# Catalytic isofunctional reactions – expanding the repertoire of shuttle and metathesis reactions
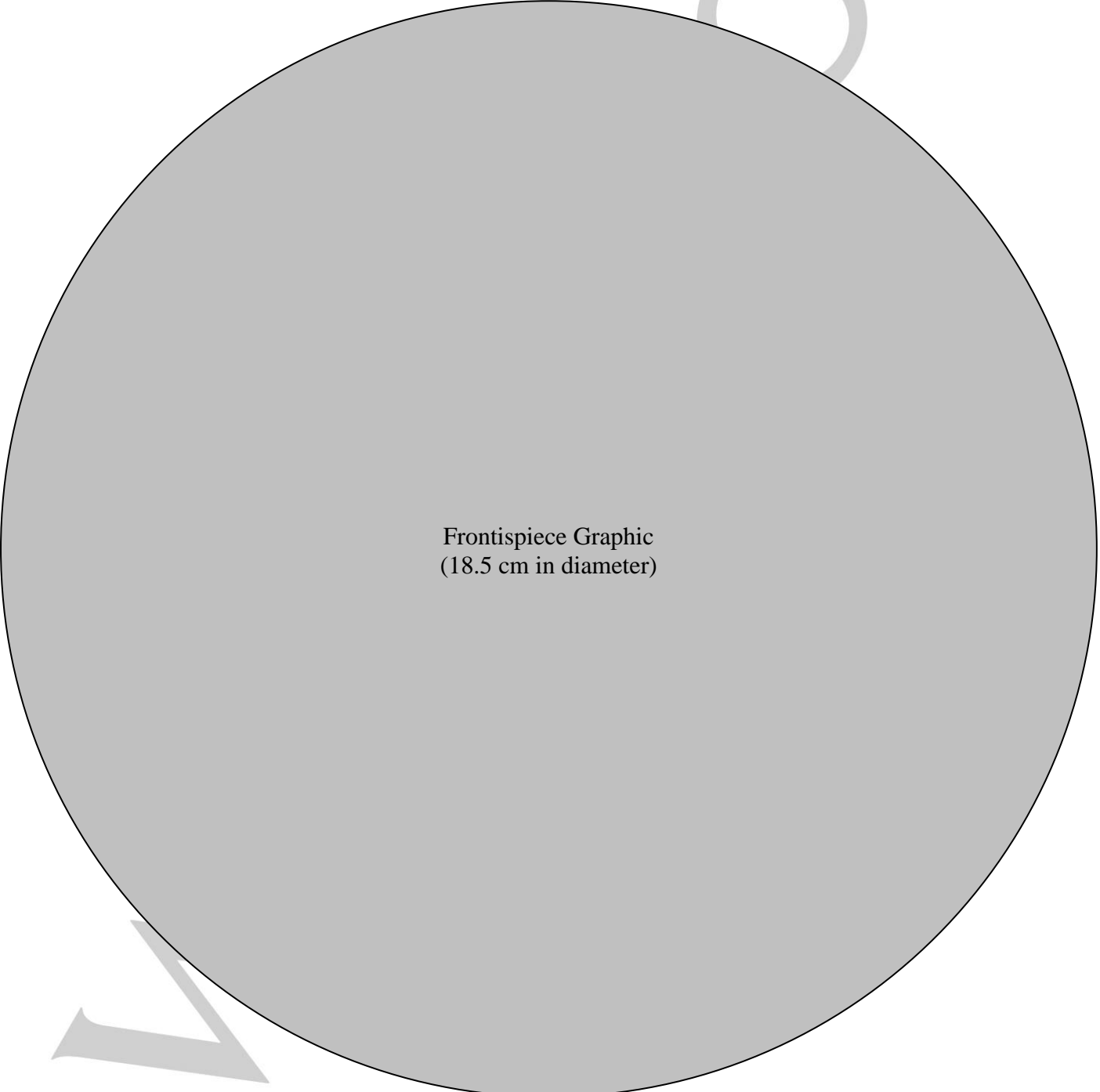
Benjamin N. Bhawal and Bill Morandi*[a,b]

Dedication ((optional))

Frontispiece Graphic
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**Abstract:** Transfer hydrogenation, alkene metathesis and alkyne metathesis possess great value to the synthetic chemistry community. One of the key features of these processes is their reversibility which can be attributed to the presence of the same number and type of functional groups in both the reactants and products, making these reactions isofunctional. These classic reactions have recently inspired the development of novel shuttle and metathesis reactions that offer great promise for synthetic chemistry. This review describes and systematically categorizes both recent and older examples of shuttle and metathesis reactions other than transfer hydrogenation and alkene/alkyne metathesis.
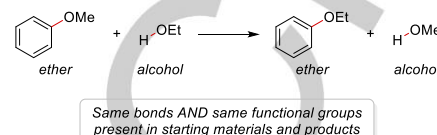
## 1. Introduction

Transfer hydrogenation,[1] alkene metathesis[2] and alkyne metathesis[3] are among the most popular catalytic reactions available to the synthetic practitioner, finding widespread use in a variety of fields from natural product synthesis[4] to the preparation of novel materials.[5] They have also proved exceptionally versatile, enabling the development of a broad range of novel catalytic processes. For instance, alkene metathesis has enabled various transformations including ring-closing metathesis, ring-opening metathesis polymerization and has been used in tandem with other catalytic processes,[6] while transfer hydrogenation facilitates both hydrogenation and dehydrogenation reactions as well as underpinning borrowing hydrogen reactions.[7]

An unusual feature of these reactions is that they are intrinsically reversible processes which is arguably pivotal to their synthetic utility. These reactions can be considered as isodesmic since all the bonds broken on the reactant side are reformed on the product side through bond redistribution.[8,9] However, one can delve deeper and notice that the number and type of functional groups is also conserved throughout the reaction. This can thus be considered a subclass of isodesmic reactions which for the purpose of this review we will term isofunctional reactions (Scheme 1).[10,11]
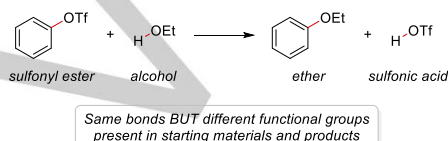
A coarse consideration of the energies of both the starting materials and products reveals that these processes should have a negligible $\Delta G°$ value or even be completely ergoneutral. This is in contrast to the vast majority of organic reactions, which tend to be exothermic and, as a consequence, the reverse process is often challenging to undertake. The ergoneutrality of isofunctional reactions vindicates why these reactions are inherently reversible. With regards to organic reactions, isofunctional reactions can be classified in three different groups. The first group consists of

unimolecular isomerization and rearrangement reactions that convert a single starting material into a single product (Scheme 2A). Notable examples include some sigmatropic reactions, such as the Cope rearrangement[12] and dyotropic rearrangements.[13] Among the reactions involving more than one starting material or product, two groups of transformations can be differentiated: shuttle catalysis reactions[14] and metathesis reactions. In a shuttle



*A. Illustrative example of an isofunctional, isodesmic reaction (this review)*

*ether*   *alcohol*   *ether*   *alcohol*

*Same bonds AND same functional groups present in starting materials and products*

*B. Illustrative example of a non-isofunctional, isodesmic reaction (not covered)*

*sulfonyl ester*   *alcohol*   *ether*   *sulfonic acid*

*Same bonds BUT different functional groups present in starting materials and products*

**Scheme 1.** Examples of an isofunctional reaction and a non-isofunctional reaction.

catalysis reaction, a donor molecule and an acceptor molecule can be clearly identified in a process wherein a payload (the shuttled group) is transferred from a donor molecule to an acceptor molecule (Scheme 2B). Although these reactions are isodesmic and thus keep the total number and type of bonds constant throughout the reaction, they involve a change in the number of bonds in each reaction partner. Transfer hydrogenation,[1] a reaction which involves hydrogen transfer between an alcohol donor and a ketone acceptor, is perhaps the most illustrative example of this type of reaction. By contrast, in a metathesis reaction, two chemical moieties are interchanged between two reactants (Scheme 2C). Thus, there is no clear donor or acceptor molecule that can be identified and the number of bonds remains constant for all reaction partners throughout the reaction. Alkene metathesis is probably the most recognizable example of a metathesis reaction.[2]
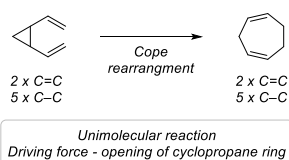
One key challenge pertaining to isofunctional reactions is that their intrinsic reversibility calls for strategies to control the position of the equilibrium to obtain synthetically useful yields of the desired product. A thermodynamic strategy to drive the reaction forward alters the ground state energy of one of the reaction components to favor formation of the desired product, for example through ring strain release. An example of this strategy can be found in the Cope rearrangement of cyclopropane-containing dienes (Scheme 2A),[15] a reaction that proceeds with high yields to the rearranged product. The position of the equilibrium can also be altered through Le Chatelier's principle. This can be most simply achieved by using one of the reaction components in a large excess, a strategy commonly employed in transfer hydrogenation (Scheme 2B).[1] The removal of one of the by-products, for example through evaporation, precipitation or even irreversible conversion to a secondary product, is another

[a]    Dr. B. N. Bhawal, Prof. Dr. B. Morandi
       Max-Planck-Institut für Kohlenforschung
       45470 Mülheim an der Ruhr (Germany)

[b]    Dr. B. N. Bhawal, Prof. Dr. B. Morandi
       Laboratorium für Organische Chemie
       ETH Zürich
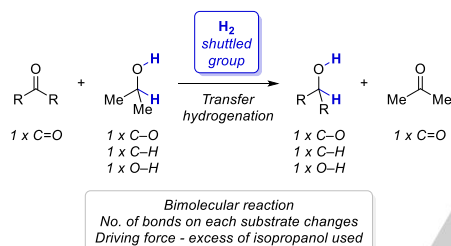       8093 Zürich, (Switzerland).
       E-mail: morandib@.ethz.ch

example of this strategy. For instance, ethylene extrusion is a common driving force in alkene metathesis reactions (Scheme 2C).[2]

In this review article, several examples of isofunctional reactions are discussed with regards to their mechanism and synthetic utility. The primary focus of this review will be on shuttle catalysis beyond transfer hydrogenation (Section 2) and metathesis reactions beyond alkene and alkyne metathesis (Section 3). Because rearrangements,[12,13] isomerizations,[16] transfer hydrogenation,[1] alkene metathesis[2] and alkyne[3] metathesis are beyond the scope of this review, interested readers are encouraged to consult several other recently published reviews on these topics. Additionally, only examples using homogeneous catalysis will be included. There are, though, many examples of isofunctional reactions mediated by enzymes[17] or heterogeneous catalysts.[18]
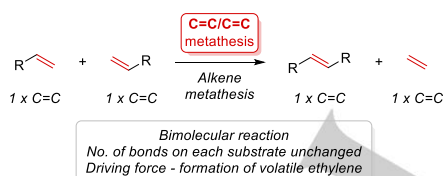
*A. Example of an isomerization/rearrangement reaction*



2 x C=C
5 x C–C

*Cope rearrangment*

2 x C=C
5 x C–C

*Unimolecular reaction*
*Driving force - opening of cyclopropane ring*

*B. Example of a shuttle catalysis reaction*



**H$_2$**
*shuttled group*

*Transfer hydrogenation*

1 x C=O

1 x C–O
1 x C–H
1 x O–H

1 x C–O
1 x C–H
1 x O–H

1 x C=O

*Bimolecular reaction*
*No. of bonds on each substrate changes*
*Driving force - excess of isopropanol used*

*C. Example of a metathesis reaction*



**C=C/C=C metathesis**

*Alkene metathesis*

1 x C=C

1 x C=C

1 x C=C

1 x C=C

*Bimolecular reaction*
*No. of bonds on each substrate unchanged*
*Driving force - formation of volatile ethylene*

**Scheme 2.** Comparison of different classes of isofunctional reactions.

## 2. Shuttle catalysis

Transfer hydrogenation is one of the classic examples of a catalytic isofunctional reaction. It involves transfer of hydrogen from a donor molecule to an acceptor molecule and, since it is reversible, it can be applied to achieve either hydrogenation or dehydrogenation. As it has been extensively reviewed previously,[1] it will not be discussed further. However, it is informative to consider transfer hydrogenation in the context of shuttle catalysis which can be viewed as an extension of the transfer hydrogenation paradigm to include transfer of any group or functionality between molecules.[14,19] This unlocks the potential for numerous other, reversible transfer processes to be envisaged. In a shuttle catalysis process, a shuttled group is transferred from a donor molecule to an acceptor molecule. Because these reactions are isofunctional it is usually possible to reversibly transfer the shuttled group thus providing a platform for performing both functionalization and defunctionalization reactions under similar conditions. In a forward, functionalization process, the shuttled group is transferred from a sacrificial donor and in a reverse, defunctionalization process, the shuttled group is transferred to a sacrificial acceptor. This type of process is particularly attractive in instances where it is desirable to avoid using the bare shuttled group, possibly due to its toxicity or instability.
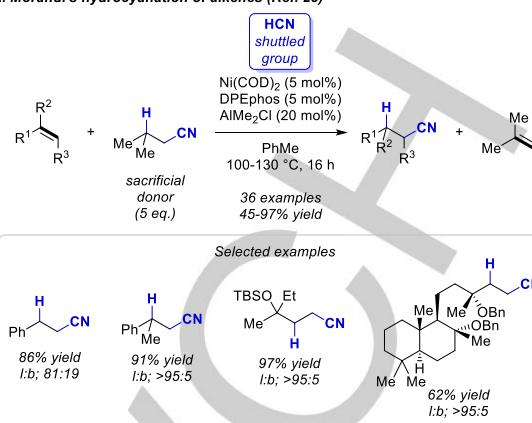
## 2.1. HCN transfer

Nitriles are a key functional group often found in bioactive compounds and also serve as versatile intermediates for organic synthesis.[20] A practical and atom economical method for the preparation of nitriles is hydrocyanation enabling access from readily available alkene precursors.[21] However, the prerequisite for toxic HCN gas has hampered the use and development of this reaction in the laboratory. The use of surrogates such as acetone cyanohydrin is a potential alternative but these reagents also suffer from high toxicity.[22] In 2016, the group of Morandi reported the use of a simple, markedly less toxic aliphatic nitrile as a HCN donor in a shuttle catalysis process (Scheme 3A).[23] Isovaleronitrile proved to be an efficient donor and, using a Ni catalyst in combination with an Al-Lewis acid, a wide array of alkenes proved amenable to hydrocyanation. Isobutene is formed as a by-product and, due to its volatility, provides a driving force for the reaction. Although the reaction is no longer completely atom economical, the replacement of toxic HCN gas with relatively benign and inexpensive isovaleronitrile arguably poses a greater benefit. For larger scale applications, inexpensive butyronitrile could be employed as HCN donor and solvent. This process could also be extended to the hydrocyanation of alkynes in a non-isofunctional process (an aliphatic nitrile is converted into an alkenyl nitrile).

In the same report, the group of Morandi capitalized on the intrinsic reversibility of isofunctional processes to achieve the dehydrocyanation of aliphatic nitriles (Scheme 3B). Thus, using the same catalytic system and norbornadiene as a HCN acceptor, the synthesis of alkenes, including both terminal and internal, from various aliphatic nitriles was achieved. The switch in selectivity to favor defunctionalization of the nitrile is dictated by the release of ring strain upon transfer of HCN to norbornadiene.

This transfer hydrocyanation is proposed to proceed via oxidative addition of the C−CN bond to form Ni complex **1** followed by β-hydride elimination to give Ni-hydride **2** (Scheme 3C). At this stage, the alkene ligand generated can undergo alkene exchange and insertion of the Ni−hydride complex **3** across the new alkene ligand then reductive elimination delivers the product nitrile. Computational studies corroborated this proposal and also illuminated the role of the Lewis acid co-catalyst which was shown to assist the initial, rate-determining oxidative addition step by binding to the nitrile.[24] In the absence of the Lewis acid, the barrier for the oxidative addition is considerably larger and thus the reaction is unlikely to be feasible at practical temperatures.

As discussed in the intro, the development of transfer hydrogenation procedures has opened up the possibility to perform borrowing hydrogen processes. Inspired by this, the group of Morandi have exploited their HCN transfer protocol to develop a Mizoroki-Heck reaction using aryl nitriles as electrophiles under acidic conditions.[25] They have also demonstrated the cyanation of aromatic chlorides and triflates using butyronitrile as a cyanide donor.[26]
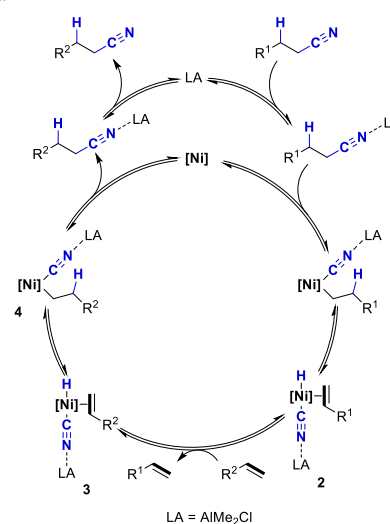


*A. Morandi's hydrocyanation of alkenes (Ref. 23)*

*B. Morandi's dehydrocyanation of aliphatic nitriles*

*C. Mechanism*

LA = AlMe₂Cl
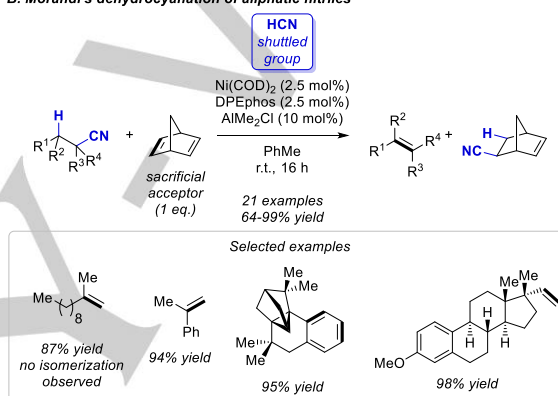
**Scheme 3.** Ni/Lewis acid co-catalyzed HCN transfer from aliphatic nitriles.

