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CONSTRUCTION OF CYCLIC ETHER-FUSED TRICYCLIC NAPHTHOQUINONE DERIVATIVES BY INTRAMOLECULAR CYCLIZATION REACTION

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Abstract – Cyclic ether-fused tricyclic naphthoquinones are major pharmacophores because they have attractive biological activities represented by antitumor and antibacterial properties. An enormous number of related compounds have been synthesized especially in the last two decades. The methodology for the construction of its skeleton is roughly classified into two types: 1) intermolecular cyclization of naphthoquinones and alkenes, 2) intramolecular cyclization of functionalized naphthoquinones. From the viewpoint of the reagents, a wide range of them from classical Brønsted acids to Lewis acids including fifth period elements have been applied to construct skeletons. The choice of appropriate reagent and reaction conditions against the substrate is the key to accomplishing the regio- and/or stereo-selective synthesis of these compounds, though it seems difficult at first glance to decide how because numerous numbers of actual examples have been presented. Therefore, in this review, we have decided to summarize the methods of constructing the tricyclic naphthoquinones limited by type 2 reactions while systematically classifying the substrates and reagents.

DEDICATION

Authors dedicate this article to prof. Kiyoshi TOMIOKA as honor of his 70th birthday.

CONTENTS

1. INTRODUCTION

Naphthoquinone, classified as 1,2-naphthoquinone (1,2-NQ) and 1,4-naphthoquinone (1,4-NQ), is a ubiquitous organo-cyclic compound. Numerous natural products including naphthoquinone skeleton represented by lawsone and Vitamin K have been found, and they are widely applied in the fields of

dyes,[1] functional materials,[2] agrochemicals,[3] and medicinal chemistry.[4] Although several reviews have been published focusing on the construction of the naphthoquinone framework,[5] there are no examples of articles which totally cover this area because a huge number of actual methodologies have been presented. Among naphthoquinones, cyclic ether-fused tricyclic naphthoquinone derivatives (TNQs) are recognized

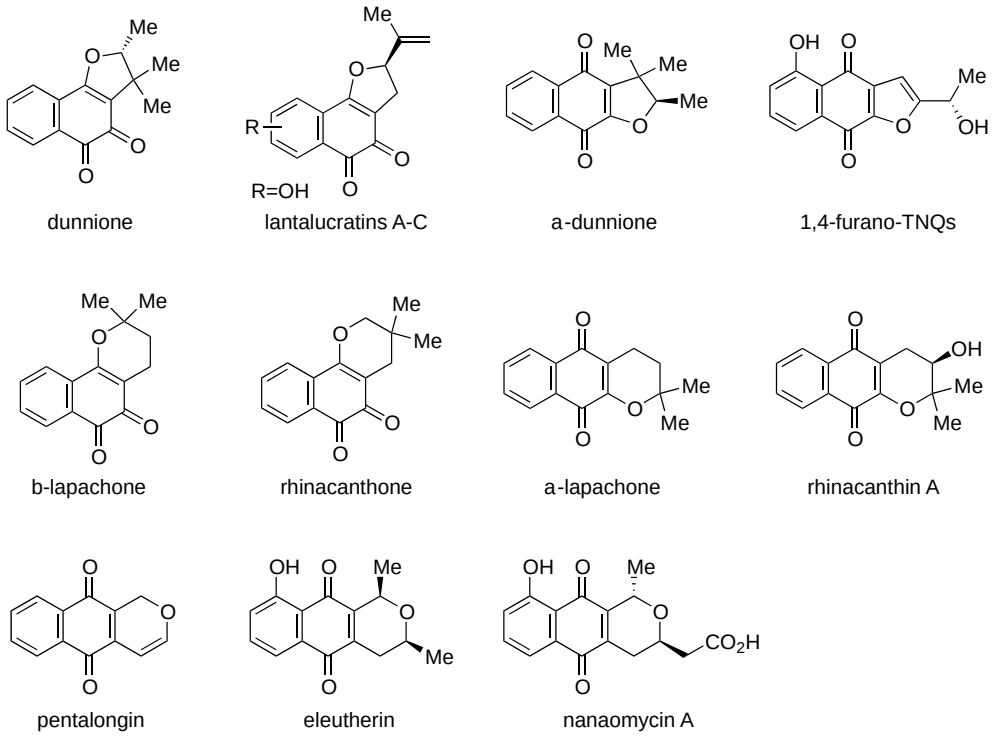
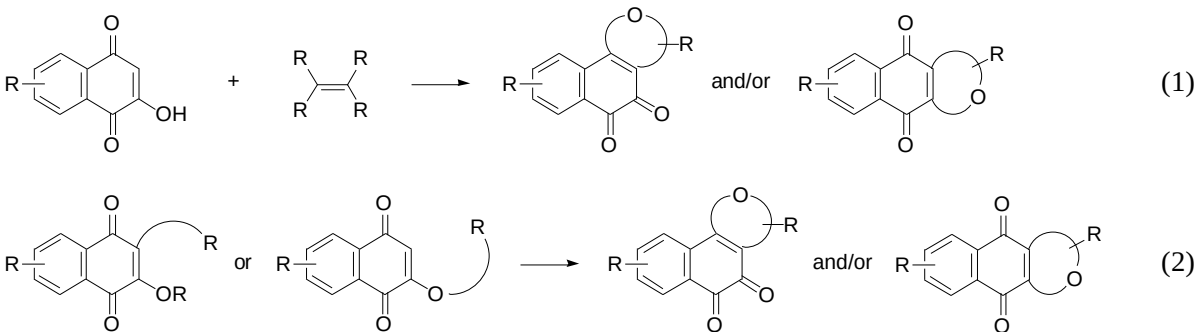


Chart 1. Representative biologically active natural products including TNQ skeletons

as an important pharmacophore due to its potential of various remarkable biological activities, e.g. antitumor, antibacterial, and dementia-related.[6] In addition, there are many biologically active natural products including TNQ skeletons as illustrated in Chart 1.[7] These major compounds have been derivatized by many research groups in the field of medicinal chemistry. A general chemical synthetic route toward TNQs is roughly classified into two types as shown in the following equations:



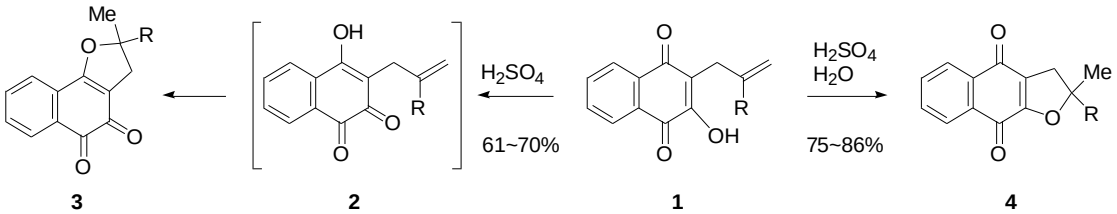
In eq (1), TNQs are constructed by intermolecular cyclization using 2-hydroxy-1,4-naphthoquinones and alkenes (alkynes). In the latter type, as shown in eq (2), TNQs are constructed by intramolecular cyclization starting from 3-substituted 2-alkoxy-1,4-naphthoquinones or 2-alkoxy-1,4-naphthoquinones. In both types, the cyclic ether moiety was made at the end of the synthesis in most cases. The reagents that were used for cyclization are diverse and many examples of the synthesis of each type have been reported mainly during the past three decades. In this article, we summarize the methods to construct the cyclic ether-fused tricyclic naphthoquinones by limiting them to intramolecular cyclization reactions. The following sections are classified by the feature of reagent that was utilized for the cyclization reaction.[8]

2. BRØNSTED ACID PROMOTED CYCLIZATION

Brønsted acid is the most commonly used reagent for cyclization to construct the cyclic ether moiety of TNQs. In this section, the reagents are classified into three sections (2.1–2.3) based on the application frequency.

2.1. H_2SO_4

Sulfuric acid is the most frequently used reagent to form TNQs by intramolecular cyclization reaction. In 1982, Valderrama and collaborators reported intramolecular cyclization of 3-hydroxyalkyl-1,4-naphthoquinone utilizing sulfuric acid (details are described in 2.1.2).[9] About two decades later, Kongkathip and collaborators reported an obvious explanation of this type of reaction including a reaction mechanism (Scheme 1).[10] Namely, substrates **1** were cyclized selectively to form 1,2-TNQs (**3**) utilizing concentrated H_2SO_4. On the other hand, 1,4-TNQs (**4**) were obtained as a sole product under aqueous conditions. They explained the regioselectivity by the difference in the reaction intermediates. Under the former condition, tautomerization of **1** occurs first to generate intermediates **2** in the presence of concentrated sulfuric acid, whereas under the latter condition, protonation of olefin occurs faster than protonation of carbonyl group of **1**.



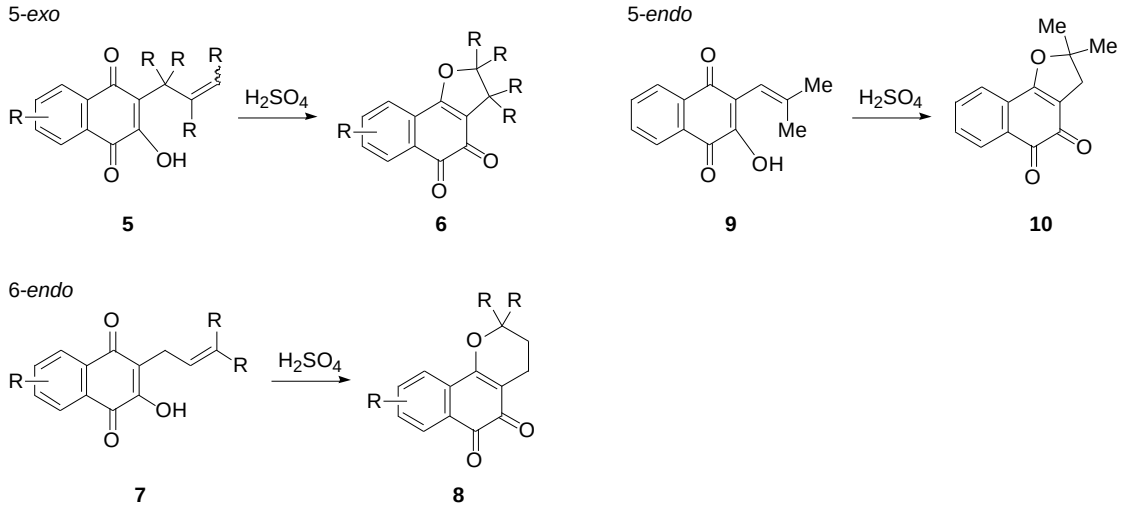
3 2 1 4

Scheme 1. H_2SO_4 Promoted regioselective cyclization of alkenyl 1,4-NQs **1**

2.1.1. Concentrated H_2SO_4

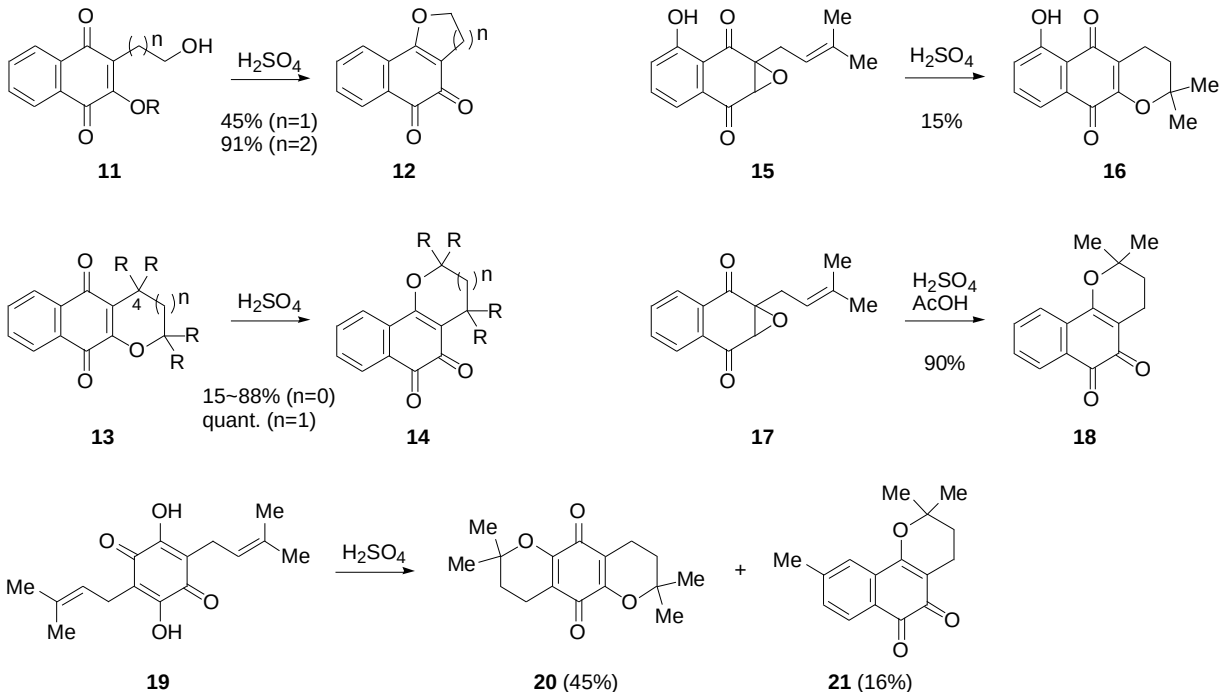
The reactions utilizing concentrated H_2SO_4 have been applied for various alkenyl 1,4-NQs, and the reported examples are summarized in Scheme 2. The substrates can be classified into three types

depending on the course of cyclization. The substrates **5**, containing an allylic side chain with mono-substituent group at the terminal alkene underwent 5-*exo*-*trig* type cyclization to afford **6**.[11–19] On the other hand, the reaction was dominated 6-*endo*-*trig* type cyclization when the substrates **7**, containing allylic side chain with di-substitutent groups at the terminal alkene was utilized.[16,18–38] These differences



