

# Masked Ketenes as Dienophiles in the Diels–Alder Reaction\*

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The Diels–Alder reaction is one of the most powerful, well-established, and versatile reactions in organic chemistry; however, its application in certain settings remains a challenge as a result of functional group incompatibility. In this review, we examine the methods in which masked ketenes can be employed as dienophiles, taking particular note of applications in complex settings.

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## Introduction

The Diels–Alder (DA) reaction is one of the most important transformations in synthetic organic chemistry. It has played a central role in the development of reactivity theory,<sup>[1–3]</sup> and has enjoyed a great number of elegant and creative applications in both the academic and industrial setting.<sup>[4–8]</sup> Despite almost a century of research,<sup>[9]</sup> the DA reaction remains a highly active area of study, and current fields of interest include the development of new catalytic asymmetric reactions,<sup>[10]</sup> incorporation of DA reactions into domino sequences,<sup>[11,12]</sup> the elucidation of natural product biosyntheses,<sup>[13–17]</sup> and the development of diene-transmissive DA reactions.<sup>[18–22]</sup>

Although the DA reaction has been used to access a vast array of structural motifs, the reaction is not without limitation.

For example, the need to electronically match the diene and dienophile often necessitates the incorporation of superfluous functionality that must be removed or modified during subsequent steps.<sup>[23,24]</sup> In a similar vein, some functionality is not tolerated and must be masked during the cycloaddition. One such example, and the focus of the present review, is the incompatibility of ketenes as dienophiles. Ketenes react via a hetero-DA–Claisen rearrangement sequence,<sup>[25,26]</sup> as exemplified by the reaction between butadiene (**1**) and ketene (**2**),<sup>[27]</sup> yielding formal [2+2] cycloadduct 3-vinylcyclobutan-1-one (**3**) (via intermediate **4**, Scheme 1).

Many ingenious examples of masked ketenes as dienophiles have been developed, and this topic has been the focus of two reviews: the first by Ranganathan and coworkers in 1977,<sup>[28]</sup> and

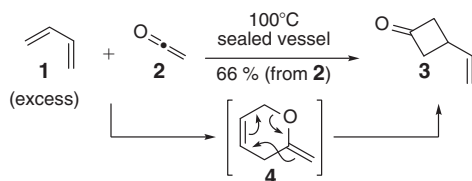


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Christopher Newton obtained his undergraduate degree from Victoria University, New Zealand, and his Ph.D. from the Australian National University under the supervision of Professor Michael Sherburn. His thesis focussed on the synthesis of novel reactive hydrocarbons and their application in the Diels–Alder reaction. In mid-2015, he began a post-doctoral stay as an EPFL Fellow in the group of Professor Nicolai Cramer, Switzerland, working in the fields of ligand design and catalytic enantioselective C–H functionalization.

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Scheme 1. Thermal reaction between butadiene and ketene.

the second by Aggarwal and coworkers in 1999,<sup>[29]</sup> and as such, the history and development of this field have already been covered. Our intention here is to revisit masked ketene equivalents within the confines of complex molecule synthesis, to best highlight their utility and relevance. Although we have made all efforts to conduct a comprehensive evaluation of the entire field, we focus herein on what we consider to be the most important developments and applications. We have elected to limit our study to the most common mode of reactivity, namely normal electron-demand DA reactions incorporating carbodienes, thus best enabling a comparative study. In addition, we restrict discussion to the most step-economic methodologies,<sup>[30]</sup> specifically those examples that require two or fewer steps post DA to unmask the ketone functionality.

### Masked Ketenes as Dienophiles in the Diels–Alder Reaction

#### Vinyl Acetates

Vinyl acetate derivatives constitute a large family of masked ketene dienophiles, the first of which was developed by Bartlett and Tate in 1956 (Scheme 2).<sup>[31]</sup> In their report, cyclopentadiene (**5**) was reacted with 1-cyanovinyl acetate (**6**) at 100°C, providing DA adduct **7** in 62% yield. Ketone **8** was subsequently accessed in excellent yield, albeit under quite forcing conditions, by exposure to a refluxing solution of aqueous NaOH.

Several structural variations to 1-cyanovinyl acetate (**6**) have since been reported (Fig. 1). For example, replacement of the nitrile group with an ester (dienophile **9**) or ketone (dienophile **10**) are both tolerated; however, in both cases the unmasking sequence requires more steps than the parent cyano-dienophile.<sup>[32]</sup> Modifications of the acetate functionality are also known: in 1997, MaGee reported the incorporation of a more electron-withdrawing 2,4-dinitrobenzoate moiety (dienophile **11**), providing an increase in DA reactivity of ~5–6 times (comparable reactivity with acrylonitrile (**35**), discussed in the section *Acrylonitriles*).<sup>[33]</sup> In addition, Vogel and coworkers demonstrated that by the incorporation of chiral auxiliaries,<sup>[34–39]</sup> such as in tartaric acid-derived dienophile **12**,<sup>[34]</sup> enantiomerically pure ketones were accessible via this methodology.

The majority of applications involving vinyl acetates as masked ketenes utilize the parent 1-cyanovinyl acetate (**6**) (Scheme 3). In 1994, Bull et al. applied this methodology to the synthesis of several steroid derivatives containing bridged bicyclic D-rings.<sup>[40]</sup> In the example depicted, oestrone-derived furan **13** was reacted with 1-cyanovinyl acetate (**6**) to provide the DA adduct **14** in 32% yield, along with other isomers (17%). The ketone was then unmasked under basic conditions, with concurrent cleavage of the second acetate moiety, yielding  $\alpha$ -hydroxyester **15** in 82% yield.

