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Perspective

C–C Bond Forming Reactions Enabled by Vitamin B_{12}—Opportunities and Challenges

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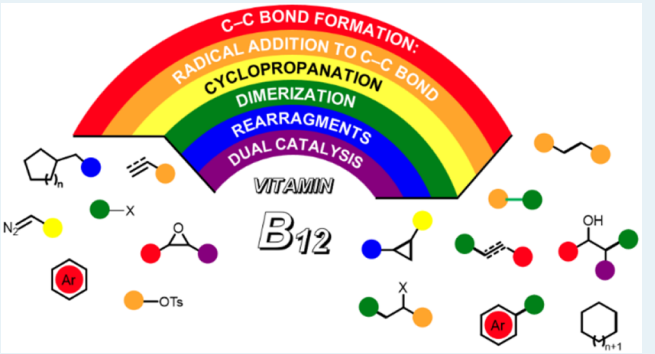
ABSTRACT: Cobalt not only is an essential micronutrient for mammals but also marks itself as important in organic synthesis, especially in the field of catalysis. Various useful reactions, such as alkene hydroformylation, hydrogenation, heterofunctionalizations of carbon–carbon double bonds, C–H activation, and cross-coupling reactions, have been realized with the aid of this metal. At the same time, cobalt deserves special attention as a catalyst for radical processes; in fact, in the form of vitamin B_{12}, it was designed by Nature as a reversible carrier for radicals. Since this molecule is a native Co-complex, it is very attractive for the development of sustainable transformations, and it has already been demonstrated that vitamin B_{12} and its derivatives mediate numerous reactions that have found applications in both the construction of complex molecules and the degradation of polyhalogenated pollutants. However, in this Perspective, we focus the readers' attention on radical C–C bond forming reactions catalyzed by vitamin B_{12}, which are particularly important as a tool for the synthesis of important molecules in a greener manner. We also ponder over the challenges that remain to be addressed and the solutions that are expected to come.



KEYWORDS: *cobalt catalysis, vitamin B_{12}, cobalamin, corrinoids, radicals*

1. INTRODUCTION

Growing concerns about the environment, and hence stringent environmental regulations, demand from the chemical industry that serious steps be taken to improve the sustainability and greenness of their processes. Among these processes, ca. 90% are catalytic and are often based on scarce, toxic, and expensive metals, such as Pd, Pt, Ru, Ir, etc.[1] In this regard, the quest for greener and more efficient catalysts has been at the forefront of chemical research, and as a consequence, a great deal of focus has been devoted to processes mediated by earth-abundant transition metals and organocatalysts. In this context, Co-catalysis has been found to facilitate numerous transformations, even reactions such as cross-coupling, mainly dominated by Pd or Ni, C–H activation, or various classes of hydrogenation or hydrofunctionalizations.[2] Impressive advances have also been made in the Co-mediated radical reactions that often take their roots in enzymatic processes involving vitamin B_{12}.

Since its first isolation in 1948, vitamin B_{12}, also known as cobalamin, has challenged researchers representing biology, chemistry, medicine, and related sciences.[3−5] Apart from studies on antipernicious anemia, vitamin B_{12} catalysis is the most explored area of cobalamin-related research, as in Nature, this molecule is a cofactor for many enzymatic reactions; rearrangements involve adenosylcobalamin (**4**), while methyl transfer requires methylcobalamin (**3**; Figure 1A). Regardless of the type of cofactor, the formation and cleavage of the Co–C bond play a crucial role and account for this Co-complex catalytic activity. In developed bioinspired reactions, these types of organometallic species are involved in the generation of radicals that engage in numerous types of unique radical transformations. In fact, vitamin B_{12} catalysis has already proven to be an increasingly valuable tool for facile radical functionalizations, as well as for the assembly and decomposition of organic molecules.

In this Perspective, with the issue of sustainability in mind, we focus on radical transformations enabled by vitamin B_{12} and closely related compounds as greener alternatives to synthetic Co-complexes. In particular, synthetically useful C–C bond forming reactions and the underlying mechanistic principles are discussed in detail, putting aside a plethora of functional group transformations.

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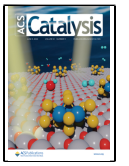

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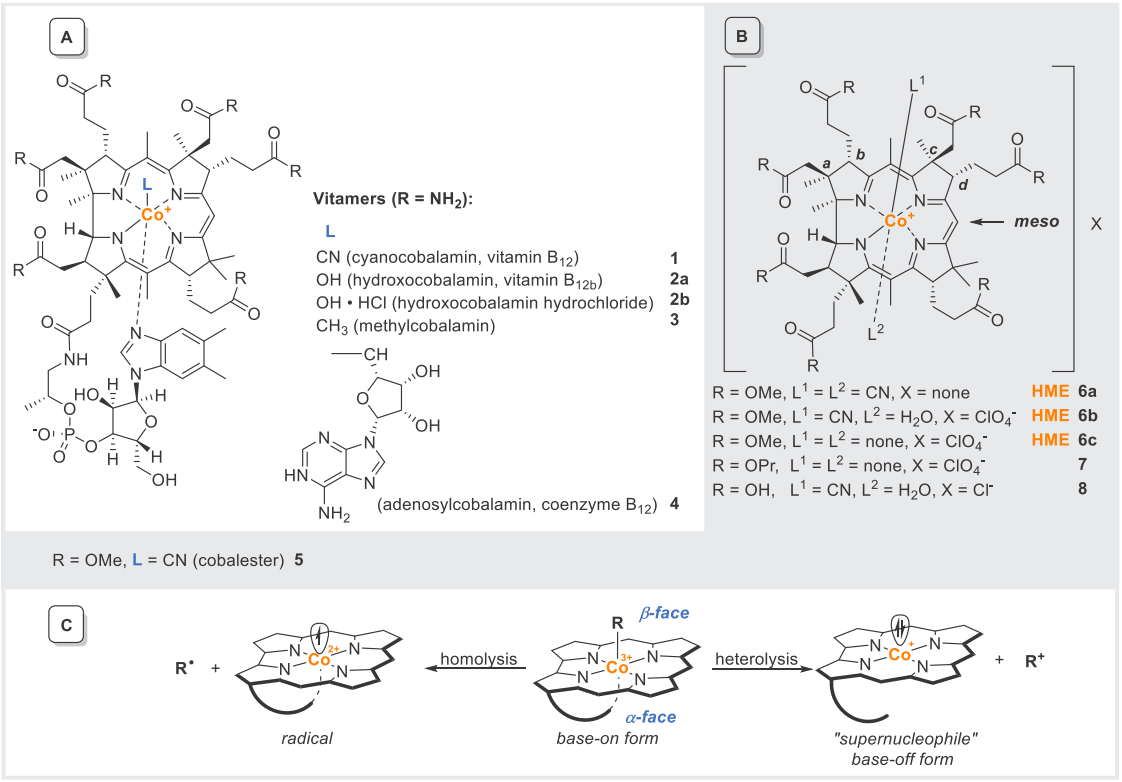

Figure 1. Structure of vitamin B_{12} (A) and its derivatives (B). Dissociation of the Co−carbon bond in vitamin B_{12} derivatives (C).

Furthermore, cooperative catalysis has enabled the discovery of a growing number of transformations leading to products that are otherwise difficult to access, which has had an impact on vitamin B_{12} catalysis and is also highlighted. However, details on dehalogenation, bioinspired by enzymatic processes, and the most extensively studied reaction catalyzed by vitamin B_{12} are not given here. The proclivity of vitamin B_{12} to catalyze this process is, however, reflected in this article, as dehalogenation frequently serves as the first step of more complex sequences leading to the formation of a new C−C bond or is often encountered as a side reaction. Inspiring enzymatic transformations involving cobalamins are also not covered here, and the readers should refer to excellent reviews that have been published on this subject.[5−7]

This Perspective is not by any means comprehensive but provides a concise update (highlighting particularly the period from 2015 through March 2022) on this continuously progressing area of bioinspired catalysis and aims to stimulate its further development not only in academic but also in industrial environments. Being a native cobalt complex and having the advantage of being water-soluble, vitamin B_{12} is perfectly suited for the development of green, sustainable catalytic transformations, and such discoveries are expected in the near future.

2. VITAMIN B_{12}—STRUCTURE AND CATALYTIC ACTIVITY

Chemically speaking, vitamin B_{12} is a stable metal complex with a cobalt ion in the +3 oxidation state coordinated with four nitrogen atoms of a corrin ring, the nitrogen atom of benzimidazole (part of the so-called nucleotide loop), and various residue groups (L) that differentiate vitamin B_{12} into different so-called vitamers (Figure 1A). Due to its complexity, for commercial use, vitamin B_{12} is biologically manufactured by fermentation, although the possibility of total synthesis has been demonstrated in a seminal decade-long work by the Woodward and Eschenmoser groups.[8,9] As a consequence, all modifications in the structure of vitamin B_{12} that may have an impact on its catalytic activity are made via transformations of the parent molecule. Along this line, various hydrophobic derivatives of vitamin B_{12} (**5**−**8**; Figure 1B), that are soluble in common organic solvents, have been devised and have extended the application of vitamin B_{12} catalysis, because the solubility of a native vitamin B_{12} is limited to water and other polar solvents such as DMSO, MeOH, EtOH, and DMF (to some extent). Although most of them contain cobalt in the +3 oxidation state, some (namely, compounds **6c** and **7** in Figure 1B) represent stable Co(II) complexes that are typically used under electrochemical or photochemical conditions.

