Diels-Alder reactions of 1-alkoxy-1-amino-1,3-butadienes: Direct synthesis of 6-substituted and 6,6-disubstituted 2-cyclohexenones and 6-substituted 5,6-dihydropyran-2-ones

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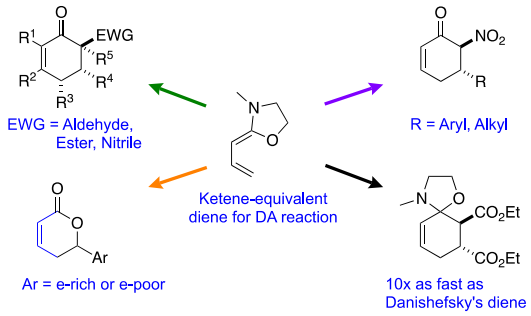
Supporting Information Placeholder



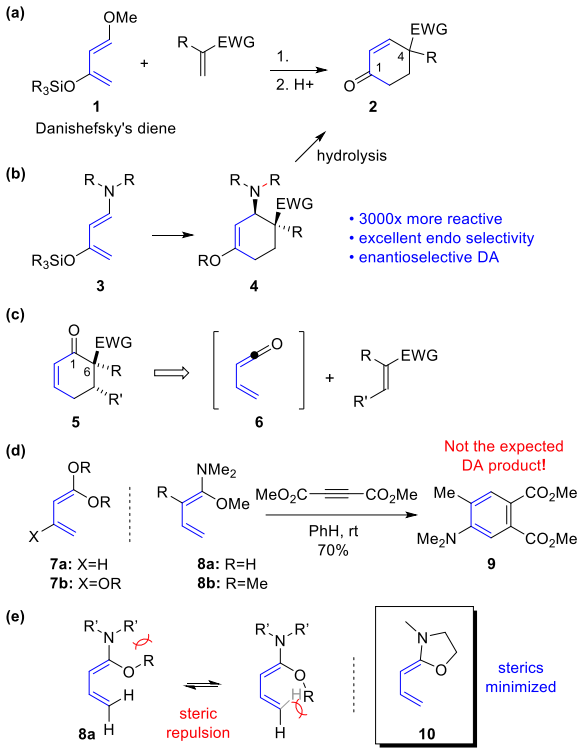
ABSTRACT: We report the cycloaddition reactions of 1-alkoxy-1-amino-1,3-butadienes. These doubly activated dienes are prepared on a multi-gram scale from crotonic acid chloride and its derivatives. The dienes undergo Diels-Alder and hetero-Diels-Alder reactions under mild reaction conditions with a variety of electron-deficient dienophiles to afford cycloadducts in good yields and excellent regioselectivities. Hydrolysis of the DA cycloadducts provides 6-substituted and 6,6-disubstituted-2-cylohexenones, which are versatile building blocks for complex molecule synthesis. The corresponding HDA cycloadducts afford 6-substituted 5,6-dihydropyran-2-ones.

The Diels-Alder (DA) reaction is one of the most important transformations in organic chemistry, providing direct access to six-membered cyclic compounds in a regio- and stereocontrolled manner, with up to four chiral centers.[1] The power of the DA reaction is evident from its indispensable role in the synthesis of numerous complex molecules.[2] Of special importance in the development of this reaction has been the advent of a suite of heteroatom-substituted dienes, which not only are more reactive but also yield a wide range of functionalized building blocks for chemical synthesis.[3] The introduction of Danishefsky's diene (**1**, Scheme 1a), for example, enabled the facile synthesis of various 4,4-disubstituted cyclohexenones (and further substituted derivatives thereof), which paved the way to many intricate natural products.[4] The development of the 1-amino-derivatives of this diene (i.e., **3**, Scheme 1b), which is considerably more reactive, opened further opportunities in synthesis,[5,6,7] including the development of enantioselective DA reactions.[8] Given the importance of 6,6-disubstituted cyclohexanone cores (**5**) as building blocks for the synthesis of complex molecules[9] and the paucity of methods to access them, we investigated various additional heteroatom-substituted butadienes and their cycloadditions and report here the results of our studies on the synthesis and DA and HDA reactions of 1-alkoxy-1-amino-1,3-butadienes.

