Abstract: Menaquinones are a class of isoprenoid molecules that have important roles in human biology and bacterial electron transport, and multiple methods have been developed for their synthesis. These compounds consist of a methylnaphthoquinone (MK) unit and an isoprene side chain, such as found in vitamin K$_1$ (phylloquinone), K$_2$, and other lipoquinones. The most common naturally occurring menaquinones contain multiple isoprene units and are very hydrophobic, rendering it difficult to evaluate the biological activity of these compounds in aqueous assays. One way to overcome this challenge has been the application of truncated MK-derivatives for their moderate solubility in water. The synthesis of such derivatives has been dominated by Friedel-Crafts alkylation with BF$_3$·OEt$_2$. This attractive method occurs over two steps from commercially available starting materials, but it generally produces low yields and a mixture of isomers. In this review, we summarize reported syntheses of both truncated and naturally occurring MK-derivatives that encompass five different synthetic strategies: Nucleophilic ring methods, metal-mediated reactions, electrophilic ring methods, pericyclic reactions, and homologation and side chain extensions. The advantages and disadvantages of each method are discussed, identifying methods with a focus on high yields, regioselectivity, and stereochemistry leading to a detailed overview of the reported chemistry available for preparation of these compounds.

Keywords: menaquinone; lipoquinone; synthesis; Friedel-Crafts alkylation; nucleophilic substitution; metal-mediated; electrophilic; pericyclic; and homologation

1. Introduction

Menaquinones are hydrophobic, isoprenoid molecules containing a methylated naphthoquinone unit and an isoprene side chain which constitutes a subgroup of lipoquinones [1–7]. There are two major structural subgroups of lipoquinones. Ubiquinones (or benzoquinones, U) are generally found in eukaryotes and Gram-negative prokaryotes, and menaquinones (or naphthoquinones, MK) generally found in Gram-positive prokaryotes. In humans, menaquinones have several biological properties, including facilitating blood coagulation. In bacteria, menaquinones are essential molecules that shuttle electrons between the membrane-bound protein complexes acting as electron acceptors and donors in the respiratory electron transport system and consequently resulting in ATP synthesis. Menaquinones are also referred to as vitamin K$_2$, a subgroup of the class of compounds categorized as vitamin K. The preparation and studies of some of these compounds have been extensive and include the preparation both by fermentation and synthesis [8–10]. The major structural variation in menaquinones involves the isoprene side chain; that is the number of isoprene units and saturation in the side chain [11]. Although these minor structural changes are deceptively simple, the specific
stereochemistry of each is required to maintain their biological action. Hence, the synthesis of these compounds requires attention to detail and often meticulous purification, which consequently leads to a decrease in yields of the desired compounds. In the following review, we will summarize reported methods and discuss the advantages and disadvantages of each, as well as identify the most suitable methods within each synthetic strategy.

Vitamin K₂ and vitamin K₁ (also referred to as phylloquinone) are natural vitamins and together make up the family of compounds known as vitamins K. The variety of the structures of vitamin K₂ depend on the number of isoprene units in the side chain. In Figure 1, we show the structures of menadione (vitamin K₃) 1, menadiol 2, vitamin K₃, and menaquinone (MK) derivatives with 1 to 9 isoprene groups in the side chain. The abbreviation used for the menaquinones in this manuscript will indicate the number of isoprene units in the side chain. For example, MK-1 describes a menaquinone with one isoprene unit, and MK-9, the major MK-derivative found in the Mycobacteria, contains nine isoprene units [12]. If the MK-derivative contains isoprene units that are saturated, it will be indicated by the addition of a Roman numeral to specify the location of the isoprene unit numbered from the naphthoquinone. For example, MK-9(II-H₂) is the major MK-derivative active as the electron transport agent in the Mycobacterium tuberculosis. It is a MK-9 derivative with the second isoprene group saturated [6]. When more than one isoprene units are saturated, such as the three units in vitamin K₁, the nomenclature will identify the location of the saturations using Roman numerals and the number of H-atoms added, such as MK-4(II,III,IV-H₆) indicating the first isoprene unit is still unsaturated [11].

The biological activities of these compounds have been studied in-depth, and most reviews that been reported have a biological-biomedical focus. In general, terpenes and isoprenoid compounds have been widely reviewed for many uses, including pharmaceutical, flavor fragrance, and possible applications in biofuel industries [13]. Naphthoquinones have been assessed for their biological activity against cancer [14], cardiovascular disease [15], tuberculosis [16,17], diabetes [18], kidney function [19], and age-related diseases [20]. The most well-known members of the naphthoquinone family are the compounds known as vitamin K. Much work has been done in this area comparing the health effects of synthetic vitamin K analogs to naturally-derived analogs [21]. The biosynthesis of vitamin K analogs have been mapped out within bacteria [22], particularly with respect to intestinal bacteria in relation to coagulation homeostasis [23], and discovery of possible drug targets to inhibit electron transport systems [24]. Another important effect caused by vitamin K₁ is the regulation of calcium uptake, particularly in bone of humans and other mammals [25].

In addition, menaquinones are hydrophobic molecules that shuttle electrons between the membrane-bound protein complexes acting as electron acceptors and donors in the respiratory electron transport system facilitating oxidative phosphorylation in bacteria [16,22]. In Mycobacteria, a menaquinone headgroup is required, whereas in a bacterium such as E. Coli, both menaquinones and ubiquinones (U-9, Figure 1) are able to serve this function [6]. In the case of Mycobacterium smegmatis, MK-9(II-H₂) was proposed as a contextual virulent factor [6], but this suggestion was later rejected when the presence of inactive MenJ protein was shown to prevent infection by the bacterium. Thus, the protein rather than the substrate was found to be the contextual virulent factor [26]. Development of inhibitors for the biosynthesis of menaquinones or other isoprene-derivatives has been explored as potential treatments [27,28].

1.1. Properties and Biological Function of Menaquinones

The structural and redox properties of menaquinones are key for their biological function. The quinone group of the menaquinones is reduced through a two-electron transport system to form a radical anion after the addition of the first electron [29–31]. After addition of the second electron, a dianion catecholate is formed, which then forms a catechol in the presence of a protic solvent (Figure 2). The two intermediates are sufficiently long-lived to be observed in aprotic solvents because the proton transfer step is slow. However, in a protic solvent the proton transfer is faster, and protonation of the intermediate radical ion occurs quickly, and the second intermediate is not
long-lived enough to be observed using electrochemistry. For MK-derivatives in cellular systems, the presence of H$_2$O renders the redox chemistry a one step process. Even though menaquinones are located in the membrane, H$_2$O is an accessible proton source. It is highly likely that the redox reaction involving fewer intermediates is important for the biological properties of these compounds. Our group has been investigating the redox properties of some menaquinone systems and found distinctly different properties in organic solvents where the MK-derivatives are soluble [12], compared to aqueous systems where the menaquinone will be interacting with a membrane or a model membrane system, such as a liposome [32].

![Figure 1. Common menaquinones and ubiquinones.](image1)

![Figure 2. The redox reaction of menaquinones showing the two steps observed in aprotic organic solvent; in the presence of a protic solvent it occurs in only one step, but the overall reaction is conserved.](image2)
The location of menaquinones in biological systems is associated with the membrane due to their hydrophobicity. These compounds have been presumed to reside inside the membrane; however, few studies have been done to investigate the specific interaction. Some computational studies have examined the association with the membrane because it is critical to understand the interaction for the electron transport action of menaquinones in bacterial systems [33]; however, less work has been done experimentally. A range of studies have been performed with ubiquinone derivatives, and evidence for the membrane association has been reported both in computational and experimental systems [34–36]. On the other hand, significantly less work has been done with the menaquinone system, but so far, the reports support the presumptions often that the menaquinone is associated with the membrane.

Despite the polarity of the quinone group, these molecules are very hydrophobic, even though this property does vary with the length and the nature of the isoprene side group. We have recently found by synthesis of truncated MK-derivatives that only MK-1, MK-2, and MK-3, including derivatives with fully or partially saturated counterparts, are soluble in aqueous solution [12,37,38]. This means that assays with MK-4, even though it is known as an enzyme substrate in vivo, may not demonstrate enzyme activity even if the aqueous assay includes surfactants [39]. This experiment was attempted for MenJ, the membrane bound enzyme reported to stereospecifically hydrogenate the second isoprene unit of MK-9 in Mycobacterium tuberculosis and Mycobacterium smegmatis. The inability of the isolated enzyme to saturate MK-4 was attributed to the poor solubility of MK-4 in vitro since it was following the study that demonstrated in vivo activity. These experiments document the need for use of the truncated MK-derivatives and caution the use of computational methods for evaluation of these systems. For example, the anticancer properties of MK-1 through MK-7 were investigated with a series of five cancer cell lines [40]. MK-1, MK-2, and MK-3 were shown to be cytotoxic, however, MK-4, MK-5, MK-6, and MK-7 did not exhibit any cytotoxic activity against any of the cell five cell lines. Based on the studies with MenJ, it seems likely that the anticancer effects of longer MK-derivatives are a consequence of the physical properties of these derivatives, and any correlations and conclusions regarding the measured activities are not based on the true cytotoxicity of these compounds, but a reflection of their hydrophobicity.

Due to the distinct hydrophobicity of menaquinones, assaying these substrates in vitro is often critical and or convenient in biological studies. Since assays are often done in aqueous solution, this can cause problems if the substrates are menaquinones with longer isoprene side chains, because the longer naturally occurring MK-derivatives are often insoluble in aqueous solution. Contrary to common belief, the addition of surfactants in such assays is often insufficient to solubilize these compounds. The approach we have used to overcome this challenge is to synthesize water soluble, truncated MK-substrates [41]. To this end, the small, truncated MK-derivatives, MK-1 through MK-3, are somewhat soluble in aqueous assays with added surfactants, which makes these MK-derivatives excellent substrates for biological studies. We have recently used this approach in studies of MenJ documenting the effectiveness of this approach [26].

