacts with various aldimines that bear the (*R*)-phenylglycinol auxiliary to give *gem*-difluorinated β-lactams in moderate-to-good yields and, in all cases, only one pure diastereomer was obtained.[52] Chiral sulfinylimines can also be utilized to prepare chiral fluorinated β-amino esters in good-to-excellent isolated yields but with relatively lower diastereoselectivities.[53–55] When, instead of the imine, the bromodifluoroacetate bears a chiral auxiliary such as a menthol moiety, high levels of enantiocontrol are achieved (Scheme 3**,** Part (b)).[56] In this case, the cyclization eliminates the menthol auxiliary and the difluoro-β-lactams are obtained in high ee's. Moreover, chiral amino alcohol based ligands (e.g., **14**) were shown to promote enantioselective Reformatsky reactions with imines (Scheme 3**,** Parts (c) and (d))[57–58] as well as ketones.[59] Using ethyl dibromofluoroacetate (**15**) gives access to *syn*-α-bromo-α-fluoro-β-lactams,[60] which can react with Grignard reagents[61] or organoborane reagents,[62] or which can be metallated with butyllithium and then alkylated with alkyl halides or carbonyl compounds.[63]

Fluoroalkenes are similar to peptide bonds, but are resistant to enzymatic degradation, which makes them appealing functional groups for designing stable peptide-based probes. Fujii and co-workers have utilized a stereoselective Reformatsky–Honda reaction to access (*Z*)- and (*E*)-fluoroalkene-linked dipeptides (**Scheme 4**).[64] (*Z*)- and (*E*)-fluoroalkenes **19** and **21** act as trans and cis isosteres of amides **20** and **22**, respectively. When the affinities of each of these fluoroalkenes were determined at the peptide transporter PEPT1, the (*Z*)-fluoroalkene showed



Scheme 2. *gem*-Difluorinated Analogue of Ripostatin A. *(Ref. 39)*



Scheme 3. Stereoselective Syntheses of Fluoro-β-lactams by a Modified Reformatsky Reaction. *(Ref. 52,56–58)*

higher affinity, suggesting that this PEPT1 binds to the trans conformation of the peptide.[64] A similar approach was applied to the synthesis of fluoroalkene analogues of α-helical anti-HIV peptide,[65] CXCR4 antagonistic pseudopeptide,[66] and the endogenous opioid neuropeptide, Leu-enkephalin.[67]

3. Copper-Mediated Michael Addition

Kumadaki and co-workers first reported the copper-mediated Michael addition of ethyl bromodifluoroacetate with Michael acceptors (**Scheme 5**, Part (a)).[68] A subsequent report disclosed that an improved protocol—utilizing the bidentate ligand tetramethylethylenediamine (TMEDA) to promote the reaction—resulted in better yields and a simplified workup.[69] More recently, Lee and co-workers reported that introducing a protic additive, such as acetic acid, reduced the formation of side products and improved the isolated yields.[70] This approach was applied to a large-scale preparation of the antidiabetic agent, gemigliptin, a dipeptidyl peptidase-IV (DPP-IV) inhibitor (Scheme 5, Part (b)).[70]

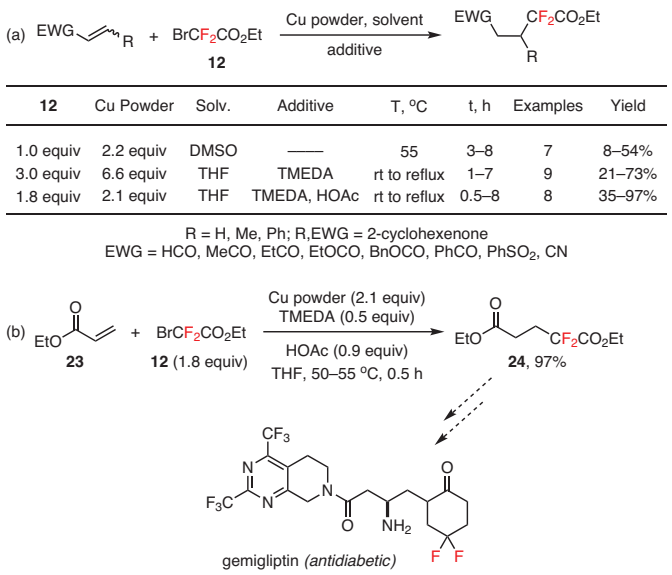
3.1. Applications of the Copper-Mediated Michael Addition

Other synthetic applications of the copper-mediated Michael addition include the construction of *gem*-difluorinated heterocyclic building blocks. For example, the reaction of ethyl bromodifluoroacetate (**12**) with acrylonitrile forms ethyl 4-cyano-2,2-difluorobutanoate, which can be cyclized to difluoropiperidine,[71] difluoroglutaric anhydride,[72] or difluoropiperidinone building blocks.[73] A major benefit of this approach is that readily available starting materials can be employed to access high-value fluorinated targets.

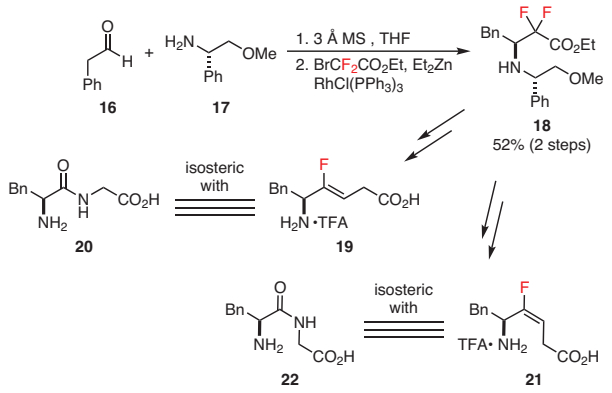
Jiráček and co-workers applied the copper-mediated Michael addition to the synthesis of a trifunctional scaffold that can be selectively derivatized for sequential bioconjugations.[74] The Michael addition of **12** to **25** led to the *gem*-difluorinated ester **26**, which was efficiently homologated into the polyamide target **27** (**Scheme 6**).[74] ^{19}F NMR was subsequently used to observe and quantify the fluorine-containing compounds in the crude mixtures of combinatorial libraries at the end of solid-phase syntheses.

4. Copper-Promoted Coupling with Vinyl and Aryl Halides

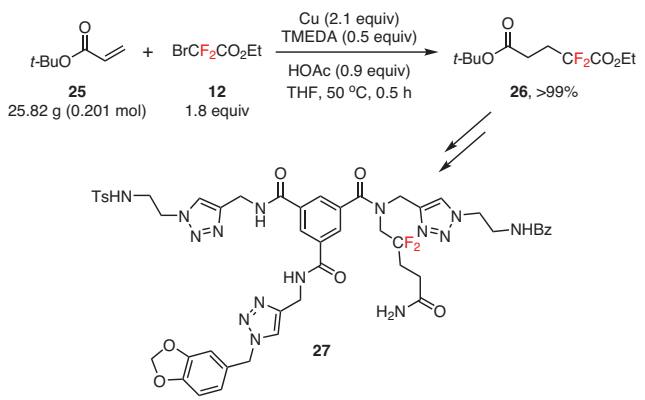
Kobayashi and co-workers reported the copper-promoted coupling of difluoroiodoacetate to vinyl and aryl halides, in which three equivalents of difluoroiodoacetate reacted with one equivalent of the alkenyl halide in DMSO.[75] ^{19}F NMR based solvent studies determined that HMPA stabilized the reactive intermediate and resulted in nearly quantitative conversion.[76] However, similar results could not be obtained with bromodifluoroacetate and, over a decade later, Kumadaki and



Scheme 5. *gem*-Difluoromethylation (a) by the Copper-Mediated Michael Addition, and (b) Its Application to the Large-Scale Synthesis of the Antidiabetic Gemigliptin. *(Ref. 68–70)*

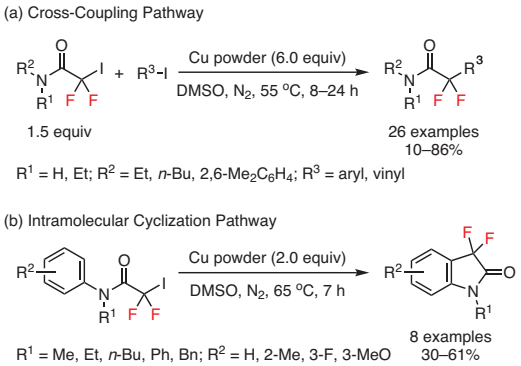


Scheme 4. Fluoroalkene-Based Peptidomimetics by the Reformatsky–Honda Reaction. *(Ref. 64)*

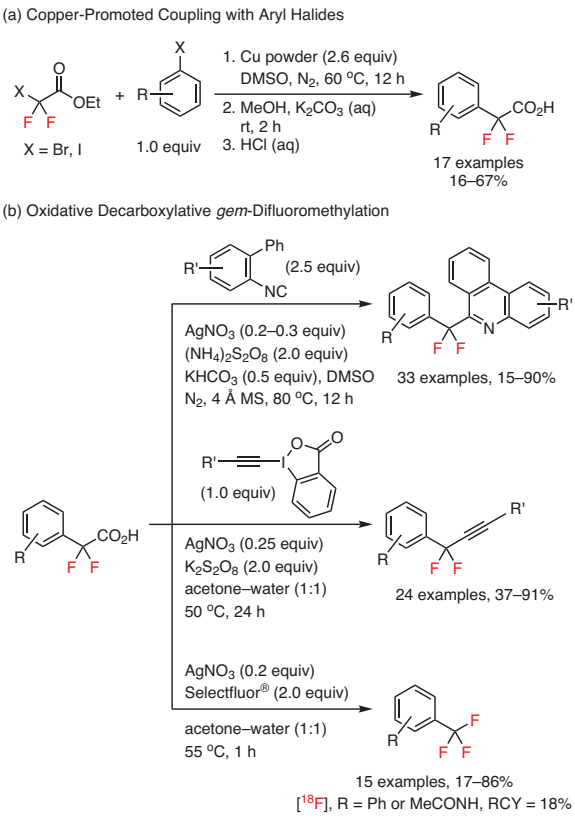


Scheme 6. *gem*-Difluorinated Trifunctional Scaffold for Sequential Bioconjugation by the Copper-Mediated Michael Addition. *(Ref. 74)*

co-workers overcame this limitation by using activated copper in DMSO and reducing the number of bromodifluoroacetate equivalents to one.[77] While these conditions led to a reduction in the formation of the double-addition byproduct, they were incompatible with alkyl and alkynyl halides.[77] Kumadaki and Kobayashi proposed different complexes as the active intermediates in the reaction, with the nature of the solvent presumably determining the type of intermediate formed.[76,77] α-Silyldifluoroacetates also participate in the reaction, with copper iodide and potassium fluoride in heated DMF promoting their coupling with aryl halides.[78] Furthermore, the reaction is not limited to fluoroacetates: Fluoroamides, fluorosulfones, and even fluoromethylbenzo-1,3-oxazoles are competent partners in this copper-promoted coupling.[79]



Scheme 7. Selectivity of the Copper-Mediated Reaction of Iododifluoroacetamides with Aryl or Alkenyl Iodides. *(Ref. 80)*



Scheme 8. (a) The Copper-Mediated Coupling of Halodifluoroacetates with Aryl Halides, and (b) Its Application in the Silver-Promoted Decarboxylative Difluoromethylation. *(Ref. 81–84)*

4.1. Applications of the Copper-Promoted Coupling with Vinyl and Aryl Halides

The products of the copper-mediated coupling reaction are distinct from those of most of the other approaches, because they do not display a β-hydroxy group. A hydroxy group at such a position is relatively difficult to deoxygenate due to the high electronegativity of the neighboring fluorines. Thus, the α,α-difluorinated ester starting materials in the Cu-mediated coupling are valuable, since a subsequent silver-catalyzed decarboxylation step can produce important difluoromethylated intermediates (**Scheme 8**).[81–84] For example, the copper-mediated arylation of a halodifluoroacetate, followed by hydrolysis, forms 2,2-difluoro-2-phenylacetic acids which can then be decarboxylated using Ag(I) to generate difluoromethylene-based radicals. These radicals can react with isocyanides followed by intramolecular cyclization to form difluoromethylated phenanthridines.[81] The difluoromethylene-based radicals can also be alkynylated with ethynylbenziodoxolone reagents in the presence of potassium persulfate ($K_2S_2O_8$) as oxidant.[82] Alternatively, the CF_2 radical intermediates can be labeled with ^{18}F to access aryl-[^{18}F]CF_3 compounds. This transformation can be accomplished using ^{18}F sources such as [^{18}F]KF/K222,[83] [^{18}F]Selectfluor® bis(triflate),[84] and [^{18}F]difluoromethylarenes.[84] The decarboxylation of difluoroacetic acid derivatives is versatile and can generate difluoroenolates as well (see Section 5 for more details).

The coupling reaction has found further applications in the synthesis of biologically active compounds, including anticonvulsants,[85] antifungal agents,[86] and anti-oxidizing agents.[87] For instance, Ashwood and co-workers utilized it in their search for an efficient and scalable protocol for the synthesis of a difluorinated thrombin inhibitor (**Scheme 9**).[88] The original route required treatment of ethyl 2-(2′-pyridyl)acetate with *N*-fluorobenzenesulfonimide (NFSI) at −78 °C to accomplish the

difluorination of the ester; however, another route was devised using Deoxo-Fluor® to difluorinate the product of the Grignard-mediated addition of 2-bromopyridine to diethyl oxalate, thus avoiding the use of very low temperatures. Unfortunately, both of these routes require expensive fluorinating reagents and result in relatively low yields. In contrast, a third route, employing the copper-mediated arylation of readily available ethyl bromodifluoroacetate (**12**) with 2-bromopyridine, avoided the use of expensive reagents and gave much better yields.

5. Decarboxylation Reactions

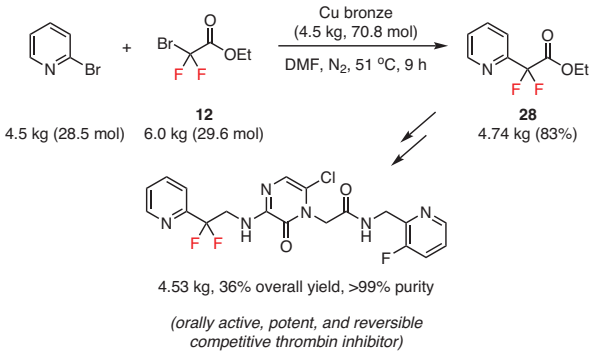
Decarboxylation reactions of difluorinated esters and acids can be used to access other valuable difluorinated compounds. Both α,α-difluoro-β-keto acids and esters can form difluoroenolates following decarboxylation in the presence or absence of a metal catalyst. Although these methods form difluoroenolates under neutral conditions, higher temperatures are frequently required, which can limit the scope of suitable starting materials. The decarboxylative aldol reactions from α,α-difluoro-β-keto acids produce α,α-difluoro-β-hydroxy ketones when heated to 100 °C, or when catalyzed by a copper-phenanthroline complex in addition to heating to 80 °C (**Scheme 10**, Parts (a) and (b)).[89,90] Moreover, palladium-catalyzed decarboxylative benzylation reactions can be employed to form α-benzyl-α,α-difluoroketones when heated to 120 °C (Scheme 10, Part (c)).[91] Similarly, α-allyl-α,α-difluoroketones can be accessed by using a palladium-catalyzed decarboxylative allylation (Scheme 10, Part (d)).[92] In the allylation reaction, the regioselectivity of the process is dependent on the ligand; for example, *t*-BuBrettPhos predominantly forms products without substituents adjacent to the difluoromethyl unit.

6. Trifluoroacetate-Release Reactions

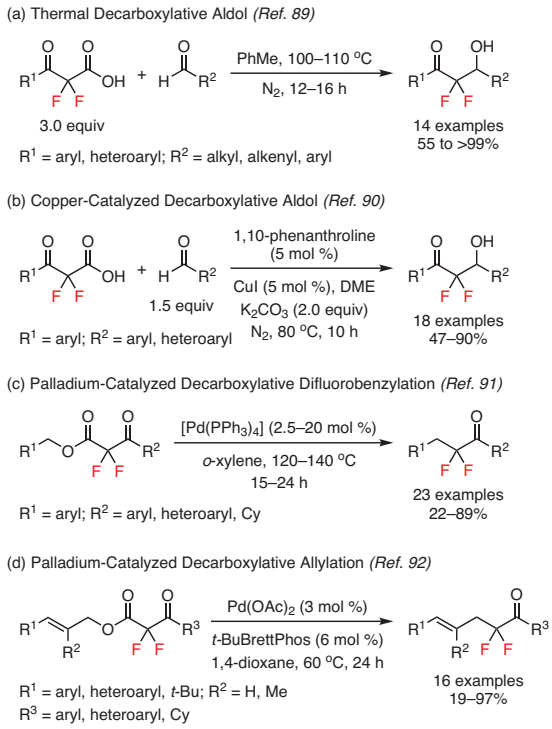
In 2011, our laboratory reported that highly fluorinated α,α-difluoro-α′-trifluoro-β-keto-*gem*-diols fragment under mild conditions to produce difluoroenolates and trifluoroacetate.[93] This method was based on the 1968 report by Prager and Ogden that hexafluoroacetone hydrate releases trifluoroacetate and fluoroform following treatment with base.[94] The production of difluoroenolates occurs nearly instantaneously in the presence of a metal salt and a mild base such as triethylamine (**Scheme 11**).[93] The difluoroenolates thus produced are very valuable, as they undergo aldol reactions with aldehydes[93] and trifluoromethyl ketones,[95] Mannich reactions with imines,[96–98] halogenation reactions,[99,100] and quenching with H_2O[101] or D_2O.[102]

6.1. Applications of Trifluoroacetate-Release Reactions

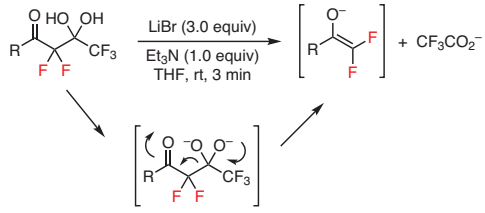
The aldol reaction of difluoroenolates generated by the trifluoroacetate-release method with a variety of aromatic and aliphatic aldehydes produces α,α-difluoro-β-hydroxy ketones in moderate-to-excellent yields (**Scheme 12**, Part (a)).[93] While this type of aldol reaction can also employ trifluoromethyl ketones



Scheme 9. The Copper-Mediated Coupling Reaction as a Key Step in a Scalable, Economical, and High-Yield Synthesis of a Thrombin Inhibitor. *(Ref. 88)*



Scheme 10. Valuable Difluoromethylated Compounds by Decarboxylation Reactions. *(Ref. 89–92)*



Scheme 11. Versatile α,α-Difluoroenolates by the Trifluoroacetate-Release Reaction *(Ref. 93)*

as electrophiles, it requires a stronger base, such as LiHMDS, to achieve good yields.[95]

Imines are also suitable electrophiles, and the scope of starting materials includes activated imines such as *N*-sulfinyl,[96] *N*-sulfonyl,[97,98] and *N*-Boc imines (Scheme 12, Part (b)).[97] This Mannich-type transformation has been applied in the synthesis of difluoromethyl-tetrahydroisoquinolines through reaction of difluoroenolates with dihydroisoquinolines that are generated in situ by visible-light photoredox catalysis.[103] The difluoroenolates can also be trapped with water or deuterated water to produce difluoromethyl ketones[101] and deuterodifluoromethyl ketones,[102] respectively.

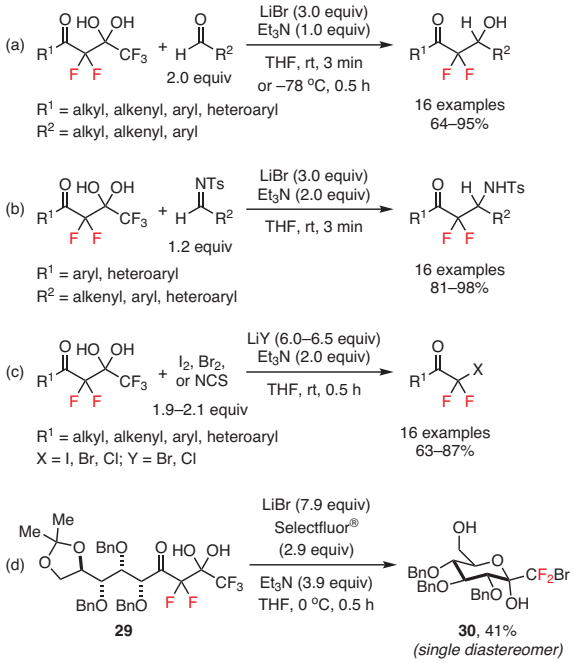
Furthermore, the difluoroenolate intermediates react with halogenation reagents such as I_2, Br_2, and NCS to generate iodo, bromo, and chlorodifluoromethyl ketones (Scheme 12, Part (c)).[99] The difluoroiodomethyl ketones serve as valuable precursors for radical-mediated additions of difluoromethylenes to alkenes[104] and alkynes, but are quite difficult to access by other synthetic methods.[105]

The difluoroenolate from pentafluoro-*gem*-diol **29** undergoes a tandem halogenation, acetonide cleavage, and cyclization to give *CF_2Br*-glucopyranose **30** as a single diastereomer in 41% yield (Scheme 12, Part (d)).[100] This route is the first reported synthesis of a *CF_2Br*-glucopyranose.

The preceding methods have allowed the rapid construction of a large number of functionalized difluoromethyl ketones, and screening of many of these difluorinated structures has led to the identification of α,α-difluoro-β-hydroxy ketone **31** as a $GABA_B$ receptor agonist (**Figure 5**).[15] Compound **31** has an EC_{50} of 24.9 μM, whereas its non-fluorinated analogue, **32**, exhibits no activity at this receptor.