The source of the catalytic activity of vitamin B_{12} lies in its ability to form organometallic species with relatively weak cobalt−carbon bonds that can undergo either homo- or heterolytic dissociation [bond dissociation energy of 126 kJ/mol for coenzyme B_{12} (**4**; Figure 1C)].[10] In the laboratory setup, the first mode is typically induced by heat or irradiation and leads to the formation of a radical and a paramagnetic Co^{2+} species with an unpaired electron. Heterolytic dissociation of that bond gives the corresponding carbocation and Co^{+} species with highly nucleophilic character, which is often referred to as a "supernucleophile".[11,12]

Despite a variety of bioinspired C−C bond forming reactions mediated by corrinoids, most of them share a similar mechanistic pathway that involves the generation of an organometallic species and subsequent homolytic cleavage of the Co−carbon bond (Scheme 1). In particular, it begins with the reduction of cobalt(III) or cobalt(II) to the cobalt(I) form

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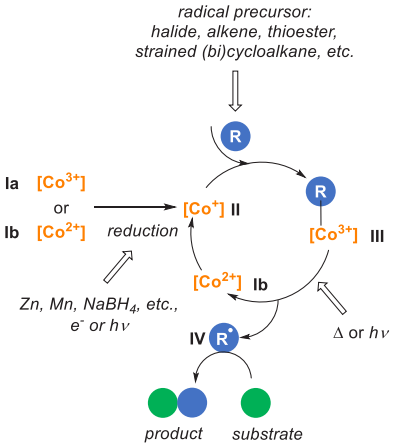
Scheme 1. General Mechanism of C−C Bond Forming Reactions Catalyzed by Vitamin B_{12}



typically using chemical reductants (e.g., Zn, Mn, or $NaBH_4$), although electrochemical and photochemical approaches have also proved successful (*vide infra*). The reduced species **II** (supernucleophile) reacts with an electrophilic substrate often via the S_N2 mechanism to form a Co−C bond whose subsequent homolysis generates radical **IV**, which can engage in various reactions, and cobalt(II) species **Ib**, which upon reduction returns to the catalytic cycle (Scheme 1).

3. C−C BOND FORMING REACTIONS CATALYZED BY VITAMIN B_{12} AND ITS DERIVATIVES

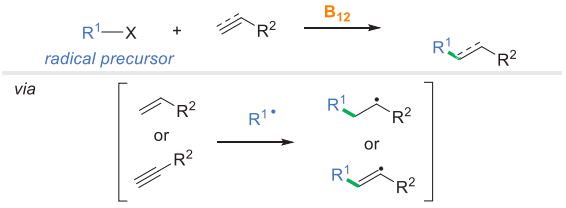
C−C bond forming reactions are fundamental transformations of synthetic organic chemistry enabling the assembly or extension of a carbon skeleton. Such transformations are of paramount importance in medicinal chemistry, agrochemical production, and natural product synthesis, particularly if they are performed under sustainable conditions. In this regard, the unique mechanistic pathway by which vitamin B_{12} works inspired researchers to probe its catalytic activity in organic reactions, including dehalogenation, addition to double bonds, ring expansion, or C−H functionalization, etc., some of which are discussed below in more detail. By combining vitamin B_{12} with other transition metal catalysts, the scope of potential transformations can be further expanded.

3.1. Radical Addition to the Carbon−Carbon Multiple Bonds. Alkenes are well-known radical acceptors,[13] and their compatibility with radicals generated via vitamin B_{12} chemistry has been extensively explored. Other radical acceptors, such as alkynes or arenes, have also been disclosed. As radical precursors, alkyl halides and pseudo-halides have been used predominantly, but with the field evolving, new groups of compounds have proved suitable as well.

3.1.1. Alkylation of Alkenes and Alkynes. Additions. In protic solvents, α,β-unsaturated carbonyl compounds typically undergo hydrogenation in the presence of reduced cobalamin. However, when a radical source, for example, an alkyl halide, is present, this reactivity can be altered, and alkylation of alkenes or alkynes occurs (Scheme 2).

A process involving the addition to an electron deficient alkene (e.g., α,β-unsaturated carbonyl compound) is commonly referred to as the Giese-type reaction. The new carbon−carbon bond is formed due to interactions between the singly occupied molecular orbital (SOMO) of the free radical and the lowest unoccupied molecular orbital (LUMO) of the alkene (for

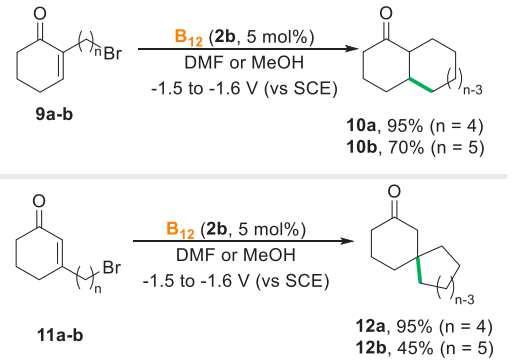
Scheme 2. Vitamin B_{12}-Catalyzed Addition to a Carbon−Carbon Multiple Bond



nucleophilic radicals) or, accordingly, the SOMO and the highest occupied molecular orbital (HOMO) (for electrophilic radicals).[14]

Reactions of alkyl halides with alkenes containing an electron-withdrawing group constitute one of the most frequently studied reactions among those catalyzed by vitamin B_{12}. In the 1980s, this approach has been demonstrated in the electrocyclization of a series of unsaturated bromo derivatives **9** and **11** leading to the formation of fused rings **10** or spirocycles **12** depending on the structure of the substrate (Scheme 3).[15,16] This methodology

Scheme 3. Intramolecular Radical Conjugate Addition Catalyzed by Vitamin B_{12}



was later extended to the synthesis of five-membered *O*-heterocycles via cyclization of the corresponding 6-bromoalkynes.[17] Furthermore, the synthesis of 1-decalone was realized in microemulsions containing hexadecyltrimethylammonium bromide,[18,19] as well as using metallopolyion films of cobalt corrin vitamin B_{12} hexacarboxylate and poly(L-lysine) covalently attached to carbon electrodes.[20]

An intermolecular variant of this reaction was demonstrated in the reaction of steroid-derived bromides and iodides **13** with activated alkenes **14**, emphasizing that vitamin B_{12} catalysis is a suitable tool for late-stage functionalizations of complex molecules (Scheme 4).[16] It is important to note that this protocol utilizes secondary alkyl halides that are known to be less reactive for the generation of alkylcobalamins and are, therefore, rarely explored in vitamin B_{12} catalysis. The reactivity of Michael acceptors **14** is reflected in the stereoselectivity of this reaction. Highly reactive reagents lead predominantly to α-substituted stereoisomers, while for less reactive disubstituted olefins, thermodynamically more stable β-derivatives are formed. The addition of amine (e.g., Et_3N) has a beneficial impact on the diastereoselectivity of the vitamin B_{12}-catalyzed Giese-type addition, while in the presence of only NH_4Cl, the *syn*:*anti* ratio decreased from 99:1 to 82:18.[21]

In 1994, Scheffold and Busato portrayed vitamin B_{12} (**2b**) as a suitable tool for the synthesis of the complex molecule **17**−

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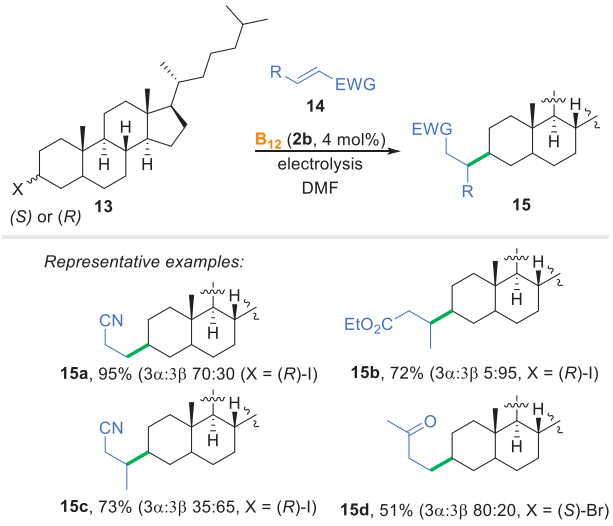
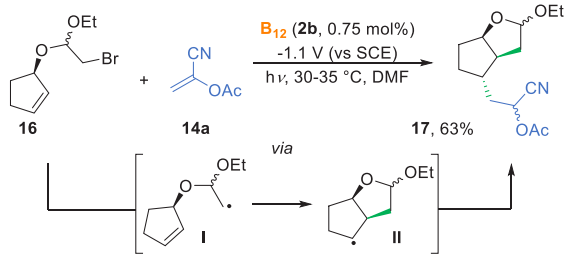
Scheme 4. Intermolecular Radical Conjugate Addition Catalyzed by Vitamin B_{12}



methyl jasmonate (Scheme 5).[22] Specifically designed bromide **16** reacts with the reduced form of the catalyst to give alkyl

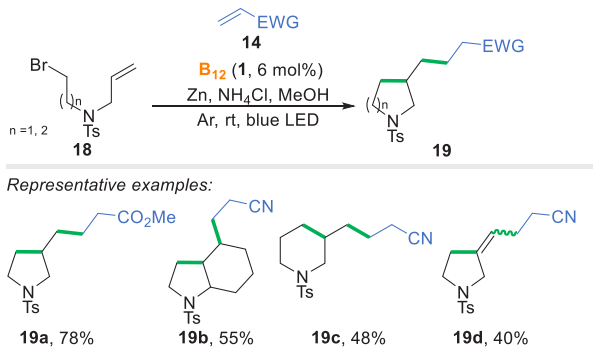
Scheme 5. Tandem Radical Cyclization and Conjugate Addition in the Synthesis of a Jasmone Derivative



cobalamin. Homolysis of the Co−C bond generates primary radical **I**, which cyclizes with the formation of secondary radical **II**, which precedes conjugate addition.

