Unimolecular Fragment Coupling: A New Bond-Forming Methodology via the Deletion of Atom(s)

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ABSTRACT: Unimolecular fragment coupling (UFC) is defined as a reaction format, wherein atom(s) located in the middle of a molecule are extruded, and the remaining fragments are coupled. UFC is a potentially powerful strategy that is an alternative to transition-metal-catalyzed cross-coupling because the target chemical bond is formed in an intramolecular fashion, which is inherently beneficial for chemoselectivity and stereoselectivity issues. In this Perspective, we will present an overview of the recent advances in UFC reactions, which encompass those proceeding through the elimination of CO_2, CO, SO_2, isocyanates, N_2, or single atoms primarily via transition metal catalysis.

Unimolecular Fragment Coupling (UFC)
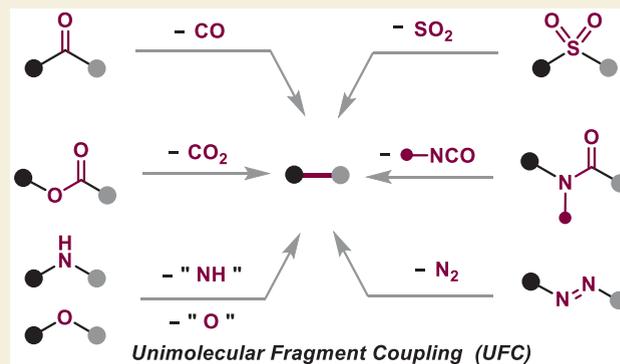
INTRODUCTION

Transition-metal-catalyzed cross-coupling stands as a powerful method for constructing C−C and C−heteroatom bonds, which has enabled extensive applications in the synthesis of natural products, pharmaceuticals, and organic materials.[1−4] However, the use of organic halides as electrophiles and organometallic reagents as nuculeophiles raises issues of preparation of these compounds and the generation of stoichiometric metal waste (Scheme 1A). Although these issues have been solved, in part, by the emergence of C−H functionalization[5−11] and the use of halogen-free electrophiles,[12−23] the scope of such sophisticated methods remains substantially limited compared with the classical cross-coupling reactions.

A conceptually distinct approach is unimolecular fragment coupling (UFC), wherein the formation of a new chemical bond occurs through the elimination of atom(s) from the middle of the substrate, which is followed by recombination of the remaining fragments (Scheme 1B). Typical starting materials for UFC are common carbonyl compounds, which can be synthesized via well-established methods, such as condensation of readily available feedstock materials. The key feature of UFC is that the target chemical bond is formed in an intramolecular fashion, which is inherently beneficial for chemoselectivity and stereoselectivity issues because of the entropic advantage. For example, palladium-catalyzed decarboxylation of allylic esters is a typical example of UFC in which a new C−C bond is forged by extruding CO_2 (Scheme 1C,

top).[24,25] Unlike intermolecular coupling reactions, this reaction proceeds without adding external nucleophiles or electrophiles, which allows the sensitive functional groups that react with such external reagents to be tolerated (see Schemes 8 and 21 for additional examples of chemoselective UFC). Since the starting esters are, in principle, prepared by condensation of the corresponding allylic alcohol and carboxylic acid using a suitable catalyst, the overall process is regarded as a C−C bond formation from those substrates by eliminating H_2O and CO_2, which highlights the potential advantage of UFC over classical cross-coupling reactions in terms of atom economy.[26−30] Moreover, the intramolecular nature of the reaction enables a number of enantioselective variants because of the facile assembly of an ordered transition state compared with that of the corresponding intermolecular reactions.[31] Several UFC reactions require no transition metal catalysts and, instead, are mediated either by organic reagents or photoirradiation. For example, the deletion of nitrogen from secondary benzylamines is mediated by the reaction with an anomeric amide reagent (Scheme 1C, bottom).[32−36] Although

Scheme 1. Definition of Unimolecular Fragment Coupling

A | Cross-coupling

organometallics   *metal waste*

B | Unimolecular fragment coupling (UFC)

readily available   *no metal waste*

L: atom(s)

C | Examples of UFC

Table 1. List of Ligands

R = H: IMes·HCl   R = H: IPr·HCl   SIPr·HCl
R = Me: IMes^{Me}·HCl   R = Me: IPr^{Me}·HCl

IOMe·HCl   MeO-bipy   phen

dcype   n = 2: dppe   dppf   dcypt (R = cyclohexyl)
= 3: dppp   dcppt (R = cyclopentyl)
= 4: dppb

XPhos   BrettPhos   RuPhos   XantPhos

(Ar = 4-MeOC$_6$H$_4$)
pmdba   (Ar = 4-CF$_3$C$_6$H$_4$)   PS-DPPBz
(S)-(CF$_3$)$_3$-^{t}BuPHOX
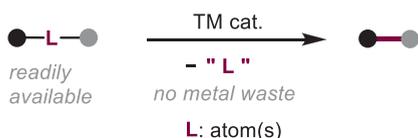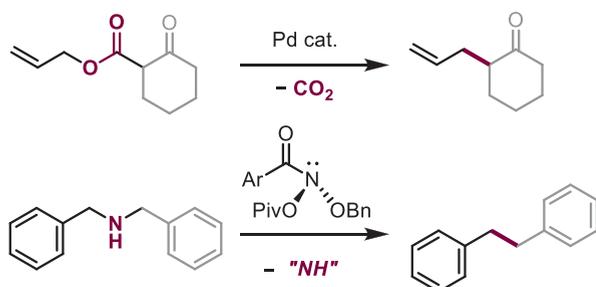
stoichiometric reagents are necessary, new $C(sp^3)-C(sp^3)$ bonds are formed from readily available aliphatic amines in a nonconventional manner.

In this Perspective, UFC reactions are overviewed on the basis of the classification of eliminated atom(s), such as CO_2, CO, and single atoms, and their scope, limitations, and mechanism are briefly summarized (Scheme 2). Because UFC

Scheme 2. Summary of UFCs Reported to Date
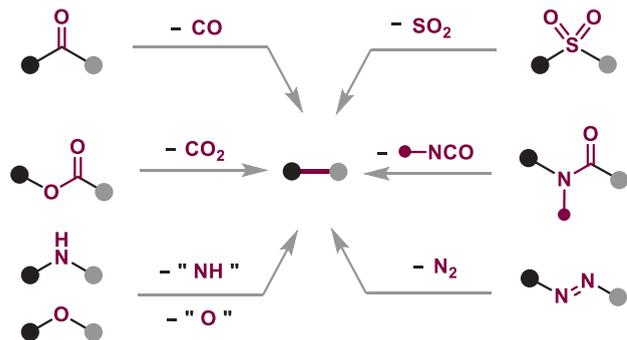
serves as a potential alternative to cross-coupling, reactions in which one of the fragments is a single atom are not covered (i.e., decarbonylation of aldehydes or acid chlorides), and examples included in this Perspective are basically limited to acyclic compounds, although elimination of atom(s) from the cyclic skeleton is known to be a useful ring contraction strategy.[37−39]

■ LIST OF LIGANDS IN THIS PERSPECTIVE

Structures of the ligands used in this Perspective, together with their abbreviations, are listed in Table 1.
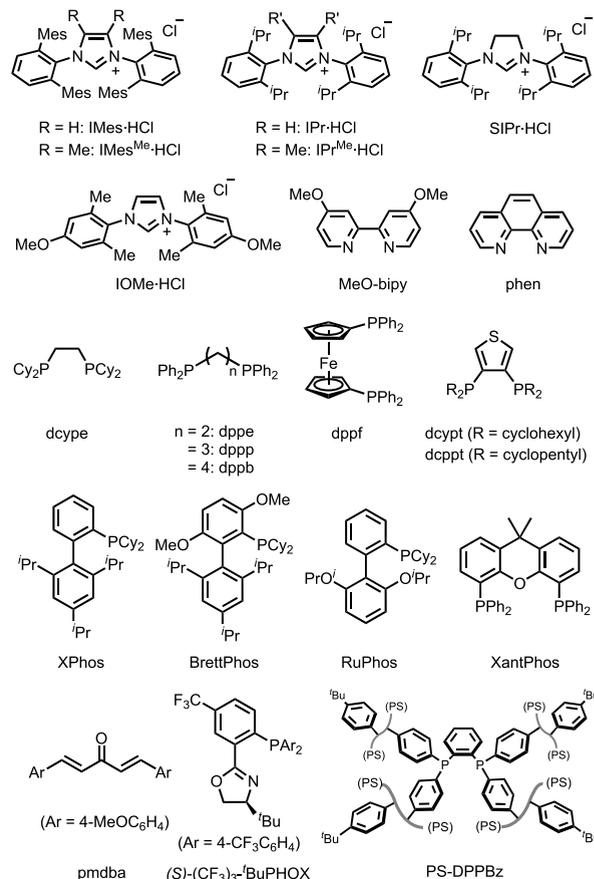
■ ELIMINATION OF CO$_2$ FROM ESTERS AND THEIR DERIVATIVES (DECARBOXYLATION)

Esters are among the most common functional groups, which are prevalent among organic molecules and easily accessible by condensation of carboxylic acids and alcohols.[40,41] Therefore, if reliable methods for deleting CO_2 from esters could be developed, a range of C−C and C−heteroatom bonds could be formed from feedstock materials without the generation of metal- or halogen-containing waste. In fact, catalytic decarboxylation of esters has long been a subject of investigation. A typical mechanism for decarboxylative UFC of esters involves the oxidative addition of a C(alkoxyl)−O bond to give intermediate **A**, in preference to an intrinsically more reactive C(acyl)−O bond, and the extrusion of CO_2 via the cleavage of a C(acyl)−C bond with the coupling of remaining fragments through reductive elimination from intermediate **B** (Scheme 3). However, the requisite bond cleavage processes are challenging for the majority of esters, which limits the scope of the decarboxylative UFC.

