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Enantioselective Addition of Alkynes to α,α-Dichlorinated Aldehydes

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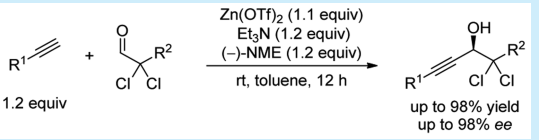
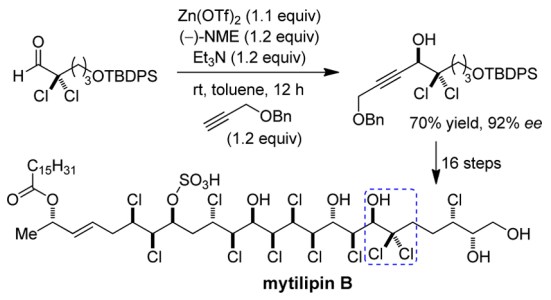
Supporting Information

ABSTRACT: Enantioselective addition of terminal alkynes to α,α-dichlorinated aldehydes employing $Zn(OTf)_2$/NME is disclosed. The propargylic alcohols obtained are accessed in good yields and high enantioselectivity from easily accessible α,α-dichloroaldehydes. The method opens new strategic opportunities for the synthesis of chlorinated natural products, such as the chlorosulfolipids.



There are numerous bioactive natural products that incorporate C_{sp3}-bound chlorides.[1] These have served as a source of inspiration for the development of methods enabling their stereoselective synthesis.[2] An often-occurring structural motif in chlorinated lipids is *gem*-dichlorides in proximity to a stereogenic center, such as a secondary alcohol. We have previously reported the implementation of Zn^{II}-mediated enantioselective alkyne additions to aldehydes[3] in the total synthesis of undecachlorosulfolipid A, also known as mytilipin B (Scheme 1).[4,5] Herein, we document that the reaction can be extended to a collection of other α,α-dichloroaldehydes to furnish products in useful yields and high enantiocontrol.

Scheme 1. Example of Asymmetric Addition of an Alkyne to a Dichlorinated Aldehyde in the Synthesis of Mytilipin B



The presence of chiral propargylic alcohols in synthetic routes to natural products and pharmaceuticals makes them highly valuable buildings blocks.[6] Various methods for the asymmetric synthesis of propargylic alcohols have been disclosed. These include direct addition of metalated nucleophilic acetylenes to prochiral aldehydes[7] or the asymmetric reduction of alkynyl ketones.[8] Since the Zn^{II}-mediated enantioselective addition of alkynes to aldehydes was described by our group,[3] there has been widespread use of this method by the synthetic community.[9] This simple and mild reaction constitutes a powerful means to access intermediates employed in the synthesis of complex molecules.[10]

The first addition of an alkyne to α,α-dichlorinated aldehyde was reported by Maruoka and co-workers in 1998.[11] They employed an aluminum-based alkynylation using phenylacetylene and 2,2-dichlorodecanal to give adducts as racemates. An asymmetric version of this reaction was also disclosed using aluminum alkoxides, although α,α-dichlorinated aldehydes were not tested.[12]

In approaching the methodological studies described herein, the strong electrophilic nature and low stability of these aldehydes were of concern, in particular, whether the initial conditions reported for the sole example of Zn-mediated addition[4a] would be extendable to other substrates. Additionally, we were interested in investigating whether the additions would give rise to adducts that in turn would be amenable to further synthetic elaboration.

The α,α-dichlorinated aldehydes in this study were synthesized from the corresponding aldehydes via dichlorination of their enamines following a known procedure.[13,14] However, they were not amenable to purification by silica gel chromatography, and accordingly, they were either purified by distillation or used without purification. We were pleased to find that conditions employed in the mytilipin B synthesis[4a] could be employed with a wide range of substrates, as shown in Scheme 2.

This method exhibits wide substrate scope and is compatible with various functional groups on both the alkyne and the aldehyde moieties (Scheme 2). The ^1H NMR of the unpurified product always showed conversion to a greater extent than 85%.[15] The method shows tolerance for a wide range of protecting groups and functional groups, including primary chlorides. The configuration of product **3c** was confirmed by X-ray crystallography, and for all other adducts, the absolute configurations were determined by analogy.[16] In the study, the addition to give **3c** was carried out at 1 mmol scale to give products in equally high yield and selectivity, consistent with the use of the reaction in the total synthesis of mytilipin B.