1.2. Synthetic Strategy for the Preparation of Menaquinones

Contemplating the many synthetic strategies available, consideration of the structure and the application of the MK-derivatives may be important when choosing the appropriate method for synthesis. So far, our group has focused on the preparation of truncated MK-derivatives, where the syntheses are relatively short and direct [12,37,38]. Therein, we used Friedel-Crafts alkylation using BF$_3$·OEt$_2$ as a Lewis acid catalyst. This use of electrophilic aromatic substitution is one of the most common across the literature for the synthesis of this family of compounds. This is most likely because it occurs over two steps from commercially available starting materials. For example, for our synthesis of MK-2, we begin by reducing menadione 1 with 10% Na$_2$S$_2$O$_4$ at room temperature for 30 min to produce menadiol 2 in ~84% yield (Scheme 1) [12]. Then menadiol 2 underwent alkylation with commercially available geraniol in the presence of BF$_3$·OEt$_2$, producing MK-2 in 20.1% yield.
This approach may be direct, but it generally results in low yields (<30%) and a mixture of isomers. Although biological studies do not require very much sample, consistently low yielding reactions are not suitable for multi-step syntheses at large scales, such as longer MK-derivatives where the key step is a Friedel-Crafts alkylation.

![Scheme 1. Friedel-Crafts alkylation using BF₃·OEt₂ and commercially available materials [12].](image)

Two reviews [42,43] have been published that focus on the synthesis of the biologically relevant vitamin K₁. In this review, we summarize the syntheses of MK-derivatives reported in recent history. This includes menaquinones of varying side chain lengths, which include many types of vitamin K₂ derivatives, as well as vitamin K₁. This review will highlight the five most common synthetic strategies used for preparation of truncated and full-length MK-derivatives: nucleophilic ring methods, metal-mediated and radical reactions, electrophilic ring methods, pericyclic reactions, and side chain extensions (Figure 3). Each class of reactions will be summarized, identifying the advantages and disadvantages of each. This will allow an evaluation of each strategy based on the overall yields of the synthesis, regioselectivity, and the stereoretention of the first isoprene (α) unit from the ring. Other comparisons concerning the number of steps, competing side reactions, and safety will also be presented, which will result in a summary identifying the most attractive synthetic strategies from each category for preparation of this class of compounds.

![Figure 3. 5 Main synthetic strategies from across the literature for the synthesis of menaquinone derivatives.](image)
2. Nucleophilic Ring Methods

2.1. Enolate Alkylation

In 1974, Snyder and Rapoport published a comprehensive report detailing their attempts to synthesize menaquinones [44]. The main goal of their syntheses was to retain the stereochemistry of α-isoprene double bond. The first approach used enolate chemistry to alkylate the C3 position of menadiol 2. Beginning with menadiol 3a, the potassium salt 4a was formed using potassium hydride or potassium methoxide (Scheme 2). It was suspected that Claisen alkylation had occurred, but upon further analysis it was concluded that the reaction proceeded via enolate alkylation to form 5a with 97:3 E/Z. Oxidation of the ring in the presence of Ag₂O formed MK-2 in an average of 20% yield over three steps. The authors postulated the lower yield was due to competing Friedel-Crafts alkylation occurring on the C2 position. To prevent competition, the authors redeveloped the route using C1 methyl ether protected menadion 3b. Conversion of 3b to MK-2 yielded 45% with 97% E alkene (Scheme 2). Despite the improved yield, the synthesis of 3b was more complicated than the authors originally thought. Therefore, this route was abandoned for one with more accessible starting materials.

A few years later, Tabushi et al. published on the allylation of naphthoquinones using β-cyclodextrin as an inclusion catalyst, especially for synthesis of vitamin K₁ [45,46]. Menadiol 2 was alkylated at the C3 position in mild basic conditions, borate buffer (pH 9), with and without β-cyclodextrin (Scheme 3A). The yields of MK-1 were found to be 40% and 15%, respectively, showing a significant decrease in yield without β-cyclodextrin. The only byproduct observed was menadione 1 in 49% and 28% yield, respectively.

![Scheme 2. Synthesis of MK-2 via enolate alkylation [44].](image)

![Scheme 3. (A) Synthesis of MK-1 using β-cyclodextrin (β-CD) as an inclusion catalyst. (B) Steric hinderance (shown in bold) of the β-cyclodextrin scaffold preventing C2 alkylation [45,46].](image)
The results strongly indicate that β-cyclodextrin played significant role catalyzing this reaction. The authors noted the selectivity of the alkylation behaved as if it were a ligase and or oxidase. Due to the semi-conical structure of β-cyclodextrin, menadion is surrounded by the hydrophobic cavity. The C1 and C4 hydroxy groups interact with the hydrophilic exterior (Scheme 3B). The C1 hydroxy group hypothesized to be hydrogen bonding on the narrower end of the scaffold. The hydrogen bonding interactions were found to lower the pKa of the opposite hydroxy group at the C4 position. Unbound menadion has a pKa of 9.45, and bound menadion was calculated to have a pKa of ~8.90 [46]. The decrease in pKa was said to enhance the nucleophilicity of the partially charged carbanion on the C3 position. Deprotonation of the C4 hydroxy group in pH 9 medium created a more nucleophilic enolate, alkylating at the C3 position. The authors did not observe any C2-alkylated product in their trials. They postulated the sterically hindered, semi-conical shape of the β-cyclodextrin scaffold prevented C2 alkylation (Scheme 3B). Menadione 1 was the only other product formed. In both trials, 1 was produced in higher yields than MK-1. In protic solvents, menadion 2 will spontaneously oxidize to form menadione 1. In the presence of an enzyme-like cavity of β-cyclodextrin, the transformation was most likely accelerated in the buffer solution. Although menadione 1 was formed in higher yields, it can be recovered and recycled for subsequent use.

2.2. Transmetalation

After marginal success with enolate alkylations, Snyder and Rapoport shifted their focus towards more direct nucleophilic methods [44]. Bismethyl ether 2-bromomenadion 6 was transformed into 2-metallo derivatives using lithium, magnesium, and copper to react with a variety of electrophiles (Scheme 4). The authors were originally interested in using aldehydes as electrophiles; however, their attempts were unsuccessful. Removal of the resultant benzyl alcohol led to the formation of a vinyl alkene or isomerization of the α-isoprene double bond. To avoid this, prenyl halide substrates were used instead. Preliminary reactions were performed to assess the stereoretention of the α-isoprene double bond for each 2-metallo derivative. All three 2-metallo derivatives left the α-isoprene double bond virtually unaffected. Organolithium yields were 10% and 65% for geranyl chloride and bromide, respectively. The Grignard reagent was formed in 92% yield. Snyder and Rapoport continued their studies using the Grignard reagent.

![Scheme 4](https://example.com/scheme4.png)

**Scheme 4.** Synthesis of MK-2 and MK-9 using Grignard reagents [44].

To examine the utility of this method, the authors synthesized MK-2 and MK-9 (Scheme 4). The Grignard reagent was produced by stirring 6 with Mg turnings in dry THF. Geranyl bromide and solanesyl bromide were added to the solution, resulting in the respective alkylated products, 7a and 7b. Removal of the bismethyl ethers and oxidation of the ring were achieved with AgO in acidic conditions yielding 80% and 73% for MK-2 and MK-9, respectively. Both products retained the stereochemistry of the α-isoprene double bond, each with ≥98% E alkene.

Unlike Snyder and Rapoport, Sá and coworkers were successful using aldehydes as electrophiles in the early 1990s. This challenge was overcome with the use of stereocontrolled Birch hydrogenolysis conditions (BIHY) to selectively remove silyl ether protected (E)- or (Z)-α-alkenylbenzyl alcohols [47–49]. The authors applied this method towards the synthesis of MK-2 and MK-4 (Scheme 5). Using the
same starting material as Snyder and Rapoport, bismethyl ether 2-bromomenadiol 6 underwent lithium-bromide exchange to form the organolithium reagent. Commercially available aldehydes, citral 8a (68:32 E/Z) and geranylgeranial 8b (≥ 95% E), were used without further purification to assess the stereoretentive abilities of BIHY conditions. Upon nucleophilic attack, the resultant benzylic alcohols 9a and 9b were formed in ~65% and 58% yield, respectively. The alcohols were protected with TMSCl in the presence of HMDS, as used in previous reports [48,49]. In the literature, the authors used the abbreviation “HMDSZ” instead of “HMDS”, which is now more the commonly used abbreviation. The protected alcohol was then reduced in the presence of lithium metal and liquid ammonia to produce the free methylene 10. With this method, the resulting stereochemistry of 10a and 10b α-isoprene double bonds were determined to be 2:1 E/Z and ≥95% E alkene, respectively. These results reflect the stereochemistry of the aldehyde precursors and demonstrate the remarkable stereoretention of BIHY. The methyl ether protecting groups were removed using CAN to produce MK-2 and MK-4. Only the reported yield was for MK-4 in 86%.

Further improvement upon the strategies established by Snyder and Rapoport was reported by Swenton and coworkers in 1977 [50]. Therein, preliminary results were published using electrolysis to protect bismethyl 2-bromomenadiol 6 as bismethyl ketals. The authors used lithium organocuprate nucleophiles instead of Grignard reagents. In 1980, the authors published a complete study towards the synthesis of menaquinones [51]. Bismethyl ether 2-bromomenadiol 6 underwent electrolysis in a divided cell with 2% KOH and methanol, producing bisketal 11 (Scheme 6). Lithium-bromide exchange in THF and subsequent transmetalation with cuprous iodide produced the desired lithium organocuprate dimer 12. The corresponding electrophiles, prenyl bromide 13a and geranyl bromide 13b, were added to the solution and immediately carried forward to hydrolysis without purification. MK-1 and MK-2 were formed in 92% and 96% yield, respectively. The authors did not observe any evidence of the Z isomer in NMR; however, its absence could not be concluded.
Second, Hirschmann et al. reported the comparison of different Lewis and Bronsted-Lowry acid catalysts towards the synthesis of vitamin K₃ in the following year. First, Isler and Doebel detailed the synthesis of vitamin K₁ and various other racemic derivatives [53]. Second, Hirschmann et al. reported the comparison of different Lewis and Bronsted-Lowry acid catalysts towards the synthesis of vitamin K₁ [54] in an effort to improve upon existing reported methods at the time [55–61]. Most notably among those methods, Fieser reported the condensation of menadiol and phytol in the presence of oxalic acid with overall yields of 25–30% [55]. Much of the yield was lost to undesired side products, such as phytadiene and the C2-alkylated product [62]. Many of the early reports do not use protecting groups or other functional handles to induce regioselectivity.