The synthesis of 6,6-disubstituted cyclohexenones (**5**) via a Diels-Alder cycloaddition requires either vinyl ketene (**6**) or its formal equivalent (Scheme 1c). To realize this capability, several 1,1-dialkoxybutadienes have been developed and examined (**7a**) in cycloaddition reactions.[10] Notably, Sustmann reported that while 1,1-dimethoxybutadiene gave the expected cycloadducts with highly electron-deficient dienophiles such as dimethyl 2,3-dicyanomaleate, its reactions with common dienophiles such as methyl acrylate, acrylonitrile, fumaro- and maleonitrile, dimethyl fumarate, and dimethyl maleate, gave none of the cycloadducts, only polymeric materials.[10d] Among the 1,1-dialkoxybutadienes, the most important is Brassard's diene (**7b**, Scheme 1d). Although used widely for HDA and Mukaiyama aldol reactions, its successful use in DA reactions is primarily with quinone or doubly-activated

dienophiles.[11] Additionally, the cycloadducts it generates are necessarily more highly oxygenated, giving 3-alkoxycyclohexenone products, the masked form of 1,3-cyclohexanediones, rather than 2-cycohexenones. The related 1-alkoxy-1-aminobutadiene (cf., **8**), which is expected to be even more reactive, has seen limited use for DA reactions. Indeed, the reaction of **8b** with dimethyl acetylenedicarboxylate did not afford the expected DA adduct, giving instead a product (**9**) "with a substitution pattern incompatible with the normal Diels-Alder pathway."[12]

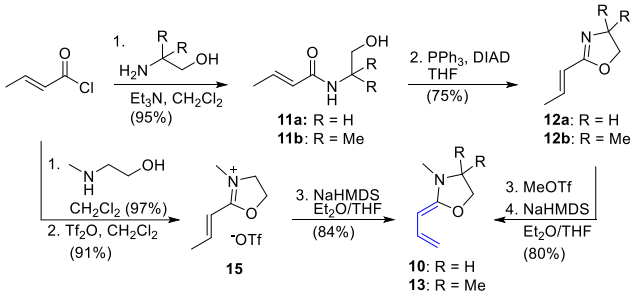
Scheme 1. Activated butadienes for Diels-Alder reactions



We reasoned that the poor DA reactivity of 1-alkoxy-1-aminobutadienes such as **8** was likely due to steric interactions that disfavor the *s*-*cis* rotamer required for DA reactions, allowing instead alternate reaction paths (Scheme 1e).[13] Given this background of literature reports, we investigated oxazolidine-fused butadiene **10**, wherein the N- and O-atoms are linked through a two-carbon unit, thereby obviating the steric issues. The desired diene was synthesized in good yield through a simple protocol starting with Woollaston's route to α,β-unsaturated oxazoline **12a** (Scheme 2).[14] This oxazoline was then converted into the desired diene in two steps via formation of the oxazolinium salt followed by deprotonation with NaHMDS. Through this route we prepared both the base diene **10** and the gem-dimethyl substituted diene **13**. An alternate synthesis of the diene was also developed to overcome the long reaction times and a difficult isolation procedure, especially the distillation of the thermally unstable oxazolines **12**. Crotonyl chloride was reacted with *N*-methylethanolamine and the resulting amide **14** was treated with triflic anhydride, which induced the desired cyclization to give oxazolonium triflate salt **15**. Deprotonation of **15** with NaHMDS then proceeds cleanly to give the desired diene in 71% overall yield from crotonyl chloride. While the diene is unstable in aqueous solutions of pH <10, we found that it can be subjected to 2M $NaOH/H_2O$ solution with no degradation. By quenching the reaction with such a solution, all polar non-volatiles can be removed by extraction, and the desired diene can be obtained pure without the need for distillation. This improved route is shorter and affords the diene in high yield, requiring no distillation or columns. Importantly, intermediate **15** is stable for an extended period of time, even when stored at room temperature. The improved route was used to prepare over 15 grams of salt **15** and 4 grams of diene **10** in a single pass.

