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Enantioselective Propargylic Oxidation

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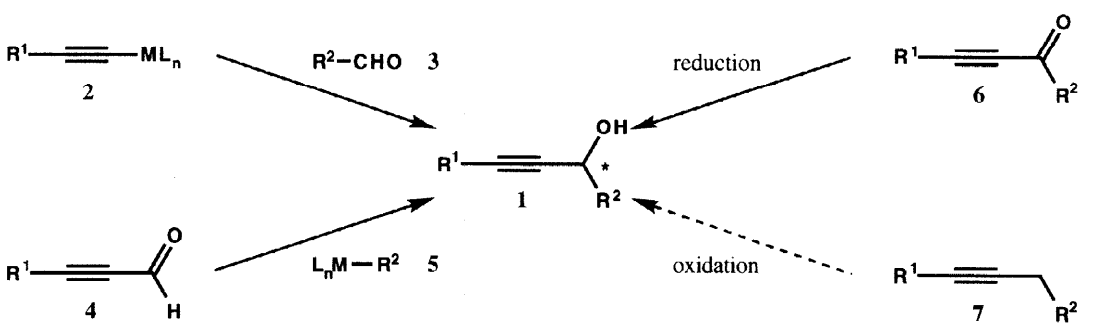
Abstract

Benzoyl esters of propargylic alcohols can be prepared in an enantioselective manner by direct copper-catalysed acyloxylation of alkynes with *t*-butyl peroxybenzoate. High product yields and reasonable levels of induction are obtained upon the oxidation of non-terminal alkynes with excess perester using copper-bisoxazoline complexes as catalysts.

Keywords: alkyne; enantioselection; catalysis; oxidation

Propargylic alcohols and their derivatives are important synthetic intermediates, and can be used for the preparation of *E* or *Z* allylic alcohols, chiral allenes[1] and a variety of other functionalised synthetic building blocks. At the present time, there are three general methods for preparation of enantiomerically pure propargylic alcohols: the addition of alkynyl organometallic reagents to aldehydes (**2+3→1**),[2] the addition of organometallic reagents to alkynyl aldehydes (**4+5→1**),[3] and the reduction of alkynyl ketones (**6→1**)[4] (**Scheme**). Although some of these methods have general applicability, many of them involve the use of air-sensitive reagents, require stoichiometric amounts of a chiral additive, or deliver propargylic alcohols of modest enantiomeric purity. In an effort to develop a novel and efficient general strategy for the direct enantioselective synthesis of propargylic alcohol derivatives that circumvents these problems, we have explored the catalytic asymmetric propargylic oxidation of unfunctionalised alkynes (**7→1**) (**Scheme**). The results of our preliminary investigations directed towards this objective are described in this *Letter*.



Scheme

As far as we are aware, the direct enantioselective synthesis of propargylic alcohols by oxidation of simple alkynes is unprecedented. Following our recent work concerning the enantioselective synthesis of allylic alcohols from unfunctionalised alkenes using an asymmetric variant of the Karash-Sosnovsky reaction,[5] we initiated a programme to develop an analogous catalytic reaction for the enantioselective oxidation of alkynes to propargylic alcohol derivatives.

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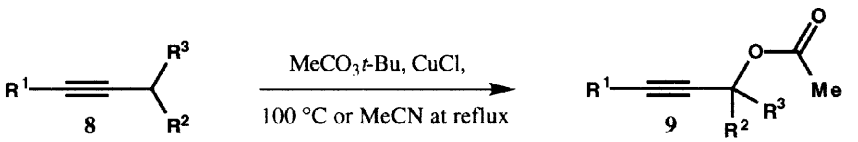
There are very few examples of propargylic oxidation using the Karash-Sosnovsky acyloxylation reaction, the first general study having been performed by Kropf and co-workers in 1977.[6] The results of that study showed that the acyloxylation of some simple alkynes could be performed under rather harsh conditions to provide esters of propargylic alcohols in low or modest yields (eq. 1). In order to establish the viability of this reaction, we commenced our studies by performing some of the reactions described by Kropf, but under milder conditions (acetonitrile, 40 °C) and with a more suitable copper(I) source [$Cu(MeCN)_4PF_6$]. Similar yields (13–51%) to those reported by Kropf were obtained when an excess of the alkyne was used.[6] Alkynes were found to be very much less reactive substrates than alkenes and reactions took several days to proceed to completion.