To address the regioselectivity challenge, Hirschmann et al. designed monoacetate 14 to influence C3 alkylation (Scheme 7). Monoacetate 14 underwent condensation with phytol in the presence of an acid catalyst to form alkylated product 15. Potassium acid sulfate, oxalic acid, Duolite C-60 cation exchange resin, and BF₃·OEt₂ produced varied results, as outlined in Table 1. Removal of the acetate protecting group was achieved using Claisen alkali conditions (dilute KOH in methanol), and oxidation with Ag₂O work up formed vitamin K₁.

Scheme 6. Synthesis of MK-1 and MK-2 featuring electrolysis as a protection method [50,51].

2.3. Friedel-Crafts Alkylation

Throughout all the strategies described in this report, the Friedel-Crafts alkylation is by far the most popular across the literature. The most common Lewis acid catalyst used for this specific transformation is BF₃·OEt₂, which became popular after Lindlar’s 1953 patent detailing its usage [52]. Two more reports of its use specifically towards the synthesis of vitamin K₁ were published in the following year. First, Isler and Doebel detailed the synthesis of vitamin K₁ and various other racemic derivatives [53]. Second, Hirschmann et al. reported the comparison of different Lewis and Bronsted-Lowry acid catalysts towards the synthesis of vitamin K₁ [54] in an effort to improve upon existing reported methods at the time [55–61]. Most notably among those methods, Fieser reported the condensation of menadiol and phytol in the presence of oxalic acid with overall yields of 25–30% [55]. Much of the yield was lost to undesired side products, such as phytadiene and the C2-alkylated product [62]. Many of the early reports do not use protecting groups or other functional handles to induce regioselectivity.

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Scheme 7. Synthesis of vitamin K₁ using Friedel-Crafts alkylation with different acid catalysts [54].
Table 1. Yields for different acid catalysts used in the synthesis of vitamin K$_1$ [54].

| Acid Catalyst | % Yield $^1$ |
|---------------|-------------|
| KHSO$_4$     | 55%         |
| Oxalic Acid  | N/A $^2$    |
| Duolite C-60 | 8%          |
| BF$_3$OEt$_2$ | 66.5%       |

$^1$ Over two steps. $^2$ No yield reported.

In 1990, Schmid et al. published a comprehensive report on the synthesis and analysis of all four stereoisomers of (E)-vitamin K$_1$ [63]. The synthesis of the naturally occurring stereoisomer showcased a unique transformation using BF$_3$OEt$_2$ as the catalyst (Scheme 8). Starting with monoaacetate 14, the free phenol was alkylated with phytol chloride 16 and potassium carbonate in 79–87% yield with 99.5% E alkene. In the presence of BF$_3$OEt$_2$, the O-alkylated product 15 was thought to have undergone a Claisen rearrangement to form C-alkylated product 17, but upon further analysis, the reaction was determined to proceed via and intramolecular Friedel-Crafts mechanism. The C-alkylated product 17 was formed in 76–80% yield and the E/Z ratio was found to be 97:3. This kind of intramolecular transformation was first reported by Yoshizawa et al. in 1982 on ubiquinone derivatives [64]. Removal of the acetyl group in basic conditions produced vitamin K$_1$ in 96.5% yield based on HPLC. The E/Z ratio of the α-isoprene double bond was determined to be 97:3, unchanged from the previous step. In 2003, the authors of a vitamin K$_1$ syntheses review [42] commented that this route has received little attention.

Scheme 8. Synthesis of vitamin K$_1$ featuring an intramolecular Friedel-Crafts alkylation [63].

Alllyl alcohols have a reputation for being intrinsically unstable towards alcohol rearrangement. To circumvent this issue, Min et al. used prenyl chlorides instead [65]. Menadiol dimethyl ether 18 was reacted with prenyl chloride 19 in presence of BF$_3$OEt$_2$ to form sulfonyl intermediate 20 (Scheme 9). Truncated prenyl chain 19 allowed for further functionalization of the side chain to make more diverse analogs, which will be discussed in detail later in Section 6.2. The authors assessed the efficacy of a large scope of Lewis acids, which are summarized in Table 2. Based on these results, AlCl$_3$ performed the best with 72% yield and all E configuration of the α-isoprene double bonds.

Scheme 9. Synthesis of truncated MK-derivatives using Friedel-Crafts alkylation [65].
The reactions resulted in 100% conversion of the starting material with each catalyst. The yields were predicted that this class of catalysts will replace homogenous BF₃·OEt₂ using partly hydroxylated magnesium and aluminum fluorides to address such concerns [66]. The authors yielded 26.5%, which is comparable to BF₃·OEt₂ in industrial applications. Therefore, these stereoisomers are purified on demand for the biological studies.

Despite the historical popularity of BF₃·OEt₂, the competition between C2/C3 alkylation continued to be a persistent challenge. Various types of protecting groups have been used to prevent competition with varying success. Due to competing side reactions, its use in industrial applications has been accused of being wasteful, inspiring researchers to identify new, more sustainable Lewis acids to minimize byproducts and maximize yield. Coman et al. developed a new class of heterogenous, partly hydroxylated magnesium and aluminum fluorides to address such concerns [66]. The authors predict that this class of catalysts will replace homogenous BF₃·OEt₂ in industrial applications. Vitamin K₁ was synthesized to illustrate this concept starting with menadiol 2 and isophytol 21 (Scheme 10). The reactions resulted in 100% conversion of the starting material with each catalyst. The yields were low and showed considerable formation of byproducts, mainly chromanol and C2-alkylated product, as shown in Table 3. The catalyst, MgF₂-57 provided the best results with respect to vitamin K₁, yielding 26.5%, which is comparable to BF₃·OEt₂.

**Scheme 10.** Synthesis of vitamin K₁ using partly hydroxylated magnesium and aluminum fluorides [66].

Despite the historical popularity of BF₃·OEt₂, the competition between C2/C3 alkylation continued to be a persistent challenge. Various types of protecting groups have been used to prevent competition with varying success. Due to competing side reactions, its use in industrial applications has been accused of being wasteful, inspiring researchers to identify new, more sustainable Lewis acids to minimize byproducts and maximize yield. Coman et al. developed a new class of heterogenous, partly hydroxylated magnesium and aluminum fluorides to address such concerns [66]. The authors predict that this class of catalysts will replace homogenous BF₃·OEt₂ in industrial applications. Vitamin K₁ was synthesized to illustrate this concept starting with menadiol 2 and isophytol 21 (Scheme 10). The reactions resulted in 100% conversion of the starting material with each catalyst. The yields were low and showed considerable formation of byproducts, mainly chromanol and C2-alkylated product, as shown in Table 3. The catalyst, MgF₂-57 provided the best results with respect to vitamin K₁, yielding 26.5%, which is comparable to BF₃·OEt₂.

**Table 2.** Friedel-Crafts alkylation of 18 with sulfonyl 19 to form 20 [65].

| Lewis Acid | % of 20 (E/Z) |
|------------|--------------|
| BF₃·OEt₂   | 0 (-)        |
| MgBr₂      | 0 (-)        |
| TiCl₄      | - 2(-)       |
| FeCl₃      | 55 (4:1)     |
| Et₂AlCl    | 56 (7:1)     |
| SnCl₄      | 56 (E)       |
| ZnBr₂      | 60 (7:1)     |
| ZnCl₂      | 67 (7:1)     |
| AlCl₃      | 72 (E)       |

1 1.2 equiv of Lewis acid was used. 2 Decomposition of the starting materials was observed.

Recently, we synthesized fully and partially saturated MK-derivatives in an effort to understand their structural and electrochemical properties in model membranes [12,37,38]. For the synthesis of MK-2(II-H₂), the condensation of isophytol 22 and menadiol 2 was accomplished in 11% yield using MgF₂-48, a Coman et al. inspired catalyst (Scheme 11). Before purification, the crude yield was determined to be 60%, consisting of regio- and stereoisomers. The regioisomers separated readily via column chromatography; however, the E/Z isomers of the C3-product required thorough purification using preparative TLC. Therefore, these stereoisomers are purified on demand for the biological studies.

**Table 3.** The catalytic results in the synthesis of vitamin K₁, K₁-chromanol, and C2-alkylated product from menadiol [66].

| Catalyst | % of Vitamin K₁ | % of K₁ Chromanol | % of C2 Product |
|----------|----------------|-------------------|-----------------|
| MgF₂-40  | 21.2           | 5.9               | 58.8            |
| MgF₂-57  | 26.5           | 21.0              | 43.7            |
| MgF₂-71  | 15.6           | 20.8              | 52.9            |
| MgF₂-87  | 0              | 0                 | 0               |
| AlF₂-50  | 7.6            | 42                | 41.2            |

1 0% conversion.
ii et al., the authors only synthesized MK-1; therefore, the stereochemical implications of the method were not addressed. However, in the case of Tabushi et al., the authors only synthesized MK-1; therefore, the stereochemical implications of the method were not addressed.

2.4. Summary

The three main nucleophilic ring methods throughout the literature include enolate alkylation, transmetalation of bromonaphthoquinone derivatives, and Friedel-Crafts alkylation. The advantages and disadvantages of each have been outlined in Table 4. Out of all nine methods presented, only three of them reported overall yields greater than 80%. These methods were Snyder and Rapoport’s aryl-Grignard reaction with prenyl bromides, Swenton and coworker’s use of electrolytically protected lithium organocuprate, and Schmid et al.’s unique intramolecular Friedel-Crafts alkylation. The first two methods also demonstrated exemplary regiocontrol due to lithium-bromide exchange with of bismethyl ether 2-bromomenadiol 6. The other methods produced regioisomers owing to prominent competition between C2 and C3 alkylation. Many methods did not utilize protecting groups or directing group manipulations to influence regiocontrol. For most of these methods, the chosen electrophiles were prenyl halides, which left the α-isoprene double bond virtually undisturbed. However, in the case of Tabushi et al., the authors only synthesized MK-1; therefore, the stereochemical implications of the method were not addressed.