## 2.2. RCHO transfer

A pioneering example of shuttle catalysis was reported by the group of Jun in 1999 (Scheme 4A).[27] They discovered that a dual catalytic system, composed of Wilkinson's catalyst and 2-amino-3-picoline **5**, enabled aldehyde transfer from a ketone to an alkene. A notable feature of this reaction is that it proceeds through a rare activation of an unstrained C−C bond. This is proposed to be aided by the picoline catalyst **5** which can form imine **6** with the ketone substrate (Scheme 4B). Subsequently, the pyridine N atom can then direct the Rh catalyst towards oxidative addition of the C−C bond forming complex **7**. The Rh catalytic cycle is then completed by β-hydride elimination to give **8**, alkene ligand exchange, insertion across the new alkene ligand and reductive elimination from **10** to regenerate the Rh catalyst. To favor the formation of the products, an excess of alkene is typically employed but the authors also suggest that the styrene by-product can polymerize under the reaction conditions,[28] providing a further driving force. Overall, this reaction is a useful complement to traditional hydroacylation processes,[29] wherein an alkene inserts directly in to an aldehyde, since there are instances where the use of the bare aldehyde is unfavorable. For instance, acetaldehyde can be a challenging substrate to work with. This is due to its volatility and carcinogenic properties and also because of its propensity to undergo side reactions such as self-aldol condensation.[30] However, with this transfer hydroacylation process, easier to handle benzylacetone can be employed as a surrogate. An extension of this work demonstrated the application of this system to the skeletal rearrangement of cyclic imines[31] and also showed that alcohols could be used as precursors for the ketones via a borrowing hydrogen strategy.[32]
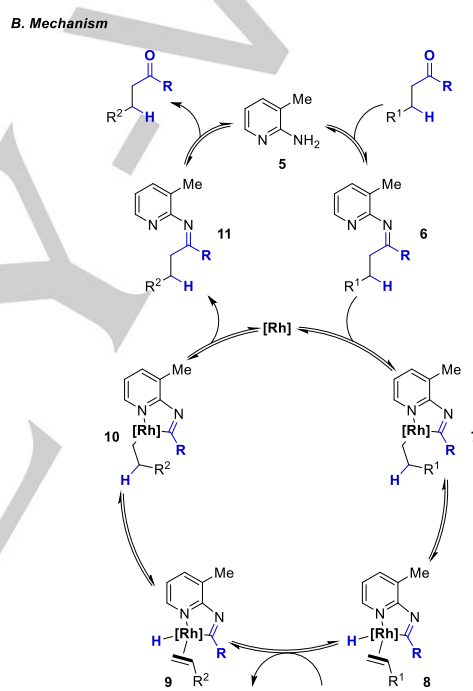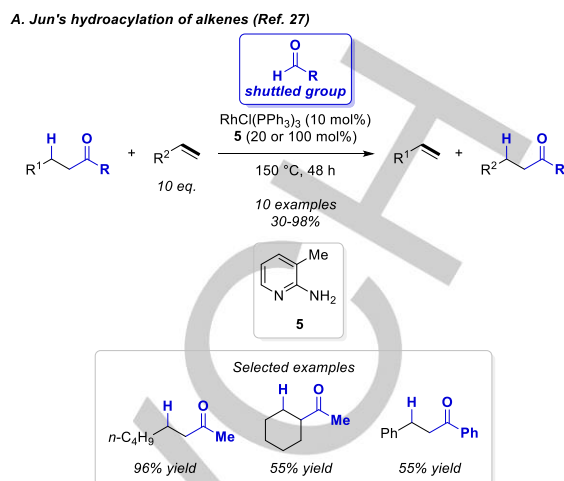


**Scheme 4.** Rh/aminopicoline co-catalyzed RCHO transfer.

## 2.3. H₂/CO transfer

Although hydroformylation is a widely employed and well studied reaction,[33] particularly in industrial applications,[34] it does suffer from some drawbacks, namely the requirement for a hazardous, gaseous mixture of hydrogen and carbon monoxide. Due to the acute toxicity of carbon monoxide, protocols employing surrogates such as formaldehyde and carbon dioxide have been explored.[35] A transfer process would be highly desirable as the toxic and flammable hydrogen-carbon monoxide mixture could be substituted for a relatively benign aldehyde. Early work from the group of Brookhart suggested that this could be possible.[36] They found that Rh catalyst **12** promoted an isomerization of *n*-butanal to afford a 1:1 mixture of *n*-butanal and *iso*-butanal (Scheme 5A). The establishment of a mixture of products implicates the reversibility of the process. Further work found that transfer hydroformylation from isovaleroaldehyde to 3,3-dimethyl-1-butene catalyzed by Rh complex **13** was also possible (Scheme 5B). The reaction is driven by formation of isobutene and gives exclusive formation of the linear aldehyde, presumably due to the steric encumbrance of the *tert*-butyl group. Although this result suggests that a forward transfer hydroformylation process is feasible, to date no general method has been developed and this remains an isolated example.



*A. Brookhart's isomerization of a linear aldehyde (Ref. 36)*
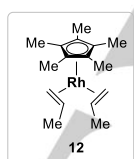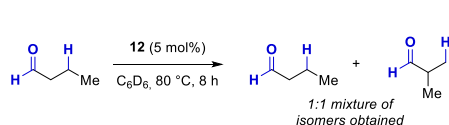
*B. Brookhart's transfer hydroformylation*
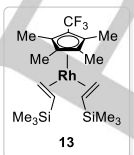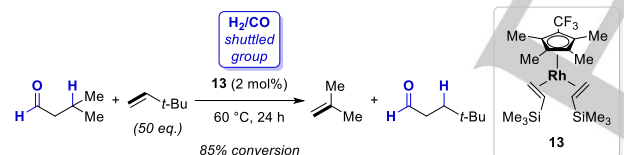
**Scheme 5.** Rh catalyzed H₂/CO transfer for isomerization of aldehydes and hydroformylation of alkenes.

Despite the numerous examples of hydroformylation, the reverse process, dehydroformylation, remained elusive until recent work from the group of Dong (Scheme 6A).[37] They reported a Rh catalyzed dehydroformylation to transform aldehydes to the corresponding alkenes by transfer of hydrogen and carbon monoxide to a strained alkene, either norbornadiene or norbornene. Despite the propensity for isomerization of the product alkene, this proved not to be an issue suggesting the process is kinetically controlled. A plausible explanation for this is that the transfer to the strained alkene leads to an exothermic reaction and is thus irreversible under these conditions. From their mechanistic studies, the group of Dong proposed that the Rh complex **15** adds oxidatively across the C−H bond of the aldehyde to form **16** (Scheme 6B). At this stage, reductive elimination of the hydride and carboxylate occurs forming Rh complex **17**. This

complex then undergoes de-insertion and β-hydride elimination to form **19**. Ligand exchange with norbornadiene leads to release of the alkene product. The microscopic reverse then occurs with norbornadiene leading to regeneration of the catalyst and formation of the by-product. Insertion of the Rh hydride complex **20** across norbornadiene to form **21** is thought to be irreversible under these reaction conditions. This mechanistic proposal was supported by DFT studies.[38]

Recently, the group of Dong used this reaction in tandem with hydrogen transfer to achieve formal dehydroxymethylation.[39] This enables direct access to alkenes from simple alcohol precursors.



*A. Dong's dehydroformylation of aldehydes (Ref. 37)*

*Selected examples*
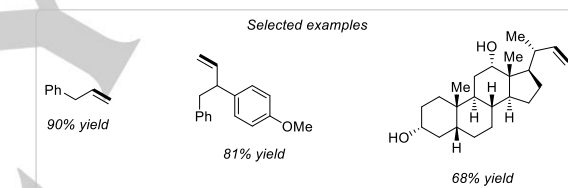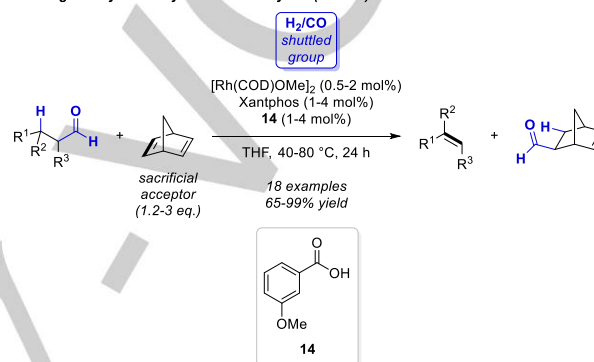
*B. Mechanism*
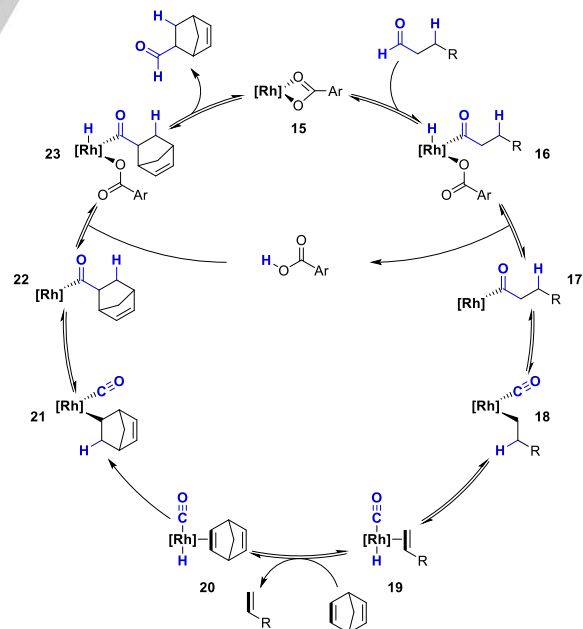
**Scheme 6.** Rh catalyzed H₂/CO transfer for the dehydroformylation of aldehydes.
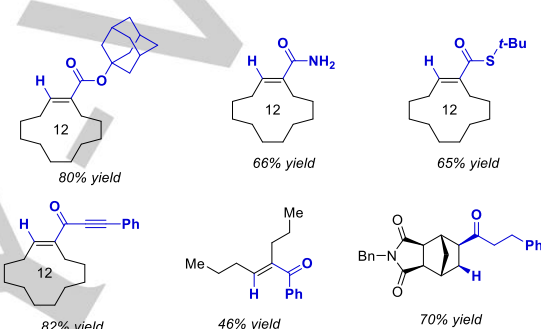
## 2.4. HCl/CO transfer

In traditional Reppe-type processes, carbon monoxide and a nucleophile react with an alkene or alkyne to afford a wide range of carbonyl derivatives.[40] This chemistry has found widespread employment in industry with one of the key routes to methyl methacrylate, the precursor to poly(methyl methacrylate), relying on this type of process.[41] However, applications in the laboratory are relatively scarce, most likely due to the requirement for pressurized, toxic CO. Another issue is the absence of a general catalyst for performing the reaction with varying nucleophiles. Instead, different catalysts are required depending on the class of nucleophile used. Hydrochlorocarbonylation, the transfer of HCl and CO, could open access to the synthesis of a wide range of carbonyl derivatives from alkenes following derivatization of the versatile acid chloride product. However, examples following Reppe-type processes are rare,[42] presumably due to the prerequisite for a combination of toxic CO and corrosive HCl. Shuttle catalysis presents a convenient solution to this issue as demonstrated by the group of Morandi (Scheme 7A).[43] They found that butyryl chloride could be used as a HCl/CO donor for the hydrochlorocarbonylation of alkenes. The formation of propene as a by-product serves as a driving force. The reaction has a limited scope with regard to alkenes but proved to be more facile with alkynes, affording α,β-unsaturated carboxylic acid derivatives in a non-isofunctional process. To demonstrate the utility of this process, the acid chloride products were directly functionalized with a range of nucleophiles to afford esters, amides, thioesters and ketones (Scheme 7B). One-pot hydrochlorocarbonylation followed by either Sonogashira, Suzuki or Kumada cross-couplings were also performed to extend the scope of ketones accessible via this methodology. The reverse dehydrochlorocarbonylation of an aliphatic acid chloride was also demonstrated using norbornene as an acceptor.
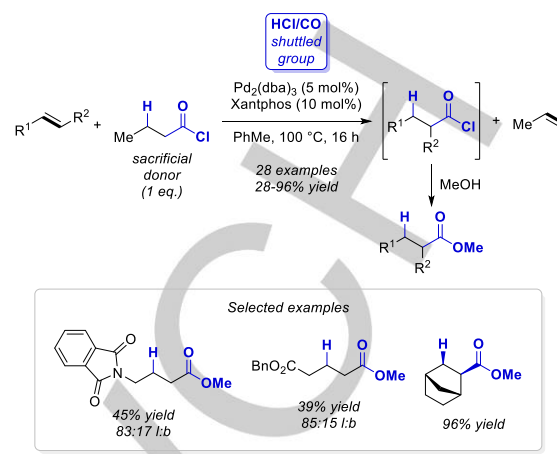


**Scheme 7.** Pd catalyzed HCl/CO transfer for the synthesis of versatile acid chlorides.

## 2.5. HMgBr transfer

Grignard reagents are among the most widely used reagents in organic synthesis and are typically synthesized by insertion of magnesium into an alkyl or aryl halide.[20] However, this procedure proceeds through radical intermediates and therefore may not be compatible with other functionalities. As an alternative, an early shuttle catalysis process was reported in 1962 by Cooper and Finkbeiner (Scheme 8).[44,45,46] They demonstrated that *n*-propyl magnesium bromide could act as a source of "HMgBr" for Ti catalyzed hydromagnesiation. Although hydromagnesiation has been demonstrated using RMgH and MgH$_2$, this represents a more practical procedure due to the poor availability and instability of the parent reagents.[47] Further work demonstrated a range of transition metals also able to catalyze the transfer but the number of examples were often limited.[48]



*Cooper and Finkbeiner's transfer hydromagnesiation (Ref. 44)*
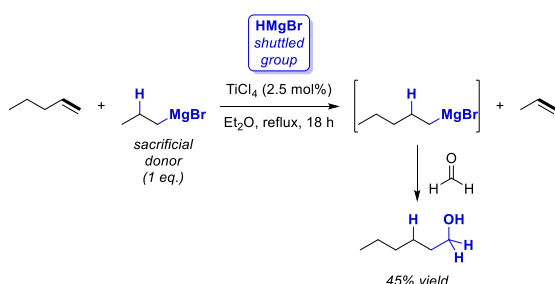
**Scheme 8.** Ti catalyzed HMgBr transfer.

More recently, the group of Shirakawa and Hayashi performed an isomerization of secondary alkyl Grignard reagents to the more stable primary reagents using an Fe-Cu co-operative catalysis system (Scheme 9A).[49] The Fe catalyst is proposed to form Fe complex **24** through transmetallation of FeCl$_3$ with the Grignard reagent (Scheme 9B). Isomerization occurs through β-hydride elimination and reinsertion across the alkene to form the isomeric complex **26**. This complex then undergoes transmetallation with the cuprate **27**, which is formed by transmetallation between CuBr and the starting Grignard reagent, to complete the Fe catalyst cycle. Cuprate **27** is generated from **28** by transmetallation with the starting Grignard reagent, leading to extrusion of the newly formed product Grignard reagent. Following on from this work, they used the same system to facilitate transfer hydromagnesiation from cyclopentylmagnesium bromide to a range of alkenes and alkynes (Scheme 9C).[50] Cyclopentylmagnesium bromide is a good source of HMgBr as it is unable to form a more stable primary Grignard reagent. Thus transfer to the alkene, which is able to form a primary Grignard reagent, is strongly favored and only one equivalent of the donor is required.