Allylic and Benzylic Esters

The first solution to the selectivity issue between the cleavage of a C(alkoxyl)−O bond and a C(acyl)−O bond in esters during the oxidative addition event involves the use of allylic esters. The preferential cleavage of a C(alkoxyl)−O bond is achieved by the formation of a stable π-allylmetal intermediate. In 1980, the groups of Tsuji[42] and Saegusa[43] independently reported a palladium-catalyzed decarboxylative allylation of enolates with allylic esters, which represents one of the earliest examples of UFC (Scheme 4). In these reactions, the use of

Scheme 3. Generalized Mechanism for Decarboxylative UFC
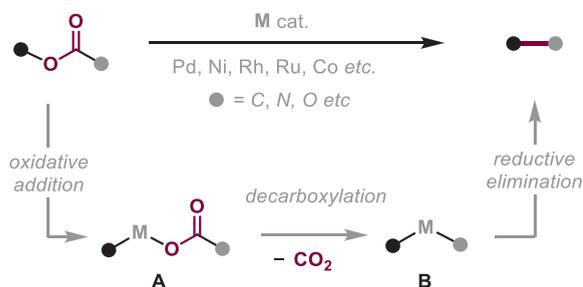
Scheme 4. Early Works: Pd-Catalyzed Decarbonylative UFC of Allylic Esters

Tsuji, 1980

Saegusa, 1980

Table 2. Pd-Catalyzed Decarboxylative Allylation

Selected examples of carbon nucleophiles

α-cyano anion
Saegusa, 1980

acrylonitrile
Saegusa, 1980

azaallyl anion
Tunge, 2006

α-sulfonyl anion
Weaver & Tunge, 2006

α-nitro anion
Tsuji, 2007

α-heteroaryl anion
Weaver & Tunge, 2007

coumarin
Tunge, 2009

acetylide
Tunge, 2005

o-nitroarene
Jana, 2014

Selected examples of heteroatom nucleophiles

amine
Tunge, 2005

ether
M'Leux, 1981
Tsuji, 1985

selenide
Tunge, 2008

allylic esters derived from β-keto acids is also essential for a successful UFC because the stability of the carbanion that is generated after decarboxylation is crucial.

Since these early works, allylic esters have served as a useful platform for the development of decarboxylative UFC. The scope has been expanded to include benzylic esters in which the formation of a similar π-benzylmetal intermediate is involved. Regarding the fragments derived from carboxylic acids, nucleophiles other than enolates can also be coupled, as listed in Table 2.[24,25] Decarboxylation occurs efficiently when stabilized carbanions are generated, as in the case of enolates. Carbanions with a pK_a of conjugate acids of >25 either require high temperatures or will not react.[25] Several heteroatom nucleophiles can also be used for decarboxylative UFC via the use of carbamates and carbonates.

Recent efforts have focused on overcoming the pK_a limitation during the decarboxylation step. Tunge and co-workers reported palladium/photoredox dual-catalyzed decarboxylative UFC reactions in which the decarboxylation is promoted by single-electron oxidation of the carboxylate to acyloxy radicals, which are prone to decarboxylation under mild conditions (Scheme 5A).[44,45] It is noteworthy that this dual catalysis strategy allows for the decarboxylative allylation of esters that do not undergo coupling via conventional two electron mechanisms: those derived from 2-arylacetic acids[44] and α-amino acids.[45] The catalytic mechanism proposed by Tunge et al. is shown in Scheme 5B. Oxidative addition of an allylic ester to Pd(0) initially generates a π-allylpalladium complex and a carboxylate anion **C**. This relatively electron-rich carboxylate is then oxidized by a photoactivated Ir(III) catalyst, which immediately induces radical decarboxylation to generate a benzyl radical. The resultant Ir(II) species simultaneously reduces the allyl—Pd(II) species **E** by a single
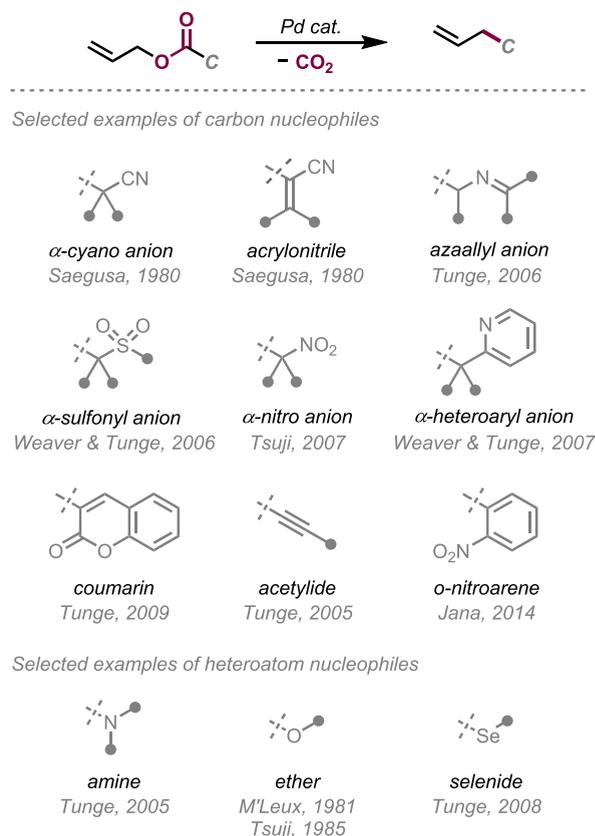
electron, which results in homolysis to provide an allyl radical and regenerate the active Pd(0) and Ir(III) catalysts. Radical cross-coupling between an allyl radical and a benzyl radical provides the final decarboxylative UFC product. Although the scope of the fragment derived from 2-arylacetic acids is limited to those bearing an amino group, this is complementary to the classical decarboxylative UFC in which an electron-withdrawing group is required for decarboxylation to occur.

MacMillan and co-workers also independently developed a nickel/photoredox dual-catalyzed decarboxylative UFC of amino acid anhydrides (Scheme 6).[46] Similar to allylic esters, acid anhydride substrates can avoid the selectivity issue in the oxidative addition step since the bond that must be cleaved is a relatively reactive C(acyl)—O bond. A carboxyl group in α-amino acids can be substituted by a range of acyl groups via decarboxylation.

Nonallylic Esters

Examples of decarboxylative UFC using esters other than allylic or benzylic systems are currently limited because catalysts that can activate nonallylic C—O bonds in preference to normally more reactive C(acyl)—O bonds are less explored. Doi, Sato and co-workers reported a palladium-catalyzed decarboxylative UFC of α-acyloxyketones bearing an alkyne moiety, which is triggered by the activation of a C(sp³)—O bond α to a carbonyl group (Scheme 7, top).[47] The key to success is the coordination of the Pd(0) complex to a ketone, which facilitates the activation of a C(sp³)—O bond at the α-position to form a Pd enolate intermediate. While alkynylation at the α-position of ketones by cross-coupling reactions often suffers from the undesired dimerization of alkynes, such byproducts can be avoided in this decarboxylative UFC. The

Scheme 5. Palladium/Photoredox Dual-Catalyzed Decarboxylative UFC of Allylic Esters
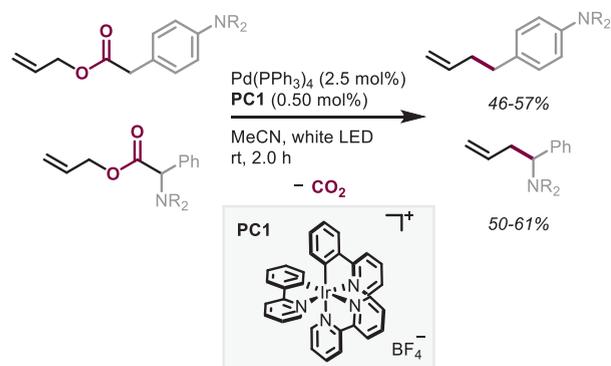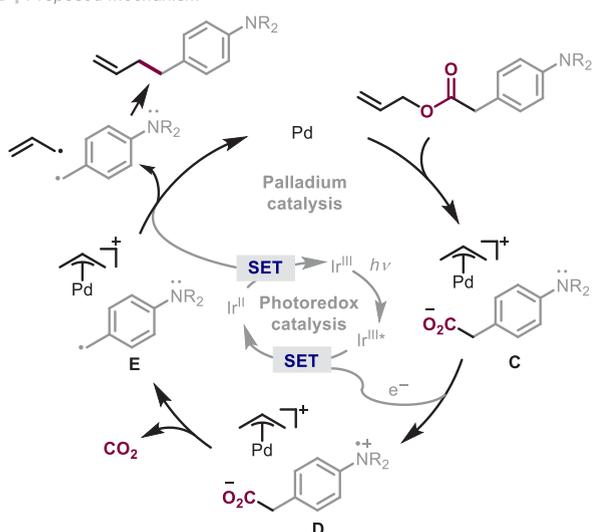
Scheme 6. Nickel/Photoredox Dual-Catalyzed Decarboxylative UFC of Acid Anhydrides

Scheme 7. Pd-Catalyzed Decarbonylative UFC of α-Acyloxyketones

proceed as is frequently observed in the metal-catalyzed decarboxylation of benzoic acid derivatives.

During the past decade, tremendous progress has been made in transition-metal-catalyzed C(aryl)−O bond activation for cross-coupling reactions.[12−23] Decarboxylative UFC, however, via C(aryl)−O bond activation, is extremely rare. Sawamura, Chatani, and Tobisu et al. reported the nickel-catalyzed decarboxylative UFC of aryl carbamates, which forms aromatic amines (Scheme 8).[49] In this reaction, a bisphosphine ligand

Scheme 8. Nickel-Catalyzed Decarboxylative UFC of Aryl Carbamates
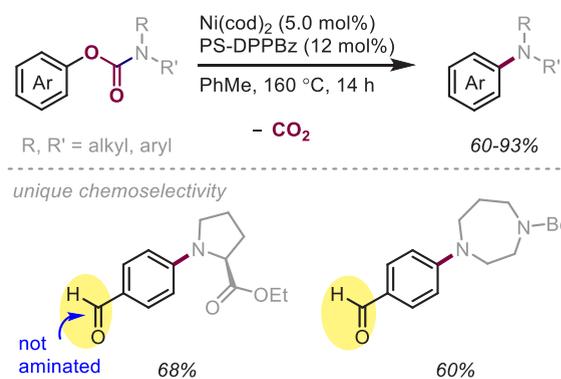
immobilized on a polystyrene support (PS-DPPBz) is crucial for an efficient reaction rather than using simpler phosphine ligands, such as dcype or PCy3, which are normally effective for the nickel-catalyzed cross-coupling reactions of unreactive phenol derivatives. The unique constrained and isolated environment of the bisphosphine unit in PS-DPPBz allows for selective 1:1 ligand-to-metal complexation and suppresses the undesired comproportionation induced by the encounter of Ni(0) and Ni(II) species to form less active Ni(I) complexes. The synthetic advantage of this decarboxylative amination is that a range of electrophilic functional groups that can react with amines (e.g., a formyl group) can be tolerated because no free amines are needed for this amination. This chemoselectivity is not possible with the common catalytic intermolecular amination of aryl halides and represents a characteristic feature of UFC.