6.2. Synthesis of Highly Fluorinated *gem*-Diols

The highly fluorinated *gem*-diols employed in the trifluoroacetate-release reactions are typically synthesized from methyl ketones in a two-step process: trifluoroacetylation with trifluoroethyl trifluoroacetate[106] followed by difluorination with Selectfluor® (**Scheme 13**, Part (a)).[93] This approach can produce pentafluoro-*gem*-diols[93] or tetrafluoro-*gem*-diols depending upon the reaction conditions, while monofluorination can be partially controlled by reducing the equivalents of Selectfluor®.[107] Fang, Wu, and co-workers subsequently disclosed that using copper nitrate in a mixture of water and acetonitrile can produce the tetrafluoro-*gem*-diols in substantially higher yields.[108] Alternatively, the



Scheme 12. Applications of Difluoroenolates Generated by the Trifluoroacetate-Release Method. *(Ref. 93,98–100)*

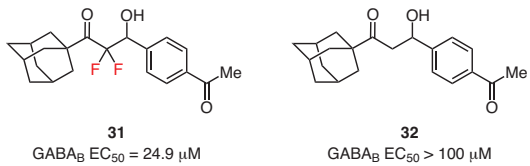
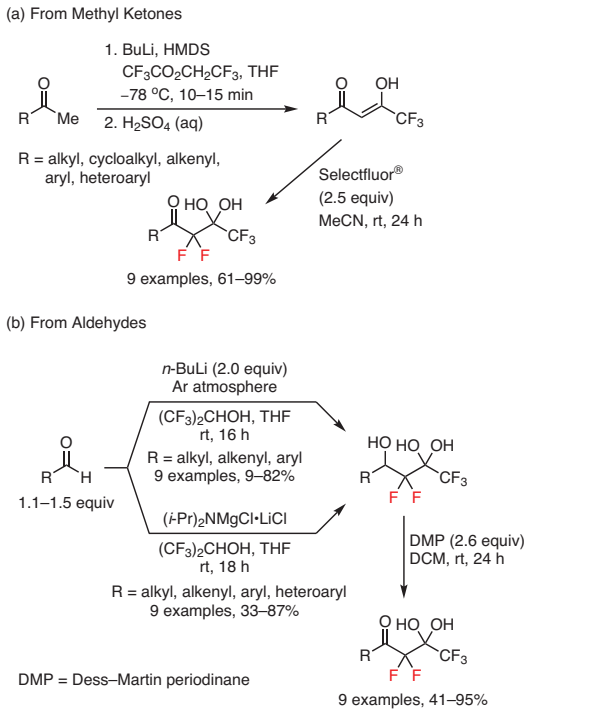


Figure 5. α,α-Difluoro-β-hydroxy Ketone **31** as a $GABA_B$ Receptor Agonist. *(Ref. 15)*



Scheme 13. Highly Fluorinated *gem*-Diol Precursors from Aldehydes and Methyl Ketones. *(Ref. 93,110,111)*

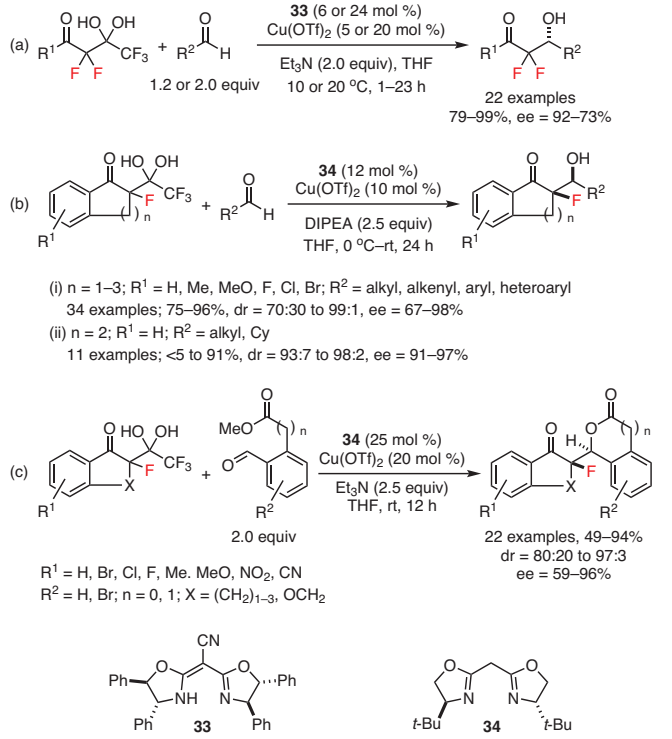
highly fluorinated *gem*-diols can be accessed from aldehydes in two steps by addition of difluoroenolates generated from hexafluoroisopropanol, followed by oxidation of the newly formed β-hydroxy group to a β-keto group (Scheme 13, Part (b)). In this approach, the intermediate, lithium pentafluoropropen-2-olate, is formed by treating hexafluoroisopropanol with two equivalents of *n*-BuLi.[100,109,110] A recent modification relies on the intermediacy of magnesium pentafluoropropen-2-olate generated from $(i\text{-Pr})_2$NMgCl•LiCl and hexafluoroisopropanol.[111]

6.3. Stereoselective Trifluoroacetate-Release Reactions

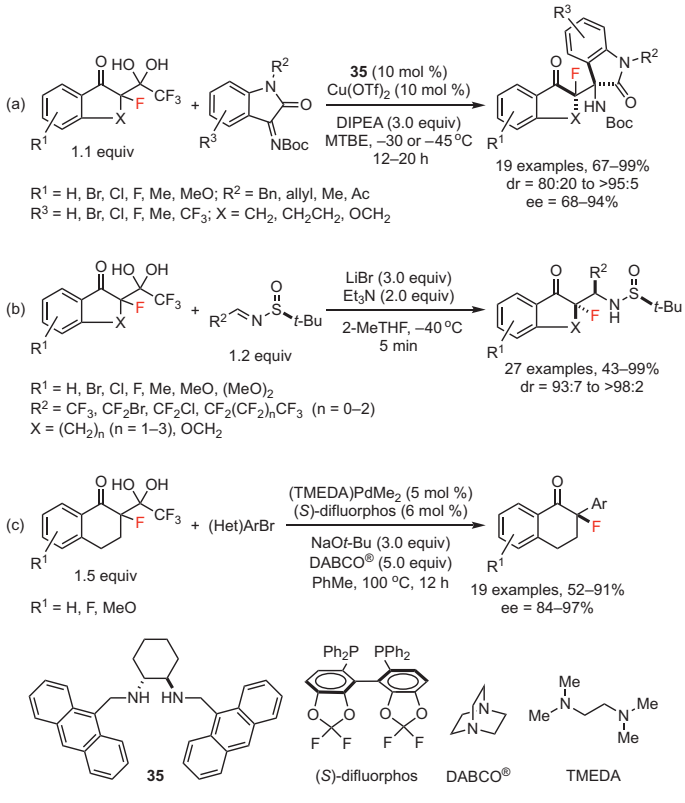
Historically, the development of asymmetric reactions with difluoroenolates has been challenging. While some success in this regard has been achieved with the Reformatsky reaction, stoichiometric amounts of chiral ligands are usually required. Recently, this limitation has been dramatically overcome, because the mild and homogeneous conditions of the trifluoroacetate-release process lend themselves well to catalytic and stereoselective methodologies. Consequently, catalytic, asymmetric reactions have been reported which exploit fluoroenolates produced from the release of trifluoroacetate in the presence of different types of ligands such as bis(oxazoline) (BOX), thiourea, diamine, and monophosphine ligands. Zhang and Wolf reported a catalytic, enantioselective trifluoroacetate-release aldol reaction, in which α,α-difluoro-β-hydroxy ketones are synthesized using copper(II) triflate and the chiral bidentate BOX ligand **33** (**Scheme 14**, Part (a)).[112] Han and co-workers utilized a similar method in the catalytic, asymmetric synthesis of C–F quaternary stereogenic centers by using the *tert*-butyl-substituted BOX ligand **34**, first with aromatic aldehydes[113] and later with alkyl aldehydes (Scheme 14, Part (b)).[114] In a subsequent paper, an aldol–cyclization cascade was designed to create 2-fluoro-isobenzofuran-1(*3H*)-one with high diastereoselectivities and enantioselectivities (Scheme 14, Part (c)).[115]

Stereoselective Mannich-type reactions have also been developed for fluoroenolates generated from the release of trifluoroacetate. For example, cyclic α-tetrafluoro-*gem*-diols react with isatin-derived ketimines in the presence of chiral diamine ligand **35** (**Scheme 15**, Part (a))[116] and react with chiral *N*-sulfinylimines in the absence of any ligand (Scheme 15, Part (b))[117] to generate quaternary α-fluoro-β-keto-amines highly diastereoselectively. Furthermore, Zhou, Hartwig, and co-workers used the trifluoroacetate-release protocol in catalytic, enantioselective palladium-mediated α-arylation reactions with $(TMEDA)PdMe_2$ and (*S*)-difluorphos as ligand. The resulting coupling products are obtained in good yields and high levels of enantiomeric excess (Scheme 15, Part (c)).[118]

Several other methods employ chiral urea- and thiourea-based ligands for enantioselective monofluoroalkylations with



Scheme 14. Catalytic, Asymmetric Aldol Reactions of Fluoroenolates Generated by the Release of Trifluoroacetate. *(Ref. 112–115)*

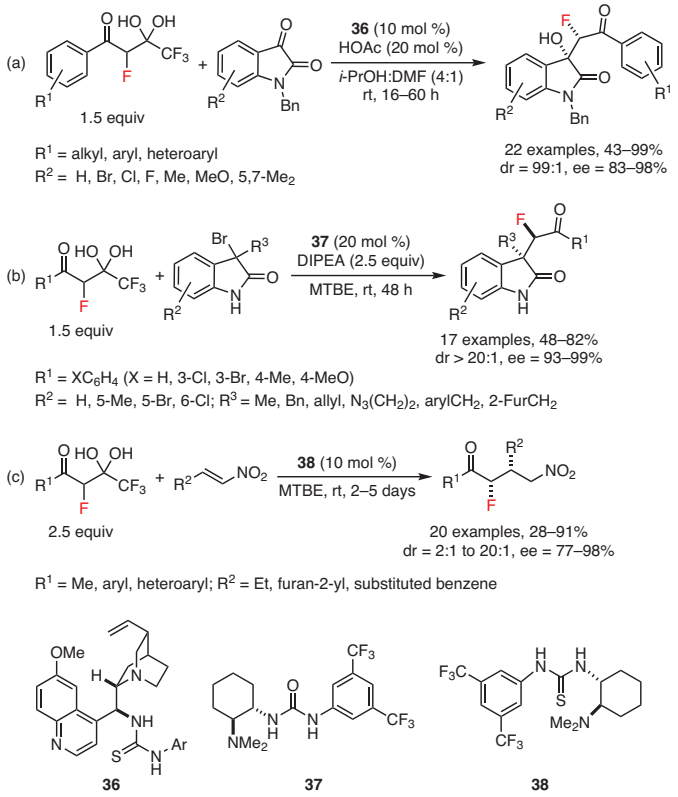


Scheme 15. Catalytic, Asymmetric Mannich and Cross-Coupling Reactions of Fluoroenolates Generated by the Release of Trifluoroacetate. *(Ref. 116–118)*

fluoroenolates generated in situ by the trifluoroacetate-release method. For example, Fang, Wu, and co-workers used thiourea ligand **36** to synthesize 3-hydroxyoxindoles by the aldol reaction of fluoroenolates with indoline-2,3-diones (**Scheme 16**, Part (a)).[108] Similarly, Hong, Wang, and collaborators achieved the asymmetric synthesis of 3-alkyloxindoles by utilizing chiral ligand **37** and 3-bromo-oxindoles as precursors (Scheme 16, Part (b)).[119] Moreover, the asymmetric monofluoroalkylation of nitro-olefins, albeit with diminished stereocontrol, has been realized by using a Michael-type addition of in situ generated fluoroenolates in the presence of chiral ligand **38** (Scheme 16, Part (c)).[120]

7. Conclusions and Outlook

The preparation of difluorinated organic compounds from difluoroenolates is a powerful and versatile synthetic tool for chemists. Both fluorinating reagents and fluorinated building blocks play a fundamental role in the production of fluorinated enolates. Recently, the application of difluoroenolate intermediates in synthesis has advanced substantially with the discovery of catalytic and asymmetric methodologies. Most of these innovations have been achieved through the mild generation of the fluorinated enolates by release of trifluoroacetate, or, to a lesser extent, by decarboxylation of suitable precursors. Both of these approaches require the cleavage of a carbon–carbon bond, which is a rare and challenging task for chemists, because most of the emphasis in synthetic chemistry is on the creation of carbon–carbon bonds.[121] We anticipate that, in the future, the chemistry of fluorinated organic molecules will be explored, not only through the synthesis of these important targets, but also by cleaving them to unleash valuable reactive fluorinated intermediates that can be elaborated further into useful and desired products.



Scheme 16. Asymmetric Monofluoroalkylations with Fluoroenolates Generated in Situ by the Release of Trifluoroacetate. *(Ref. 108,119,120)*

8. References

(1) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Acena, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422.
(2) Littich, R.; Scott, P. J. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1106.
(3) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *Chem. Soc. Rev.* **2011**, *40*, 3496.
(4) Fujiwara, T.; O'Hagan, D. *J. Fluorine Chem.* **2014**, *167*, 16.
(5) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.
(6) Nemoto, H.; Nishiyama, T.; Akai, S. *Org. Lett.* **2011**, *13*, 2714.
(7) Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N. *J. Am. Chem. Soc.* **2010**, *132*, 18199.
(8) Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Soc., Chem. Commun.* **1992**, 595.
(9) Differding, E.; Ofner, H. *Synlett* **1991**, *2*, 187.
(10) Ruppert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *25*, 2195.
(11) Riofski, M. V.; Hart, A. D.; Colby, D. A. *Org. Lett.* **2013**, *15*, 208.
(12) Doherty, A. M.; Sircar, I.; Kornberg, B. E.; Quin, J., III; Winters, R. T.; Kaltenbronn, J. S.; Taylor, M. D.; Batley, B. L.; Rapundalo, S. R.; Ryan, M. J.; Painchaud, C. A. *J. Med. Chem.* **1992**, *35*, 2.
(13) Fäh, C.; Hardegger, L. A.; Baitsch, L.; Schweizer, W. B.; Meyer, S.; Bur, D.; Diederich, F. *Org. Biomol. Chem.* **2009**, *7*, 3947.
(14) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813.
(15) Han, C.; Salyer, A. E.; Kim, E. H.; Jiang, X.; Jarrard, R. E.; Powers, M. S.; Kirchhoff, A. M.; Salvador, T. K.; Chester, J. A.; Hockerman, G. H.; Colby, D. A. *J. Med. Chem.* **2013**, *56*, 2456.
(16) Moore, C. L.; Leatherwood, D. D.; Diehl, T. S.; Selkoe, D. J.; Wolfe, M. S. *J. Med. Chem.* **2000**, *43*, 3434.
(17) Quero, C.; Rosell, G.; Jiménez, O.; Rodriguez, S.; Bosch, M. P.; Guerrero, A. *Bioorg. Med. Chem.* **2003**, *11*, 1047.
(18) Takahashi, L. H.; Radhakrishnan, R.; Rosenfield, R. E., Jr.; Meyer, E. F., Jr.; Trainor, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 3368.
(19) Decostanzi, M.; Campagne, J.-M.; Leclerc, E. *Org. Biomol. Chem.* **2015**, *13*, 7351.
(20) Choppin, S.; Ferreiro-Medeiros, L.; Barbarotto, M.; Colobert, F. *Chem. Soc. Rev.* **2013**, *42*, 937.
(21) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2568.
(22) McBee, E. T.; Pierce, O. R.; Christman, D. L. *J. Am. Chem. Soc.* **1955**, *77*, 1581.
(23) Hallinan, E. A.; Fried, J. *Tetrahedron Lett.* **1984**, *25*, 2301.
(24) Kuroboshi, M.; Ishihara, T. *Bull. Chem. Soc. Jpn* **1990**, *63*, 428.
(25) Soengas, R. G. *Tetrahedron: Asymmetry* **2010**, *21*, 2249.
(26) Poisson, T.; Belhomme, M. C.; Pannecoucke, X. *J. Org. Chem.* **2012**, *77*, 9277.

(27) Aslam, N. A.; Babu, S. A.; Sudha, A. J.; Yasuda, M.; Baba, A. *Tetrahedron* **2013**, *69*, 6598.
(28) Si, C.; Fales, K. R.; Torrado, A.; Frimpong, K.; Kaoudi, T.; Vandeveer, H. G.; Njoroge, F. G. *J. Org. Chem.* **2016**, *81*, 4359.
(29) Yao, H.; Cao, C.-R.; Jiang, M.; Liu, J.-T. *J. Fluorine Chem.* **2013**, *156*, 45.
(30) Cheguillaume, A.; Lacroix, S.; Marchand-Brynaert, J. *Tetrahedron Lett.* **2003**, *44*, 2375.
(31) Nadon, J. F.; Rochon, K.; Grastilleur, S.; Langlois, G.; Dao, T. T.; Blais, V.; Guerin, B.; Gendron, L.; Dory, Y. L. *ACS Chem. Neurosci.* **2017**, *8*, 40.
(32) Ellipilli, S.; Ganesh, K. N. *J. Org. Chem.* **2015**, *80*, 9185.
(33) Madaiah, M.; Prashanth, M. K.; Revanasiddappa, H. D. *Tetrahedron Lett.* **2013**, *54*, 1424.
(34) Fujimoto, T.; Tomata, Y.; Kunitomo, J.; Hirozane, M.; Marui, S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6409.
(35) Schuler, M.; Silva, F.; Bobbio, C.; Tessier, A.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2008**, *47*, 7927.
(36) Schuler, M.; Monney, A.; Gouverneur, V. *Synlett* **2009**, *20*, 1733.
(37) Médebielle, M.; Hohn, S.; Okada, E.; Myoken, H.; Shibata, D. *Tetrahedron Lett.* **2005**, *46*, 7817.
(38) Fang, X.; Yang, X.; Zhao, M.; Di, Q.; Wang, X.; Wu, F. *J. Fluorine Chem.* **2009**, *130*, 974.
(39) Tang, W.; Liu, S.; Degen, D.; Ebright, R. H.; Prusov, E. V. *Chem.—Eur. J.* **2014**, *20*, 12310.
(40) Aikawa, K.; Asano, M.; Ono, K.; Habuka, N.; Yano, J.; Wilson, K.; Fujita, H.; Kandori, H.; Hara, T.; Morimoto, M.; Santou, T.; Yamaoka, M.; Nakayama, M.; Hasuoka, A. *Bioorg. Med. Chem.* **2017**, *25*, 3330.
(41) Boyer, N.; Gloanec, P.; De Nanteuil, G.; Jubault, P.; Quirion, J.-C. *Eur. J. Org. Chem.* **2008**, 4277.
(42) Akahoshi, F.; Ashimori, A.; Sakashita, H.; Yoshimura, T.; Eda, M.; Imada, T.; Nakajima, M.; Mitsutomi, N.; Kuwahara, S.; Ohtsuka, T.; Fukaya, C.; Miyazaki, M.; Nakamura, N. *J. Med. Chem.* **2001**, *44*, 1297.
(43) Chen, S.; Bartkovitz, D.; Cai, J.; Chen, Y.; Chen, Z.; Chu, X.-J.; Le, K.; Le, N. T.; Luk, K.-C.; Mischke, S.; Naderi-Oboodi, G.; Boylan, J. F.; Nevins, T.; Qing, W.; Chen, Y.; Wovkulich, P. M. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1247.
(44) Hilpert, H.; Guba, W.; Woltering, T. J.; Wostl, W.; Pinard, E.; Mauser, H.; Mayweg, A. V.; Rogers-Evans, M.; Humm, R.; Krummenacher, D.; Muser, T.; Schnider, C.; Jacobsen, H.; Ozmen, L.; Bergadano, A.; Banner, D. W.; Hochstrasser, R.; Kuglstatter, A.; David-Pierson, P.; Fischer, H.; Polara, A.; Narquizian, R. *J. Med. Chem.* **2013**, *56*, 3980.
(45) Giovani, S.; Penzo, M.; Brogi, S.; Brindisi, M.; Gemma, S.; Novellino, E.; Savini, L.; Blackman, M. J.; Campiani, G.; Butini, S. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3582.
(46) Gauthier, D. R., Jr.; Sherry, B. D.; Cao, Y.; Journet, M.; Humphrey, G.; Itoh, T.; Mangion, I.; Tschaen, D. M. *Org. Lett.* **2015**, *17*, 1353.
(47) Yang, Y.-Y.; Meng, W.-D.; Qing, F.-L. *Org. Lett.* **2004**, *6*, 4257.
(48) Yang, Y.-Y.; Xu, J.; You, Z.-W.; Xu, X.; Qiu, X.-L.; Qing, F.-L. *Org. Lett.* **2007**, *9*, 5437.
(49) Kumamoto, H.; Kawahigashi, S.; Wakabayashi, H.; Nakano, T.; Miyaike, T.; Kitagawa, Y.; Abe, H.; Ito, M.; Haraguchi, K.; Balzarini, J.; Baba, M.; Tanaka, H. *Chem. Commun.* **2012**, *48*, 10993.
(50) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549.
(51) Honda, T.; Wakabayashi, H.; Kanai, K. *Chem. Pharm. Bull.* **2002**, *50*, 307.
(52) Tarui, A.; Kondo, K.; Taira, H.; Sato, K.; Omote, M.; Kumadaki, I.; Ando, A. *Heterocycles* **2007**, *73*, 203.
(53) Staas, D. D.; Savage, K. L.; Homnick, C. F.; Tsou, N. N.; Ball, R. G. *J. Org. Chem.* **2002**, *67*, 8276.
(54) Soloshonok, V. A.; Ohkura, H.; Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yamazaki, T. *Tetrahedron Lett.* **2002**, *43*, 5445.
(55) Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yasuda, N.; Uekusa, H.; Ono, T.; Berbasov, D. O.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 7448.
(56) Tarui, A.; Ozaki, D.; Nakajima, N.; Yokota, Y.; Sokeirik, Y. S.; Sato, K.; Omote, M.; Kumadaki, I.; Ando, A. *Tetrahedron Lett.* **2008**, *49*, 3839.
(57) Tarui, A.; Ikebata, T.; Sato, K.; Omote, M.; Ando, A. *Org. Biomol. Chem.* **2014**, *12*, 6484.
(58) Tarui, A.; Nishimura, H.; Ikebata, T.; Tahira, A.; Sato, K.; Omote, M.; Minami, H.; Miwa, Y.; Ando, A. *Org. Lett.* **2014**, *16*, 2080.
(59) Fornalczyk, M.; Singh, K.; Stuart, A. M. *Chem. Commun.* **2012**, *48*, 3500.
(60) Tarui, A.; Kawashima, N.; Sato, K.; Omote, M.; Miwa, Y.; Minami, H.; Ando, A. *Tetrahedron Lett.* **2010**, *51*, 2000.
(61) Tarui, A.; Kondo, S.; Sato, K.; Omote, M.; Minami, H.; Miwa, Y.; Ando, A. *Tetrahedron* **2013**, *69*, 1559.
(62) Tarui, A.; Miyata, E.; Tanaka, A.; Sato, K.; Omote, M.; Ando, A. *Synlett* **2015**, *26*, 55.
(63) Tarui, A.; Kawashima, N.; Kawakita, T.; Sato, K.; Omote, M.; Ando, A. *J. Org. Chem.* **2013**, *78*, 7903.
(64) Niida, A.; Tomita, K.; Mizumoto, M.; Tanigaki, H.; Terada, T.; Oishi, S.; Otaka, A.; Inui, K.; Fujii, N. *Org. Lett.* **2006**, *8*, 613.
(65) Oishi, S.; Kamitani, H.; Kodera, Y.; Watanabe, K.; Kobayashi, K.; Narumi, T.; Tomita, K.; Ohno, H.; Naito, T.; Kodama, E.; Matsuoka, M.; Fujii, N. *Org. Biomol. Chem.* **2009**, *7*, 2872.
(66) Narumi, T.; Tomita, K.; Inokuchi, E.; Kobayashi, K.; Oishi, S.; Ohno, H.; Fujii, N. *Tetrahedron* **2008**, *64*, 4332.
(67) Karad, S. N.; Pal, M.; Crowley, R. S.; Prisinzano, T. E.; Altman, R. A. *ChemMedChem* **2017**, *12*, 571.
(68) Sato, K.; Tamura, M.; Tamoto, K.; Omote, M.; Ando, A.; Kumadaki, I. *Chem. Pharm. Bull.* **2000**, *48*, 1023.
(69) Sato, K.; Nakazato, S.; Enko, H.; Tsujita, H.; Fujita, K.; Yamamoto, T.; Omote, M.; Ando, A.; Kumadaki, I. *J. Fluorine Chem.* **2003**, *121*, 105.
(70) Kim, B. C.; Park, A.; An, J. E.; Lee, W. K.; Lee, H. B.; Shin, H. *Synthesis* **2012**, *44*, 3165.
(71) Giacoboni, J.; Clausen, R. P.; Marigo, M. *Synlett* **2016**, *27*, 2803.
(72) Moens, M.; Verniest, G.; de Schrijver, M.; ten Holte, P.; Thuring, J.-W.; Deroose, F.; de Kimpe, N. *Tetrahedron* **2012**, *68*, 9284.
(73) Surmont, R.; Verniest, G.; Thuring, J. W.; Macdonald, G.; Deroose, F.; de Kimpe, N. *J. Org. Chem.* **2010**, *75*, 929.