A similar concept has been applied very recently to the synthesis of pyrrolidine (and piperidine) derivatives **19**. The reaction proceeds via a sequence of debromination, radical cyclization with the formation of an *N*-heterocycle, followed by conjugate addition (Scheme 6).[23] This protocol enables the efficient synthesis of substituted heterocycles **19** in as fast as 15 min and is also compatible with internal alkenes and alkynes,

Scheme 6. Tandem Radical Cyclization and Conjugate Addition Leading to Pyrrolidines



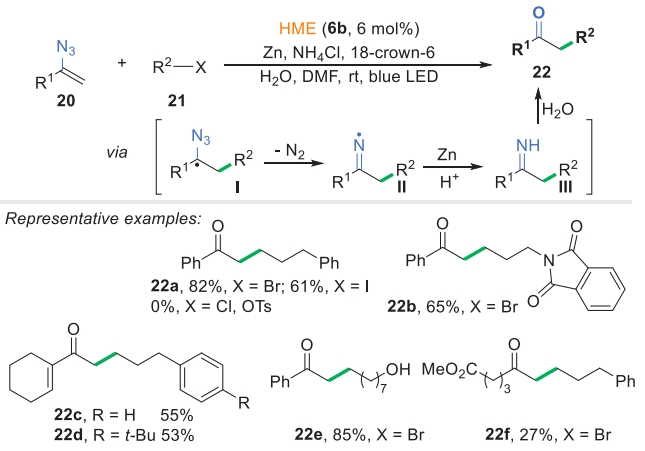
correspondingly leading to bicyclic product **19b** or the derivative with the exocyclic double bond **19d**.

This protocol enables the efficient synthesis of substituted heterocycles **19** in as fast as 15 min and is also compatible with internal alkenes and alkynes, correspondingly leading to bicyclic product **19b** or the derivative with the exocyclic double bond **19d**.

With an increasing demand for the use of greener energy sources in chemical synthesis and following the developments in the field of photocatalysis, the visible light-driven reducing system based on Rose Bengal for derivative **6c** was developed and applied in the addition of a radical originated from (3-bromopropyl)benzene to methyl acrylate giving the desired product in 47% yield.[24] This approach eliminated the need for chemical reductant use, but in order to be successful it required a prereduced Co(II) form of the catalyst.

Most of the examples shown previously utilized *α,β*-unsaturated derivatives of carboxylic acids as radical acceptors, but other types of alkene acceptors are also compatible with vitamin B_{12} catalysis. In this context, very recently, a methodology utilizing electron rich vinyl azides **20** as acceptors of radicals was devised (Scheme 7).[25] Under the developed

Scheme 7. Addition of Alkyl Radicals to Vinyl Azides 20 Catalyzed by HME (Heptamethyl Ester Cobyrinate, 6b)



conditions, electrophilic alkyl halide generates a C-centered nucleophilic radical that adds to the azide with the formation of the azido C-centered radical **I**, which fragments to the corresponding iminyl radical **II**. Subsequent reduction, protonation, and hydrolysis lead to desired ketone **22**. The crucial addition of 18-crown-6-ether is worth noting, the role of which, however, is not well understood. Desired products form not only from aryl vinyl azides but also from *α,β*-unsaturated and alkyl vinyl azides **20**, which is unusual behavior for the latter azides.

Under the developed conditions, electrophilic alkyl halide generates a C-centered nucleophilic radical that adds to the azide with the formation of the azido C-centered radical **I**, which fragments to the corresponding iminyl radical **II**. Subsequent reduction, protonation, and hydrolysis lead to desired ketone **22**. The crucial addition of 18-crown-6-ether is worth noting, the role of which, however, is not well understood. Desired products form not only from aryl vinyl azides but also from *α,β*-unsaturated and alkyl vinyl azides **20**, which is unusual behavior for the latter azides.

Not only alkyl halides but also pseudo-halides are suitable as a radical source in vitamin B_{12}-catalyzed reactions. In this context,

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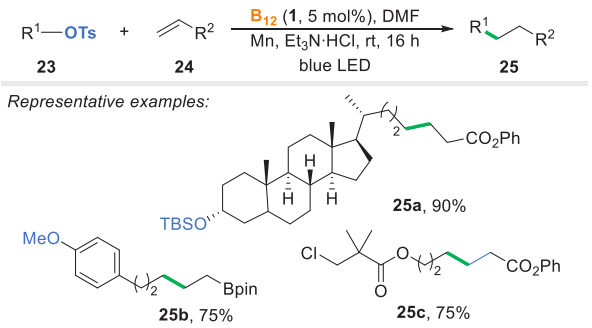
Komeyama and co-workers reported alkyl tosylates **23** as suitable precursors of alkyl radicals in vitamin B_{12}-catalyzed reactions (Scheme 8).[26] In this scenario, the reduced Co(I)

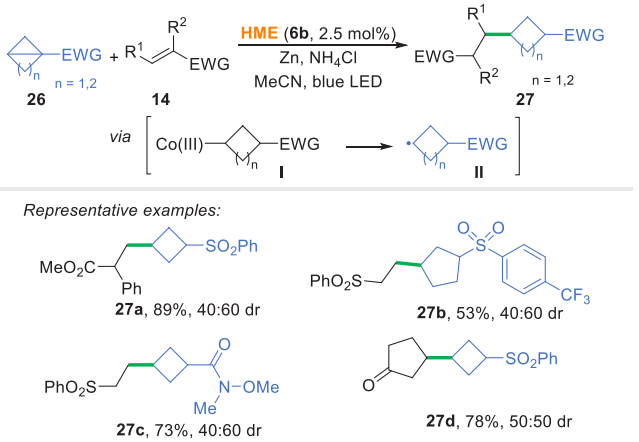
Scheme 8. Alkyl Tosylates 23 as a Source of Radicals in Vitamin B_{12}-Catalyzed Reactions



form reacts with pseudohalide **23**, giving an alkyl cobalamin as an intermediate. Crucial to the successful outcome of this process was the choice of a suitable proton donor (the best being $Et_3N{\cdot}HCl$). Interestingly, choosing manganese instead of zinc, a commonly used reductor, resulted in a higher yield of the product (61% vs 51%). The reaction is highly chemoselective, and silyl, alkyl, and phenyl ethers remained intact under the developed conditions.

Another interesting class of radical precursors compatible with Giese-type addition is strained rings. In 2020, the application of bicyclo[1.1.0]butane derivative (BCB) **26** in this reaction was demonstrated (Scheme 9). These compounds

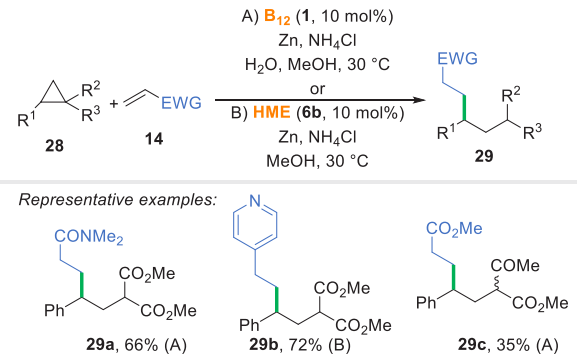
Scheme 9. HME-Catalyzed Giese-Type Addition of BCB to Olefins



react with a reduced form of the catalyst at the bridgehead carbon atom to give cyclobutylcobalamin derivatives **I** and after homolysis of the Co(III)−C bond generate secondary nucleophilic radical **II**, which adds to an electron deficient olefin serving as a SOMOphile.[27] The postulated mechanism is supported by the isolation and the unique X-ray structure of the Co(III)−alkyl complex **I**. The intermediate retains a square-pyramidal geometry around the central cobalt ion, and the Co−C bond is oriented toward the less sterically hindered β-face of the corrin ring (see Figure 1). Without the need for reoptimization, the reaction conditions could be applied to bicyclo[2.1.0]pentanes.

The polarity-reversal strategy utilizing the transformation of the initially electrophilic center into a nucleophilic radical, on which this work is also based, allowed the formation of a C−C bond between the electrophilic olefin **14** and what in the starting donor−acceptor cyclopropane **28** was an electron deficient carbon (Scheme 10).[28] In this particular case, the thermal

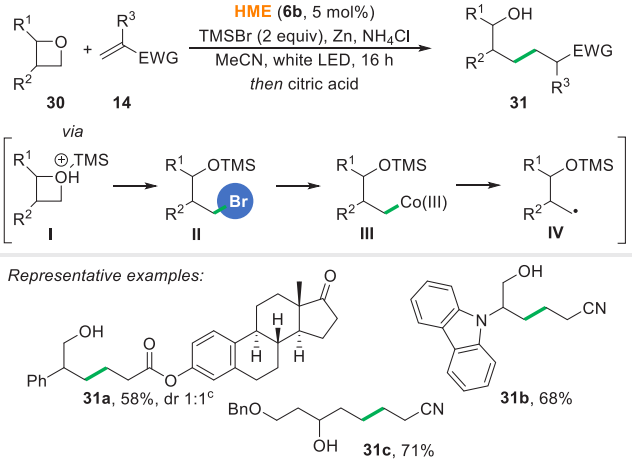
Scheme 10. Vitamin B_{12}-Catalyzed Reaction of Donor−Acceptor Cyclopropanes with Olefins



activation was more efficient than the photochemical one. For 1,1- and 1,2-disubstituted olefins, vinyl ethyl sulfone, vinyl pyridines, and 2-vinylpyrazine, the yield increased substantially when the catalyst was changed from cobalamin to HME (**6b**).

The idea of generation of radicals through the opening of strained rings was later adapted to heterocycles, namely oxetanes (**30**, Scheme 11).[29]

Scheme 11. HME-Catalyzed Generation of C-Centered Radicals from Oxetanes 30



In contrast to the reactions of carbocycles presented above, this approach proceeds via the TMSBr-mediated opening of the oxetane ring, leading to the formation of the alkyl bromide **II**, which serves as a radical precursor. This reaction is compatible with a wide range of alkyl- and aryl-substituted oxetanes **30** as well as functionalized electrophilic alkenes **14**, including menthol and estrone derivatives, which indicate that the developed methodology is suitable for late-stage functionalizations.