The following year, the group of Thomas reported a transfer hydromagnesiation of styrenes to produce α-aryl carboxylic acids, following reaction in situ with CO$_2$ (Scheme 10A).[51] In this process, ethyl magnesium bromide acts as a HMgBr donor and the

reaction is conducted by an Fe catalyst and a tridentate bis(imino)pyridine ligand **29**. Release of volatile ethene
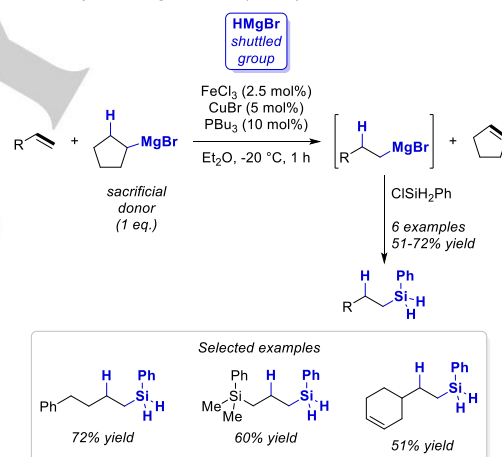


*A. Isomerization of secondary Grignard reagent to primary Grignard reagent (Ref. 49)*
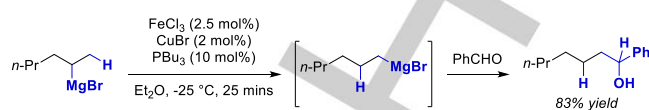
*B. Mechanism*
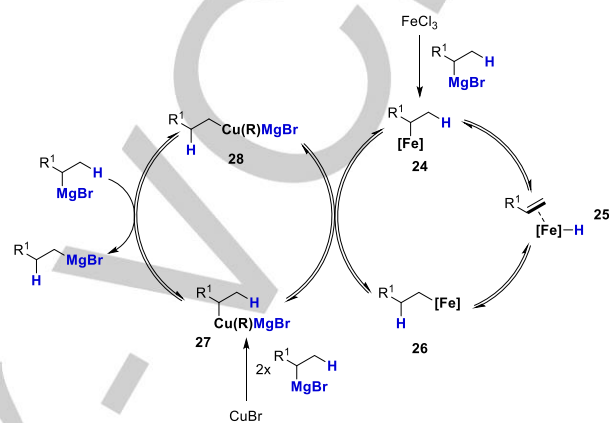
*C. Skirakawa and Hayashi's HMgBr transfer (Ref. 50)*

*Selected examples*

**Scheme 9.** Fe/Cu co-catalyzed HMgBr transfer.

provides a driving force for the reaction and only 1.2 equivalents of the donor are required. Following mechanistic investigations (Scheme 10B),[52] the authors proposed that the reaction proceeds by transmetallation between the Grignard reagent and the catalyst to give complex **30** followed by β-hydride elimination. Hydrometallation of the styrene ligand in **32** and subsequent transmetallation affords the Grignard product which is trapped by reaction with CO$_2$. In contrast to the work by the groups of Shirakawa and Hayashi, this reaction displays selectivity for the formation of the secondary, α-aryl Grignard intermediate rather than the primary, β-aryl Grignard intermediate. The authors suggest that this likely arises from preferential formation of a more stable benzylic anion. This would be true if the reaction is truly

under thermodynamic control. However, under kinetic control formation of the α-aryl Grignard intermediate could be favored due to stabilization of the Fe−C bond by the adjacent π-system. Follow up work illustrated the versatility of the intermediate Grignard reagent formed to access a variety of products using this Fe catalyzed transfer hydromagnesiation.[53]

In 2016, the group of Xi reported a Ti catalyzed hydrocarboxylation process, that depending on the substrate, afforded either the linear or branched products (Scheme 11).[54] This process relies on the transfer of HMgBr from a simple donor, *i*-propylmagnesium bromide, to the acceptor alkene and subsequent trapping of the newly formed Grignard reagent with $CO_2$. If styrene derivatives are employed as acceptors, a preference for the branched product is exhibited. Similarly, with conjugated dienes the branched product is preferentially formed with reaction occurring on the less substituted alkene. However, in the case of non-conjugated, terminal alkenes the linear product is favored. Even with allyl benzene, where it could be conceived that migration of the double bond could occur, only the linear product was isolated.

In 2012, the group of Nakamura reported an Fe catalyzed transfer hydromagnesiation using alkynes as acceptors in a non-isofunctional process.[55] Again, EtMgBr was used as a HMgBr donor and $FeCl_2$ was employed as catalyst but no ligand was required.
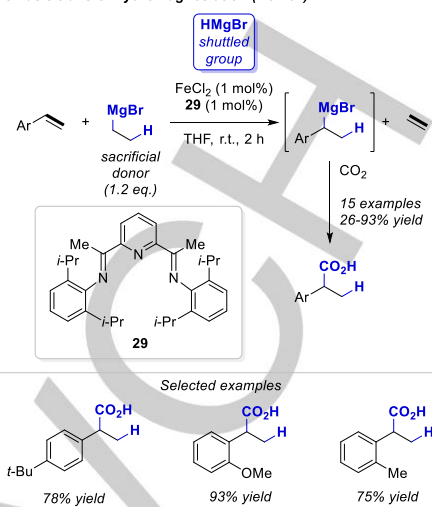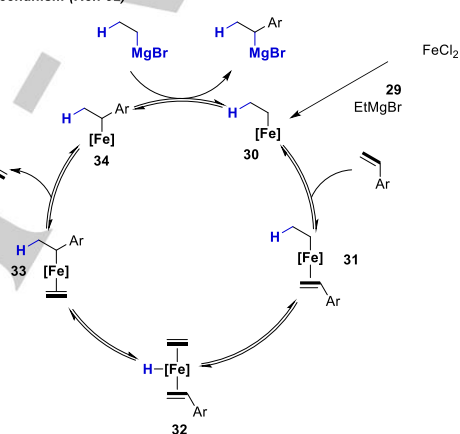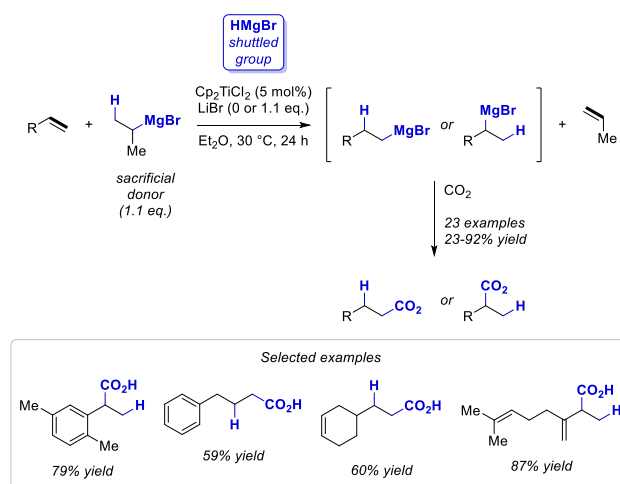


**Scheme 10.** Fe catalyzed HMgBr transfer for the synthesis of α-aryl carboxylic acids.
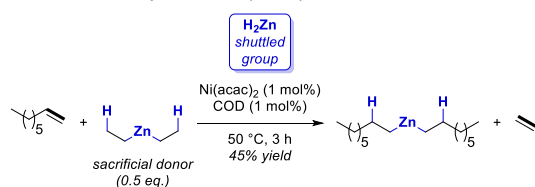
*Xi's transfer hydromagnesiation (Ref. 54)*



**Scheme 11.** Ti catalyzed hydrocarboxylation of alkenes via HMgBr transfer.

## 2.6. H₂Zn transfer

Organozinc reagents stand aside Grignard reagents as being among the most powerful organometallic reagents for organic synthesis.[20,56] Traditional methods for their preparation have relied upon insertion of activated Zinc into an organohalide or by transmetallation with another organometallic species. The demand for organozinc reagents has spurred further developments for their preparation and one valuable addition to the repertoire of methods available is the transfer hydrozincation reaction discovered by the group of Knochel in 1995. This opens access to organozincs from widely available alkene precursors (Scheme 12).[57] The authors found that Ni(acac)$_2$ and cyclooctadiene catalyzed the reaction of monosubstituted alkenes with diethylzinc to form a new diorganozinc with concomitant generation of ethene providing a suitable driving force. Derivatization of the newly formed diorganozinc was performed including oxidation to afford the formal, anti-Markovnikov hydration product.
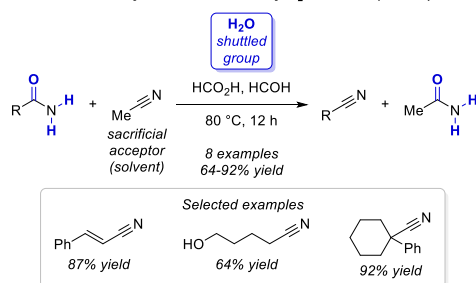


**Scheme 12.** Ni catalyzed ZnH$_2$ transfer for the synthesis of diorganozincs from alkenes.

## 2.7. H₂O transfer

A key method for the preparation of nitriles is the dehydration of primary amides but harsh reagents are traditionally required for conducting this transformation.[58] A shuttle catalysis process for this transformation was reported by the group of Mioskowski wherein the conversion of a primary amide to a nitrile was achieved by transfer of water to acetonitrile, the sacrificial acceptor (Scheme 13).[59] A combination of paraformaldehyde and formic acid was shown to effect the dehydration of various primary amides. Although these reagents were used in excess the aldehyde could be employed in catalytic quantities albeit affording lower yields of the product. The authors proposed that the reaction proceeds by transfer of water from the primary amide to acetonitrile, which was the solvent for the reaction thus favoring the dehydration of the amide starting material. To verify this proposition, a reaction in which acetonitrile was replaced with benzonitrile was conducted and led to formation of benzamide.
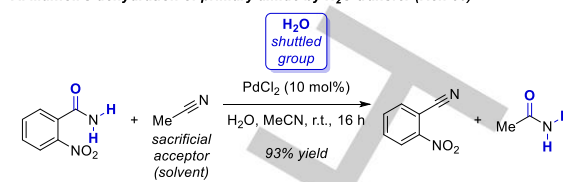

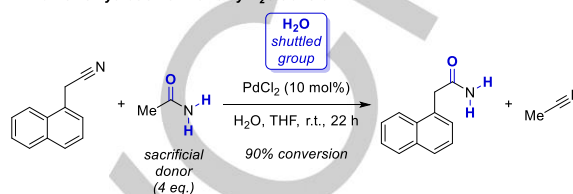
Scheme 13. Paraformaldehyde/formic acid catalyzed H₂O transfer for the synthesis of nitriles from primary amides.



Scheme 14. Pd catalyzed H₂O transfer between primary amides and nitriles.

Later, the group of Maffioli found that Pd catalysts were able to promote the dehydration of primary amides by transfer of water to acetonitrile (Scheme 14A).[60] It was noted that acetonitrile was critical to the success of the reaction and when substituted with benzonitrile, benzamide formation could be detected. Having observed the hydration of benzonitrile, the authors explored the reversibility of this reaction and found that acetamide could be used in excess to induce hydration of aromatic and aliphatic nitriles using catalytic PdCl₂ thus demonstrating the reversibility of the process (Scheme 14B). A similar method was reported later by the group of Dai again using Pd catalysis.[61]

Although the conversion of nitriles to amides and vice versa via H₂O transfer is an important transformation, arguably a related H₂S transfer to interconvert nitriles and thioamides would be of greater benefit due to the gaseous nature and acute toxicity of H₂S. To date one example exists in the literature of the synthesis of thioamides from nitriles using thioacetamide as a H₂S donor.[62] This, though, relies on a saturated solution of excess HCl in dimethylformamide.

## 2.8. Transfer of carbene, silylene and related reactive intermediates

Three-membered cyclic compounds such as epoxides and cyclopropanes[20] are well-documented intermediates for organic synthesis. By contrast, silacyclopropanes have received relatively minimal attention despite the widespread usage of organosilicon reagents.[63] A plausible explanation for this is the lack of methods available for their preparation. One method involves transfer of a silylene intermediate from a silacyclopropane to an alkene. Early methods relied on thermal decomposition of a silacyclopropane **35** to generate a reactive silylene intermediate in situ.[64] More recently, the group of Woerpel demonstrated that Ag salts are effective catalysts for this decomposition enabling silylene transfer to proceed at cryogenic temperatures with addition to alkene occurring stereospecifically and also with high diastereoselectivites (Scheme 15A).[65] Following detailed mechanistic studies on the silacyclopropanation of styrene (Scheme 15B), a catalytic cycle was proposed.[66] The results obtained indicate that the Ag catalyst **36** first cleaves the strained silacyclopropane via sigma bond metathesis and following β-silyl elimination forms silylsilver complex **38**. Following ligand exchange, electrophilic attack of the silyl group into the alkene affords **40** from which the product silacyclopropane is formed by sigma bond metathesis.
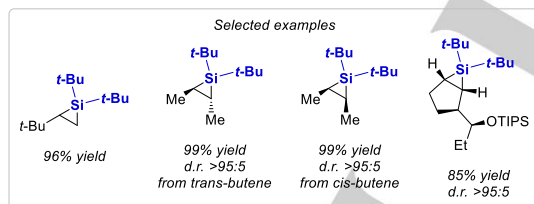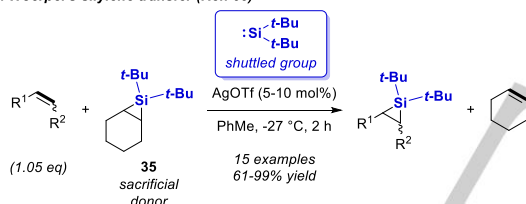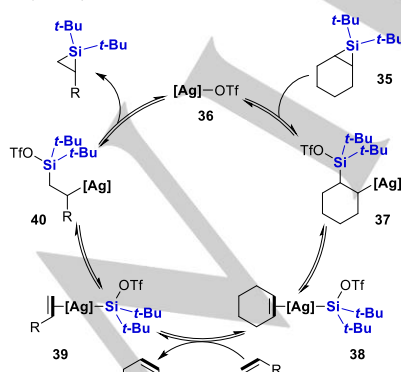


**Scheme 15.** Ag catalyzed silylene transfer.

A related process for the transfer of :SO to form an episulfoxide from alkenes was reported by the group of Simpkins (Scheme 16A).[67] A trans-stilbene derived epi-sulfoxide proved to be an effective :SO donor and the reaction proceeds at room temperature using a Rh catalyst. Norbornene and norbornadiene, though, proved to be the only substrates that worked, possibly due to the release of ring strain upon transfer of :SO. The transfer of sulfenium was also achieved using propylene sulfide as a donor and the same Rh catalyst (Scheme 16B).
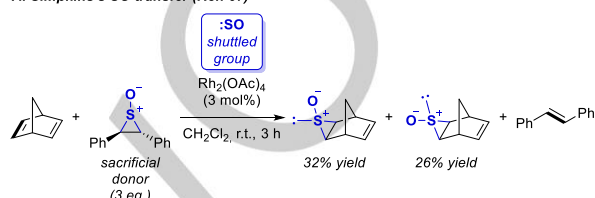


**Scheme 16.** Rh catalyzed SO and sulfenium transfer.

In 2003, a Mo catalyzed sulfur transfer was reported by Adam and co-workers (Scheme 17).[68] They identified phenylthiirane to be a productive sulfenium donor and using Mo complex **41** they were able to effect the episulfidation of a range of cyclic E- and Z-alkenes. Allenes also proved amenable to episulfidation under these reaction conditions.
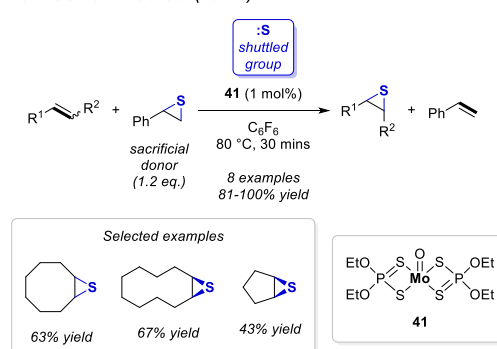


**Scheme 17.** Mo catalyzed sulfenium transfer for the synthesis of thiiranes.

The group of Denmark has also demonstrated the transfer of sulfenium and selenenium to form thiiraniums and seleniraniums respectively from alkenes in an uncatalyzed process.[69] Cyclopropanes are oft prepared from alkenes by reaction with a carbene that is typically generated in situ from a diazo compound.[70] However, as there are some diazo compounds that

are significantly unstable, the development of a carbene transfer process is desirable. In 1976, Gassman and co-worker reported a carbene transfer from ethylcyclopropane to electron deficient alkenes using W catalysis (Scheme 18).[71] The yields, unfortunately, are low for this transformation but it should be noted that methylene is transferred in this process. Traditionally diazomethane, a notoriously explosive chemical, is used as a precursor for methylene and thus using ethylcyclopropane presents an obvious advantage.
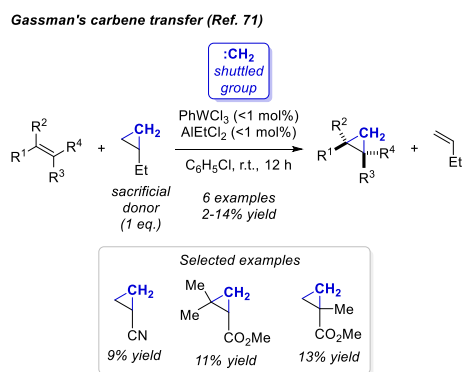


**Scheme 18.** W catalyzed carbene transfer.

## 3. Metathesis Reactions

Alkene metathesis has emerged as one of the most important metal catalyzed reactions available to the synthetic practitioner.[2] Aside from finding widespread application in organic synthesis, it is used in various other branches of chemistry. For instance, it has had a significant influence on polymer synthesis, valorization of bio-renewables and dynamic combinatorial chemistry. Reasons for the success of this reaction include the functional group tolerance of modern alkene metathesis catalysts as well as the distinctive mechanism by which the reaction proceeds. The analogous alkyne metathesis reaction has also provided countless applications in total synthesis, supramolecular chemistry and polymer sciences.[3]

Taking into consideration the impact that alkene and alkyne metathesis reactions have had in synthetic chemistry, it should come as no surprise that other metathesis processes invoking exchange across other types of bonds have been sought. A wide range of isofunctional metathesis processes have subsequently been developed and these can be classified by two simple considerations.