(74) Vaněk, V.; Pícha, J.; Fabre, B.; Buděšínský, M.; Lepšík, M.; Jiráček, J. *Eur. J. Org. Chem.* **2015**, 3689.
(75) Taguchi, T.; Kitagawa, O.; Morikawa, T.; Nishiwaki, T.; Uehara, H.; Endo, H.; Kobayashi, Y. *Tetrahedron Lett.* **1986**, *27*, 6103.
(76) Kitagawa, O.; Taguchi, T.; Kobayashi, Y. *Chem. Lett.* **1989**, *18*, 389.
(77) Sato, K.; Kawata, R.; Ama, F.; Omote, M.; Ando, A.; Kumadaki, I. *Chem. Pharm. Bull.* **1999**, *47*, 1013.
(78) Fujikawa, K.; Fujioka, Y.; Kobayashi, A.; Amii, H. *Org. Lett.* **2011**, *13*, 5560.
(79) Jiang, H.; Lu, W.; Yang, K.; Ma, G.; Xu, M.; Li, J.; Yao, J.; Wan, W.; Deng, H.; Wu, S.; Zhu, S.; Hao, J. *Chem.—Eur. J.* **2014**, *20*, 10084.
(80) Zhu, J.; Zhang, W.; Zhang, L.; Liu, J.; Zheng, J.; Hu, J. *J. Org. Chem.* **2010**, *75*, 5505.
(81) Wan, W.; Ma, G.; Li, J.; Chen, Y.; Hu, Q.; Li, M.; Jiang, H.; Deng, H.; Hao, J. *Chem. Commun.* **2016**, *52*, 1598.
(82) Chen, F.; Hashmi, A. S. K. *Org. Lett.* **2016**, *18*, 2880.
(83) Verhoog, S.; Pfeifer, L.; Khotavivattana, T.; Calderwood, S.; Collier, T. L.; Wheelhouse, K.; Tredwell, M.; Gouverneur, V. *Synlett* **2016**, *27*, 25.
(84) Mizuta, S.; Stenhagen, I. S. R.; O'Duill, M.; Wolstenhulme, J.; Kirjavainen, A. K.; Forsback, S. J.; Tredwell, M.; Sandford, G.; Moore, P. R.; Huiban, M.; Luthra, S. K.; Passchier, J.; Solin, O.; Gouverneur, V. *Org. Lett.* **2013**, *15*, 2648.
(85) Smith, G. R.; Brenneman, D. E.; Zhang, Y.; Du, Y.; Reitz, A. B. *J. Mol. Neurosci.* **2014**, *52*, 446.
(86) Hoekstra, W. J.; Garvey, E. P.; Moore, W. R.; Rafferty, S. W.; Yates, C. M.; Schotzinger, R. J. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3455.
(87) Sato, K.; Nishimoto, T.; Tamoto, K.; Omote, M.; Ando, A.; Kumadaki, I. *Heterocycles* **2002**, *56*, 403.
(88) Ashwood, M. S.; Alabaster, R. J.; Cottrell, I. F.; Cowden, C. J.; Davies, A. J.; Dolling, U. H.; Emerson, K. M.; Gibb, A. D.; Hands, D.; Wallace, D. J.; Wilson, R. D. *Org. Process Res. Dev.* **2004**, *8*, 192.
(89) Huang, D.-K.; Lei, Z.-L.; Zhu, Y.-J.; Liu, Z.-J.; Hu, X.-J.; Mao, H.-F. *Tetrahedron Lett.* **2017**, *58*, 3394.
(90) Yuan, J.-W.; Liu, S.-N.; Mai, W.-P. *Org. Biomol. Chem.* **2017**, *15*, 7654.
(91) Yang, M.-H.; Hunt, J. R.; Sharifi, N.; Altman, R. A. *Angew. Chem., Int. Ed.* **2016,** *55*, 9080.
(92) Yang, M.-H.; Orsi, D. L.; Altman, R. A. *Angew. Chem., Int. Ed.* **2015**, *54*, 2361.
(93) Han, C.; Kim, E. H.; Colby, D. A. *J. Am. Chem. Soc.* **2011**, *133*, 5802.
(94) Prager, J. H.; Ogden, P. H. *J. Org. Chem.* **1968**, *33*, 2100.
(95) Zhang, P.; Wolf, C. *J. Org. Chem.* **2012**, *77*, 8840.
(96) Xie, C.; Wu, L.; Mei, H.; Soloshonok, V. A.; Han, J.; Pan, Y. *Org. Biomol. Chem.* **2014**, *12*, 7836.
(97) Xie, C.; Wu, L.; Zhou, J.; Mei, H.; Soloshonok, V. A.; Han, J.; Pan, Y. *J. Fluorine Chem.* **2015**, *172*, 13.
(98) Xie, C.; Wu, L.; Mei, H.; Soloshonok, V. A.; Han, J.; Pan, Y. *Tetrahedron Lett.* **2014**, *55*, 5908.
(99) John, J. P.; Colby, D. A. *J. Org. Chem.* **2011**, *76*, 9163.
(100) Hazlitt, R. A.; John, J. P.; Tran, Q.-L.; Colby, D. A. *Tetrahedron Lett.* **2016**, *57*, 1906.
(101) Leng, D. J.; Black, C. M.; Pattison, G. *Org. Biomol. Chem.* **2016**, *14*, 1531.
(102) Sowaileh, M. F.; Han, C.; Hazlitt, R. A.; Kim, E. H.; John, J. P.; Colby, D. A. *Tetrahedron Lett.* **2017**, *58*, 396.
(103) Li, W.; Zhu, X.; Mao, H.; Tang, Z.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2014**, *50*, 7521.
(104) Chen, H.; Wang, J.; Wu, J.; Kuang, Y.; Wu, F. *J. Fluorine Chem.* **2017**, *200*, 41.
(105) Wang, D.; Wu, J.; Huang, J.; Liang, J.; Peng, P.; Chen, H.; Wu, F. *Tetrahedron* **2017**, *73*, 3478.
(106) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.
(107) Sloop, J. C.; Boyle, P. D.; Fountain, A. W.; Pearman, W. F.; Swann, J. A. *Eur. J. Org. Chem.* **2011**, 936.
(108) Saidalimu, I.; Fang, X.; He, X.-P.; Liang, J.; Yang, X.; Wu, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 5566.
(109) Qian, C.-P.; Nakai, T. *Tetrahedron Lett.* **1988**, *29*, 4119.
(110) Jiménez, O.; Bosch, M. P.; Guerrero, A. *J. Org. Chem.* **2005**, *70*, 10883.
(111) Hazlitt, R. A.; Tran, Q.-L.; Sowaileh, M. F.; Colby, D. A. *J. Org. Chem.* **2017**, *82*, 2231.
(112) Zhang, P.; Wolf, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 7869.
(113) Xie, C.; Wu, L.; Han, J.; Soloshonok, V. A.; Pan, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 6019.
(114) Zhang, L.; Xie, C.; Dai, Y.; Mei, H.; Han, J.; Soloshonok, V. A.; Pan, Y. *J. Fluorine Chem.* **2016**, *184*, 28.
(115) Sha, W.; Zhang, L.; Zhang, W.; Mei, H.; Soloshonok, V. A.; Han, J.; Pan, Y. *Org. Biomol. Chem.* **2016**, *14*, 7295.
(116) Liu, X.; Zhang, J.; Zhao, L.; Ma, S.; Yang, D.; Yan, W.; Wang, R. *J. Org. Chem.* **2015**, *80*, 12651.
(117) Xie, C.; Dai, Y.; Mei, H.; Han, J.; Soloshonok, V. A.; Pan, Y. *Chem. Commun.* **2015**, *51*, 9149.
(118) Jiao, Z.; Beiger, J. J.; Jin, Y.; Ge, S.; Zhou, J. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 15980.
(119) Wu, C.; Li, G.; Sun, W.; Zhang, M.; Hong, L.; Wang, R. *Org. Lett.* **2014**, *16*, 1960.
(120) Saidalimu, I.; Fang, X.; Lv, W.; Yang, X.; He, X.; Zhang, J.; Wu, F. *Adv. Synth. Catal.* **2013**, *355*, 857.
(121) Han, C.; Kim, E. H.; Colby, D. A. *Synlett* **2012**, *23*, 1559.

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Munia F. Sowaileh was born in Amman, Jordan. She received her B.S. degree in pharmacy in 2010 and her M.S. degree in medicinal chemistry in 2013 from Jordan University of Science

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David A. Colby earned a Pharm.D. degree in 2001 from the University of Iowa, and received his Ph.D. degree in chemistry in 2006 from the University of California, Irvine. He completed postdoctoral training at the Scripps Research Institute, and is currently Associate Professor of Medicinal Chemistry in the Department of BioMolecular Sciences at the University of Mississippi. His research program aims to design drugs from naturally occurring molecules, and spans the fields of medicinal chemistry, fluorine chemistry, and natural product synthesis. He moved to the University of Mississippi in 2014, and had previously been a faculty member at Purdue University with appointments in the Department of Medicinal Chemistry and Molecular Pharmacology as well as the organic division of the Department of Chemistry.

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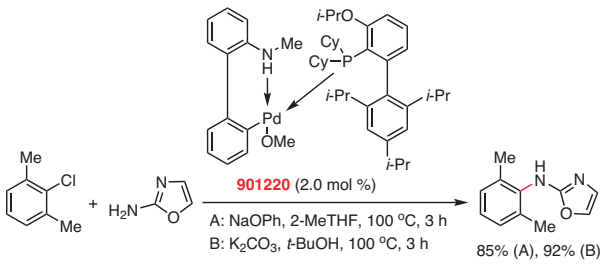

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Olsen, E. P. K.; Arrechea, P. L.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2017**, *56*, 10569

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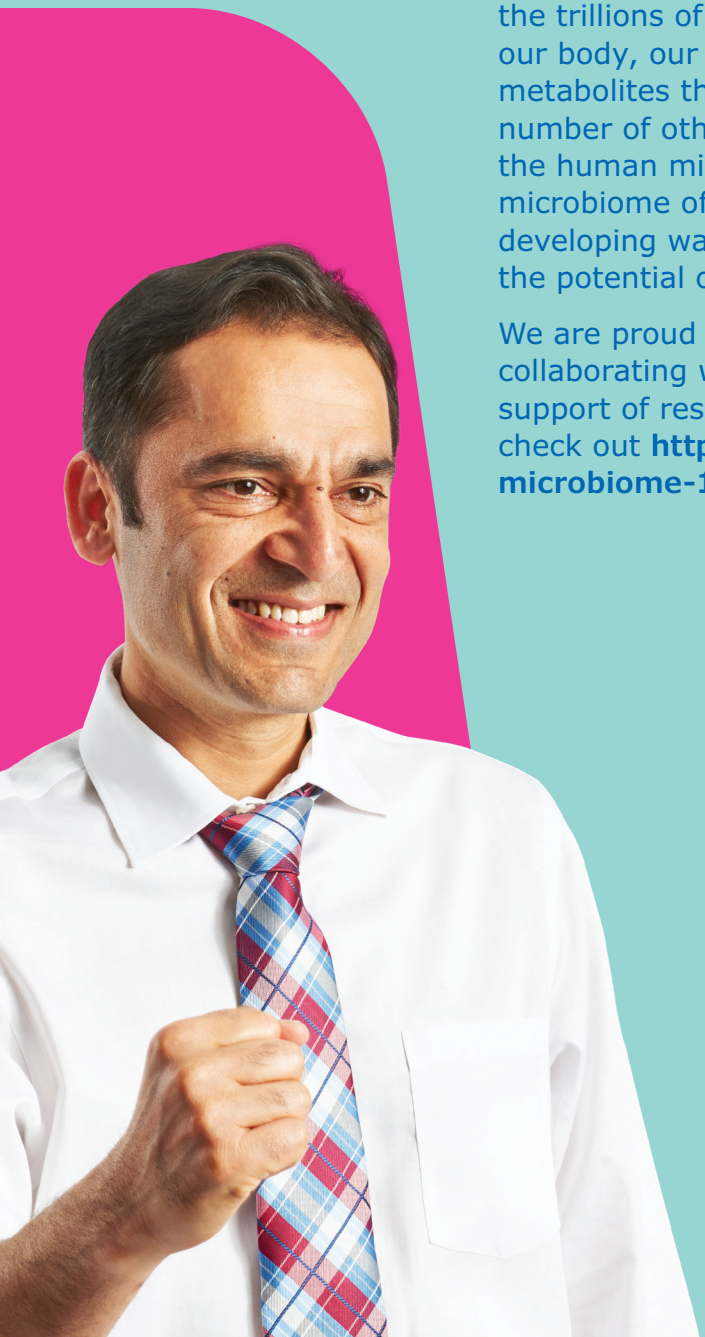

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Professor Keary M. Engle of the Department of Chemistry at The Scripps Research Institute kindly suggested that we offer three new nucleophilic fluorinating reagents that are complementary to TBAF hydrate: TBAF(pTol$_3$COH)$_2$ (**809578**), TBAF(9-Ph-9-fluorenol)$_3$ (**900016**), and TBAF(pin)$_2$ (**900021**). These fluoride–alcohol complexes, first described by Professor Véronique Gouverneur of the Chemistry Research Laboratory at the University of Oxford, are more stable and less hygroscopic than TBAF and are more convenient to handle. By attenuating fluoride nucleophilicity through hydrogen bonding, the complexes allow the controlled release of fluoride in solution, making them highly useful in organic synthesis.

Engle, K. M.; Pfeifer, L.; Pidgeon, G. W.; Giuffredi, G. T.; Thompson, A. L.; Paton, R. S.; Brown, J. M.; Gouverneur, V. *Chem. Sci.* **2015**, *6*, 5293.

$(n\text{-Bu})_4N^+ F^-$	$(n\text{-Bu})_4N^+ F^-$	$(n\text{-Bu})_4N^+ F^-$
$[(4\text{-}MeC_6H_4)_3COH]_2$	(9-Ph-9-fluorenol)$_3$	$[Me_2C(OH)C(OH)Me_2]_2$
809578	**900016**	**900021**
TBAF(pTol$_3$COH)$_2$	TBAF(9-Ph-9-fluorenol)$_3$	TBAF(pin)$_2$

809578	TBAF(pTol$_3$COH)$_2$	1 g
900016	TBAF(9-Ph-9-fluorenol)$_3$	1 g
900021	TBAF(pin)$_2$	1 g

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ABOUT OUR COVER

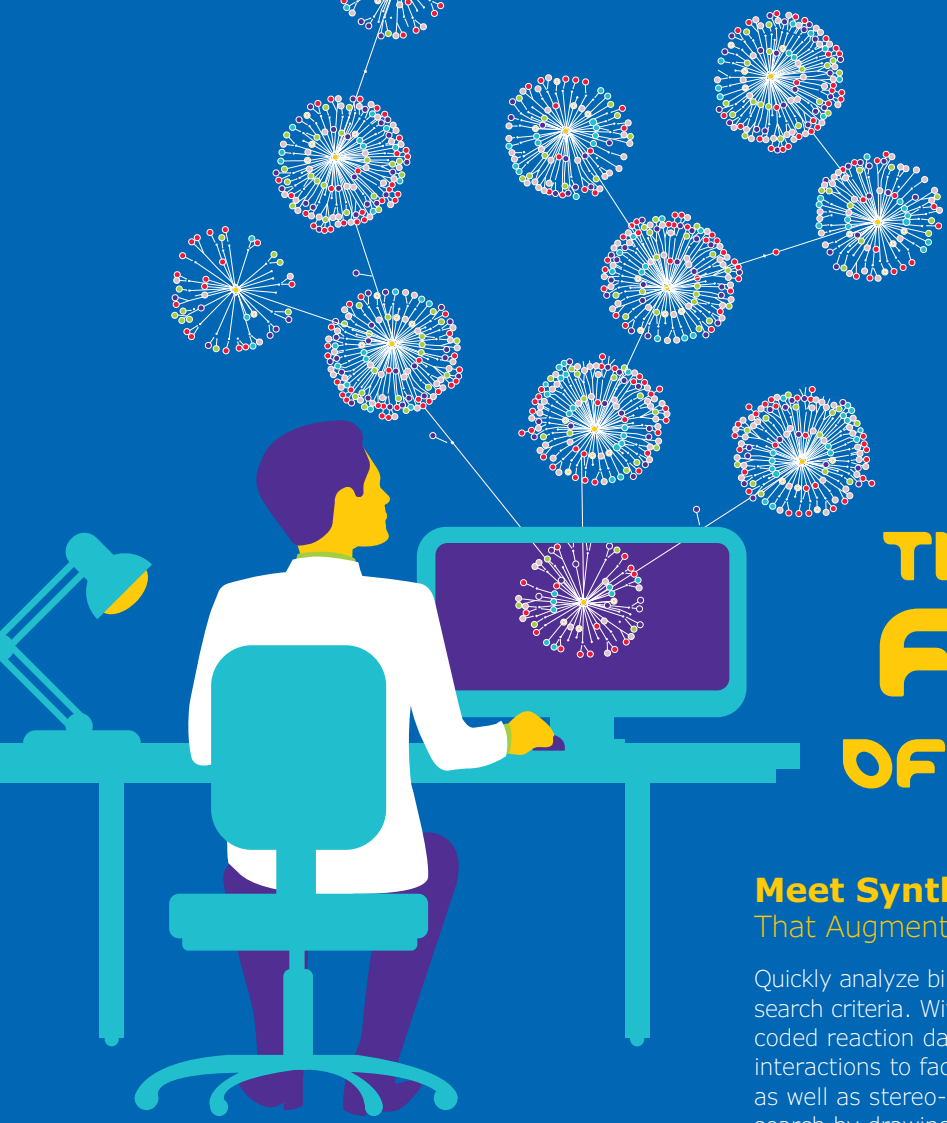
On Their Way to Camp (oil on board, 48.9 x 75.2 cm) was painted in 1873 by the famed American painter (Jonathan) Eastman Johnson (1824–1906). Born and raised in Maine, he received his early apprenticeship in Boston and his rigorous multi-year artistic training in Europe (Düsseldorf, The Hague, and Paris), where he was influenced by, among others, Emanuel Gottlieb Leutze and the works of seventeenth-century Flemish and Dutch masters. In the U.S., he acquired a favorable reputation at an early age, had wealthy and influential patrons, and was able to fetch high prices for his compositions. While he painted in several locales (Augusta, Washington DC, Northern Wisconsin, and Cincinnati) he created most of his work while residing in Manhattan and Nantucket. He exhibited widely and was in much demand during his lifetime.

Detail from ***On Their Way to Camp***. Photo courtesy National Gallery of Art, Washington, DC.

He is best-known as a portraitist and a meticulous painter of realistic scenes of ordinary people carrying on their everyday activities in simple, often outdoor, settings. ***On Their Way to Camp*** is one charming, fully finished, and particularly important example of the latter genre and was born out of sketches he made on his many trips to maple sugar camps in New England. His legacy endures today, not only through his well-known sketches and paintings, but also through his other important contributions to the art world.*

Paul Mellon Fund and Gift of Jo Ann and Julian Ganz, Jr., National Gallery of Art, Washington, DC.

** To find out more about Eastman Johnson's enduring legacy to the art world, visit **SigmaAldrich.com/Acta***



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Keywords. phosphorus ylides; sulfur ylides; green synthesis; CO_2 activation; Wittig olefination; carbene precursor; C^1 synthon.

Abstract. The present review highlights relevant recent examples (2013–2018) of sustainable synthetic reactions involving phosphorus and sulfur ylides. These examples include catalytic, halide- and base-free Wittig olefination reactions and P-ylides as CO_2 activators. They also include sustainable protocols for the synthesis of S-ylides and recent applications of these as C^1 synthons, carbene precursors, and in selected rearrangement reactions.

Outline

1. Introduction

Phosphorus and sulfur (sulfonium and sulfoxonium) ylides are widely utilized reagents in organic chemistry, and are traditionally employed for olefination and cyclization reactions. Although these transformations opened new pathways in organic synthesis, their environmental footprint is still a relevant issue since both of these classes of ylides are typically used in stoichiometric amounts, and the unavoidable byproducts formed (phosphine or sulfur oxides) must be separated from the reaction mixture and disposed of at the end of the process, highlighting the need for "greener" options. In this context, the present review showcases recent examples of ylide-based synthetic reactions that are characterized by an improved environmental footprint.

2. Phosphorus Ylides

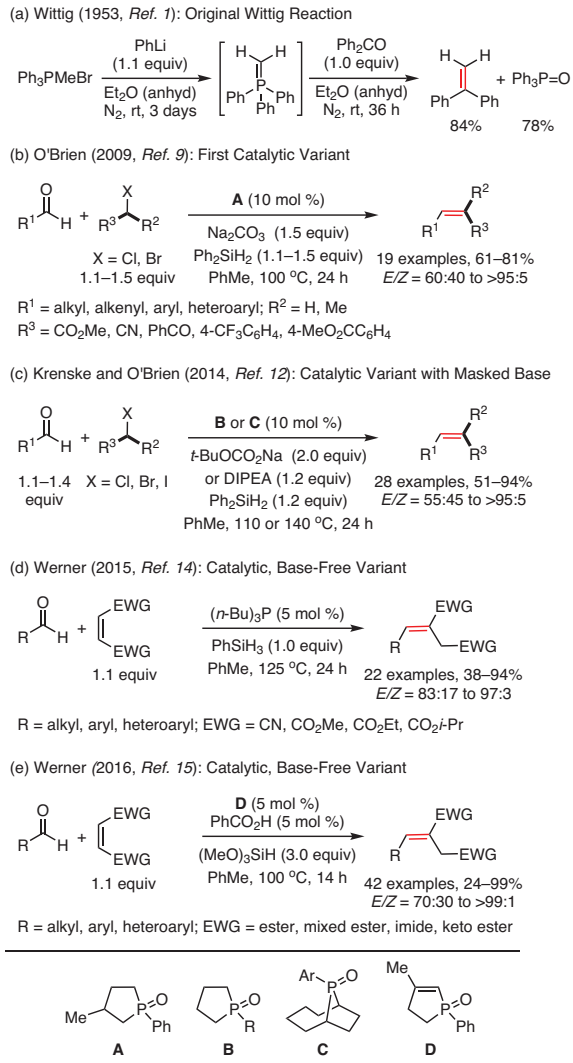
2.1. Greener Wittig reactions

2.1.1. Catalytic

The Wittig reaction is rightly considered one of the most effective and versatile pathways for the synthesis of a carbon–carbon double bond starting from carbonyl compounds (e.g., aldehydes or ketones). The first example was described in 1953 by Georg Wittig,[1] who reported the formation of 1,1′-diphenylethene upon heating triphenylphosphonium ylide with benzophenone (**Scheme 1**, Part (a)).

The protocol reported by Wittig required the use of a strong base in stoichiometric amounts to deprotonate the starting phosphonium salt and form the reactive ylide intermediate. The driving force for the reaction is the formation of the olefin product with a concurrent irreversible formation of an equimolar amount of triphenylphosphine oxide (Ph_3PO) as a byproduct. Despite these significant limitations with respect to sustainability and atom economy, the initial report by Wittig was a milestone in olefin synthesis and has resulted in a reliable, versatile, and widely applicable procedure with demonstrated synthetic

utility. However, the phosphine oxide byproduct still represents a waste that hampers product recovery and purification and gives rise to environmental and safety concerns because it is either incinerated or the starting phosphine regenerated at a high chemical cost (harsh conditions, use of reducing agents). Moreover, the poor atom economy associated with the classical Wittig protocol has prompted several research groups to develop catalytic alternatives in which substoichiometric amounts of the phosphine, or suitable synthetic equivalents, are utilized. In particular, research efforts have been aimed at reducing the formation of phosphorus(V) byproducts without compromising the protocol efficiency.[2] For example, a promising approach involves the use of catalytic variants, in which the phosphine oxide is reduced in situ, thus allowing phosphorus turnover and utilization of substoichiometric amounts of the phosphorus



Scheme 1. Evolution of the Wittig Reaction: from Stoichiometric to Catalytic.

ylide (vide infra). Nevertheless, the most common reduction pathways of phosphine oxide to phosphine require the use of harsh reducing agents such as lithium aluminum hydride ($LiAlH_4$) or trichlorosilane ($HSiCl_3$), which may not be compatible with some of the reagents or the desired products.

A different approach relies on the use of alternatives to P-based ylides such as arsenic-,[3-6] tellurium-,[7] or antimony-based ones.[8] All have been successfully employed in catalytic Wittig reactions, since the respective oxides are much easier to reduce thanks to their weaker element–oxygen bond strengths. However, these protocols are not applicable on a large scale due to the high toxicity of these elements.

The first successful example of a phosphine-based, catalytic Wittig reaction protocol was proposed in 2009 by O'Brien and co-workers.[9] Diphenylsilane was found to be a suitable reducing agent, transforming selectively the precatalyst, 3-methyl-1-phenylphospholane-1-oxide (**A**, 10 mol %), into the corresponding phosphine, while keeping all of the other components unaltered. The in situ generated phosphine reacted with activated alkyl halides (containing electron-withdrawing groups) in the presence of a base, such as Na_2CO_3, to generate the corresponding stabilized phosphonium ylides. These reacted with a series of aldehydes to form the desired alkenes (61–81%, *E/Z* = 60:40 to >95:5) and regenerate the precatalyst (Scheme 1, Part (b)).[9] In 2013, O'Brien and co-workers reported an alternative protocol utilizing an organic base, *N,N*-diisopropylethylamine (DIPEA)—which is soluble in organic solvents—to replace heterogeneous sodium carbonate.[10] The same group also observed that the presence of a Brönsted acid, such as 4-nitrobenzoic acid, facilitates the reduction of phosphine oxide to the point that the reaction could be performed at room temperature. In particular, using 1-*n*-butylphospholane-1-oxide, phenylsilane as the reducing agent, and 4-nitrobenzoic acid, the first example of a room-temperature, catalytic Wittig reaction (RT-CWR) was efficiently performed.[11] Moreover, using this protocol, green solvents such as ethyl acetate and cyclopentyl methyl ether (CPME) proved to be effective alternatives to THF and toluene. RT-CWR allowed for the synthesis of 16 olefins in 61–91% isolated yields and very good *E* diastereoselectivities, with the *E/Z* ratio typically in the range of 80:20 to >95:5.

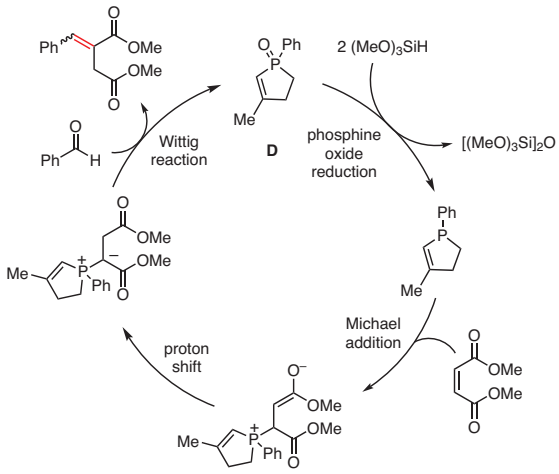
Krenske, O'Brien, and co-workers recently improved the experimental design of the catalytic Wittig reaction by extending its applicability to semi-stabilized [pK_a (DMSO) = 17–18] and unstabilized ylides [pK_a (DMSO) = 22–25]. The key to this improvement was the choice of base, which has to be sufficiently strong to abstract the ylide-forming proton of the phosphonium salt (**Scheme 2**, Step III) without compromising the rest of the CWR. Sodium *tert*-butoxycarbonate ($NaOCO_2t$-Bu), which slowly releases NaO*t*-Bu, was chosen as the masked base (Scheme 1, Part (c) and Scheme 2).[12] To further lower the pK_a of the ylide-forming proton, electron-withdrawing groups such as CF_3 were introduced into the phenyl ring of the phosphine oxide precatalyst, thus decreasing the electron density of the phosphorus center. The proposed mechanism shown in Scheme 2, however, fails to account for the fate

of the starting silane, which is bound to form an Si–O bond that represents the driving force for the reaction as well as its limitation in terms of atom economy.