The initial studies were aimed at assessing the cycloaddition

Scheme 2. Synthesis of oxazolidine-fused-butadienes



capability of the new dienes. Upon heating a solution of diene **10** and methacrolein in toluene at 60 °C for 2 h, the diene was fully consumed and yielded a 3:1 mixture of two products, as observed by NMR. The major product was the expected cycloadduct and the minor product was tentatively assigned to be the HDA adduct.[15a] The major product was unstable to silica gel but can be hydrolyzed to give the desired 6,6-disubstituted cyclohexanone **17a** (Scheme 3). The analogous reaction with the gem-dimethylated diene **13** gave a cycloadduct (cf., **16**, 30%) that was column stable, allowing confirmation of its structure. However, the DA reaction proceeded significantly more slowly, so diene **13** was not investigated further.[15b]

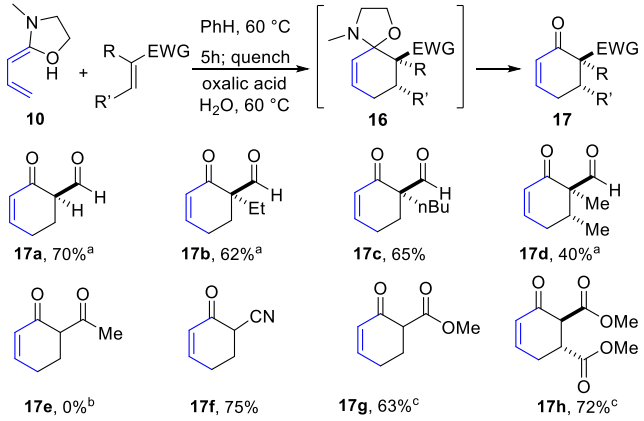
Various parameters were examined to improve the reaction outcome with diene **10**. When carried out in toluene at room temperature, the reaction required 10 h to go to completion and gave a similar ratio of the two products. In hydrogen bond donor solvents (e.g., *t*-BuOH), the reaction rate of the HDA reaction increased and the reaction gave a lower proportion of the desired DA cycloadduct. The best outcome, albeit by a small margin, was obtained when the reaction was performed in benzene. Upon optimization, the DA reaction and the hydrolysis could be performed in a single procedure that afforded ketone **17a** in 70% isolated yield.

To evaluate the generality of the protocol, diene **10** was reacted with several common dienophiles (Scheme 1). Ethyl- and *n*-butyl-acroleins reacted analogously to methacrolein and afforded the respective 6,6-disubstituted-

2-cyclohexenones in good yields. We were delighted to find that even tiglic aldehyde participated in the cycloaddition to give, after hydrolysis, tri-substituted cyclohexenone **17d**. The reactions with acrylonitrile, and methyl acrylate proceeded well, as did the reaction with methyl maleate. Unfortunately, the reaction with methyl vinyl ketone gave none of cycloadduct 17e.[15c]

The useful reactivity shown by diene **10** in DA reactions with traditional dienophiles motivated us to examine its reactions with nitroalkenes (Scheme 4). While nitroethylene is reported to react at room temperature with highly active dienes like cyclopentadiene, the DA reaction of β-arylnitroethylenes generally requires higher temperatures or special activation modes.[16] In light of this limitation, we were delighted to observe that oxazolidine-fused butadiene **10** reacted rapidly at room temperature with β-nitrostyrene to give a cycloadduct (cf., **18**), which upon quenching with aqueous oxalic acid gave the expected 6-nitro-substituted cyclohexenone **19a** in 75% yield.[17] Several additional β-arylnitroethylenes and two β-alkyl-substituted nitroethylenes were subjected to the cycloaddition/hydrolysis protocol, and all gave the cyclohexanone products in good to excellent yields. Nitroethylenes with aryl units possessing donor groups or withdrawing groups worked equally well, as did naphthyl- and heteroaryl-substituted nitroethylenes. Noteworthy are the two