The first differentiation, based on bond multiplicity,[72] can be made between metathesis reactions involving either triple bonds (e.g. alkyne metathesis), double bonds (e.g. alkene metathesis) or single bonds (e.g. alkane metathesis). The second differentiation can be made depending on whether the metathesized bonds are the same or not (Scheme 19). In Type 1 reactions, the same type of chemical bond is cleaved in the two different reaction partners. For example, in alkene metathesis two alkene bonds are exchanging their substituents. By contrast, Type 2 reactions involve exchange of the substituents between two chemically different bonds. An example is provided by carbonyl/alkene metathesis, wherein the substituents on the carbonyl groups and the alkene group are redistributed.
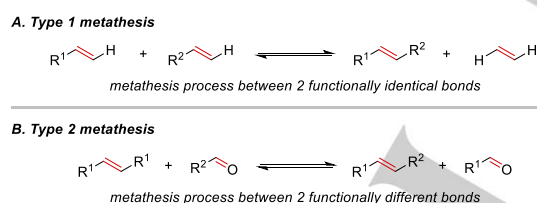


**Scheme 19.** Comparison of Type 1 and Type 2 metathesis reactions.

Due to the reversibility of isofunctional metathesis processes, an equilibrium mixture will form in the absence of a suitable driving force. The number of possible products accessible through a given metathesis reaction is strongly dependent on whether the bonds involved are directional or not (Scheme 20).[73] For instance, if non-directional bonds (e.g. an alkene bond) are employed, both sides of the bond can be transferred leading to several possible products. By contrast, directional bonds (e.g. an imine bond) help ensure that a given bond will only react at a single position, limiting the number of possible products. If two non-directional bonds are involved, as in alkene metathesis, a total of 10 compounds, including 8 new products, can be formed. If one

directional bond and one non-directional bond are involved, for example in a hypothetical alkene/imine metathesis reaction, the total number of possibilities is reduced to 9 with 7 new products formed. Finally, if two directional bonds are employed, for example in imine/imine metathesis, only 2 new products can be formed in addition to the starting materials. Bond directionality thus greatly affects the number of possible products that can form in different metathesis reactions and has a strong impact on selectivity considerations. It should also be noted that for this analysis the stereochemistry of the double bonds has not been considered. If one does take this into consideration, each reaction would lead to the formation of a substantially greater number of products.
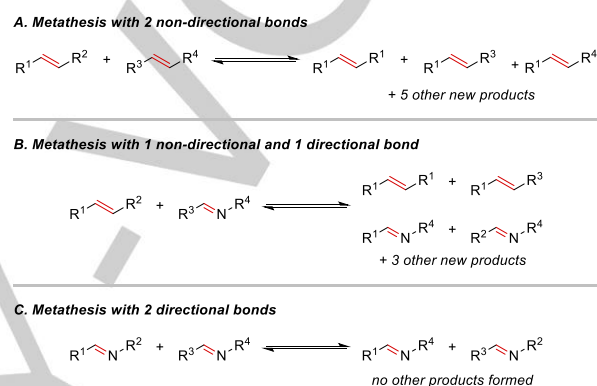


**Scheme 20.** Impact of the directionality of the metathesized bonds on the number of potential products.

Further complications can arise if there are more than one bond that can be metathesized in the starting materials. For instance, in a C−N/C−N metathesis of tertiary amines it is possible to exchange any of the 3 different substituents on each amine (Scheme 21). In the simplest case, where each amine has the same substituents (e.g. reaction between trimethylamine and triethylamine) then only 2 new products can be formed. However, if all the substituents on the 2 different tertiary amines are different (i.e. 6 different N-alkyl groups are present), then a total of 56 products can be formed, including the 2 starting materials.
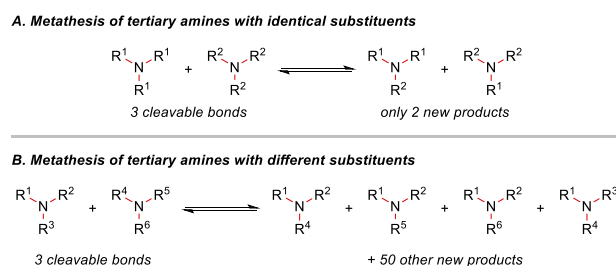


**Scheme 21.** Complications arising from the number of bonds that can undergo the metathesis process.

This section is mainly divided according to the bond type involved in the metathesis reactions with the first part focusing on the

metathesis of multiple bonds and the second part on the metathesis of various single bonds. Several of the examples included in this section only demonstrate the reversibility of their respective metathesis process by the establishment of an equilibrium. Although this is arguably not as useful synthetically, these examples are still included as they are of potential interest for further synthetic development and are also of relevance in the field of dynamic covalent chemistry.[74]
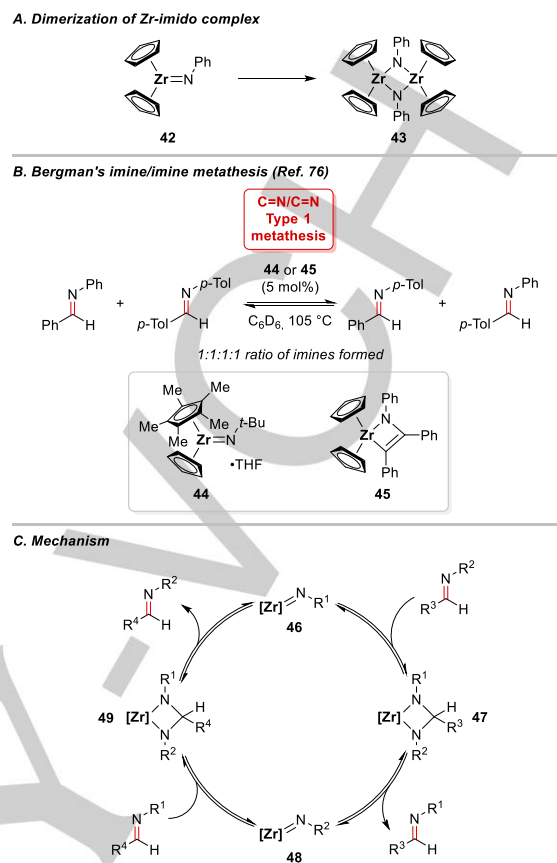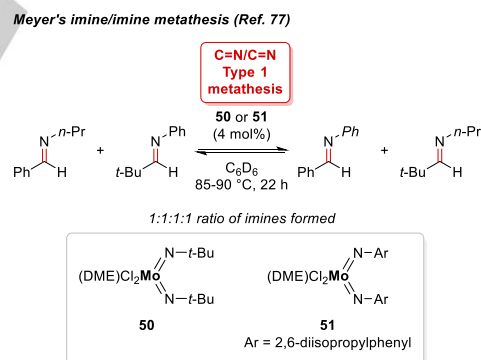
## 3.1. Imine/imine metathesis

The reversible formation of C=N containing functional groups such as imines, oximes and hydrazones from aldehydes are among the foremost reactions employed in the field of dynamic combinatorial chemistry.[74] Features including reversibility, fast reaction times and compatibility with aqueous solvents make these processes ideal for such studies. The success of these reactions and alkene metathesis has encouraged the examination of imine/imine metathesis as an alternative, $H_2O$ free protocol. There are several early reports of Brønsted acid catalysts capable of executing this reaction.[75] Another promising avenue for conducting imine metathesis is through a process analogous to alkene metathesis. This was the focus of work from the group of Bergman using Zr-imido complexes.[76] Initial attempts to develop a catalytic process were hampered by the propensity of Zr-imido complex **42** to irreversibly form dimer **43** (Scheme 22A). To inhibit this deleterious pathway, two strategies were conceived; the first introduces a bulkier Cp* ligand to disfavor dimerization, the second uses diphenylacetylene to stabilize the catalyst since this undergoes a reversible cycloaddition with Zr-imido complexes more rapidly than the undesired dimerization. Thus the catalytic imine metathesis of various *N*-aryl and *N*-alkyl imines was achieved, using catalysts **44** and **45**, as demonstrated by the establishment of an equilibrium between the initial and newly formed imines (Scheme 22B). The authors verified that the reaction proceeds through diazametallacyclobutane intermediates **47** and **49** and proposed a mechanism homologous to that of alkene metathesis proceeding through reversible [2+2] cycloaddition of the imine substrates and imido complexes **46** and **48** to give the diazametallacyclobutane intermediates **47** and **49** (Scheme 22C). It should be noted that since imine bonds are directional a smaller set of products are obtained in comparison to alkene metathesis.

The group of Meyer contemporaneously discovered that Mo complexes **50** and **51** are also efficient catalysts for imine/imine metathesis, as evidenced by the equilibration of two imines (Scheme 23).[77] Notably, both aryl and aliphatic aldimines were tolerated in this reaction. Since the Mo complexes contain two reactive sites, the authors were unable to determine if a mechanism analogous to alkene metathesis is operative. Further work from the Meyer group identified a Ta catalyst[78] and an iminophosphorane catalyst[79] capable of conducting imine/imine metathesis.

Other research in this area has shown that Ti,[80] Re[81] and Nb[82] complexes also catalyze imine-imine metathesis. Imine/imine metathesis via carbonyl intermediates[83] and imine/amine metathesis[84] have also been studied with a view to applications in dynamic combinatorial chemistry.



**Scheme 22.** Zr catalyzed imine/imine metathesis.



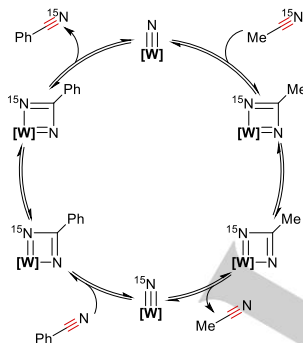**Scheme 23.** Mo catalyzed imine/imine metathesis.

## 3.2. Nitrile/nitrile metathesis

With alkyne metathesis finding widespread usage in the synthetic community,[3] the extension of this type of metathesis process to nitriles has garnered attention. In 2003, the group of Chisholm found that W complex **52** could catalyze nitrogen atom exchange between two nitriles (Scheme 24A).[85] Using $^{15}$N labeled acetonitrile, the formation of $^{15}$N labeled benzonitrile from unlabeled benzonitrile was detected by $^{15}$N NMR. The authors proposed that the reaction proceeds through a reversible [2+2] cycloaddition as in alkyne metathesis (Scheme 24B). Support for this hypothesis was provided by isotope labeling of the nitrile carbon in acetonitrile which was found not to be incorporated into benzonitrile. As with imine/imine metathesis, both partners in the nitrile/nitrile metathesis are directional and hence only 2 new products are formed in the reaction.
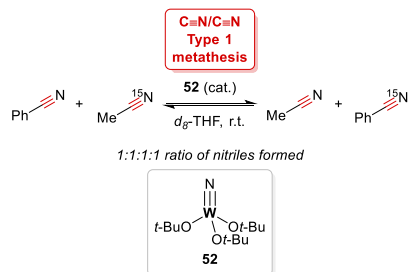


**Scheme 24.** W catalyzed nitrile/nitrile metathesis.

In 2005, the group of Johnson discovered that Mo catalyst **53** exhibited good activity for nitrile/nitrile metathesis (Scheme 25).[86] Initially, they were aiming to promote alkyne/nitrile metathesis (vide infra) but did not observe any formation of the expected alkylidyne complex. Studies using $^{15}$N labeled acetonitrile, though, showed that a nitrogen exchange between the nitrido complex and acetonitrile was taking place. Subsequently, they displayed that complex **53** could be applied to the scrambling of nitrogen atoms between acetonitrile and benzonitrile. To date, this reaction remains more of a mechanistic curiosity but there is potential to use this method for the synthesis of $^{15}$N labeled nitriles which are of value for NMR studies.
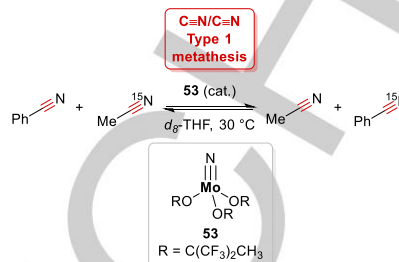


**Scheme 25.** Mo catalyzed nitrile/nitrile metathesis.

### 3.3. Nitrile/alkyne metathesis

The development of nitrile/nitrile metathesis hinted at the possibility of achieving nitrile/alkyne metathesis. This would provide a valuable alternative to alkyne metathesis given the relatively facile access to nitrile containing compounds. Additionally, the directionality of the nitrile bond should impart greater control over the reaction. However, early attempts were inhibited by the greater stability of Mb- or W-nitride complexes over the corresponding alkylidyne complexes.[87] The group of Johnson found that introduction of fluorinated alkoxides into W-nit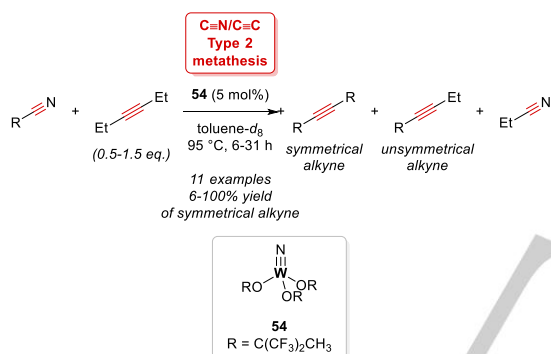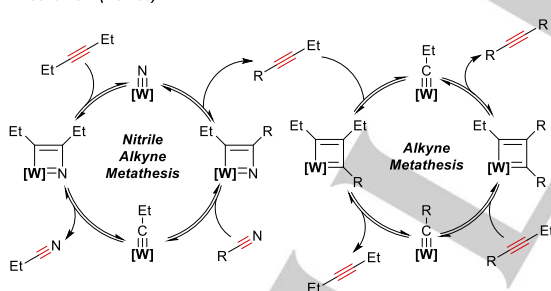ride complex **54** permitted exchange of a nitrido ligand for an alkylidyne ligand.[88] Encouraged by this result, they investigated the ability of **54** to catalyze nitrile/alkyne metathesis and found that reaction of aryl nitriles with 3-hexyne afforded a mixture of the aryl nitrile along with the symmetrical and unsymmetrical alkyne products plus propionitrile (Scheme 26A). Following optimization, various symmetrical alkynes were prepared by reacting the parent nitrile with 3-hexyne.

nitrido and alkylidyne complexes (Scheme 26B). Alkyne cross metathesis, which also proceeds via a [2+2]-cycloaddition-cycloreversion mechanism, leads to formation of the symmetrical alkyne product.

Recently, the group of Fürstner have explored a similar reaction between Schrock alkylidynes and diazoniums as an alternative pathway to nitriles.[90] This has led to the development of a Rh catalyzed metathesis of diazoniums and azobenzene.[91] However, as this reaction is not isofunctional, it will not be discussed further.



**Scheme 26.** W catalyzed nitrile/alkyne metathesis.

Further studies from the group of Johnson highlighted the critical role of the alkoxide species in establishing an equilibrium.[89] Different catalyst resting states were found with -OC(CF$_3$)(CH$_3$)$_2$ alkoxide ligands favoring W-nitrido species and -OC(CF$_3$)$_2$CH$_3$ ligands preferring carbyne species. Complex **54**, with -OC(CF$_3$)$_2$CH$_3$ ligands, proved more active with all the steps for the nitrile/alkyne cross metathesis catalytic cycle proving reversible. DFT studies indicate that the reaction proceeds via [2+2]-cycloaddition-cycloreversion to interconvert between the
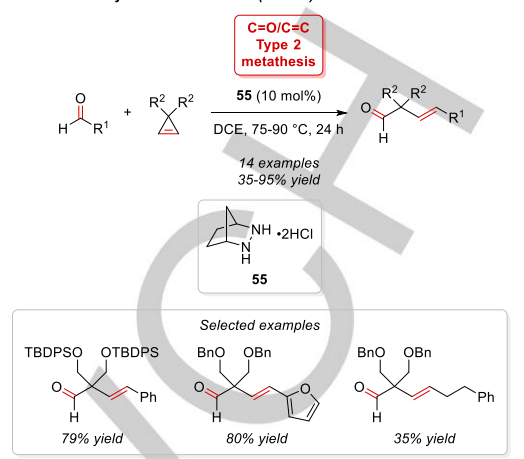
### 3.4. Carbonyl/alkene metathesis

The transformation of a carbonyl group into an alkene is a fundamental reaction in organic synthesis.[20] Traditionally this has been realized through the Wittig reaction and other related methodology, including Horner-Wadsworth-Emmons, Peterson and Julia type reactions, which have been readily adopted by the synthetic community. Due to the greater strength of the C=O bond in comparison to the C=C bond, these methods rely upon the concomitant formation of a strong bond in the by-product as a driving force. In the case of the Wittig reaction, the formation of the P=O bond delivers this driving force. As a consequence, a drawback of these methods is the stoichiometric waste by-products formed which can be challenging to separate from the desired product. Attempts to develop a catalytic process with a mechanism akin to alkene metathesis have been inhibited by the irreversible formation of a metal oxo species. Thus, these processes have required a stoichiometric amount of metal.[92,93]

Recently, alternative approaches to execute carbonyl/alkene metathesis have been developed. The first of these, from the group of Lambert, utilizes an organocatalytic reaction manifold (Scheme 27A).[94] Bicyclic hydrazine **55** was found to catalyze the carbonyl-alkene metathesis of cyclopropenes and aldehydes to form β,γ-unsaturated aldehydes. Mechanistically, the reaction is proposed to be initiated by condensation of the catalyst and aldehyde to form hydrazonium **56** (Scheme 27B). Isomerization of the geometry of the C=N bond occurs rapidly and (*E*)-**56** undergoes [3+2] cycloaddition with the cyclopropane, forming adduct **57**. Following proton transfer, cycloreversion occurs, driven by the opening of the cyclopropane ring, to yield hydrazonium **59** which, upon hydrolysis, gives the product and regenerates the hydrazine catalyst **55**. To support this proposal, (*Z*)-**56** was synthesized and found to react with cyclopropene to afford the product. Additionally, intermediate **56** was observed by ^{1}H NMR during the course of the reaction.