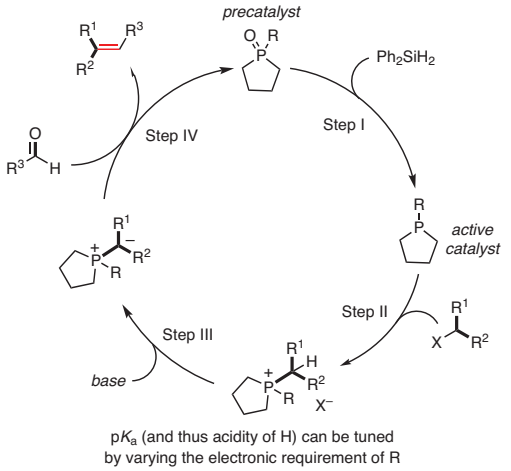
Werner and co-workers reported the first example of a catalytic enantioselective Wittig reaction[13] and described the reaction conditions for a highly efficient, catalytic, and base-free Wittig protocol (Scheme 1, Part (d)).[14] The proposed catalytic cycle consists of three steps: An initial Michael addition of $(n\text{-Bu})_3P$ to a substituted alkene acceptor (diethyl maleate) and a subsequent [1,2]-H shift lead to the corresponding ylide under base-free conditions. In the second step, the ylide formed in situ reacts with the aldehyde starting material to afford succinates and $(n\text{-Bu})_3P{=}O$. In the last step of the catalytic cycle, $(n\text{-Bu})_3P$ is regenerated in situ by reaction of $(n\text{-Bu})_3PO$ with phenyl silane ($PhSiH_3$). After protocol optimization, 22 succinate derivatives were obtained in good-to-excellent yields of up to 94%. Moreover, in the case of aromatic and heteroaromatic aldehydes, very good *E*/*Z* selectivities of up to 97:3 were obtained.

This protocol was further optimized using 3-methyl-1-phenyl-2-phospholene 1-oxide (**D**) as the precatalyst in the presence of trimethoxysilane [$(MeO)_3SiH$] as the in situ reducing agent.[15] The influence of Brönsted acid on the reduction of the phosphine oxide was also investigated. Using benzoic acid (5 mol %), nine activated olefins and 33 aldehydes (aliphatic, aromatic, and heteroaromatic) were converted into 42 highly functionalized alkenes in isolated yields of up to 99%. In all cases, good-to-excellent selectivity for the *E* isomer was observed, and the proposed scheme (**Scheme 3**)[15] parallels that proposed by Krenske and O'Brien.

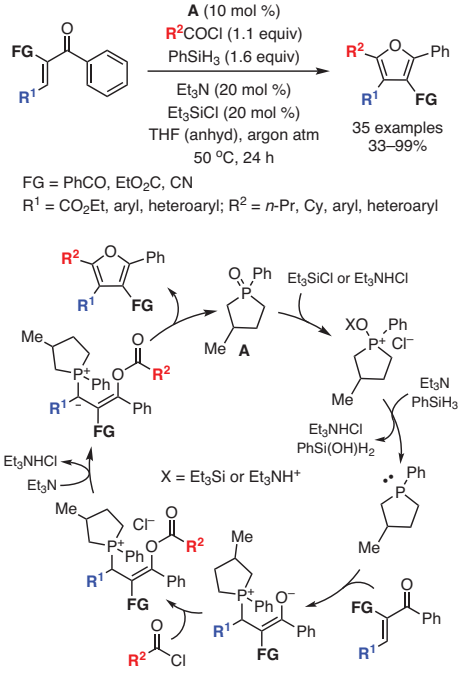
The scope of the catalytic Wittig reaction has been extended by Lin and co-workers to the intramolecular synthesis of highly functionalized furans.[16] In this protocol, α-substituted chalcones react with an acyl chloride in the presence of a phosphine oxide precatalyst (10 mol %) and Et_3N (20 mol %). Phenylsilane ($PhSiH_3$) is used as a reducing agent (1.6 equiv) and Et_3SiCl (20 mol %) as a promoter of the reduction of the phosphine oxide. Moreover, the in situ generated byproduct (Et_3NHCl) was also found to accelerate the reduction of the phosphine oxide. Using the optimized reaction conditions, 35 highly functionalized furans were synthesized in 33–99% isolated yields (**Scheme 4**).[16]



Scheme 3. Werner's Proposed Mechanism for the Base-Free, Catalytic Wittig Reaction. *(Ref. 15)*



Scheme 2. Krenske and O'Brien's Proposed Mechanism of a Catalytic Wittig Reaction Utilizing a Masked Base. *(Ref. 12)*



Scheme 4. Lin's Intramolecular Catalytic Wittig Olefination Leading to Highly Functionalized Furans. *(Ref. 16)*

All the catalytic Wittig protocols described so far constitute significant improvements on the classic Wittig reaction. Notably, for the first time, the phosphine oxide byproduct could be employed as the precatalyst in catalytic amounts. However in these CWR protocols, an equimolar amount of byproduct is always formed, since the silane reducing agent is used in stoichiometric quantities, is quantitatively oxidized, and has to be disposed of at the end of the reaction. A desirable evolution of this chemistry would thus rely on the development of catalytic reductions of the phosphine oxide.

A life cycle analysis (LCA) of the catalytic Wittig reaction developed by O'Brien versus the classic stoichiometric analogue was carried out by Huijbregts and co-workers by evaluating two quantitative measures: the global warming potential over 100 years (GWP 100a developed by the International Panel for Climate Change) expressed in CO_2 equivalents and the cumulative energy demand (CED, the total energy consumption for the life cycle inventory). The CED, in particular, is considered a proxy for the total environmental burden of a process. The process data included the quantities of all reagents and solvents necessary to produce 1 mole of olefin. The LCA followed a cradle-to-gate analysis for all materials employed, including contributions to prepare Ph_3P, silane, and aldehyde, but excluding subsequent use of the olefin and waste treatment of the chemicals produced. The comparison showed a clear advantage of the catalytic variant in reducing energy consumption, greenhouse gas (GHG) emissions, and waste generation (**Scheme 5**).[17] The authors concluded that, even though the catalytic Wittig reaction conditions require the use of additional reagents such as sodium carbonate, this contributed only marginally to its environmental impact when compared to the classic Wittig reaction. In contrast, the advantages of using silanes as sacrificial reducing agents in the catalytic reaction are clearly demonstrated by the reduction of CED and GHG emissions when compared to the use of stoichiometric quantities of triphenylphosphine in the classic reaction protocol.

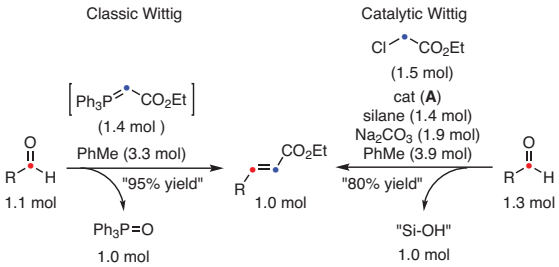
2.1.2. Halide- and Base-free

Aiming to improve the sustainability of the Wittig protocol, we reported the first example of a simple, versatile, and sustainable halide- and base-free Wittig vinylation.[18] This sustainable pathway for the synthesis of vinyl derivatives from aldehydes and ketones was performed in two steps. In the first, the Wittig vinylating agent, methyltriphenylphosphonium methylcarbonate ($[Ph_3PCH_3][CH_3OCO_2]$, **1**), was readily prepared by quaternarization of triphenylphosphine (TPP) in the presence of the nontoxic methylating agent dimethyl carbonate.[18] Remarkably, this reaction step is characterized by a 100% atom economy. The XRD crystal structure of **1** revealed a short distance between the methylcarbonate oxygen and the P-CH_3 methyl group (3.174 Å at 100 K), suggesting a significant H-bonding in the solid state. This proximity represents strong evidence of a latent ylide, which could be formed via a "counterion-mediated" deprotonation.

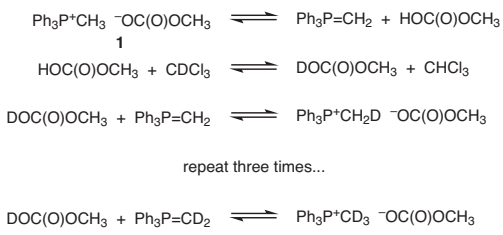
A preliminary study demonstrated that when treating **1** with a 15-fold molar excess of $CDCl_3$, a hydrogen–deuterium exchange occurs between the P-CH_3 protons (pK_a > 20) of the phosphonium salt and deuterium of $CDCl_3$ (pK_a = 25), leading to the quantitative formation of the deuterated analogue $[Ph_3PCD_3][CH_3OCO_2]$ presumably via the proposed mechanism shown in **Scheme 6**.[18]

The second step, the halide- and base-free Wittig vinylation protocol, was effected by reacting the model carbonyl substrate benzaldehyde with **1** and using the bio-derived 2-Me-THF as solvent. Styrene was quantitatively obtained after only 40 minutes at 80 °C. The reaction was optimized and its scope extended to 8 aromatic and aliphatic carbonyl compounds, leading to the corresponding alkenes in good-to-excellent yields (**eq 1**).[18]

We then carried out an evaluation of the efficiency and environmental impact of our protocol vis-à-vis three existing ones that follow the classic Wittig process (**Table 1**).[18-21] Applying three simple green chemistry metrics [atom economy (AE, %), environmental factor (EF), and mass index (MI)] to the Wittig reaction of piperonal as a model reaction, we found that the calculated AE values of the four methods are all intrinsically low due to the need for stoichiometric amounts of the phosphonium ylide and the resulting formation of stoichiometric amounts of triphenylphosphine oxide. Nonetheless the halide- and base-free protocol is still slightly more atom-efficient (29.5%), due to the absence of halides and of added bases. Sheldon's EF



Scheme 5. Huijbregts's Comparison of the Quantitative Environmental Impact of the Classic Wittig Reaction (Left) Versus the Catalytic Variant Developed by O'Brien and Co-workers (Right). *(Ref. 17)*



Scheme 6. Proposed Mechanism of the Hydrogen–Deuterium Exchange for the Wittig Vinylation Agent ($[Ph_3PCH_3][CH_3OCO_2]$, **1**). *(Ref. 18)*

appears to favor Stevenson's process due to an exceptionally high yield reported by using purely stoichiometric amounts (1.0 equiv) of phosphonium salt and BuLi. In contrast, the MI of our protocol is significantly more advantageous (9.60) than those of the other three (15.70–19.31) due to the high conversion and selectivity achieved in the presence of low amounts of solvent (methylenedioxystyrene/2-Me-THF = 0.150 g/mL) and the resulting positive effects on the reaction rate. In all cases, chromatography solvents were not included in the calculations.

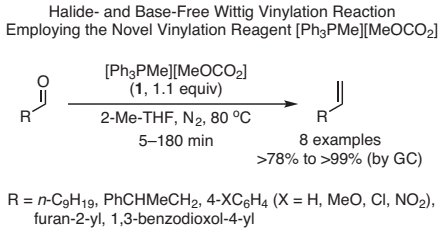
2.2. Organocatalysis for CO_2 activation

Among other applications, ylides, and in particular disyline bisphosphine adducts, have been efficiently employed for carbon dioxide (CO_2) transformation into desirable and economically competitive products. CO_2 is a thermodynamically inert molecule that is formed at the end of any carbon-based combustion process. Therefore, relatively high-energy co-reagents are often used to promote its reduction. In these processes, CO_2 activation is pivotal for its effective transformation.

The first nonmetal-mediated, direct CO_2 reduction to CO at room temperature was reported in 2011 by Kato, Baceiredo, and co-workers who utilized a bench-stable disilyne bis(phosphine) adduct (**eq 2**).[22] The adduct was characterized by a peculiar ligand effect of phosphine toward the Si^I center, whereby the phosphine ligands behave as weakly σ-donating ligands without a π-accepting character and induce a strong π donor–acceptor character in the Si^I centers. Consequently, the Si–Si fragment in the disilyne bis(phosphine) adduct exhibits some multiple-bond character. Owing to this peculiar property, the disilyne bis(phosphine) adduct showed high reactivity with CO_2, and, upon mixing with CO_2 at room temperature, it reacted with four equivalents of the latter, formally extracting three oxygen atoms and capturing one CO_2 molecule. Three molecules of CO and one molecule of the aminosilicate were generated, and the aminosilicate structure was confirmed and fully characterized by NMR analysis and XRD crystal structure determination.

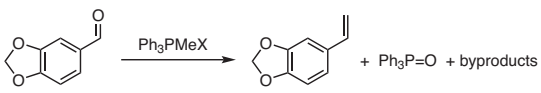
It is well known that phosphorus ylides are powerful and versatile nucleophilic reagents in organic synthesis. In 1966, Matthews et al. reported the first CO_2 adduct of a P-ylide formed from the nucleophilic addition of the ylide to CO_2.[23a] More recently, Zhou, Lu, and co-workers synthetized a series of P-ylide-CO_2 adducts, and showed them to be very efficient metal- and halogen-free organocatalysts for a number of reactions that transform CO_2 into useful fine chemicals under mild conditions (**Scheme 7**).[23b] One adduct in particular (**2**; R^1 = R^2 = Me) proved to be very stable even at 80 °C.

These catalysts were tested in the cycloaddition of CO_2 with terminal epoxides leading to cyclic organic carbonates. In particular, ylide adduct **2** (R^1 = H, R^2 = *n*-Pr; 5 mol %)



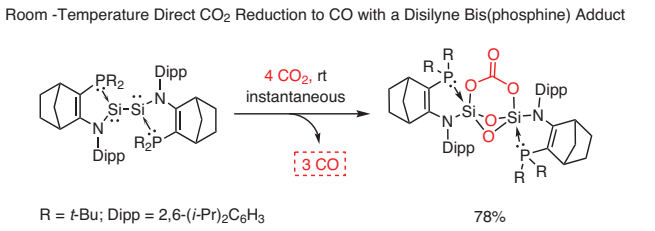
eq 1 *(Ref. 18)*

Table 1. Calculated Green Metrics for the Synthesis of 3,4-Methylenedioxystyrene by Various Wittig Reaction Protocols

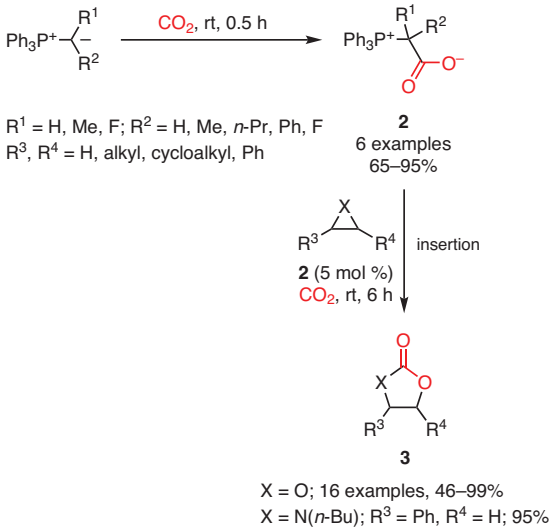


Protocol By	Ref.	X	AE	EF	MI
Gaset (1982)	19	I	22.9%	4.34	15.85
Stevenson (2006)	20	Br	25.9%	2.99	15.70
Joullié (2007)	21	Br	25.9%	3.90	19.31
Perosa (2015)	18	$MeOCO_2$	29.5%	3.82	9.60

AE = atom economy; EF = environmental factor; MI = mass index



eq 2 *(Ref. 22)*



Scheme 7. P-Ylides–CO_2 Adducts Prepared by Zhou, Lu, and Co-workers for Use as Organocatalysts for Activating CO_2 toward a Number of Useful Transformations. *(Ref. 23b)*

promoted a quantitative conversion of propylene oxide into propylene carbonate (98% yield) at room temperature after 4 h in the absence of any additional solvent. At 100 °C, 100% selectivity and 78% yield of propylene carbonate was achieved with a very low loading (0.5 mol %) of the same ylide adduct. After protocol optimization, the same organocatalyst (5 mol %) was used for the synthesis of 16 different cyclic organic carbonates in 46–99% yields (Scheme 7).[23b] The authors proposed a mechanism whereby the P-ylide activates the free CO_2 by forming a P-ylide adduct. Being less sterically hindered, the acetate fragment of this CO_2 complex is more nucleophilic than the starting P-ylide. After the epoxide starting material is activated through coordination to the central P^+ unit on the P-ylide, the activated CO_2 anion simultaneously attacks the less substituted C–O bond of the epoxide. A final intermolecular cyclization produces the cyclic carbonate and regenerates the P-ylide, which re-enters the catalytic cycle (**Scheme 8**).[23b] The P-ylides–CO_2 adducts were effective catalysts also for the insertion of CO_2 into aziridines and for the reduction of CO_2 with 9-BBN in the presence of anilines to form the corresponding *N*-methyl- and *N*-formylanilines.[23b]

3. Sulfonium and Sulfoxonium Ylides

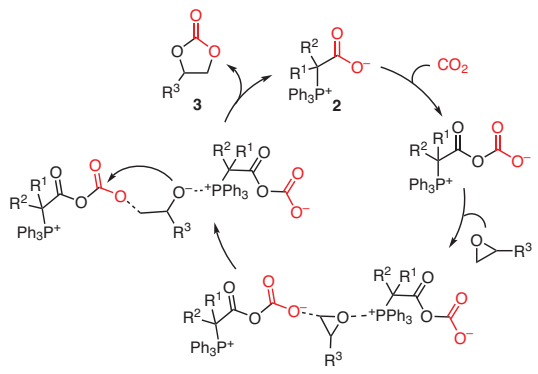
Sulfur-based ylides are among the most versatile reagents in organic synthesis, providing easy access to nucleophilic C^1 synthons. They have been successfully applied in a large number of synthetically relevant transformations, leading to the construction of small rings such as epoxides, aziridines, and cyclopropanes (**Scheme 9**); multicyclic heterocycles; or to ring expansions of lactones and lactams.[24–25] Notably, all of the above-mentioned transformations can be carried out with high levels of diastero- and/or enantioselectivity,[26–27] highlighting the importance and wide applicability of sulfur-based ylides in contemporary organic synthesis in both academia and industry.[28] Moreover, the synthetic relevance of these transformations is attested to by the number of recent review articles focusing on the various synthetic applications of sulfur-based ylides: their use as diazocarbonyl equivalents in metal-catalyzed insertion reactions;[29] the development of metal-, organo-, and photocatalytic asymmetric cyclization protocols based on sulfur ylides;[30] advances in transition-metal-catalyzed sulfonium or sulfoxonium ylide reactions;[31] synthesis and reactivity of vinyl sulfonium and vinyl sulfoxonium ylides;[32] and propargylic sulfides.[33]

Sulfur ylides are zwitterions, typically constituted by carbanions with an adjacent positive sulfur atom. Their stability depends on their molecular structure, in particular on the electronic delocalization of the negative charge of the carbanionic center and on the nature and type of substituents on the sulfur atom. For example, the presence of carbonyl groups attached to the carbanionic center—as is the case in ketosulfonium and ketosulfoxonium ylides—results in less reactive sulfur ylides, whereas the presence of a heteroatom attached to the sulfur center increases the ylide stability (Scheme 9).

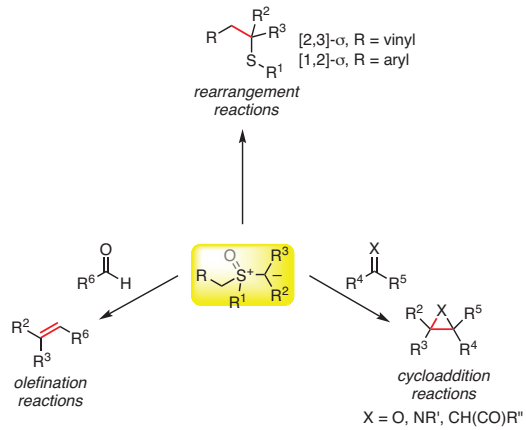
Sulfur ylides are accessed mainly through (i) hydrogen abstraction from sulfonium and sulfoxonium salts, and (ii) reaction between a sulfide or sulfoxide with a metal–carbene complex that is typically derived from a diazo compound.[29,34] The second approach is far less studied, since sulfur-based ylides are considered safer and more stable synthetic alternatives to the highly reactive diazo compounds. Thus, the development of new methods for the preparation of these ylides, especially the more stable ones (e.g., substituted ketosulfonium and ketosulfoxonium ylides), is still of great interest. Additionally, the development of truly sustainable synthetic methodologies for the preparation of sulfur ylides is still an open challenge.

3.1. Sustainable Synthesis of Sulfur Ylides: the Case of β-Keto Thioethers

The preparation of β-keto thioethers, which are biologically and agrochemically relevant S-containing compounds, can serve as an example of a sustainable application of S-ylides in



Scheme 8. Proposed Catalytic Cycle for the Insertion of CO_2 into Epoxides Promoted by P-Ylide–CO_2 Adducts. *(Ref. 23b)*



Scheme 9. The Reactivity of Sulfur Ylides.

synthesis. These compounds are bench-stable solids employed synthetically as benzothiophenes and Julia reagent precursors.[35] They are traditionally prepared via metal-catalyzed S–H insertion into diazocarbonyl compounds or via nucleophilic substitution from haloketones in the presence of thiolates. While the former methodology requires the use of highly reactive reagents (diazocarbonyl compounds), the latter consists of a multistep reaction sequence with superstoichiometric amounts of base and is characterized by poor regiochemical control. Moreover, haloketones are unstable, noncommercially available, and irritating (lachrymatory) reagents, typically prepared starting from toxic and reactive precursors (e.g., Br_2 or NBS). Dias and Burtoloso have reported a sustainable method for synthesizing β-keto thioethers starting from easily prepared keto sulfoxonium ylides and commercially available aryl thiols (**Scheme 10**, Part (a)).[36] This organocatalytic reaction involves an initial, rate-determining thiol addition to the sulfoxonium ylide formed in situ, followed by an irreversible nucleophilic displacement of DMSO and formation of the β-keto thioether product. The β-keto thioethers were synthesized with high chemoselectivity, and the protocol was applied to a diverse library of substituted aryl thiols (25 examples, yields up to 94%).[36]

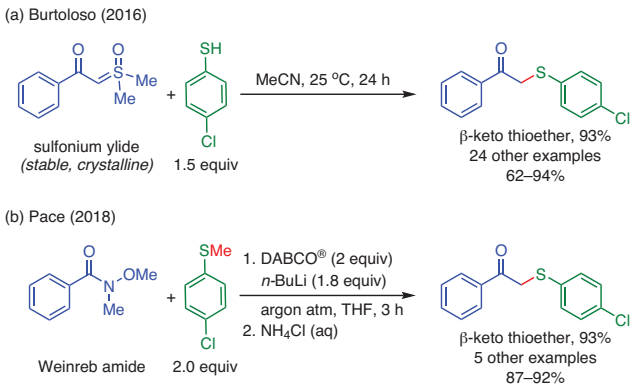
More recently, Pace and co-workers described the reaction of Weinreb amides with α-functionalized methyllithium reagents derived from thiols (carbenoid nucleophiles generated in situ), which gave rise to the corresponding β-keto thioethers in high yields and selectivity (Scheme 10, Part (b)).[37] Notably, this protocol was also applicable to the preparation of α-thioacetal-like methyl ketones.

Biju and co-workers developed a simple and sustainable methodology for the selective preparation of α-functionalized β-oxo arylthioethers (**Scheme 11**).[38] The reported procedure is mild, does not use transition metals, and works well for a broad range of substituted alkyl allyl thioether and aryne [generated from 2-(trimethylsilyl)aryl triflates] precursors. The reaction proceeds through a sulfur ylide intermediate generated from the aryne and alkyl allyl thioether, followed by an intramolecular [2,3]-sigmatropic Stevens rearrangement resulting in the formation of new carbon–sulfur and carbon–carbon bonds, respectively. Moreover, the conversion of the β-oxo arylthioethers into useful aryl heteroaryl thioethers and substituted pyridazines was demonstrated in one case by following a two-step procedure consisting of an initial ozonolysis and subsequent intramolecular condensations.

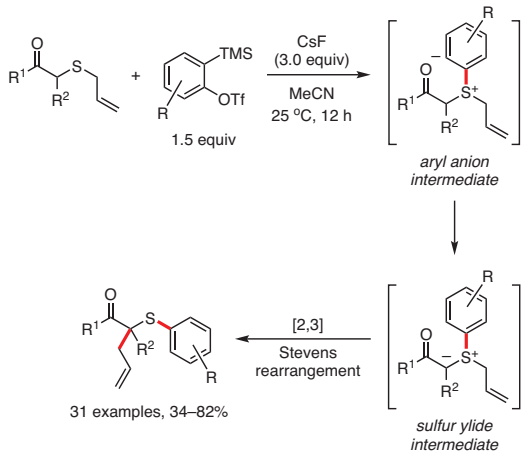
Maulide and co-workers reported an S^{IV}, transition-metal-free divergent process for the selective preparation of stabilized sulfonium ylides from active methylene compounds, indoles, or pyrroles; and for the direct α-arylation of carbonyl compounds (**Scheme 12**).[39] Selectivity toward one reaction pathway or the other is likely due to the structure of the S^{IV} ylide intermediate and counteranion basicity, with the more basic anions favoring S-alkylation and the less basic ones promoting the Lewis acid reactivity of the S^{IV} intermediate.