Scheme 2. Regioselective cyclization of alkenyl 1,4-NQs utilizing conc. H_2SO_4

can be rationally explained by the stability of the carbocation intermediate. The substrates **9** containing a vinyl side chain underwent 5-*endo*-*trig* type cyclization.[16,17,19,25,30,32,35,37,39] Concentrated H_2SO_4 is also

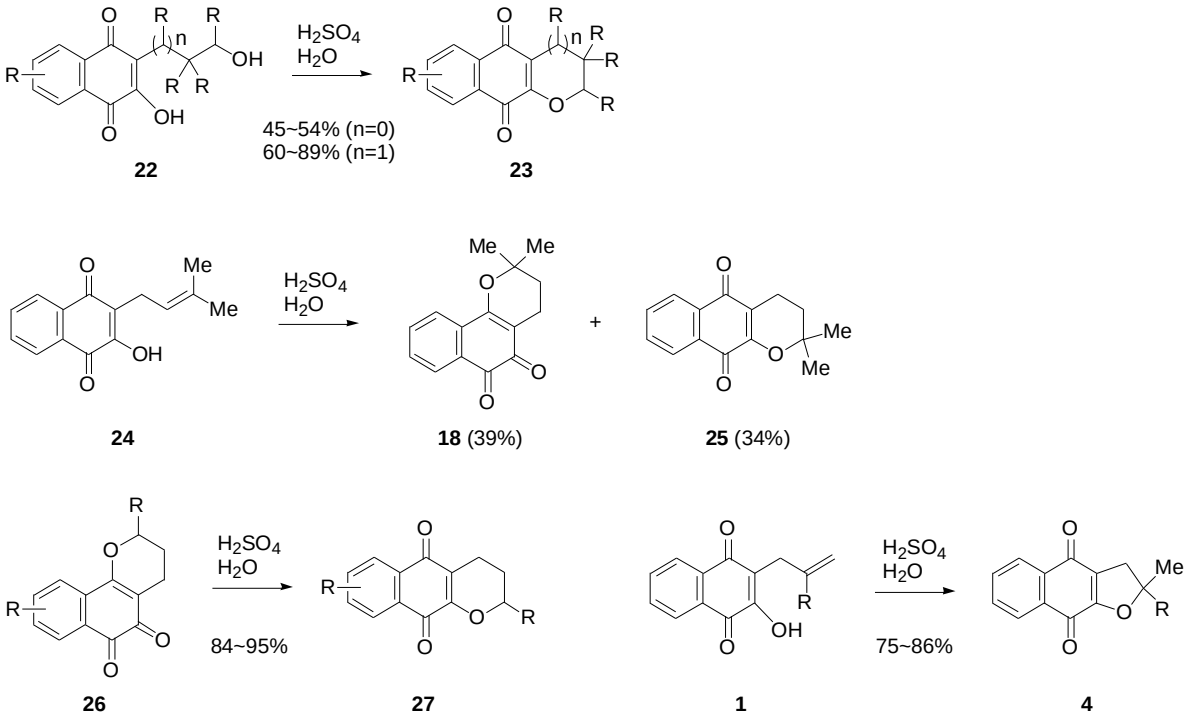


Scheme 3. Regioselective cyclization of various substrates utilizing conc. H_2SO_4

utilized to construct the corresponding TNQs from various kinds of substrates (Scheme 3). 1,4-NQs containing a hydroxyalkyl side chain (**11**) were selectively cyclized to afford 1,2-TNQs (**12**).[10,40] TNQs (**13**) can be transformed into **14** by the treatment of concentrated H_2SO_4, and this phenomenon indicates that there is an equilibrium relationship between 1,2-TNQs and 1,4-TNQs under acidic conditions.[41–43] In addition, a rearrangement occurs during the isomerization process if the substrates **13** contain a quaternary carbon atom at 4-position.[42] 1,4-NQ related compounds (**15** and **17**) which involve oxiranyl moiety underwent cyclization to obtain **16** and **18**, respectively, and the regioselectivities of these products depend on the reagents and substituent group of the substrates.[44,45] A symmetric dihydroxybenzoquinone **19**, containing two alkenyl substituents underwent dual cyclization to yield **20**, and unexpected 1,2-TNQ (**21**) was also obtained as a minor product via air oxidation.[46]

2.1.2. Aqueous H_2SO_4

The reactions utilizing aqueous H_2SO_4 have been applied to various alkenyl 1,4-NQs, and the reported examples are summarized in scheme 4. In an early study, hydroxyalkyl 1,4-NQs (**22**) were found to be cyclized in the presence of aqueous H_2SO_4 under heated conditions.[9] The same type of reactions were reported thereafter.[10,47] Similar reaction with different substrate **24** has also reported, and in this case, the product became a mixture of 1,2-TNQ (**18**) and 1,4-TNQ (**25**).[45,48] The transformation of 1,2-TNQs (**26**) into 1,4-TNQs (**27**) has been reported,[49–51] and the results were completely different from the reaction utilizing concentrated H_2SO_4. The reaction of *exo*-alkenyl 1,4-NQs (**1**) underwent 5-*exo*-*trig* type

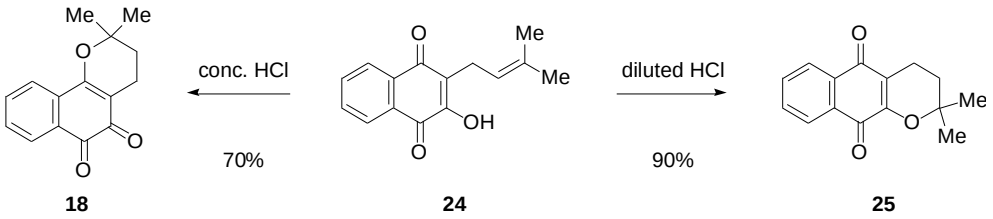


Scheme 4. Cyclization of various substrates utilizing aqueous H_2SO_4

cyclization to afford five-membered 1,4-TNQs (**4**) as a sole product in good yields.[10]

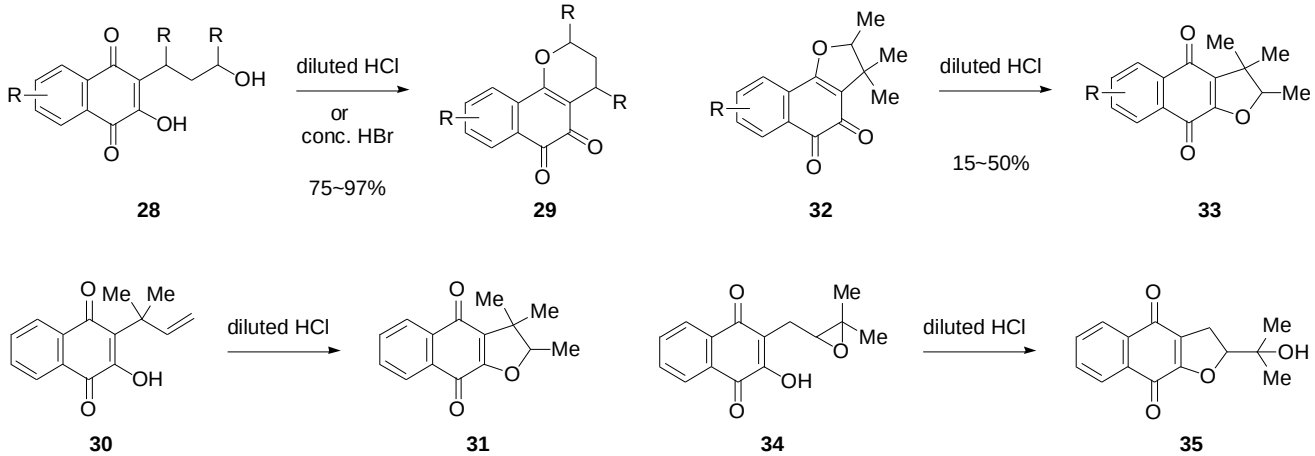
2.2. Hydrogen halides

Hydrogen halides, especially for hydrochloric acid, have been utilized for cyclization of many 1,4-NQs. There are similarities in the cyclization of 1,4-NQs utilizing H_2SO_4 as a reagent (Scheme 5). Namely, 1,4-NQ (**24**) is selectively converted to 1,2-TNQ (**18**) in the presence of concentrated HCl,[27] while the reaction occurs in a different pathway to afford 1,4-TNQ (**25**) under more diluted conditions.[52,53]



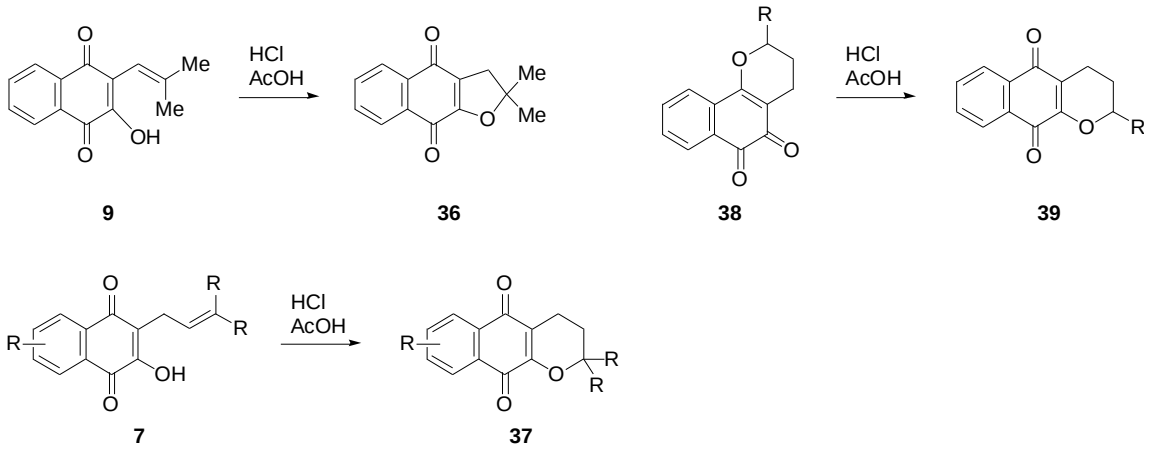
Scheme 5. HCl Promoted regioselective cyclization of alkenyl 1,4-NQ (**24**)

Reported examples of HCl promoting cyclization of various substrates are summarized in scheme 6. 1,4-NQs (**28**), which include the alkoxyalkyl group, were cyclized to afford 1,2-TNQs (**29**) by the treatment of diluted hydrochloric acid[27,50] or concentrated hydrobromic acid.[9] In this case, the regioselectivity of cyclized adduct is the same regardless of the kind of hydrogen halides utilized. By the treatment of diluted HCl, 1,4-NQ (**30**) and 1,2-TNQs (**32**) are converted to 1,4-TNQs (**31**[53] and **33**[42]), respectively, and the trend of these reactions are similar as in the case of aqueous H_2SO_4. Diluted HCl smoothly promotes the ring opening of epoxide moiety of 1,4-NQ (**34**), and subsequent 5-*exo*-*trig* type cyclization occurs to afford alkoxyalkylated 1,4-TNQ (**35**).[54]