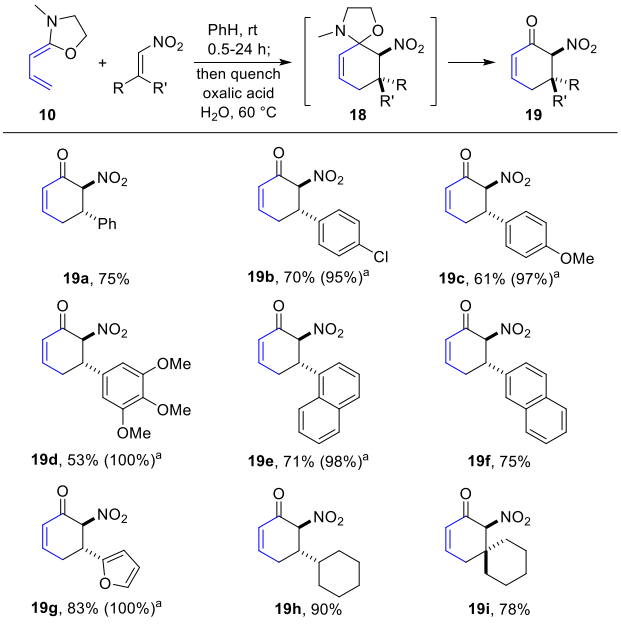
Scheme 3. Diels-Alder reactions of diene 10 with dienophiles



(a) DA reactions run in a sealed tube. (b) Expected cycloadduct not formed. (c) Mixture of keto and enol forms.

alkyl-substituted β-nitroalkene products, especially the spiro-fused bicyclic compound **19i**, which was formed in 78% yield. The present method offers a simple route to various 6-nitrocyclohexenones, the chemistry of which appears to have been scarcely investigated.[18]

Scheme 4. Diels-Alder reactions of diene 10 with nitroalkenes

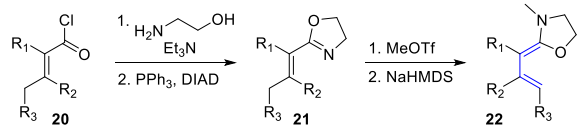


(a) Yield in parentheses is the NMR yield of the cycloadduct (**18**).

We next turned our attention to the preparation and DA reactivity of more substituted analogs of diene **10** (Scheme 5). Three different dienes were synthesized using the first protocol described above, starting with the requisite acid chlorides. The procedures transferred well and enabled the synthesis of gram quantities of the different dienes, which were isolated as colorless liquids that were stored under an inert atmosphere. The dienes reacted with several common dienophiles to afford, after in situ hydrolysis of the cycloadducts, the expected cyclohexanone products in good overall yields (Scheme 6).[19] Given the robustness of diene preparation and the generality of the DA reactions, the present method provides facile access to various functionalized mono- and bicyclic systems that should prove of value in complex molecule synthesis.

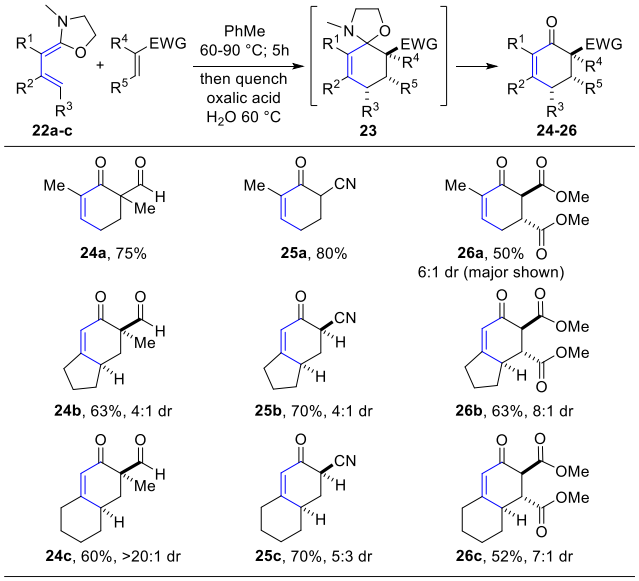
To further expand the scope of cycloadditions of diene **10**, we examined its HDA reaction with aldehydes, which would provide a

Scheme 5. Synthesis of substituted oxazolidine-butadienes



entry	R^1	R^2, R^3	product	yield (%)	product	yield (%)
1	Me	H	**21a**	68	**22a**	70
2	H	-$(CH_2)_3$-	**21b**	75	**22b**	83
3	H	-$(CH_2)_4$-	**21c**	60	**22c**	80