Later, the group of Franzén reported another organocatalytic carbonyl/alkene metathesis reaction (Scheme 28A).[95] This method utilizes catalytic trityl tetrafluoroborate as a Lewis acid to effect the intermolecular cross metathesis of various benzaldehydes with *geminal*-dimethyl substituted alkenes to afford trans-substituted styrenes. An excess of the aldehyde substrate was required to drive the reaction to high conversion and acetone was produced as a by-product. The authors propose that the reaction proceeds by attack of the alkene into the Lewis acid activated aldehyde **60** with formation of the more stable tertiary carbocation dictating the regioselectivity observed in **61** (Scheme 28B). An oxetane intermediate **62** is then formed by attack of the O lone pair into the carbocation. This oxetane breaks down to give a benzylic carbocation **63** which then expels the product and Lewis acid bound acetone **64**.
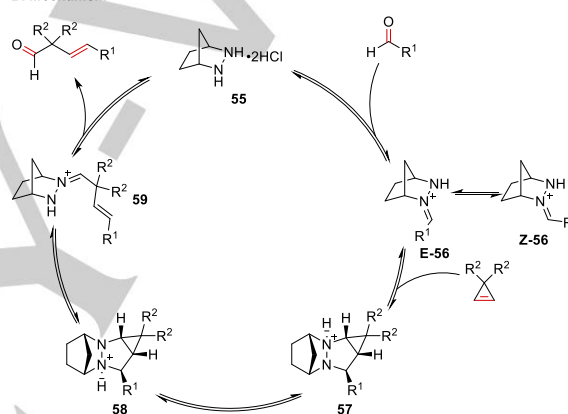


**Scheme 27.** Hydrazine catalyzed carbonyl/alkene metathesis.

In 2016, the group of Schindler reported an Fe catalyzed ring-closing, carbonyl/alkene metathesis (Scheme 29A).[96] They found that aryl ketones reacted with *geminal*-dimethyl substituted alkenes to form either a cyclopentene or cyclohexene product with concomitant release of acetone as a by-product. The reaction exhibited broad functional group tolerance and proved applicable to the synthesis of tetra-substituted alkenes. While *geminal*-dimethyl substituted alkenes afforded the highest reaction yields, other alkenes bearing cis or trans aryl groups also proved to be suitable substrates. Detailed mechanistic studies were performed to elucidate the mechanism of this process (Scheme 29B).[97] EPR studies indicate the binding of $FeCl_3$ to the carbonyl and, with *geminal*-dimethyl substituted alkenes, attempts to trap any potential carbocation intermediates failed. As a consequence, the authors propose that formation and fragmentation of the intermediate oxetane **66** is concerted and this was ratified by DFT studies. The Schindler group have also applied this methodology towards the synthesis of polycyclic aromatic hydrocarbons[98] and dihydropyrroles.[99]

**A. Franzén's carbonyl/alkene metathesis (Ref. 95)**



*Selected examples*

59% yield    59% yield    51% yield
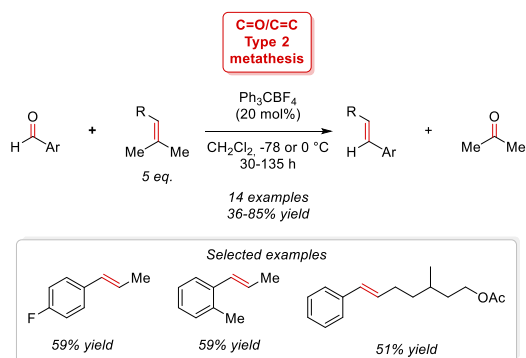
**B. Mechanism**
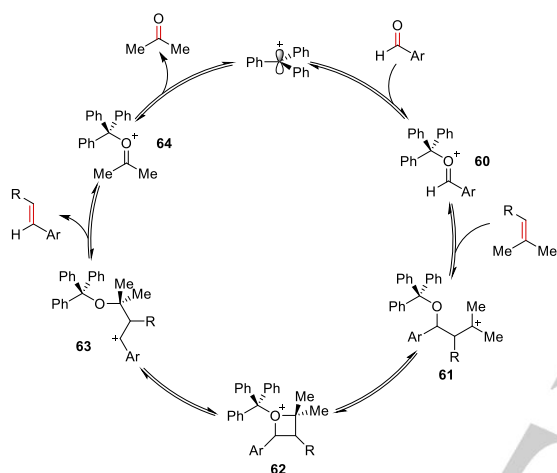


**Scheme 28.** Tritylium catalyzed carbonyl/alkene metathesis.

Shortly after the initial publication from the group of Schindler, the group of Li also reported an FeCl$_3$ catalyzed ring-closing, carbonyl/alkene metathesis.[100] Their protocol is similar to that employed by Schindler and co-workers, with the exception that aryl substituted alkenes were studied. A notable finding in their work, though, was the synthesis of 2,5-dihydropyrroles (Scheme 30). Using FeCl$_3$ as catalyst alone failed to afford the desired product but addition of excess allyltrimethylsilane **68** proved effective in promoting the reaction. Currently, the role of the silane is unclear but it is possible that it is either coordinating to the catalyst to generate a more active species or it serves as a scavenger for the benzaldehyde by-product.

In the above examples, only the intermolecular cross metathesis or intramolecular ring-closing metathesis could be achieved with the catalysts investigated. Recently, the groups of Ho and Nguyen demonstrated that tropylium salt **69** is a more versatile catalyst for carbonyl/alkene metathesis.[101] Aside from proving effective in both cross metathesis and ring-closing metathesis reactions, the investigators were also able to perform ring-opening carbonyl/alkene metathesis to prepare γ,δ- or δ,ε-unsaturated ketones from aldehydes and cyclic alkenes (Scheme 31). The scope of the alkene reaction partner was largely limited to 1-methylcyclopentene as no reaction was observed with larger rings and problems were encountered with smaller rings due to the

volatility of the substrates. The authors also noted that the methyl group on the alkene appears to be necessary for the reaction as no product was obtained with cyclopentene or 1-phenylcyclopentene. Recently, the group of Schindler disclosed their approach to ring-opening carbonyl/alkene metathesis using GaCl$_3$ as the catalyst.[102]

Another catalyst system to promote carbonyl/alkene metathesis was reported by the group of Tiefenbacher.[103] Using a supramolecular host and HCl they were able to perform a ring-closing metathesis to produce cyclopentenes and cyclohexenes. Control experiments verified that the reaction proceeds within the cavity of the supramolecular host and it is thought that the host stabilizes a putative cationic intermediate through a cation-π interaction. The Tiefenbacher group have previously demonstrated the suitability of the supramolecular host for conducting cationic cascade reactions.[104]

**A. Schindler's FeCl$_3$ catalyzed carbonyl/alkene metathesis (Ref. 96)**



*Selected examples*

99% yield    76% yield    52% yield    59% yield    87% yield
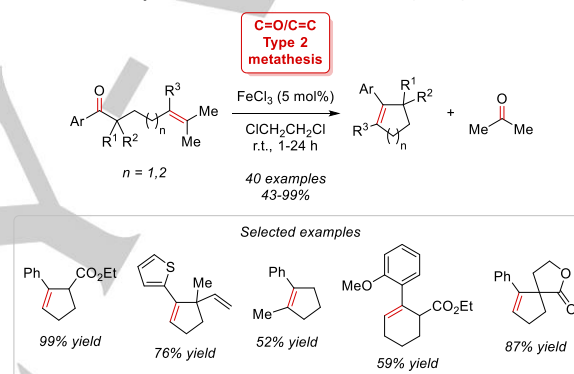
**B. Mechanism (Ref. 97)**
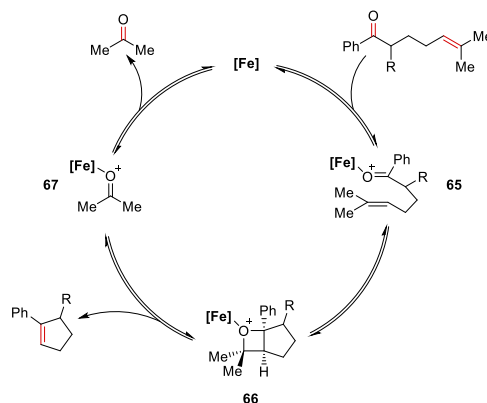


**Scheme 29.** Fe catalyzed ring-closing carbonyl/alkene metathesis.

*Li's ring-closing carbonyl/alkene metathesis (Ref. 100)*
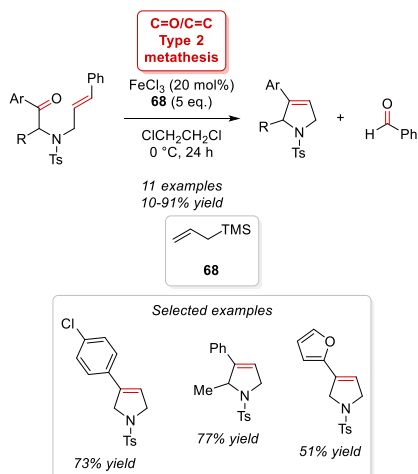


**Scheme 30.** Fe catalyzed ring-closing carbonyl/alkene metathesis for the synthesis of dihydropyrroles.

*Ho & Nguyen's ring-opening carbonyl/alkene metathesis (Ref. 101)*
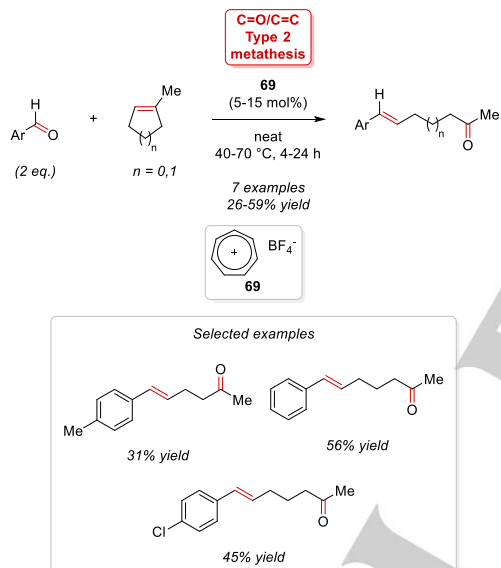


**Scheme 31.** Tropylium catalyzed ring-opening carbonyl/alkene metathesis

## 3.5. C−N metathesis reactions with amides

While transesterification is a well established synthetic transformation,[105] the related transamidation reaction, a C−N/N−H, Type 2 metathesis process, is relatively less well developed. An obvious challenge for transamidation is the low reactivity of the amide group and thus harsh conditions are required. The acidic NH proton in secondary amides also poses problems and thus early reports used stoichiometric quantities of Lewis acids to promote the reaction.[106] In 2003, the groups of Gellman and Stahl disclosed the first catalytic transamidation reaction using either Ti(NMe$_2$)$_4$ or Sc(OTf)$_3$.[107] This has instigated the development of several other transamidation processes, from both the Gellman and Stahl groups[108] and others, typically using Lewis acid catalysts.[109] More recently, the groups of Garg[110] and Szostak[111] have described Ni- or Pd catalyzed transamidations of activated Boc-protected amides, although these reactions are not isofunctional.

The groups of Gellman and Stahl have also developed a Type 1 C−N/C−N metathesis of secondary amides (Scheme 32).[112] This reaction is initiated by *N*-benzyldiacetamide **70** and a base, with NaHMDS, KHMDS and KH all proving effective. The reaction tolerates both *N*-aryl and *N*-alkyl substrates with only *N*-alkyl/*N*-alkyl pairs failing to establish an equilibrium. This was attributed to enolization of the imide intermediates interfering with the reaction process. To circumvent this issue, non-enolizable *N*-alkyl amides were tested and these were able to form an equilibrium mixture.

*Gellman & Stahl's imide initiated amide/amide metathesis (Ref. 112)*



*Forward reaction: **71**:**72** = 1:0.73*
*Reverse reaction: **71**:**72** = 1:0.66*

*12 other examples*
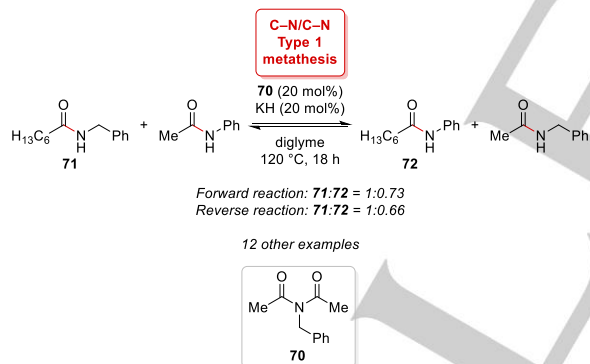
**Scheme 32.** Imide initiated C−N/C−N metathesis of secondary amides.

Follow-up work from Gellman, Stahl and co-workers identified Zr(NMe$_2$)$_4$ as a suitable catalyst for the C−N/C−N metathesis of tertiary amides, which proceeds at room temperature (Scheme 33).[108e] Only N-alkyl amides were investigated but the reaction exhibits improved tolerance for enolizable amides. In the reaction of *N*-aryl amides, higher temperatures were required. Time-course experiments identified that equilibrium is established within minutes in both the forward and reverse reactions.

*Gellman and Stahl's Zr catalyzed amide/amide metathesis (Ref. 108e)*



*Forward reaction: **73**:**74**:**75**:**76** = 20:26:26:28*
*Reverse reaction: **73**:**74**:**75**:**76** = 20:26:26:28*

*11 other examples*
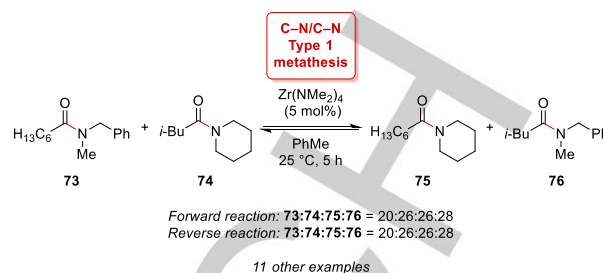
**Scheme 33.** Zr catalyzed C−N/C−N metathesis of tertiary amides.

## 3.6. C−N metathesis reactions with amines

The development of the borrowing hydrogen strategy has unleashed a plethora of novel catalytic methodologies.[7] Notable among these is the use of alcohols as alkylating reagents via in situ formation of a carbonyl intermediate. Alternatively, amines can be used as an alkylating source in what can be considered a metathesis reaction. Early work in this area was undertaken by the group of Concilio who demonstrated that secondary amines could be obtained from the parent primary amine with concomitant formation of ammonia using a Ru catalyst (Scheme 34).[113,114]

*Concilio's C–N/N–H metathesis (Ref. 113)*



**Scheme 34.** Ru catalyzed alkylation of amines via borrowing hydrogen strategy.

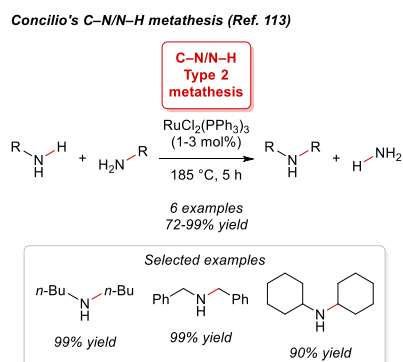More recently, the group of Beller found that Shvo's catalyst **77** could effect the alkylation of anilines using primary amines as an alkyl donor (Scheme 35A).[115] Formation of ammonia as a side product provides a driving force for this reaction although an excess of aniline is also employed. Key to the success of this reaction is that only the primary amine can undergo dehydrogenation to form an iminium intermediate (Scheme 35B). This can then be attacked by the aniline, which following elimination of ammonia and hydrogenation of the imine leads to product formation. However, it is also possible for the alkyl amine to attack into the iminium intermediate and this leads to formation of a secondary amine which is also an effective alkyl source. This was the focus of further work from the same group, who identified that secondary or even tertiary amines could be deployed as an alkyl source.[116] This is particularly attractive in the case of volatile primary amines with short alkyl chains as they can be substituted for a secondary or tertiary amine instead. Alkylation of alkyl amines such as 1-adamantylamine, wherein dehydrogenation to form an imine is not possible, was also developed[117] and reaction of anilines with cyclic secondary amines was shown to afford pyrrolidine or piperidine substituted aromatics.[118] This latter reaction involves a double dehydrogenation of the cyclic substrate.

*A. Beller's C-N/N-H metathesis of amines (Ref. 115)*
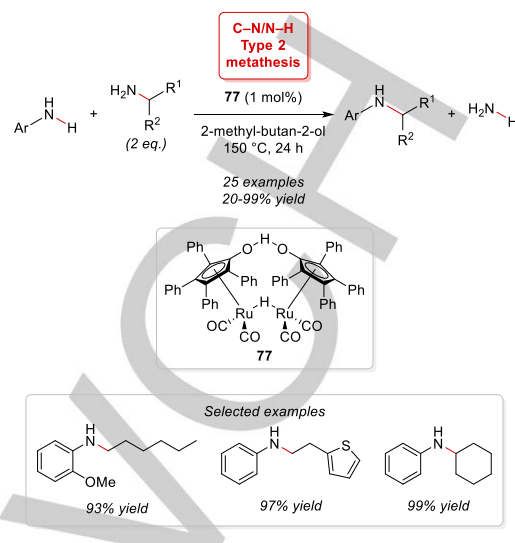


*B. Mechansim*
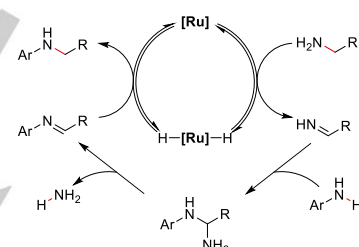


**Scheme 35.** Ru catalyzed alkylation of anilines using amines as an alkyl source.

A limitation of the work by the group of Beller was the requirement for one of the amines to be unable to undergo dehydrogenation (i.e. an aniline or *tert*-alkyl amine). This minimizes the possibility of side reactions occurring but narrows the scope of the methodology. However, the group of Williams found that, using an Ir catalyst, aliphatic amines could be selectively alkylated with di-*iso*-propylamine to afford *N*-alkyl-*N*-*iso*-propylamines (Scheme 36).[119] At this junction, the reasons behind this selectivity are unclear although the use of an excess of (*i*-Pr)$_2$NH and the volatility of (*i*-Pr)NH$_2$ are likely to play a role. The authors, demonstrated, though, that dibenzylamine can form under the reaction conditions in the absence of (*i*-Pr)$_2$NH. However, submitting dibenzylamine to the reaction conditions in place of benzylamine led to formation of *N*-*iso*-propyl-*N*-benzylamine suggesting that the reaction is self-correcting.
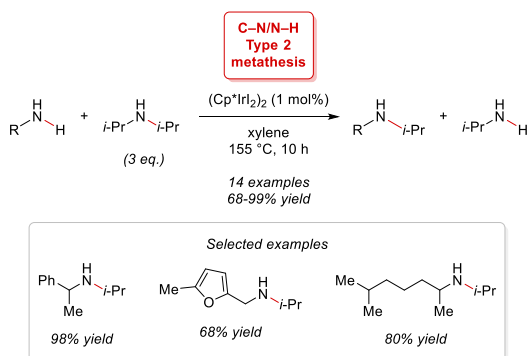
**Scheme 36.** Ir catalyzed alkylation of amines using (*i*-Pr)$_2$NH as an alkyl source.