Furthermore, 1,1-disubstituted arylalkenes have the capacity of generating tertiary radicals in the presence of vitamin B_{12} (see section 3.3. for more details). Van der Donk et al. demonstrated their utility in radical additions to internal alkenes (Scheme

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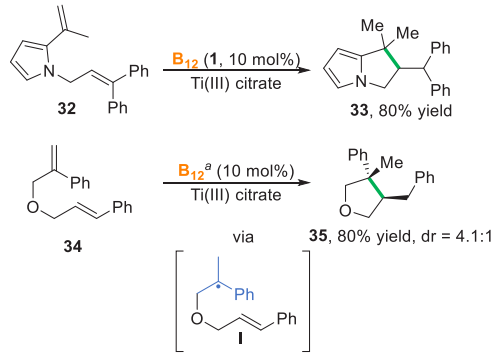
12).[30,31] Because these alkenes themselves do not form radicals under the developed conditions, it was possible to selectively

Scheme 12. Vitamin B_{12}-Catalyzed Cyclization of Arylalkenes 32 and 34[a]

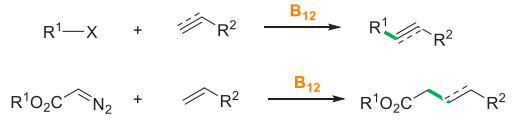


[a]Form of vitamin B_{12} not specified.

obtain cyclic products **33** and **35** via an intramolecular reaction, where internal alkenes served exclusively as radical acceptors.

Coupling reactions have been recognized as one of the most versatile tools for the construction of carbon−carbon bonds and have been widely applied for the synthesis of valuable organic compounds.[32,33] Although they typically rely on palladium-based catalysts, recent studies have shown the possibility of performing Heck- or Sonogashira-type reactions in a greener manner, including the use of vitamin B_{12} catalysis (Scheme 13).

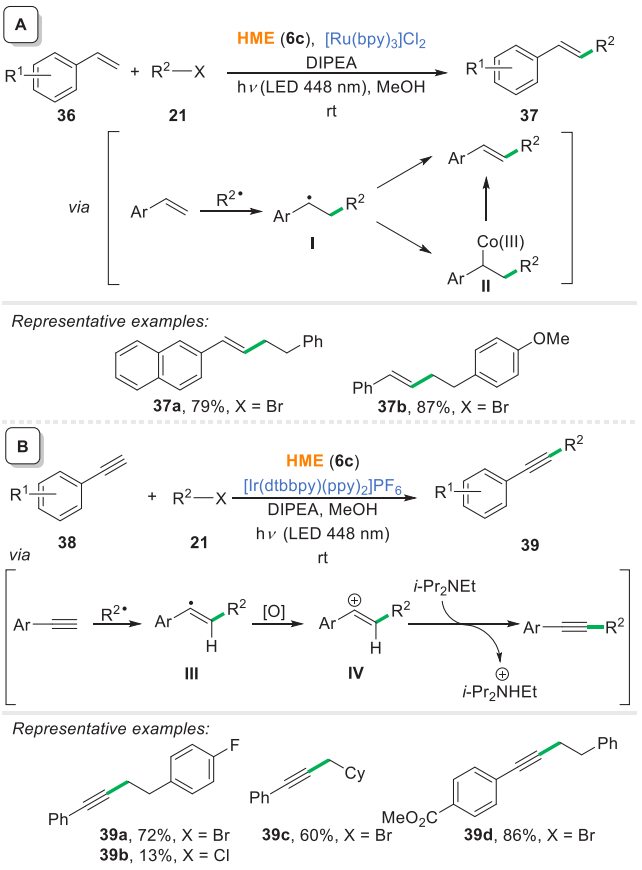
Scheme 13. Vitamin B_{12}-Catalyzed Coupling of Radical Precursors and Unsaturated Hydrocarbons



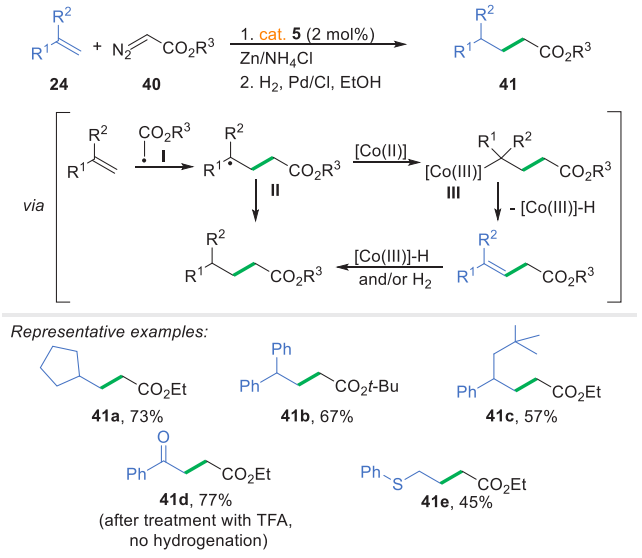
In 2019, the Hisaeda group reported a Heck-type reaction in which a radical, formed from alkyl halide after the alkyl Co-complex homolysis, adds to styrene derivatives (Scheme 14A).[34] The Co(II) species (**6c**) in this process is reduced under photochemical conditions to the supernucleophilic Co(I) species that reacts with halide **21** in a manner typical for the vitamin B_{12} catalysis. Soon after their initial report, the scope of this transformation was extended to alkynes **38** as coupling partners, but this required the use of an iridium complex as a photocatalyst (Scheme 14B).[35]

In 2016, a methodology that combines alkenes **24** and ethyl diazoacetate (**40**) to form a Heck-type linear alkylation product **41**, instead of cyclopropanes (as reported by Zhang and co-workers), was proposed (Scheme 15).[36] The reaction is catalyzed by cobalester **5**, a nontoxic vitamin B_{12} derivative, and leads to the formation of the desired product along with a small quantity of its saturated analogue. The well-known activity of vitamin B_{12} and its derivatives in the dehalogenation process is manifested here as chloro- and bromo-substituted arenes are transformed into the respective products with the loss of the halogen atom. Furthermore, cobyrinates with various substituents at the *c*-, *d*-, and *meso*-positions were tested in the model reaction of 1,1-diphenylethylene with ethyl diazoacetate.[37] This study revealed the impact of the structure of the catalyst on the ratio of the saturated and unsaturated products;

Scheme 14. Coupling Reaction Catalyzed by HME



Scheme 15. Cobalester-Catalyzed Olefin sp^2 C−H Alkylation with Diazo Reagents



functionalizations of heptamethyl ester cobyrinate (**6a**) at the *meso*-position with either an electron-withdrawing or electron-donating group diminished the ratio from 17:1 to as low as 7:1.

Very recently, Lewis and co-workers demonstrated that a variant of the transcription factor, CarH, catalyzes this reaction with improved yields and selectivity compared with the sole vitamin B_{12} induced reaction.[38] A preference for the unsaturated

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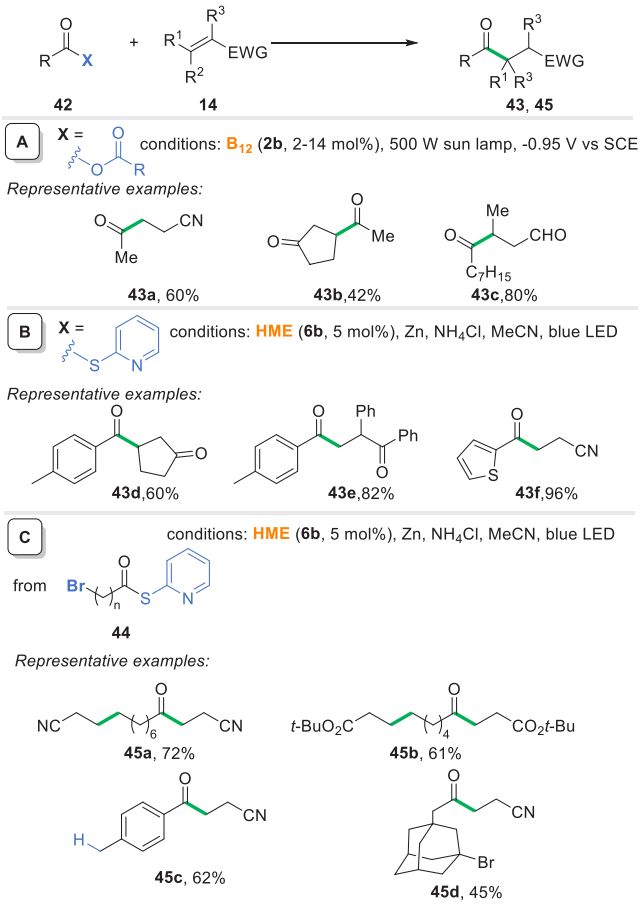
product results from the strong cage effect that prevents the formation of alkane via free-radical side reactions.

3.1.2. Acylation of Alkenes. So far, we have discussed reactions in which the crucial step is the generation of alkyl radicals from various precursors. In 1983, Scheffold et al. showed that vitamin B_{12} catalysis can also provide access to acyl radicals (Scheme 16A).[16,39]

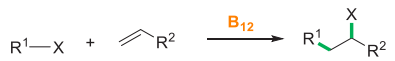
Scheme 16. Vitamin B_{12}-Catalyzed Generation of Acyl Radicals



The combination of visible light irradiation and electrochemical reduction of vitamin B_{12} enables the generation of acyl radicals from acid anhydrides that subsequently react with olefins **14** to give ketones **43** in moderate to high yields. It is worth mentioning that acyl chlorides were reacting poorly under these reaction conditions. On the contrary, more recently studied 2-*S*-pyridyl thioesters are better precursors of acyl radicals compared to not only acid anhydrides but also other stable active esters.[40] Their higher reactivity stems from the stronger electrophilic character of the carboxyl group. The reaction requires visible light irradiation to facilitate homolysis of the acyl Co-complex. A variety of alkyl and (hetero)aryl thioesters, as well as electron deficient olefins, are compatible with the developed conditions (Scheme 16B). When specifically designed reagent **44** containing alkyl chains with bromide at one end and a thioester moiety at the other are subjected to these reaction conditions, products **45** of consecutive addition of an alkyl radical and then an acyl radical can be obtained in a selective manner (Scheme 16C).[41] Kinetic studies revealed that the cobalt−alkyl complex is formed almost instantly and at a much faster rate compared with the corresponding cobalt−acyl complex. In the presence of a tertiary bromide, however, acyl radicals are generated selectively. In contrast, for reactive benzyl halides the competing dehalogenation predominates.

