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# Applications of Danishefsky's dienes in asymmetric Oxo-Diels-Alder reactions

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ABSTRACT

Applications of Danishefsky's dienes in catalytic asymmetric hetero-Diels-Alder (AHDA) reactions or specifically, their asymmetric Oxo-Diels-Alder (AOxo-DA) reactions with appropriate dienophiles are highlighted in detail, including the preparation of catalysts with discussion from a mechanistic points of view. Danishefsky's dienes are effective and useful compounds for the synthesis of optically active six-membered rings such as dihydropyrones, dihydropyridones and dihydropyrans. Due to the broad range of the overall subject, we have limited ourselves, to the recent developments in the utility of Danishefsky's dienes in the reaction with carbonyl compounds (aldehydes, ketones and 1,2-dicarbonyl compounds) in asymmetric Oxo-Diels-Alder (AOxo-DA) reactions.

## Contents

## 1. Introduction

The Diels-Alder reaction was discovered in 1928.[1] Since then, it has been a key reaction in synthetic organic chemistry especially in the construction of six-membered rings as scaffolds in the structure of natural products. A variety of Diels-Alder reactions have opened a gateway to promote the art of synthetic organic chemistry. Diels-Alder reactions drew a lot of attention because of their extensive applications due to its essentiality for the synthesis of compounds required in academia, as well as industry and the synthesis of several other significant compounds needed of life today.

One of the most important variants of the Diels-Alder reaction is the asymmetric hetero-Diels-Alder (AHDA) reaction.[2] The Diels-Alder reaction undoubtedly, is one of the most important C—C bond-forming reactions, as well as being remarkable in carbon–heteroatom bond formation. Thus, it provides several approaches for the highly efficient catalyzed stereoselective synthesis of optically active six-membered ring compounds including heterocycles such as dihydropyrans, and dihydropyrones, etc. When one of the substrates has at least one heteroatom in its structure, the Diels-Alder reaction is called the hetero-Diels-Alder (HAD) reaction, thus, when a stereoselective hetero-Diels-Alder

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*Abbreviations:* CAB, a stable chiral (acy1oxy)borane; TBME, *tert*-butyl methyl ether; EDOT, 3,4-ethylenedioxythiophene; CAN, a chiral Ce(IV) complex from ammonium cerium(IV) nitrate; TADDOL, α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanols; 5-C1-BIPOL, 5,5′-dichloro-4,4′,6,6′-tetramethylbiphenol; BINOL, binaphthol; TBS, *tert*-butyldimethylsilyl; DPENTf, (*R*,*R*)-1,2-*N*,*N*′-bis-(trifluoromethanesulfonylamino)-1,2-diphenylethane; DABNTf, (*R*)-2,2′-bis-(trifluoromethanesulfonylamino)-1,1′-binaphthyl; TBDPS, *tert*-butyldiphenylsilyl; PMB, 4-methoxybenzyl ether; TFA, trifluoroacetic anhydride; PEG, poly(ethylene glycol); DMF, dimethylformamide; $Ti(O^iPr)_4$, titanium isopropoxide; TBAT, tetrabutylammonium triphenyldifluorosilicate; TMSF, trimethylenesulfide; (−)-DIOP, (−)-2,3-D-isopropylidine-2,3-dihydroxy-l,4-bis(diphenylphosphino)butane; (−)-CHIRAPHOS, (−)-(2*S*,3*S*)-bis(diphenylphosphino)butane; BNP, (1,1′-binaphthyl-2,2′-diylphosphate); TON, turnover numbers; Phebox, 2,6-bis(oxazolinyl)phenyl.

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reaction is under discussion it is called asymmetric hetero-Diels-Alder (AHDA) reaction.[3] The first AHDA reaction of carbonyl groups with appropriate dienes was achieved and reported by Danishefsky et al. who reacted benzaldehyde with 1-*tert*-butoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene.[4]

Frequently, these conversions are Lewis acid catalyzed reactions. The stereoselective variants of these reactions are particularly popular since they lead to enantiomerically pure six-membered heterocycles, which partly unsaturated, with at least one stereogenic center. This class of compounds have broad applications as precursors or starting materials for the total synthesis of several naturally occurring compounds and other complex and highly functionalized heterocyclic moieties.[5]

In 1974, Danishefsky et al. developed an electron-rich diene which due to its significance has become the so-called 'Danishefsky's diene (Fig. 1).[6]

It was first synthesized by the reaction of trimethylsilyl chloride with 4-methoxy-2-buten-one in the presence of zinc chloride. The zinc chloride is a Lewis acid that activates the oxygen for promoting the reaction with silicon (Scheme 1).