Hu and co-workers reported a decarboxylative UFC for the synthesis of aniline derivatives via palladium-catalyzed

use of bulky silyl groups, such as triisopropylsilyl (TIPS) and *tert*-butyldimethylsilyl (TBS), at the alkyne terminal is essential to deliver the desired products in good yields. The decarboxylative UFC of esters also occurs with α-acyloxyketones bearing polyfluoroaryl groups, such as pentafluorophenyl and 1,6-difluorophenyl, to form α-polyfluoroarylated ketones (Scheme 7, bottom).[48] The presence of two fluorine atoms at the ortho positions is required for this decarboxylation to

decarboxylation from *N*-aroyloxycarbamates, which can be generated in situ by reacting aryl carboxylic acids with Boc-NHOH (Scheme 9).[50] The authors suggest that this UFC is

Scheme 9. Pd-Catalyzed Decarboxylative UFC of *N*-Aroyloxycarbamate
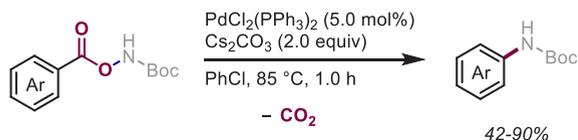
likely to proceed through oxidative addition of the N−O bond to Pd(0), decarboxylation, and reductive elimination. This reaction exhibits excellent functional group tolerance, which enables the synthesis of diverse aniline derivatives. Unlike other metal-mediated decarboxylation reactions of benzoic acid derivatives, electron-withdrawing groups at the ortho position are not required for an efficient reaction.

ELIMINATION OF CO FROM CARBONYL COMPOUNDS (DECARBONYLATION)

Carbonyl compounds, such as aldehydes, ketones, esters, amides, and many others, are among the most prevalent and essential functional groups in organic molecules. Consequently, the development of catalytic methods for removing a carbonyl group from carbonyl compounds promises widespread utility in a range of bond formation processes. In fact, such decarbonylation reactions have been investigated most extensively among UFC reactions.[51] Similar to decarboxylative UFC, transition-metal-mediated decarbonylative UFC proceeds through the activation of a C−C or C−heteroatom bond of the substrate via oxidative addition and extrusion of CO followed by reductive elimination (Scheme 10). Initial oxidative addition of a C−C or C−heteroatom

Scheme 10. Generalized Mechanism for Transition-Metal-Mediated Decarbonylative UFC
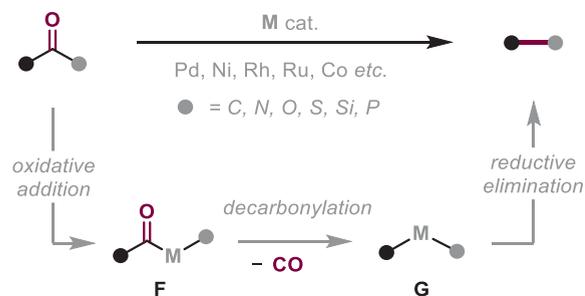
bond is often the most challenging step and dictates the scope of substrates. The strong binding of an eliminated CO to the catalyst often deactivates the catalyst, and this poses a hurdle for developing a decarbonylative UFC.

Ketones

Although the decarbonylation of ketones represents an attractive strategy for forming a C−C bond from readily available feedstock, the difficulty in activating a C(=O)−C bond in ketones has rendered its development a daunting challenge. The relief of ring strain serves to facilitate the oxidative addition of C−C bonds and is successfully used in

the metal-mediated decarbonylation of cyclobutanone derivatives.[52−61] The first example of the decarbonylation of acyclic ketones was reported in 2004 by Brookhart et al. A stoichiometric amount of a rhodium complex was found to mediate the decarbonylation of diaryl ketones to form biaryl products (Scheme 11A).[62] In addition to the decarbonylation

Scheme 11. Rh- and Ni-Mediated Decarbonylative UFC of Unstrained Ketones
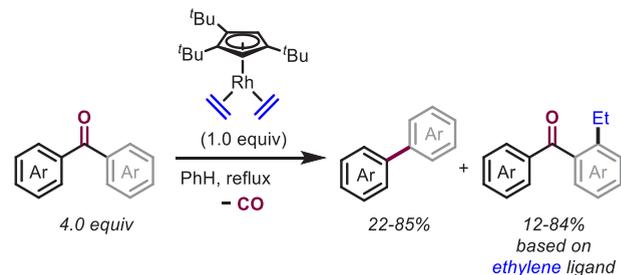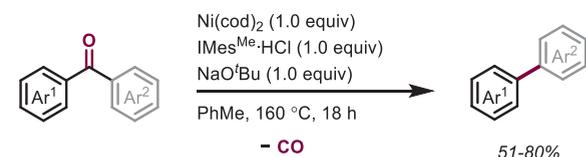
products, the *ortho*-ethylated aromatic ketones were obtained via the insertion of an ethylene ligand into the *ortho*-C−H bond of aromatic ketones. In 2017, Tobisu and Chatani et al. reported that a decarbonylative UFC of diaryl ketones can also be promoted by a nickel complex (Scheme 11B).[63] Although a highly electron-donating *N*-heterocyclic carbene ligand is essential for the generation of a nickel center that is sufficiently electron-rich to facilitate the challenging oxidative addition of a C(=O)−C bond, the electron-rich nature of the nickel also strengthens the binding of the eliminated CO, which thereby inhibits the regeneration of a coordinatively unsaturated nickel species. Although researchers continue to search for catalytic variants that could solve this issue of CO poisoning, these reactions demonstrate the potential power of decarbonylative UFC for biaryl synthesis from simple ketone substrates.

Catalytic decarbonylative UFC reactions have been successful when ketones bearing a directing group or relatively activated ketones are used as substrates. Directing groups have been widely exploited for the activation of various robust chemical bonds because of their ability to form a stable metallacycle via chelation with transition metals.[10] Early works by the groups of Suggs,[64−66] Jun,[67−71] and Murai and Chatani[72] have demonstrated that the C(=O)−C bonds of ketones can be activated with the aid of a directing group, which sets the stage for application to catalytic decarbonylative UFC. Shi and co-workers developed a Rh-catalyzed decarbonylative UFC of unstrained ketones with a pyridyl directing group (Scheme 12A).[73] This decarbonylation exhibits a high tolerance of functional groups, including alkenyls, alkyls, aryls, and heteroaryls. The pyridine directing group facilitates both the oxidative addition of the C(=O)−C bond and the dissociation of CO by forming a stable five-membered rhodacycle intermediate. Wei and co-workers reported the nickel-catalyzed decarbonylation of bi(hetero)aryl ketones bearing either a pyridine or a pyrimidine group (Scheme

Scheme 12. Rh- and Ni-Mediated Decarbonylative UFC of Unstrained Ketones

A │ *Shi, 2012*
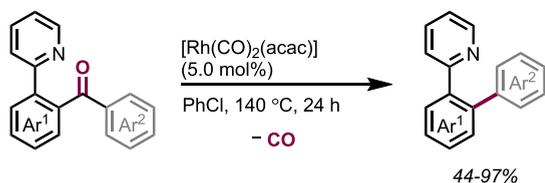
B │ *Wei, 2018 & 2020*
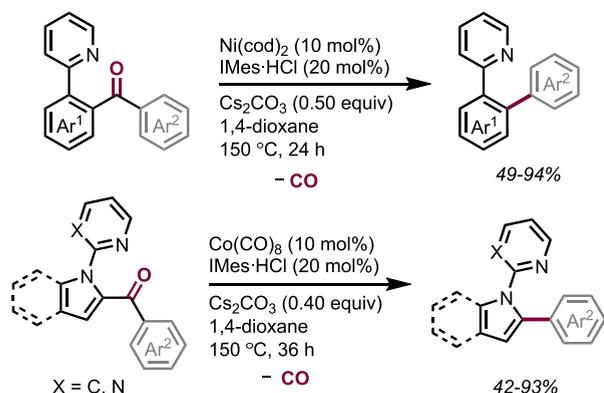
12B, top).[74] A combination of Ni(cod)$_2$ and an electron-rich *N*-heterocyclic carbene (NHC) ligand is crucial for this catalytic decarbonylation to proceed. The pyrimidine directing group on the indole skeleton can be removed from the decarbonylation products upon treatment with NaOEt in

DMSO at 100 °C to form the corresponding N−H indole derivatives. Wei et al. also disclosed a Co-catalyzed variant via a similar directing group strategy (Scheme 12B, bottom).[75]

A decarbonylative UFC of 1,2- and 1,3-diketones was reported by Teranishi et al. in 1974, albeit with low efficiency and a limited substrate scope (Scheme 13A).[76] This early work is a pioneering example of the decarbonylation of carbonyl compounds without strain or a directing group. Alkynyl ketones also serve as suitable substrates for catalytic decarbonylation, presumably because of the coordinating ability of the alkyne moiety. In 1969, Müller and co-workers reported the Wilkinson's complex-mediated decarbonylative UFC of conjugated diynones to generate diynes.[77] A few decades later, Dong and co-workers developed a rhodium-catalyzed decarbonylative UFC of monoyones[78] and diynones[79] to produce disubstituted alkynes and 1,3-diynes, respectively (Scheme 13B-i). Bidentate phosphine ligands with large bite angles were reported to be effective for these reactions. Dong also reported a rhodium-catalyzed decarbonylation of alkynyl *α*-diones (Scheme 13B-ii).[80] Single and double eliminations of CO from alkynyl *α*-diones occur in a controlled fashion to give alkynyl ketones **1** and aryl alkynes **2** by a judicious choice of ligands and reaction temperatures.

Acyl cyanides have been used in a catalytic UFC for the synthesis of nitriles. In 1967, Bergmann and co-workers reported the decarbonylative UFC of aryl cyanides using a RhCl(PPh$_3$)$_3$ catalyst (Scheme 13C-i).[81] This approach was also applicable to acyl chlorides and acyl bromides, which allowed for the generation of aryl halides via decarbonylation reactions. However, this UFC requires extremely harsh reaction conditions (300 °C), and the applicable substrates are limited to reactive acyl cyanides, such as naphthoyl and *p*-

Scheme 13. Catalytic Decarbonylative UFC of Diketones, Alkynyl Ketones, and Acyl Cyanides