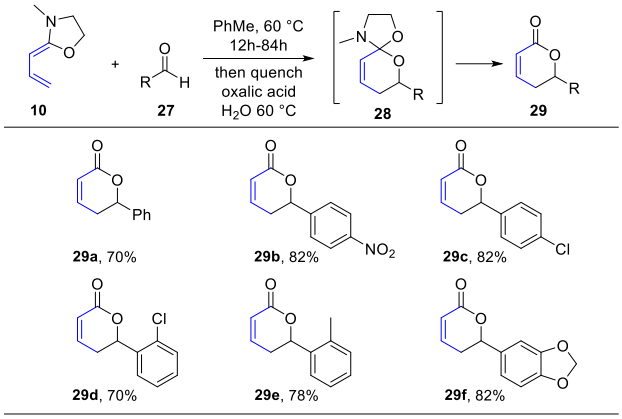
Scheme 6. Diels-Alder reactions of substituted oxazolidine-butadienes with various dienophiles



simple and direct route to 6-substituted dihydro-2-pyrones. This subunit is found in many bioactive natural products and, consequently, is the subject of much synthesis work.[20] As noted above, we had observed the formation of a labile side-product, which was presumed to be the hetero Diels-Alder adduct. To capitalize on this observation, we carried out the reaction of **10** with benzaldehyde (PhH, 60 °C) and were delighted to observe the clean formation of cycloadduct **28**, as confirmed by NMR. As the cycloadduct proved labile to isolation, the reaction was quenched directly with aqueous oxalic acid, which promoted its hydrolysis to afford the α,β-unsaturated δ-lactone product **29a** in 70% yield. Given the simplicity of the procedure, we examined the HDA reaction of **10** with several common aldehydes and found the process to be useful for both electron-poor and electron-rich aromatic aldehydes (Scheme 7). Aliphatic aldehydes were unreactive under the conditions used.

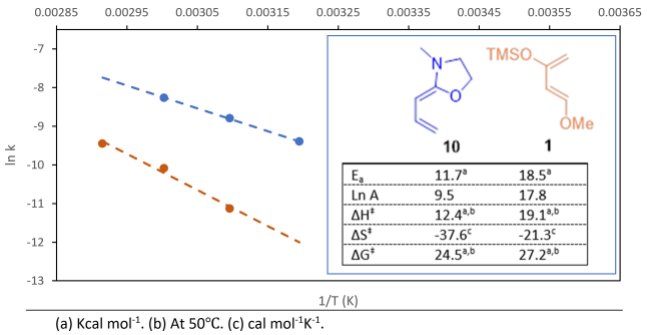
The breadth of facile reactions observed with diene **10a** and its more substituted derivatives motivated us to benchmark its reactivity against other highly reactive dienes, such as Danishefsky's diene(**1**), 1-amino-3-siloxybutadiene (**3**), and its carbamate derivative (**30**). The kinetic measurements were carried out at 60 °C in C_6D_6 and the product concentrations were monitored by ^{1}HNMR. The second order rate constant for the reaction between diene **10** and diethyl fumarate in benzene was determined to be $2.7x10^{-4}$ $M^{-1}s^{-1}$ (Table 1).[15b] For diene **1** and carbamate diene **30**, the rate constants

Scheme 7. Hetero-DA rxn of diene 10 with aromatic aldehydes



are $4.1x10^{-5}$ $M^{-1}s^{-1}$ and $3.5x10^{-5}$ $M^{-1}s^{-1}$, respectively. Also listed are the reported rate constants for the reaction between the 1-amino-3-siloxy diene **3** and diethyl fumarate at 17 °C, and with methacrolein at 17 and 60 °C.[21] The results show that while Danishefsky's diene **1** and carbamate diene **30** react with fumarate at approximately the same rate, diene **10** reacts nearly 7x faster. All three dienes reacted 2-3x faster in chloroform. Interestingly, although dienes **3** and **10** have similar heteroatom substituents, the latter is considerably less reactive, likely due to the steric hindrance from the cis-oriented oxygen.

To get further insight on the relative reactivities of the dienes, we determined the activation parameters for the DA reactions of diethyl fumarate with dienes **1** and **10** (Figure 1). As expected, the activation energy (E_a) for the reaction with Danishefsky's diene was found to be substantially larger than that with diene **10**. Arrhenius plots extrapolated from the kinetic data indicate a much larger difference in the relative reactivity of dienes **1** and **10** at room temperature.[15b] Interestingly, above 140 °C, diene **1** is predicted to react faster with diethyl fumarate than diene **10**.