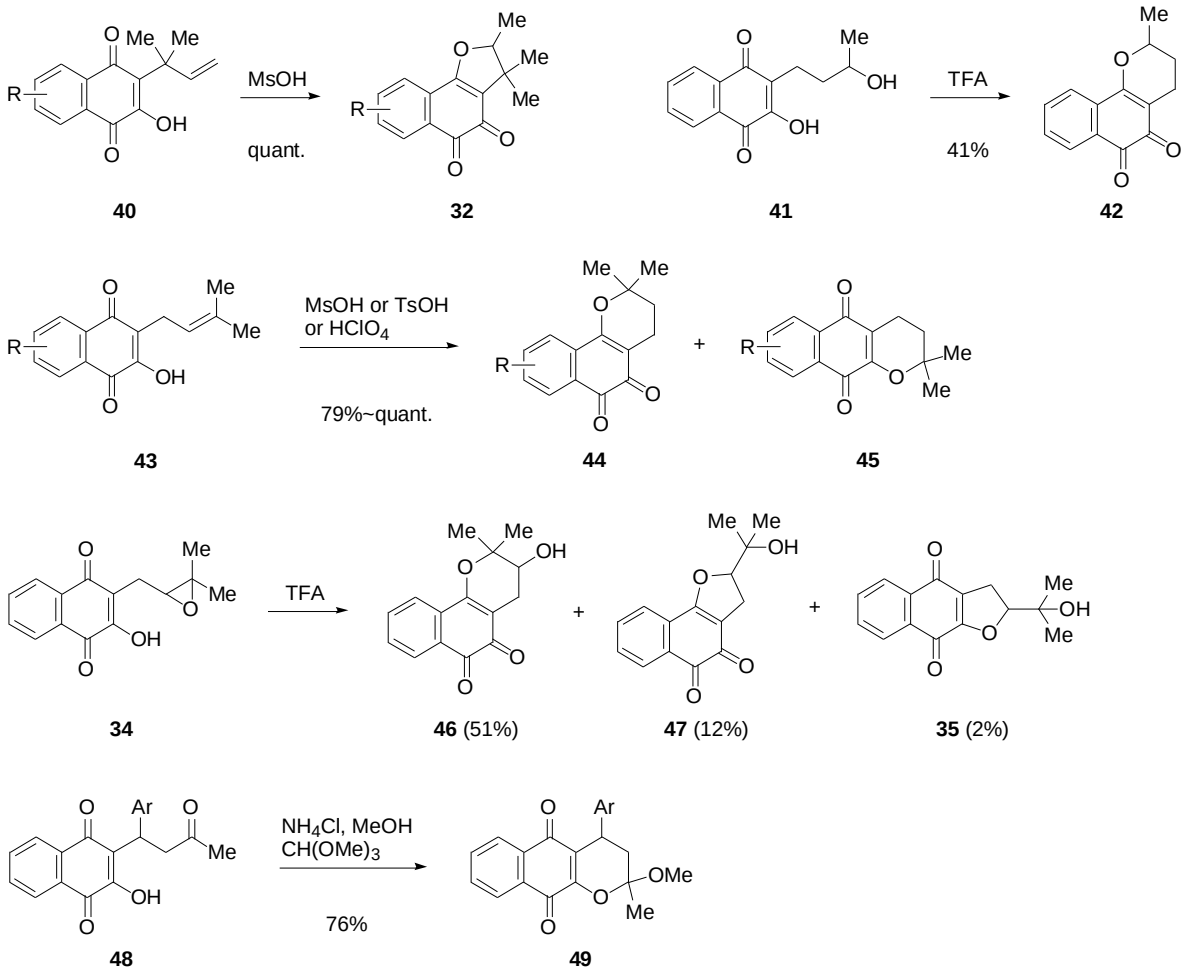


Scheme 6. Cyclization of various substrates utilizing HCl

1,4-NQs, and the reaction occurs in the same course as in the case of utilizing diluted HCl (Scheme 7). 1,4-NQs (**7** and **9**), and 1,2-TNQs (**38**) are converted into the corresponding 1,4-TNQs (**36**,[33,55,56] **37**,[31,33,36,55,57–59] and **39**[51]), respectively under the aforementioned conditions.



Scheme 7. Cyclization of various substrates utilizing HCl/AcOH



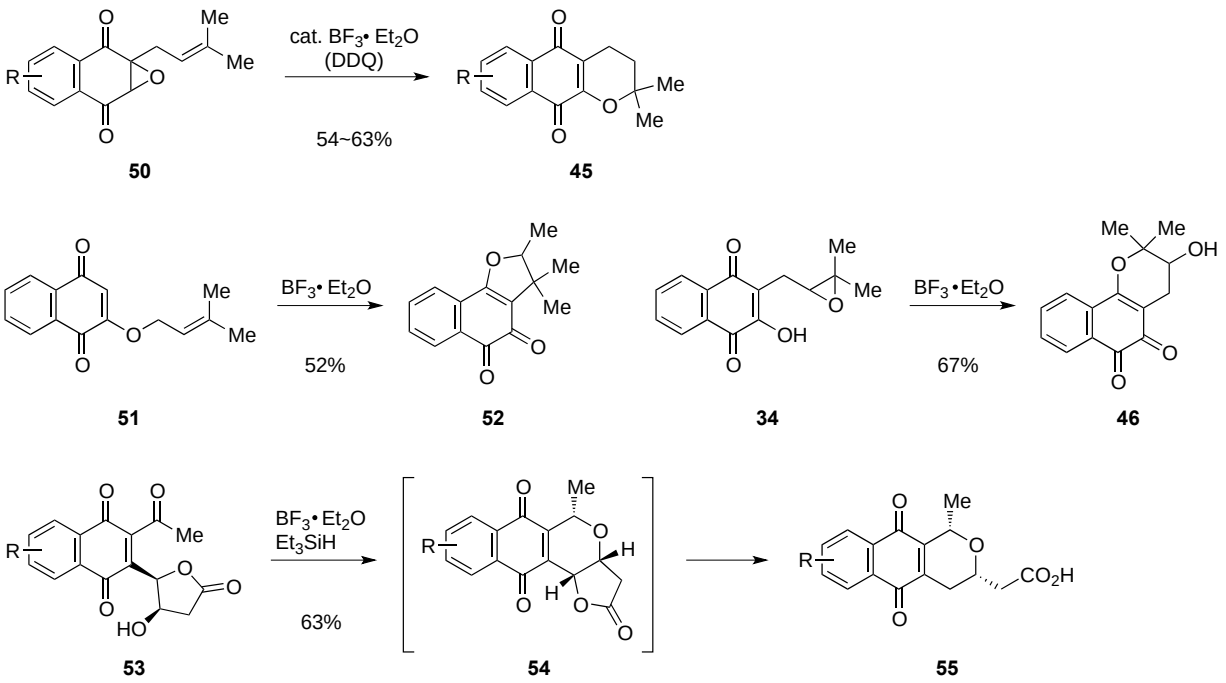
Scheme 8. Cyclization of various substrates utilizing other Brønsted acids

2.3. Other Brønsted acids

Other kinds of Brønsted acids, besides H_2SO_4 and hydrogen halides, have been also utilized for cyclization of various 1,4-NQs. The summary of reported examples is described in Scheme 8. Organosulfonic acids, such as methane sulfonic acid (MsOH), *p*-toluene sulfonic acid (TsOH), and trifluoroacetic acid (TFA) are often utilized for this type of cyclization. Regioselective cyclization occurred by the treatment of *exo*-alkenyl 1,4-NQs (**40**) with MsOH,[42] and by the treatment of alkoxyalkyl 1,4-NQ (**41**) with TFA,[51] respectively. The product ratios of 1,2-TNQs (**44**) and 1,4-TNQs (**45**) are variable depending on the substituent groups and reaction conditions when the cyclization of 1,4-NQs (**43**) was carried out in the presence of MsOH,[60] TsOH,[61] and $HClO_4$.[60] By the treatment of epoxy-1,4-NQ (**34**) with TFA afforded a mixture of TNQs (**35**, **46**, and **47**).[18] There is an example of weak acid promoted cyclization of 1,4-NQs (**48**) that was reported by Valderrama and collaborators in 1984.[62] By the treatment of 1,4-NQ (**48**) with a mixed reagents of ammonium chloride, methanol, and trimethyl orthoformate, 1,4-TNQs (**49**) were obtained by the formation of cyclic ketal.

3. LEWIS ACID PROMOTED CYCLIZATION

Lewis acids are versatile reagents for the cyclization of variety sort of substrates to construct TNQs. In most cases, a stoichiometric amount of Lewis acid was utilized, and in general, 1,4-TNQs are obtained as a major product by the usage of stoichiometric amount of these Lewis acids. On the other hand, 1,2-TNQs are mainly obtained by the usage of catalytic amount of Lewis acids. The factors of the regioselectivity in



Scheme 9. Cyclization of various substrates utilizing $BF_3 \cdot Et_2O$

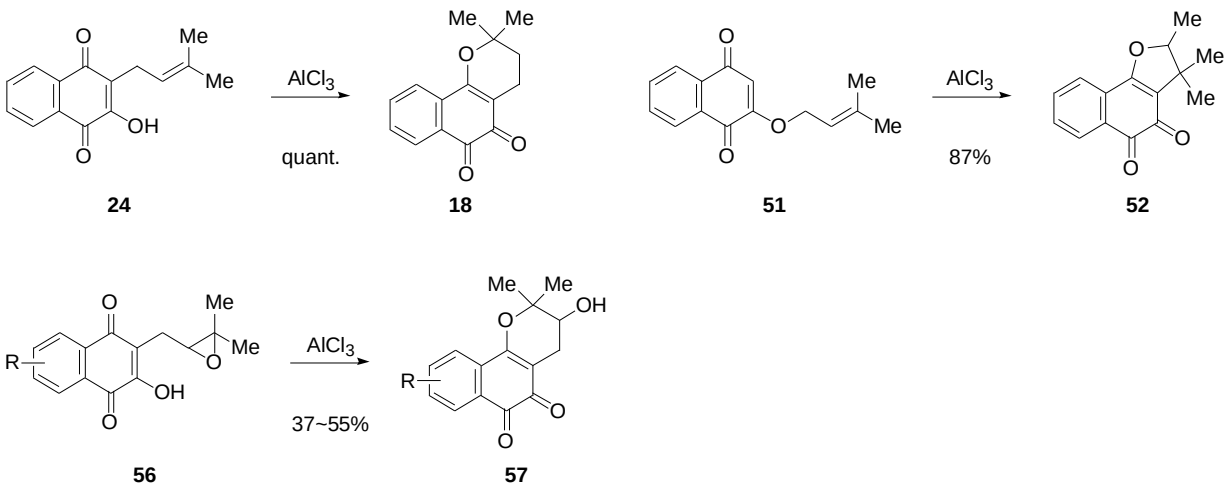
the cyclization are not only the amount of Lewis acid but also the acidity and molecule size. In this section, the reagents are classified into eight sections (3.1–3.8) based on the order of the periodic table of the centre element constituting the Lewis acid.

3.1. $BF_3 \cdot Et_2O$

The reported examples for the formation of TNQs utilizing $BF_3 \cdot Et_2O$ are summarized in Scheme 9. The first example of the application of Lewis acid promoted cyclization of 1,4-NQs was reported by Matsumoto's group in 1985.[44] According to their study, epoxy-1,4-NQs (**50**) can be successfully converted to 1,4-TNQs (**45**) in the presence of catalytic amount of $BF_3 \cdot Et_2O$. In addition, small improvement of the yield was observed when 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was utilized together with $BF_3 \cdot Et_2O$. A method of selective formation of five-membered 1,2-TNQ (**52**) was reported, and the yield of the product was moderate.[63] The cyclization involves two processes, namely, first Claisen rearrangement and second intramolecular 5-*exo* cyclization of terminal alkene. In another case, 6-*endo-trig* type cyclization occurs when epoxy-1,4-NQ (**34**) is treated with $BF_3 \cdot Et_2O$.[64] In 2008, Brimble's group reported a unique methodology for the construction of 1,4-TNQs (**55**) with mixed Lewis acid/reductant system.[65] The reaction of **53** first occurred in the six-membered lactol formation followed by reduction of lactol generate intermediate **54**, and subsequent ring opening of γ–lactone afforded **55**.

3.2. $AlCl_3$

The reported examples for the formation of TNQs utilizing $AlCl_3$ are summarized in scheme 10. In all cases, stoichiometric amounts of $AlCl_3$ were utilized. In the presence of $AlCl_3$, six-membered 1,2-TNQs