3.1.3. Difunctionalizations of Alkenes. Alkene difunctionalization reactions provide a convenient way of transforming readily available substrates containing double bonds with a potentially high level of atom economy as two positions are modified in one process (Scheme 17). Among several difunctionalization strategies, atom transfer radical addition (ATRA) appears to be particularly suitable for vitamin B_{12} catalysis.[42]

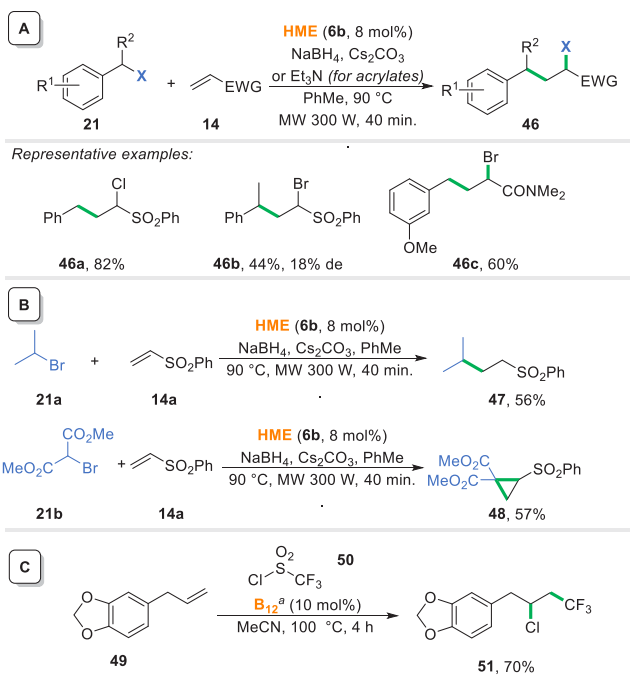
Scheme 17. General Scheme of Vitamin B_{12}-Catalyzed Alkene Difunctionalizations



Activated olefins, such as α,β-unsaturated carbonyl compounds in B_{12} catalysis, typically serve as radical acceptors with the formation of conjugate addition products. Atom transfer radical addition enables the difunctionalization of such olefins by adding to both the α- and β-positions of alkenes. Cobalt complexes known in atom transfer radical polymerization have not been explored in ATRA until recently. Along this line, the reaction of organic halides **21** with olefin **14** catalyzed by heptamethyl ester cobyrinate (**6b**) leads to α-chloro- or bromo-substituted products **46** (Scheme 18A).[43]

Some bromides, however, gave intermediates prone to subsequent reactions, furnishing dehalogenated product **47** or cyclopropane **48** (Scheme 18B). Unactivated olefin **49** has also been explored in related studies on chlorotrifluoromethylation

Scheme 18. Cobyrinate-Catalyzed Atom Transfer Radical Addition (A and B). Vitamin B_{12}-Catalyzed Chlorotrifluoromethylation of Alkenes (C)[a]



[a]Form of vitamin B_{12} not specified.

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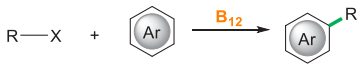
(Scheme 18C).[44] Although most substrates were converted using the cobalt(II) porphyrin complex (CoClTPP), vitamin B_{12} was also compatible with this transformation, and when used with an alkene derived from cinchona alkaloids, a higher diastereoselectivity was observed compared to the CoClTPP-catalyzed reaction (6.4:1 vs 1.4:1).

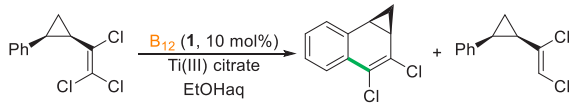
3.1.4. Radical Addition to Arenes. Halogenated compounds have attracted the attention of synthetic chemists, particularly due to the increasing application of fluorinated derivatives in pharmaceuticals.[45,46] In the context of vitamin B_{12} catalysis, the synthesis of halogenated compounds was demonstrated using aromatic compounds that can also serve as acceptors of polyhalogenated radicals generated from the corresponding halides by removal of one halogen atom (Scheme 19).

Scheme 19. General Scheme of Vitamin B_{12}-Catalyzed Reactions of Arenes



An early example of this approach was shown by van der Donk et al. in their studies on the dehalogenation of perchloroethylene containing the phenyl group in its structure.[47] The specifically designed phenyl-substituted cyclopropane derivative **52** in the presence of reduced vitamin B_{12} furnished predominantly a cyclic product **53** resulting from the addition of a radical to the phenyl ring, thus corroborating the participation of radical anions and/or vinyl radical in the reaction (Scheme 20).

Scheme 20. Vitamin B_{12}-Catalyzed Cyclization via Dechlorination of Chlorinated Alkenes

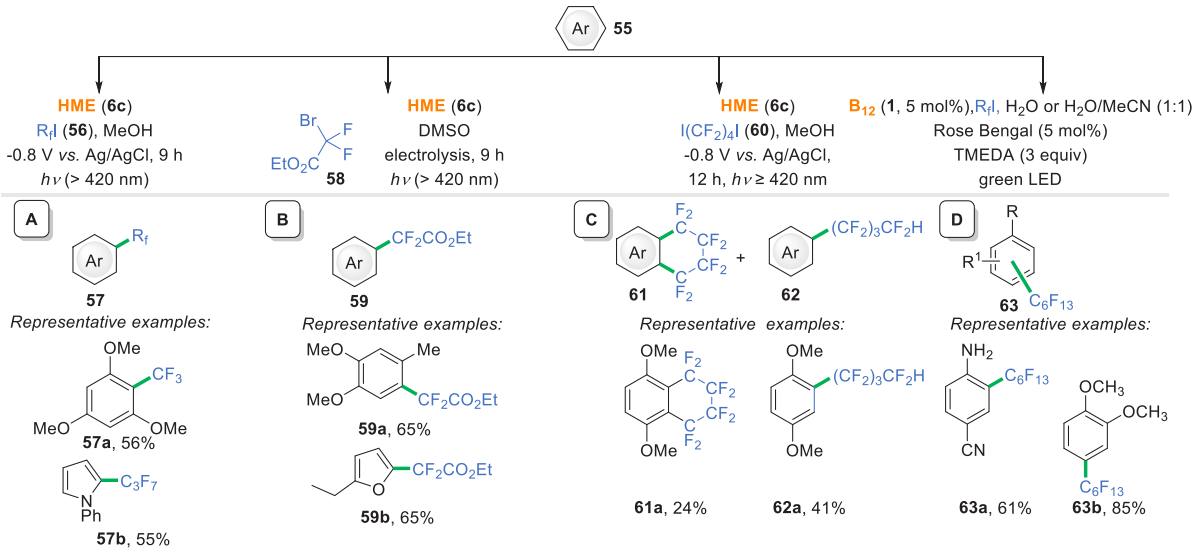


Almost two decades later, fluorinated halides were explored in a variety of transformations relying on the addition of a radical to arene. In 2017, the Hisaeda group reported trifluoromethylation and perfluoroalkylation of arenes **55** catalyzed by heptamethyl cobyrinate **6c** (Scheme 21A). In this reaction, an active Co(I) species is generated by electrochemical reduction of the precatalyst. Subsequent formation of the Co-fluoroalkyl intermediate from the corresponding iodide and its homolysis under visible light irradiation are the source of the radical that adds to an (hetero)arene.[48] This approach was then extended to difluoroacylation (Scheme 21B)[49] and perfluoroalkylation (Scheme 21C)[50] although the latter lacked selectivity, leading to the formation of a mixture of cyclic **61** and acyclic products **62**. These reactions required a careful choice of electrolysis parameters to facilitate the reduction of Co(II), whose reduction potential is ca. −0.6 V vs Ag/AgCl. A slightly more negative potential (−0.8 V) delivered higher yields; however, when it was further increased, the formation of byproducts was more pronounced. Perfluorination of indole and aniline derivatives was also accomplished using an imine/oxime-type cobalt complex that mimics vitamin B_{12} activity.[51] Although that complex gave the desired products in higher yields, native vitamin B_{12} also proved to be an efficient catalyst for the perfluorohexylation of aniline and alkoxy-substituted benzenes (Scheme 21D).[52] In this protocol, under visible light irradiation Rose Bengal promoted reduction of Co(III) and Co(II) to the Co(II) and Co(I) forms, respectively.

The addition of vitamin B_{12}-generated radicals to unsaturated bonds emerged as a practical tool to construct new C−C bonds. Although most comprehensively studied, this reactivity is not limited to electron deficient alkenes/alkyl halide combinations. Alkynes, electron rich alkenes, and arenes are compatible with this approach as well and can serve as acceptors of both alkyl and acyl radicals (generated from a variety of precursors) in inter- and intramolecular transformations alike.

3.2. Cyclopropanation. The cyclopropane ring is an important moiety present in the structure of many natural products, and its formation has been a challenge for synthetic chemists.[53] The synthesis of cyclopropane derivatives employing vitamin B_{12} catalysis has been realized using several distinct approaches although only two, relying on either the dechlorination of the corresponding alkyl chlorides or the application of

Scheme 21. Vitamin B_{12}-Catalyzed Syntheses of Fluorinated Arenes



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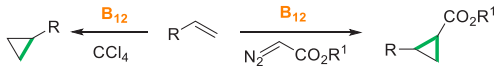
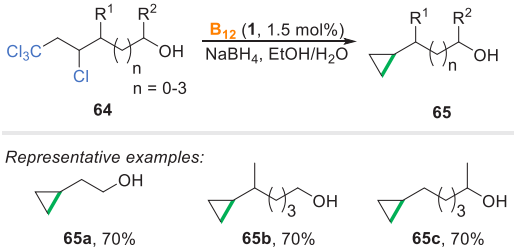
diazo compounds, have been demonstrated for a broader scope of substates (Scheme 22).

