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TBOxCr^{III}Cl-Catalyzed Enantioselective Synthesis of 1,3-Butadien-2-ylcarbinols

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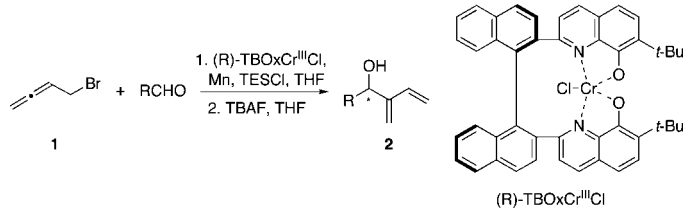
ABSTRACT



A highly enantioselective synthesis of 1,3-butadien-2-ylcarbinols is achieved by using the TBOxCr^{III}Cl catalyst and homoallenylbromide 1. This method can be further extended to the enantio- and regioselective propargylation of aldehydes.

2-Substituted-1,3-dienes, of general structure **2**, represent an increasingly important group of compounds due to their synthetic versatility. These molecules are highly useful precursors for the synthesis of several natural products.[1] One of the highly useful features of this class of compounds is the 1,3-diene moiety that can be utilized for the construction of functionalized cyclohexene rings.[2] Besides the obvious Diels−Alder reaction, alkyl(1,3-butadien-2- yl)carbinols have been successfully used in various other reactions.[3]

Until the present day, several protocols for the synthesis of this type of compounds have been published and they can be classified into two general classes. One of the pathways entails generation of 1,3-butadienyl-2-metal reagents which then add to a carbonyl group.[4] Another approach to 1,3-butadien-2-carbinols is based on the utility of 2,3-butadienyl-1-metal reagents.[5] Some of these methods suffer from difficulties associated with low regioselectivity and/or reactivity. In some instances, the protocol requires starting materials which are prepared in several synthetic steps, thereby rendering the method more tedious. Another drawback of some methods is the use of toxic reagents, such as tin compounds, as a source of the 1,3-butadiene moiety.

More recently, conceptually different methods for the preparation of 1,3-butadien-2-carbinol derivatives have been introduced.[6] In 2005, Alcaraz and co-workers reported the double homologation of 2,3-epoxy-1-bromides using dim-

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ethylsulfonium methylide to generate 1,3-butadien-2-ylcarbinols.[6a] The terminal alkyne−ethylene cross metathesis approach described by Diver et al. can also be used successfully for the synthesis of dienyl acetates and silyl and benzyl ether derivatives.[6b,c] Chan's report of an indium-based Barbier-type of reaction between 1,4-dibromo-2-butyne and aldehyde in aqueous media is noteworthy from the standpoint of atom economy and environmental issues.[6d]

Among the aforementioned accounts, there are only a few reports of enantioselective transformations.[5a,c,d,6a,b,e] Even though these reactions provide products with high yields and enantioselectivities, the scope of the substrates is not extensive.

We wish to report an enantioselective synthesis of 1,3-butadien-2-ylcarbinols using tethered bis(8-quinolinato) (TBOx) chrominum complex (TBOxCr^{III}Cl) and bromoallene **1**.

The TBOxCr^{III}Cl catalyst, developed in our group, was shown to be a highly effective catalyst for several asymmetric redox processes.[7] On the basis of the catalytic redox Cr(II)/Cr(III)−Mn system pioneered by Fürstner et al.,[8] TBOxCr^{III}Cl catalyst efficiently promotes a pinacol coupling reaction of aldehydes,[7a] asymmetric Nozaki−Hiyama allylation reaction of aldehydes,[7b] and allenylation reaction of aldehydes.[7c] These reactions proceed exceedingly well with use of low catalyst loadings to yield products in a highly diastereo-/enantioselective fashion.

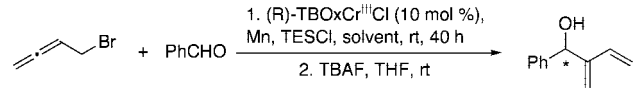
Encouraged by the reactivity of our catalyst with allyl- and propargylhalide substrates, we have turned our attention to bromoallene **1** as an alternative substrate for the Cr-catalyzed reactions.

We were interested in exploring the reactivity of bromoallene **1** in Cr-catalyzed addition to aldehydes, since it presents a more challenging substrate due to the possible formation of regioisomers. To our surprise, when bromoallene **1** was treated with TBOxCr^{III}Cl−Mn in the presence of benzaldehyde and TESCl only the 1,3-butadiene product was observed. Screening of the solvents commonly used with this catalytic system (Table 1, enteries 1−4) showed THF to be the most effective affording the product with highest yields and ee values (entry 4). Further investigation of the reaction conditions indicated that 2.0 equiv of bromoallene provided **2** in slightly higher yield.

With these optimized conditions, reactions with several aldehydes have been carried out and the results are summarized in Table 2.

The reaction proceeded well for a series of aldehydes providing adducts with good to moderate yields and high enantioselectivities. Electron-rich aldehydes afford 2-substituted 1,3-butadienes with higher yields in contrast to electron-poor aldehydes which exhibited decreased reactivity. Generally, high levels of enantioselectivity were maintained for all of the carbonyl substrates used.

Table 1. Optimization of Reaction Conditions[a]



1 2

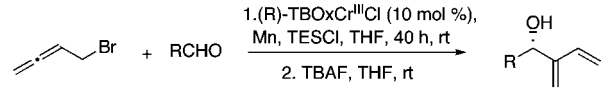
entry	solvent	yield (%)[b]	ee (%)[c]
1	MeCN	37	86
2	DME	35	87
3	MeCN:DME (1:3)	40	84
4	THF	41	90

[a] Reactions were carried out with 2.0 equiv of **1**, 1.0 equiv of PhCHO, 3.0 equiv of Mn, and 1.0 equiv of TESCl. [b] Yields of the isolated products. [c] Determined by HPLC analysis.