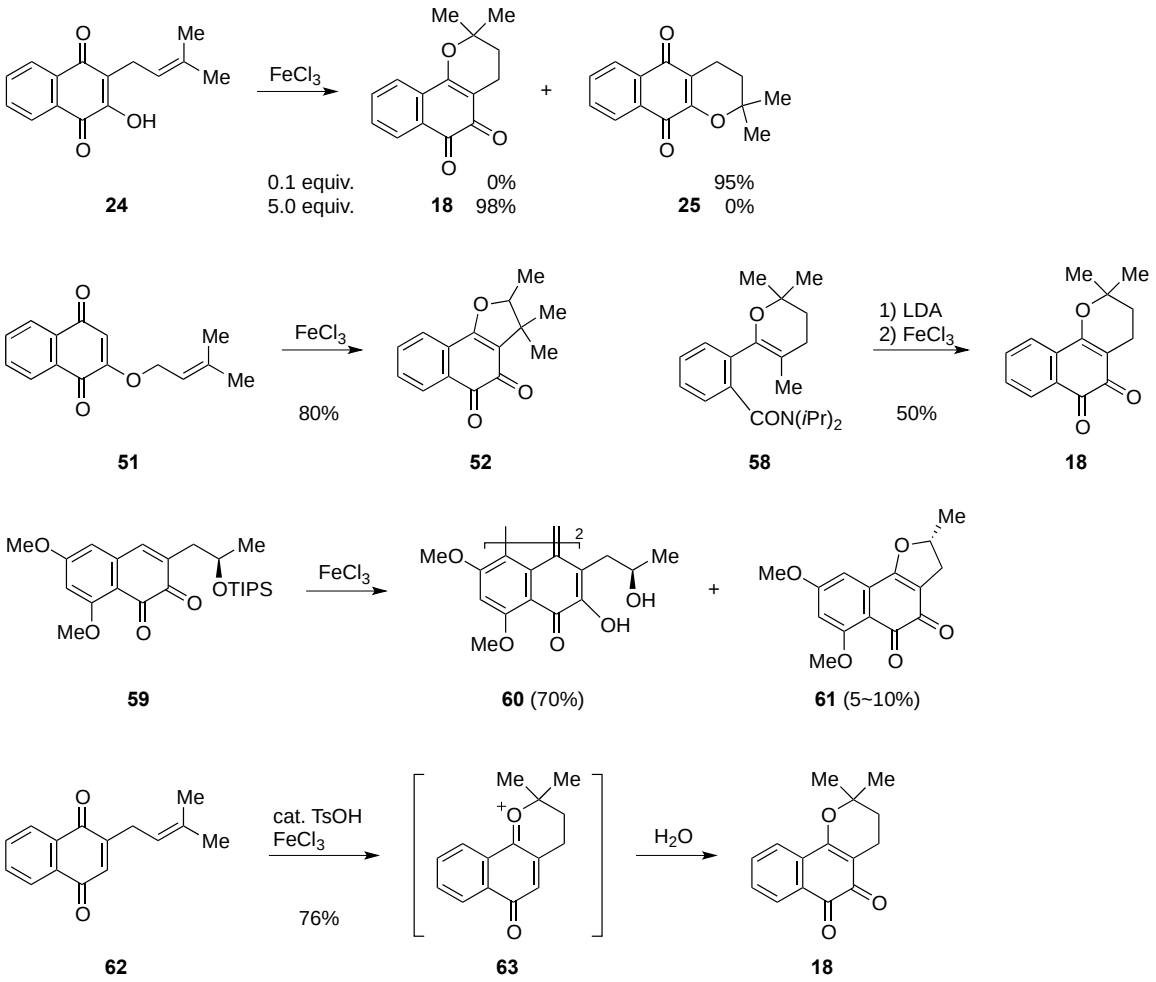


Scheme 10. Cyclization of various substrates utilizing $AlCl_3$

(**18** and **57**) were obtained in moderate to excellent yield from 1,4-NQ (**24**)[66] and epoxy-1,4-NQs (**56**),[18] respectively. $AlCl_3$ promoted five-membered ring formation starting from alkoxy-1,4-NQ (**51**) was also reported.[63]

3.3. $FeCl_3$

The reported examples of the formation of TNQs utilizing $FeCl_3$ are summarized in Scheme 11. In the cyclization of 1,4-NQ (**24**), the regioselectivity was completely regulated by the amount of $FeCl_3$ which was utilized for the reaction. Namely, 1,4-TNQ (**25**) was selectively obtained in the presence of catalytic amount of $FeCl_3$,[43] whereas 1,2-TNQ (**18**) was the only product when the reaction was conducted with the excess amount of $FeCl_3$.[66,67] In the reaction of **51**, **58**, **59**, and **62**, Stoichiometric amount of $FeCl_3$ was utilized. The alkoxy-1,4-NQ (**51**) was able to convert into five-membered 1,2-TNQ (**52**) via Claisen rearrangement.[63] In 2001, Merlic and collaborators treated the 1,2-NQ (**59**) with $FeCl_3$ for the purpose of synthesizing dimer **60**, and five-membered 1,2-TNQ (**61**) was obtained as a side product via an intramolecular oxa-Michael addition reaction.[68] Katoh's group reported a method of constructing 1,2-TNQs which involves intramolecular cyclization-oxidation process.[69] According to their article, 1,4-NQ (**62**) was cyclized to generate intermediate **63** with the treatment of mixed reagent system as shown in Scheme 11, and following oxidation with water afforded 1,2-TNQ (**18**) in good yield. There is



Scheme 11. Cyclization of various substrates utilizing $FeCl_3$

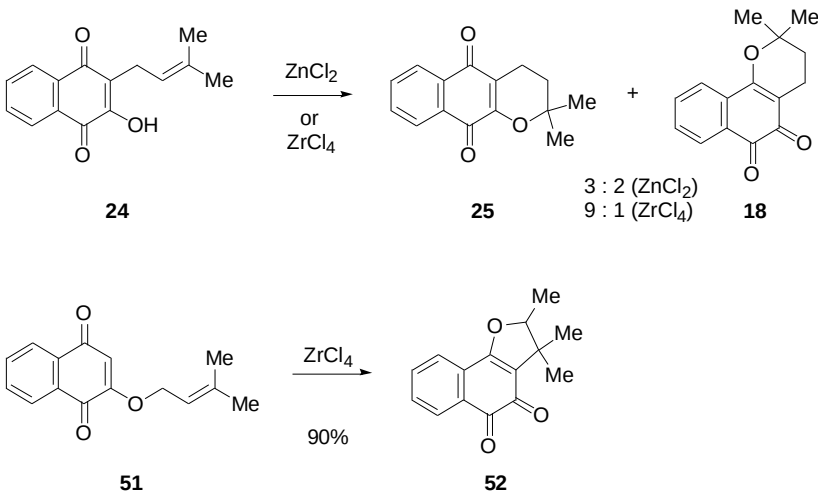
an unusual method for the construction of 1,2-TNQs (**18**) reported by Snieckus and collaborators in 1993.[70] According to their article, the reaction involves two processes. The "remote metalation" occurs at the conjugated methyl group by the treatment of **58** with lithium diisopropylamide (LDA), and subsequent cyclization-oxidation occurs in the presence of $FeCl_3$.

3.4. $ZnCl_2$

$ZnCl_2$ promoted cyclization was report by two research groups and the results are described in Scheme 12. By the treatment of 1,4-NQ (**24**) with stoichiometric amount of $ZnCl_2$, 1,4-TNQ (**25**) was obtained as a major product together with 1,2-TNQ (**18**).[61,66] The regioselectivity was relatively poor in contrast to the other Lewis acids.

3.5. $ZrCl_4$

$ZrCl_4$ promoted cyclization was reported by two research groups and the results are described in Scheme 12. The cyclization of 1,4-NQ (**24**) utilizing a stoichiometric amount of $ZrCl_4$ afforded 1,4-TNQ (**25**) as a major product together with 1,2-TNQ (**18**).[66] In this reaction, the regioselectivity was much better than in the case of $ZnCl_2$, and it was noteworthy that 1,4-TNQ was the major product despite utilizing a stoichiometric amount of Lewis acid. $ZrCl_4$ can be also applied to the cyclization of alkoxy-1,4-NQ (**51**) to obtain 1,2-TNQ (**52**) as a sole product.[63]



24 **25** **18** **51** **52**

Scheme 12. Cyclization of 1,4-NQs **24** and **51** utilizing $ZnCl_2$ or $ZrCl_4$

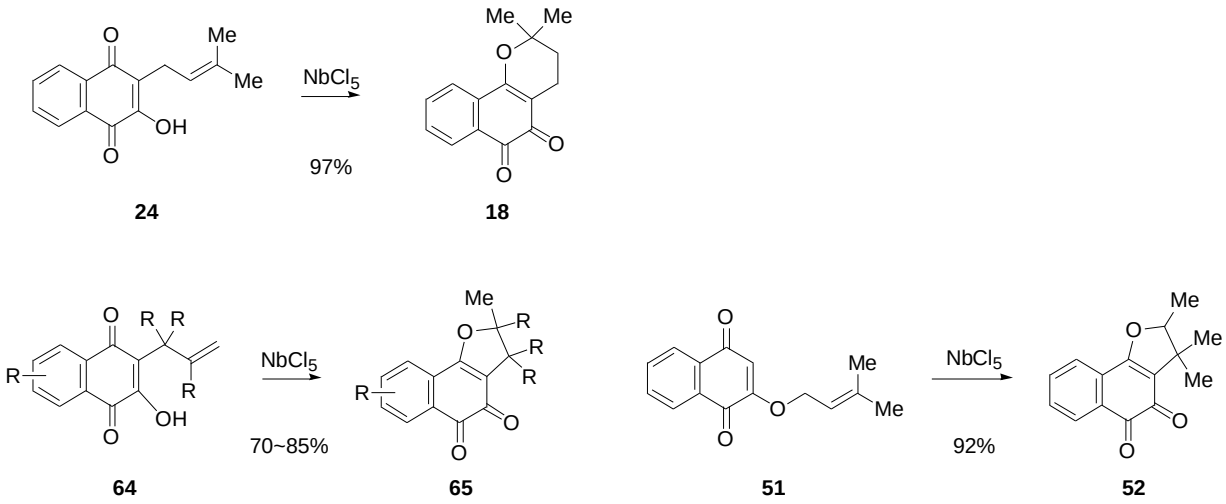
3.6. $NbCl_5$

A study of $NbCl_5$ promoted cyclization of 1,4-NQs was reported by Zhang's group and all examples for the formation of TNQs utilizing $NbCl_5$ are summarized in Scheme 13. As a common reaction condition, 5 equivalents of $NbCl_5$ was utilized to realize the complete regioselectivity and high yield of 1,2-TNQs. 6-*endo-trig* type cyclization of 1,4-NQ (**24**) occurred to obtain 1,2-TNQ (**18**) in excellent yield with complete selectivity.[66] On the other hand, 5-*exo-trig* type cyclzation of *exo*-alkenyl 1,4-NQs (**64**)

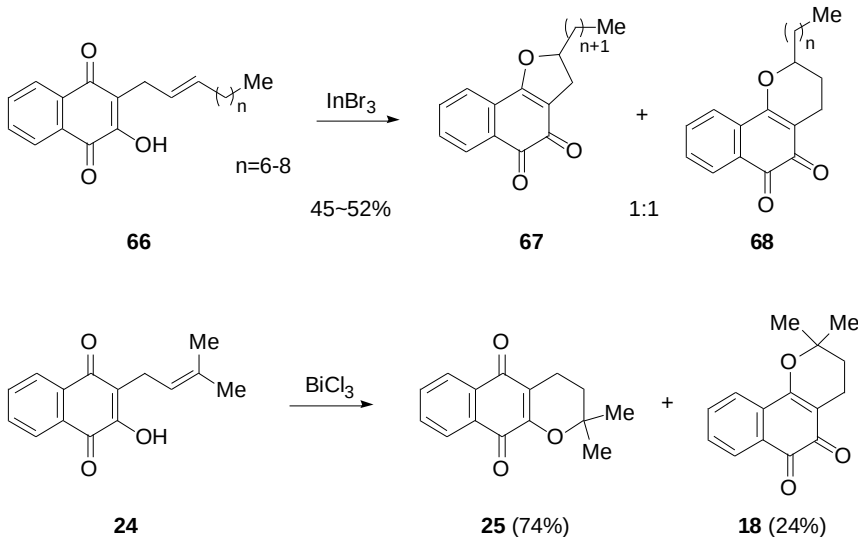
selectively occurred at room temperature to obtain 1,2-TNQs (**65**) in good to high yield.[53,63,71] In contrast to the reactions of **43** and **64**, the cyclization of alkoxy-1,4-NQ (**51**) requires high temperature probably because it involves a Claisen rearrangement.[63]

3.7. $InBr_3$

In 2015, Lima's group reported an example of $InBr_3$ promoted cyclization of 1,4-NQ (**66**) involving a long alkyl side chain (Scheme 14).[72] In the presence of excess $InBr_3$, the cyclization occurred at room temperature to afford a mixture of 5-*exo* and 6-*endo* product (**67** and **68**) in low yield. It was noticed that $InBr_3$ is reusable.



Scheme 13. Cyclization of various substrates utilizing $NbCl_5$



Scheme 14. Cyclization of 1,4-NQs (**24** and **66**) utilizing $InBr_3$ or $BiCl_3$

3.8. $BiCl_3$

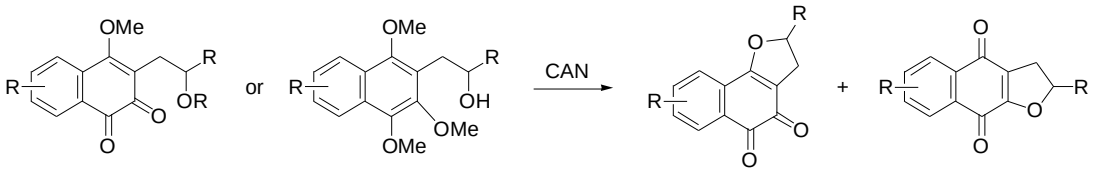
One example of $BiCl_3$ promoting cyclization of 1,4-NQ (**24**) was reported by Zhang's group (Scheme 14).[66] In the presence of excess $BiCl_3$, cyclization occurred at room temperature to afford 1,4-TNQ (**25**) as a major product together with 1,2-TNQ (**18**) in excellent yield with moderate regioselectivity. It seems a similar regioselectivity in the case of utilizing $ZrCl_4$.

4. OXIDANT PROMOTED CYCLIZATION

Conversion of naphthalene derivatives to naphthoquinones has been achieved oxidatively by numerous oxidants. In this section, two types of ring formation pathways are exemplified. One is by the oxidation of hydroxy or alkoxy substituted naphthalene and the subsequent ring closure is by way of nucleophilic addition of oxygen function such as hydroxy groups, and the other is by activation of olefin functions including in the substituents with various oxidants such as *m*-CPBA, H_2O_2, PhI=O, and the subsequent ring closure to form 1,2- or 1,4-TNQs.