Table 4. Summary of nucleophilic ring methods.

| Methods | Advantages | Disadvantages |
|---------|------------|---------------|
| **Section 2.1. Enolate Alkylations** |
| Snyder and Rapoport Enolate Alkylation [44] | -Stereo retention of α-isoprene double bond (97% E-alkene) -3 step synthesis (not including starting material) | -Low yields (20–45%) -C2 alkylation competition via Friedel-Crafts alkylation -Unviable synthesis of starting material |
| Tabushi et al. β-cyclodextrin inclusion catalyst [45,46] | -Regiocontrol via sterically hindered nature of β-cyclodextrin -Menadione is the only byproduct -1 step synthesis | -Low yields (40% with inclusion catalyst) -Competition between C3 alkylation and C3 protonation -Only synthesized MK-1 |
| **Section 2.2. Transmetalations** |
| Snyder and Rapoport Grignard reaction [44] | -Regiocontrol through lithium-bromide exchange -Stereo retention of the α-isoprene double bond (≥95%) -Alkylation step is high yielding (>95%) -3 step synthesis (not including starting material) | -Need to prepare starting material 6 |
| Saá and coworkers BIHY Reduction [47–49] | -Stereo retention of the α-isoprene double bond during BIHY reduction | -Moderate yields for nucleophilic addition (58–65%) and BIHY reduction (53–70%) -5 step synthesis (not including starting material) |
Table 4. Cont.

| Methods | Advantages | Disadvantages |
|---------|------------|---------------|
| Swenton and coworkers | -Unique use of electrolysis as a protection method<br>-High yields for all reported steps (≥85%)<br>-Regiocontrol through lithium bromide exchange<br>-Stereoretention of α-isoprene double bond (<5% Z-alkene estimated)<br>-Deprotection of bisketals to menaquinone ring structure via hydrolysis, no oxidation required | -Lithium organocuprate nucleophile only used one of two bisketal rings—poor atom economy<br>-Difficult purification because of unreacted starting materials<br>-5 step synthesis (not including starting material) |
| Electrolysis & Lithium Organocuprate | | |
| [50,51] | | |
| Section 2.3. Friedel-Crafts Alkylation | | |
| Hirschmann et al. Friedel-Crafts Alkylation Lewis Acid Analysis [54] | -Favors C3 alkylation over C2 due to monoacetate 14<br>-Avoided formation of undesired byproducts (phytadiene and chromanol)<br>-Monoacetate 14 was the only recoverable byproduct<br>-2 step synthesis (not including starting material) | -Low to moderate yields (8–66.5%) depending on acid catalyst used (Table 1)<br>-Stereoretention of the α-isoprene double bond was not discussed |
| Schmid et al. Intramolecular Friedel-Crafts [63] | -Features unique intramolecular Friedel-Crafts alkylation at C3 position<br>-High yields (76–96.5%) throughout all steps<br>-Stereoretention of α-isoprene double bond<br>-3 step synthesis (not including starting material) | -Need to prepare starting material 22 |
| Min et al. Friedel-Crafts Alkylation Lewis Acid Analysis [65] | -Stereoretention of α-isoprene double bond with AlCl₃<br>-Produced a functional handle for chain extension methods<br>-1 step synthesis (not including starting material) | -Low to moderate yields (0–72%) depending on Lewis acid used |
| Coman et al. [66] and Koehn et al. [38] Heterogenous Lewis Acid Catalysts | -Predicted industrial benefit to replace BF₃·OEt₂<br>-Performed without protecting groups, but could benefit from them<br>-1 step synthesis (not including starting material) | -Universally low yields (0–26.5%)<br>-Poor regiocontrol to prevent C2 alkylation<br>-Difficult purification<br>-Synthesis of partly hydroxylated metal fluorides requires the use of dangerous aqueous HF [67,68] |

3. Metal-Mediated and Radical Reactions

3.1. Cross-Coupling

After the incorporation of transmetalation, synthetic efforts were shifted to investigate cross-coupling reactions. In 1973, Sato et al. used π-allylnickel chemistry to synthesize vitamin K₁ and MK-9 after initial success with MK-1 [69]. For this method, π-allylnickel complexes 24 and 28 were formed in situ using allyl bromides 23 and 27 with Ni(CO)₄ (Schemes 12A and 13A). Vitamin K₁ was synthesized from diacate 25 and π-allyl complex 24 in MPD at 50 °C for 5 h to form the expected alkylated product 26 in 75% yield (Scheme 12B). The acetate protecting groups were removed in mild basic conditions, and the oxidation was achieved using FeCl₃, producing vitamin K₁ in 93% over two steps. The observed E/Z ratio was 8:2 with respect to the α-isoprene double bond. For MK-9, the same starting material diacate 25 and π-allyl complex 28 were heated to 50 °C for 16 h to form alkylated product 29 in 52% yield (Scheme 13A). MK-9 was produced in 85% yield and 7:3 E/Z using the same methods of deprotection and oxidation (Scheme 13B).
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Scheme 12. (A) Formation of π-allylnickel complex. (B) Synthesis of vitamin K1 using π-allylnickel cross-coupling [69].

Stille et al. published the synthesis of vitamin K1 using trimethylstannane derivatives to cross couple phytlyl bromide in 1983 [70]. 2-Bromomenadiol 30 was protected with TBSCl in 95% yield (Scheme 14). Lithiation with t-BuLi and transmetalation with trimethyltin chloride formed 31 in 77% yield over two steps. Phytlyl bromide was then coupled with 31 in the presence of ZnCl2 forming 32. PCC was used to deprotect and oxidize the ring to form vitamin K1 in 40% yield over two steps.
In 1990, Liebeskind and Foster discovered an unexpected transformation that appeared useful towards the synthesis of MK-derivatives [71], which was previously mentioned in a review of syntheses of vitamin K and analogs [42]. MK-1 was synthesized using ring-strained dione 33 and propyne, forming alcohol 34 (Scheme 15). Then alcohol 34 underwent a Liebeskind-Moore rearrangement in the presence of Bu3SnOMe to form the stannylated product 35 in 49% over two steps. From there, MK-1 was synthesized in 90% yield using Stille cross-coupling conditions with Pd(0) and prenyl bromide.

Scheme 15. Synthesis of MK-1 featuring Liebeskind-Moore rearrangement to ring expansion [71].

3.2. Coordination Complex

An intriguing approach to the synthesis of MK-derivatives was developed by Dötz et al. in 1986. Using pentacarbonyl(methoxyphenylcarbene)chromium(0) complex 36 and an alkyne (Scheme 16), the quinone ring was formed via carbonylation [43,72,73]. This approach provided access to several different naphthoquinone derivatives using functionalized alkynes. The authors synthesized vitamin K1 and MK-1 through MK-3 to illustrate this transformation. Phenyllithium reacted with one of the carbonyl ligands (CO) on Cr(CO)6, and then was methylated by trimethyloxonium tetrafluoroborate to form complex 36. Vitamin K1 and MK-1 through MK-3 were formed by using alkynes 37a or 37b, respectively. Upon addition, the alkyne displaced another molecule of CO, to form intermediate complex 38. The resulting menadiol ring 39a/b was coordinated to Cr(CO)3. To make this route more sustainable, the authors determined Cr(CO)3 could be regenerated by pressurizing the system with CO to displace Cr(CO)3 and liberate the alkylated product 40a/b. Oxidation with standard oxidizing agents afforded the menaquinone products accordingly. The yields of each reaction were not reported in Rüttimann’s 1986 review [43].
Scheme 16. Synthesis of MK-derivatives using unique Cr(CO)$_6$ mediated ring formation [43,72,73].

In 1980, Liebeskind et al. designed a synthesis of naphthoquinones using bis(triphenylphosphine)phthaloylcobalt complex 41 (Scheme 17A). Ring formation was achieved upon addition of an alkyne in the presence of AgBF$_4$ [74]. In 1986, an update was published wherein the authors describe an improved cobalt complex to increase the yield of the reaction and minimize the amount of AgBF$_4$ required [75]. The updated complex 42 replaced the triphenylphosphine ligands with pyridine and dimethylglyoxime (Scheme 17B).

Scheme 17. (A) Original cobalt complex synthesized by Liebeskind et al. for this transformation. (B) Synthesis of MK-1 and MK-2 using the updated catalyst [74,75].

This new complex was more tolerant towards different Lewis acids as well as hydrated salts, which was demonstrated by the formation of 44 using complex 42, as shown in Table 5. MK-1 and
MK-2 were synthesized using alkynes 43a and 43b, cobalt complex 42 and Lewis acid in the form of CoCl$_2$-6H$_2$O at 80 °C producing MK-1 and MK-2 in 94% and 86% yield, respectively.

### Table 5. Effects of Additives on 2,3-diethyl-1,4-naphthoquinone 44 formation at 80 °C [75].

| Additive (1 Equiv) | GC Yield % of 44 |
|--------------------|------------------|
| None               | 25  52  77       |
| AgBF$_4$           | 80  82  -         |
| BF$_3$-OEt$_2$     | 74  79  82       |
| SnCl$_2$           | 41  39  70       |
| CoCl$_2$-6H$_2$O   | 59  83  91       |
| CoCl$_2$(anhyd)    | 61  86  86       |
| p-CH$_3$PhSO$_2$H  | 14  31  76       |
| CH$_3$CO$_2$H      | 23  47  74       |

### 3.3. Radical Reactions

#### 3.3.1. Metal-Mediated Radical Reactions

In 1972, Jacobsen and Torssell reported the use of allyl radicals produced via decarboxylation of carboxylic acids to alkylate quinones. Upon mixing silver nitrate and ammonium peroxodisulfite, Ag$^+$ and S$_2$O$_8^{2-}$ produce the radical, Ag$^{2+}$ as shown in Equation (1). Then Ag$^{2+}$ abstracts an electron from the carboxylic acid to produce CO$_2$ and a radical species R as shown in Equation (2) [76]. The authors were concerned about possible rearrangement of the position of isoprene double bond [77]. 4-Methyl-3-pentenoic acid 45 formed the 3,3-dimethylallyl radical 46, which resonates between $\alpha,\alpha$ and $\gamma,\gamma$ positions (Scheme 18A).

\[
\text{Ag}^+ + \text{S}_2\text{O}_8^{2-} \rightarrow \text{Ag}^{2+} + \text{SO}_4^{-} + \text{SO}_4^{2-} \quad (1)
\]

\[
\text{Ag}^{2+} + \text{RCOOH} \rightarrow \text{R}^- + \text{CO}_2 + \text{H}^+ + \text{Ag}^+ \quad (2)
\]

**Scheme 18.** (A) Radical formation via decarboxylation. (B) Synthesis of MK-1 using this method [76,77].
The more stable tertiary radical, \( \alpha,\alpha\)-dimethylallylquinone, was expected; however, only \( \gamma,\gamma\)-dimethylallylquinone was observed, favoring the more stable alkene. MK-1 was produced in 70\% yield using 45 (Scheme 18B), leaving the question of \( E/Z \) alkene isomerization unanswered:

The question of \( \alpha \)-isoprene double bond stereoretention was later answered by Yamago et al. in 2000 with preliminary results of the radical coupling of quinones with organotellurium reagents [78,79]. Geranyl bromide (73:23 \( E/Z \)) 47 was converted to the corresponding tolyltelluride 48 in 41\% yield with complete retention of stereochemistry (Scheme 19A). Then the tolyltelluride 48 was photochemically coupled to menadione 1 to produce MK-2 in 44\% yield with complete retention of stereochemistry (Scheme 19B). This reaction was previously mentioned in a review by Daines et al. in 2003 [42].