In 2007, Hansen et al.<sup>[41]</sup> demonstrated that the core framework of (–)-colchicine<sup>[42]</sup> could be accessed via a DA reaction between fused furan **16** and 1-cyanovinyl acetate (**6**), which, following hydrolysis of the crude mixture of cycloadducts, gave

ketones **18** as a 1 : 1 mixture of atropisomers in 77% yield over the two steps.

Notably, vinyl acetates as masked ketene equivalents are best suited to reaction with cyclic dienes. Only a few examples that employ acyclic dienes have been reported, and significant isomerization of the alkene into conjugation is observed in all cases as a result of the basic conditions employed during the unmasking procedure.<sup>[32,33]</sup>

#### Acrylonitriles

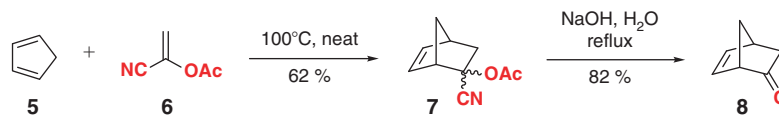
2-Chloroacrylonitrile was first employed as a masked ketene in the DA reaction by Paasivirta and Kreiger in 1965.<sup>[43,44]</sup> Arguably the most famous application came 4 years later from the Corey laboratory within the total synthesis of several prostaglandin natural products (Scheme 4).<sup>[45,46]</sup> In their report, unstable 5-substituted cyclopentadiene **19** was reacted with 2-chloroacrylonitrile (**20**), in the presence of a copper Lewis acid catalyst, providing bicyclic adduct **21** as a mixture of diastereoisomers in over 90% yield. Basic conditions were used to generate ketone **22**, presumably via an  $\alpha$ -chloro amide intermediate,<sup>[47]</sup> which was ultimately converted into ( $\pm$ )-prostaglandin-F<sub>2 $\alpha$</sub> . Notably, Corey's synthesis of ketone **22** (or related derivatives) has become a benchmark by which the efficiency of many new ketene equivalents is measured.

In 1972, Evans demonstrated that under non-catalyzed conditions, 2-chloroacrylonitrile (**20**) is notably more reactive in the DA reaction than 1-cyanovinyl acetate (**6**), and reacts with a higher degree of orientational selectivity with unsymmetrical dienes.<sup>[48]</sup> In the same study, Evans also furthered their utility by developing alternative unmasking reaction conditions, namely Na<sub>2</sub>S in refluxing ethanol, conditions that are frequently reported to be higher-yielding.<sup>[48,49]</sup>

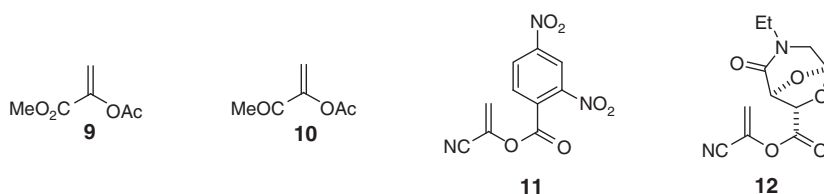
Alternative unmasking conditions were also established by Banwell et al., who in studies directed towards the synthesis of paclitaxel, observed that both KOH and Na<sub>2</sub>S were unsuitable, necessitating development of an alternative protocol (Scheme 5).<sup>[50]</sup> In this example, a DA reaction between diene **23** and 2-chloroacrylonitrile (**20**) was performed at high temperature, providing cycloadduct **24** in excellent yield. Using conditions adapted from an earlier paper by Selikson and Watt,<sup>[51]</sup> the organolithium derived from **24** was treated with O<sub>2</sub> to yield an  $\alpha$ -cyanohydroperoxide intermediate, followed by cyanohydrin formation with SnCl<sub>2</sub>, and finally treatment with NaOH gave the final product, ketone **25**, in 58% yield.

While conducting structure–activity relationship studies on morphine analogues, Lewis et al. reported a thermal DA reaction between thebaine (**26**) and 2-chloroacrylonitrile (**20**), providing a 4 : 1 crude mixture of *endo* (with respect to the more electron-withdrawing nitrile substituent) and *exo* isomers **27** and **28**, which were subsequently isolated in 43 and 7% yields respectively after crystallization.<sup>[52]</sup> Formation of ketone **29** was achieved under standard basic conditions, and the analgetic activity of this substrate, along with a handful of other derivatives, was explored, leading to the discovery of two substrates more potent than morphine.<sup>[53]</sup>