Danishefsky's diene (Kitahara diene) is actually an organosilicon compound with the IUPAC name of *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene. The methoxy group promotes the highly regioselective additions. The diene was proven to react with carbonyl compounds,[7] alkenes,[8] alkynes,[9] imines[10] and nitro-olefins.[11]

This diene has two prominent features: (a) it is highly electron rich, and (b) the functionalities are easily removed after the addition is performed, generating an α,β-unsaturated ketone in a six-membered ring system.[6]

In connection with a variety of synthetic objectives, it would be useful to realize that transformations of this kind is generally limited.[12,13] The nature of X and Z should be carefully considered. It shows high reactivity and high specificity with respect to diene **I** in its reactions with unsymmetrical dienophiles of the type **II**, where Y is an electron withdrawing groups such as carbonyl, cyano, etc.[14] The character of X should allow for conversion of the XC=C type of enol derivative in **III** into the ketone found in **IV** and **V**. The function Z should be selected for easy β-elimination, thus allowing the transformation of **IV** → **V**. Indeed, the direct transformation of **III** → **V** may also be possible.[15] Alternatively, the Z group in **IV** may be maintained for purposes of protection of a latent enone or possibly for its own functionality. Finally, of course, the diene **I** should be readily prepared and accessible (Scheme 2).

Noticeably, there are other variants on the Danishefsky's diene, as shown below in Scheme 3.[6]

Since this diene is very electron-rich it is expected to be very reactive in Diels-Alder and HDA reactions (Scheme 4).

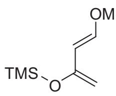
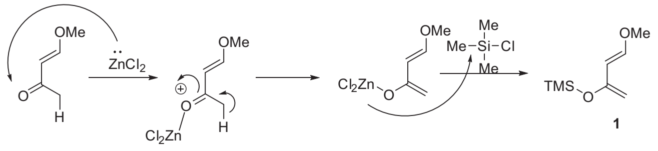
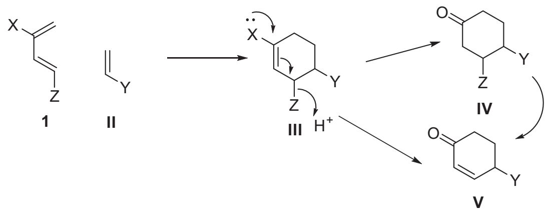


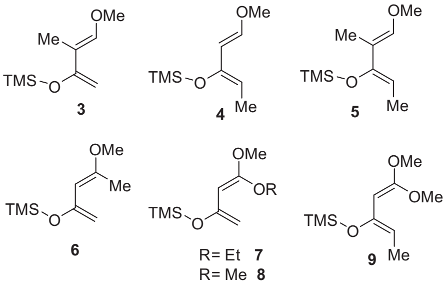
**Figure 1.** Danishefsky's diene.



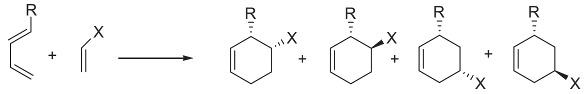
**Scheme 1.** Synthesis of Danishefsky's diene.



**Scheme 2.** The nature of X and Z should result in high reactivity and high versatility of specificity on diene **I** in its reactions with unsymmetrical dienophiles of the type **II**.



**Scheme 3.** Various modified Danishefsky's dienes.

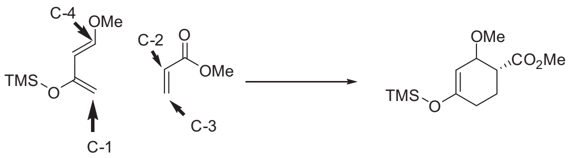


**Scheme 4.** Reactivity of Danishefsky's diene.

Generally, Diels-Alder reactions afford a mixture of regioisomeric products. Notably Danishefsky's diene shows a strong regiochemical tendency for the silyl ether being oriented near the more electron deficient part of the dienophile. The dienophile depicted in Scheme 5 is more electron withdrawing at C3 than at C2, thus, it reacts easily with the silyl ether diene to afford a single regioisomeric product. The reason for the observed high regioselectivity is attributed to electron-richness of C1 of the diene relative to C4 (Scheme 5).

Two mechanistic pathways have been suggested for the Lewis acid catalyzed HDA reactions. (a) A conventional Diels-Alder cycloaddition and (b) generation of the HDA adduct via a Mukaiyama-aldol reaction approach when a carbonyl compound is employed or a Mannich-type reaction for an imine is involved (Scheme 6).[16]

The mechanistic investigations of $BF_3$-catalyzed HDA reactions of carbonyl compounds **2a** with *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-dimethyl-1,3-butadiene[17] **5** (Scheme 6) revealed that the



**Scheme 5.** Strong regiochemical inclination for the silyl ether being oriented stated near the more electron deficient part of the dienophile.