![Scheme 19. (A) Synthesis of geranyltelluride reagents. (B) Synthesis of MK-2 with organotelluride radical alkylation [78,79].](image)

3.3.2. Non-Metal-Mediated Radical Reactions

In 2019, we continued our pursuit to synthesize menaquinone analogs with various levels of saturation within the side chain [38]. For analogs with the first isoprene unit saturated, we employed chemistry developed by Coppa et al. in 1991. Therein, different methods for homolytic methylation of quinones with alkyl iodides were discussed [80]. In one such method, menadione 1 reacted with a saturated alkyl iodide in the presence of benzoyl peroxide to form the C3-alkylated product 49 (Scheme 20A).

![Scheme 20. (A) General synthesis of menaquinones with alkyl iodides [80]. (B) Synthesis of MK-2 (I,II-H4) [38].](image)
The results varied, with yields ranging from 68 to 93%. Prominent competition between the C3-alkylated product and the C3-self-coupling aryl product was observed, showing 32–94% the C3 aryl product in some trials. We saw the parallels between the substrates used by Coppa et al. and the saturated prenyl side chains required for our studies. Menadione 1 was coupled with alkyl iodide 50 to synthesize MK-2(I,II-H4) in 17% yield (Scheme 20B).

3.4. Summary

The three main metal-mediated and radical methods reported in the literature included organometallic cross-coupling, the use of coordination complexes, and both metal and non-metal mediated radical reactions. The advantages and disadvantages of each have been outlined in Table 6. Only four methods reported moderate to high yields (65–100%) across the synthesis. Liebeskind and Foster used Stille coupling for the key alkylation step (90%). Liebeskind et al., again, reported high yields (77%) using the updated cobalt complex to aid the cycloaddition of alkynes to the coordinated phthaloyl group. Jacobsen and Torssell achieved moderate yields (70%) in the alkylation of quinones with radicals generated by the decarboxylation of prenyl carboxylic acids. Lastly, Coppa et al. also used radical alkylation of quinones using short-chain alkyl iodides in the presence of benzoyl peroxide. Regiocontrol for these methods was achieved in three ways: (1) transmetalation of organolithium reagents to different organometalates; (2) asymmetric alkynes coordinating to symmetric complexes; and 3) selective abstraction of aryl hydrogens adjacent to the carbonyl. Complete stereoretention was observed during Stille et al.’s cross-coupling of arylstannanes and phytlyl bromide in the presence of ZnCl2, Dötz et al.’s cycloaddition using stereopure alkynes, and

Table 6. Summary of metal-mediated reactions.

| Methods                              | Advantages                                                                 | Disadvantages                                                                 |
|--------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| **Section 3.1. Cross-Coupling**      |                                                                           |                                                                               |
| Sato et al.                          | -No coordination complex synthesis required                               | -The yields drop at the cross-coupling, especially for the much longer prenyl side chains, MK-9 (52%) |
| *π*-Allylnickel Cross Coupling [69]   | *π*-allyl complex is formed in situ                                       | Authors note E/Z ratio is tunable depending on the solvent, but the yields drop as a result |
|                                     | -Moderate to high yields (52–93%) across the syntheses                    |                                                                               |
|                                     | -E/Z ratio of the α-isoprene double bond (7:3 E/Z for MK-9)               |                                                                               |
|                                     | -3 step synthesis (not including starting material)                        |                                                                               |
| Stille et al.                        | -High yields (77%) for the formation of the arylstannane                 | -Low yield for cross-coupling (40% over two steps)                           |
| Aryl Stannane Cross Coupling [70]    | -The regiochemistry of the system is controlled by transmetalation at C3 position | Requires the use of t-BuLi                                                   |
|                                     | -Allylic transposition was not observed in analogous synthesis of myrcene [70] | -5 step synthesis (not including starting material)                          |
| **Section 3.2. Coordination Complex** |                                                                           |                                                                               |
| Liebeskind and Foster Ring Expansion to Stille Coupling [71] | -Stille coupling achieved high yields (90%) | Low yield for key Liebeskind-Moore rearrangement (40% over two steps) |
|                                     | -3 step synthesis (not including starting material)                        | -Only synthesized MK-1                                                       |
| Dötz et al. Chromium Complex         | -No coordination complex synthesis required                              | Known adverse health effects related to hexavalent chromium                 |
| Carbonylation [72,73]                | -E/Z ratio of the α-isoprene double bonds was retained throughout the synthesis | No yields reported in Rüttimann’s 1986 review [43]                           |
|                                     | -The regiochemistry of the system is controlled by the alkynes 37a and 37b | -5 step synthesis (not including starting material)                          |
|                                     | -Cr(CO)6 is recyclable                                                    |                                                                               |
Table 6. Cont.

| Methods                                    | Advantages                                                   | Disadvantages                                                                 |
|--------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------------------------|
| Liebeskind et al. Cobalt Complex Cycloaddition [75] | -High yields (>86%)                                        | -The authors did not address α-isoprene double bonds isomerization               |
|                                           | -Simple coordination complex synthesis required using commercially available materials |                                                                                |
|                                           | -The regiochemistry of the system is controlled by the alkyne 43a and 43b |                                                                                |
|                                           | -1 step synthesis (not including catalyst)                  |                                                                                |

Section 3.3. Radical Reactions

- Moderate yields (70%)
- Regiocontrolled through aryl hydrogen abstraction
- Selective for γ,γ-alkene product of MK-1
- 1 step synthesis

- Only synthesized MK-1

Yamago et al. Radical Organotelluride [78,79]

- Regiocontrolled through aryl hydrogen abstraction
- Stereoretention of the α-isoprene double bond across all steps
- 2 step synthesis

- Low yields for both formation of tolyltelluride and radical coupling (~40%)
- Known adverse health effects related to working with tellurium and tellurium compounds

Coppa et al. [80] & Koehn et al. [80]

Benzoyl Peroxide Initiated Radical Alkylation

- Moderate to high yields of straight chain alkyl iodides (68–93%) [80]
- 1 step synthesis (not including starting material)

- Koehn et al. reported very low yields (17%) for this transformation with a branched alkane
- Substantial α-isoprene double bond isomerism
- Competing reactions interfere with C3-alkylated product (C3-C3, and C2 alkylation)

4. Electrophilic Ring Methods

4.1. 1,2-Addition versus 1,4-Addition

In the late 1970s and early 1980s, Naruta published two reports independently and published one with Maruyuma, reporting the use of prenyl stannanes for the synthesis of biologically important quinones, focusing on vitamin K1 and MK-2 [81–83]. Using menadione 1, trans and cis isomers with respect to the α-isoprene double bond were synthesized using geranyl and neryl trimethylstannanes, 51a and 51b, respectively, in the presence of BF3·OEt2 (Scheme 21A). The yields were 30% and 41% for the respective trans and cis products with the configuration of the double bond mostly maintained for each product. Trans-MK-2 was found to have 95% E alkene, and the cis isomer was found to have 76% Z alkene. Using the same conditions, vitamin K1 was synthesized in 48% using phytly trimethylstannane 52 (> 95% E) (Scheme 21B). The product was found to have 96% E alkene configuration, showing complete stereoretention.

Scheme 21. The synthesis of (A) MK-2 and (B) vitamin K1 using alkylstannanes [81–83].
Although the major product for all trials was the 1,4-addition product, 1,2-addition accounted for a large portion of the undesired byproducts. For cis-MK-2 and vitamin K₁, the C2 isomer was isolated in 13% and 14% yield, respectively. The 1,2 addition is hypothesized to add the least hindered carbonyl carbon of menadione 1, which then undergoes a [3,3] sigmatropic rearrangement, similarly described by Araki et al. [84] and Evans and Hoffmann [85] in Section 5.3. The rearrangement places the prenyl chain on the C2 carbon with the preexisting methyl group. In addition to prominent mechanistic competition, the yields are low across all steps. This method does, however, feature complete retention of stereochemistry of the α-isoprene double bond, as detailed in Table 7.

### Table 7. Summary of electrophilic ring methods.

| Methods                              | Advantages | Disadvantages                                   |
|--------------------------------------|------------|-------------------------------------------------|
| Naruta and Maruyama.                 | -Stereo retention of the α-isoprene double bond | -Low yields for both formations (30–48%)         |
| Organostannane                        | -1 step synthesis (not including starting materials) | -Prominent competition between C2 and C3 alkylation |
| Michael Addition [81–83]             |            |                                                 |

### 5. Pericyclic Reactions

#### 5.1. Diels-Alder Reactions

In a review published by Rüttimann in 1986 [43], synthetic advancements of the preparation of vitamin K₁ were presented, detailing methods from traditional substitutions, organometallic reactions, and pericyclic reactions. Therein, Rüttimann and coworkers explored the use of Diels-Alder reactions to form the naphthoquinone unit of vitamin K in a previously unpublished synthesis inspired by the work of Troll and Schmid. [86]. Dihydroisobenzofuranone 53 was reacted with activated alkyne dienophile 54 (96:4 E/Z) at 80 °C overnight to form the Diels-Alder adduct 55 (Scheme 22). Deprotection of the silyl ethers was achieved using methanol, and reduction of C2 methyl ester to a methyl group with sodium bis(2-methoxyethoxy)aluminum hydride in toluene under reflux formed the substituted menadiol. Oxidation with air in slightly acidic conditions produced vitamin K₁ in ~50% yield over four steps. The configuration of the isoprene double bond was not disturbed, resulting in 93–96% E alkene.