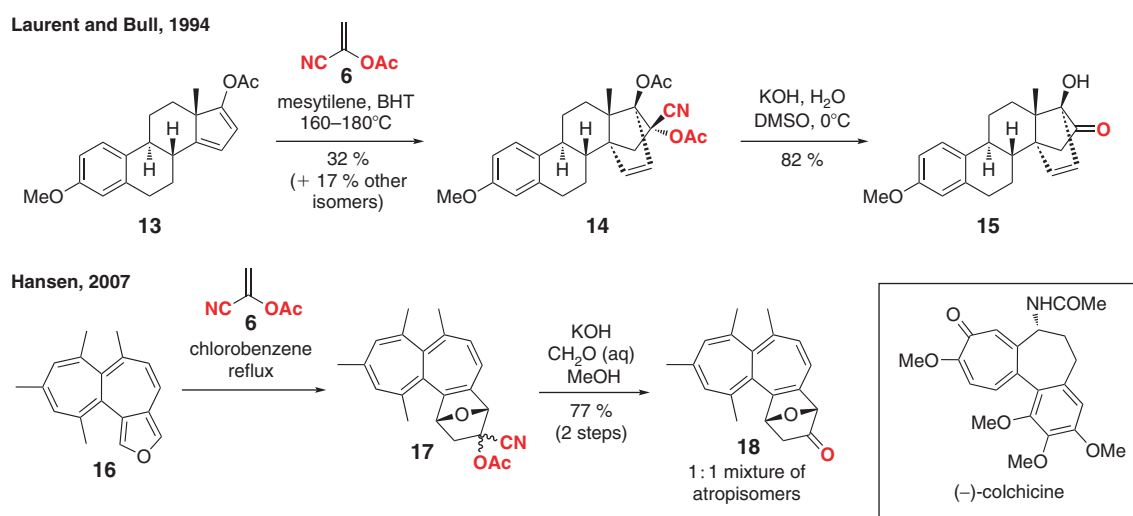
2-Chloroacrylonitrile (**20**) has also found application as a ketene equivalent in the industrial sector as part of a multigram route to a preclinical candidate.<sup>[54]</sup> In this example from Abele and coworkers, the masked ketene underwent a DA reaction with cyclic diene **30** on 800-g scale, utilizing (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO) as a polymerization inhibitor, to provide intermediate cycloadduct **31** as a mixture of isomers. The silyl enol ether was cleaved on treatment with a



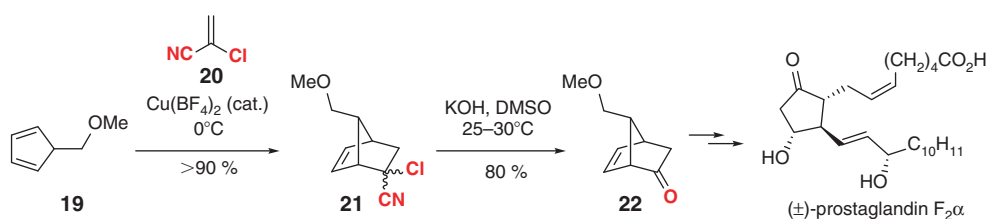
**Scheme 2.** Earliest report of 1-cyanovinyl acetate as a masked ketene in the DA reaction.



**Fig. 1.** 1-Cyanovinyl acetate derivatives as ketene equivalents.



**Scheme 3.** Selected applications of 1-cyanovinyl acetate as a ketene equivalent.



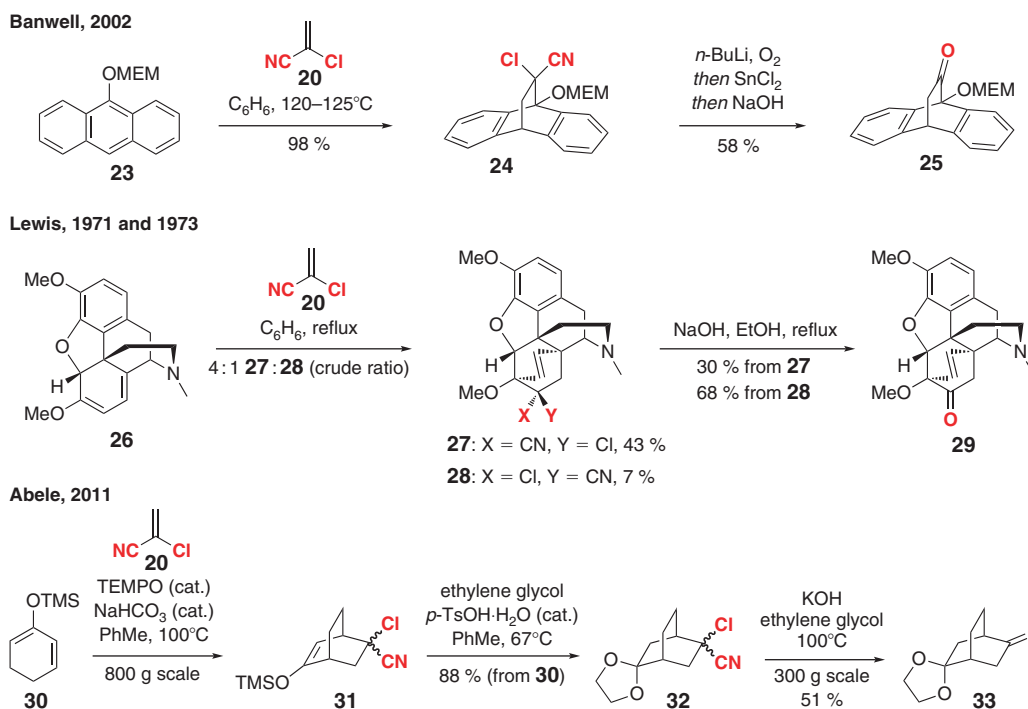
**Scheme 4.** Application of 2-chloroacrylonitrile in the synthesis of prostaglandins by Corey et al.

catalytic quantity of acid in the presence of ethylene glycol, followed by in situ protection of the intermediate ketone to yield ketal **32** in 88 % overall yield from diene **30**. Finally, hydrolysis under basic conditions, conducted on a 300-g scale, provided the target **33** in 51 % yield.