Related investigations have been conducted towards the development of C−N/C−N metathesis processes of tertiary amines.[120] Currently, these reactions are limited in scope but do hold potential as preliminary results.

## 3.7. C−P metathesis reactions

Phosphine ligands have played an important role in the advent of transition metal catalyzed reactions.[121,122] However, it has been known that, under catalytic conditions, phosphine ligands can undergo aryl group exchange.[123] There have been several studies investigating this reaction and various transition metals have been shown to effect aryl group exchange including Co, Ni, Ru, Rh, Pd and Os. With Pd, the reaction is proposed to proceed via reductive elimination of a phosphine ligand and an aryl group from a Pd complex to form a tetraarylphosphonium salt. At this juncture, oxidative addition occurs and if there are different aryl groups present then this leads to scrambling of the aryl groups on the phosphine. This reaction manifold has been applied to the synthesis of various tetraarylphosphonium salts which have subsequently been applied as an aryl group source in cross-coupling reactions.[124]
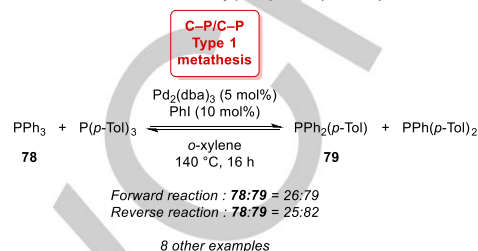
In 2017, the group of Morandi advanced this methodology to conduct $C(sp^2)$−P/$C(sp^2)$−P metathesis.[125] Initial studies examined the cross metathesis of triphenylphosphine with various arylphosphines (Scheme 37A). A catalytic mixture of $Pd_2(dba)_3$ and iodobenzene was used to generate the arylpalladium halide required to facilitate aryl group exchange. This reaction yields a mixture of phosphines and in all cases a nearly identical distribution was obtained for the forward and reverse reaction. Aryl groups bearing different functional groups were tolerated in the reaction including heterocycles. Reaction with alkyl substituted phosphines was not observed. Following this work, the ring-closing $C(sp^2)$−P/$C(sp^2)$−P metathesis of various bisphosphines was also performed to afford novel P-heterocycles (Scheme 37B). Reaction with axially chiral substrates such as BINAP led to loss of chirality but with SPINAP, wherein racemization is more challenging, no depreciation in enantiopurity was detected.

Contemporaneously, the group of Chatani and Tobisu also reported a Pd catalyzed $C(sp^2)$−P/$C(sp^2)$−P ring-closing metathesis for the formation of P-heterocycles from bisphosphines (Scheme 38A).[126] Unlike the work from Morandi and co-workers, addition of aryl iodide was not required and the authors propose that the reaction does not necessarily proceed via oxidative addition of a phosphonium intermediate (Scheme 38B). Instead, chelation assisted $C(sp^2)$−P oxidative addition is speculated to be occuring. Reductive elimination from the resulting intermediate **80** affords cyclic phosphonium intermediate **81** and phosphopalladate **82**. The phosphole is formed by oxidative addition mediated by the phosphopalladate which forms **83** that can then undergo reductive elimination to reform Pd(0) and triphenylphosphine as a by-product.

The group of Chatani and Tobisu have also developed another route to phosphole derivatives via a Type 2 $C(sp^2)$−P/$C(sp^2)$−H ring-closing metathesis (Scheme 39A).[127] In contrast, to the other work discussed in this section, this reaction requires a monophosphine as a starting material as opposed to a bisphosphine. Purification is also simplified as benzene is produced as the only side product. Mechanistic probes led the authors to propose a catalytic cycle wherein the Pd catalyst undergoes cyclometalation to form **84**, followed by reductive

elimination giving a neutral Pd species and phosphonium **85** (Scheme 39B). The phosphonium can then undergo oxidative addition, forming the phosphole product and Pd complex **86**. Closure of the catalytic cycle is realized by reaction of **86** with acetic acid, which is formed in the initial cyclometalation.



**Scheme 37.** Pd catalyzed C−P/C−P metathesis.

*A. Chatani & Tobisu's ring-closing metathesis of bisphosphines (Ref. 126)*



9 examples
52-94% yield

isolated as
phosphine oxide

*Selected examples*

93% yield  82% yield  73% yield  94% yield
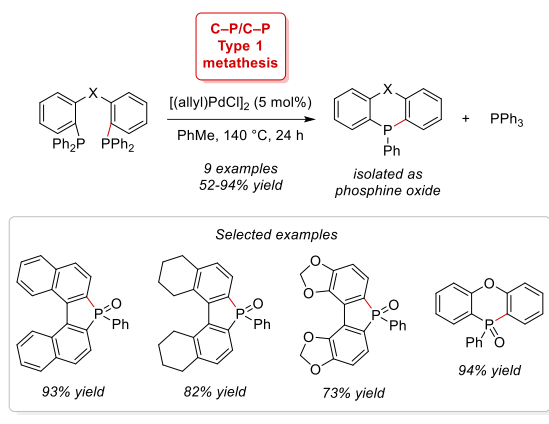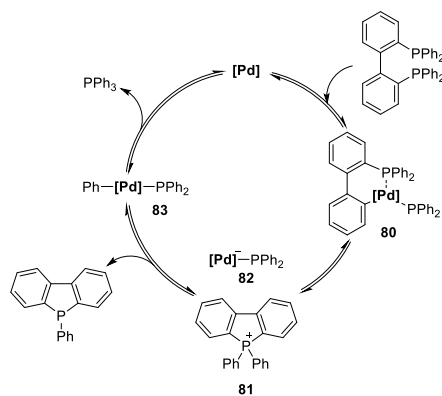
*B. Mechanism*



**Scheme 38.** Pd catalyzed ring-closing C−P/C−P metathesis.

*A. Chatani & Tobisu's ring-closing metathesis of monophosphines (Ref. 127)*



19 examples
54-94% yield

isolated as
phosphine oxide

*Selected examples*

69% yield  84% yield  85% yield

*B. Mechanism*



**Scheme 39.** Pd catalyzed ring-closing C−P/C−H metathesis.

### 3.8. C−O metathesis reactions

There are various C−O metathesis reactions that are crucial both in nature and in the chemical industry. Transesterification is probably the pro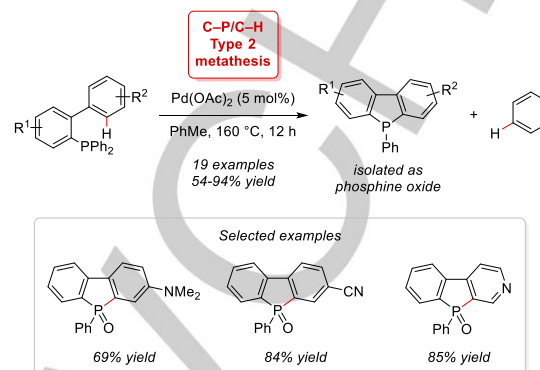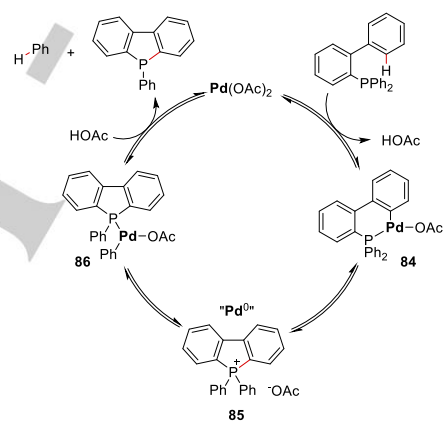totype example and has found significant applications including the production of polyesters and biofuels.[105] Other C−O metathesis reactions include transacetalization, transketalization and orthoester exchange.[128] Significant research has examined these transformations, particularly in the field of dynamic combinatorial chemistry, and in some cases asymmetric methodology has been elaborated.[129] However, given the extensive amount of research in this area, no further discussion will be included in this review.

By contrast, processes invoking substituent exchange of ethers, another key O-functionality, are considerably less prevalent. Progress in this field was made by the group of Morandi.[130] They found that Lewis acidic Fe(OTf)$_3$ could promote the cyclization of diethers to form cyclic ethers through a ring-closing C(sp$^3$)−O/C(sp$^3$)−O metathesis (Scheme 40A). Although in the majority of the examples gaseous dimethylether is formed as the by-product, the authors found that this is not necessarily the driving force for the reaction as diethers that form less volatile dialkyl ethers as a by-product gave comparable yields. In addition, attempts to perform ring-opening metathesis of tetrahydropyran through reaction with dibutyl ether were met with failure. Further mechanistic studies led the authors to propose a mechanism for the reaction wherein one ether is activated by the Lewis acid and the other ether can thus attack in to form a cyclic oxonium **88** (Scheme 40B). The product is consequently formed by attack of a putative Fe methoxide species.

A related C(sp$^2$)−O/O−H metathesis of aryl ethers was just reported by the groups of Murai and Takai.[131] They found that Bi(OTf)3 was an effective catalyst to activate aryl methyl ethers for transetherification with simple aliphatic alcohols. Ring-closing C(sp$^3$)−O/O−H metathesis was also demonstrated.
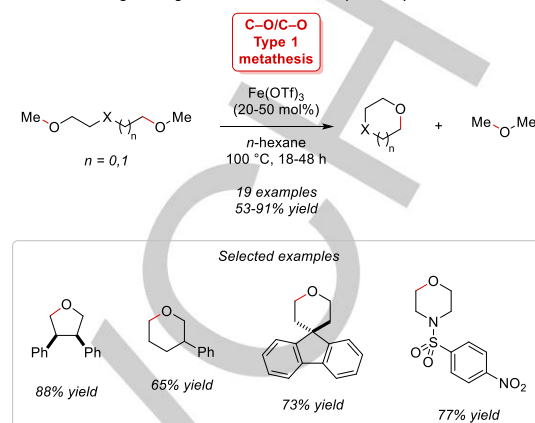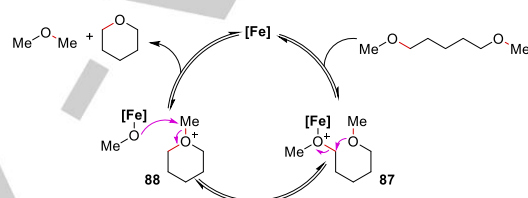


**Scheme 40.** Pd catalyzed ring-closing C−P/C−H metathesis.

## 3.9. C−S metathesis reactions

As with C−O metathesis, several C−S metathesis reactions have been developed with a view to applications in dynamic combinatorial chemistry.[74] These include thioester exchange,[132] a process analogous to transesterification, thioacetal exchange[133] and probably most importantly disulfide exchange.[134] This latter process plays a crucial role in biological systems including protein folding.[135]

By comparison, metathesis reactions with aromatic thioethers are scarce despite their prevalence across the molecular sciences.[136] Cross-coupling processes analogous to the Buchwald-Hartwig reaction have emerged that provide expedient access to this motif.[137] A metathesis process, wherein one of the substituents can 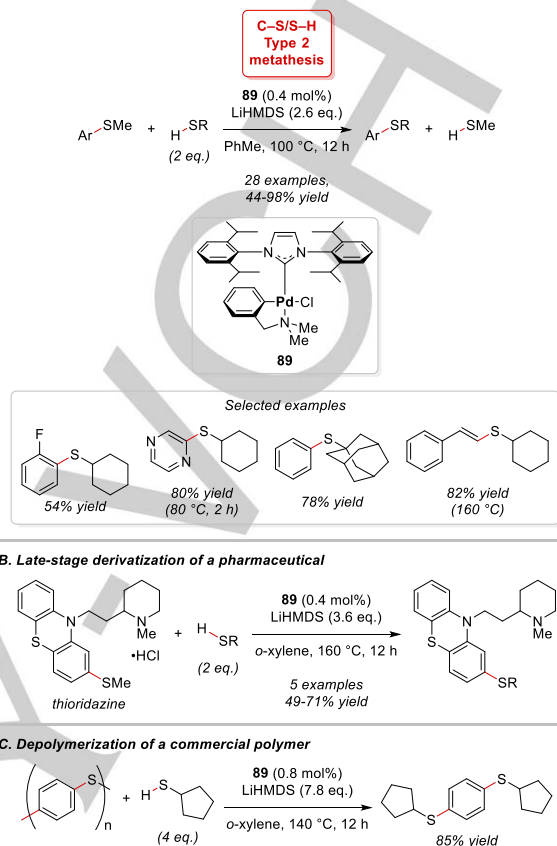be exchanged with another, would be complementary to cross-coupling methodologies as it would enable the facile diversification of thioethers. There have been sporadic reports of C−S metathesis reactions[138] but the first general method was reported in 2017 by the group of Morandi.[125] They developed a C(sp²)−S/S−H metathesis reaction using Pd precatalyst **89** with LiHMDS used to generate a thiolate in situ (Scheme 41A). They found that the aromatic methyl thioethers reacted with thiols to afford novel aromatic alkyl thioethers. An excess of the thiol was required and it is proposed that the poor solubility of the lithium thiomethoxide by-product provides sufficient driving force to favor formation of the products. This is supported by the diminished yields obtained when using either NaHMDS or KHMDS. This procedure demonstrated a wide tolerance to substituents on the aromatic ring and also proved effective with bulky thiol substrates. It was applied to the rapid, late-stage generation of a library of thioridazine derivatives, an anti-psychotic that was recently removed from the market due to severe side effects (Scheme 41B). Another niche application was found in the depolymerization of polyphenylene sulfide (PPS), which cleanly furnishes a monomeric unit with no oligomers detected at the end of the reaction (Scheme 41C).

Remarkably, the metathesis of thiophenols was also amenable under similar reaction conditions and again exhibited good tolerability, particularly with bulky thiols (Scheme 42A).[125] Notably, no homodimerization products were observed although it was possible to achieve this in the absence of an aliphatic thiol (Scheme 42B). Diphenylselenide could also be procured through a C(sp²)−Se/Se−H metathesis by subjecting selenophenol to the reaction conditions (Scheme 42C).

Finally, C(sp²)−S/C(sp²)−S cross metathesis was also demonstrated (Scheme 42D).[125] An equimolar mixture of two diaryl sulfides **90** and **91** gave a mixture of the starting materials plus the cross metathesis product **92**. Subjecting the mixed diaryl sulfide **92** to the same reaction conditions gave a nearly identical mixture of products, underlining the reversible nature of the process. A co-catalytic amount of lithium thiophenolate, generated in situ by reaction of thiophenol and LiHMDS, was required as an initiator for the reaction to proceed. An unusual feature of this Type 1 metathesis is that it is realized through subsequent C(sp²)−S/S−H metathesis processes.



**Scheme 41.** Pd catalyzed C−S/S−H metathesis with aromatic thioethers.

**A. Morandi's C–S/S–H metathesis with thiophenols (Ref. 125)**

C–S/S–H
Type 2
metathesis

**89** (0.4 mol%)
LiHMDS (3.9 eq.)

Ar–SH  +  H–SR  $\xrightarrow{\text{o-xylene, 160 °C, 12 h}}$  Ar–SR  +  H–SH

(2 eq.)