A │ *1,2- and 1,3-Diketones*

Teranishi, 1974

C │ *Acyl cyanides*

i) Bergmann, 1967

ii) Murahashi, 1986

iii) Rueping, 2017

B │ *Alkynyl ketones*

i) Dong, 2013 & 2015

ii) Dong, 2015
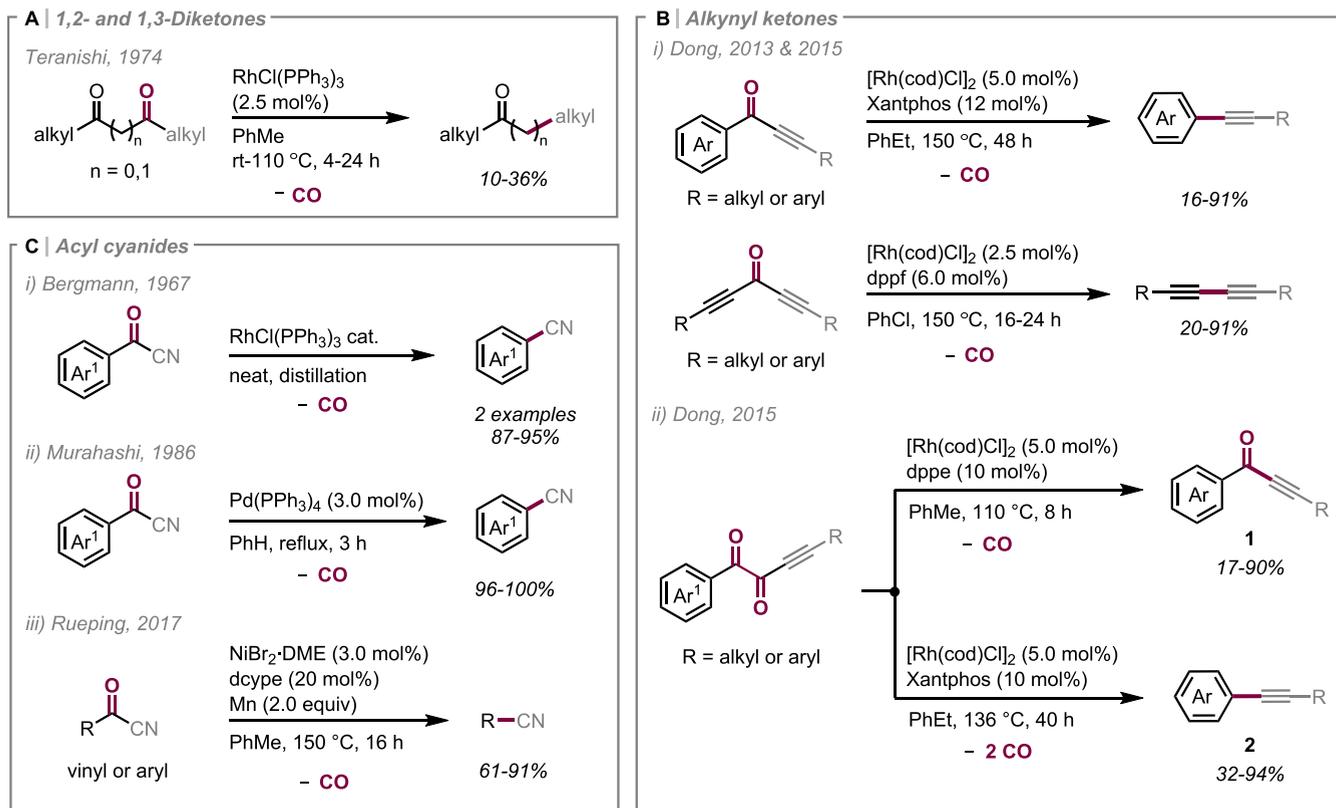
chlorobenzoyl cyanides. In 1986, Murahashi and co-workers discovered that acyl cyanides undergo decarbonylative UFC under mild reaction conditions by using a palladium catalyst, which has allowed a broader range of substrates to be decarbonylated (Scheme 13C-ii).[82] Recently, a nickel-catalyzed protocol for the UFC of acyl cyanides was also reported by Rueping et al. (Scheme 13C-iii).[83]

Decarbonylation of aliphatic ketones can proceed under photoirradiation conditions via the homolytic cleavage of a C—C bond. Although the reactions in solution are normally sluggish because of a number of side products formed through intermediate radical pairs, photodecarbonylation in the crystalline state can occur in high yields because the constrained environment can suppress undesired intermolecular reaction pathways. Garcia-Garibay et al. demonstrated that photodecarbonylation of ketones in crystals is a powerful method for constructing vicinal stereogenic all-carbon quaternary stereocenters (Scheme 14A).[84] Limited atomic

Scheme 14. Photoinduced Decarbonylation of Ketones
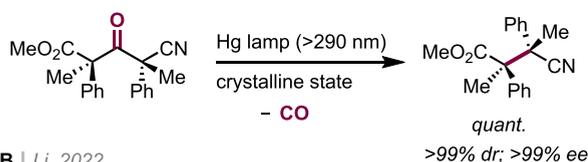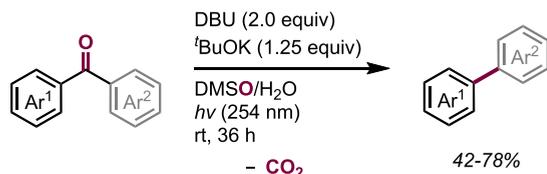
and molecular motion in crystals allows for the complete retention of the stereochemical configuration in the starting ketones. Recently, Li et al. reported that decarbonylation of diaryl ketones can also occur under photochemical conditions (Scheme 14B).[85] The addition of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) and a strong base in DMSO are essential for this reaction. The carbonyl group of the ketone substrate is eliminated as CO_2 by incorporating an additional oxygen atom from DMSO. The reaction is proposed to be initiated by the reaction of a photoexcited diaryl ketone with DMSO to form a dioxy diradical intermediate. This intermediate is subsequently reduced by DBU via photoinduced single-electron transfer to form a radical anion, which extrudes CO_2 with 1,2-migration of an aryl group to construct a biaryl product.

Acylsilanes

Decarbonylative UFC is also applicable to carbon—silicon bond formation by use of silyl-substituted carbonyl compounds as substrates. A pioneering example of this reaction was reported by Narasaka and co-workers, who demonstrated that decarbonylation of bis(silyl)ketones could be catalyzed by a palladium catalyst to form disilane (Scheme 15A).[86] Independent works by the groups of Rueping[87] and Tobisu[88] demonstrated that nickel serves as a suitable catalyst for the formation of C—Si bonds by decarbonylative UFC of acylsilanes (Scheme 15B-i and -ii). The reaction is initiated by the oxidative addition of a C(=O)—Si bond in acylsilanes to a nickel catalyst. Interestingly, this UFC is catalyzed by

Scheme 15. Catalytic Decarbonylation of Acylsilanes
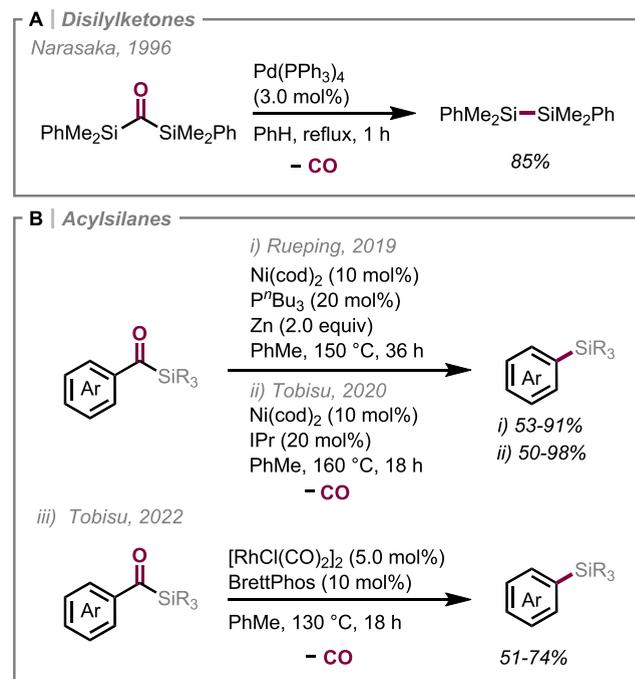
$Ni(IPr)(CO)_3$, which is in sharp contrast to the nickel-mediated decarbonylation of ketones, wherein a CO-bound nickel complex is inactive for the activation of C(=O)—C(aryl) bonds. This is presumably because C(=O)—Si bonds are weaker than C(=O)—C(aryl) bonds, which allows the nickel species to maintain its activity in the presence of CO. Quite recently, Tobisu et al. also reported a rhodium-catalyzed variant in which BrettPhos serves as an appropriate ligand. (Scheme 15B-iii).[89] This study showcases the capability of a rhodium(I) complex to facilitate the oxidative addition of C(=O)—Si bonds in acylsilanes.

Esters

Although the decarboxylative UFC of esters has been extensively studied, the *decarbonylative* UFC of esters for the synthesis of ethers is extremely rare. In 2017, Yamaguchi and Itami et al. reported a decarbonylative UFC of phenyl esters derived from pyridine 2-carboxylic acid derivatives using either nickel- or palladium catalysts to furnish the corresponding 2-pyridyl aryl ether derivatives (Scheme 16).[90] The 2-pyridine or related 2-azine moiety is essential for this process because of their electron-withdrawing and/or coordinating nature, which facilitates a reductive elimination to form a C(aryl)—O bond.[91]

Scheme 16. Ni-Catalyzed Decarbonylative UFC of Pyridyl Esters
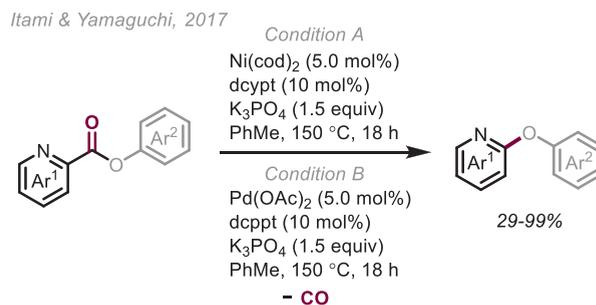
Scheme 17. Catalytic Decarbonylative UFC of Thioesters

A | Pd catalysis

i) Yamamoto, 1987

Pd(PCy$_3$)$_2$ (5 mol%)

PhMe, 100 °C, 3.0 h

− CO

100%

ii) Kambe & Kuniyasu, 2006

R = vinyl or aryl

Pd(PPh$_3$)$_4$ (5.0 mol%)

PhMe, reflux, 1.0 h

− CO

3-92%

iii) Sanford, 2018

R = vinyl or aryl

Pd[P(o-tol)$_3$]$_2$ (10 mol%)

PAd$_2$Bn (20 mol%)

p-xylene

130 °C, 20 h

− CO

27-85%

iv) Lee, 2020

PdCl$_2$ (10 mol%)

PPh$_3$ (20 mol%)

K$_3$PO$_4$ (1.5 equiv)

PhMe, 150 °C, 18 h

− CO

30-85%

C | Ni-catalyzed mono- and double- decarbonylative UFC

Wei, 2019

Ni(cod)$_2$ (10 mol%)

PPh$_3$ (20 mol%)

1,4-dioxane

160 °C, 22 h

− CO

3

63-86%

Ni(cod)$_2$ (10 mol%)

IPr^{Me}·HCl (20 mol%)

Cs$_2$CO$_3$ (20 mol%)

1,4-dioxane

160 °C, 22 h

− 2 CO

4

57-77%

B | Ni catalysis

i) Wenkert, 1991

R^1 = alkyl, vinyl, aryl

R^2 = Me, Et, Ph

NiCl$_2$·H$_2$O (2.0 equiv)

Zn (2.0 equiv)

DMF

23-80 °C, 0.5-48 h

− CO

R^1—SR^2

42-86%

ii) Sanford, 2018

R = vinyl or aryl

Ni(cod)$_2$ (10 mol%)

PCy$_3$ (20 mol%)

PhMe, 130 °C, 20 h

− CO

28-99%

iii) Szostak, 2018

NiCl$_2$(dppp) (10 mol%)

Na$_2$CO$_3$ (1.5 equiv)