3.2. Sulfur Ylides as C^1 Precursors

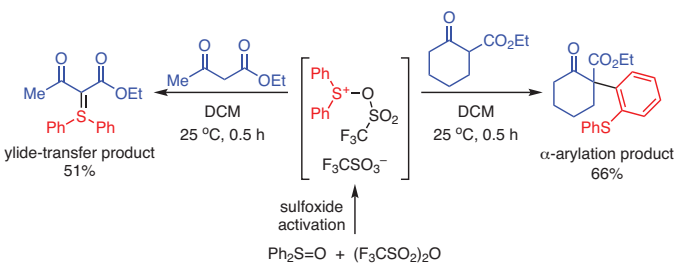
As mentioned previously, reactive sulfur-containing species, such as sulfur-based ylides, are typically generated by sulfide



Scheme 10. Representative Examples of Sustainable Syntheses of β-Keto Thioethers. *(Ref. 36,37)*



Scheme 11. Synthesis of α-Substituted β-Oxo Arylthioethers via a [2,3]-Stevens Rearrangement of Sulfur Ylide Intermediates Generated from the Reaction of Alkyl Allyl Thioethers with in Situ Generated Arynes. *(Ref. 38)*



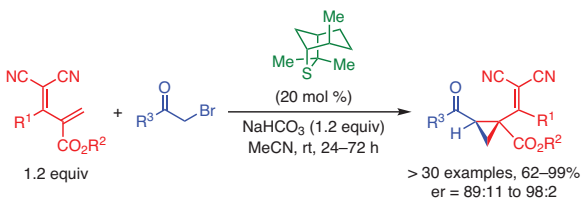
Scheme 12. Divergent Reactivity of Stabilized S-Ylides with β-Keto Esters. *(Ref. 39)*

alkylation with an alkyl halide followed by deprotonation. This sequence can be performed in situ or, for the most stable ylides, in a previous synthetic step, but it has a detrimental impact on the sustainability of the overall process in terms of step-economy, atom economy, and environmental compatibility. As a consequence, sustainable alternative protocols for this alkylation–deprotonation sequence have been developed. These require the use of base-nonsensitive Michael acceptors, thus allowing a one-pot reaction in which the sulfide is regenerated as the reaction progresses, resulting in sulfide loadings as low as 20 mol %.[40] Despite these positive developments, direct sulfide catalysis is rather underexplored, and only scattered results have been reported so far.[26,41-42] Recently, Li and co-workers reported the first example of effective, sulfide-based enantioselective organocatalysis using halide substrates bearing an electron-withdrawing group. An efficient, metal-free cyclopropanation protocol via direct sulfide catalysis was developed and applied to different electron-deficient halides including α-brominated ketones, esters, and amides. The reaction generated vinylcyclopropanes featuring a quaternary chiral center (>30 examples) with yields of up to 99% and enantiomeric ratios (er) of up to 98:2 (**eq 3**).[43] The protocol is characterized by mild operating conditions, the use of inexpensive sulfides, and by being highly regio- and diastereoselective.

A similar approach was reported by Huang and co-workers who developed a transition-metal-free Suzuki-type cross-coupling between benzyl halides and boronic acids via a 1,2-metalate shift involving a zwitterionic boron "ate" intermediate. The reaction takes place through a novel catalytic cycle using commercially available sulfides as organocatalysts and involving formation of the corresponding sulfonium salts as the rate-determining step. Rearrangement to a reactive sulfur ylide, oxidative addition of the boronic acid to form the boron "ate" complex, 1,2-metalate shift, and protodeboronation lead to the final C(sp^3)–C(sp^2) coupling product (**eq 4**).[44] This approach eliminates possible undesirable homocoupling reactions for substrates with multiple aryl halide substituents, and enables a modular synthesis of unsymmetrical, highly functionalized diarylmethanes from polyhalogenated substrates by using sequential cross-coupling steps.

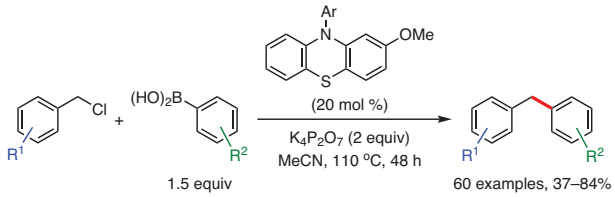
The reaction of S-ylides as nucleophiles in cycloadditions with aldehydes, ketones, and ketenes is well established[45] and has become an important synthetic tool for the stereoselective preparation of epoxides, aziridines, and cyclopropane moieties,[46] respectively. In contrast, a thorough understanding of the reactivity patterns occurring between S-based ylides and Michael acceptors is still lacking. Achieving this understanding is complicated by the fact that most Michael acceptors do not behave analogously, and require a case by case study. It has been noted, however, that in the presence of selected Michael acceptors, S-ylides undergo [4 + 1] rather than [2 + 1] cycloaddition to form the corresponding 5-membered rings. These reactions generally occur in the presence of a transition-metal Lewis acid catalyst. In 2012, Bolm and co-workers were the first to report the selective formation of enantioenriched dihydropyrazoles from the [4 + 1] cycloaddition of conjugated azoalkenes (generated in situ from the corresponding α-haloketones) and sulfoxonium ylides.[47] The protocol, however, required the use of a chiral Cu-BINAP catalyst. Later, Lu, Lan, Xiao, and co-workers reported the first example of an iron-catalyzed decarboxylative [4 + 1] cycloaddition that leads to a wide range of functionalized indoline products starting from readily available vinyl benzoxazinanones and sulfur ylides.[48] These initial observations led to the development of catalyst-free [4 + 1] cycloadditions starting from 1,2-diaza-1,3-dienes (DDs) and S-ylides. Thus, Wang, Fang, and co-workers have synthesized a small library of 5-(trifluoromethyl)pyrazolines through a catalyst-free [4 + 1] annulation of α-halo hydrazone derivatives with trifluoroethyldiphenylsulfonium triflate. In this reaction, the reactive DDs are generated in situ under mild conditions, and are readily trapped by reaction with the activated but unstable trifluoroethylidenesulfur ylide (**Scheme 13**, Part (a)).[49] The same year, Shao, Chen, and co-workers reported a substrate-controlled protocol for the selective synthesis of bicyclic 4,5-dihydropyrazoles, starting from DDs and stabilized S-ylides under mild conditions. In particular, they noted that, when the DDs include a cyclopentene ring, the corresponding trans bicyclic 4,5-dihydropyrazolones were obtained in moderate-to-good yields (Scheme 13, Part (b)). Intriguingly, when acyclic DDs were employed, the corresponding 5,6-diazaspiro[2.4]-hept-6-en-4-ones (formal [2 + 1]-cycloaddition products) were obtained selectively.[50]

Structurally similar azaoxyallyl cation intermediates are typically involved in [3 + m]-cycloaddition reactions that lead to



R^1 = H, Ph, aryl, heteroaryl; R^2 = Me, Et, *t*-Bu
R^3 = Me, Ph, aryl, heteroaryl, phenoxy, anilino, chromon-2-yl

eq 3 *(Ref. 43)*



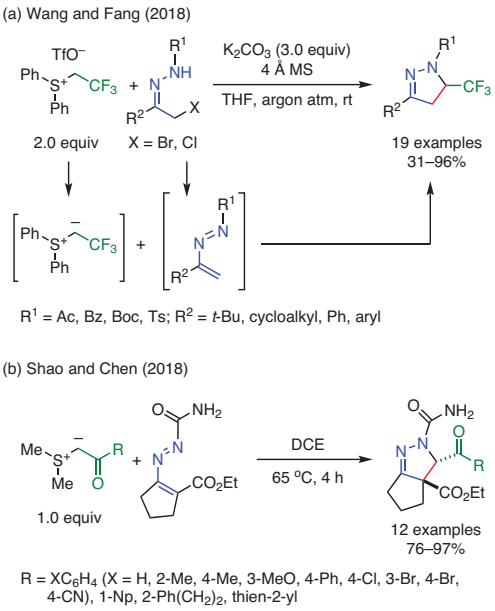
Ar = 4-MeOC$_6$H$_4$
R^1 = MeO, MeS, CF_3O, CO_2Et, CN, alkyl, Ph, aryl, halogen
R^2 = Ph_2N, MeS, alkyl, alkoxy, phenoxy, siloxy, Ph, aryl, heteroaryl, halogen

eq 4 *(Ref. 44)*

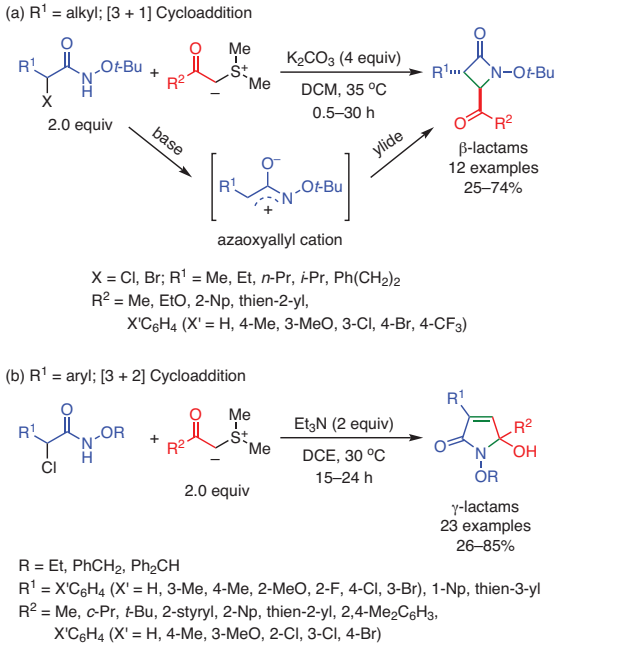
N-heterocycles.[51] The azaoxyallyl cations—generated in situ from α-halohydroxamates in the presence of base—were recently used by Liu, Chen, and co-workers as three-atom units in cycloaddition reactions with sulfur ylides.[52] The expected [3 + 1] cycloaddition products (β-lactams) were formed diasteroselectively (dr > 19:1) and in acceptable yields (up to 74%) only when starting from α-alkyl-substituted α-halohydroxamates (**Scheme 14**, Part (a)).[52] Moreover, moderate enantioselectivity was observed when chiral sulfur ylides were employed. When α-aryl-substituted α-halohydroxamates were used, an unexpected [3 + 2] cycloaddition reaction took place leading to the selective formation of γ-lactams instead (Scheme 14, Part (b)). In this case and for the first time, sulfur ylides stabilized by a vicinal ketone group acted as two-carbon cycloaddition partners.[52]

Maulide and co-workers extended the range of applications of azaoxyallyl derivatives by developing a new carbonyl olefination approach that relies on the formation of an intermediate *N*-iminylaziridine. Upon thermal decomposition, the three-membered-ring intermediate, prepared in a one-pot fashion by addition of a sulfoxonium ylide to an azine, leads to formation of the desired olefin in good-to-high yields (**Scheme 15**).[53] This procedure is applicable to a wide range of alkyl- and aryl-substituted aldehydes, enals, and alkyl-substituted sulfoxonium ylides. This methodology represents a novel carbonyl olefination approach when compared to the Wittig, Julia, Peterson, and Tebbe olefinations. It selectively delivers trans-disubstituted olefins and dienes from α,β-unsaturated carbonyls, and opens new reactivity pathways for sulfoxonium ylides. The same laboratory extended the use of stabilized S-ylides to heterocyclic targets, reporting a novel strategy for the synthesis of 2-amino-4,5-dihydrothiophenes (21 examples, yields up to 95%) upon [3 + 2] cycloaddition between nitro-olefins and thiouronium ylides. The latter compounds act as push–pull 1,3-dipoles resulting in fine-tuning of the reaction outcome based on the relative stability of the thiocarbonyl ylide: obtaining reduced yields for less stabilized ylides and observing a complete shutdown of reactivity when the ylide is "overstabilized".[54]

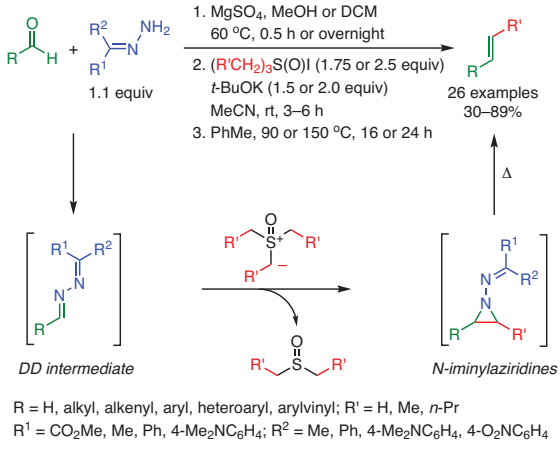
Prop-2-ynylsulfonium salts are a relatively new class of S-ylides that has shown borderline reactivity between C[1]



Scheme 13. Catalyst-free Reactivity of in Situ Generated 1,2-Diaza-1,3-dienes and S-Ylides. *(Ref. 49,50)*



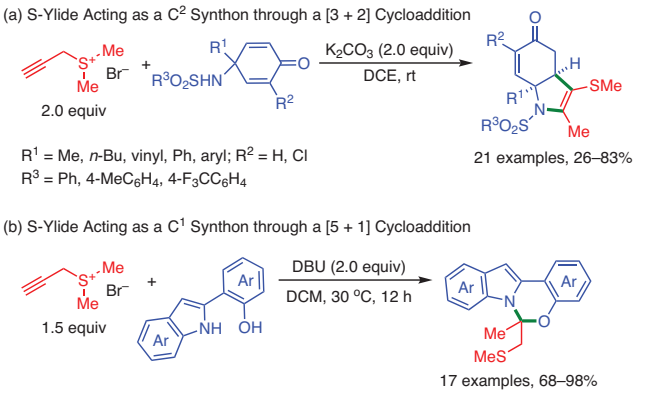
Scheme 14. Divergent Reactivity of Azaoxyallyl Halides with S-Ylides. *(Ref. 52)*



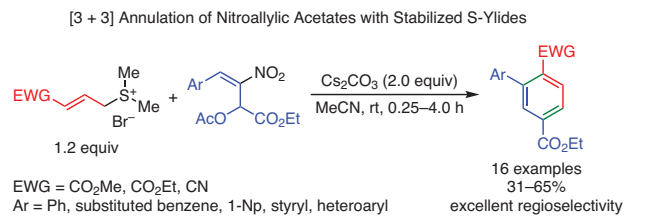
Scheme 15. Maulide's Novel Olefination of Activated Carbonyl Compounds with Sulfoxonium Ylides. *(Ref. 53)*

and C^2 synthons. For example, Huang and co-workers have reported a method to construct hydroindol-5-ones containing a methylthiogroup via [3 + 2] cycloaddition of prop-2-ynylsulfonium salts and *p*-quinamines (**Scheme 16**, Part (a)).[55] In this context, prop-2-ynylsulfonium salts isomerize into the corresponding allenic sulfonium salts acting as C^2 synthons with formation of the corresponding organosulfur bicyclic compounds. A year later, the same research laboratory reported the first formal [5 + 1]-annulation reaction between S-ylides and 2-(1*H*-indol-2-yl)-phenols, leading to a library of indole-fused 4*H*-benzo[*e*][1,3]-oxazines (Scheme 16, Part (b)).[56] In this reaction, the prop-2-ynylsulfonium salt participates with its electrophilic β-carbon atom, acting as a novel C^1 synthon and allowing for the formation under mild conditions of the corresponding polycyclic oxazolines bearing a thioether substituent in good-to-high yields.

G.-L. Wu and Q.-P. Wu have developed a metal-free domino reaction that is based on S-ylides and is selective for 4,5-disubstituted 1,2,3-(*NH*)-triazoles. The protocol involves an initial coupling between sulfur salts and aldehydes followed by the introduction of sodium azide. It is interesting to note that when the sulfur salts react with the aldehydes in the presence of L-proline, olefinic sulfur salt intermediates form instead of the expected epoxides; once formed, these intermediates undergo facile cyclization with azide ion.[57]



Scheme 16. The Reactivity of Propargyl-Substituted S-Ylides as C^1 and C^2 Synthons. *(Ref. 55,56)*



eq 5 *(Ref. 59)*

Nitroallylic derivatives are synthetically relevant reaction partners for annulation reactions, forming functional and biologically relevant derivatives.[58] When nitroallylic acetates were reacted with crotonate-derived stabilized S-ylides, Satham and Namboothiri selectively formed 2-arylterephtalates, which are formal precursors of farnesyltransferase inhibitors as well as potential monomers for polymerization reactions. The reaction occurs in a regioselective fashion through a cascade process consisting of two consecutive Michael additions (an initial intramolecular S_N2' followed by an intramolecular *6-endo-trig* cyclization) and two base-catalyzed eliminations (**eq 5**).[59]

Fan and co-workers developed a novel, highly efficient approach for the synthesis of spirocyclopentenyl *para*-dienones building blocks, relying on a base-mediated tandem spirocyclopropanation/rearrangement reaction of vinyl *para*-quinone methides (*p*-VQMs) with sulfonium salts. A series of highly functionalized spirocycles were thus prepared in good yields (up to 96%) and diastereoselectivities (up to 14:1 dr) under mild, metal-free conditions.[60]

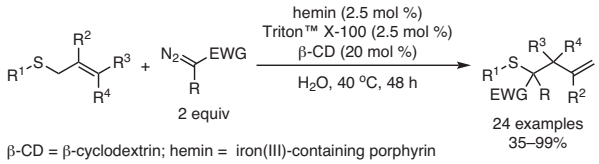
3.3. Sulfur Ylides as Carbene Precursors

Since their discovery in 1960, sulfonium and sulfoxonium ylides have been extensively employed as carbene precursors in transition-metal-catalyzed reactions, most likely because they are safer and more stable alternatives to diazo compounds.[29,31,61] The chemistry of metal carbenoids generated from diazo compounds has an established role in organic synthesis, particularly in cyclopropanations and insertion reactions into C–H and X–H (X = N, O, S, P, Se) bonds. The same chemistry can conceivably be accessed with metal carbenoids derived from sulfonium and sulfoxonium ylides. However, the generation of metal carbenoids from the ylides is much more challenging, especially because the reverse reaction—the formation of sulfonium ylides from the combination of metal carbenoids with sulfides—is facile and well-studied. In an effort to increase the sustainability of the Doyle–Kirmse reaction, one of the most commonly employed strategies to synthesize sulfonium ylides—the reaction between an allyl sulfide and a diazo reagent—was performed in aqueous solvent using hemin, a porphyrin-based catalyst. To ensure phase homogeneity, amphiphilic additives such as cyclodextrin (CD) and Triton™ X-100 were added. The protocol is characterized by high catalytic activity and broad functional-group tolerance, producing the corresponding homoallyl sulfides selectively in up to 99% yield (**eq 6**).[62]

The same protocol was extended to benzyl phenyl sulfide, observing selective formation of the [1,2]-Stevens and Sommelet–Hauser rearrangements products. Selectivity toward one type of rearrangement or another could be predicted based on the electronic properties of the substituents on the benzyl group together with solvent effects. Electron-donating or weak electron-withdrawing groups lead to the [1,2]-Stevens rearrangement, whereas strong electron-withdrawing substituents in the para position favor the Sommelet–Hauser rearrangement.[63] Fasan and co-workers reported the first example of a biocatalytic [2,3]-sigmatropic rearrangement

involving allylic sulfides and diazo reagents.[64] This variant of the Doyle–Kirmse C–C bond-forming reaction was efficiently catalyzed by engineered variants of sperm whale myoglobin. The protocol worked highly efficiently for a variety of sulfide substrates and α-diazo esters. Moreover, the reaction with propargylic sulfides led to the formation of substituted allenes. The active-site mutations increased the catalytic efficiency of the hemoprotein, modulated the enantioselectivity, and allowed the identification of Mb(L29S,H64V,V68F) as a myoglobin variant that is capable of effecting asymmetric Doyle–Kirmse reactions with enantiomeric excesses up to 71%.[64]

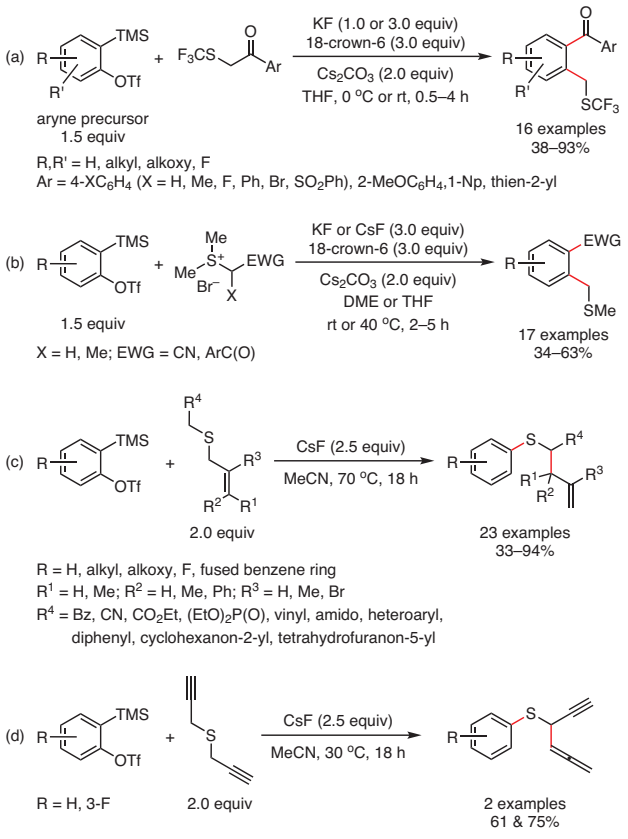
Hemin-Catalyzed Sulfonium Ylide Formation and Subsequent [2,3]-Sigmatropic Rearrangement in Aqueous Medium



β-CD = β-cyclodextrin; hemin = iron(III)-containing porphyrin

EWG = CO_2Me, CO_2Et, CO_2t-Bu, CO_2Bn, TMS
R = H, Ph, 1-Np; R^2 = H, Me; R^3 = H, Me, Ph; R^4 = H, Me
R^1 = Me, Et, *n*-Hex, Bn, 2-Pyr, 2-Np, XC_6H_4 (X = H, 3-Me, 4-Et, 4-MeO, 4-Br, 4-F, 4-NO_2)

eq 6 *(Ref. 62)*



Scheme 17. Novel Reactivity of S-Ylides with Arynes Opening the Door to Pharmaceutically Relevant Benzophenones and Sulfides. *(Ref. 65–67)*

3.4. Novel Reactivity of Sulfur-Based Ylides

Sulfur-based ylides are sources of active methylenes, thanks to their 1,2-dipolar nature, whereby the electron-rich carbon is stabilized by the adjacent electropositive sulfur atom. Compared with the classical metal-carbenoid-mediated [2,3]-sigmatropic rearrangement reactions, it is anticipated that a transition-metal-free method would provide an effective synthetic alternative. Mhaske and co-workers have reported a novel and efficient transition-metal-free reaction pathway for aryne insertion into substituted C–S bonds, resulting in ortho-difunctionalized arenes. The protocol requires mild reaction conditions and works with a broad range of aryne precursors and different S-ylides. For example, pharmaceutically relevant *ortho*-(trifluoromethylmercaptomethyl)-substituted benzophenones (16 examples, up to 93%) were prepared upon aryne insertion into α-(trifluoromethyl)thiomethyl ketones (**Scheme 17**, Part (a)).[65] With S-aryl/alkyl sulfonium salts, the same reaction led to ortho-substituted thioanisoles in good-to-moderate yields (17 examples, up to 63%; Scheme 17, Part (b)).[66] Moreover, Tan, Xu, and co-workers have reported a highly efficient aryne-induced [2,3]-sigmatropic rearrangement of allyl and propargyl thioethers, in which the S-ylide intermediate was generated in situ (Scheme 17, Parts (c) and (d)).[67] This approach had a broad substrate scope and allowed the selective synthesis of a library of highly functionalized sulfides in good yields (25 examples, up to 94%).[67]

4. Conclusion

In conclusion, and despite the healthy number of exciting research findings that have been disclosed so far, the "greening" of reactions based on phosphorus and sulfur ylides is still a research field in its infancy. The examples highlighted in the present review have demonstrated the viability of using phosphorus and sulfur ylides to discover and develop more environmentally friendly and sustainable processes, and should provide more impetus for further research in this emerging area of synthetic chemistry.