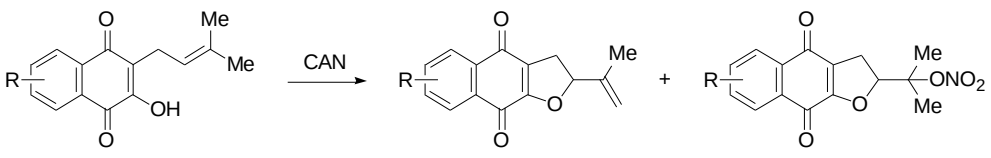
4.1. CAN

In numerous oxidants, cerium diammonium nitrate (CAN) is most frequently used. CAN oxidation of naphthol derivatives including alkoxy naphthalenes ordinarily afford both 1,2- and 1,4-NQs with low selectivity. On the other hand, formation of TNQs by intramolecular cyclization with CAN oxidation often shows fruitful selectivity to form 1,2-TNQs. Kimachi and Ogata's group achieved the highly selective 1,2-TNQs construction utilizing 1,2,4-trimethoxynaphthalene derivatives (2-hydroxy-1,4-naphthoquinone reduced equivalent) with aqueous CAN solution.[73–77] In this reaction, the authors suggest that CAN oxidation initiates the formation of 1,2- or 1,4-NQs unselectively, and then follows a highly stereoselective intramolecular ring closure to form 1,2-TNQs (Scheme 15). Campillo et al. introduced the synthesis of linear furano-naphthoquinones **73** and **74** (1,4-TNQs) with 2equiv of CAN



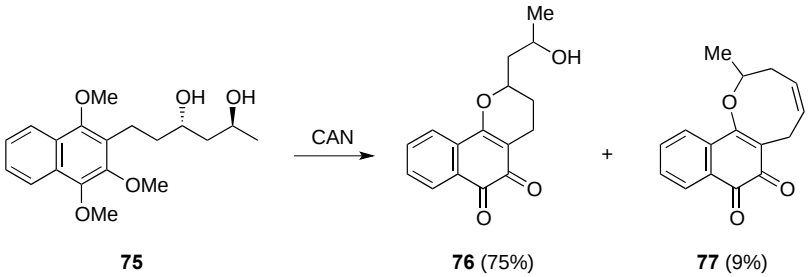
69 **70** **71** (56~84%) **72** (trace)

Scheme 15. Cyclization of **69** and **70** utilizing CAN



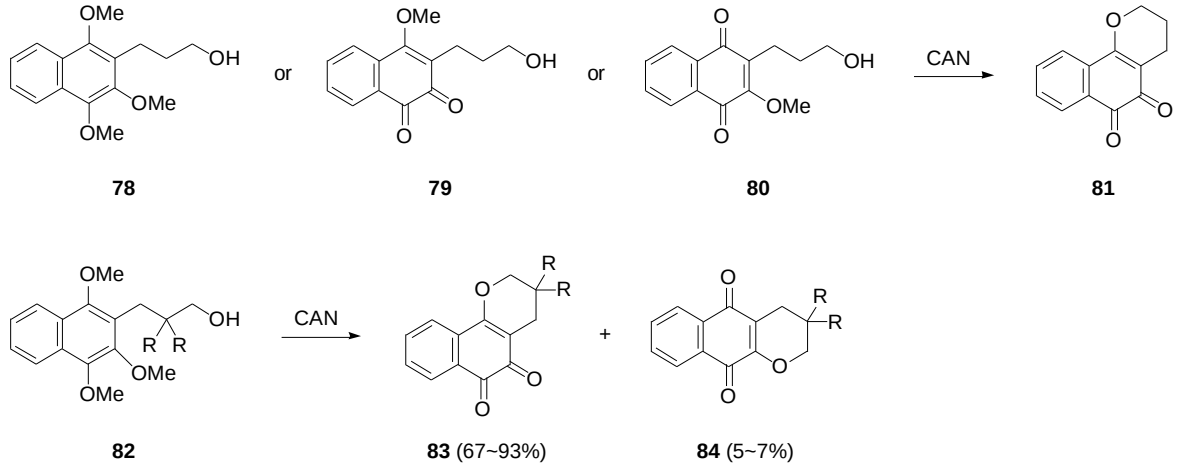
43 **73** (15%) **74** (19%)

Scheme 16. Cyclization of **43** utilizing CAN



Scheme 17. Construction of 1,2-TNQs (**76** and **77**) from trimethoxynaphthalene derivative (**75**) utilizing CAN

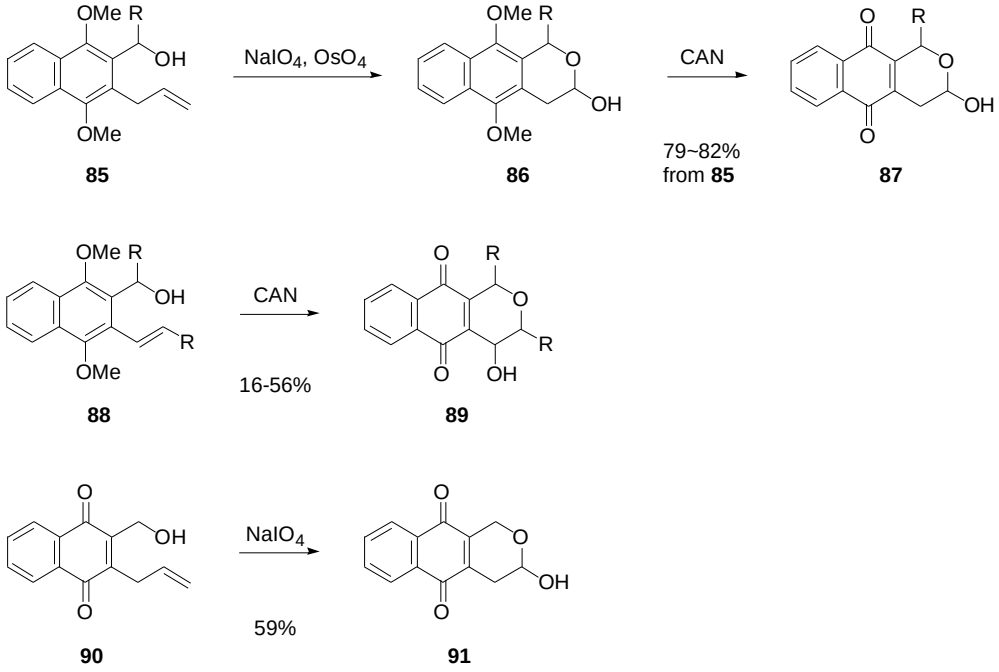
(Scheme 16).[48,78,79] Trialkoxynaphthalenes (**75**) having two or more hydroxy groups in the molecule afford cyclized 1,2-TNQs (**76** and **77**), which the formation of six-membered ring is preferentially observed according to the Baldwin ring closure rules (Scheme 17).[49,51] Hydroxypropyl substituent containing naphthalenes (**78**) or NQs (**79** and **80**), which is an appropriate side chain for the formation of a six-membered ring, obtain pyranonaphtho-1,2-quinone (**81**) same as the result that hydroxyethyl substituent containing substrates afforded furanonaphtho-1,2-quinones. This ring constructing system applied for the total synthesis of biologically active naturally occurring rhinacanthone (**83**: R=Me). The authors achieved a convenient five-step synthesis of target molecule with 78% over-all yield starting



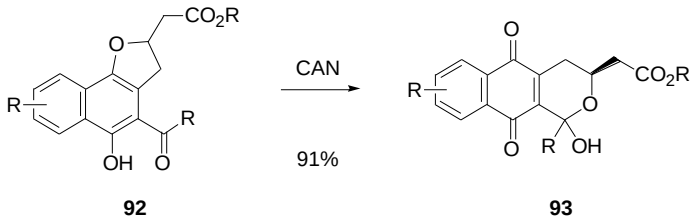
Scheme 18. Cyclization of hydroxypropyl subtituent containing substrates to 1,2-TNQs (pyranonaphtho-1,2-quinones) utilizing CAN

from commercially available 1,2,4-trimethoxynaphthalene (Scheme 18).[75] Pyranol coupled naphthalene compound (**86**) is constructed by a periodic acid and osmium tetraoxide system, and then selectively oxidized to the desired 1,4-TNQs (**87**).[80] This methodology is applied for the synthesis of the series of antimicrobials (Scheme 19). The study on the convenient preparation of 1,4-TNQs by the same methodology described above was extended by Kesteleyn et al.[80,81] Nucleophilic cyclization preferentially occurred in 6-*endo* manner to form **89**. This CAN oxidation also proceeded exclusively to

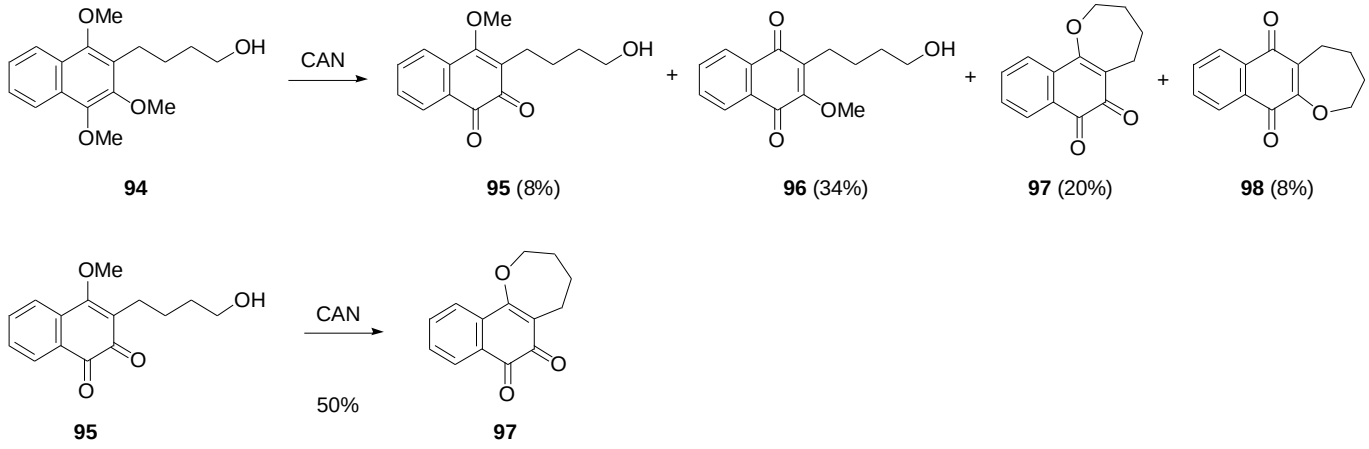
form 1,4-TNQs. An additional example of the exclusive formation of 1,4-TNQ with the same concept described above was carried out utilizing $NaIO_4$ instead of CAN by Pialat et al. in 1998.[82] Dihydrofuran



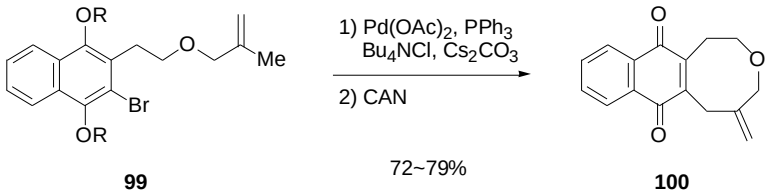
Scheme 19. Specific synthesis of 1,4-TNQs (**87**, **89**, and **91**) utilizing CAN or $NaIO_4$