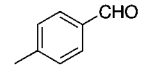
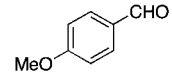
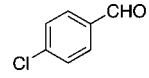
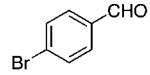
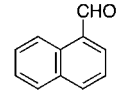
Encouraged by the high regioselectivity observed in the dienylation reaction, we were interested in the reactivity of simple propargyl bromide as a substrate for Cr-catalyzed reaction. Interestingly, the formation of (*R*)-homopropargyl alcohol of benzaldehyde occurred exclusively (Scheme 1). Therefore the TBOxCr^{III}Cl−Mn system can be effectively employed in an enantioselective propargylation of aldehydes.

Comparison of the optical rotation value with previously published data revealed that products have (*R*)-absolute

Table 2. Scope of the Dienylation Reaction[a]



1

entry	RCHO	yield (%)[b]	ee (%)[c]
1	PhCHO	41	90
2		45	89
3		47	90
4		34	85
5		32	86
6		28	85

[a] Reactions were carried out with 2.0 equiv of bromoallene **1**, 1.0 equiv of aldehyde, 3.0 equiv of Mn, and 1.1 equiv of TESCl. [b] Yields of the isolated products. [c] Determined by HPLC analysis with Chiracel OB-H column.

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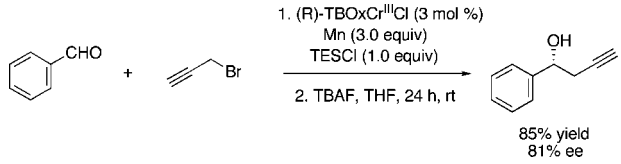
Scheme 1. Highly Regioselective Propargylation of Benzaldehyde



configuration. This observation is consistent with our results of the allylation[7b] and allenylation[7c] reactions of aldehydes catalyzed by (*R*)-TBOxCr^{III}Cl. On the basis of these observations we could propose two plausible transition states that could occur during the reaction (Figure 2).

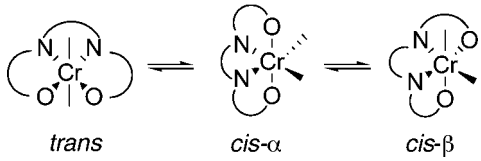


Figure 1. Possible geometries of the octahedral chromium center in TBOxCr^{III}Cl complex.

TBOxCr^{III}Cl may have a total of three geometric isomers (Figure 1), given that it adapts octahedral coordination geometry.

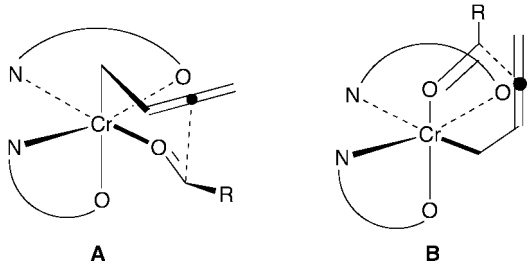


Figure 2. Possible transition states leading to (*R*)-alcohols

The X-ray structures of *rac*-TBOxCrCl revealed that TBOxH ligand is bound to the chromium center in a *cis*-β configuration. The crystal structure of TBOx(EtOH)$_2$Cr^{III}Cl also showed that the two reactive sites are positioned *cis* to each other and fit closely into the concave site of the TBOxCr^{III} complex.[7a]

Although the free TBOxH ligand has C_2-symmetry, the produced *cis*-β metal complex does not. Thus, the metal center of the resulting *cis*-β complex is chiral and two of the coordination sites are nonequivalent. Owing to the C_2-symmetry of the ligand we do not need to worry about the possible generation of two stereoisomers.

Considering the geometry of the *cis*-β configuration of the metal center, two transition states that lead to (*R*)-alcohols can be envisioned (Figure 2). In the transition state **A**, the allenyl moiety is bonded axially to chromium while the aldehyde adopts an equatorial orientation. Clearly, the aldehyde coordinates to chromium through its oxygen electron pair in the *trans* manner to the aldehyde's *R*-group. In such a spatial arrangement, nucleophilic attack of the dienyl moiety occurs at the Re-face of the aldehyde to deliver (*R*)-alcohol. The transition state **B** involves opposite coordination of the substrates. More specifically, the allenyl moiety is now bonded to chromium in the equatorial position and aldehyde adopts the axial position. In this assembly, aldehyde coordinates to the metal center in a similar fashion as in **A** leaving its Re-face open for the addition of dienyl moiety (Figure 2).

A noteworthy feature of this reaction is high regioselectivity for the addition of organochromium species. In our previous studies regarding S_Ei' processes for propargyl and allenyl metal reagents, intermediate organometallic species generated from trimethylsilyl-substituted alkynes reacted at their less hindered site.[9] In contrast to those accounts, here we observe the formation of 1,3-butadienyl products which arise exclusively from the addition of organochromium intermediate where chromium is located at a more sterically hindered site.

In summary, we have developed a method for the enantioselective synthesis of 1,3-diene-2-ylcarbinols using chiral tethered bis(8-quinolinato) ligand (TBOxH) developed in our laboratory. The protocol described provides products with high ee values and moderate yields under mild reaction conditions. The TBOxCr^{III}Cl catalyst circumvents the difficulties generally associated with the regioselectivity of the reaction. Furthermore, the method does not require the use of toxic reagents used in previous enantioselective syntheses of this class of compounds.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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