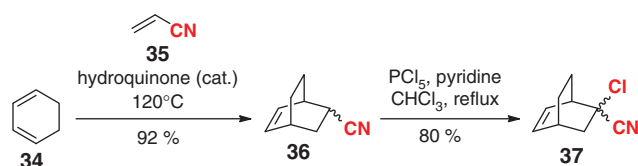
In 1968, Brown demonstrated that selective chlorination of acrylonitrile DA adducts was possible, thus establishing a new masked ketene dienophile.<sup>[55]</sup> In a representative example from Maiti,<sup>[56]</sup> cyclohexadiene (**34**) was reacted neat with acrylonitrile (**35**) at elevated temperatures, followed by exposure of cycloadduct **36** to  $\text{PCl}_5$  in the presence of excess pyridine, to deliver the ketone precursor **37** in good overall yield (Scheme 6). Despite

Brown reporting the overall sequence to be higher-yielding than analogous examples with 2-chloroacrylonitrile,<sup>[55]</sup> and the fact that acrylonitrile is a more reactive dienophile,<sup>[54]</sup> the additional chlorination step appears to be a large enough deterrent to prevent this methodology from becoming widely adopted.

As with vinyl acetate derivatives, the use of 2-chloroacrylonitrile (**20**) as a ketene equivalent is restricted to reaction with cyclic (or 1,1-disubstituted<sup>[57–59]</sup>) dienes, as a result of the basic conditions required for their unmasking. When acyclic dienes are employed, elimination of HCN is a competitive process,<sup>[60,61]</sup> representing a significant limitation to this methodology.



**Scheme 5.** Selected applications of 2-chloroacrylonitrile as a ketene equivalent.



**Scheme 6.** Application of chloroacrylonitrile as a masked ketene dienophile in the DA reaction by Maiti et al.

### Nitroalkenes

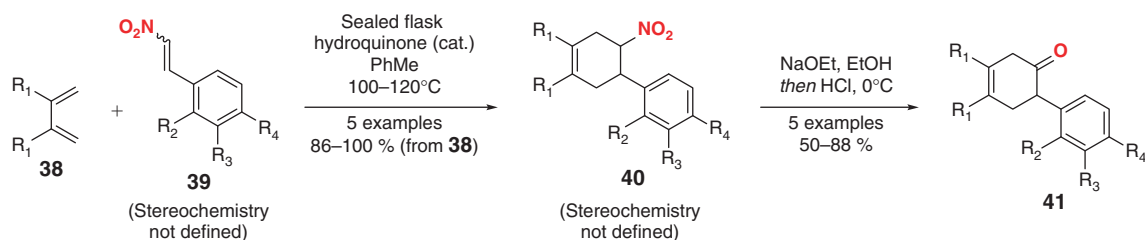
To the best of our knowledge, the first examples of masked ketenes as dienophiles in the DA reaction were disclosed by Wildman and Wildman in 1951.<sup>[62]</sup> In their report, symmetrical butadienes **38** were reacted with  $\beta$ -nitrostyrenes **39** in hot toluene (Scheme 7). The DA cycloadducts **40** were then subjected to a Nef reaction, yielding a small library of non-conjugated (and non-bridged) ketones **41**, a motif that is not accessible via the methodologies discussed earlier.

In 1974, Ranganathan et al. reported the first example that utilized nitroethylene as a masked ketene, while simultaneously demonstrating that this dienophile exhibits significantly higher DA reactivity than known alternatives, namely acrylonitrile (**35**), 2-chloroacrylonitrile (**20**), and 2-chloroacryloyl chloride (**61**) (see below), making it more suitable for sensitive or unreactive dienes.<sup>[63]</sup> However, despite the advantage of their higher DA reactivity, nitroalkenes as ketene equivalents frequently suffer from difficulties associated with the Nef reaction.<sup>[64–67]</sup> Nevertheless, successful reports in the context of target-oriented synthesis are known (Scheme 8). In 1985, Myers and Corey<sup>[68]</sup> reacted 2-hydroxy-5-iodobenzoic acid (**43**)-derived cyclohexadiene **44** in a DA reaction with nitroethylene (**45**), employing *N,N*-dibornylamine as a buffer owing to the acid sensitivity of **44**. The reaction proceeds with complete orientational and stereoselectivity, yielding nitroalkane **46** in