1,4-dioxane

160 °C, 15 h

− CO

72-98%

iv) Rueping, 2018

R = vinyl or aryl

NiCl$_2$ (10 mol%)

dppp (20 mol%)

Mg (2.0 equiv)

PhMe, 150 °C, 36 h

− CO

70-98%

v) Yamaguchi, 2018

Het

Ni(OAc)$_2$ (5.0 mol%)

P^{n}Bu$_3$ or dppb

(10-20 mol%)

Na$_2$CO$_3$ (2.0 equiv)

DMF or PhMe

150 °C, 12 h

− CO

Het

0-95%

D | Rh catalysis

i) Yamamoto, 1987

R = vinyl, aryl

RhCl(PPh$_3$)$_3$

(1.0 equiv)

DMF or PhMe

100 °C, 3-9 h

− CO

R—SPh

43-100%

ii) Szostak, 2021

[Rh(cod)Cl]$_2$

(2.0 mol%)

PhMe, 160 °C, 15 h

− CO

70-98%

Thioesters

Transition-metal-mediated C−S bond activation of thioesters is commonly utilized in cross-coupling reactions with external nucleophiles.[92] Decarbonylation of thioesters is similarly catalyzed by various transition metals. The first decarbonylative UFC of thioesters was reported by Yamamoto et al. in 1987 using Pd(PCy$_3$)$_2$ as the catalyst (Scheme 17A-i).[93] Since then, several other palladium-based catalyst systems have been developed, which has significantly broadened the scope of substrates to include vinyl, aryl, and heteroaryl groups that could be thiolated (Scheme 17A-ii, iii, and iv).[94−96]

Examples of the nickel-catalyzed decarbonylative UFC of thioesters are summarized in Scheme 17B. Since the pioneering work by Wenkert and co-workers using 2.0 equiv of a nickel complex,[97] several groups have accomplished catalytic reactions by adding suitable ligands (Scheme 17B).[95,98−100] Wei and co-workers also reported a nickel-catalyzed decarbonylation of α-keto thioesters (Scheme 17C).[101] The selectivity between single and double decarbonylation is controlled by the electronic characteristics of the ligand. When a phosphine ligand, such as PPh$_3$, was employed, the monodecarbonylated products **3** were selectively obtained to form thioesters. In contrast, using NHC as a ligand results in

a second decarbonylation of the thioester, which leads to the formation of doubly decarbonylated diaryl sulfide products **4**.

Rhodium complexes also serve as catalysts for the decarbonylative UFC of thioesters. In contrast to an early finding by Yamamoto and co-workers that 1.0 equiv of RhCl(PPh$_3$)$_3$ is required for decarbonylation of thioesters (Scheme 17D-i),[93] Szostak and co-workers reported that decarbonylation proceeds catalytically when [Rh(cod)Cl]$_2$ alone is used as the catalyst without phosphine ligands, inorganic bases, or other additives (Scheme 17D-ii).[102] It should be noted that aryl chlorides and bromides are compatible, although these are problematic in decarbonylation when using other metal catalysts.

Amides

Despite isoelectronic relationship between amides and esters, decarbonylative UFCs of amides remain underdeveloped because C($=$O)−N bonds are, in general, considerably stronger than C($=$O)−O bonds.[103] Rueping and co-workers reported a nickel-catalyzed decarbonylative UFC of amides derived from pyridine 2-carboxylic acid (Scheme 18A).[104]

Scheme 18. Ni-Catalyzed Decarbonylative UFC of Amides
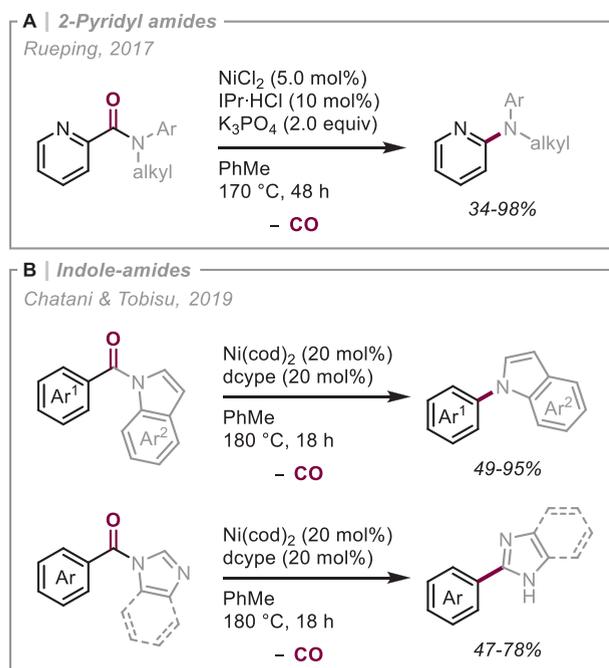
Similar to the work by Yamaguchi et al. on the decarbonylation of esters, the scope of substrates is limited to 2-azinecarboxyamide derivatives, presumably because N-heteroarenes serve as a directing group to facilitate oxidative addition/reductive elimination processes. Chatani and Tobisu et al. developed a decarbonylative UFC of N-acylated N-heteroarenes (Scheme 18B, top).[105] This transformation is complementary to the common cross-coupling of aryl halides with NH-heteroarenes in that benzoic acid derivatives can serve as an aryl source. This catalytic UFC is promoted by a nickel catalyst in conjunction with a strong σ-donor bidentate phosphine ligand, i.e., dcype, which facilitates the dissociation of CO from the nickel center and allows for regeneration of the active catalyst. It is noteworthy that the use of N-acylated imidazoles as substrates results not only in the elimination of carbon monoxide but also

in a 1,2-shift of the imidazole ring, which leads to the formation of 2-arylated imidazoles (Scheme 18B, bottom).

Acylphosphines

The palladium-catalyzed decarbonylative UFC of acylphosphonates via C($=$O)−P bond activation was reported by Nakazawa and Miyoshi in 1992 (Scheme 19A).[106] An oxidative

Scheme 19. Catalytic Decarbonylative UFC to Form a C−P bond
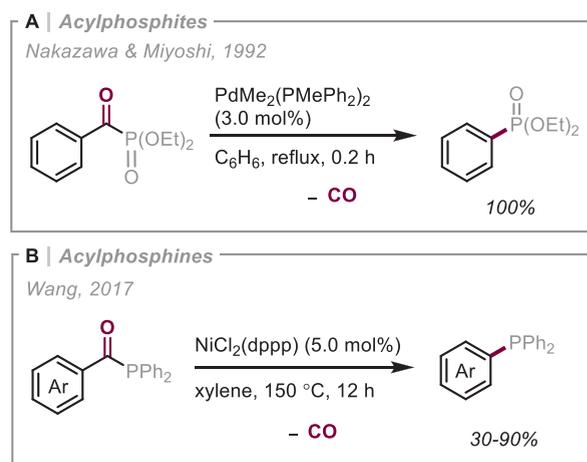
addition complex in which a palladium moiety inserts into a C($=$O)−P bond of the substrate was successfully isolated, which provided a concrete experimental basis for the mechanism of this UFC. Recently, Wang et al. developed a nickel-catalyzed decarbonylative UFC of acylphosphines, which established a simple route for the synthesis of unsymmetrically substituted triarylphosphines (Scheme 19B).[107] Since acylphosphines can be prepared by phosphination of benzoic acid derivatives, the use of aryl halides can be avoided in the arylation of phosphines.

■ ELIMINATION OF SO₂ FROM SULFONES

Among organosulfur compounds, sulfones occupy a unique position for use in synthetic organic chemistry because of their strong electron-withdrawing ability, which stabilizes α-anions and also serves as a good leaving group.[108−112] Given that sulfones are readily available building blocks, the UFC of sulfones with the elimination of SO$_2$ (desulfonylative UFC) would provide useful bond-forming methods that could be applicable in the late stages of synthetic schemes.[113] An early example of such an elimination of SO$_2$ from sulfones is exemplified by the Ramberg−Bäcklund reaction[114−120] in which α-halo dialkyl sulfones are converted to alkenes via thiirane dioxide intermediates, although this reaction is not classified as UFC. In 1985, Kamigata et al. reported a Ru-catalyzed desulfonylative UFC of dialkenyl sulfones to synthesize 1,3-butadiene derivatives (Scheme 20A).[121] Although this reaction represents one of the earliest examples of the desulfonylative UFC of sulfones, this transformation is exclusively limited to divinyl sulfones, which leaves its broader synthetic potential largely untapped.

In 2018, Yorimitsu and co-workers utilized 2-azaaryl aryl sulfones as effective substrates for desulfonylative UFC (Scheme 20B-i).[122] The use of Ni(cod)$_2$ and NHC ligands efficiently promotes UFC to give heterobiaryl products in good