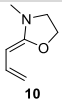
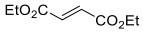
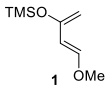
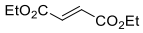
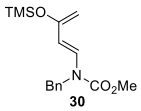
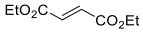
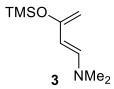
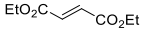
(a) Kcal mol^{-1}. (b) At 50°C. (c) cal $mol^{-1}K^{-1}$.

Figure 1. Arrhenius plots and activation parameters for the reaction of dienes **1** and **10** with diethyl fumarate in toluene; [diene]0 = 0.2M, [dienophile]0 = 0.6 M. Rate constants for **1** measured at 50, 60, and 70 °C. Rate constants for **10** measured at 40, 50, and 60 °C.

As the results above demonstrate, 1-amino-1-oxobutadienes represent an important addition to the family of reactive, heteroatom-substituted dienes. The parent diene can be synthesized in one step from a stable triflate salt precursor, and it and all related dienes can be prepared on a multigram-scale. The new dienes undergo

Diels-Alder reactions with a broad range of dienophiles to afford, after in situ hydrolysis, a variety of 6-substituted-2-cyclohexenones, which should prove to be versatile building blocks for the synthesis of complex molecules. The HDA reactions of the parent diene with aldehydes give direct access to 6-substituted 5,6-dihydro-2-pyrones. Kinetics experiments indicate that the new diene, despite its added steric interactions, is significantly more reactive than other highly active dienes such as Danishefsky's diene, especially at lower temperatures. Further expansion of the chemistry of these dienes, especially the development of enantioselective DA or HDA reactions or reactions with other heterodienophiles, is expected to greatly enhance their usefulness in chemical synthesis.

Table 1. Rate constants for DA reactions of some reactive dienes

entry	diene	dienophile	temperature (°c)	k_2 ($M^{-1}s^{-1}$)	relative rate
1[a]	 **10**		60	2.6×10^{-4}	7.1
2[a]	 **1**		60	4.1×10^{-5}	1.1
3[b,c]	**1**		17	3.6×10^{-6}	0.1
4[a]	 **30**		60	3.5×10^{-5}	1.0
5[a,b]	 **3**		17	1.5×10^{-3}	42.8
6[a,b]	**3**		17	2.0×10^{-3}	57.1
7[b,d]	**3**		60	2.0×10^{-2}	571.4
8[b,c]	**3**		17	1.2×10^{-2}	342.9

(a) Run in C_6D_6. (b) Values from Kozmin et al.[24] (c) Run in CDCl3 (d) Run in Tol-d_8.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, and copies of NMR spectra (PDF)

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Author Contributions

‡PKE and NDD contributed equally to the work. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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[9] The 6,6-disubstituted cyclohexanone motif, or its further modified derivative, is found in numerous natural products, including platencin, welwitindolinones, cyanthiwigin B, acutifolone A, and lycopoclavamine A.

[10] Such dienes have been shown to be effective primarily with highly activated dienophiles. See: (a) Banville, J.; Grandmaison, J.-L.; Lang, G.; Brassard, P. "Reactions of ketene acetals. Part I. A simple synthesis of some naturally occurring anthraquinones," *Can. J. Chem.* **1974**, *52*, 80–87; (b) Mitchell, W. L. Ph.D. Thesis, Imperial College, London, U.K. 1978; (c) Ley, S. V.; Mitchell, W. L.; Radhakrishnan, T. V.; Barton, D. H. R. "The synthesis and Diels–Alder reactions of 2-prop-2-enylidene-1,3-dioxolan," *J. Chem. Soc., Perkin Trans. 1* **1981**, 1582-1584; (d) Sustmann, R.; Tappanchai, S.; Bandmann, H. "(*E*)-1-Methoxy-1,3-butadiene and 1,1-dimethoxy-1,3-butadiene in (4+2) cycloadditions. A mechanistic comparison," *J. Am. Chem. Soc.* **1996**, *118*, 12555-12561.