5. References

(1) Wittig, G.; Geissler, G. *Justus Liebigs Ann. Chem.* **1953**, *580,* 44.
(2) Lao, Z.; Toy, P. H. *Beilstein J. Org. Chem.* **2016**, *12,* 2577.
(3) Shi, L.; Wang, W.; Wang, Y.; Huang, Y.-Z. *J. Org. Chem.* **1989**, *54,* 2027.
(4) Dai, W.-M.; Wu, A.; Wu, H. *Tetrahedron: Asymmetry* **2002**, *13,* 2187.
(5) Zhu, S.; Liao, Y.; Zhu, S. *Org. Lett.* **2004**, *6,* 377.
(6) Cao, P.; Li, C.-Y.; Kang, Y.-B.; Xie, Z.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* **2007**, *72,* 6628.
(7) Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* **2002**, *67,* 5320.
(8) Liao, Y.; Huang, Y.-Z. *Tetrahedron Lett.* **1990**, *31,* 5897.

(9) O'Brien, C. J.; Tellez, J. L.; Nixon, Z. S.; Kang, L. J.; Carter, A. L.; Kunkel, S. R.; Przeworski, K. C.; Chass, G. A. *Angew. Chem., Int. Ed.* **2009**, *48,* 6836.
(10) O'Brien, C. J.; Nixon, Z. S.; Holohan, A. J.; Kunkel, S. R.; Tellez, J. L.; Doonan, B. J.; Coyle, E. E.; Lavigne, F.; Kang, L. J.; Przeworski, K. C. *Chem.—Eur. J.* **2013**, *19,* 15281.
(11) O'Brien, C. J.; Lavigne, F.; Coyle, E. E.; Holohan, A. J.; Doonan, B. J. *Chem.—Eur. J.* **2013**, *19,* 5854.
(12) Coyle, E. E.; Doonan, B. J.; Holohan, A. J.; Walsh, K. A.; Lavigne, F.; Krenske, E. H.; O'Brien, C. J. *Angew. Chem., Int. Ed.* **2014**, *53,* 12907.
(13) Werner, T.; Hoffmann, M.; Deshmukh, S. *Eur. J. Org. Chem.* **2014**, 6630.
(14) Schirmer, M.-L.; Adomeit, S.; Werner, T. *Org. Lett.* **2015**, *17,* 3078.
(15) Schirmer, M.-L.; Adomeit, S.; Spannenberg, A.; Werner, T. *Chem.—Eur. J.* **2016**, *22,* 2458.
(16) Lee, C.-J.; Chang, T.-H.; Yu, J.-K.; Madhusudhan Reddy, G.; Hsiao, M.-Y.; Lin, W. *Org. Lett.* **2016**, *18,* 3758.
(17) Van Kalkeren, H. A.; Blom, A. L.; Rutjes, F. P. J. T.; Huijbregts, M. A. J. *Green Chem.* **2013**, *15,* 1255.
(18) Cattelan, L.; Noè, M.; Selva, M.; Demitri, N.; Perosa, A. *ChemSusChem* **2015**, *8,* 3963.
(19) Le Bigot, Y.; Delmas, M.; Gaset, A. *Synth. Commun.* **1982**, *12,* 107.
(20) Aslam, S. N.; Stevenson, P. C.; Phythian, S. J.; Veitch, N. C.; Hall, D. R. *Tetrahedron* **2006**, *62,* 4214.
(21) Faler, C. A.; Joullié, M. M. *Org. Lett.* **2007**, *9,* 1987.
(22) Gau, D.; Rodriguez, R.; Kato, T.; Saffon-Merceron, N.; de Cózar, A.; Cossío, F. P.; Baceiredo, A. *Angew. Chem., Int. Ed.* **2011**, *50,* 1092.
(23) (a) Matthews, C. N.; Driscoll, J. S.; Birum, G. H. *Chem. Commun.* **1966**, 736. (b) Zhou, H.; Wang, G.-X.; Zhang, W.-Z.; Lu, X.-B. *ACS Catal.* **2015**, *5,* 6773.
(24) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97,* 2341.
(25) Sheng, Z.; Zhang, Z.; Chu, C.; Zhang, Y.; Wang, J. *Tetrahedron* **2017**, *73,* 4011.
(26) Piccinini, A.; Kavanagh, S. A.; Connon, S. J. *Chem. Commun.* **2012**, *48,* 7814.
(27) Marsini, M. A.; Reeves, J. T.; Desrosiers, J.-N.; Herbage, M. A.; Savoie, J.; Li, Z.; Fandrick, K. R.; Sader, C. A.; McKibben, B.; Gao, D. A.; Cui, J.; Gonnella, N. C.; Lee, H.; Wei, X.; Roschangar, F.; Lu, B. Z.; Senanayake, C. H. *Org. Lett.* **2015**, *17,* 5614.
(28) Zhurakovskyi, O.; Türkmen, Y. E.; Löffler, L. E.; Moorthie, V. A.; Chen, C. C.; Shaw, M. A.; Crimmin, M. R.; Ferrara, M.; Ahmad, M.; Ostovar, M.; Matlock, J. V.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2018**, *57,* 1346.
(29) Burtoloso, A. C. B.; Dias, R. M. P.; Leonarczyk, I. A. *Eur. J. Org. Chem.* **2013**, 5005.
(30) Lu, L.-Q.; Li, T.-R.; Wang, Q.; Xiao, W.-J. *Chem. Soc. Rev.* **2017**, *46,* 4135.
(31) Neuhaus, J. D.; Oost, R.; Merad, J.; Maulide, N. *Top. Curr. Chem.* **2018**, *376,* 15.
(32) Mondal, M.; Chen, S.; Kerrigan, N. J. *Molecules* **2018**, *23,* 738.
(33) Vizer, S. A.; Sycheva, E. S.; Al Quntar, A. A. A.; Kurmankulov, N. B.; Yerzhanov, K. B.; Dembitsky, V. M. *Chem. Rev.* **2015**, *115,* 1475.
(34) Koval, I. V. *Russ. Chem. Rev. (Engl. Transl.)* **1995**, *64*, 141.
(35) Bahlinger, A.; Fritz, S. P.; Wennemers, H. *Angew. Chem., Int. Ed.* **2014**, *53,* 8779.
(36) Dias, R. M. P.; Burtoloso, A. C. B. *Org. Lett.* **2016**, *18,* 3034.
(37) Senatore, R.; Ielo, L.; Urban, E.; Holzer, W.; Pace, V. *Eur. J. Org. Chem.* **2018**, 2466.
(38) Thangaraj, M.; Gaykar, R. N.; Roy, T.; Biju, A. T. *J. Org. Chem.* **2017**, *82,* 4470.
(39) Huang, X.; Patil, M.; Farès, C.; Thiel, W.; Maulide, N. *J. Am. Chem. Soc.* **2013**, *135,* 7312.
(40) McGarrigle, E. M.; Myers, E. L.; Illa, O.; Shaw, M. A.; Riches, S. L.; Aggarwal, V. K. *Chem. Rev.* **2007**, *107,* 5841.
(41) Wu, H.-Y.; Chang, C.-W.; Chein, R.-J. *J. Org. Chem.* **2013**, *78,* 5788.
(42) Huang, M.-T.; Wu, H.-Y.; Chein, R.-J. *Chem. Commun.* **2014**, *50,* 1101.
(43) Li, Q.-Z.; Zhang, X.; Zeng, R.; Dai, Q.-S.; Liu, Y.; Shen, X.-D.; Leng, H.-J.; Yang, K.-C.; Li, J.-L. *Org. Lett.* **2018**, *20,* 3700.
(44) He, Z.; Song, F.; Sun, H.; Huang, Y. *J. Am. Chem. Soc.* **2018**, *140,* 2693.
(45) Li, Z.; Jangra, H.; Chen, Q.; Mayer, P.; Ofial, A. R.; Zipse, H.; Mayr, H. *J. Am. Chem. Soc.* **2018**, *140,* 5500.
(46) Ledingham, E. T.; Merritt, C. J.; Sumby, C. J.; Taylor, M. K.; Greatrex, B. W. *Synthesis* **2017,** *49,* 2652.
(47) Chen, J.-R.; Dong, W.-R.; Candy, M.; Pan, F.-F.; Jörres, M.; Bolm, C. *J. Am. Chem. Soc.* **2012**, *134,* 6924.
(48) Wang, Q.; Qi, X.; Lu, L.-Q.; Li, T.-R.; Yuan, Z.-G.; Zhang, K.; Li, B.-J.; Lan, Y.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2016**, *55,* 2840.
(49) Wang, Z.; Yang, Y.; Gao, F.; Wang, Z.; Luo, Q.; Fang, L. *Org. Lett.* **2018**, *20,* 934.
(50) Shao, J.; Chen, W.; Zhao, M.; Shu, K.; Liu, H.; Tang, P. *Org. Lett.* **2018**, *20,* 3992.
(51) Xuan, J.; Cao, X.; Cheng, X. *Chem. Commun.* **2018**, *54,* 5154.
(52) Li, C.; Jiang, K.; Ouyang, Q.; Liu, T.-Y.; Chen, Y.-C. *Org. Lett.* **2016**, *18,* 2738.
(53) Niyomchon, S.; Oppedisano, A.; Aillard, P.; Maulide, N. *Nat. Commun.* **2017**, *8,* 1091.
(54) Neuhaus, J. D.; Angyal, P.; Oost, R.; Maulide, N. *J. Org. Chem.* **2018**, *83,* 2479.
(55) Jia, P.; Zhang, Q.; Jin, H.; Huang, Y. *Org. Lett.* **2017**, *19,* 412.
(56) Jia, P.; Huang, Y. *Adv. Synth. Catal.* **2018**, *360*, 3044.
(57) Wu, G.-L.; Wu, Q.-P. *Adv. Synth. Catal.* **2018**, *360,* 1949.
(58) Nair, D. K.; Kumar, T.; Namboothiri, I. N. N. *Synlett* **2016**, *27,* 2425.
(59) Satham, L.; Namboothiri, I. N. N. *J. Org. Chem.* **2018**, *83*, 9471.
(60) Zhang, X.-Z.; Deng, Y.-H.; Gan, K.-J.; Yan, X.; Yu, K.-Y.; Wang, F.-X.; Fan, C.-A. *Org. Lett.* **2017**, *19,* 1752.
(61) Oost, R.; Neuhaus, J. D.; Merad, J.; Maulide, N. Sulfur Ylides in Organic Synthesis and Transition Metal Catalysis. In *Modern Ylide Chemistry: Applications in Ligand Design, Organic and Catalytic Transformations*; Gessner, V. H., Ed.; Springer: Cham, Switzerland, 2018; pp 73–115.
(62) Xu, X.; Li, C.; Tao, Z.; Pan, Y. *Green Chem.* **2017**, *19,* 1245.

(63) Xu, X.; Li, C.; Xiong, M.; Tao, Z.; Pan, Y. *Chem. Commun.* **2017**, *53,* 6219.
(64) Tyagi, V.; Sreenilayam, G.; Bajaj, P.; Tinoco, A.; Fasan, R. *Angew. Chem., Int. Ed.* **2016**, *55,* 13562.
(65) Ahire, M. M.; Khan, R.; Mhaske, S. B. *Org. Lett.* **2017**, *19,* 2134.
(66) Ahire, M. M.; Thoke, M. B.; Mhaske, S. B. *Org. Lett.* **2018**, *20,* 848.
(67) Tan, J.; Zheng, T.; Xu, K.; Liu, C. *Org. Biomol. Chem.* **2017**, *15,* 4946.

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Trimethylsilyldiazomethane ($TMSCHN_2$) in Carbon–Carbon and Carbon–Heteroatom Bond-Forming Reactions


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Keywords. trimethylsilyldiazomethane; TMSD; $TMSCHN_2$; homologation; insertion; carbene; cycloaddition.

Abstract. Trimethylsilyldiazomethane, a safe and stable substitute for diazomethane, has emerged as an indispensable modern synthetic tool that has found wide applications in a variety of synthetic transformations. This selective review provides an overview of the significant developments in chemistry that have occurred mainly over the last decade and a half, and focuses on application examples that demonstrate the novelty, value, and power of this reagent.

Outline

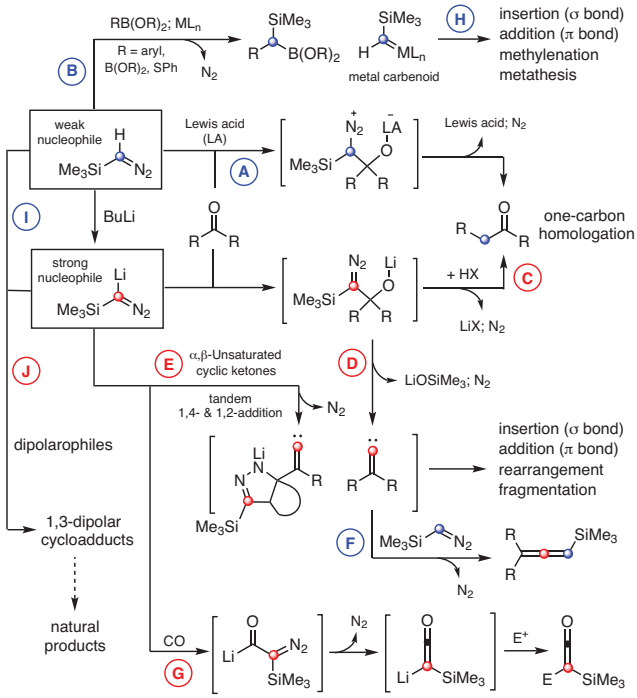
1. Introduction

Trimethylsilyldiazomethane ($TMSCHN_2$ or TMSD)[1] has been used most commonly in Lewis acid promoted one-carbon homologation reactions with various acyclic and cyclic carbonyl compounds (**Scheme 1**, Path **A**).[2] Similarly, the one-carbon insertion into C–B, B–B, and B–S bonds serves as an effective platform for installing polysubstituted sp^3-hybridized carbon centers bound to different p-block elements (Scheme 1, Path **B**). As opposed to neutral $TMSCHN_2$, the corresponding lithiated reagent, $TMSC(Li)N_2$, is a much stronger nucleophile; it thus reacts readily with a broader range of carbonyl compounds to generate, not only one-carbon insertion products (Scheme 1, Path **C**), but also alkylidene carbene intermediates (Scheme 1, Path **D**). These highly reactive unsaturated carbenes can participate in insertion reactions with N–H, O–H, O–Si, C–Si, and N–Li bonds to form hetero- or carbocycles, or in addition reactions with alkenes to form alkylidenecyclopropanes. With appropriate structural elements, alkylidene carbenes can also undergo rearrangement or fragmentation to form either terminal or internal alkynes. α,β-Unsaturated cyclic ketones react with 2 equivalents of $TMSC(Li)N_2$ in tandem 1,4- and 1,2-addition to generate an adduct (Scheme 1, Path **E**), that can subsequently follow the reaction course in Path **D**. Moreover, the insertion of an alkylidene carbene with $TMSCHN_2$ generates a silylallene (Scheme 1, Path **F**), and the insertion of $TMSC(Li)N_2$ with CO results in the formation of ketenes and their derivatives (Scheme 1, Path **G**).

Transition-metal complexes (ML_n) of Ru, Rh, Ni, and Pd react with $TMSCHN_2$ to form the corresponding carbenoids (Scheme 1, Path **H**), which participate in cycloaddition, C–H insertion, and metathesis processes. Moreover, $TMSCHN_2$ serves as a

1,3-dipole that undergoes cycloadditions with electron-deficient alkenes, alkynes, and carbon–heteroatom multiple bonds, forming structurally diverse heterocycles (Scheme 1, Paths **I** and **J**). $TMSC(Li)N_2$ is an anionically activated 1,3-dipole that displays higher reactivity toward electron-deficient dipolarophiles thus expanding the scope of the $TMSCHN_2$-based dipolar cycloaddition chemistry. The merits of $TMSCHN_2$ and $TMSC(Li)N_2$ in various C–C and C–heteroatom bond-forming reactions have been exploited for the synthesis of various natural products, including *ent*-kaurane diterpenoid steviol, scillasciloside E-1, amathaspiramides, plantensimycin, and delnudine.

Because of its higher stability and lower volatility, $TMSCHN_2$ is considered a safer alternative to diazomethane owing to the potential explosivity, flammability, and pulmonary toxicity of the latter. However, it is important to keep in mind that great caution needs to be exercised at all levels during its handling because of its potentially fatal toxicity following inhalation.[3]



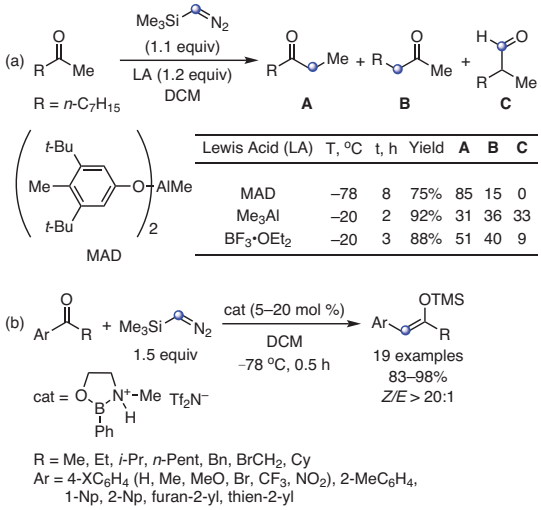
Scheme 1. Outline of Common Transformations of $TMSCHN_2$ and $TMSC(Li)N_2$.

2. Homologation Reactions

2.1. Insertion into C(O)–C and C(O)–H Bonds

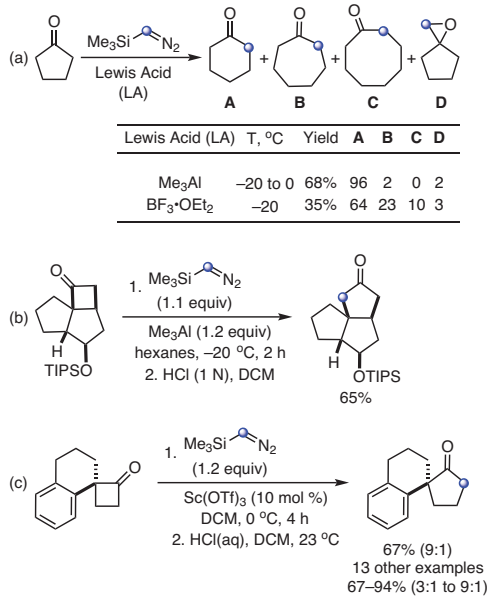
One-carbon homologations have been achieved via insertion of $TMSCHN_2$ into C(O)–C and C(O)–H bonds aided by Lewis acids. For the homologation of acyclic ketones, bulky Lewis acids such as methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide (MAD) provide improved selectivity for the homologated product (**Scheme 2**, Part (a)).[4,5] A new, highly stereoselective synthesis of monohomologated (*Z*)-silyl enol ethers has been achieved through the oxazaborolidinium ion catalyzed reaction of TMSD with alkyl aryl ketones (Scheme 2, Part (b)).[6]

The homologation of cyclopentanone is dependent on Lewis acid and reaction conditions (**Scheme 3**, Part (a)),[4] whereas the homologation of cyclobutanones consistently results in monohomologation. The regioselectivity of group migration depends on the overall environment of the cyclobutanone. For



Lewis Acid (LA)	T, °C	t, h	Yield	A	B	C
MAD	–78	8	75%	85	15	0
Me_3Al	–20	2	92%	31	36	33
$BF_3{\cdot}OEt_2$	–20	3	88%	51	40	9

Scheme 2. Single Homologation through Trimethylsilyldiazomethane Insertion into Acyclic Ketones. *(Ref. 4–6)*



Lewis Acid (LA)	T, °C	Yield	A	B	C	D
Me_3Al	–20 to 0	68%	96	2	0	2
$BF_3{\cdot}OEt_2$	–20	35%	64	23	10	3

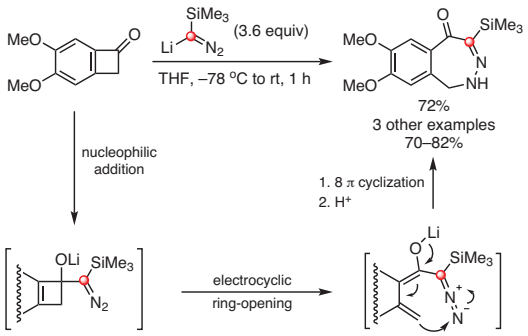
Scheme 3. Homologation of Cyclopentanone and Cyclobutanones with Trimethylsilyldiazomethane. *(Ref. 4,7a,8)*

example, in the formation of a triquinane skeleton, the migration of a more substituted carbon occurs selectively when catalyzed by $AlMe_3$ (Scheme 3, Part (b)),[7a] whereas the homologation of cyclobutanone derivatives with spiro-α,α-dibenzylic substituents provides cyclopentanone derivatives after migration of a less substituted carbon[7b] in the presence of $Sc(OTf)_3$ as catalyst (Scheme 3, Part (c)).[8]

In contrast to cyclobutanone derivatives, the ring-expansion of benzocyclobutenone takes a completely different course. This is a consequence of an extra π system, which causes the alkoxycyclobutene moiety to undergo electrocyclic ring-opening followed by 7-endo cyclization between an extended enolate and a diazo functionality, leading to 2,3-benzodiazepin-5-one (**Scheme 4**).[9]

Unlike the Lewis acid catalyzed ketone homologation with $TMSCHN_2$, which often involves insertion of more than one carbon atom, the corresponding homologation with $TMSC(Li)N_2$ generates an anionic intermediate, which, when protonated, ensures insertion of a single carbon (**Scheme 5**).[10] For example, protonation of such an intermediate with MeOH at low temperature followed by silica gel treatment provides the highest yield of ring-expanded five- to eight-membered-ring product with a minimal amount of epoxide byproduct. Unless electronically biased, unsymmetrical cyclic ketones display preferential migration of a less-substituted carbon center.

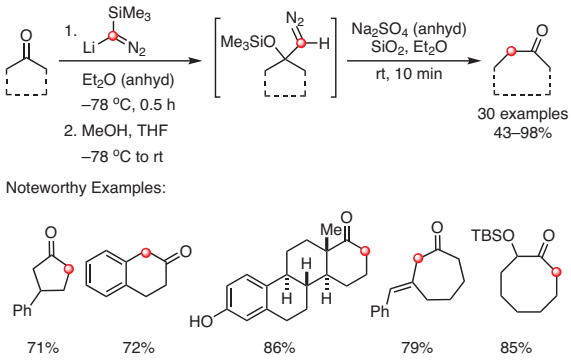
The product distribution of the one-carbon homologation of aldehydes by insertion of $TMSCHN_2$ into the C(O)–H bond is dependent on the nature of the catalyst. While the one-carbon homologation with $InCl_3$ as a Lewis acid catalyst generates the corresponding homologated α-trimethylsilyl ketones, that with $Sc(OTf)_3$ provides mainly silyl enol ethers, and a mixture of these products was obtained with other Lewis acids such as $BF_3•OEt_2$, $ZnCl_2$, and $MgBr_2$ (**Scheme 6**, Part (a)).[11] In contrast, the one-carbon homologation of cyclic β-alkoxyenals with $TMSCHN_2$ catalyzed by TMSOTf results in ring-expansion that is initiated by Mukayama-type 1,4-addition of $TMSCHN_2$ followed by migration of an sp^2-hybridized carbon and desilylation (Scheme 6, Part (b)).[12]



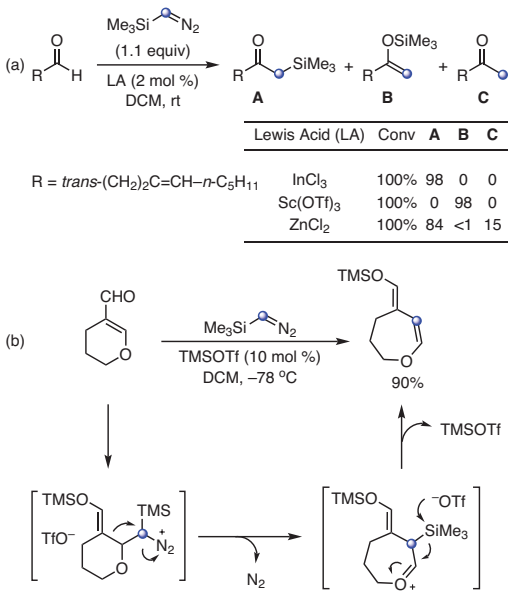
Scheme 4. $TMSC(Li)N_2$ Enabled Synthesis of 2,3-Benzodiazepines from Benzocyclobutenes. *(Ref. 9)*

2.2. Insertion into C–B, B–B, and B–S Bonds

$TMSCHN_2$ readily reacts with alkyl- and arylboronic acids and boronates to effect a one-carbon homologation via insertion into the C–B bond. This insertion reaction is the consequence of an initial interaction between the empty p orbital on the central boron atom and the weakly nucleophilic carbon center of $TMSCHN_2$ to generate a zwitterionic intermediate. For instance, an alkyl catechol boronate reacts with $TMSCHN_2$ to generate a one-carbon homologated alkyl *gem*-silyl boronate (**Scheme 7**, Part (a)).[13a] An aryl *gem*-silyl boronate was similarly obtained from the reaction of $TMSCHN_2$ with boroxines.[13b] Based on the one-carbon insertion into a C–B bond by $TMSCHN_2$, a robust and scalable synthesis of homoallylic alcohols was achieved



Scheme 5. New, Selective One-Carbon Homologation of Cyclic Ketones Employing a Nucleophile Activation Strategy. *(Ref. 10)*



Scheme 6. One-Carbon Homologation of Aldehydes with Trimethylsilyldiazomethane. *(Ref. 11,12)*

(Scheme 7, Part (b)).[14] Insertion of $TMSCHN_2$ into a B–B bond such as in B_2Pin_2 afforded the one-carbon-homologation product $(Bpin)_2HC(SiMe_3)$, which readily reacted with cyclohexanone upon treatment with lithium tetramethylpiperidide to provide a *gem*-silyl boronate-containing tetrasubstituted alkene (Scheme 7, Part (c)).[15] Similarly, insertion of $TMSCHN_2$ into the B–S bond of PhS–Bpin followed by deborylative alkylation with NaO*t*-Bu and alkyl halide provided the corresponding alkylated α-silyl sulfides (Scheme 7, Part (d)).[16]

2.3. Insertion into sp-Hybridized Carbons

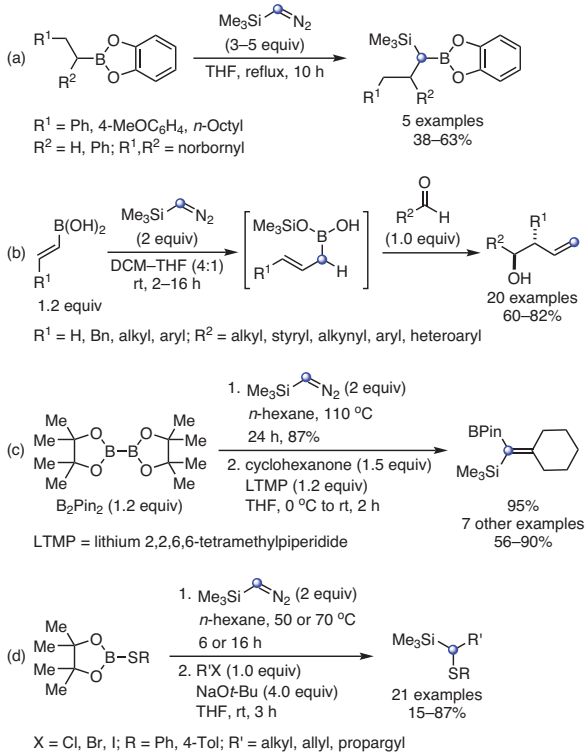
The reaction between CO and $TMSC(Li)N_2$ generates, after extrusion of N_2, lithium silylethynolate ($LiOC{\equiv}CSiMe_3$) which readily participates in the ketenylation reaction of epoxides and aziridines. The aluminum reagent generated from lithium silylethynolate and Me_3Al reacts efficiently with epoxides to provide alkoxy ketenes, which spontaneously cyclize to afford 2-trimethylsilyl-γ-lactones (**Scheme 8**, Part (a)).[17a] Similarly, the reaction of lithium silylethynolate with aziridines generates α-silyllactam enolates, which upon addition of excess aldehyde undergo a Peterson-type olefination to deliver α-alkylidene lactams in good yields (Scheme 8, Part (b)).[17b] When the reaction of $TMSC(Li)N_2$ with ^{11}CO to form ^{11}C-labeled silylethynolate was followed by reaction with 3-diazopyrazole, it provided ^{11}C-labeled pyrazolotriazine-1*H*-4-one (Scheme 8, Part (c)).[18] This ^{11}C-labeled bioactive compound could be used for positron emission tomography (PET).