Scheme 22. General Scheme of Vitamin B_{12}-Catalyzed Cyclopropanations



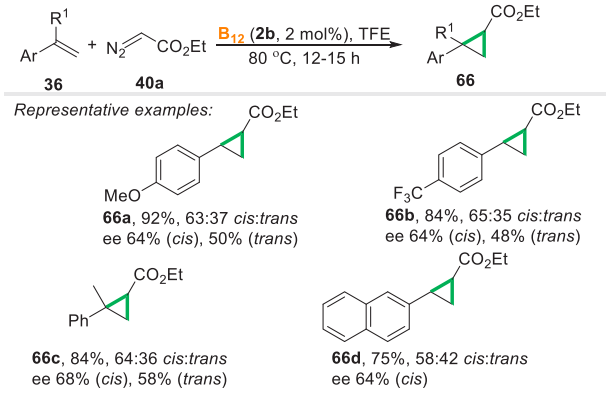
The first methodology was applied for the transformation of alkenes into tetrachloroinated derivatives **64** using CCl_4. These intermediates provided cyclopropane derivatives **65** after subsequent dechlorination (Scheme 23). The reaction proceeds under mild conditions and employs sodium borohydride as a reductant.[54]

Scheme 23. Vitamin B_{12}-Catalyzed Formation of Cyclopropanes



Cyclopropanation of alkenes with diazo compounds has been established for several transition metal catalysts based on Cu, Pd, Ni, and Rh. In 2004, Zhang demonstrated that this transformation can be efficiently catalyzed by vitamin B_{12} (Scheme 24).[55] The mechanism of this reaction is believed to involve the

Scheme 24. Vitamin B_{12}-Catalyzed Cyclopropanation of Alkenes with Ethyl Diazoacetate



reduction of vitamin B_{12} by ethyl diazoacetate (**40a**) to the Co(II) species that reacts with a second molecule of diazo reagent **40a** to form Co-carbene with concomitant release of nitrogen. Subsequent transfer of the carbene to styrene **36** affords the desired cyclopropane **66**. Although the reaction represents an example of challenging asymmetric transformations catalyzed by vitamin B_{12}, the obtained diastereo- and enantioselectivities are expectedly moderate.

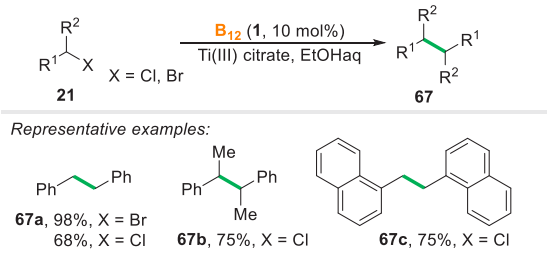
Under electrochemical conditions, vitamin B_{12} catalyzes the generation of a radical from dichloromethane that after addition to alkene forms a cyclopropane ring. This approach was demonstrated for a single substate—styrene that was transformed to cyclopropylbenzene or, in the presence of a proton donor, (3-chloropropyl)benzene.[56]

3.3. Dimerization of Alkyl Halides and Alkenes. Alkyl halides have been extensively studied in dehalogenation catalyzed by vitamin B_{12}. This was inspired by biological processes, and the development of this area has also been driven by the possibility of applying this methodology to the removal of persistent halogenated compounds such as DDT from the environment. While in that case dehalogenation is useful, generally this process can also be a source of undesired reactivity resulting in decomposition in halogen-containing substrates. Given that vitamin B_{12} dehalogenation proceeds with the formation of radicals, it is expected that under certain conditions the corresponding dimers will form (Scheme 25).

Scheme 25. General Scheme of Vitamin B_{12}-Catalyzed Dimerization of Alkyl Halides

In 1996, the Rusling group reported this reactivity for benzyl bromide **21**;[19,57] later van der Donk performed detailed mechanistic investigations and found that the presence of the Co(II) species diminishes the rate of recombination of two benzyl radicals (Scheme 26).[30] Thus, the addition of reducing

Scheme 26. Vitamin B_{12}-Catalyzed Dimerization of Alkyl Halides



reagents, such as Ti(III) citrate or Zn, is required. Under the optimized conditions, various benzyl bromides and chlorides **21** gave dimers **67** in good yields, with dehalogenation being observed as a side reaction. As expected, the recombination of two radicals is not a stereoselective process.

The dimerization of alkyl bromides **21** often serves as a model reaction to probe the catalytic activity of vitamin B_{12}-based catalysts. For instance, cobalester (**5**), an amphiphilic derivative of vitamin B_{12},[58,59] and heptapropyl ester cobyrinate (**7**) trapped on an indium tin oxide electrode by sol—gel reactions[60] were found to be efficient in catalyzing the dimerization of benzyl bromides **21**. For cobalester (**5**), it was hypothesized that the presence of the nucleotide loop increases the yield of dimerization because of weakening of the organometallic C—Co bond resulting from intramolecular coordination of the nucleotide to the cobalt ion.[58] In another study, a hybrid catalyst composed of hydrophobic vitamin B_{12} derivative **6c** and a hyperbranched polymer was tested in the dimerization of (2-bromoethyl)benzene under photoreductive conditions.[61] This system enabled a higher local concentration of benzyl radical that resulted in a more efficient formation of the dimer **66** (rather than ethylbenzene) in comparison with the monomeric

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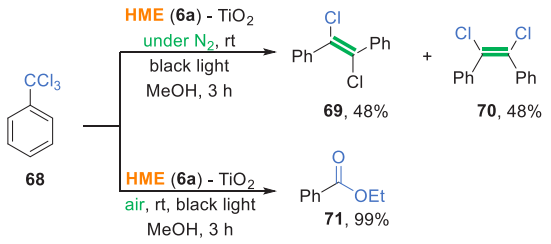
B_{12} (31% vs 2% yield of the dimer) and facilitates the recovery of the catalyst.

An alternative catalytic system, based on derivative **6a** and TiO_2, under a nitrogen atmosphere, promotes partial dechlorination and dimerization of trichlorinated organic compound **68** leading to chlorinated alkenes **69** and **70** (Scheme 27).[62] Interestingly, under aerobic conditions in the presence of alcohols (or amines), formation of esters **70** (or amides, respectively) is observed.

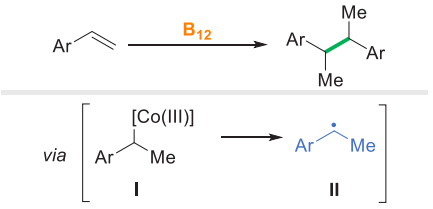
Scheme 27. Vitamin B_{12}-Catalyzed Dechlorination/Dimerization of Trichloromethylbenzene



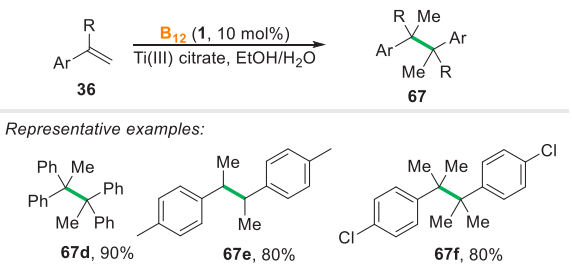
More complex aliphatic halides containing the hydroxy group are prone to subsequent reactions, as Petrović has shown for γ- and δ-bromoalkanols.[63] In the presence of protic solvents (ethanol and water), these bromo derivatives undergo dehydrobromination, oxidative allylic coupling, and hydration. It is also worth mentioning that vitamin B_{12}-catalyzed dehalogenation itself can be employed for the efficient synthesis of the corresponding alkenes in a unimolecular process, as recently demonstrated by West et al.[64]

In a similar manner to alkyl halides, some alkenes, e.g., styrene derivatives **36**, can directly form alkyl−cobalt species **I**, being a source of radical **II**, which can undergo dimerization (Schemes 28 and 29) or can add to alkene (see section 3.1.1).

Scheme 28. Vitamin B_{12}-Catalyzed Coupling of Alkenes



Scheme 29. Vitamin B_{12}-Catalyzed Dimerization of Arylalkenes



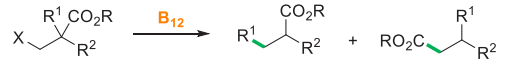
Under reductive conditions (Ti(III) citrate or Zn), vitamin B_{12} was established as an effective catalyst for the homocoupling of arylalkenes **36** (Scheme 29).[30] The reaction proceeds regioselectively with the formation of the new bond between two benzylic carbons. However, the stereochemical outcome of this coupling lacks selectivity, leading to an equimolar mixture of diastereomeric products **67** for 1,1-disubstituted alkenes. The reaction is believed to involve the usual alkyl cobalamin.

Simple arylalkenes **36** (α- and β-methylstyrene) dimerize also in the presence of HME **6c**.[65] In general, native vitamin B_{12} (**1**), with the nucleotide loop coordinated to the cobalt ion ("base-on" form), facilitates dimerization more efficiently compared with derivatives with a noncoordinating "loop" (77−80% yield vs 8−75% after 1 h).[66] However, when the reaction time was extended to 24 h, the catalyst in the "base-off" form delivered an excellent yield of dimerization. In a search for a more sustainable approach, it was discovered that a hybrid catalyst based on cobyrinic acid **8** and TiO_2 under UV irradiation promotes dimerization without the need for a chemical reductant.[67]

3.5. Radical Rearrangements. Vitamin B_{12}-catalyzed radical rearrangements constitute a class of reactions that are closely related to processes occurring in Nature that are enabled by vitamin B_{12}-dependent enzymes such as methylmalonyl-CoA mutase, glutamate mutase, and α-methyleneglutarate mutase.[6] In the context of new C−C bond formation reactions, catalytic systems inspired by enzymatic reactions have been explored primarily for 1,2-migration of functional groups and ring expansion.