The method tolerates olefins (**3d**) and arenes in the aldehyde substrate (**3e**), giving good results in yields and enantiose-

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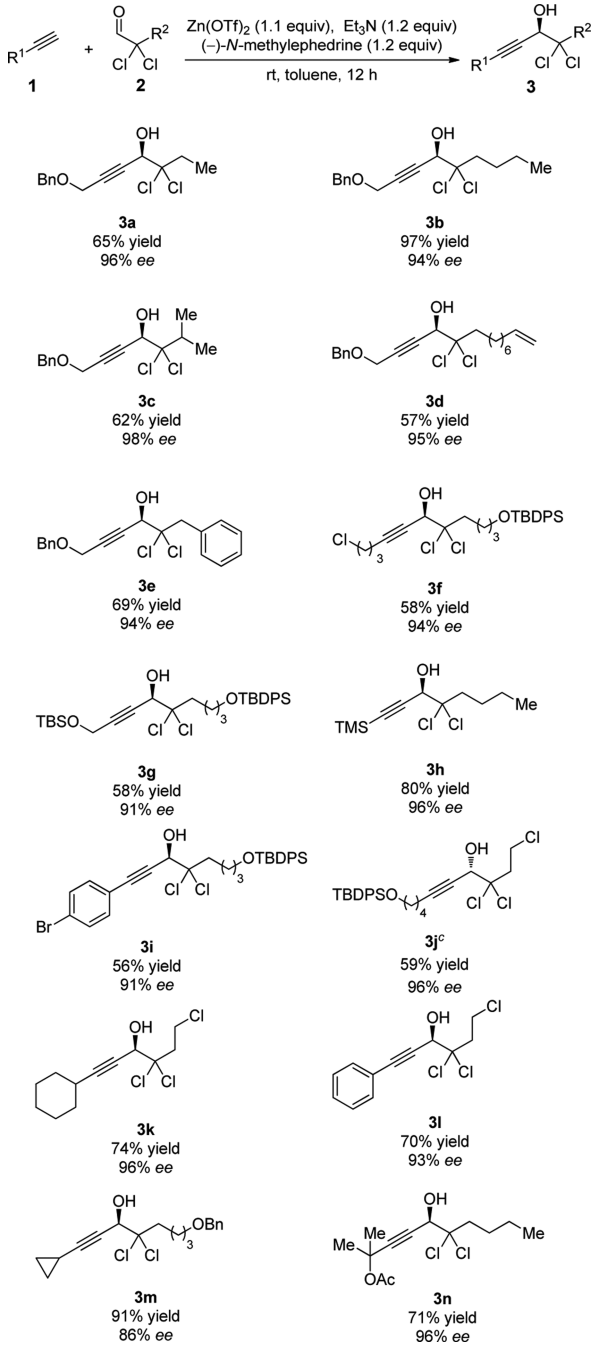
Scheme 2. Asymmetric Alkynylations of α,α-Dichlorinated Aldehydes[a,b]



[a]Standard procedure: **1a–n** (1.2 equiv), **2a–n** (1 equiv), $Zn(OTf)_2$ (1.1 equiv), Et_3N (1.2 equiv), (−)-NME (1.2 equiv), toluene, 24 °C, 12 h. [b]Yields of purified products. [c]Compound **3j** was synthesized by employing (+)-NME.

lectivities. The reaction can be carried out in the presence of silyl-protected alcohols or ethers (products **3f**, **3g**, or **3m**), thus providing opportunities for further elaboration of the products. Additionally, a primary chloride is compatible in this Zn^{II}-mediated process, and no side products derived from its elimination are observed (see products **3j–l**). When the aldehyde was used in excess (1.5 equiv of **2c**), comparable yields were obtained under otherwise identical conditions.

A range of functionalized alkynes was also examined, and the appended side chains serve as a second point for further synthetic elaboration of the products. In this regard, the substitution in the α-position to the alkyne moiety was well tolerated to furnish adducts in up to 96% ee and in good yields (**3h,i,k–n**). Likewise, the alkyne can bear an ether or silyl ether group without any adverse effect on enantioselectivity (for example, **3b**, **3g**, or **3j**). However, when free alcohols were present in the alkyne the reaction did not proceed well (yields lower than 40%). The use of 6-chloro-1-pentyne (**1f**) demonstrates that primary chlorides can be present in both fragments of the molecule.

In summary, we have disclosed a substantive expansion of the Zn^{II}-mediated asymmetric addition of alkynes to include additions to α,α-dichlorinated aldehydes, which proceed to furnish adducts in greater than 86% ee. The scope as well as attendant yield and enantiomeric excesses observed are promising for the application of the method in the synthesis of a variety of chlorinated natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03692.

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

X-ray data for compound **3c** (CIF)

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Notes

The authors declare no competing financial interest.

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(15) The reaction is difficult to follow by TLC due to the low stability of the α,α-dichlorinated aldehydes on silica. Therefore, the reactions were run for 12 h as a standard reaction time.

(16) CCDC 1432243 (**3c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

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