Scheme 20. Specific cyclization to synthesize 1,4-TNQs (**93**) utilizing CAN



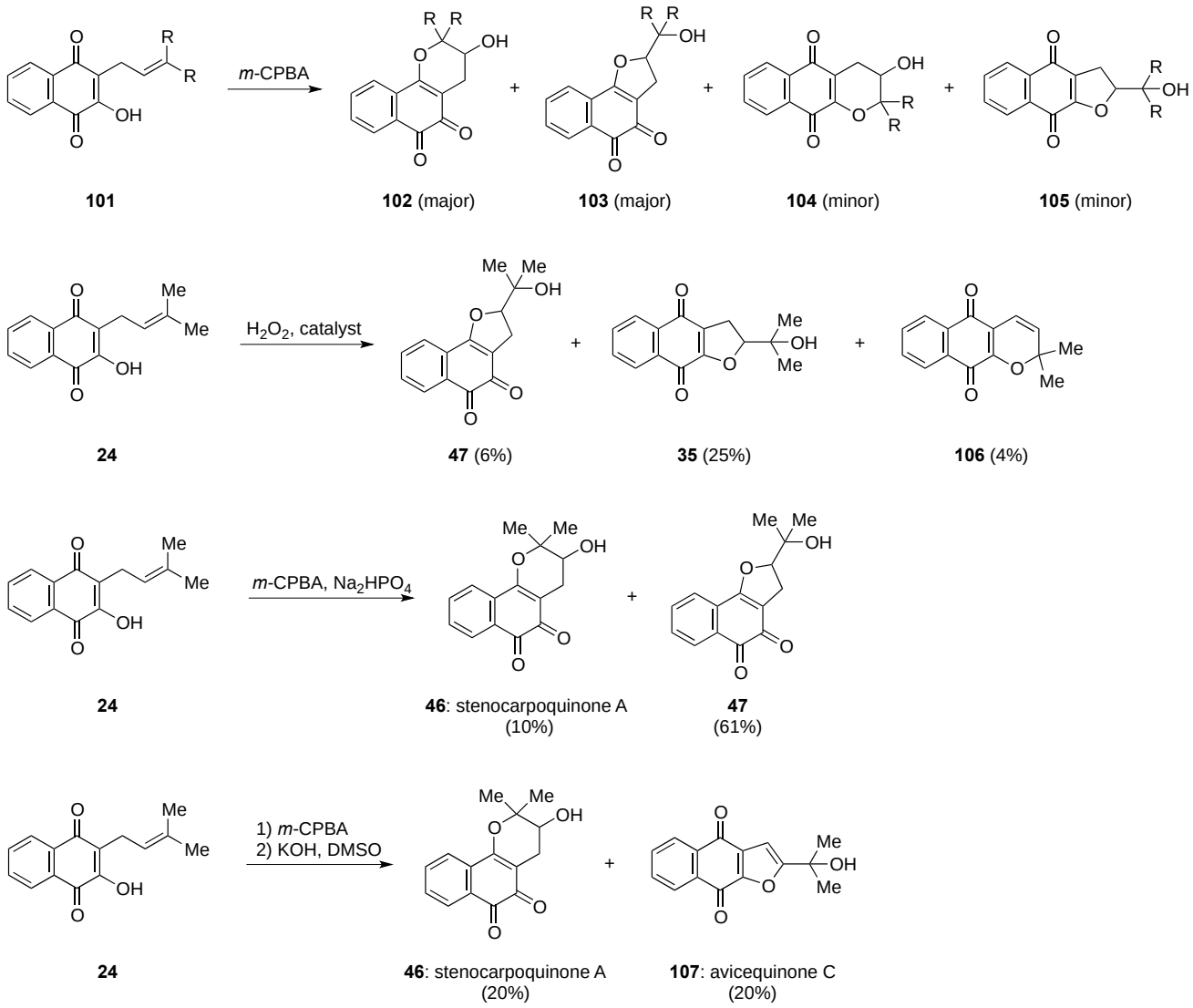
Scheme 21. Cyclization of **94** and **95** to 1,2-TNQs (**97**) and 1,4-TNQs (**98**) utilizing CAN



99 **100**

Scheme 22. Specific cyclization of 1,4-dialkoxynaphthalenes to 1,4-TNQ (**100**) utilizing CAN

containing tricyclic naphthol derivative **92** is selectively oxidized to **93**.[83,84] CAN oxidation may afford 1,4-naphthoquinone derivative and then give the hemiketal (**93**) intramolecularly in a specific manner (Scheme 20). The formation of a seven-membered ring is also favorable, but slower than that of five- or six-membered ring formation according to Baldwin's rules. The authors showed plausible reaction path



101 **102** (major) **103** (major) **104** (minor) **105** (minor)

24 **47** (6%) **35** (25%) **106** (4%)

24 **46**: stenocarpoquinone A (10%) **47** (61%)

24 **46**: stenocarpoquinone A (20%) **107**: avicequinone C (20%)

Scheme 23. 1,2- and 1,4-TNQs synthesis utilizing *m*-CPBA or H_2O_2 as oxidant by way of olefinic epoxidation

and mechanism to form **97** and **98** by way of **95** and **96** (Scheme 21).[75] Specific formation of eight-membered cyclic ether fused 1,4-TNQ (**100**) was achieved by Ray et al. (Scheme 22).[85] First of all, the starter **99** was converted to tricyclic naphthol utilizing the intramolecular Heck reaction by 8-*endo-trig* type cyclization and then specifically oxidized to 1,4-TNQ.

4.2. Peroxide

In this section, the reactions which the third ring structures are introduced by peracid or peroxide oxidation are exemplified. The main hints of the concept in this section are coming from biosynthetic route of naturally occurring naphthoquinones such as lapachol.

The oxidant *m*-chloroperbenzoic acid (*m*-CPBA) and hydrogen peroxide (H_2O_2) are utilized for the epoxide formation of olefinic function in the side chain and in situ intramolecular nucleophilic cyclization to form TNQs. The rapid cyclizations of epoxide intermediates with poor selectivity are observed. In each case, epoxide intermediates are not isolated probably due to their instability (the similar trend of this type of compound **56** is described in scheme 35, in section 7). This epoxide-mediated oxidative cyclization of lapachol (**101**: R=Me) with peracid, well researched by Campillo et al., afforded 1,2-TNQs (**102** and **103**) with moderate selectivity (1,2-TNQs/1,4-TNQs=84/15) (Scheme 23).[10,18,23,24,27,48,54,86–90] The result is the same in the reaction with H_2O_2.[88]

The epoxide formation of the olefinic function in the side chain of lapachol (**24**) utilizing *m*-CPBA and the following TNQs construction were also studied by Ribeiro et al. (Scheme 23).[54] Some natural furano- and pyrano-naphthoquinones were introduced in basic conditions as an economic and simple method to obtain biologically active TNQs in good yield. The authors showed the cytotoxicity of the derived compounds against the tested tumor cells.

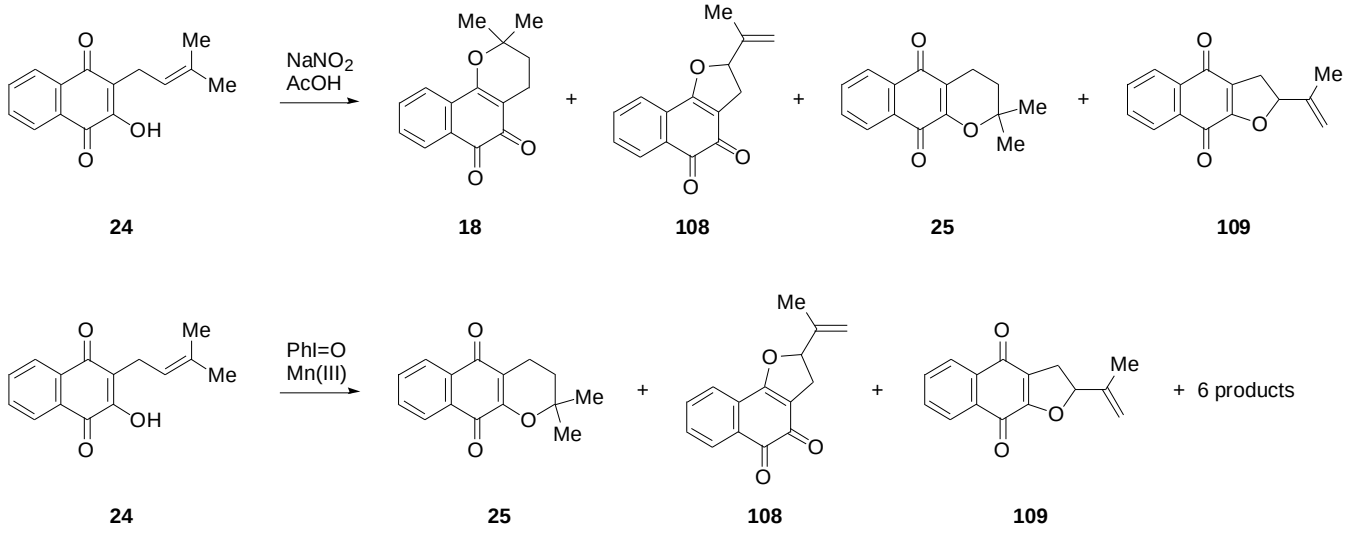
4.3. Other oxidants

Other kinds of oxidants, besides CAN and peroxide, have been also utilized for formation of various 1,2-TNQs and 1,4-TNQs. The examples utilizing other reaction conditions such as $NaNO_2$ and gracial AcOH combination to synthesize α-lapachone, β-lapachone, dehydro-α-lapachone, dehydroiso-α-lapachone and dehydroiso-β-lapachone were achieved by Krishna et al. (Scheme 24).[87,91]

The authors used Mn(III) salen complex for biomimetic in vitro oxidation model of lapachol (Scheme 24).[92] The oxidized reaction mixture was used as the potential phase I metabolites in vivo plasma analysis of biological evaluations. Acid catalyzed oxidative formation of TNQ utilizing HNO_3 and AgO, shown by Ghera et al. also led to 1,4-TNQ (**111**) (Scheme 25).[93]

The unique oxidation of TNQ formation was achieved by Yamamoto and collaborators.[94] RCM reaction to form 1,4-dihydropyran is precedent the DDQ oxidation, which is utilized for oxidative aromatization of 1,4-dihydropyran to form **113** (Scheme 26).

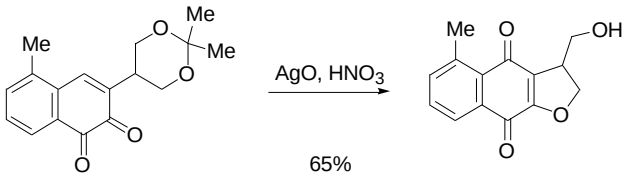
Synthetic methodologies for various naphthoquinones are studied by Kongkathip et al. As a part of their



24 **18** **108** **25** **109**

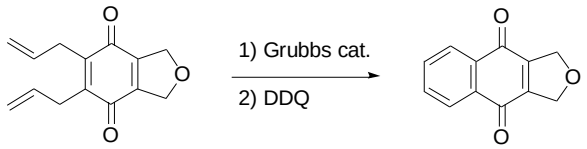
24 **25** **108** **109**

Scheme 24. Cyclization of **29** to 1,2- and 1,4-TNQs utilizing $NaNO_2$/AcOH or PhI=O/Mn(III) reagent system



110 **111**

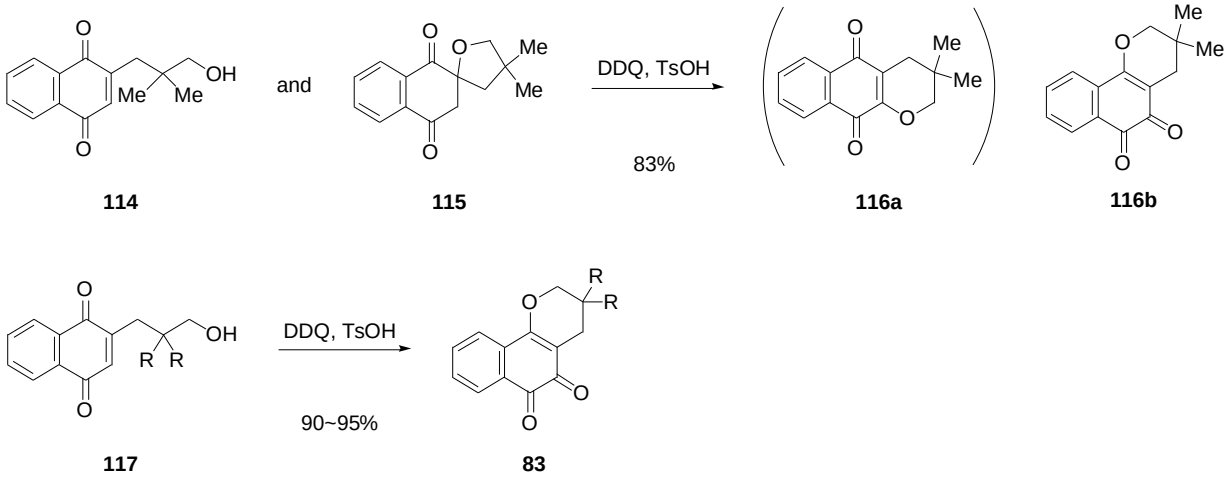
Scheme 25. Acid catalyzed oxidative cyclization to form **111** utilizing AgO and HNO_3



112 **113**

Scheme 26. RCM reaction containing 1,4-TNQ (**113**) formation utilizing DDQ as aromatizing oxidant

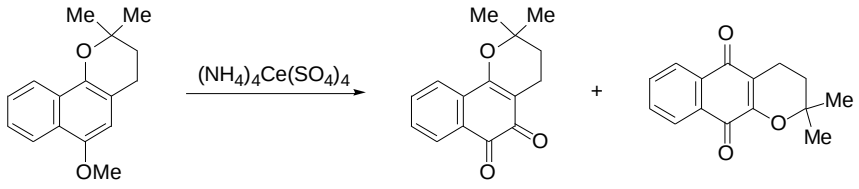
studies, an example of utilizing DDQ with TsOH for the cyclization of 1,4-NQs (**117**) is shown in scheme 27.[10,95,96] The pioneering work of this type of cyclization was reported in 1991.[97] Namely, the synthesis of important intermediate **116b** (rhinacanthone) was carried out from **114** including spiro compound **115** by DDQ oxidation with TsOH (The structure of the compound **116a** was revised to **116b** by Kodama et al.[7f]) Instead of CAN, CAS (cerium tetraammonium sulfate) was also utilized to synthesize 1,2-TNQs and 1,4-TNQs. Lee et al. carried out CAS promoted oxidation of lapachenole (**118**) to form β-lapachone (**18**) with a small amount of 1,4-TNQ (**25**).[98]