In analogy to the formation of ketene from the combination of CO and $TMSC(Li)N_2$, allenes can be generated from the reaction of alkylidene carbenes and $TMSCHN_2$ (Scheme 8, Part (d)).[19] The empty p orbital of alkylidene carbenes readily reacts with the weakly nucleophilic carbon center of $TMSCHN_2$ to generate a zwitterionic intermediate that can undergo $E1_{CB}$-type elimination of N_2, generating silyl-substituted allenes.

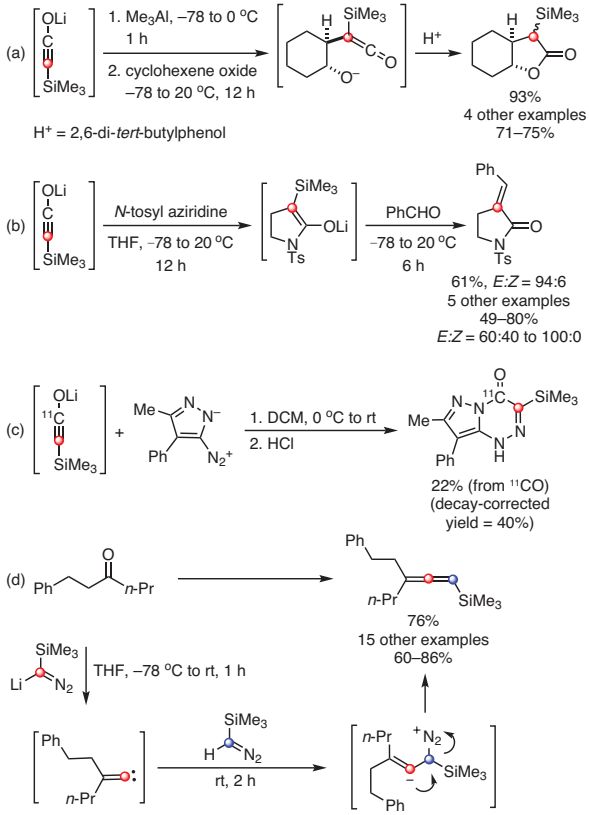
3. Reactions Involving an Alkylidene Carbene

3.1. Insertion into C–H and C–Si Bonds

An alkylidene carbene can be generated from the reaction of a ketone with $TMSC(Li)N_2$, and its highly electrophilic nature promotes an effective C–H insertion reaction to generate typically cyclopentene products. The C–H insertion into a bridgehead C–H bond constitutes a particularly versatile strategy for the construction of bridged carbocycles. In the synthesis of the tricyclic core of platensimycin, alkylidene-based C–H insertion was employed as the key step, where high selectivity for the bridgehead C–H_a bond was observed (**Scheme 9**, Part (a)).[20]



Scheme 7. One-Carbon Insertions into C–B, B–B, and B–S Bonds. *(Ref. 13–16)*



Scheme 8. Trimethylsilyldiazomethane-Enabled Ketenylation and Allenylation Reactions. *(Ref. 17–19)*

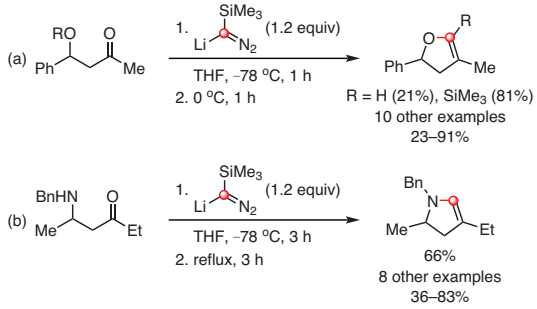
This selectivity is considered to be a consequence of the slightly deactivated nature of the C–H_b bond as compared to the C–H_a because of the high electronegativity of the geminal oxygen atom. The alkylidene-carbene-based insertion into bridgehead C–H bonds was also employed in the synthesis of the ABC ring system of delnudine (**Scheme 9**, Part (b)).[21]

The high reactivity of an alkylidene carbene can also promote the insertion reaction into C–Si bonds to generate silyl-substituted cyclopropenes. Thus, the preparation of α-silyl ketones from the $InCl_3$-catalyzed reaction of $TMSCHN_2$ and aldehydes followed by treatment of the α-silyl ketones with $TMSC(Li)N_2$ leads to the formation of alkylidene carbene intermediates, which undergo an insertion reaction preferentially with the proximal C–Si bond over the distal C–H bond or π bond to generate the silyl-substituted cyclopropenes (**Scheme 9**, Part (c)).[22]

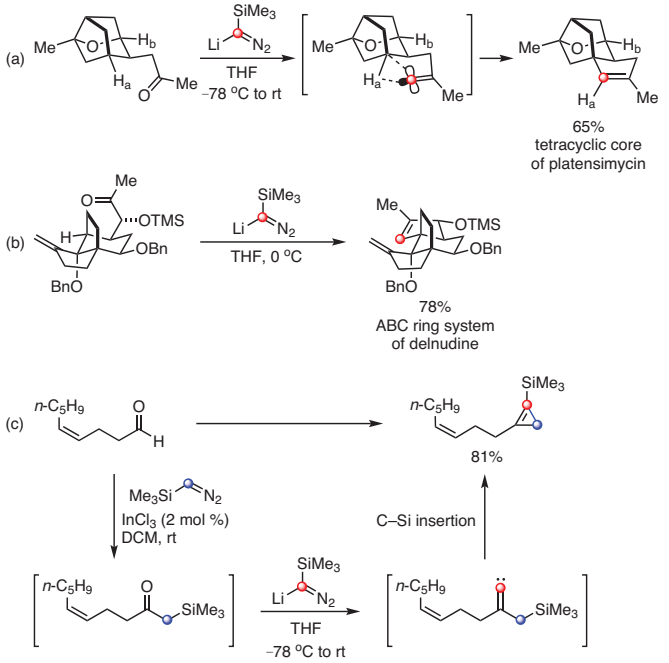
3.2. Insertion into Other σ Bonds and Fragmentation

Alkylidene carbenes generated from the reaction between ketones and $TMSC(Li)N_2$ can readily form 2,3-dihydrofuran derivatives after insertion into O–H and O–Si bonds that are positioned at the β carbon of the ketone (**Scheme 10**, Part (a)).[23] The insertion into O–Si bonds is more efficient than that into O–H bonds, and in some cases a group migration process competes with the insertion into alkynes. Similarly, alkylidene carbenes generated from β-amino ketones insert into N–H bonds to form dihydropyrroles (**Scheme 10**, Part (b)). Reactions of $TMSC(Li)N_2$ with *ortho*-acyl-*N*-substituted anilines generated either 3-substituted indoles or *ortho*-alkynyl-*N*-substituted anilines depending on the nature of the nitrogen substituent.[24,25] It was observed that *N*-Ts and *N*-Boc favored N–H bond insertion by the alkylidene carbene to form indole derivatives, whereas with the *N*-pivaloyl substituent the Colvin rearrangement outcompeted the N–H bond insertion to form the alkyne as the major product.

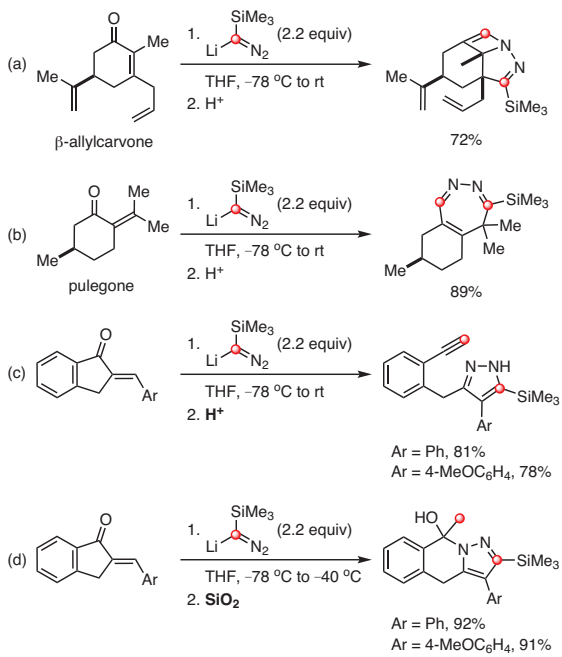
The reaction between cyclic α,β-unsaturated ketones and $TMSC(Li)N_2$ selectively engages in 1,4-addition followed by cyclization to form fused pyrazolines after protonation. Thus, β-allylcarvone underwent sequential 1,4- and 1,2-additions with 2 equivalents of $TMSC(Li)N_2$ to form a lithium pyrazolinate-fused cyclohexylidene carbene. The carbene then provided a tricyclic product via an N–Li bond insertion followed by protonation (**Scheme 11**, Part (a)).[26] A related alkylidene carbene derived



Scheme 10. Alkylidene Carbene Insertion into O–H, O–Si, and N–H Bonds. *(Ref. 23)*



Scheme 9. Applications of Alkylidene Carbene Insertions into C–H and C–Si Bonds in the Synthesis of Alkaloids and Antibacterial Agents. *(Ref. 20–22)*



Scheme 11. Alkylidene Carbene Insertion into N–Li and Grob-type C–C Bond Fragmentation. *(Ref. 26)*

from pulegone underwent an N–Li bond insertion followed by a cycloreversion to form a bicyclic 4*H*-1,2-diazepine derivative (Scheme 11, Part (b)).[26] On the other hand, a spirobicyclic lithium pyrazolinate-fused cyclopentylidene carbene derived from benzylidene indanone selectively engaged in a C–C fragmentation process to predominantly generate pyrazole derivatives containing a terminal alkyne moiety (Scheme 11, Part (c)).[26] Interception of the 1,4/1,2-bis adduct of $TMSC(Li)N_2$ before elimination of a lithium silanolate by quenching with SiO_2 at low temperature induced a different course of C–C bond fragmentation to generate as the major product benzo-fused bicyclic pyrazoles containing a hemiaminal moiety (Scheme 11, Part (d)).

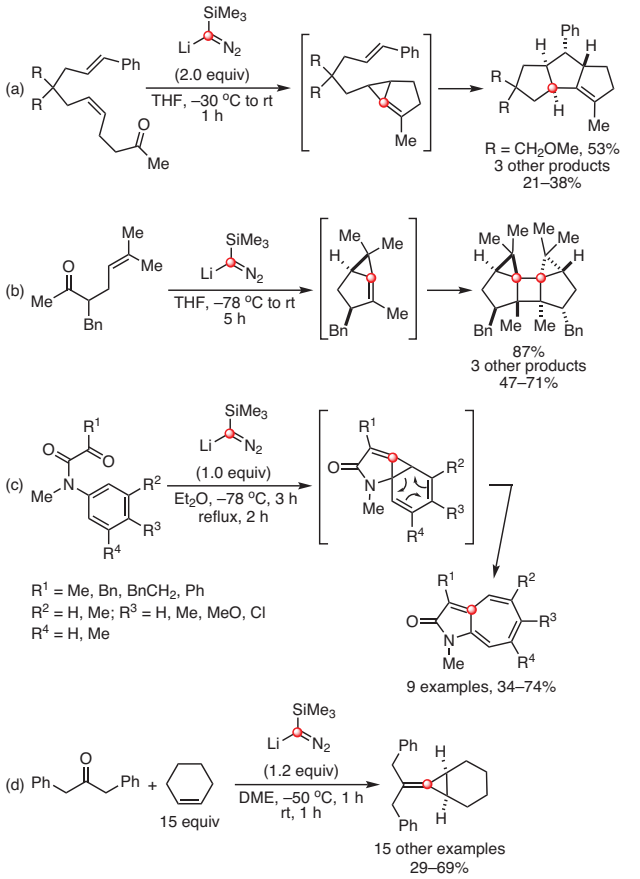
3.3. Addition to Alkenes and Formation of Alkynes

The alkylidene carbenes generated from the reaction between $TMSC(Li)N_2$ and ketones can undergo an intramolecular [2 + 1] cycloaddition to form a highly strained bicyclo[3.1.0]hex-1-ene intermediate. C–C bond fragmentation of the strained three-membered ring of this intermediate generates a trimethylenemethane diyl, which undergoes intramolecular [3 + 2] cycloaddition to provide a linearly fused triquinane derivative (**Scheme 12**, Part (a)).[27] In contrast, structurally simpler bicyclo[3.1.0]hex-1-enes that do not contain a tethered alkene participate in a dimerization reaction via a [2 + 2] cycloaddition (Scheme 12, Part (b)).[28] The alkylidene carbene generated from an α-ketoanilide readily undergoes a [2 + 1] cycloaddition with a proximal aromatic π system to form a norcaradiene moiety, which rearranges to form a cycloheptatriene product (Scheme 12, Part (c)).[29] Moreover, alkylidene carbenes can undergo intermolecular [2 + 1] cycloaddition with external alkenes to form cyclopropylidene derivatives (Scheme 12, Part (d)).[30]

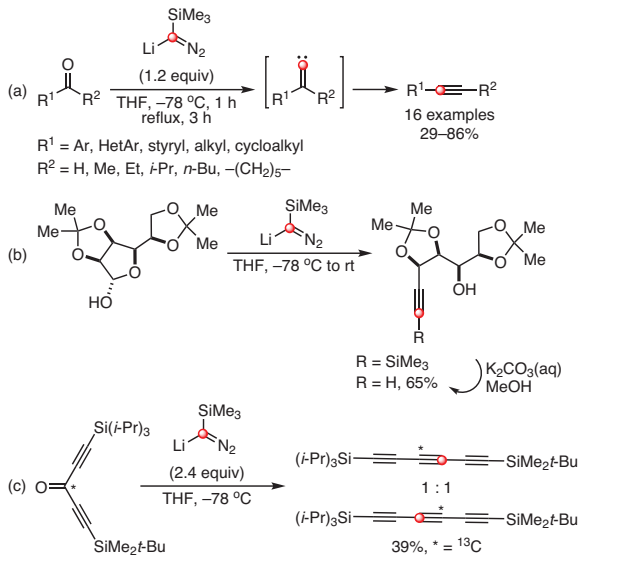
The reaction of $TMSC(Li)N_2$ with aldehydes and alkyl aryl/alkenyl/alkynyl ketones to generate alkynes constitutes a robust and efficient one-step method for the preparation of terminal alkynes from aldehydes and internal alkynes from ketones.[31] For example, treating alkyl aryl ketones with $TMSC(Li)N_2$ provides the corresponding internal alkynes (**Scheme 13**, Part (a)).[32] This transformation has been widely applied in complex-molecule synthesis such as in the synthesis of kedarcidin[33a] and of the hikizimycin core starting from sugar-based hemiacetals (Scheme 13, Part (b)).[33b] It was shown that group migration generally occurs in the order of H > sp^2-C ~ sp-C > sp^3-C, but groups of similar characteristics don't display strong selectivity in the migration. For example, a terminally differentiated, ^{13}C-labeled bisalkynyl ketone provided a mixture of two isotopomers in a 1:1 ratio upon treatment with $TMSC(Li)N_2$ (Scheme 13, Part (c)).[34]

4. Reactions Involving Metal-Alkylidene Formation

$TMSCHN_2$ readily reacts with various transition-metal complexes of Ni, Ru, Rh, and Cu to form the corresponding metal carbenoids that can engage in a variety of transformations.



Scheme 12. Intra- and Intermolecular Addition of Alkylidene Carbenes to π bonds. *(Ref. 27–30)*



Scheme 13. Alkyne Synthesis through the Colvin Rearrangement Enabled by Reaction of $TMSC(Li)N_2$ with Ketones. *(Ref. 32–34)*

4.1. With Ni and Pd Complexes

1,3-Dien-6-yne readily participated in a highly efficient [4 + 2 + 1] cycloaddition with $TMSCHN_2$ in the presence of $Ni(cod)_2$ to form a bicyclo[5.3.0]decane system in good yield and excellent diastereoselectivity (**Scheme 14**, Part (a)).[35] It was proposed that the reaction proceeds through formation of a Ni-carbenoid species in different manifolds of pathways, including a metathesis cascade initiated by an initially formed Ni-carbenoid, or an initial oxidative cyclization of the diene-yne by a Ni(0) complex followed by $TMSCHN_2$ insertion to form a Ni-carbenoid species.

Similarly, Pd(0) complexes promote the reactions of $TMSCHN_2$ with various reagent classes such as benzyl bromides to generate styrenes[36a] and vinylic halides (Scheme 14, Part (b)).[36b] With vinylic halides, the initial oxidative addition forms a vinyl-Pd(II) complex that induces insertion of $TMSCHN_2$ to form a vinyl-Pd(II)–carbenoid complex. Subsequently, vinyl group migration generates a π-allyl-Pd(II) complex, which reacts with a nucleophile such as secondary amine or the anion of malononitrile or malonate to generate the double-bond-transposed vinyl silanes.[36c] The reaction of 2-bromostyrene derivatives with $TMSCHN_2$ catalyzed by Pd(0) complexes proceeds via a formal [4 + 1] annulation to generate polycyclic aromatic compounds (Scheme 14, Part (c)).[37]

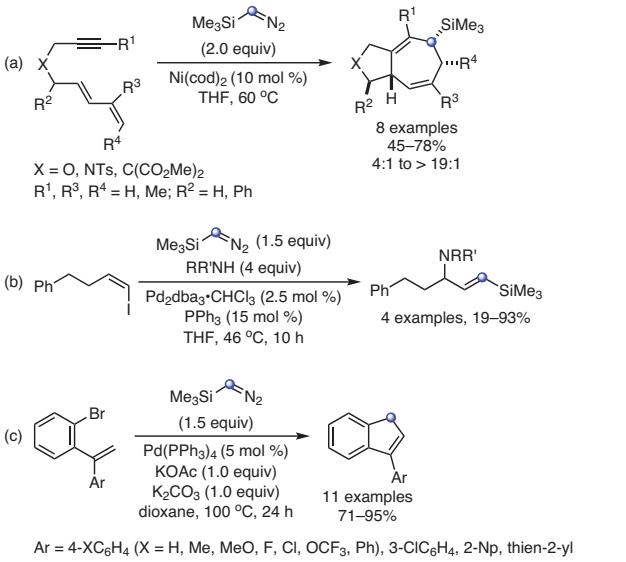
4.2. With Ru, Rh, and Cu Complexes

Ruthenium complexes such as [Cp*Ru(cod)Cl] readily react with $TMSCHN_2$ to generate Ru-alkylidenes, which undergo a metathesis reaction with alkynes to generate 1,3-dienes with good stereoselectivity (**Scheme 15**, Part (a)).[38] In contrast, under almost identical conditions, TsN-tethered 1,6-enynes are converted into bicyclo[3.1.0]hexanes, where the cyclopropane moiety probably arises from reductive elimination from the metallacyclobutane intermediate (Scheme 15, Part (b)).[39] The putative vinyl Ru-carbenoids display yet another mode of reactivity involving C–H insertion to generate cyclopentane derivatives (Scheme 15, Part (c)).[40] $[RhCl(PPh_3)_3]$ brings about efficient methylenation of aldehydes and ketones in the presence of $TMSCHN_2$, 2-propanol, and triphenylphosphine.[41] This alkenylation protocol was employed by Baran and co-workers for the conversion of an α-hydroxyketone intermediate into the corresponding allylic alcohol during the synthesis of the kaurane family natural product steviol (Scheme 15, Part (d)).[42] In the catalytic methylenation of aldehydes and ketones, copper complexes were substituted for the rhodium complex, and (IPr)CuCl was identified as one of the most effective catalysts in most cases, including the conversion of perillaldehyde into the corresponding triene (Scheme 15, Part (e)).[43]

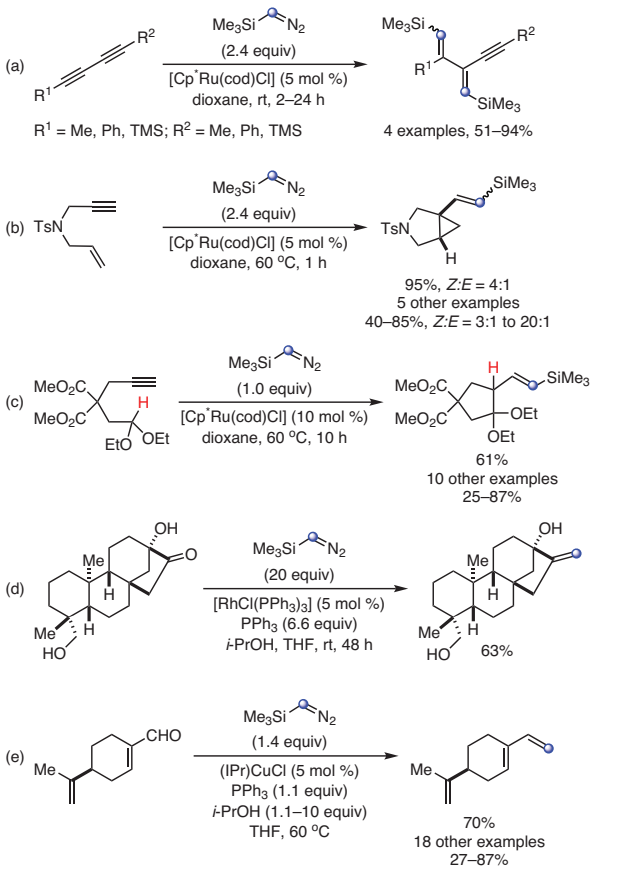
5. Addition Reactions

5.1. With Alkenes

The relatively high reactivity of the diazo group toward electron-deficient alkenes has been exploited in the auxiliary-based, Lewis acid catalyzed asymmetric [3 + 2] dipolar



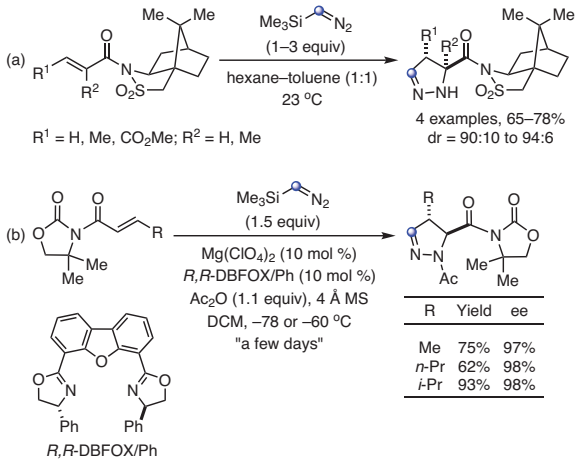
Scheme 14. Reactions Involving Ni and Pd Carbenoids. *(Ref. 35–37)*



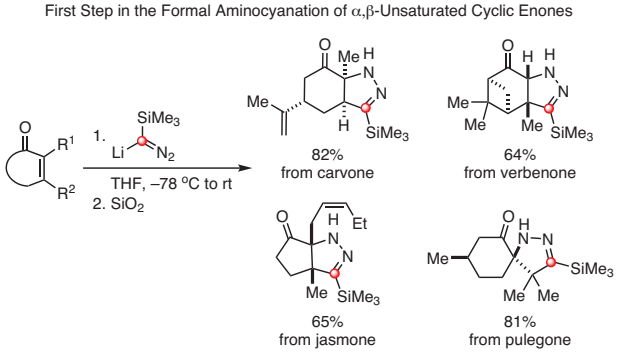
Scheme 15. Noteworthy Applications of Ru, Rh, and Cu Carbenoids in Synthesis. *(Ref. 38–40,42,43)*

cycloaddition. The reactions of $TMSCHN_2$ with camphor sultam bound α,β-unsaturated carbonyl compounds proceeded at room temperature to generate Δ^2-pyrazolines after spontaneous loss of the trimethylsilyl group. While relatively high diastereoselectivity was observed in all cases, the α-methyl substituted substrate resulted in the highest selectivity (94:6) (**Scheme 16**, Part (a)).[44a] This dipolar cycloaddition approach to establishing a chiral C–N bond was taken advantage of in the synthesis of *ent*-stellettamide A.[44b] A chiral Lewis acid catalyzed approach was also developed for this cycloaddition, where the reaction between achiral oxazolidinone-bound α,β-unsaturated carbonyl compounds and $TMSCHN_2$ was effectively catalyzed by a chiral Mg–DBFOX complex (Scheme 16, Part (b)).[45] An unusual observation in this reaction was that the more sterically hindered substituents at the β position of the substrates provided significantly higher yields.