Scheme 20. Catalytic Desulfonative UFC of Sulfones, Solfonates, and Sulfoamides
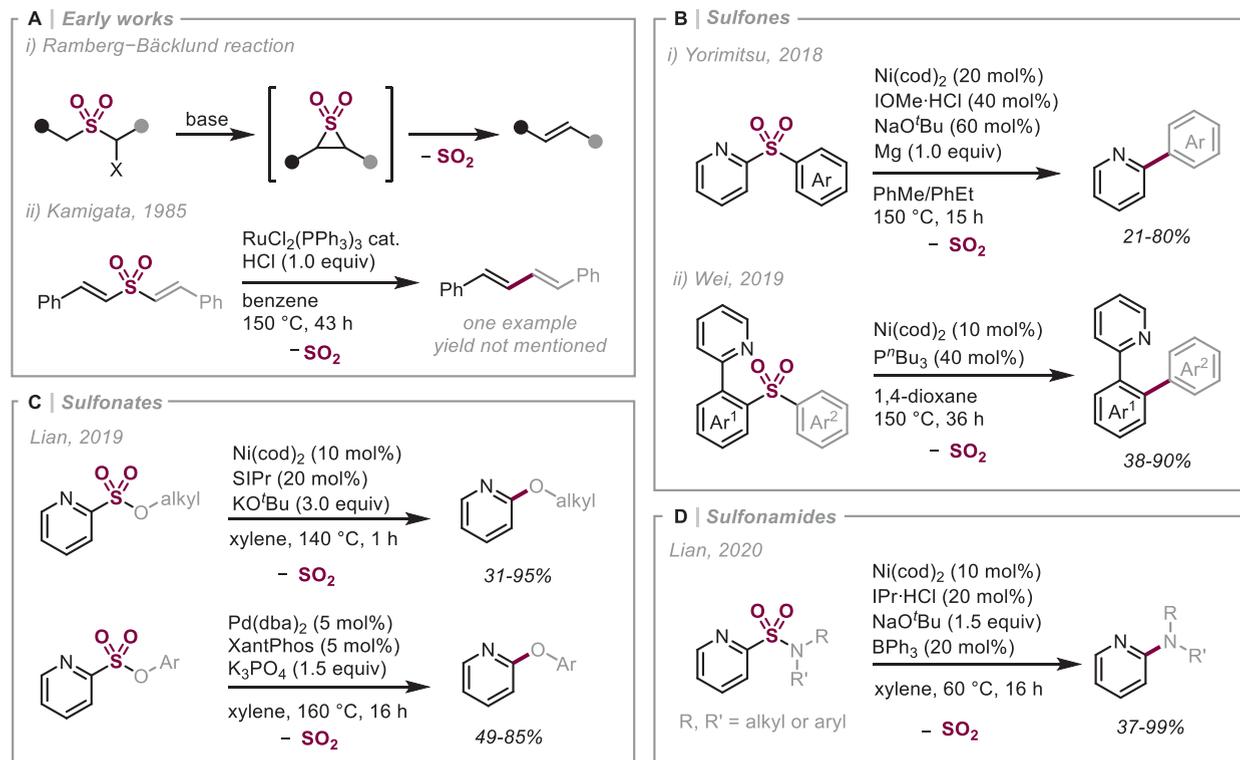
yields. The addition of Mg turnings is not essential but it helps improve the yield, possibly by reducing undesirably oxidized nickel species. This reaction exhibits high levels of functional group compatibility, such as Cl, CN, and esters. A mechanism was proposed on the basis of a Ni(0)/(II) catalytic cycle, which involves the oxidative addition of a C(aryl)−SO$_2$ bond, the elimination of SO$_2$, and the reductive elimination, as is proposed for other forms of UFC. A 2-azaaryl ring (e.g., 2-pyridyl) in the substrate is necessary for smooth desulfonylative UFC, which suggests that the coordination of nitrogen to the nickel catalyst would accelerate the oxidative addition step and/or that the electron-withdrawing nature of a 2-azaaryl ring facilitates the elimination of SO$_2$ by stabilizing the resultant diaryl nickel(II) complex. Wei and co-workers also reported that biaryl sulfone derivatives with a 2-pyridyl group at the ortho position also participate in Ni-catalyzed desulfonylative UFC (Scheme 20B-ii).[123] The utilization of the pyridyl moiety as the directing group enables the cleavage of the C(aryl)−SO$_2$ bond, which results in the formation of a wide variety of biaryl derivatives. UFC via the extrusion of SO$_2$ is not limited to C−C bond formation, and other heteroatoms such as O and N could also be used as internal nucleophiles. Lian and co-workers reported a nickel- and palladium-catalyzed desulfonylative UFC of sulfonates bearing a 2-pyridine group to forge the C−O bond (Scheme 20C).[124] Again, the presence of a 2-pyridyl group in the substrates is essential, possibly because of its role as a directing group. In this reaction, alkyl sulfonates participate in an intramolecular desulfonylative C−O coupling, which is facilitated by nickel catalysts, to form aryl alkyl ethers. Conversely, aryl sulfonates undergo analogous elimination of SO$_2$ with the aid of a palladium catalyst, which leads to the formation of diaryl ethers. The C−N bond formation by SO$_2$ extrusion is also possible by the use of sulfonamides (Scheme 20D).[125] In this reaction, the addition of a catalytic amount of

a Lewis acid, BPh$_3$, improves the yield of desired products, possibly by the activation of substrates through coordination to either the pyridine nitrogen or the sulfonyl oxygen atom(s).

ELIMINATION OF RNCO FROM AMIDES

An amide group is a common functionality found in both natural and non-natural compounds. A variety of amide derivatives can be readily prepared from amine and carboxylic acid feedstocks by reliable condensation protocols.[126−128] Therefore, amides are definitely one of the most attractive substrates for UFC. Nevertheless, as of 2022, only two examples of UFC involving amide compounds have been reported. Both of these involve the elimination of CO (i.e., decarbonylative UFC) to form C−N bonds (see Scheme 18).[104,105] In view of the great success of the catalytic decarboxylation of esters (Table 2), one could envision that another mode for the UFC of amides would be the elimination of isocyanate, in which an entire amide group is deleted. However, the process requires the activation of unactivated C−N bonds, which renders such a UFC of amides a daunting challenge. In 2022, Tobisu and co-workers reported the first UFC of amides with the extrusion of isocyanate.[129] An amide functionality [i.e., −C(=O)−NAr−] can be deleted from a range of N-allylamides to form C−C, C−N, and C−S bonds (Scheme 21A). It should be noted that a formyl group is tolerated under these UFC conditions, which highlights the unique chemoselectivity of this method when compared with common intermolecular allylic amination reactions. This reaction is triggered by the oxidative addition of a C(allyl)−N bond to give a stable π-allylpalladium complex, which exists as an equilibrium mixture between neutral (**I**) or ion-paired (**I′**) forms (Scheme 21B). The elimination of isocyanate from π-allylpalladium species, followed by reductive elimination, gives a UFC product and regenerates the Pd(0) species. DFT

Scheme 21. Pd-Catalyzed Deisocyanative UFC of *N*-Allylamides

converted into an allyl group by *N*-alkylation followed by palladium-catalyzed UFC to provide **7** in 86% yield. While the synthetic modification of aminoquinoline-based directing groups has been confined to hydrolysis to produce the corresponding carboxylic acids, the UFC strategy developed in this investigation expands the range of product derivatization in C−H functionalization reactions.

Tobisu and co-workers also demonstrated that the eliminated isocyanate can be captured when substrates bearing a tethered nucleophile are used. The overall process can be viewed as a catalytic transposition of an amide group from the middle to the terminal of the molecule (Scheme 23).[130]

■ ELIMINATION OF N₂ FROM 1,2-DIAZENES AND THEIR DERIVATIVES

1,2-Diazenes represent a class of nitrogen-bridged compounds and could be attractive substrates for UFC with the elimination of molecular nitrogen (N_2). Indeed, it is well-known that 1,2-diazenes can eliminate N_2 by heating at high temperatures or by UV irradiation, which leaves behind carbon-centered radicals that can combine to form C−C bonds, particularly in the case of cyclic 1,2-diazenes (Scheme 24A).[131,132] However, the current state of this chemistry has several limitations. First, synthesis of 1,2-diazenes is nontrivial. For example, 1,2-dialkyldiazenes are prone to isomerize to hydrazones, which are inactive for the elimination of N_2. Second, the elimination of N_2 from 1,2-diazenes normally requires high temperatures or UV irradiation, which induces side reactions by the generated reactive radical species. Therefore, implementation of this process in UFC would require (a) hassle-free synthesis of unsymmetrical 1,2-diazenes or their precursors, (b) mild conditions for their fragmentation, and (c) controlled radical pair combination.

In 2011, Movassaghi and co-workers reported a controlled and stereoselective synthesis of homo- and heterodimeric hexahydropyrroloindoles by the expulsion of N_2 from 1,2-diazenes (Scheme 24B).[133] The sulfamide **8**, which can be easily synthesized by the reaction of the corresponding amine and sulfuryl chloride in the presence of 4-dimethylaminopyridine (DMAP) , is oxidized with *N*-chlorosuccinimide (NCS) and 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) to afford the desired 1,2-diazene **9** via the elimination of SO_2. Photolysis of the crude 1,2-diazene **9** in ᵗBuOH leads to stereocontrolled C−C bond formation and produces the UFC product in 70% yield in 2 steps. Movassaghi et al. also disclosed the total synthesis of highly complex natural products using this 1,2-diazene-based UFC strategy.[134−137]

Quite recently, Lambert and co-workers developed a simple yet effective method for the elimination of N_2 from 1,2-

calculations revealed that the elimination of isocyanate from allylic amides is endoergic, and the trimerization of isocyanate ($\Delta G = -7.4$ kcal/mol) provides the driving force for this UFC, which renders the overall process thermodynamically favorable.

To showcase the synthetic utility of this deisocyanative UFC, it is applied to the catalytic transformation of an amide directing group, which is used for C−H bond functionalization reactions (Scheme 22). For example, an amide group bearing an 8-aminoquinoline moiety in **5** facilitates the arylation of an inert C(sp³)−H bond by using a palladium catalyst to generate **6**. The 8-aminoquinoline-based directing group in **5** can be

Scheme 22. 8-Aminoquinoline Amide as a Convertible Directing Group
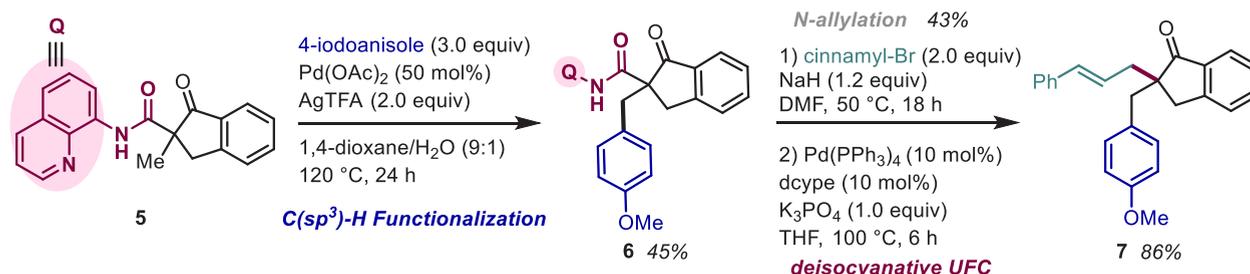
Scheme 23. Pd-Catalyzed Migratory UFC of *N*-Allylamides

Tobisu, 2023

Pd(PPh₃)₄ (10 mol%)
dcype (10 mol%)

PhMe, 100 °C, 18 h

(Ar = *p*-CF₃C₆H₄)

cut → *paste*

92%

selected examples

56%

77%
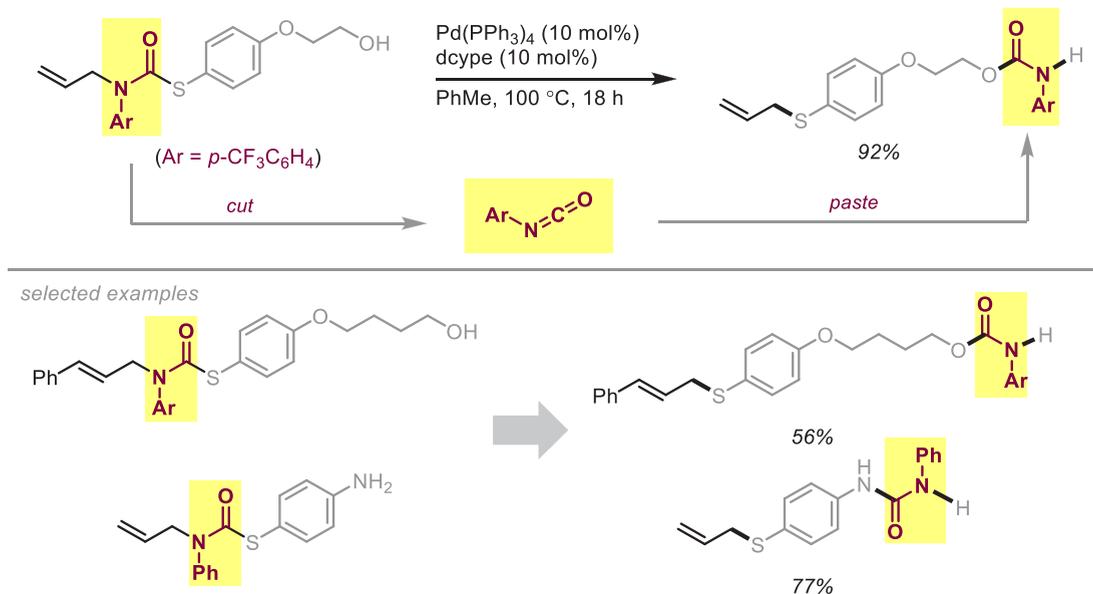
diazenes (Scheme 24C).[138,139] Primary amines are converted to 1,2-dialkyldiazenes by treatment with *O*-nosylhydroxyl-amines followed by visible light photocatalysis to trigger their in situ elimination of N_2. This transformation can also be viewed as a novel method to convert primary amines to $C(sp^3)-C(sp^3)$ cross-coupled products. Because of the mild conditions, a wide range of functional groups are compatible, including carboxylic acids, unprotected alcohols, and tertiary amines.