114 **115** **116a** **116b**

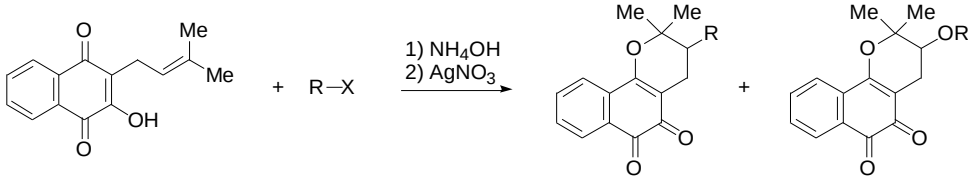
117 **83**

Scheme 27. Cyclization of 2-substituted 1,4-NQs and its spiro type isomers to form 1,2-TNQs (**83** and **116b**) utilizing DDQ



118 **18** (48%) **25** (17%)

Scheme 28. Synthesis of **18** and **25** utilizing CAS



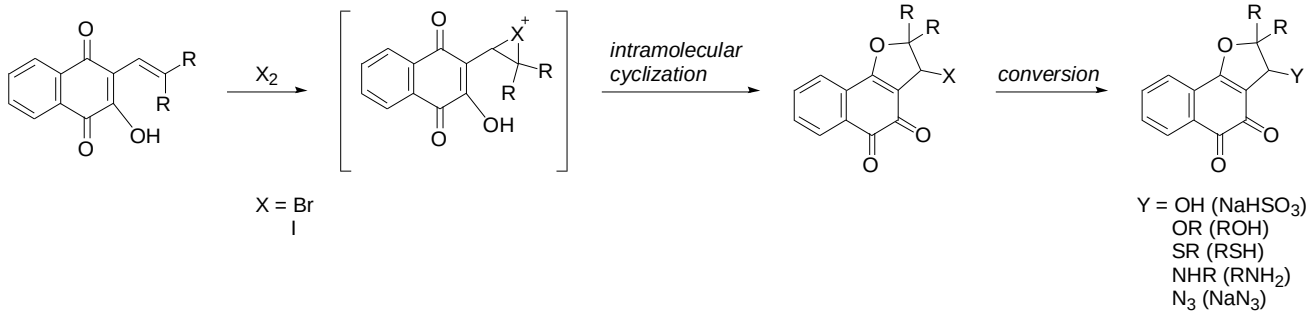
24 **119** (1~4%) **120** (1~2%)

Scheme 29. AgX Promoted synthesis of 1,2-TNQs (**119** and **120**) utilizing ammonia alkaline $AgNO_3$

Lapachol silver salt prepared from aqueous ammonia solution of $AgNO_3$ was exposed to allyl or simple alkyl halides to obtain the desired **119** and **120** even in low yields.[99]

5. ELECTROPHILIC HALOGENATION ASSISTED CYCLIZATION

Halogen is a representative and useful agent to construct TNQs by electrophilic halogenation assisted intramolecular cyclization of alkenyl NQs, and the general reaction pathway is described in Scheme 30. The reaction is not merely simple but this method has been applied by many people probably due to the wide convertibility of halogen substituent groups of the cyclized adducts. This section is classified into two sections by the type of halogen atoms within the reagent which was utilized for cyclization.



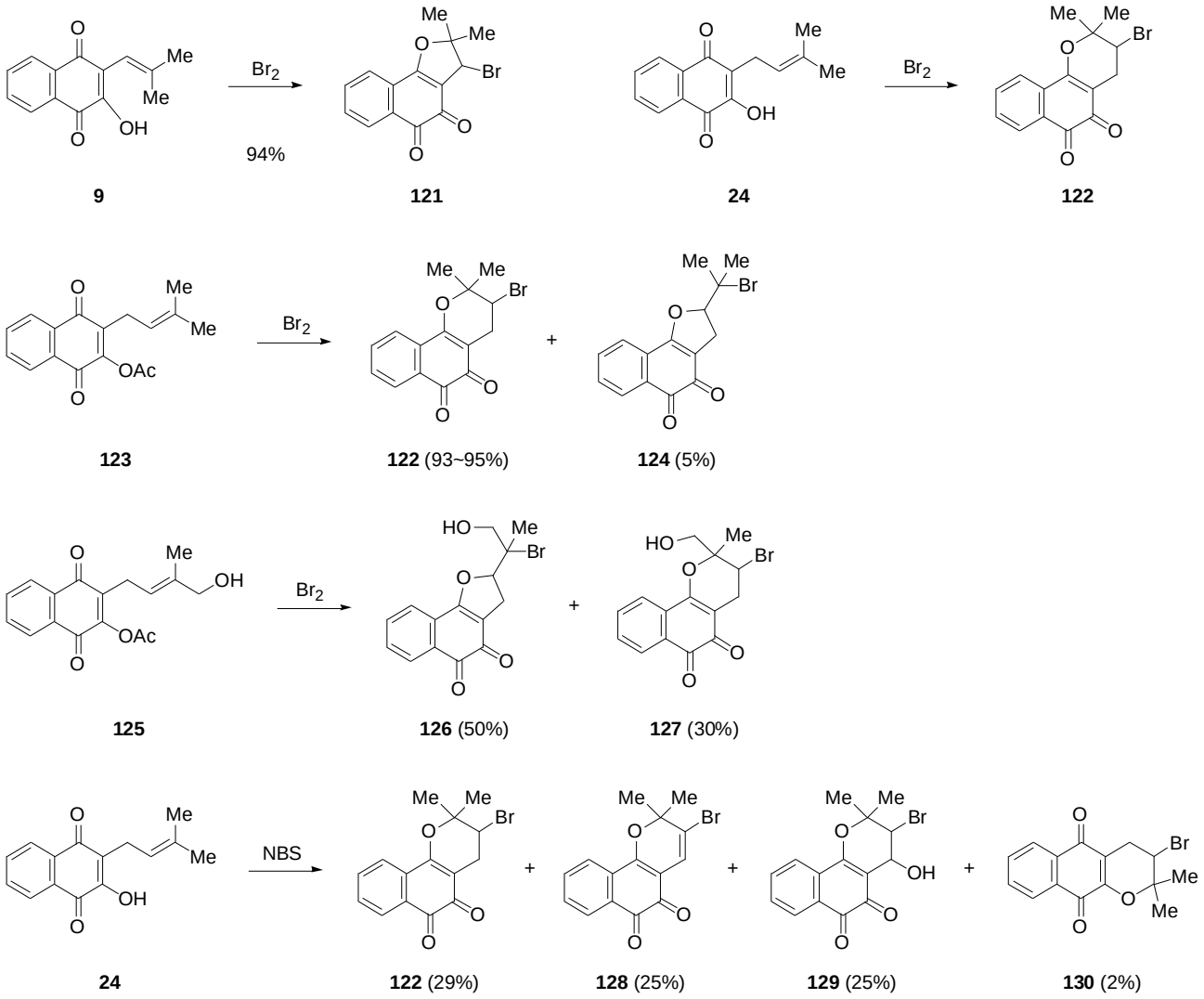
Scheme 30. General reaction pathway of halogen assisted cyclization of NQs and subsequent conversion of halogen substituent groups

5.1. Molecular bromine or NBS

The reported examples for the formation of TNQs utilizing molecular bromine or *N*-bromosuccinimide (NBS) are summarized in Scheme 31. In general, the cyclization conditions of NQs with those reagents have a tendency to be selectively formed the 1,2-TNQs. The first demonstration of the bromination assisted cyclization of 1,4-NQs was reported by Castro's group in 2006.[11] According to their article, 1,4-NQ (**9**) was smoothly cyclized to afford the brominated 1,2-TNQ (**121**) with excellent yield by 5-*endo-trig* type cyclization. After their report, many research groups re-examined this method with the same substrate **9** to extend the potential of **121** by derivatization at bromo-substituted moiety especially in the field of medicinal chemistry.[17,29,33–36,39,58,59,100–108] The reaction has been carried out in halogen-containing solvents such as methylene chloride or chloroform under mild conditions. Six-membered 1,2-TNQ (**122**) can be synthesized from 1,4-NQ (**24**) under the same conditions as mentioned above.[19] The 1,4-NQ (**123**) which is an *O*-acetylated compound of **24** is a good substrate for a regioselective cyclization, and six-membered isomer **122** was obtained as a major product in excellent yield by the exposure to bromine.[24,30,48] A bromo-cyclization of alkoxyalkene substituted 1,4-NQ (**125**) was reported by Eyong and Baskaran's group in 2015, and the regioselectivity of corresponding products 1,2-TNQs (**126** and **127**) was inadequate although 80% of the total yield of the products was obtained.[89] The cyclization of **24** utilizing NBS was reported by Campillo and collaborators in 2006.[48] The reaction characteristically occurred upon a 1,2-TNQs (**122**, **128**, and **129**) selective formation although there are many kinds of products.

5.2. Molecular iodine

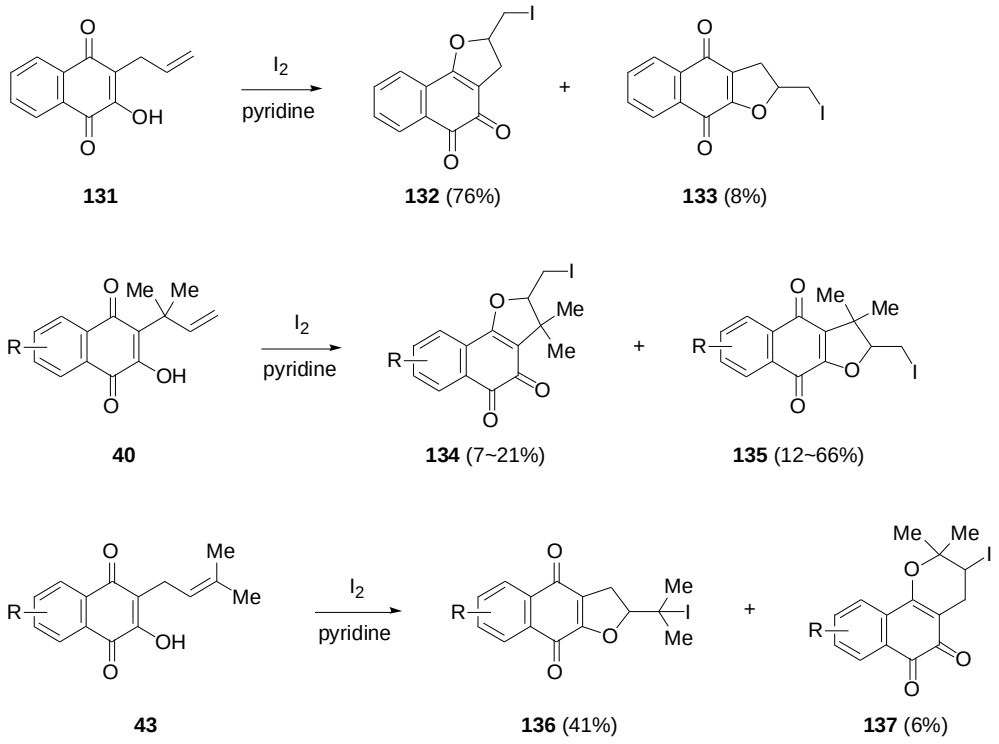
Molecular iodine has been also utilized for the formation of TNQs, and the reactions can be classified in two types between stoichiometric and catalytic reactions. The reactions have different trends especially for the regioselectivity of the cyclized adducts in contrast to the bromine case as described in the above section. In this section, the reported examples of these reactions are summarized as in the following two subsections.