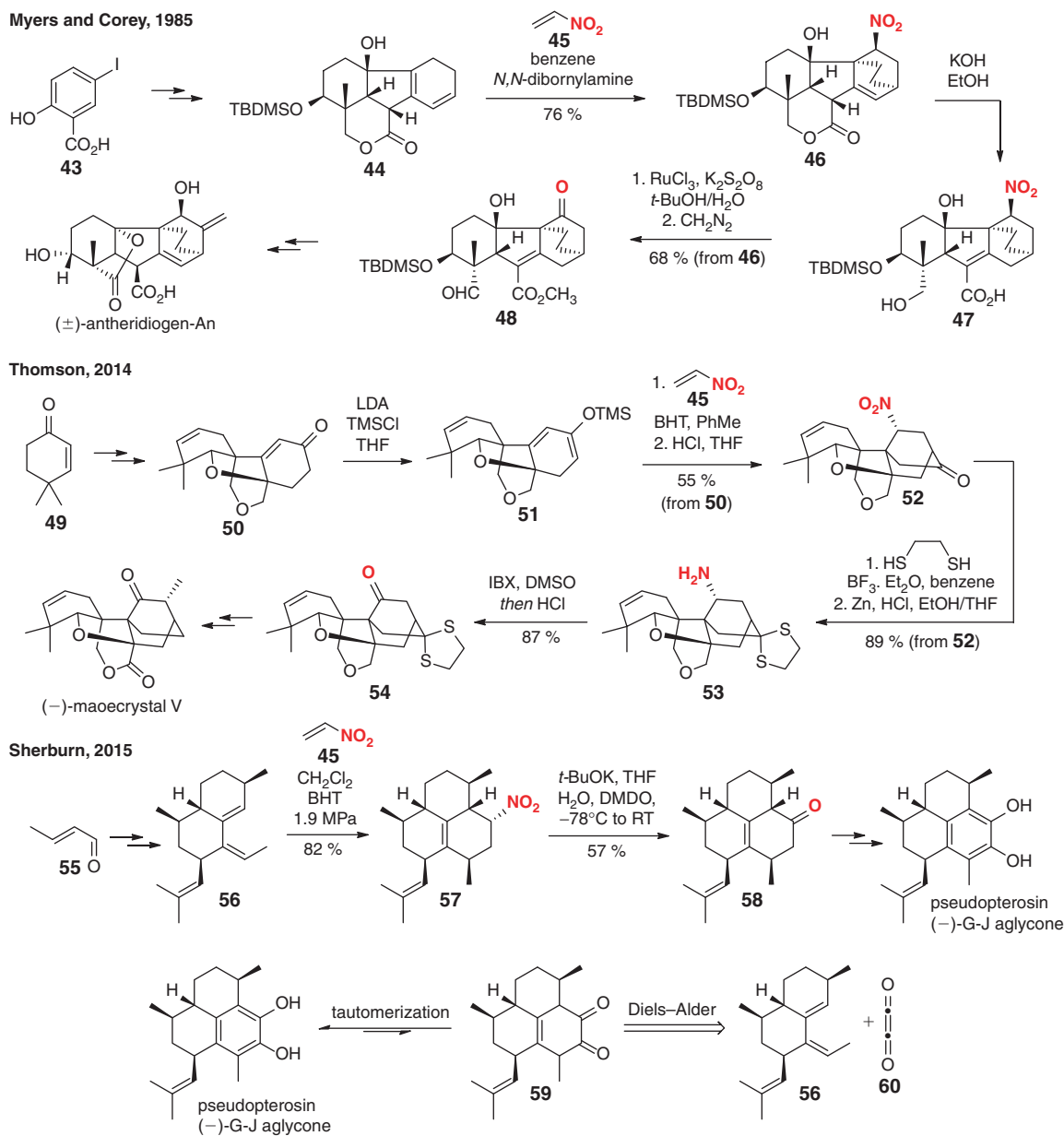
76% yield. Following lactone hydrolysis and olefin isomerization to carboxylic acid **47**, potassium ruthenate oxidation served to both oxidize the primary alcohol and induce a novel oxidative Nef reaction. Finally, esterification with diazomethane delivered ester **48**, which was subsequently converted into the plant hormone ( $\pm$ )-antheridiogen-An.

More recently, Thomson et al. disclosed an elegant example of nitroethylene as a masked ketene within an enantioselective total synthesis of (–)-maoecrystal V from 4,4-dimethylcyclohexenone (**49**).<sup>[69]</sup> Treatment of  $\alpha,\beta$ -unsaturated ketone **50** with dithium diisopropylamide (LDA) and trimethylsilyl chloride (TMSCl) provided activated diene **51**, which underwent a DA reaction with nitroethylene (**45**), followed by silyl enol ether hydrolysis, to give ketone **52** in 55% yield. A two-step procedure was used to unmask the ketone, beginning with dithiane protection, followed by in situ reduction of the nitro group to yield amine **53**. Finally, oxidation with 2-iodoxybenzoic acid (IBX)<sup>[70,71]</sup> revealed the ketone **54** in 86% yield. From this intermediate, only four steps were required to complete the synthesis of the natural product.

The final example of nitroethylene as a masked ketene comes from a 2015 total synthesis of the pseudopterosin (–)-G–J aglycone by Sherburn et al.<sup>[72]</sup> In this report, highly unreactive *Z*-substituted diene **56** (accessed in only six steps from crotonaldehyde (**55**)) was subjected to a high-pressure DA reaction, providing tri-cycle **57** in 82% yield as a single regio- and diastereoisomer. The ketone was unmasked via treatment with potassium *tert*-butoxide (*t*BuOK) and dimethyldioxirane (DMDO),<sup>[73]</sup> providing the target material **58** in 57% yield. Oxidation to the catechol was achieved in two steps, thus completing the shortest synthesis of a pseudopterosin to date.<sup>[74]</sup> As identified by Sherburn and coworkers, this retrosynthetic disconnection of the aglycone via its 1,2-diketone tautomer **59** formally represents a DA reaction between diene **56** and ethylene dione (**60**), a reagent for which a synthetic equivalent has yet to be developed.