Although the origin of the high efficiency of a radical–radical recombination generated from 1,2-diazenes in these examples remains unclear, the choice of the solvent (i.e., the solvent-cage-controlled radical pair combination)[140,141] and the use of mild reaction conditions, such as visible light instead of UV, are apparently important.

■ ELIMINATION OF A SINGLE ATOM

Deletion of a single atom from the middle of the molecule represents a unique strategy for developing an uncommon mode of UFC.[142−145] In general, the elimination of stable molecules, such as CO_2 and CO, is one of the most important driving forces for promoting UFC. In contrast, the elimination of a single atom cannot occur directly because a single atom is extremely unstable. Therefore, a generalized sequence of UFC that involves the oxidative addition/extrusion of a small molecule/reductive elimination cannot be applied, and a mechanistically distinct approach must be devised. In the following examples, formal extrusion of a single atom is accomplished by converting it into a stable molecule. In this section, we focus on single atom deletions of acyclic compounds.

In 2017, Shi and co-workers reported the nickel-catalyzed removal of an oxygen atom from dibenzyl ethers to synthesize 1,2-diarylethanes (Scheme 25A).[146] In this reaction, the addition of a stoichiometric amount of B_2pin_2 and Zn dust is essential, likely as an oxygen acceptor. A Ni(0)/Ni(I)/Ni(III) catalytic cycle is proposed for this reaction (Scheme 25B). First, the oxidative addition of a C−O bond in the ether substrate to Ni(0) forms Ni(II) intermediate **K**, which is

subsequently reduced by Zn to generate Ni(I) complex **L**. This Ni(I) facilitates a second oxidative addition involving another ether substrate, which leads to the formation of Ni(III) species **M**. Subsequent reductive elimination from **M** forms a C(benzyl)−C(benzyl) bond, along with the regeneration of Ni(I) species **N**, which is further reduced to Ni(0) by zinc. Although the role of B_2pin_2 is not entirely clear, it could serve as a coreductant, as well as a Lewis acid, to activate ethers toward oxidative addition. It should be noted that when unsymmetrically substituted diarylmethyl ethers are used, crossover products are observed, which is in agreement with the proposed mechanism in which two molecules of the ether substrate are involved.

As mentioned above, esters undergo UFC with the elimination of either CO_2 (Table 2) or CO (Scheme 16). A third class of UFC for esters involves deoxygenation in which the oxygen atom in an alkoxy group is selectively removed from esters (Scheme 26, bottom). This transformation represents the editing of an ester framework to a ketone, which can be viewed as a "retro Baeyer−Villiger reaction".[147−149]

Quite recently, Tobisu and co-workers realized this type of deoxygenative UFC of esters by the dual use of nickel and photoredox catalysts using PPh₃ as a stoichiometric reductant (Scheme 27A).[150] Various allyl benzoate derivatives can be converted into the corresponding deoxygenated ketones in the presence of NiCl₂(dme)/phenanthroline and {Ir[dF(CF₃)-ppy]₂(dtbbpy)}PF₆ catalysts, along with PPh₃ (1.2 equiv), under irradiation of visible light. A possible mechanism is depicted in Scheme 27B. The oxidative addition of an allylic ester to Ni(0) initially gives a cationic π-allyl nickel **P** and a carboxylate anion **O**. In parallel, the photoexcited Ir(III)* induces a single-electron transfer (SET) oxidation of PPh₃, which generates a triphenylphosphine radical cation. The phosphine radical cation subsequently reacts with a carboxylate **O** to generate phosphoranyl radical **Q**, which immediately undergoes *β*-scission to homolytically cleave a C(=O)−O bond, which generates acyl radical **R**, along with phosphine oxide.[151−155] The acyl radical **R** is then captured by a cationic

Scheme 24. Photoinduced Deletion of N₂ of 1,2-Diazenes

A | *N₂ deletion from 1,2-diazene*

Prior work

1,2-diazene — $- N_2$ — *radical pair* — several side products

---

B | *Movassaghi, 2011*

1) NCS (12 equiv)
BEMP (15 equiv)
THF, 23 °C, 15 min
$- SO_2$

2) Hg lamp (280 nm)
^{t}BuOH, rt, 5 h
$- N_2$

68%
(over 2 step)

8, R = CO₂Me; R' = CO₂Bn

via **9**

BEMP

C | *Lambert, 2023*

R'—NH₂ + NsO—N(H)—R''

1) 2,6-lutidine (2.0 equiv)
MeCN, rt, 12 h

2) **PC3** (2.0 mol%)
blue LED
MeCN, rt, 24 h

R—R''

38-91%

R', R'' = 1° or 2° alkyl
Ns = 2-nitrobenzenesulfonyl

via R—N=N—R'

PC3

Scheme 25. Ni-Catalyzed Deoxygenative UFC of Dibenzyl Ethers

A | *Shi, 2017*

NiBr₂(glyme) (10 mol%)
dppb (20 mol%)
B₂pin₂ (1.0 equiv)
Zn dust (2.5 equiv)

PhMe/THF
115 °C, 12 h
$- $ "O"

37-80%

B | *Proposed mechanism*

X = Bn or Bpin

Scheme 26. Catalytic UFC of Esters

decarboxylation
cat. Pd, Ni, Ir *etc.*
$- O=C=O$
well-known
for allylic esters

decarbonylation
cat. Ni
$- CO$
two examples

deoxygenation
cat.
$- $ "O"
Tobisu, 2023

π-allyl nickel species, which results in the formation of the π-allyl nickel complex **S** and provides the UFC product by reductive elimination.

The deoxygenative UFC of allylic esters could also be used to substitute the oxygen atom with a two-carbon unit (Scheme 28). When allylic esters bearing a pendant alkene group (i.e., **10**) are reacted with the Ni/photoredox dual catalysts under visible light irradiation, the acyl radical **T** generated via the extrusion of an oxygen atom undergoes 6-exo cyclization to give the alkyl radical intermediate **U**, which is subsequently captured by a cationic π-allylnickel to give the swapped product **11** in 53% yield.

In recent years, several reactions involving the removal of a nitrogen moiety from amines with a stoichiometric amount of reagents have been reported. Thermal decomposition of 1,1-diazene, a nitrogen-stabilized nitrene, is known to generate a new C−C bond by breaking two C−N bonds (Scheme 29A).[156−161] If one could generate 1,1-diazene from secondary amines in an efficient manner, then overall nitrogen deletion

from secondary amines could be realized. Lu and co-workers reported that sulfamoyl azides **13**, which are synthesized by the reaction of secondary amines **12** with N₃SO₂N₃, can generate 1,1-diazene **W** via a Curtius-type rearrangement upon heating at 80 °C, which immediately undergoes the elimination of N₂ to forge a new C−C bond (Scheme 29B).[33] One of the substituents in secondary amine substrates must be an arylmethyl group for an efficient reaction. Levin and co-workers developed a one-step procedure for a nitrogen atom deletion reaction directly from secondary amines **12** using an anomeric amide **15** (Scheme 29C).[32] Nucleophilic substitution at the nitrogen center of **15** by a secondary amine generates hydrazide **X**, which subsequently undergoes the migration of an OBn group to the carbonyl to produce 1,1-diazene **W** (the HERON reaction). The resultant 1,1-diazene **W** extrudes N₂ to form a product under these conditions, which allows a one-pot procedure for nitrogen deletion from secondary amines. The reaction exhibits wide functional group tolerance and has been applied to the synthesis of complex bioactive compounds as long as one of the substituents is an arylmethyl group (see Scheme 30).

Scheme 27. Nickel/Photoredox Dual-Catalyzed Deoxygenative UFC of Allylic Esters

A | *Tobisu, 2023*

NiCl₂(dme) (15 mol%)
phen (23 mol%)
PC2 (1.0 mol%)
PPh₃ (1.2 equiv)

PhMe/MeCN/TFE
blue LED
40 °C, 17 h

31–81%

– "O"

B | *Proposed mechanism*
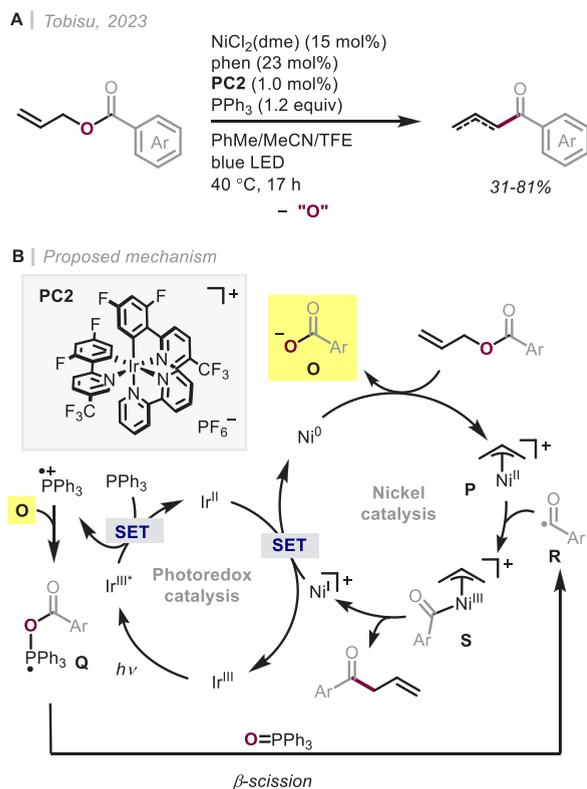
Scheme 28. Deoxygenative Insertion of a Tethered Alkene into Allylic Esters

Tobisu, 2023

NiCl₂(dme) (15 mol%)
phen (23 mol%)
PC2 (1.0 mol%)
PPh₃ (1.2 equiv)

TFE/toluene/MeCN
blue LED
40 °C, 18 h

11 *53%*

substitution of an oxygen atom by a C2 unit
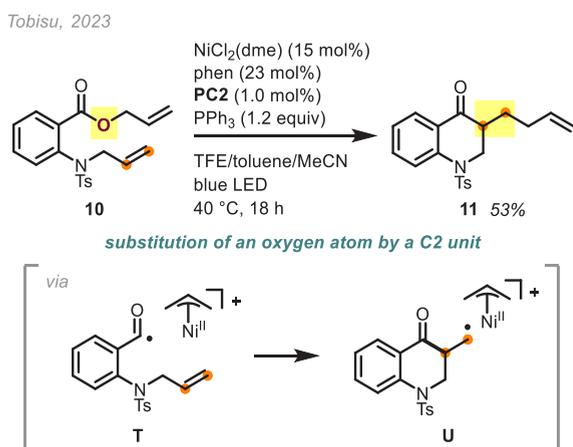
APPLICATION OF UFC IN THE SYNTHESIS OF PHARMACEUTICAL AND NATURAL PRODUCTS

Although the UFC reactions described above still require further improvement in terms of scope, some of them were successfully used for the synthesis of pharmaceuticals and natural products (Scheme 30).