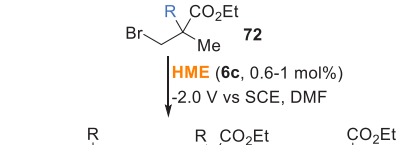
3.5.1. Migration of a Functional Group. 1,2-Migration of a functional group is an intramolecular process of exchange of a functional group and a hydrogen atom connected to neighboring carbon atoms (Scheme 30).

Scheme 30. General Scheme of Vitamin B_{12}-Catalyzed Migration of a Functional Group



Several studies on vitamin B_{12}-based catalytic systems confirmed that processes typically facilitated by methylmalonyl-CoA mutase can also be translated into synthetically useful procedures.[68,69] The electrocatalytic conditions for the rearrangement of the carbon skeleton of esters **72** are very efficient (Scheme 31).[68−71] Both the steric and electronic properties of

Scheme 31. HME-Catalyzed Migration of a Functional Group



		73	74	75
a	R = CN	62%	30%	2%
b	COMe	3%	3%	91%
c	CO_2Et	n/a	15%	80%
d	CO_2t-Bu	44%	29%	24%
e	CO_2Cy	47%	24%	22%
f	CO_2Ph	43%	29%	19%

the migrating group impose a strong impact on the selectivity of this process. In particular, the migratory capacity of the functional group increases in the following order, CN < CO_2R < COR, and as far as esters are considered, the smaller the ester group, the higher the yield of the rearranged product **75**. By controlling the electrolysis potential, the reactivity and selectivity of this process improved.[72] Although vitamin B_{12}

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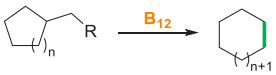
has been used primarily under homogeneous conditions, in 2015, a heterogeneous catalyst—the metal−organic framework (MOF) **6c**—was reported.[73] Under visible light irradiation, this system facilitated the 1,2-migration of the acetyl group with up to 68% yield.

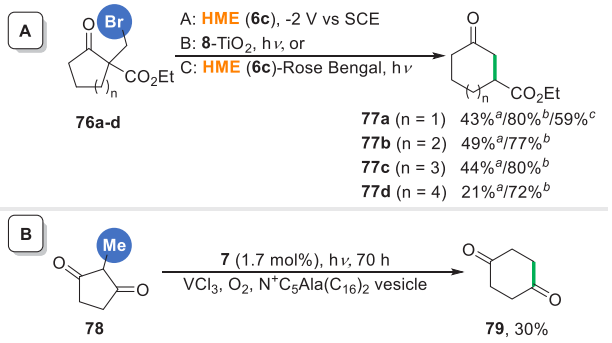
3.5.2. Ring Expansion. In certain cases, the migration reaction can lead to ring expansion, which is a valuable class of transformations enabling the synthesis of cyclic compounds that are difficult to obtain through direct cyclization (Scheme 32). Vitamin B_{12} catalysis has also contributed to this field.

Scheme 32. General Scheme of Vitamin B_{12}-Catalyzed Ring Expansion



Usually, halogenated cyclic compounds were used as precursors of expanded rings. Along this line, an electrochemical approach that allowed the transformation of five- to eight-membered cyclic ketones **76a−d** into the corresponding six- to nine-membered derivatives **77a−d** was reported (Scheme 33A).[74] Hybrid catalysts **8**-TiO_2[75] or HME **6c** merged with

Scheme 33. Cobyrinate-Catalyzed Ring-Expansion of Cyclopentanone Derivatives[a−c]



[a]Yields of the products under conditions A. [b]Yields of the products under conditions B. [c]Yields of the products under conditions C.

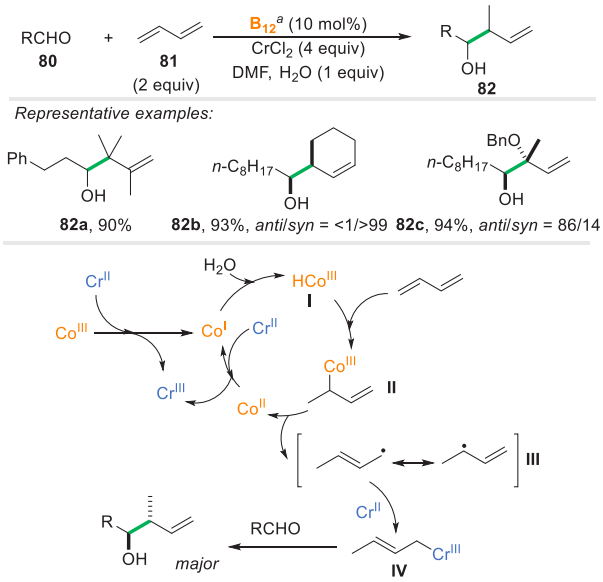
Rose Bengal[24] exhibited an improved efficiency in these types of transformation. The report by Murakami, however, demonstrated that the rearrangement of unactivated five-membered carbonyl compounds **78** into the corresponding six-membered ones **79** is also feasible (Scheme 33B).[76] For this, heptapropyl cobyrinate **7** and vanadium trichloride under an aerobic atmosphere have been utilized. The role of vanadium trichloride is not only to reduce Co(III) to Co(II) but also to activate molecular oxygen. The yields of these reactions were low unless a membrane system based on an alanine-derived vesicle was used.

4. VITAMIN B_{12} COOPERATIVE CATALYSIS

Combining two or more transition metal catalysts opens a new avenue for the synthesis or functionalization of structurally complex molecules and has been intensely investigated in recent years.[77] Such strategies have also started to have their impact on vitamin B_{12} catalysis. To date, such reactions are represented by a catalytic system based on only Co/Cr and Co/Ni.

4.1. Vitamin B_{12}−Chromium Dual Catalysis. The addition of various reagents to a carbon−carbon double (or triple) bond is the most often encountered type of reaction in vitamin B_{12} catalysis, in contrast to the addition to the carbonyl group. This was achieved by the cooperative action of vitamin B_{12} with chromium catalysis. With regard to that, the Takai group proposed a novel way of functionalizing 1,3-dienes **81** (Scheme 34).[78] It involves chromium(II) chloride and leads to

Scheme 34. Vitamin B_{12}-Catalyzed Reaction between Aldehydes 80 and 1,3-Dienes 81[a]



[a]Form of vitamin B_{12} not specified.

the formation of the corresponding alcohols **82** through the 1,2-addition of allylchromium(III) intermediate **IV** to aldehydes **80**. The proposed mechanism starts with the reduction of vitamin B_{12} to the Co(I) form with $CrCl_2$ and then the subsequent water-mediated formation of cobalt(III) hydride **I**. The hydrocobaltation of diene **81** leads to the formation of an allylcobalt(III) species **II**, which after homolysis leads to an allyl radical **III**, which can be trapped with Cr(II) to form allylchromium(III) **IV**, which in the last step adds to aldehyde. Regarding the scope, dienes **81** with various patterns of substituents and aliphatic aldehydes **79** are well tolerated. Moreover, the selective addition to the aldehyde occurs in the presence of the ketone moiety.

4.2. Vitamin B_{12}−Nickel Dual Catalysis. With a general shift toward sustainable chemistry, earth-abundant nickel-based complexes have emerged as an interesting alternative to precious metal catalysts.[79] Features such as a variety of oxidation states (from Ni(0) to Ni(IV)) or the formation of highly reactive organometallic species result in diverse mechanistic pathways only possible using nickel catalysts. An interesting approach to expand the scope of vitamin B_{12} catalysis is to merge it with nickel complexes. It has enabled coupling of either aryl or alkyl halides as well as *N*-acyl-glutarimides with radical precursors. These reactions rely on nucleophilic cobalt species obtained by reduction of vitamin B_{12}, which delivers radicals that engage in the nickel catalytic cycle.

4.2.1. Coupling of Tosylates and Halides and Homocoupling of Tosylates. In 2017, Komeyama et al. revealed a methodology that combines Ni and vitamin B_{12} catalysis in the cross-coupling of aryl halides **21** and alkyl tosylates **23** (Scheme 35A).[80] In this reaction, the alkyl radical generated from the

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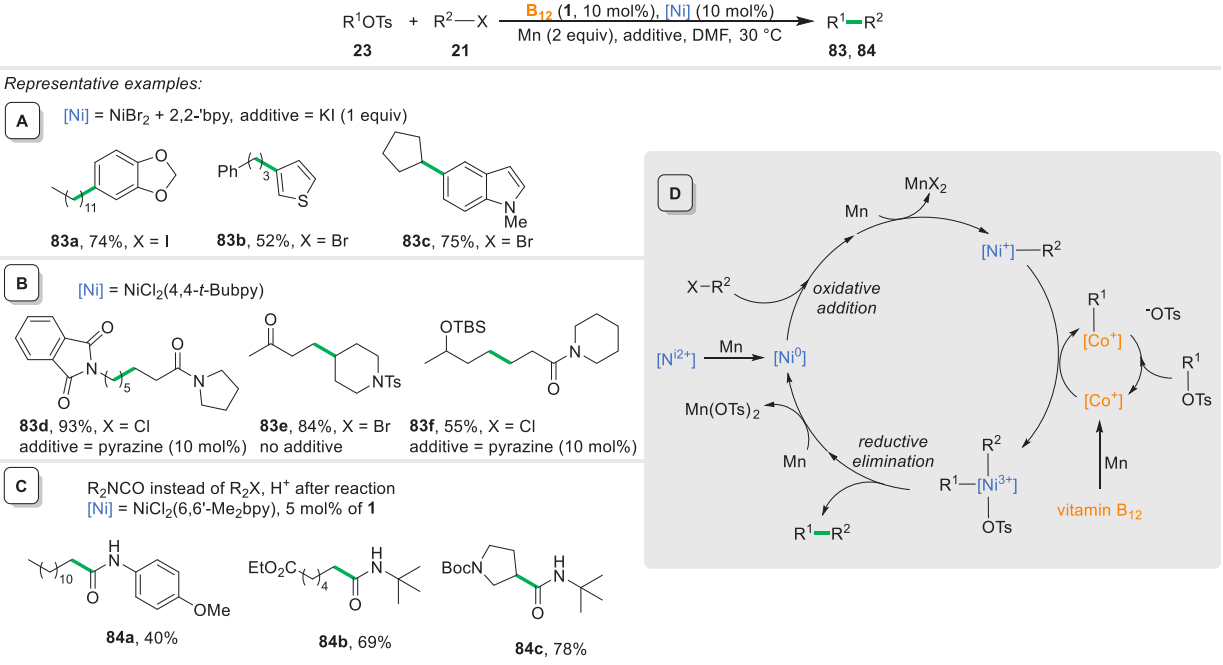
Scheme 35. Cross-coupling of Tosylates with Halides or Isocyanides