**Scheme 7.** Earliest report of nitroalkenes as masked ketenes in the DA reaction by Wildman and Wildman.



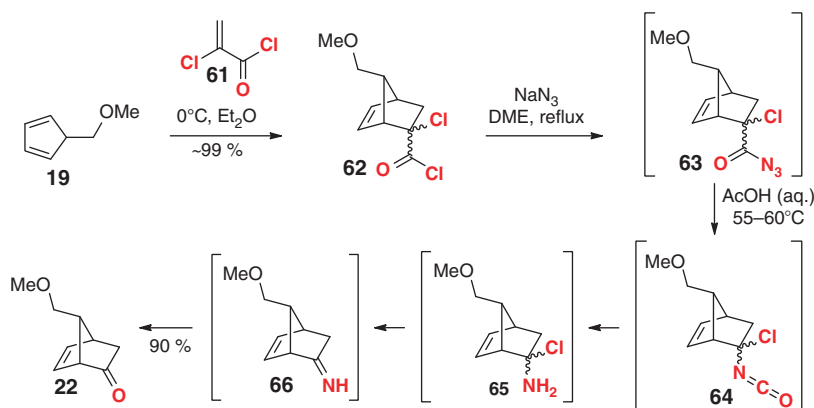
**Scheme 8.** Selected applications of nitroethylene as a ketene equivalent.

Although not yet realized, there is opportunity for an enantioselective sequence incorporating nitroalkenes as masked ketenes, as enantioselective DA reactions of nitroethylene<sup>[75]</sup> and substituted derivatives<sup>[76,77]</sup> are known.

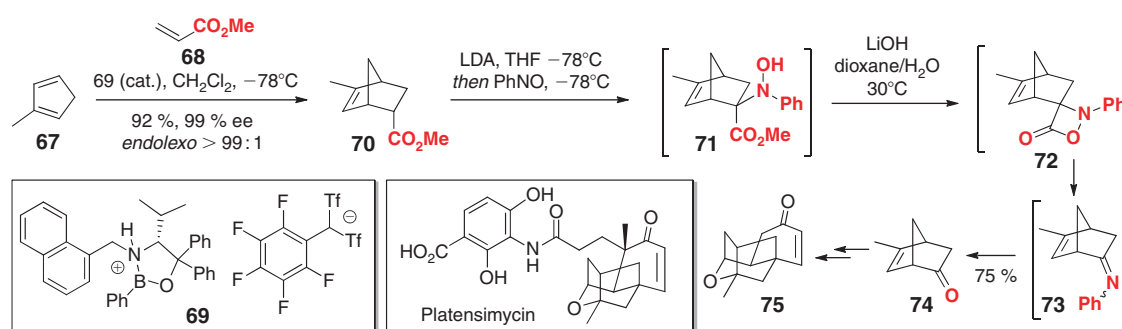
#### 2-Chloroacryloyl Chloride

In further studies directed towards the synthesis of prostaglandin natural products (see [Scheme 4](#) for earlier work), Corey et al. reported the development of an improved, highly reactive





Scheme 9. Application of 2-chloroacryloyl chloride as a masked ketene by Corey et al.



Scheme 10. The application of methyl acrylate as a ketene equivalent by Yamamoto et al.

ketene equivalent (comparable in reactivity with maleic anhydride) that avoids the need for a strong base during the unmasking procedure (Scheme 9).<sup>[78]</sup> Thus 2-chloroacryloyl chloride (**61**) was reacted (under non-catalyzed conditions) with substituted cyclopentadiene **19** at 0°C, which, following concentration of the reaction under reduced pressure, yielded DA adduct **62** in quantitative yield. The crude material was subsequently heated with sodium azide in anhydrous dimethoxyethane (DME), followed by the addition of ethanoic acid, providing the target ketone **22** in excellent yield. Mechanistically, the reaction proceeds via an initial acyl substitution, giving intermediate azide **63**. A Curtius rearrangement then provides isocyanate **64**, which under the aqueous reaction conditions breaks down to provide amine **65**. The ketone is formed via subsequent elimination and hydrolysis. This interesting approach has not found much favour in the literature, perhaps in part owing to the intermediacy of a potentially dangerous azide, or as a result of difficulties associated with the synthesis<sup>[79]</sup> and handling of the dienophile. Notably, Corey also demonstrated 2-chloroacryloyl chloride (**61**) could be successfully employed with acyclic dienes, with little to no isomerization of the alkene into conjugation during ketone unmasking.

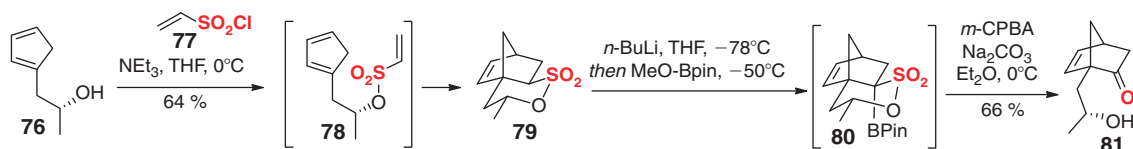
### Acrylates

Although examples of acrylates as masked ketene equivalents have been known for many years, their application typically requires several synthetic steps to reveal the ketone.<sup>[80–83]</sup> However, in 2007, Yamamoto and coworkers published an efficient unmasking procedure as part of a formal synthesis of platensimycin (Scheme 10).<sup>[84]</sup> Utilizing their earlier described DA reaction between 2-methylcyclopenta-1,3-diene (**67**) and