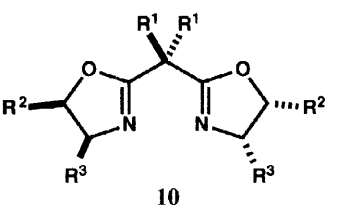


(1)

R^1 = H, Me, Et, Ph, $SiMe_3$ R^2 = H, Me R^3 = Me, Et, *n*-Pr 20–70%

After confirming that is was possible to accomplish propargylic oxidation using the Karash-Sosnovsky reaction, we turned our attention to the development of an asymmetric variant of the reaction. Bisoxazolines were selected as candidate ligands because we[5] and others[7] had found them to be highly effective for the enantioselective acyloxylation of alkenes. The ligands **10a–e** and **11** were chosen as representative examples of this class of ligands (**Figure**).[8] Preliminary investigations were then undertaken to discover whether it was possible to perform the reaction enantioselectively and to gauge how ligand structure influences yields and levels of asymmetric induction.

a	R^1 = H	R^2 = H	R^3 = Ph
b	R^1 = Me	R^2 = H	R^3 = Ph
c	R^1 = H	R^2 = Ph	R^3 = Ph
d	R^1 = H	R^2 = H	R^3 = CMe_3
e	R^1 = Me	R^2 = H	R^3 = CMe_3



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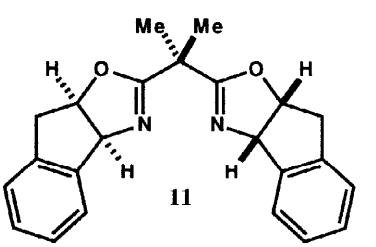

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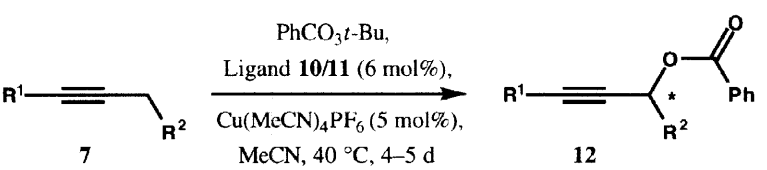
Figure

In preliminary ligand-screening studies, the enantioselective oxidation reactions of 3-hexyne (**7a**) and 1-hexyne (**7b**) were performed using a slight excess of the bisoxazoline ligand relative to the copper salt and *t*-butyl peroxybenzoate as the oxidant (eq. 2). These reactions were much cleaner and higher yielding than those performed using the Kropf procedure.[6] Although the non-terminal alkyne **7a** underwent oxidation in good yield, the terminal alkyne **7b** was oxidised in modest yield (16–47%) irrespective of the particular bisoxazoline ligand used (**Table 1**). Low levels of asymmetric induction were obtained in all cases, but those reactions involving ligands without *gem*-dimethyl substitution between the oxazoline rings (**10a**, **10c** and **10d**) provided products with very low ee (≤12%). The product yields were found to be largely unaffected by the structure of bisoxazoline ligand employed.

The results of the screening studies revealed that bisoxazoline **10b** was the most satisfactory ligand of those investigated (**Table 1**). This was consistent with our findings concerning the allylic acyloxylation reaction, which indicated that phenyl-substituted bisoxazolines were generally superior to *t*-butyl-substituted bisoxazolines as ligands in these oxidation reactions.[5]

a	R^1 = Et	R^2 = Me	
b	R^1 = H	R^2 = *n*-Pr	
c	R^1 = Me	R^2 = Et	
d	R^1 = Ph	R^2 = *n*-Pr	
e	R^1 = $SiMe_3$	R^2 = *n*-Pr	



(2)

Table 1. Enantioselective propargylic oxidation of 3-hexyne (**7a**) and 1-hexyne (**7b**) using copper-bisoxazoline complexes as catalysts (eq. 2)

Substrate[a]	Ligand	Yield 12 (%)[b]	ee (%)[c]
7a	**10b**	80	21
7b	**10b**	41	21
7a	**10e**	81	13
7b	**10e**	35	7
7a	**11**	67	7
7b	**11**	41	19

a A four-fold excess of the alkyne was used. *b* Yield of isolated material after purification by column chromatography. *b* Enantiomeric excesses were determined by chiral HPLC analysis.