16 examples,
37-92% yield

*Selected examples*

MeO–C6H4–S–n-C8H17
76% yield

Ph–S–CH2CH2–NMe2
60% yield

Ph–S–(bornyl)
92% yield

**B. Homo-metathesis of thiophenol**

C–S/S–H
Type 2
metathesis

**89** (0.4 mol%)
LiHMDS (1.5 eq.)

Ph–SH  +  H–S–Ph  $\xrightarrow{\text{o-xylene, 160 °C, 12 h}}$  Ph–S–Ph  +  H–SH

76% yield
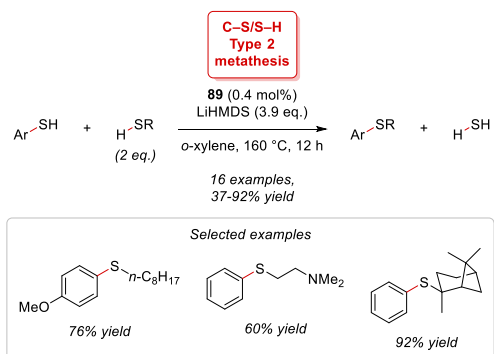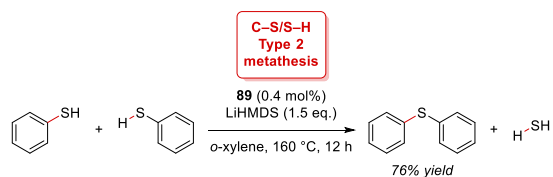
**C. Homo-metathesis of selenophenol**

C–Se/Se–H
Type 2
metathesis

**89** (0.4 mol%)
LiHMDS (1.5 eq.)

Ph–SeH  +  H–Se–Ph  $\xrightarrow{\text{o-xylene, 160 °C, 12 h}}$  Ph–Se–Ph  +  H–SeH

96% yield
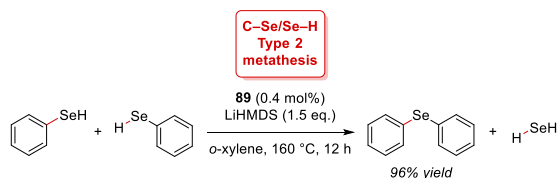
**D. Equilibration of diarylthioethers**

C–S/C–S
Type 1
metathesis

*Forward reaction*
**90**:**91**:**92** = 27:21:5
*Reverse reaction*
**90**:**91**:**92** = 26:20:54

**89** (0.4 mol%)
PhSH (10 mol%)
LiHMDS (50 mol%)

Ph–S–Ph  +  Ar–S–Ar  $\rightleftharpoons$  Ph–S–Ar
**90**         **91**                              **92**
              Ar = 4-MeOC6H4

Ph–S–H

C–S/S–H
Type 2
metathesis

C–S/S–H
Type 2
metathesis

Ph–S–H

Ph–S–Ph  +  Ph–S–Ar
      +  Ar–S–H
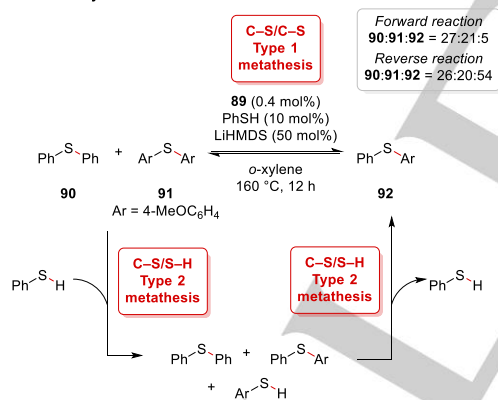
**Scheme 42.** Pd catalyzed C−S/S−H metathesis with aromatic thiophenols.

## 3.10. C−halogen metathesis reactions

The oxidative addition of alkyl halides has gained a lot of attention recently in efforts to extend the utility of cross-coupling reactions to form $C(sp^3)$−$C(sp^3)$ and $C(sp^3)$−$C(sp^2)$ bonds.[139] However, Ir and Rh complexes have been known to effect this process with simple alkyl iodides since the 1960s.[140] Moreover, it has also been demonstrated that this process can be reversible and this facet was exploited by Lyons to achieve a halogen exchange reaction between alkyl halides (Scheme 43).[141] It was shown that a Rh complex was effective in promoting halide exchange between a monohalide and either dichloromethane or dibromomethane. The dihalomethane was used in a 10-fold excess to ensure complete conversion of the monohalide. Reactions were conducted under a pressurized CO atmosphere but no carbonylation of the alkyl halides was observed.
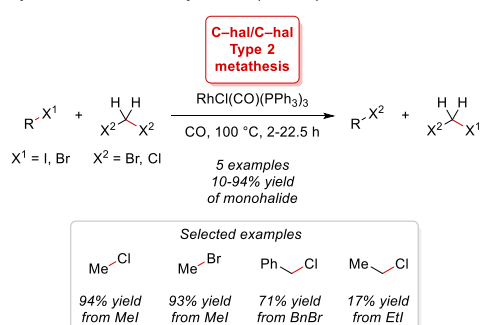


**Scheme 43.** Rh catalyzed C−hal/C−hal metathesis.

A related C−halogen/C−H Cu catalyzed metathesis reaction of alkynes has also been developed. The group of Hein chose to pursue the study of the kinetics of this reaction given its relevance to Glaser-Hay and Cadiot-Chodkiewicz couplings.[142]

## 3.11. C−C metathesis reactions

Performing reactions through the cleavage of C−C bonds remains a significant challenge in organic synthesis, particularly in the case of non-polarized C−C bonds.[143] Common strategies to achieve this have relied on release of ring strain, cleavage of 1,3-diketones or through intramolecular chelation. For inst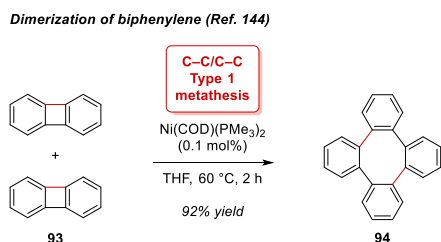ance, an early example of a C−C/C−C metathesis reaction emerged for the preparation of tetraphenylene **94** from biphenylene **93** (Scheme 44).[144] This reaction has been developed using Ni, Pd and Pt catalysts and relies on the release of ring strain.

*Dimerization of biphenylene (Ref. 144)*



**Scheme 44.** Ni catalyzed synthesis of tetrabenzocyclooctatetraene **93** via C−C/C−C metathesis.

Another early example of a C−C metathesis reaction that does not rely on a typical strategy for cleaving C−C bonds is the transfer alkylation of *tert*-butyl groups between aromatics through Friedel-Crafts type reactivity and is promoted by Lewis acids.[145] As a result of this reactivity, *tert*-butyl groups have been engaged as positional protecting groups in the synthesis of aromatics. High conversions are typically achieved by performing the reaction in an excess of toluene with 4-*tert*-butyltoluene formed as a by-product.

To circumvent the challenge of breaking a C−C single bond, the groups of Goldman and Brookhart instead used transfer hydrogenation and alkene metathesis in tandem to achieve a formal C−C/C−C metathesis (Scheme 45A).[146] In this Ir/Mo co-catalyzed process, the C−C bond is transformed into a C=C bond by transfer hydrogenation and, although this bond is stronger than the C−C bond, substituent exchange can be easily induced by alkene metathesis (Scheme 45B). This leads to the formation of new alkenes which, following hydrogenation, affords the alkane product. An unusual feature of this reaction is the combination of two catalytic isofunctional reactions, transfer hydrogenation and alkene metathesis, that results in a novel isofunctional reaction. It should be noted that there is no control over this reaction and that a complex mixture of linear alkanes is obtained. This results from the lack of directionality associated with the C−C bond and also the potential for any of the C−C bonds to be cleaved, including in the products.

In 2012, the group of Arisawa and Yamaguchi reported an unusual acyl transfer catalyzed by a Rh complex (Scheme 46).[147] They initially demonstrated that asymmetrically substituted diarlypropan-2-one **97** disproportionated to form the two symmetrically substituted diarlypropan-2-ones **98** and **99**. A statistical distribution of products is obtained suggesting a reversible process is operative. Following this result, the authors

found that a similar catalyst system enabled acyl exchange between phenyl benzyl ketones and thioesters.

More recently, the group of Zhou reported a compelling example of C−C/C−H metathesis using a lanthanide catalyst (Scheme 47A).[148] In their work, Lu([N(SiMe₃)₂]₃ catalyzed alkynyl exchange between propargyl amines and terminal alkynes. An impressive substrate tolerance was exemplified in this reaction with a variety of functional groups on either alkyne tolerated. Secondary propargyl amines were required for the success of the reaction although aryl, benzyl and methyl substituted propargylamines all proved effective. To ensure good yields of the product progarylamine, an excess of terminal alkyne was employed. On the basis of their mechanistic studies, the authors propose a catalytic cycle wherein the Lu catalyst initially deprotonates the amine to form Lu complex **100** (Scheme 47B). This undergoes β-alkynyl elimination to form **101** and, at this stage, the alkynyl ligands can be exchanged and insertion of the alkynyl across the imine gives complex **103**. The catalytic cycle is completed by exchange of the propargylamine ligand leading to formation of the product.

*A. Goldman & Brookhart's C−C/C−C metathesis of simple alkanes (Ref. 146)*
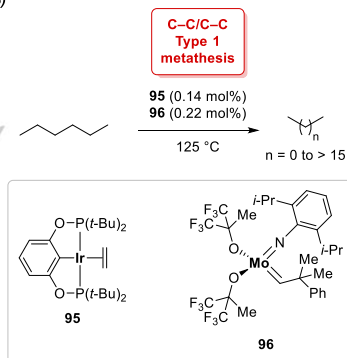


*B. Pathway of formal alkane metathesis*
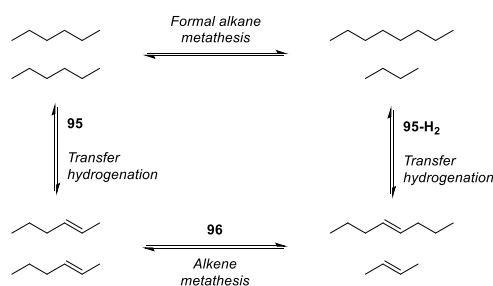


**Scheme 45.** Ir/Mo co-catalyzed formal alkane metathesis.

*Arisawa & Yamaguchi's C–C/C–C metathesis (Ref. 147)*

**Scheme 46.** Rh catalyzed C−C/C−C metathesis.

*A. Zhou's alkynyl group exchange of propargylamines (Ref. 148)*

**Scheme 47.** Lu catalyzed C−C/C−H metathesis with propargyl amines and alkynes.
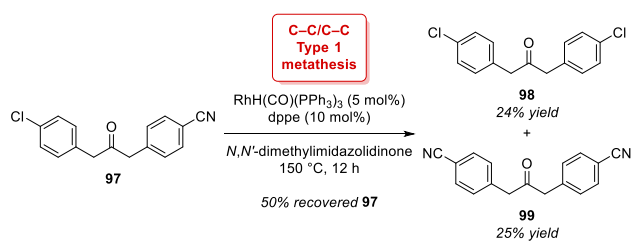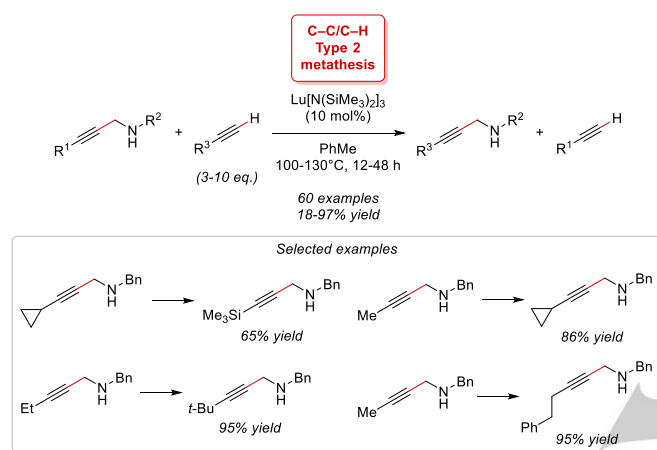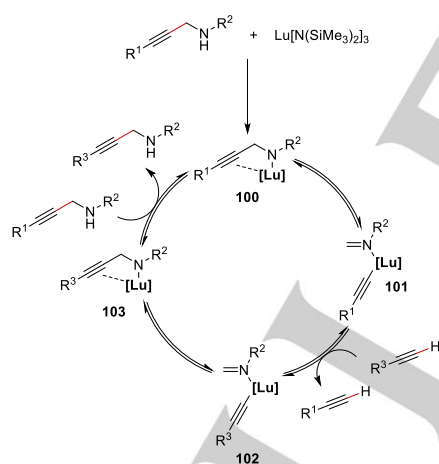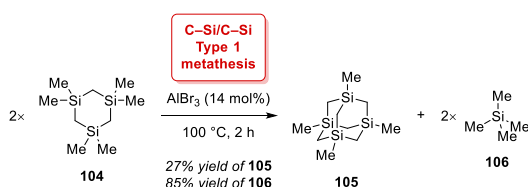
### 3.12. C−Si metathesis reactions

There are numerous early examples of C−Si/C−Si metathesis reactions mainly for the preparation of organosilanes.[149] For instance, it was shown that reaction of trisilacyclohexane **104** yields tetrasilaadamantane **105** upon heating with AlBr₃ (Scheme 48). Concomitant extrusion of volatile tetramethylsilane **106** likely provides a driving force for this reaction that enables rapid access to structurally complex, caged compounds.

**Scheme 48.** Lewis acid catalyzed C−Si/C−Si metathesis of organosilanes.

Alkene metathesis is one of the most powerful catalytic reactions available to the synthetic community.[2] However, due to the non-directional nature of the alkene bond, it does suffer in some cases from poor product selectivity.[150] In particular, cross metathesis between two alkenes can often be plagued by formation of self-metathesis products. A parallel approach to achieving formal cross alkene metathesis has been developed by the group of Wakatsuki that relies on single-bond metathesis (Scheme 49A).[151] Using RuCl(CO)H(PPh₃)₃, a C−Si/C−H bond metathesis between vinylsilanes and mono-substituted alkenes was realized. This reaction is driven by release of ethene and gives novel vinylsilanes in good yields and, in most cases, a preference for the E isomer. Mechanistic studies suggested a mechanism wherein the Ru hydride **107** undergoes hydrometallation with the vinylsilane to give **108** (Scheme 49B). At this stage, β-silicon elimination occurs giving complex **109** and ethene. Silylmetallation of the alkene followed by β-hydride elimination regenerates the catalyst and leads to formation of the vinylsilane product. This reaction has been applied to the synthesis of complex vinylsilanes including novel ferrocenes and macrocycles.[152] Since this is a metathesis of 2 directional bonds, less products are obtained then would be through an alkene metathesis.

Recently, the groups of Zhang and Hou reported a C−Si/Si−H metathesis of arylhydrosilanes for the preparation of diarylsilanes (Scheme 50).[153] This reaction was found to be efficiently catalyzed by the Lewis acidic B(C₆F₅)₃, which has recently proved to be proficient in the activation of Si−H bonds.[154] Initially, the homometathesis of various arylhydrosilanes was studied and was found to afford the corresponding diarylsilane in good yields. The scope was largely limited to aryl groups bearing an amine meta to the silyl group but di(ferrocenyl)dimethylsilane also proved amenable. This reaction is postulated to be driven by the formation of volatile dimethylsilane as a by-product. Using the same system, the cross metathesis of meta-aminoarylhydrosilanes with various simpler hydrosilanes was accomplished.
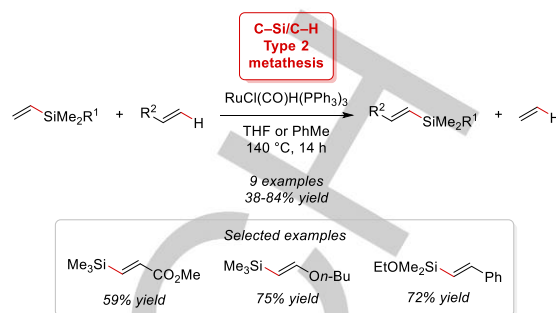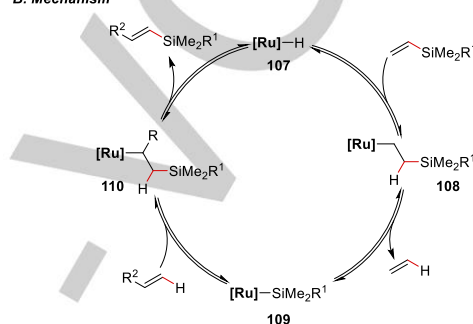
**Scheme 49.** Ru catalyzed C−Si/C−H metathesis as an alternative to alkene metathesis.

**A. Zhang & Hou's homometathesis of arylhydrosilanes (Ref. 153)**



*Selected examples*
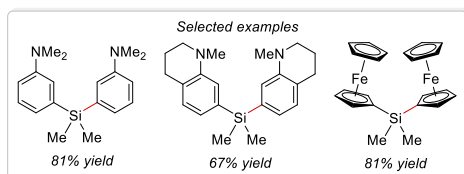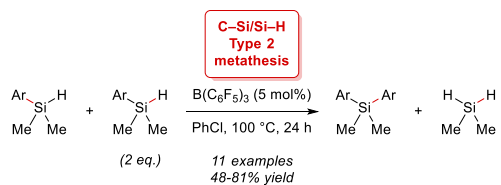


**B. Zhang & Hou's heterometathesis of arylhydrosilanes**



*Selected examples*
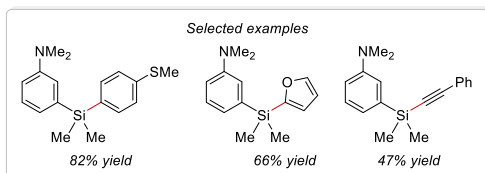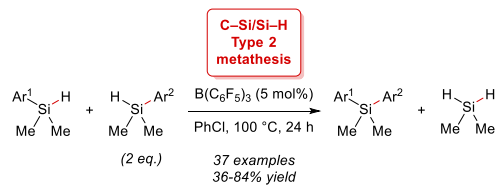


**Scheme 50.** B(C$_6$F$_5$)$_3$ catalyzed C−Si/Si−H metathesis for the synthesis of diarylsilanes.

### 3.13. C−B and C−Ge metathesis reactions

As discussed earlier, alkene metathesis can be problematic due to the potential for homo-metathesis occurring and the non-directional nature of the alkene bonds. To circumvent these issues an alternative reaction relying on C−Si/C−H metathesis was developed. This methodology was extended to the reaction of vinyl boronates[155] and vinyl germanes[156] with mono-substituted alkenes using a Ru-hydride complex by the group of Marciniec. No homo-metathesis products were obtained, although an excess of the mono-substituted alkene was employed.