Scheme 31. Cyclization of various substrates utilizing Br_2 or NBS

5.2.1. Stoichiometric reaction utilizing molecular iodine

The reported examples of cyclization reaction of NQs utilizing stoichiometric amount of iodine are summarized in Scheme 32. The pioneering work came out in 2006 by Castro et al.[11] According to their article, two isomers of the products (**132** and **133**) were obtained from *exo*-alkenyl 1,4-NQ (**131**) by the treatment of molecular iodine and pyridine in methylene chloride in less than 40% yield with slight regioselectivity. After their report, reaction conditions have been improved by Silva et al., and in 2015, the total yield of the products finally reached up to 84% with 90:10 regioselectivity.[17,34,36,59,109] An example of cyclization of functionalized 1,4-NQs (**40**) utilizing iodine was reported by Padrón and Misico's group in 2010.[79] According to their article, the regioselectivity of the products (**134** and **135**) were variable depending on the substituent groups on the aromatic ring under mild conditions. In addition, they also reported a reaction utilizing 1,4-NQs (**43**) under the same reaction conditions. In this case, 1,4-TNQs (**136**) were obtained as a major product with good regioselectivities. Seven years later, Silva's

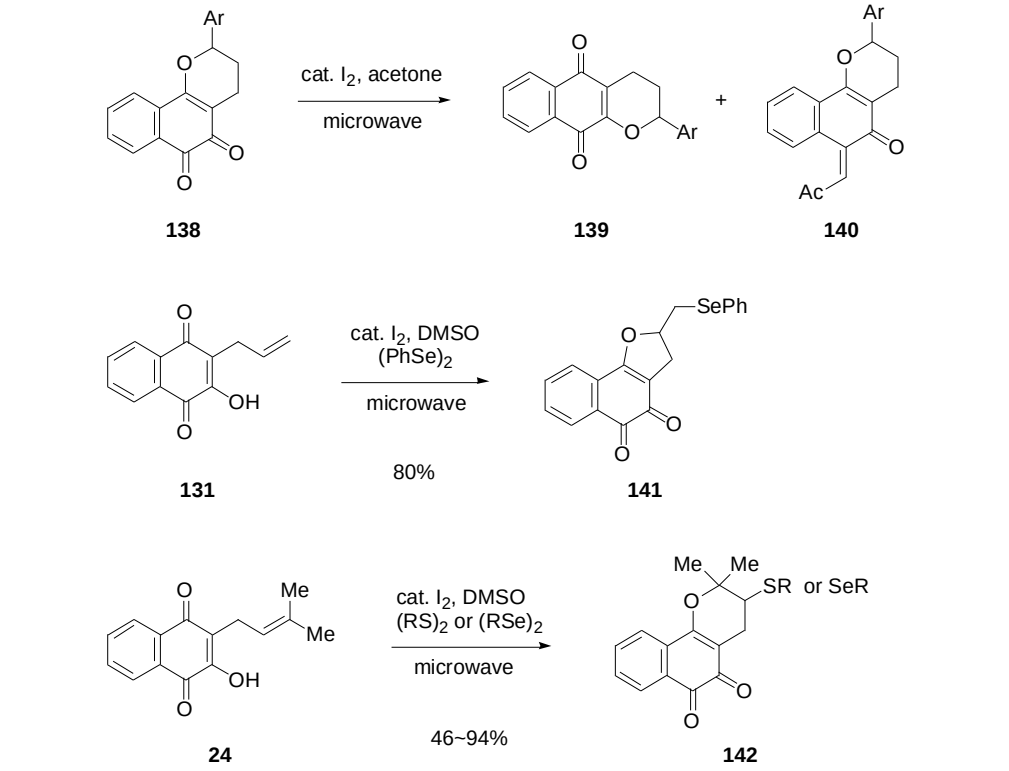


Scheme 32. Cyclization of 1,2-NQs utilizing stoichiometric amount of I_2

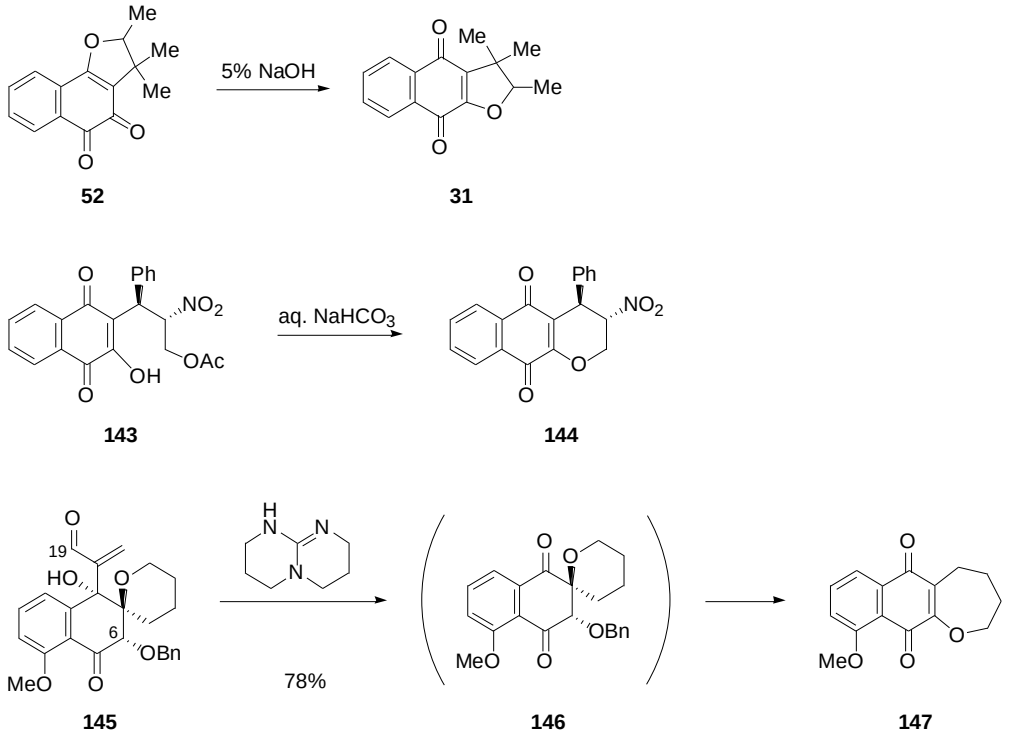
group re-examined this reaction utilizing **43** without substituent group on the aromatic ring under the same reaction conditions.[19]

5.2.2. Catalytic reaction utilizing molecular iodine

In the type of catalytic reaction utilizing molecular iodine was first demonstrated for the molecular conversion of 1,2-TNQ (**138**) into 1,4-TNQs (**139**) in 2011 by Ferreira and her colleagues (Scheme 33).[110] According to their article, the reaction was proceeded quickly in acetone in the presence of a catalytic amount of iodine under microwave irradiation. The aldol condensation between **138** and acetone also occurred during the reaction, and the product ratios of **139** and **140** depended on the substituent group on the aromatic rings. Molecular iodine could be applied for the one-pot functionalization of 1,4-NQs (Scheme 33). Silva's group recently reported a method of the tandem cyclization-arylselenylation reaction utilizing *exo*-alkenyl 1,4-NQ (**131**) as a substrate.[111] The reaction was smoothly promoted in the mixed reagent system of catalytic amount of iodine, dimethyl sulfoxide (DMSO), and diphenyl diselenide under microwave irradiation, the arylselenylated 1,2-TNQ (**141**) was selectively obtained in high yield. The DMSO acts as a re-oxidizing agent of iodine in the mixed reagent system. This reagent system was also applied for 1,4-NQ (**24**). Namely, a similar reaction occurred to yield the corresponding 1,2-TNQs (**142**) with complete regioselectivities when **24** was treated with a catalytic amount of iodine, DMSO, and organo-chalchogen reagents.[59,111,112]



Scheme 33. Catalytic reaction utilizing I_2 with various substrates



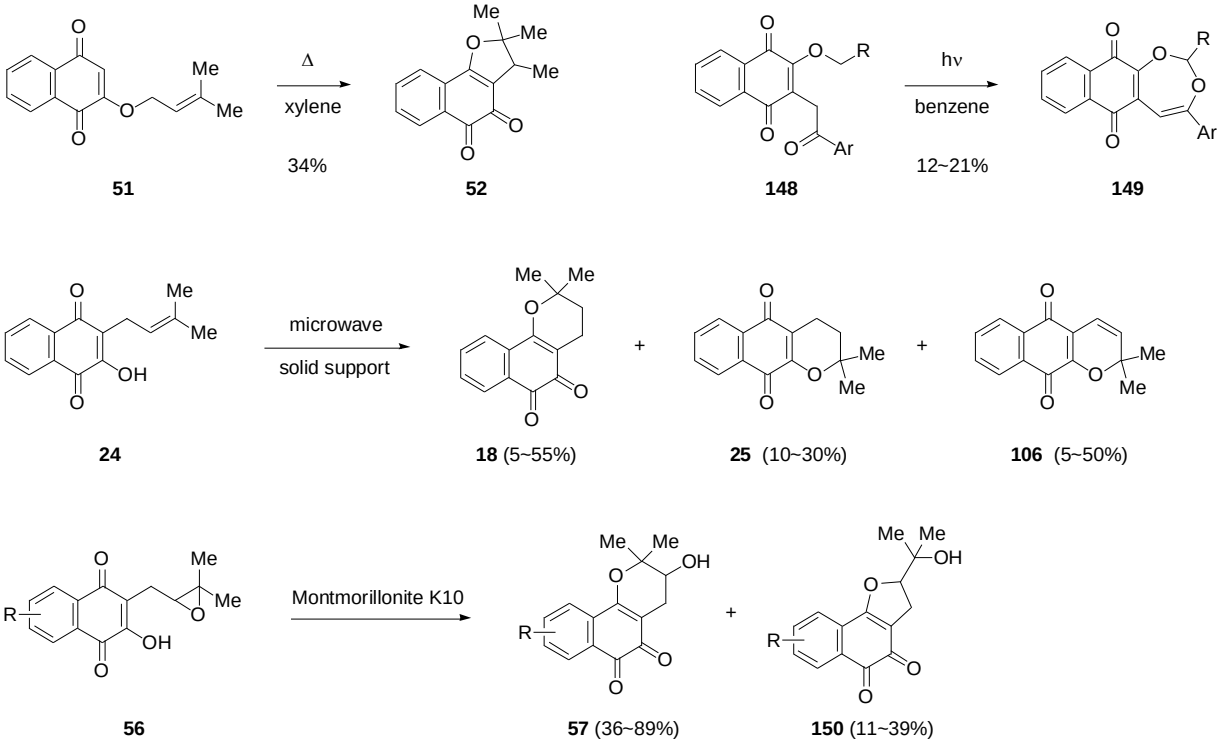
Scheme 34. Cyclization of various substrates utilizing bases

6. BASE-PROMOTED CYCLIZATION

The way for a formation of TNQs utilizing bases is also known as a minor method in comparison to utilizing acids, and the reported example is described in Scheme 34. The first application was reported by Cooke and collaborators in 1950 utilizing aqueous sodium hydroxide.[113] 1,2-TNQ (**52**) was converted to 1,4-TNQ (**31**) by the treatment of this base via ring opening reaction by hydrolysis. A simple S_N2 type cyclization of functionalized 1,4-NQ (**143**) was reported by Pericas's group, and the corresponding product **144** was obtained with retention of configuration at stereo centres under aqueous weak basic condition.[114] In 2015, Suzuki and Ohmori's group reported an extraordinary method for constructing 7-membered 1,4-TNQ (**147**).[115] According to their study, the aldol reaction of **145** at C6 and C19 positions was failed in the presence of bulky amine (1,5,7-triazabicyclo[4.4.0]dec-5-ene: TBD) during the synthesis of natural product: naphthospironone A, **147** was obtained in good isolated yield as a side product. The proposed mechanism for formation of **147** was explained in their article as follows, 1,4-addition of TBD occurred at *exo*-methylene moiety first, and subsequent retro-aldol reaction generate intermediate **146**, base-promoted elimination to cleave the six-membered ether ring, and finally the product **147** was obtained by addition-elimination reaction.

7. OTHER TYPES OF CYCLIZATION

Several unusual methodologies besides those described in the sections 2–6 were reported up to present, and the actual methods are described in Scheme 35. A thermal cyclization reaction of alkoxy-1,4-NQ (**51**)



Scheme 35. Cyclization of various substrates and conditions

was reported by Park and Kwak in 2009, and the corresponding product **52** was obtained under reflux condition utilizing xylene as a solvent.[13,16] The methods are supposed to be applicable for simple substrates with less substituent groups because of its harsh condition. One example of photochemical cyclization of 1,4-NQs (**148**) were reported by Matsumoto and collaborators in 1980.[116] Seven-membered "unique" 1,4-TNQs (**149**) were obtained in moderate to high yield under irradiation of **148** utilizing 30W high pressure Hg lamp. The microwave-assisted cyclization of 1,4-NQ (**24**) was originally reported in 2006 by Singh and his collaborators.[117] According to their study, the regioselectivity of each product was variable depending on the reaction conditions such as the sort of solid support and irradiation time. Four years later, another group also carried out their method utilizing the same substrate.[45] Recently, a similar reaction of epoxy-1,4-NQs (**56**) utilizing acidic support solid (Montmorillonite K10) was reported by Koketsu's group.[18] According to their report, substrates **56** were prepared in situ by the epoxidation of alkenes utilizing *m*-CPBA due to the instability of themselves. The six-membered 1,2-TNQs (**57**) were obtained as a major product and the regioselectivities were variable depending on the substituent group of **56**.

8. SUMMARY

All of methods introduced in this article are summarized in Table 1. By looking at this table, there are

Table 1. The summary of reported methods for the construction of TNQs by intramolecular cyclization[a]

Reagents	1,2-TNQs		1,4-TNQs		Selectivity	Functional group tolerance
	Furano-	Pyrano-	Furano-	Pyrano-		
conc. H_2SO_4	21	28	0	1	G	P
aq. H_2SO_4	0	2	2	8	M	M
HX	0	1	6	13	G	M
other [H^+]	2	4	1	3	M	M
Lewis acids	10	12	0	8	G	G
CAN	1	3	3	4	G	G
peroxides	3	3	3	2	M	M
other [O]	2	6	4	4	M	M
Br_2 or NBS	23	6	0	1	M	G
I_2	8	5	9	1	P	G
bases	0	0	1	1	G	M
others	3	3	0	2	M	G

[a] The numbers described in this table are total counts of reported examples based on the classification of the type of substrates that include re-examinations of utilizing the same substrates, and the capital abbreviations are as follows: G=good, M=moderate, P=poor. Examples of seven- and eight-membered ring formation were excluded.

characteristic trends of the cyclized adduct depending on which reagents were utilized. We expect this article will be helpful in a future study of TNQs and related compounds.

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