![Scheme 22](image)

**Scheme 22.** Previously unpublished synthesis of vitamin K₁ inspired by Troll & Schmid [43].

Using insights gained from the previous route, Rüttimann continued to explore the use of Diels-Alder reactions to synthesize vitamin K₁. He and Büchi designed an auxiliary-directed route using cyclopentadiene as the corresponding diene (Scheme 23) [87]. *Endo*-Diels-Alder adduct 56 was formed at room temperature using menadione 1 and cyclopentadiene in 93% yield. Formation of adduct 56 switched the C3 hybridization from sp² to sp³, decreasing the pKa. Upon deprotonation by a strong base (e.g., potassium amide, sodium amide, or potassium t-butoxide (which is referred to as potassium t-butanolate in the source literature)) a stable carbanion is formed, allowing regioselective alkylation at the C3 position with a variety of electrophiles.
Scheme 23. Synthesis of vitamin K1 using Diels-Alder approach with cyclopentadiene auxiliary [43].

Alkylation with phytol bromide (≥98% E) gave the predicted product 57. The authors found that some O-alkylation product was formed in trace amounts, however it was cleaved with acidic aqueous work up and easily separated. Alkylated adduct 57 was formed in approximately 90% yield over three steps. Due to the intrinsic instability of adduct 57, slow decomposition was observed at room temperature. Retro-Diels-Alder reaction was induced at high temperatures to remove the auxiliary group quickly, producing vitamin K1 in quantitative yield [87].

5.2. Anionic Diels-Alder Reactions

In contrast to traditional Diels-Alder reactions where neutral species form adducts, anionic Diels-Alder reactions have been another useful method to form the naphthoquinone unit. In 1995, Tso and Chen published a one-pot synthesis applicable towards the synthesis of vitamin K1, and MKs-1, 2, and 9 (Scheme 24) [88]. The dienophiles used were alkyl phenylsulfone 58 and alkyl bromides 59a–d for vitamin K1, MK-1, MK-2, and MK-9, respectively. Isobenzofuranone 61 was deprotonated with NaHMDS, then 60a–d were attacked forming the intermediate 62. Elimination of the benzenesulfonate produced the desired products vitamin K1, MK-1, MK-2, and MK-9 in moderate yields, 60–64%. The configuration of the α-isoprene unit was found to be >98% E alkene for all substrates.

Scheme 24. Synthesis of vitamin K1, MK-1, 2, and 9 using anionic Diels-Alder approach [88].

Nearly twenty years later, Mal et al. suggested better atom economy could be obtained in comparison to the work done by Tso and Chen. In an effort to improve the atom economy of anionic Diels-Alder reactions, the authors replaced the phenylsulfone moiety with a nitrile 63 (Scheme 25) [89]. Using this method, the authors synthesized different C3-alkylated MK-derivatives using specifically...
designed dienophiles. For the synthesis of MK-1 and MK-2, methyl acrylate derivatives 64a and 64b were used. It is important to note the synthesis of 64b produced a mixture of ~3:1 of E/Z isomers with respect to the methyl acrylate alkene, as determined by NMR. It is unclear to us whether that were used. It is important to note the synthesis of 68a.

Since MK-1 was the only product synthesized, there were 55% and 40% yield, respectively. The ratio of 64a/b with dienophiles 64a/b in 73% and 65% yield, respectively. Demethylcarboxylation of adducts 65a/b was achieved using a second round of LiOT-Bu in THF under reflux to form MK-1 and MK-2 in 55% and 40% yield, respectively. The ratio of E/Z ratio of MK-2 was found to be 5:3.

Scheme 25. Synthesis of MK-1 and MK-2 using anionic Diels-Alder approach with improved atom economy [89].

5.3. [3,3] Sigmatropic Rearrangements-Cope

[3,3] Sigmatropic rearrangements were also used to synthesize menaquinones, as shown in Daines et al. 2003 review [42]. In 1976, Evans and Hoffmann took advantage of the Cope rearrangement to synthesize MK-1 (Scheme 26A) [85]. Using masked ketone 66, the unprotected carbonyl was attacked with prenylmagnesium bromide, forming ketone 67 in one step. Interestingly, the authors discovered that prenylmagnesium bromide added to the carbonyl in a reverse prenylated fashion 68a (Scheme 26B). The C1-reverse prenylated product 68a set the transition state 68b for a Cope rearrangement, 68b to 69a, producing C3-prenylated product 69a. Upon quenching with saturated NH₄Cl, as shown in intermediate 69b, the C3 methoxy group was removed to reform ketone 67 (Scheme 26B). Deprotection of the masked ketone was achieved using AgF in mild conditions to form MK-1 in 71% yield over two steps. Since MK-1 was the only product synthesized, there E/Z ratio of the α-isoprene double bond was not considered, nor were the effects of this synthesis on longer prenyl chains.

Scheme 26. (A) Synthesis of MK-1 using prenylmagnesium bromide to Cope rearrangement. (B) Specific mechanism of the Cope rearrangement [85].
In contrast to more conventional alkylating reagents, Araki et al. used organoindium reagents for the allylation of various quinones [84]. Throughout many trials with a wide scope of benzoo- and naphthoquinone derivatives, organoindium reagents were found to selectively add to the least hindered carbonyl in 1,2-addition (Scheme 27A). Therefore, when choosing between the C1 and C4 carbonyl groups, 2-bromomenadione 70 was attacked at the less hindered C1 ketone with prenylindium 71 to form reverse prenylated intermediate 72a (Scheme 27B). Following addition, the reverse prenyl group underwent a Cope rearrangement, 72b to 73a, analogous to the system reported by Evans and Hoffmann. After oxidation with Ag2O, MK-1 was produced in 67% over two steps. This synthesis did not address the possibility of alkene isomerization, however, in other trials reported in the same paper [84], the authors reported geranylindium 74a and nerylindium 74b rearrangements on menadione 1, producing 75a and 75b in 85% and 95% yield, respectively (Scheme 27C). Each product showed a total loss of stereoretention, ~50/50 E/Z. The authors hypothesized the same trend would have been seen using 2-bromomenadione 70; therefore, stereocontrol of the α-isoprene double bond continues to be an important challenge with Cope rearrangements.

Scheme 27. (A) Synthesis of MK-1 using organoindium reagents. (B) Closer look into the Cope rearrangement. (C) Attempted synthesis of MK-2 using geranyl 74a and neryl 74b organoindium rearrangement. [84].

5.4. Summary

Across the literature, the common types of pericyclic reactions are Diels-Alder cycloadditions and [3,3] sigmatropic rearrangements, specifically Cope rearrangements. The advantages and disadvantages of each method have been outlined in Table 8. Rüttimann et al. achieved high yields with a cyclopentadiene auxiliary-directed Diels-Alder reaction. For all methods described in this section, the asymmetry of certain reagents controlled the regioselectivity of the reaction. For example, the asymmetry of the dienophiles involved in the Diels-Alder reactions controlled the regiochemistry of the adduct. The Cope rearrangement reactions were regiocontrolled by using starting materials
with leaving groups on the desired position, protecting groups, and by taking advantage of steric hinderance. For all Diels-Alder reactions described, except for the work done by Mal et al., complete retention of stereochemistry was observed for the \( \alpha \)-isoprene double bond. In the case of Mal et al., the reported \( E/Z \) ratio for dienophile \( 64b \) was \( \sim 3:1 \) \( E/Z \) by NMR for the methyl acrylate dienophile. The \( E/Z \) ratio of the product MK-2 was found to be \( 5:3 \) \( E/Z \). It is unclear to us whether this was a result of the Diels-Alder reaction or due to isomeric starting material. For all Cope rearrangements, it can be inferred that a complete loss of stereocontrol would be observed due to the reverse-prenyl addition to the carbonyl, as observed by Araki et al. using geranyl and nerylindium reagents with menadione 1.

**Table 8. Summary of pericyclic reactions.**

| Methods | Advantages | Disadvantages |
|---------|------------|---------------|
| **Section 5.1. Diels-Alder** | | |
| Rüttimann et al. Diels-Alder Reaction inspired by Troll & Schmid [43] | -High regiocontrol through the symmetry of dihydroisobenzofuranone diene -Stereoretention of \( \alpha \)-isoprene double bond (≥ 93%) | -Overall low yields (~50% over four steps) -Synthesis of starting materials -4 step synthesis (not including starting material) |
| Rüttimann et al. Auxiliary-Directed Diels-Alder [43] | -Uses commercially available starting materials (menadione and cyclopentadiene) -High regiocontrol through adduct 66 -Stereoretention of \( \alpha \)-isoprene double bond -Cyclopentadiene can be recycled -High yields throughout the synthesis (≥90%) | -Slight competition between C-alkylation and O-alkylation -5 step synthesis |
| **Section 5.2. Anionic Diels-Alder** | | |
| Tso and Chen Anionic Diels-Alder [88] | -One-pot synthesis -High regiocontrol through asymmetry of dienophile -Stereoretention of \( \alpha \)-isoprene double bond across all steps (>98%) -3 step synthesis (not including starting material) | -Moderate yields (60–64%) -Requires the synthesis of starting materials |
| Mal et al. Anionic Diels-Alder with Improved Atom Economy [89] | -Improved atom economy -High regiocontrol through asymmetry of dienophile -2 step synthesis (not including starting material) | -Low to moderate yields (40–73%) -Unclear if it is due to stereocchemistry of starting material or caused by the reaction |
| **Section 5.3. [3,3] Sigmatropic Rearrangements- Cope** | | |
| Evans and Hoffmann Grignard-Promoted Cope Rearrangement [85] | -Regiocontrol achieved through protected naphthoquinone -Cope rearrangement to achieve C3 alkylation -Moderate yields (71% over two steps) -2 step synthesis (not including starting material) | -No consideration of the isomerization of the isoprene double bond |
| Araki et al. Organoindium-Promoted Cope Rearrangement [84] | -Regiocontrol achieved through less hindered 1,2-addition of organoindium reagent -Cope rearrangement to achieve C3 alkylation -Moderate yields (67% over two steps) -2 step synthesis (not including starting material) | No stereoretention observed in Cope rearrangement |
6. Homologation & Side Chain Extension Methods