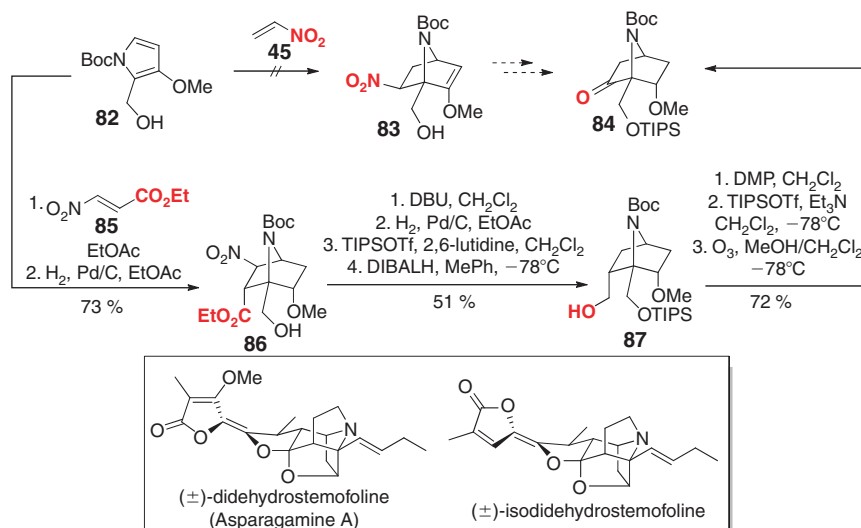
methyl acrylate (**68**), employing **69** as a Brønsted acid-assisted chiral Lewis catalyst, cycloadduct **70** was accessed in 92% yield, and with excellent enantio-, diastereo-, and regioselectivity.<sup>[85]</sup> The ketone was subsequently unmasked in a one-pot operation by treatment with LDA and PhNO, followed by warming in the presence of LiOH. Mechanistic studies<sup>[86]</sup> indicate the reaction proceeds via initial formation of *N*-hydroxylamine **71**, followed by intramolecular transesterification to spiro-oxazetidinone intermediate **72**. Extrusion of CO<sub>2</sub> to yield imine **73**, followed by hydrolysis to ketone **74**, completes the unmasking. This intermediate was converted in eight steps to complex polycycle **75**, thus intercepting an intermediate from Nicolaou's 2006 total synthesis of platensimycin.<sup>[87]</sup> Yamamoto's unmasking procedure has since been applied in simple systems by a handful of other researchers,<sup>[88,89]</sup> however, attempts in more complex settings have not been met with success.<sup>[82]</sup>

### Vinylsulfonyl Chloride

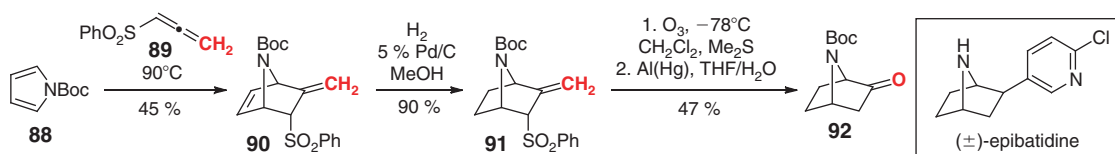
An elegant strategy to control the orientational selectivity of DA reactions with unsymmetrical dienes was disclosed by Metz, Fleischer, and Fröhlich.<sup>[90]</sup> In their study, depicted in Scheme 11, a sulfonyl tether was introduced via a simple substitution reaction of alcohol **76** with vinylsulfonyl chloride (**77**), providing intermediate **78**, which underwent an intramolecular DA reaction in situ to yield tri-cycle **79** in 64% yield. The ketone was then revealed in a two-step sequence, by lithiation and subsequent trapping with 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (MeO-Bpin), providing tri-cycle **80**. This intermediate was not isolated, but rather treated with



**Scheme 11.** The use of a sulfonylether to control DA orientational selectivity.



**Scheme 12.** Overman and coworkers' 2003 synthesis of  $(\pm)$ -didehydrostemofoline and  $(\pm)$ -isodidehydrostemofoline



**Scheme 13.** Formal synthesis of  $(\pm)$ -epibatidine via the use of an allenic dienophile.

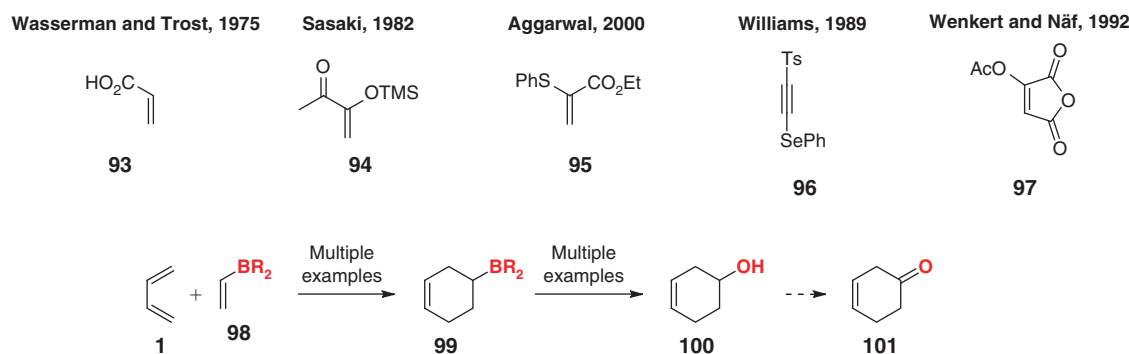
*meta*-chloroperoxybenzoic acid (*m*-CPBA), resulting in a chemoselective oxidation to the target ketone **81**. Notably, the authors demonstrated that reaction of diene **76** with 1-cyanovinyl acetate (**6**) provided a complex mixture of orientational regioisomers, highlighting the advantage of their new strategy. However, this approach necessitates appropriate proximate functionality, limiting its application. Despite this restriction, the strategy has since been implemented by Winterfeldt et al. in an enantioselective total syntheses of (–)-myltaenol.<sup>[91]</sup>