## 3.14. Functional group metathesis reactions

As discussed earlier metathesis reactions can be categorized as either type 1 processes, wherein the bonds being cleaved are of the same nature, or type 2 processes, wherein the bonds participating in the reaction are not the same. However, with regards to single bond metathesis reactions, the majority of the type 2 processes covered thus far in this review involve exchange of substituents across a X−H bond. This ultimately means that a hydrogen atom is exchanged with a functional group and vice versa. A potentially attractive alternative would be to develop functional group metathesis reactions wherein two functional groups can be interconverted.

Although, the interconversion of one functional group into another group is a common theme in synthetic reactions, there are subtle advantages to this novel paradigm. A key benefit would be the ability to carry out the interconversion in both directions under roughly similar conditions. The organic chemistry community has developed a myriad of functional group transformations to date but typically these are irreversible and if the reverse transformation is desired a whole new strategy, typically requiring either a new catalyst or reagent, has to be designed.

An example of a functional group metathesis process was described by the group of Morandi.[157] In their work, they demonstrated that, under Pd catalysis, aryl iodides and aroyl chlorides can exchange their iodide and acid chloride functionalities. The reversibility of this process was demonstrated through a simple control reaction wherein either iodo-benzoyl chloride **111** or diiodobenzene **112** and dicarboxylic acid chloride **113** were subjected to the reaction conditions resulting in an equilibrium mixture of **111**, **112** and **113** (Scheme 51A).

Having demonstrated that this reaction is reversible, the development of protocols to procure aroyl chlorides from aryl iodides and vice versa were considered. A central problem is the requirement to identify a suitable driving force to ensure good conversion towards the desired product. For the transformation of aryl iodides into aroyl chlorides, either a sterically congested or electron deficient aroyl chloride were employed (Scheme 51B). For the reverse transformation, iodobenzene could be used in excess or an electron rich aryl iodide, which leads to the formation of a push-pull stabilized aroyl chloride, could be used to drive the reaction (Scheme 51C).

Mechanistically, this reaction is somewhat unusual as it involves two reaction partners that are typically electrophiles for transition metal catalyzed cross-couplings. The authors proposed that the use of a metathesis active ligand is imperative to the exchange of the aryl group substituents (Scheme 52). Following test reactions, they noticed that if either of the aryl iodide or aroyl chloride reaction partner were submitted to the reaction conditions alone, the phenyl groups on the Xantphos ligand would undergo exchange with the aryl groups. A mechanism was subsequently proposed that involves oxidative addition with either the aryl iodide or aroyl chloride and, in the case of the latter, subsequent deinsertion of the carbonyl. At this stage, reductive elimination occurs to afford phosphonium species **116** or **120**. These can then undergo oxidative addition which leads to scrambling of the aryl groups on both the aryl iodide and aroyl chloride. Support of this hypothesis was provided by isolation of one of the phosphonium salts. This was used in place of the Xantphos ligand in the reaction and found to be catalytically competent. In addition, a similar correlation between the reaction rates and substitution pattern on the aromatic rings was observed for both C−P metathesis and the functional group metathesis.

Simultaneously, the group of Arndtsen also reported the Pd catalyzed metathesis of aroyl chlorides and aryl iodides.[158] As part of their program on the synthesis of carbonyl containing aromatics, they identified this reaction manifold as a valuable, CO-free pathway to aroyl chlorides (Scheme 53A). They found that electron deficient aroyl chlorides were suitable "COCl" sources for the metathesis. However, following their mechanistic studies they proposed a different mechanism for the reaction (Scheme 53B). They suggested that, following oxidative addition of the aroyl chloride and aryl iodide on separate Pd centers and deinsertion of carbon monoxide, the two Pd centers **123** and **128** exchange their halide ligands.

**A. Reversibility of functional group metathesis between aryl iodides and aroyl chlorides (Ref. 157)**
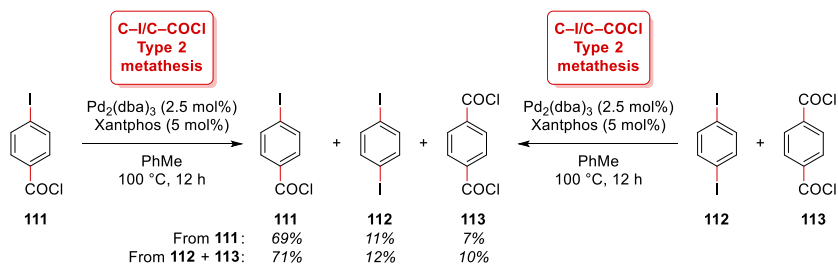


**B. Morandi's synthesis of aroyl chlorides from aryl iodides**



*Selected examples*
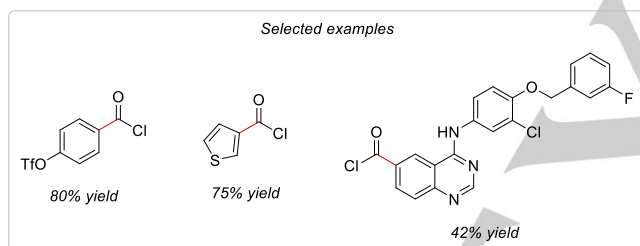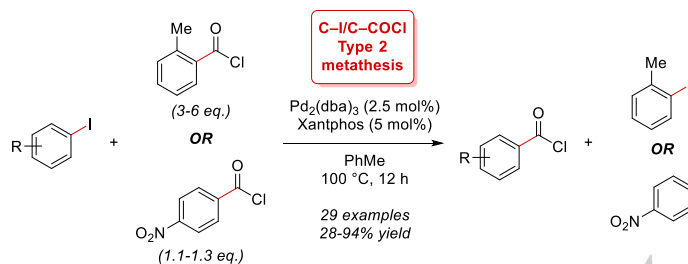


**C. Morandi's synthesis of aryl iodides from aroyl chlorides**



*Selected examples*
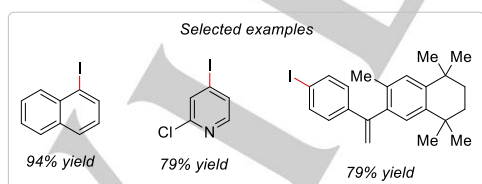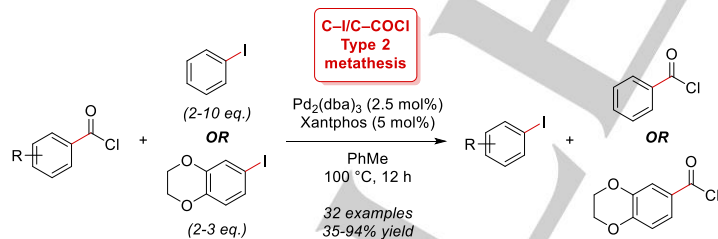


**Scheme 51.** Morandi's Pd catalysed metathesis of aryl iodides and aroyl chlorides.
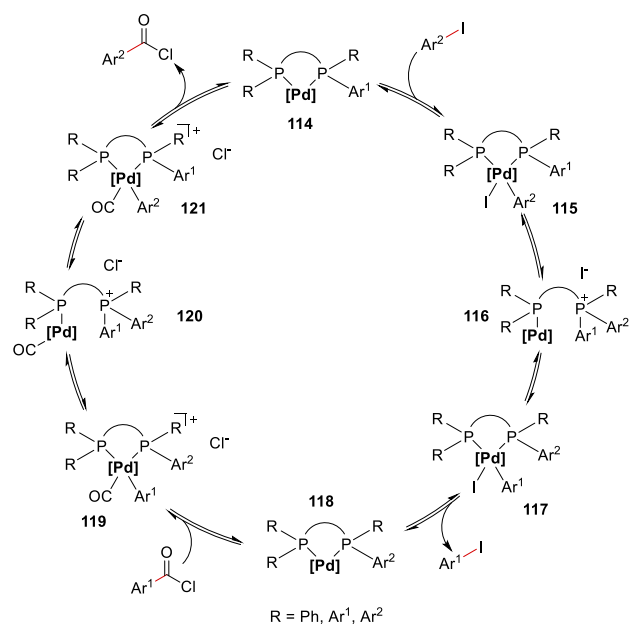
**Scheme 52.** Proposed mechanism for the metathesis of aryl iodides and aroyl chlorides.

*A. Arndtsen's synthesis of aroyl chlorides from aryl iodides (Ref. 158)*



*Pd-cat = (Xantphos)Pd(4-C$_6$H$_4$NO$_2$)(I)*

*Selected examples*

80% yield

82% yield

84% yield

85% yield
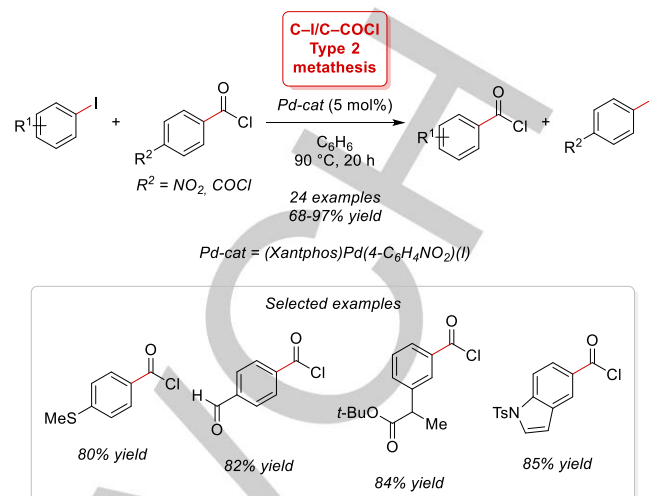
*B. Proposed mechanism*
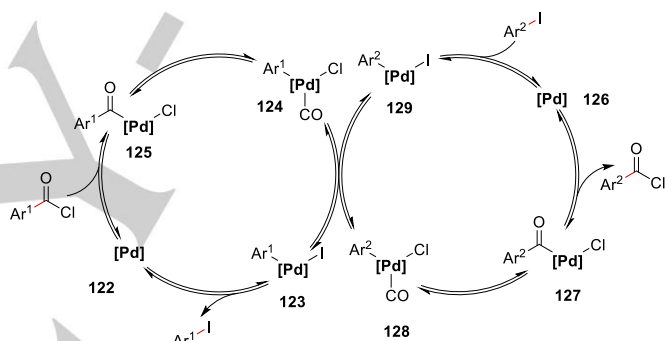


**Scheme 53.** Arndtsen's Pd catalysed metathesis of aryl iodides and aroyl chlorides.

## 3.15. Mixed bond multiplicity metathesis reactions

Transamination is a key biological transformation that facilitates the synthesis of nonessential amino acids.[159] This process reversibly transforms a ketone to a primary amine while simultaneously converting a primary amine into a ketone. An important example is the synthesis of aspartic acid from oxaloacetate and glutamate, with α-ketoglutarate formed as a by-product (Scheme 54). In this process, all functional groups present in the starting materials are also present in the products and the reaction is reversible. Although it does not bear an obvious resemblance to other metathesis reactions, it can be considered a special case wherein formally a double bond is cleaved in one of the reactants and replaced with two single bonds. Congruently, the two single bonds in the other reactant are replaced with a double bond to give an isofunctional reaction.

Transamination provides a simple pathway for the preparation of α-amino acids and given the value of this motif in organic synthesis, non-enzymatic methods for conducting this transformation have been sought.[160] This has led to the development of asymmetric procedures opening access to enantioenriched, non-natural α-amino acids and other chiral amines.

Extension of this class of metathesis reactions to other functionalities is likely to unlock exciting new synthetic transformations.
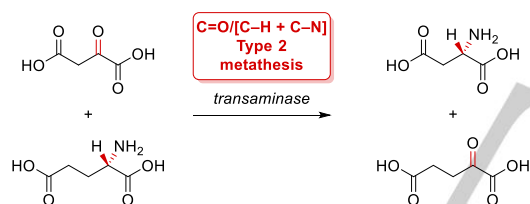


**Scheme 54.** Biocatalytic transamination for the synthesis of aspartic acid.

## 4. Summary and Outlook

This review describes recent advances in the development of catalytic isofunctional processes that go beyond the classics, transfer hydrogenation, alkene metathesis and alkyne metathesis. An impressive array of reactions has already been reported but there is considerable scope for further progress. Given the breadth of the field, there are countless other reactions that can be contemplated that fall within either the shuttle catalysis or metathesis paradigm.

In shuttle catalysis, reactions enabling the shuttle of carbene, nitrene or oxo groups is highly underdeveloped, despite the enormous potential of those reactions to provide a safer and milder alternative to diazo compounds or highly reactive hypervalent iodine reagents. Furthermore, most shuttle catalysis reactions involve the transfer of a HX equivalent. Difunctionalizations, wherein two functional groups are transferred, could be an attractive area for future research particularly for the transfer of hazardous reagents such as $F_2$. Finally, shuttle catalysis reactions that use a single bond as the acceptor could have a transforming impact on organic synthesis. As an example, a reaction that could take a C-H bond and a C-OH bond and transfer an oxo group between them would provide a means to both oxidize simple hydrocarbons as well as deoxygenate biomass-sourced alcohols.

Multiple bond metathesis reactions have seen considerable recent progress. Due to the limited number of organic triple and double bonds, there are fewer transformations that remain to be discovered, although there is still ample room for further catalyst development and reaction design. By contrast, single bond metathesis reactions remain rare compared to the number of possible reactions that could be developed in this area. In particular, many reactions involving the metathesis of traditionally inert bonds, such as C−C, C−N, C−O and C−F bonds remain elusive or limited. We anticipate that the development of these metathesis reactions would have an enormous impact on synthesis because of the ubiquity of these bonds across all the molecular sciences.

While the development of novel isofunctional reactions is a valuable target for synthesis, further catalyst and reaction design is also required in trying to emulate the power of the classical reactions. The advent of methods analogous to transfer hydrogenation and alkene metathesis and that exhibit high functional group tolerance and synthetic utility will undoubtedly be beneficial across the molecular sciences. This should unlock more sophisticated applications in synthesis such as using shuttle catalysis processes as a key step of borrowing functional group reactions.[25,26] Metathesis reactions are also fundamentally appropriate for applications in neighboring areas such as polymer chemistry, supramolecular chemistry and dynamic combinatorial chemistry. When considering the enabling power of alkene and alkyne metathesis in these research fields, the development of new metathesis processes should similarly instigate exciting interdisciplinary applications.

In conclusion, we hope that the examples of catalytic isofunctional reactions collected in this review will offer inspiration to the reader for further developments in a field that offers a broad and diverse

range of opportunities. Given the success of transfer hydrogenation and alkene/alkyne metathesis, one can imagine the potential impact such endeavors can have.

## Acknowledgements

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[11] We believe that the concept of isofunctionality used in this review to describe the conservation of the functional groups throughout a chemical reaction is a very intuitive one that should help organic chemists identify this type of reactions. However, we are aware that what can be considered the same functional group can be a subjective topic. For the purpose of this review, we have followed the IUPAC definition of a functional group: "The functional group is an atom, or a group of atoms, that has similar chemical properties whenever it occurs in different compounds. It defines the characteristic physical and chemical properties of families of organic compounds." See: P. Müller, *Pure Appl. Chem.* **1994**, *66*, 1077-1184.

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Biographical information

Benjamin N. Bhawal was born in 1988 in Glasgow, UK. He completed his undergraduate studies at the University of Cambridge in 2010. He continued his education at the same university under the supervision of Prof. Steven Ley. After completing his doctoral studies, he joined the group of Prof. Fabien Gagosz at École Polytechnique as a postdoctoral research associate. Subsequently he moved to the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr to work under the tutelage of Prof. Bill Morandi in 2016 with funding from the Leverhulme Trust. He is currently a postdoctoral associate in the same group at the ETH Zürich.

Bill Morandi was born in 1983 in Fribourg, Switzerland. He studied at the ETH Zurich from 2003–2008, earning a B.Sc. in Biology and a M.Sc. in Chemical Biology as an Oskar-Jeger Scholar. As a doctoral student supported by the Swiss Chemical Industry Funds in the Laboratory of Prof. Erick M. Carreira, he then developed new, safer synthetic methodologies using in situ generated diazo compounds. In 2012, he moved to the California Institute of Technology to work under the guidance of Prof. Robert H. Grubbs as a Swiss National Science Foundation postdoctoral fellow, where he focused on catalytic oxidation reactions. In 2014, he was awarded an independent Max Planck Research Group Leader position by the Max Planck Society to start his independent research program at the Max-Planck-Institut für Kohlenforschung. Since July 2018, he is a Professor at the Laboratorium für Organische Chemie of the ETH Zurich where he holds a chair in synthetic organic chemistry. His independent research program targets the development of new concepts in catalysis to transform broadly available feedstocks, such as polyols and hydrocarbons, into valuable building blocks for applications in medicine and materials science.
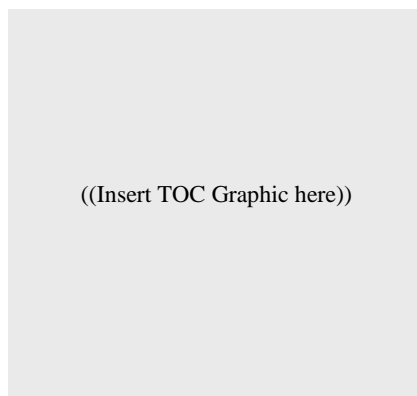
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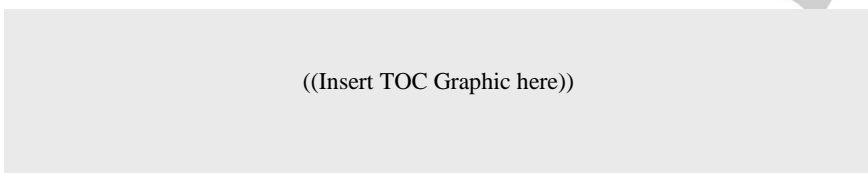
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