6.1. Homologation

In 1998, Lipshutz et al. designed a route to install a one carbon functional handle at the C3 position to enable the synthesis of a wide variety of MK-derivatives [90]. Menadione 1 was reacted with formaldehyde and hydrogen chloride gas to form 3-chloromethylene menadione 76 in 87% yield (Scheme 28). The introduction of the chloromethyl group allows for reactions that were previously less approachable, like S_N2 substitutions and organometallic cross-couplings. Using 3-chloromethylene menadione 76 as the starting material, the authors used Negishi cross-coupling conditions to take advantage of the stereoselective installation of alkenes based on the configuration of the organoalane species [91–94]. For example, phytyl alkyne 79 underwent Negishi carboalumination to form organoalane 77 (Scheme 29). Vitamin K_1 and MK-3 were synthesized using this method (Scheme 28). For the synthesis of vitamin K_1, 3-chloromethylene menadione 76 was coupled with phytylalane 77 in the presence of the nickel catalyst which is formed in situ using nickel (II) chloride, triphenylphosphine, and n-BuLi. Vitamin K_1 was formed in 88% with exclusively E configuration. MK-3 was prepared similarly, but instead with farnesylalane 78, in 93% yield with E configuration at the α-isoprene double bond.

![Scheme 28](image)

Scheme 28. Synthesis of MK-3 and vitamin K_1 via C3 homologation and Negish cross-coupling conditions [90].

![Scheme 29](image)

Scheme 29. Negishi carboalumination of phytyl alkyne [91–94].

In 2015, Mehta et al. published a patent covering the synthesis of stereospecific quinone derivatives [95]. Therein, the authors described methods used for the synthesis of the various lengths of prenyl side chains using a series of homologation and side chain extension reactions featuring stereoselective alkenes syntheses, such as Wittig, Horner-Wadsworth-Emmons, and Still-Gennari. For the synthesis of MK-7, 1,4-dimethoxynaphthoquinol 18 reacted with dichloro(methoxy)methane and TiCl_4 to form the C3 aldehyde 80 in 95% yield (Scheme 30). Wittig homologation of 80 was achieved using ylide 81 followed by mild acid hydrolysis to form aldehyde 82. Using phosphonate ester 83, aldehyde 82 underwent a Horner-Wadsworth-Emmons reaction to form the desired E alkene in 85% yield. The authors noted the use of Still-Gennari conditions for the synthesis of the Z alkene where appropriate. The ester was reduced to the alcohol using DIBAL-H in 91% yield, and then
immediately oxidized to aldehyde 84 using PCC in 88% yield. The resulting aldehyde 84 was protected as dithiane 85 in 94% yield. Deprotonation of the methine hydrogen of 85 with n-BuLi created a stable anionic nucleophile. Farnesylfarnesyl bromide 86 was used to form the C3-alkylated product in 83%.

The dithiane protected carbonyl was deprotected using Dess-Martin periodinane and then reduced using Wolff-Kishner conditions, producing the hydrocarbon prenyl side chain in 82% yield over two steps. Oxidation with CAN formed MK-7 in 80% yield. The authors achieved the synthesis of MK-7 in two different iterations: (1) when the entire chain was added in one step (Scheme 30), and (2) when the side chain was added on smaller segments using the same methodology, which is similarly used in Masaki et al.’s work in Section 6.2.

**Scheme 30. Synthesis of MK-7 using dithiane anion side chain extensions [95].**

### 6.2. Side Chain Extensions

Another popular method across the literature is the continued functionalization of truncated prenyl chains that were installed using the previously described methods. In 1984, Masaki et al. developed a synthetic route to lengthen the prenyl chain starting with prenyl bromides (Scheme 31) [96,97]. This served as the starting material for the synthesis of vitamin K1 and MK-4. The common electrophiles across all trials were prenyl bromides 92, synthesized in 70–90% yield from the corresponding prenyl alcohols 91 using PBr3 (Scheme 32). For the synthesis of vitamin K1 (Scheme 31), prenyl bromide 87 was coupled to tosylate 88. Deprotonation of the tosylate methine hydrogen created a stable anion to attack 87 to form the alkylated product 89 in 72% yield. Removal of the tosyl group was achieved using modified Bauvault-Blanc desulfurization conditions in 70% yield. Deprotection of tosylate 89 obtained 90 in 70% yield, and thus vitamin K1 was produced in 70% yield in the presence of CAN. For the synthesis of MK-4, Masaki et al. approached the synthesis with two different iterations (Scheme 33). Starting with benzyl ether protected polypropyl bromide 93a and 93b, the same alkylating conditions were used to extend the chain using tosylates 94a and 94b to form products 95a and 95b in 86% and 87% yield, respectively. Desulfurization of the prenyl chain produced the hydrocarbon side chain of MK-4 in 68–73% yield. The authors noted HPLC analysis showed isomeric byproducts in 5–7%, likely formed during the desulfurization step.
This reaction yielded 90% over two steps with 93:7
installed using the organocuprate reagent formed with hexahydrofarnesyl bromide 97, performing a SN2 substitution with the ester protecting group, forming the extended side chain in 51–79% yield. In contrast to Masaki et al.’s approach with tosylates, Schmid et al. used organocuprate reagents as nucleophiles to install the remaining hydrocarbon chain for vitamin K1 [63]. Installation of the first prenyl group was achieved via coupling of organocuprate reagent of bismethyl ether 2-bromomenadiol 6 with isoprene oxide in a 1,4-addition (Scheme 34). The resulting alcohol was protected as ester 96. This reaction yielded 90% over two steps with 93:7 E/Z configuration. The rest of the phytol chain was installed using the organocuprate reagent formed with hexahydrofarnesyl bromide 97, performing a SN2 substitution with the ester protecting group, forming the extended side chain in 51–79% yield. Oxidation of the ring was achieved with CAN with 77–86% yield to form vitamin K1.
Scheme 34. Synthesis of vitamin K₁ using organocuprate reagents to extend the length of the side chain [63].

6.3. Summary

Homologation and side chain extension methods comprise a separate category from the others despite the use of similar techniques because they provide a functional handle that enables more diverse reactions that were previously less accessible. Homologation describes the addition of one carbon-containing group to the C3 position, which is then further functionalized to synthesize the rest of side chain. Side chain extension methods have one or two isoprene units attached to the ring which were installed using previously described methods to then add the remainder of the chain using a different method, allowing for continued iterative additions. The advantages and disadvantages of each method have been outlined in Table 9. Nearly all described methods produced moderate to high yields throughout all steps, except for the organocuprate substitution demonstrated by Schmid et al., which produced low yields compared to the rest of the synthesis. Regiocontrol for these methods was achieved by the preinstalled carbons or prenyl chains connected to the ring which make the subsequent reactions chemoselective. Stereoretention of the α-isoprene double bond was achieved in three ways: (1) using stereospecific methodology, like Negishi carboalumination and cross-coupling; (2) stereoselective alkene syntheses; and (3) taking advantage of the stereochemical outcome of SN₂ substitutions.

Table 9. Summary of homologation and side chain extension methods.

| Methods                              | Advantages                                                                 | Disadvantages                                |
|--------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------|
| Section 6.1. Homologation            |                                                                             |                                               |
| Lipshutz et al. Homologation to Negishi Cross-Coupling [90] | - High yields throughout the synthesis (87-93%)                             | - Requires the use of hydrogen chloride gas   |
|                                      | - Method is applicable to a wide scope of benzo- and naphthoquinones       |                                               |
|                                      | - Stereochemistry of the α-isoprene double bond is defined by the configuration of the organoalane |                                               |
|                                      | - Regiocontrolled by the installation of the chloromethyl group at the C3 position |                                               |
|                                      | - No extraneous coordination complex synthesis required                     |                                               |
|                                      | - 3 step synthesis (including starting material)                            |                                               |
Table 9. Cont.

| Methods | Advantages | Disadvantages |
|---------|------------|---------------|
| Mehta et al. Stereoselective Alkene Syntheses [95] | -High yields throughout the synthesis for all reported steps (80–95%) -Strict use of stereoselective alkene syntheses -Methodology is applicable to full side chain extensions and smaller segments | -Requires the use of protecting groups and oxidation manipulations -11 step synthesis (not including starting material) |
| Masaki et al. Tosylate Substitution [96,97] | -Moderate to high yields throughout the synthesis (68–90%) Stereoretention of the α-isoprene double bond with minor isomerization (5–7%) Methodology is applicable to full side chain extensions and smaller segments | -4 step synthesis (not including starting material) |
| Schmid et al. Organocuprate Substitution [63] | -Achieved regio- and stereocontrol using isoprene oxide in a 1,4-addition Stereoretention of the α-isoprene double bond (97:3) Iterative methodology | -Low to moderate yields (51–79%) for alkylation step -4 step synthesis (not including starting material) |

7. Conclusions

Menaquinones are a biologically important class of isoprenoid compounds that comprise of a methylated naphthoquinone unit and an isoprene side chain of various lengths and levels of saturation. The intrinsic hydrophobicity of these compounds makes it exceedingly difficult to analyze the activity in aqueous-based in vitro assays and growth studies. The moderately water soluble, truncated derivatives, MK-1 through MK-3, have made it possible to test and measure the activities of these compounds, especially in membrane-associated proteins. The most popular method used to synthesize menaquinones and derivatives has been BF$_3$·OEt$_2$-catalyzed Friedel-Crafts reaction. This reaction typically occurs over two steps from commercially available starting material, but it generally produces low yields and a mixture of isomers. Although Friedel-Crafts alkylation is the conventional, concise method, in this review we aimed to compile and evaluate syntheses of menaquinones from all the literature to summarize the advantages and disadvantages of each route based on overall yield, regioselectivity, and stereoretention of the α-isoprene double bond, as shown in Tables 4 and 6–9.