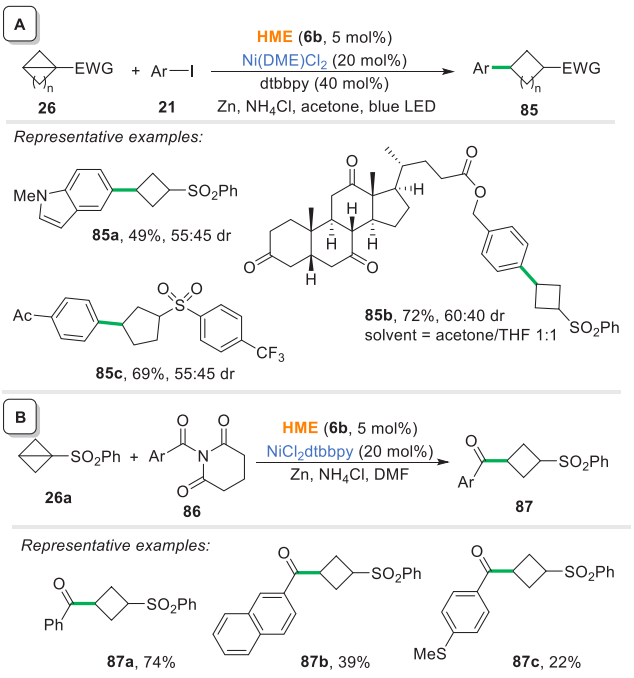


tosylate intercepts with the nickel aryl species (obtained by the oxidative addition of aryl halide **21** to the reduced nickel catalyst). Rapid reductive elimination furnishes desired product **83** and nickel catalyst, which, after reduction to its zerovalent form, can be reintroduced to the cycle (Scheme 35D). This methodology was subsequently extended, making it also compatible with alkyl halides (Scheme 35B).[81] The use of isocyanates in place of halides under similar conditions enabled the formation of the corresponding amides **84** in good yields (Scheme 35C).[82] Both alkyl and aryl isocyanates were compatible with the amidation protocol; however, a bulky alkyl tosylate **23** gave a low yield (35%), presumably due to steric hindrance between the tosylate and vitamin B_{12}. This was consistent with an increase in yield (89%) of the product obtained with a less bulky salcomine catalyst. Interestingly, the bipyridine ligand substituted at the 6,6′-positions, optimal in the amidation, was ineffective for the coupling of tosylates **23** with alkyl halides **21** and delivered only trace amounts of the products. In a related study, the Komeyama group demonstrated that zerovalent nickel species can react with alkyl cobalamins that can undergo the second transalkylation to furnish the corresponding dimers **83** from tosylates.[83]

4.2.2. Co/Ni-Catalyzed Coupling of Strained Reagents. In 2020, a related approach to the coupling reaction was proposed by the Gryko group. In it, strained cycloalkanes (mainly bicyclo[1.1.0]butanes **26**) are precursors of corresponding secondary electrophilic radicals that can be transferred to the Ni–aryl species and form products **85** after reductive elimination (Scheme 36A).[27] Replacing the aryl iodides **21** with *N*-acyl-glutarimides **86** enabled the formation of corresponding acylation products **87** (Scheme 36B).[84]

This strain-release methodology is also suitable for the regioselective ring opening of epoxides **88** with aryl halides (Scheme 37A).[85] In this reaction, it is the nucleophilic Co(I) species that is responsible for the selective opening of the epoxide ring. The calculated free Gibbs energy for the ring opening of the epoxide clearly shows that the attack of the catalyst occurs at the less hindered terminus of the ring. The

Scheme 36. Co/Ni-Catalyzed Cross-coupling of Strained Reagents



obtained Co–alkyl intermediate, after light induced homolysis, generates a primary radical that intercepts with a nickel species to form secondary alcohol **89** via cross-electrophile coupling. This selectivity toward linear product formation complements methodologies that give access to branched alcohols. In the previously described (section 3.1.1) opening of oxetanes **30**, an activated olefin **14** can be replaced with an aryl iodide **21**, which under the Co–Ni dual system conditions delivers functionalized alcohols **90** (Scheme 37B).[29] Both electron-withdrawing and electron-donating aryl iodides **21** were compatible with this reaction. Moreover, for aryl iodides containing an additional

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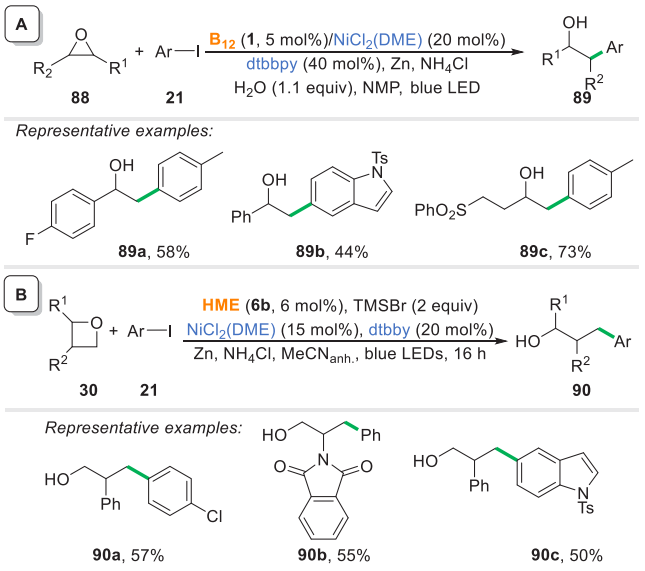
Scheme 37. Regioselective Ring Opening of Epoxides 88 and Oxetanes 30 with Aryl Halides 21



halogen atom, i.e., F, Cl, or Br, no dehalogenation of these halides was observed. While a variety of oxetanes **30** containing (hetero)aryl and functionalized alkyl substituents are reactive under the optimized conditions, phenyl-substituted oxetane, containing a methoxy substituent, performs poorly.

5. CONCLUSION AND FUTURE DIRECTIONS

In addition to the important biological role of vitamin B_{12}, its distinctive redox chemistry makes this molecule an interesting catalyst with a variety of applications, including the formation of carbon−carbon bonds, the most significant process in organic chemistry that enables the construction of carbon skeletons or their modification. This natural, nontoxic cobalt complex mediates reactions such as the addition to multiple bonds, coupling reactions, dimerizations, and functionalizations involving ring opening. In addition, rearrangements that are widely utilized for the reorganization of a carbon skeleton are also characteristic to this catalyst. The presented examples serve as an illustration of how vitamin B_{12} has evolved from being a cofactor for enzymatic and biomimetic reactions to being an effective cobalt catalyst for important C−C bond forming reactions.

Despite impressive progress, there is still plenty of space to be explored:

New Methods/New Synthetic Strategies. Intensive research in the neighboring areas of photoredox and radical chemistry, as well as cobalt catalysis, offers an inspiring environment for the development of new methodologies based on vitamin B_{12}, whose revelation we are anticipating in the near future. Challenges remain in the scope of substrates. Most reactions utilize organic halides or pseudo-halides, although recently diazo reagents and strained molecules have broadened the class of substrates that are suitable for the formation of alkyl cobalamins—the crucial intermediate in vitamin B_{12} catalysis. Additionally, by activating substrates unreactive toward vitamin B_{12}, for example with Lewis acids, as shown for oxetanes, the scope can be further expanded.

A broadening of the arsenal of catalytic reactions compatible with vitamin B_{12} chemistry can also be expected with a dual catalysis approach. Advances in this field will allow for the design of new reactions. These, we believe, will also enable inducement of a high level of stereoselectivity, which now represents a major challenge in vitamin B_{12} catalysis. Since, as a principle, the remarkable structure of natural vitamin B_{12} should remain unchanged, cooperative catalysis gives the opportunity to improve the stereoselectivity by optimizing the structure of a second chiral complex. In this context, the use of chiral Lewis acids may be promising, since they can also be utilized to induce stereoselectivity.

New Environments. More attention should be paid to the development of greener methodologies relying on native vitamin B_{12}. Due to their solubility in organic solvents, hydrophobic derivatives of vitamin B_{12} were often used in the presented transformations rather than vitamin B_{12} in its native form. The extra steps required to obtain these synthetic derivatives diminish their attractiveness for industrial applications. It is thus imperative to perform such reactions in benign solvents, as these are used in large volume and contribute greatly to chemical wastes. For vitamin B_{12}, water should be the reaction medium of choice, but alternatives may be considered, as organic compounds of interest are often insoluble in water. In this regard, lowering the catalyst loading, using benign reducing systems, and improving the TON and TOF are of significance.

An additional effort needs to be devoted to identifying efficient, robust, and sustainable reducing reagents/systems. In these terms, photocatalytic methods hold great promise, as represented by the developed examples. An increasing number of reports has indicated growing interest in this area. So far, the established systems, though effective, are not without flaws, and the ideal ones are yet to be discovered.

With increasing emphasis on the environmental impact of chemical processes, we expect more applications and studies on vitamin B_{12} catalysis to come. This is very important for the environment and, therefore, for the chemical industry.

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Author Contributions

The manuscript was written through contributions of both authors. Both authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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