[11] (a) Banville, J.; Brassard, P. "Reactions of ketene acetals. Part 7. Total syntheses of the tetramethyl ethers of the 1-acyl-2,4,5,7-tetrahydroxyanthraquinones rhodolamprometrin and rhodocomatulin," *J. Chem. Soc., Perkin Trans. 1* **1976**, 1852–1856; (b) Caron, B.; Brassard, P. "Regiospecific α-substitution of crotonic esters synthesis of naturally occurring derivatives of 6-ethyljuglone," *Tetrahedron* **1991**, *47*, 4287–4298.

[12] (a) Gillard, M.; T'Kint, C.; Sonveaux, E.; Ghosez, L. "Diels-Alder reactions of "pull-push" activated isoprenes," *J. Am. Chem. Soc*. **1979**, *101*, 5837–5839; (b) Reaction of 1-Amino-1-acyloxybutadiene with N-phenyltriazolinedione (yield unspecified): Bottomley, W. E.; Boyd, G. V. "Acylation of tertiary amides. Formation of 1-acyloxyiminium salts and 1-acyloxyenamines," *J. Chem. Soc., Chem. Commun*. **1980**, 790–791.

[13] Applications of such dienes in other reactions, especially vinylogous Mannich reactions, have been reported. For selected examples, see: (a) Denmark, S. E.; Heemstra, J. R. "Lewis base activation of Lewis acids. Vinylogous aldol addition reactions of conjugated N, O-Silyl ketene acetals to aldehydes." *J. Am. Chem. Soc.* **2006**, *128*, 1038–1039; (b) Basu, S.; Gupta, V.; Nickel, J.; Schneider, C. "Organocatalytic enantioselective vinylogous Michael reaction of vinylketene silyl-N,O-acetals," *Org. Lett.* **2014**, *16*, 274–277.

[14] Robertson, J.; Chovatia, P. T.; Fowler, T. G.; Withey, J. M.; Woollaston, D. J. "Oxidative spirocyclisation routes towards the sawaranospirolides. Synthesis of ent-sawaranospirolides C and D," *Org. Biomol. Chem.* **2010**, *8*, 226–233.

[15] (a) The minor product degraded during aqueous work-up or chromatographic purification, which prevented its isolation in pure form. (b) See Supporting Information for details. (c) The main product isolated from the reaction was tentatively assigned as the product of a Michael addition into MVK from the two position of the diene.

[16] Reaction promoted using heat: (a) Martinez, A. R.; Iglesias, G. Y. M. "Regio- and stereochemical study of the Diels-Alder reaction between (E)-3,4-dimethoxy beta-nitrostyrene and 1-(trimethylsilyloxy)buta-1,3-diene," *J. Chem Research (M*) **1998**, 0853-0858. Some dienes give apparent DA products, although likely proceeding by a stepwise process: (b) Hosokawa, S.; Matsushita, K.; Tokimatsu, S.; Toriumi, T.; Suzuki, Y.; Tatsuta, K. "The first total synthesis and structural determination of epi-cochlioquinone A," *Tetrahedron Lett.* **2010**, *51*, 5532-5536.

[17] NMR analysis of the crude reaction mixture showed a clean and nearly quantitative formation (>95%) of the DA adducts (**18**). The modest yield of the ketone products appears to reflect loss during the hydrolysis step.

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[19] The corresponding cycloheptanone-derived diene was also synthesized, and it underwent the DA reactions in comparable yields.

[20] Review: (a) Tietze, L. F.; Kettschau, G.; "Hetero Diels-Alder reations in organic chemistry," In *Stereoselective Heterocyclic Synthesis I. Topics in Current Chemistry*, Springer, Berling, Heidelberg, **1997**, vol 189, pp 1-120 and references therein;(b) Lin, L.; Kuang, Y.; Liu, X.; Feng, X. "Indium (III)-catalyzed asymmetric hetero-Diels–Alder reaction of Brassard-type diene with aliphatic aldehydes," *Org. Lett.* **2011**, *13*, 3868–3871; (c)Moriyama, M.; Nakata, K.; Fujiwara, T.; Tanabe, Y.; "Divergent asymmetric total synthesis of all four pestalotin diastereomers from (R)-glycidol," *Molecules*, **2020**, 25, 394-410.

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