We further evaluated the reactions to consider the number of steps in the synthesis, minimization of side reactions, and overall safety to highlight one representative method in each category, as outlined in Table 10. With examination of Table 10, it is possible to compare the syntheses across different approaches. As a representative of the nucleophilic ring methods, Swenton and coworkers were chosen for the clean use of electrolysis to protect the quinone as bismethyl ketals. Simple acid hydrolysis deprotection of the ketals reformed the carbonyls of the quinone without oxidizing agents. As a representative of the metal-mediated and radical reactions, Liebeskind et al. were chosen for the easily synthesized cobalt complex and internal alkynes. The updated cobalt complex was found to be more tolerant toward a wide scope of Lewis acid catalysts, and, as a result decreased the amount of catalyst required to synthesize the product. Rüttimann and Büchi designed an auxiliary-directed Diels-Alder reaction using commercially available materials, cyclopentadiene and menadione. Alkylation of the adduct occurred chemoselectively, and then facile retro-Diels-Alder formed the desired product in high yields and excellent regioselectivity. Lipshutz et al. used homologation and Negishi carboalumination and cross-coupling as side chain extension methods to attach the prenyl side chain. The stereochemistry of the α-isoprene double bond was easily installed using Negishi carboalumination of the corresponding terminal alkynyl. Finally, the representative electrophilic ring strategy was done in one synthesis of menaquinones using Michael additions was presented. The method developed by Naruta and Maruyuma retained the stereochemistry of α-isoprene double bond but was not regioselective due to competing 1,2- and 1,4-addition mechanisms.
Table 10. Summary of the best reactions within each strategy to be compared to each other.

| Strategy-                     | Advantages                                                                                                                                  | Disadvantages                                                                                       |
|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| **Nucleophilic Ring**        | -Unique use of electrolysis as a protection method                                                                                           | -Lithium organocuprate nucleophile only used one of two bisketals rings—poor atom economy           |
| 2.2. Transmetalation         | -High yields for all reported steps (≥85%)                                                                                                  | -Difficult purification because of unreacted starting materials                                    |
| Swenton and coworkers        | -Regiocontrol through lithium bromide exchange                                                                                               | -5 step synthesis (not including starting material)                                                |
| Electrolysis and             | -Stereoretention of α-isoprene double bond (≤5% Z alkene estimated)                                                                         |                                                                                                   |
| Lithium Organocuprate [50,51]| -Deprotection of bisketals to menaquinone ring structure via hydrolysis, no oxidation required                                              |                                                                                                   |
| -Unique use of electrolysis  |                                                                                                                                             |                                                                                                   |
| -High yields for all reported steps (≥85%) |                                                                                                                                             |                                                                                                   |
| -Regiocontrol through lithium bromide exchange |                                                                                                                                             |                                                                                                   |
| -Stereoretention of α-isoprene double bond (≤5% Z alkene estimated) |                                                                                                                                             |                                                                                                   |
| -Deprotection of bisketals to menaquinone ring structure via hydrolysis, no oxidation required |                                                                                                                                             |                                                                                                   |
| -5 step synthesis (not including starting material) |                                                                                                                                             |                                                                                                   |
| **Metal-Mediated**           |                                                                                                                                             |                                                                                                   |
| 3.2. Coordination Complex    | -Simple coordination complex synthesis required using commercially available materials                                                    | -The authors did not address α-isoprene double bonds isomerization                                |
| Liebeskind et al.            | -The regiochemistry of the system is controlled by the alkyne 43a and 43b                                                                     |                                                                                                   |
| Cobalt Complex Cycloaddition | -1 step synthesis (not including catalyst)                                                                                                   |                                                                                                   |
| [75]                         |                                                                                                                                             |                                                                                                   |
| **Electrophilic Ring**       |                                                                                                                                             |                                                                                                   |
| 4.1. 1,2- vs. 1,4-Addition   | -Stereoretention of the α-isoprene double bond                                                                                               | -Low yields for both formations (30–48%)                                                           |
| Naruta and Maruyuma          | -Uses commercially available starting materials (menadione and cyclopentadiene)                                                              | -Prominent competition between C2 and C3 alkylation                                               |
| Organostannane               | -High regiocontrol through adduct 66                                                                                                        |                                                                                                   |
| Michael Addition             | -Stereoretention of α-isoprene double bond                                                                                                  |                                                                                                   |
| [81,83]                      | -Cyclopentadiene can be recycled                                                                                                              |                                                                                                   |
| -High yields throughout the synthesis (≥90%) |                                                                                                                                             |                                                                                                   |
| **Pericyclic**               | -Uses commercially available starting materials (menadione and cyclopentadiene)                                                              | -Slight competition between C-alkylation and O-alkylation                                          |
| 5.1. Diels-Alder             | -High regiocontrol through adduct 66                                                                                                        |                                                                                                   |
| Rüttimann et al.             | -Stereoretention of α-isoprene double bond                                                                                                  |                                                                                                   |
| Auxiliary-Directed           | -Cyclopentadiene can be recycled                                                                                                              |                                                                                                   |
| Diels-Alder                  | -High yields throughout the synthesis (≥90%)                                                                                                 |                                                                                                   |
| [43]                         | -Slight competition between C-alkylation and O-alkylation                                                                                     |                                                                                                   |
| **Homologation & Side Chain**| -Method is applicable to a wide scope of benzo- and naphthoquinones                                                                         | -Requires the use of hydrogen chloride gas                                                          |
| Extensions                   | -Stereocchemistry of the α-isoprene double bond is defined by the configuration of the organoalane                                          |                                                                                                   |
| 6.1. Homologation            | -Regiocontrolled by the installation of the chloromethyl group at the C3 position                                                            |                                                                                                   |
| Lipshutz et al.              | -No extraneous coordination complex synthesis required                                                                                       |                                                                                                   |
| Homologation to Negishi      | -Requires the use of hydrogen chloride gas                                                                                                   |                                                                                                   |
| Cross-Coupling [90]          |                                                                                                                                             |                                                                                                   |

Although the methods described in Table 10 are short, high yielding, and selective, there are a few more methods that should be considered if a new synthetic target can accommodate a longer synthesis or the processes in Table 10 are incompatible for the particular target. The homologation method developed by Mehta et al. uses two one-carbon installations at the beginning to synthesize provide a functional handle to stereoselectively install the α-isoprene double bond, and thus can be a strong competitor to the other reactions. Even though many of the methods described have great success using prenyl halides, the reagents are expensive, particularly in comparison to synthesizing MK-derivatives from cheap prenyl alcohols. Saa & coworkers were successful in using commercially available prenyl aldehydes as electrophiles (no distillation necessary). Reduction of the resultant benzyl alcohol was achieved using Birch hydrogenolysis conditions to maintain the stereochemistry of the α-isoprene double bond. Despite the notorious use of Friedel-Crafts alkylations, Schmid et al. discovered a unique intramolecular Friedel-Crafts alkylation beginning with the O-alkylated product using BF$_3$·OEt$_2$. This route adds at two steps, not including synthesis of the starting material and one protecting group, but the additional steps improved the overall yield, as well as the regio- and stereochemistry. Lastly, even though Jacobsen and Torssell only synthesized MK-1, their method...
would most likely tolerate polyprenylcarboxylic acids based on the stereoretentive results of radical coupling with organotellurides reported by Yamago et al.

With respect to Michael additions, the method developed by Naruta and Maruyuma was plagued by competing mechanisms (1,2- vs. 1,4-addition). It appears that alkylstannanes are not chemoselective enough to produce the Michael product for C-C bonds; however, many advancements have been made regarding Michael additions in general, suggesting more regioselective Michael additions may now be available for the synthesis of menaquinone and derivatives. Recently, Michael additions have been successfully used to synthesize C-N bonds using primary amines to form new analogues for biological testing. Recently, Salunke-Gawali and coworkers have used \( n \)-alkylamines and aminophenols to synthesize naphthoquinone derivatives which have been reported to assess their antiproliferative and antibacterial activities \[98,99\]. Salunke-Gawali and coworkers used single crystal x-ray crystallography to determine the structures of these compounds. The incorporation of C-N bonds introduces more hydrogen bonding sites for both intra- and intermolecular interactions. Similarly, Zacconi et al. synthesized naphthoquinone derivatives using benzylamine and 2-phenylethylamine to evaluate their isothermal solubility in supercritical carbon dioxide \[100\]. All these MK-derived compounds were solids, compared to the typical oil produced for the all-C-atoms MK-derivatives. It would be of great interest to synthesize truncated menaquinones with \( N \)-containing isoprenyl side chains and study their redox potentials, solubility, and potential solid-state structure compared to the compounds already reported. However, as demonstrated by this review, many attractive strategies are available that could be used to synthesize potential targets even if specific geometries are required.

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Abbreviations

| Abbreviation | Full Form |
|--------------|-----------|
| β-CD: | β-cyclodextrin. |
| BIHY: | Birch hydrogenolysis. |
| CAN: | Ceric ammonium nitrate. |
| DCM: | Dichloromethane. |
| DIBAL-H: | Diisobutylaluminum hydride. |
| EtOH: | Ethanol. |
| HMDS: | Hexamethyldisilazane. |
| HMDSZ: | Outdated term, hexamethyldisilazane. |
| HMPA: | Hexamethylphosphoramide. |
| HPLC: | High performance liquid chromatography. |
| Hν: | Light. |
| Imid: | Imidazole. |
| LiOt-Bu: | Lithium tert-butoxide. |
| MeCN: | Acetonitrile. |
| MeOH: | Methanol. |
| MK: | Menaquinone, methylnaphthoquinone. |
| NaHMDS: | Sodium hexamethyldisilazane. |
| n-BuLi: | n-Butyl lithium. |
| PCC: | Pyridinium chlorochromate. |
| PPh₃: | Triphenylphosphine. |
| Pyr: | Pyridine. |
| Qt2: | Substitution nucleophilic bimolecular. |
| TBSCl: | Tert-butyl(dimethyl)silyl chloride. |
| t-BuLi: | tert-Butyl lithium. |
| t-BuOH: | tert-Butyl alcohol. |
| t-BuOK: | Potassium tert-butoxide. |
| THF: | Tetrahydrofuran. |

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