Having identified a suitable catalyst ligand, we then explored reaction stoichiometry and the application of the reaction to a wider range of alkyne substrates (**Table 2**). These studies revealed that it was possible to oxidise 3-hexyne (**7a**) using either a stoichiometric amount or an excess of *t*-butyl peroxybenzoate without significant over-oxidation, even with substrates containing two oxidisable propargylic positions. Significant double oxidation was only encountered when a very large excess of perester was used and the reaction time was extended. However, even under these conditions the double oxidation reaction was very slow and the mono-oxidation product was still the predominant product. When the oxidation reaction of 3-hexyne (**7a**) was performed using a 1:1 ratio of the alkyne and oxidant, the yields were low, so it was clear that it was best to perform the reaction using an excess of the perester.

Table 2. Enantioselective propargylic oxidation of a range of alkynes (**7a–e**) using a copper complex of the bisoxazoline **10b** as the catalyst (eq. 2)

Substrate	7:Perester	Yield 12 (%)[a]	ee (%)[b]
7a	5:1	80[c]	21
7a	1:1	38	21
7a	1:2	56[d]	21
7b	1:4	43[d]	20
7c	5:1	76[c,e]	15
7d	1:4	95[d]	51
7e	1:4	92[d]	46

a Yield of isolated material after purification by column chromatography. *b* Enantiomeric excesses were determined by chiral HPLC analysis. *c* Yield based on the amount of perester used. *d* Yield based on the amount of the alkyne used. *e* Combined yield of products resulting from oxidation at the methyl and methylene groups (~7:3 ratio in favour of oxidation at the methylene group).

Very high yields and reasonable levels of induction were obtained upon oxidation of non-terminal alkynes bearing a large non-oxidisable group (e.g. phenyl or trimethylsilyl). Terminal alkynes were oxidised in lower

yield than non-terminal alkynes even when excess oxidant was used. The high yield and good level of induction for the final example in **Table 2** are especially noteworthy because alkyne substrates of this type are readily available and the trimethylsilyl group is easily removed after oxidation to provide terminal alkynes, which can be elaborated further.

The oxidation of the alkyne **7c** is particularly interesting because this substrate possesses two non-equivalent sites for oxidation that should differ in their reactivity. Under our reaction conditions, preferential oxidation at methylene position was observed even though a statistical preference for oxidation at the methyl group, reinforced by steric effects, might be expected. This observation suggests that electronic factors are important in dictating the site of acyloxylation with non-symmetrical alkyne substrates.

The mechanism of the propargylic oxidation reaction is unclear at the present time. However, it is apparent that the generally accepted pericyclic mechanism proposed for the acyloxylation of alkenes cannot be operative in these reactions because alkyne transposition or allene formation is not encountered.[9] Thus, the pericyclic mechanism that has been proposed for allylic acyloxylation must be incorrect or a different mechanism must be operative during the propargylic oxidation reaction.

The potential synthetic scope of the enantioselective propargylic oxidation reaction is obvious. Partial hydrogenation of the oxidation products will provide *E* or *Z* allylic alcohols and their derivatives in non-racemic form. This route has significant advantages compared to the direct allylic acyloxylation of acyclic alkenes because problems associated with regiocontrol and control of alkene geometry, which are frequently encountered during the oxidation of non-terminal acyclic alkenes, will be avoided. The propargylic oxidation reaction has the additional advantage that complete and high yielding conversion of the alkyne can be accomplished when an excess of the oxidant is used.

We are currently exploring the application of the asymmetric propargylic oxidation reaction to the oxidation of more highly functionalised alkynes and investigating a new generation of catalysts to enable these reactions to be performed with higher levels of induction. The results of these studies will be reported in due course.

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