The reaction of $TMSC(Li)N_2$ with α,β-unsaturated cyclic ketones proceeds exclusively with 1,4-addition providing



Scheme 16. Asymmetric [3 + 2] Cycloadditions of $TMSCHN_2$ with Electron-Deficient Alkenes. *(Ref. 44,45)*

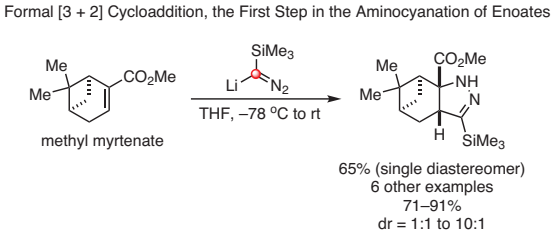


eq 1 *(Ref. 46)*

Δ^2-pyrazolines, whereas the corresponding acyclic α,β-unsaturated ketones engage in 1,2-addition to generate 1,3-enynes. The 1,4-addition appears to be a consequence of the steric interaction between the trimethylsilyl group and the cyclic framework of cyclic ketones. The reaction of $TMSC(Li)N_2$ with carvone, an α-methyl-substituted enone, affords a fused bicyclic pyrazoline in 82% yield, whereas verbenone, another trisubstituted enone containing a β-methyl substituent, leads to the corresponding pyrazoline in 64% yield. Even tetrasubstituted enones such as jasmone and pulegone provide fused and spirobicyclic pyrazolines containing vicinal quaternary carbons in 65 and 81% yields, respectively (**eq 1**).[46]

The general reactivity of α,β-unsaturated esters toward $TMSC(Li)N_2$ is similar to that of α,β-unsaturated cyclic ketones. Thus, the reaction of methyl myrtenate with $TMSC(Li)N_2$ produced the corresponding Δ^2-pyrazoline in 65% yield as a single diastereomer (**eq 2**).[47] 1,2-Addition is a more favored mode of reaction for β,β-disubstituted esters when typical methyl and ethyl esters are employed; however, β,β-disubstituted *tert*-butyl esters cleanly produce Δ^2-pyrazolines. The (*E*)-cinnamate-derived ester produced the corresponding pyrazoline as a 10:1 mixture of diastereomers, while methyl cyclopentenecarboxylate afforded a bicyclic pyrazoline in 71% yield as a single diastereomer.

On the basis of the efficient formal cycloaddition (1,4-addition–cyclization) of α,β-unsaturated esters with $TMSC(Li)N_2$, total syntheses of natural products containing an α-amino quaternary carbon such as in amathaspiramides and massadine were pursued.[47,48] For the synthesis of amathaspiramide C, a functionalized cinnamate derivative was treated with $TMSC(Li)N_2$ to directly generate a bicyclic pyrazoline. After the proton-mediated N–N bond cleavage, the cyanoester was converted into spirobicyclic Fukuyama's advanced intermediate via a three-step protocol. This route constitutes a formal synthesis of all members of the amathaspiramide family of natural products, and includes a total synthesis of amathaspiramide C.[47] Similarly, the reaction of substituted cyclopentene carboxylate with $TMSC(Li)N_2$ generated a fused bicyclic pyrazoline. Cleavage of the N–N bond in the pyrazoline led to an advanced intermediate containing all suitably functionalized carbons with the correct stereochemistry for a total synthesis of massadine, a structurally



eq 2 *(Ref. 47)*

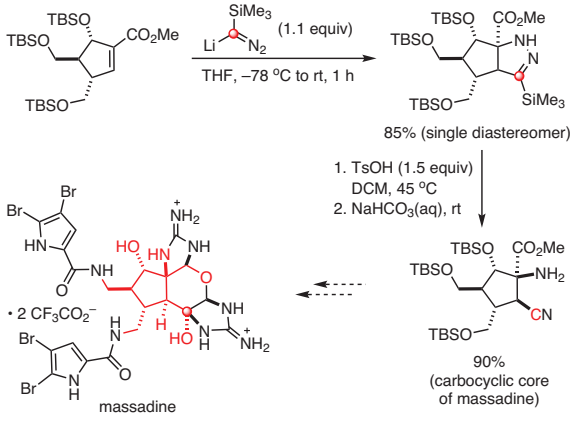
complex alkaloid which is isolated from a marine sponge and which acts as an inhibitor of geranylgeranyltransferase type I (GGTase I) (**Scheme 17**).[48]

5.2. With Alkynes

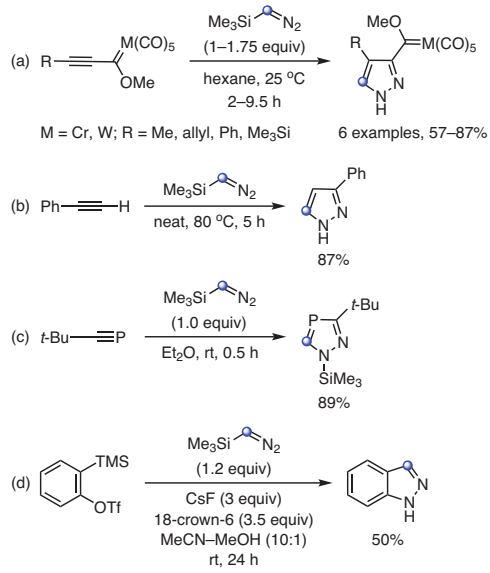
Alkynes containing a classical Fisher carbene moiety can undergo a regioselective [3 + 2] cycloaddition with $TMSCHN_2$ to provide pyrazoles, which can be oxidized to the corresponding methyl esters with cerric ammonium nitrate (CAN) (**Scheme 18**, Part (a)).[49] Electronically unactivated alkynes such as phenylacetylene still can participate in a [3 + 2] cycloaddition with $TMSCHN_2$ in the absence of solvents at relatively elevated temperatures (Scheme 18, Part (b)).[50] On the other hand, polarized heteroalkynes containing a carbon–phosphorus triple bond react with $TMSCHN_2$ at ambient temperature to form a phosphorus-containing heterocycle (Scheme 18, Part (c)).[51] Similarly, strained alkynes such as benzyne in situ generated from the Kobayashi precursor, can also readily react with $TMSCHN_2$ at room temperature to generate 1*H*-indazoles in high yields (Scheme 18, Part (d)).[52]

5.3. With sp-Carbon-Containing Multiple Bonds

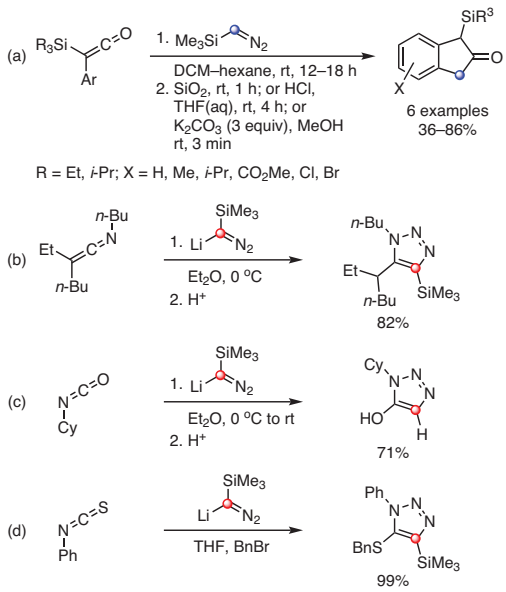
The reactivity of compounds containing an sp-hybridized carbon such as ketenes, ketenimines, isocyanates, and thioisocyanates toward nucleophiles depends mainly on the polarity of the central sp-carbon–heteroatom bond. Trialkylsilyl alkenyl ketenes are electrophilic enough to react with $TMSCHN_2$ to form zwitterionic intermediates, which undergo a Nazarov-type cyclization involving 2-oxypentadienyl cation, leading to cyclopentenones.[53] The double bond in an aromatic system also undergoes a similar annulation to generate 2-indanone derivatives from which the trimethylsilyl group can be removed by treatment with SiO_2 or dilute HCl (**Scheme 19**, Part (a)).[53] Ketenimines are less electrophilic than ketenes and require the stronger nucleophile $TMSC(Li)N_2$ for the initial bond-forming event. After forming a cyclic adduct, a series of double-bond isomerizations leads to 1,2,3-triazole products (Scheme 19, Part (b)).[54] Similarly, the reaction of isocyanate and $TMSC(Li)N_2$ generates 4-hydroxy-1,2,3-triazole after desilylation, which is the consequence of a keto-enol tautomerization (Scheme 19, Part (c)).[55] The reaction of phenyl isothiocyanate with $TMSC(Li)N_2$ affords two completely different products depending on the reaction conditions. In THF,



Scheme 17. Application of the Stereoselective Formal [3 + 2] Cycloaddition of α,β-Unsaturated Esters with $TMSC(Li)N_2$ to the Formal Total Synthesis of Massadine, an inhibitor of Geranylgeranyltransferase Type I (GGTase I). *(Ref. 48)*



Scheme 18. Cycloaddition Reactions of Trimethylsilyldiazomethane with Alkynes. *(Ref. 49–52)*



Scheme 19. Reactions with sp-Carbon-Containing Multiple Bonds. *(Ref. 53–56)*

the formation of lithio-1,2,3-triazole-5-thiolates is preferred, which can be alkylated in situ with alkyl halides to generate the final product (Scheme 19, Part (d)).[56] In contrast, in Et_2O, 2-amino-1,3,4-thiadazoles are generated in good yields. The formation of these two different classes of products is the consequence of the involvement of either the C=N bond or C=S bond of the isothiocyanate in the cycloaddition, but it is unclear whether these different kinds of products evolve from a common intermediate or two independent intermediates.

6. References

(1) (a) Hodnett, N. S. *Synlett* **2003**, 2095. (b) Shioiri, T.; Aoyama, T. Trimethylsilyldiazomethane. In *Encyclopedia of Reagents for Organic Synthesis*; Wiley, 2006; pp 1–9; https://doi.org/10.1002/047084289X.rt298.pub2 (accessed September 10, 2018).
(2) Candeias, N. R.; Paterna, R.; Gois, P. M. P. *Chem. Rev.* **2016**, *116*, 2937.
(3) Bray, P. A.; Sokas, R. K. *J. Occup. Environ. Med.* **2015**, 57, e15.
(4) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *J. Org. Chem.* **1994**, *59*, 4725.
(5) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synthesis* **1994**, *59*, 1283.
(6) Kang, B. C.; Shim, S. Y.; Ryu, D. H. *Org. Lett.* **2014**, *16*, 2077.
(7) (a) Youn, J.-H.; Lee, J.; Cha, J. K. *Org. Lett.* **2001**, *3*, 2935. (b) Maulide, N.; Markó, I. E. *Org. Lett.* **2007**, *9*, 3757.
(8) Dabrowski, J. A.; Moebius, D. C.; Wommack, A. J.; Kornahrens, A. F.; Kingsbury, J. S. *Org. Lett.* **2010**, *12*, 3598.
(9) Matsuya, Y.; Ohsawa, N.; Nemoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 13072.
(10) Liu, H.; Sun, C.; Lee, N.-K.; Henry, R. F.; Lee, D. *Chem.—Eur. J.* **2012**, *18*, 11889.
(11) Sun, C.; Li, J.; Demerzhan, S.; Lee, D. *ARKIVOK* **2011 (iv)**, 17.
(12) Lemus, C.; Poleschak, M.; Gailly, S.; Desage-El Murr, M.; Koch, M.; Deguin, B. *Chem.—Eur. J.* **2013**, *19*, 4686.
(13) (a) Goddard, J.-P.; Le Gall, T.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1455. (b) Bomio, C.; Kabeshov, M. A.; Lit, A. R.; Lau, S.-H.; Ehlert, J.; Battilocchio, C.; Ley, S. V. *Chem. Sci.* **2017**, *8*, 6071.
(14) Poh, J.-S.; Lau, S.-H.; Dykes, I. G.; Tran, D. N.; Battilocchio, C.; Ley, S. V. *Chem. Sci.* **2016**, *7*, 6803.
(15) La Cascia, E.; Cuenca, A. B.; Fernández, E. *Chem.—Eur. J.* **2016**, *22*, 18737.
(16) Civit, M. G.; Royes, J.; Vogels, C. M.; Westcott, S. A.; Cuenca, A. B.; Fernández, E. *Org. Lett.* **2016**, *18*, 3830.
(17) (a) Kai, K.; Iwamoto, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 7634. (b) Iwamoto, K.; Kojima, M.; Chatani, N.; Murai, S. *J. Org. Chem.* **2001**, *66*, 169.
(18) Nader, M. W.; Oberdorfer, F. *Tetrahedron Lett.* **2011**, *52*, 2309.
(19) Zheng, J.-C.; Yun, S. Y.; Sun, C.; Lee, N.-K.; Lee, D. *J. Org. Chem.* **2011**, *76*, 1086.
(20) Yun, S. Y.; Zheng, J.-C.; Lee, D. *J. Am. Chem. Soc.* **2009**, *131*, 8413.
(21) Lee, S.; Lee, H.-Y. *Bull. Korean Chem. Soc.* **2010**, *31*, 557.
(22) Li, J.; Sun, C.; Lee, D. *J. Am. Chem. Soc.* **2010**, *132*, 6640.
(23) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 461.
(24) Yagi, T.; Aoyama, T.; Shioiri, T. *Synlett* **1997**, 1063.
(25) Miyagi, T.; Hari, Y.; Aoyama, T. *Tetrahedron Lett.* **2004**, *45*, 6303. (b) Hari, Y.; Kanie, T.; Aoyama, T. *Tetrahedron Lett.* **2006**, *47,* 1137.
(26) O'Connor, M. J.; Sun, C.; Guan, X.; Sabbasani, V. R.; Lee, D. *Angew. Chem., Int. Ed*. **2016**, *55*, 2222.
(27) Lee, H.-Y.; Kim, W.-Y.; Lee, S. *Tetrahedron Lett.* **2007**, *48*, 1407.
(28) Zheng, J.-C.; Liu, H.; Lee, N.-K.; Lee, D. *Eur. J. Org. Chem.* **2014**, 506.
(29) Ogawa, H.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 757.
(30) Sakai, A.; Aoyama, T.; Shioiri, T. *Tetrahedron* **1999**, *55*, 3687.
(31) Habrant, D.; Rauhala, V.; Koskinen, A. M. P. *Chem. Soc. Rev.* **2010**, *39*, 2007.
(32) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107.
(33) (a) Myers, A. G.; Goldberg, S. D. *Angew. Chem., Int. Ed.* **2000**, 39, 2732. (b) Fürstner, A.; Wuchrer, M. *Chem.—Eur. J.* **2006**, *12*, 76.
(34) Bichler, P.; Chalifoux, W. A.; Eisler, S.; Shi Shun, A. L. K.; Chernick, E. T.; Tykwinski, R. R. *Org. Lett.* **2009**, *11*, 519.
(35) Ni, Y.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 11162.
(36) (a) Greenman, K. L.; Carter, D. S.; van Vranken, D. L. *Tetrahedron* **2001**, *57*, 5219. (b) Devine, S. K. J.; van Vranken, D. L. *Org. Lett.* **2007**, *9*, 2047. (c) Devine, S. K. J.; van Vranken, D. L. *Org. Lett.* **2008**, *10*, 1909.
(37) Xu, S.; Chen, R.; Fu, Z.; Zhou, Q.; Zhang, Y.; Wang, J. *ACS Catal.* **2017**, *7*, 1993.
(38) (a) Le Paih, J.; Dérien, S.; Özdemir, I.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2000**, *122*, 7400. (b) Le Paih, J.; Vovard-Le Bray, C.; Dérien, S.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2010**, *132*, 7391.
(39) Monnier, F.; Castillo, D.; Dérien, S.; Toupet, L.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5474.
(40) Cambeiro, F.; López, S.; Varela, J. A.; Saá, C. *Angew. Chem., Int. Ed*. **2012**, *51*, 723.
(41) (a) Lebel, H.; Paquet, V.; Proulx, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2887. (b) Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* **2004**, *126*, 320.
(42) Cherney, E. C.; Green, G. C.; Baran, P. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 9019.
(43) Lebel, H.; Davi, M.; Diez-González, S.; Nolan, S. P. *J. Org. Chem.* **2007**, *72*, 144.
(44) (a) Mish, M. R.; Guerra, F. M.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 8379. (b) Whitlock G. A.; Carreira, E. M. *J. Org. Chem.* **1997**, *62*, 7916.
(45) Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc.* **2000**, *122*, 10710.
(46) Sun, C.; O'Connor, M. J.; Lee, D.; Wink, D. J.; Milligan, R. D. *Angew. Chem., Int. Ed*. **2014**, *53*, 3197.
(47) O'Connor, M.; Sun, C.; Lee, D. *Angew. Chem., Int. Ed*. **2015**, *54*, 9963.
(48) Sun, C.; Lee, H.; Lee, D. *Org. Lett.* **2015**, *17*, 5348.
(49) Chan, K. S.; Wulff, W. D. *J. Am. Chem. Soc.* **1986**, *108*, 5229.
(50) Vuluga, D.; Legros, J.; Crousse, B.; Bonnet-Delpon, D. *Green Chem.* **2009**, *11*, 156.
(51) Rösch, W.; Hees, U.; Regitz, M. *Chem. Ber.* **1987**, *120*, 1645.
(52) Jin, T.; Yamamoto, Y. *Angew. Chem., Int. Ed*. **2007**, *46*, 3323.
(53) (a) Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. *J. Am. Chem.*

Soc. **1998**, *120*, 9690. (b) Dalton, A. M.; Zhang, Y.; Davie, C. P.; Danheiser, R. L. *Org. Lett.* **2002**, *4*, 2465.

(54) (a) Aoyama, T.; Katsuta, S.; Shioiri, T. *Heterocycles* **1989**, *28*, 133. (b) Aoyama, T.; Nakano, T.; Marumo, K.; Uno, Y.; Shioiri, T. *Synthesis* **1991**, 1163.

(55) Aoyama, T.; Kabeya, M.; Fukushima, A.; Shioiri, T. *Heterocycles* **1985**, *23*, 2363.

(56) (a) Aoyama, T.; Kabeya, M.; Fukushima, A.; Shioiri, T. *Heterocycles* **1985**, *23*, 2367. (b) Aoyama, T.; Kabeya, M.; Shioiri, T. *Heterocycles* **1985**, *23*, 2371.

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Daesung Lee was born in South Korea, received his B.Sc. and M.Sc. degrees in chemistry from Seoul National University. After completion of his doctorate studies at Stanford University in 1998, he spent two years of postdoctoral training at Harvard University. In 2000, he joined the Chemistry Department at the University of Wisconsin-Madison and, in 2007, he moved to the University of Illinois at Chicago. His current research interests include the development of new synthetic methods and their applications to the synthesis of biologically active natural compounds.

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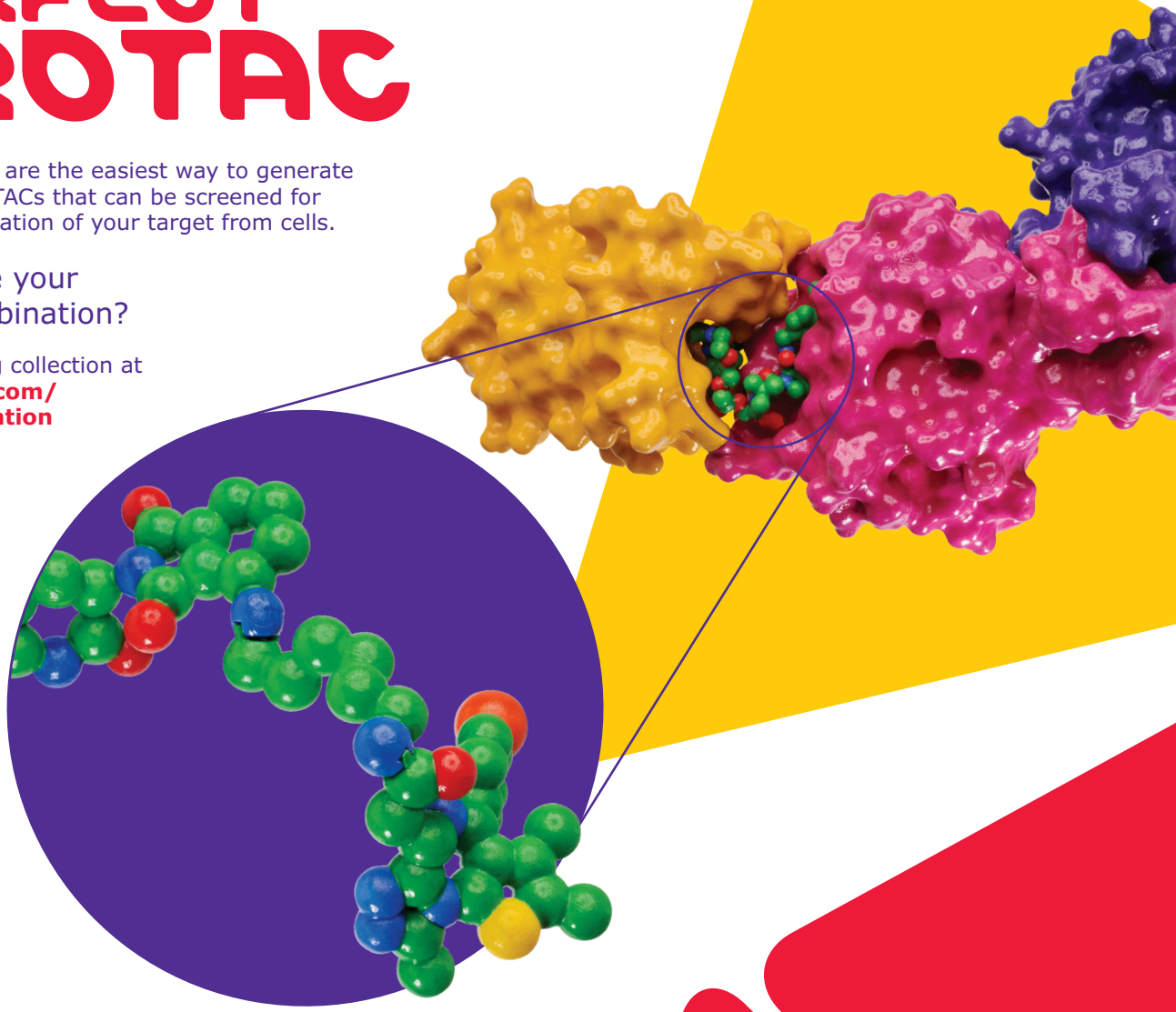

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