#### Reversing Orientational Selectivity

All of the ketene equivalents presented thus far convert the most electron-withdrawing group of the dienophile into the carbonyl. Challenges arise when the inverse orientational selectivity of the DA reaction is desired, as demonstrated by Overman and coworkers in their synthesis of  $(\pm)$ -didehydrostemofoline (asparagine A) and  $(\pm)$ -isodidehydrostemofoline (Scheme 12).<sup>[92]</sup> In their approach, an ideal route from pyrrole **82** to key intermediate **84** would employ a DA reaction with nitroethylene (**45**) (or equivalent); however, owing to the mismatched electronic properties of the two components, **83** is not accessible. Instead, a less direct route was taken, using dienophile **85**. In this case, the

nitro group behaved as a removable activating group, while the  $\alpha,\beta$ -unsaturated ester acted as the masked ketene. Following the DA reaction, the double bond was hydrogenated, giving intermediate **86** in 73% yield. Four steps were necessary to remove the nitro group, protect the alcohol, and reduce the ester, providing alcohol **87** in 51% yield. A final oxidation–silyl enol ether formation–ozonolysis sequence delivered the target **84** in 72% yield. A further 19 steps were required to furnish  $(\pm)$ -didehydrostemofoline and  $(\pm)$ -isodidehydrostemofoline, thus completing the first total syntheses of these molecules.

Allenes have also been applied as masked ketenes via ozonolysis of the exocyclic alkene post DA reaction; thus, appropriately functionalized allenic dienophiles could enable (formally) inverse orientational selectivity to that typically seen with standard masked ketenes. Although not yet applied with an unsymmetrical diene, a potentially suitable dienophile was introduced by Pavri and Trudell in their formal synthesis of  $(\pm)$ -epibatidine (Scheme 13).<sup>[93]</sup> In their study, a DA reaction between *tert*-butoxycarbonyl (BOC)-protected pyrrole **88** and sulfonyl allene **89** gave the *endo* cycloadduct **90** as the sole product in 45% yield. A regioselective hydrogenation of the 1,2-disubstituted alkene yielded the exocyclic alkene **91**, allowing for ozonolysis, followed by removal of the sulfonyl



Scheme 14. Selected masked ketenes that have yet to be applied in complex synthesis.

activating group via treatment with aluminium amalgam, providing bi-cycle **92** in 47% yield, and thus intersecting an intermediate from the 1993 total synthesis by Fletcher et al. of the natural product.<sup>[94]</sup> Although this example demonstrates that allenenes can be effective masked ketenes in DA reactions, the requisite hydrogenation before unmasking limits their utility.

### Conclusions and Future Prospects

Several known ketene equivalents have not been discussed throughout the present review, such as acrylic acid (**93**),<sup>[95,96]</sup> silyl enol ether **94**,<sup>[97]</sup>  $\alpha$ -thioacrylate **95**,<sup>[98]</sup> phenylselenoacetylene **96**,<sup>[99]</sup> and acetoxy maleic anhydride (**97**),<sup>[100]</sup> to name only a few (Scheme 14). As far as we are aware, none of these examples (or any other masked ketene equivalents not covered) have been applied outside simple settings. For some dienophiles, it is easy to understand why: **96** and **97** require three and four steps respectively for ketone unmasking, whereas silyl enol ether **94** exhibits low DA reactivity, necessitating the use of strong Lewis acids for reaction. For others, however, it is less clear why they have not been widely adopted, and perhaps they still have much to offer. In particular, we believe vinyl boranes **98** and their more highly oxidized derivatives hold great promise as masked ketenes in the DA reaction. Although much attention has been paid by Singleton and coworkers to their use as both versatile and reactive alkenyl alcohol equivalents in the DA reaction, via conversion of cycloadducts adducts **99** to **100**,<sup>[101–104]</sup> a simple oxidation to ketone **101** would represent their application as a masked ketene.

In conclusion, we hope the examples highlighted within this review demonstrate the power of masked ketenes in the DA reaction. Since the first report by Wildman and Wildman, several creative and well-executed examples have been reported, enabling the synthesis of several highly complex and biologically important natural products. However, we also hope that this survey serves to highlight the limitations of current methods. Specifically, the low DA reactivity of many ketene equivalents often necessitates reasonably forcing conditions, creating potential incompatibility issues. Although this problem has been partially addressed with the advent of more reactive ketene equivalents, most notably nitroethylene, challenges associated with the Nef reaction limit the utility of this dienophile. As yet, a true one-pot procedure where the DA reaction and unmasking can be performed together has not been disclosed; however, Corey's 2-chloroacryl chloride (**61**) is perhaps compatible. Furthermore, development of an ethylene dione (**60**) equivalent would be a valuable extension to this field, thus enabling the rapid synthesis of catechols via the DA

reaction. Other areas that would benefit greatly from further research include masked ketenes with an inverse polarity to those currently in existence, as well as advancements to intramolecular and asymmetric variants, enabling their application in more complex settings.

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