Pd-catalyzed asymmetric UFC of allylic esters via elimination of CO₂ has been employed in the synthesis of various pharmaceuticals and natural products as a powerful method to construct quaternary stereocenters. For example, the aspidosperma family can be accessed through stereodefining C–C bond formation (Scheme 30A). The stereoconvergent UFC of racemic **16** in the presence of Pd₂(pmdba)₃ and (S)-(CF₃)₃-

Scheme 29. Nitrogen Deletion of Secondary Amines

A | *N₂ deletion from 1,1-diazene*

1,1-diazene — *radical pair*
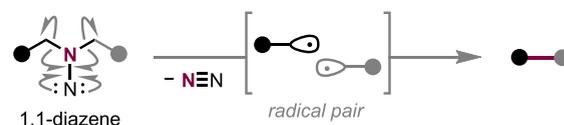
B | *Lu, 2017*
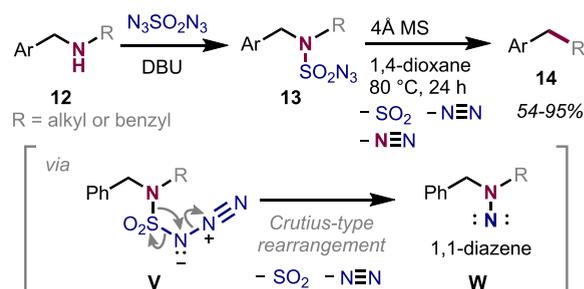
C | *Levin, 2021*
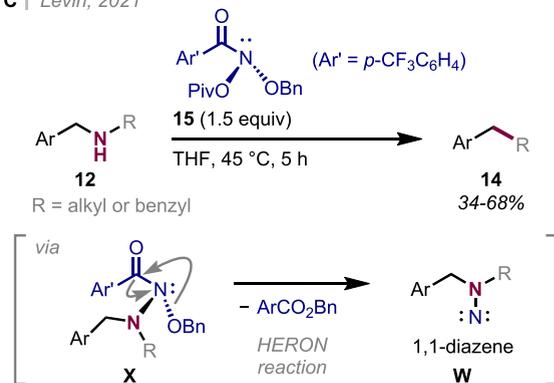
tert-BuPHOX in methyl *tert*-butyl ether (MTBE) at 60 °C delivered chiral **17** in 82% yield with 94% ee. Following the UFC, the synthesis of (+)-limaspermidine (**18**) could be completed in seven linear steps and in 31% overall yield from the tricyclic derivative **16**.[162]

Nickel/photoredox dual-catalyzed decarboxylative UFC was utilized by MacMillan and co-workers in a three-step synthesis of (±)-edivoxetine, a medicinal agent for the treatment of attention-deficit/hyperactivity disorder (ADHD) (Scheme 30B).[46] Acid **19** and acyl chloride **20** are readily coupled under the metallaphotoredox conditions (see Scheme 6) to generate ketone **21** in 68% yield via the decarboxylative UFC of an anhydride intermediate. The synthesis was completed via Grignard addition followed by HCl-mediated Boc removal to afford (±)-edivoxetine·HCl (**22**).

Despite the relatively harsh conditions (>150 °C) needed for the transition-metal-catalyzed decarbonylative UFC, it can be used for the synthesis of valuable target motifs. For example, the cobalt-catalyzed directed decarbonylation of indolyl ketones reported by Wei and co-workers was applied to the synthesis of bazedoxifene, a third-generation selective estrogen receptor modulator.[75] As shown in Scheme 30C, the key C-2 arylation is accomplished by a pyrimidine-directed decarboxylative UFC of readily accessible ketone **25**. Lian and co-workers demonstrated that the nickel-catalyzed elimination of SO₂ can be used for the synthesis of the antihistamine tripelennamine (**27**) (Scheme 30D).[125]

Scheme 30. Application of UFC in the Synthesis of Pharmaceuticals and Natural Products

Pharmaceutical and natural products synthesis by UFC strategy

A │ Metal-catalyzed decarboxylation

Pd$_2$(pmdba)$_3$ (5.0 mol%)
(S)-(CF$_3$)$_3$-^{t}BuPHOX (12.5 mol%)
TBME, 60 °C, 8 h
− CO$_2$

16　　**17** 82%, 94% ee　　(+)-limaspermidine **18**

B │ Photoredox decarboxylation

NiCl$_2$(dme) (5.0 mol%)
MeO-bipy (5.0 mol%)
PC2 (1.0 mol%)
DBU (1.3 equiv)
1,4-dioxane, blue LED
25 °C, 36 h
− CO$_2$

19　　**20**　　**21** 68%　　(±)-edivoxetine·HCl **22**

C │ Decarbonylation

Co(CO)$_8$ (10 mol%)
IMes·HCl (20 mol%)
Cs$_2$CO$_3$ (40 mol%)
1,4-dioxane
150 °C, 36 h
− CO

23　　**24** 89%　　bazedoxifene **25**

D │ Desulfonylation

Ni(cod)$_2$ (10 mol%)
IPr·HCl (20 mol%)
NaO^{t}Bu (1.5 equiv)
BPh$_3$ (20 mol%)
xylene, 60 °C, 16 h
− SO$_2$

26　　tripelennamine **27**　　49%

E │ Nitrogen atom deletion

15 (1.5 equiv)
THF, 45 °C, 5 h
− "NH"

28　　**29** 53%　　polysiphenol marine metabolite **30**

15 (1.5 equiv)
THF, 45 °C, 5 h
− "NH"

31　　**32** 66%　　pemetrexed chemotherapeutic **33**

F │ Extrusion of N$_2$

Hg lamp (350 nm)
CH$_2$Cl$_2$, rt, 3 h
− N$_2$

34　　**35** 39%　　(−)-communesin F **36**

The nitrogen atom deletion reaction developed by Levin et al. enables the synthesis of the atropoisomeric marine metabolite polysiphenol, **30**, via deletion of nitrogen from dibenzylamine **28** (Scheme 30E).[32] The previously reported

preparation of **29** relies on hydrogenation of the corresponding stilbene, the preparation of which via Wittig olefination requires diverging a common aldehyde intermediate to prepare the corresponding ylide over 3 steps. By contrast, their synthesis enables conversion of the aldehyde to the bibenzyl dimer (via an amine linchpin) without the need to divert half of the material through a phosphonium synthesis. Levin's group has also used their method in the synthesis of the folate antimetabolite pemetrexed **33**, which is used as a chemotherapeutic in the treatment of lung cancer. In this synthesis, the two functionalized fragments of the molecule are united by facile reductive amination, and nitrogen deletion subsequently forges the C−C bond.

A biomimetic enantioselective total synthesis of (−)-communesin F (**36**) featuring a 1,2-diazene synthesis from unsymmetric sulfamide/photolysis approach as a key reaction was reported by Movassaghi and co-workers (Scheme 30F).[135] The unsymmetrical sulfamide was easily synthesized by the reaction of the corresponding aryl sulfamate with aminonitrile, as implemented by DMAP. 1,2-Diazene **34** formation followed by photolysis affords UFC product **35**, which is converted to (−)-communesin F (**36**) in three steps.

CONCLUSION AND OUTLOOK

In this Perspective, the concept of UFC is defined as reactions in which a new chemical bond is formed through the elimination of an atom located in the middle of a molecule and the subsequent intramolecular coupling of the rest of the fragments. UFC has several potential advantages over common cross-coupling approaches: (i) substrates (ketones, esters, and amides, etc.) are readily accessible from feedstock materials and (ii) key bond formation occurs in an intramolecular manner, which facilitates otherwise difficult bond-forming processes with unique chemo- and stereoselectivity on the basis of the entropic advantage.

One major class of UFC is the elimination of molecules, such as CO_2, CO, and others, which is catalyzed by transition metal catalysts. As generalized in Scheme 31, the UFC requires

Scheme 31. Generalized Mechanism for Transition-Metal-Catalyzed UFC

L: CO, CO_2, SO_2 etc.
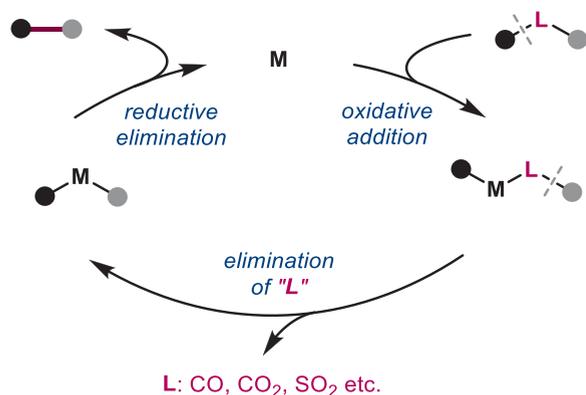
two bond activation processes through metal-mediated oxidative addition and β-elimination reactions. Because these elementary reactions are applicable to a small class of relatively reactive chemical bonds, the scope of UFC reactions has remained limited primarily to substrates that contain such reactive bonds, which includes allylic and benzylic substrates. Clearly, there is a need to broaden and diversify the scope of

substrates in order to fully demonstrate the powerful potential of the UFC strategy. Another emerging approach for UFC is the deletion of single atoms. This calls for a strategy that is completely different from that depicted in Scheme 31 since single atoms cannot be eliminated in their naked forms. Although several promising approaches have been reported, the scope of the substrates is limited primarily to allylic and benzylic systems, as is the case for UFC with the elimination of a small molecule. To overcome these limitations, research efforts should be directed to broaden the scope of chemical bonds that could be activated for use in UFC. This endeavor will be assisted not only by sophisticated transition metal catalysis but also by recent advances in single-electron processes via photoredox or electrochemistry.

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The manuscript was written through contributions of all authors.

Notes

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