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Controlling Enantioselectivity in Additions to Cyclic Oxocarbenium Ions via Transition Metal Catalysis

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Abstract

Controlling enantioselectivity in additions to oxocarbenium ions remains a challenge in asymmetric catalysis. By catalytically generating a chiral organometallic intermediate, a copper acetylide, we have developed a novel approach for additions of carbon nucleophiles to cyclic oxocarbenium ions in high enantioselectivities and yields.

Keywords

asymmetric catalysis; oxocarbenium ions; transition metals; alkyne addition; enantioselectivity

Within the field of asymmetric catalysis, a variety of methods have been established for highly enantioselective additions of carbon nucleophiles to imines, aldehydes and ketones to provide enantioenriched alcohol and amine products.¹ Many of these methods rely on the Lewis or Brønsted basicity of the electrophilic substrates to bind the electrophile to a chiral catalyst, thereby catalytically generating a chiral electrophile in situ (Figure 1). In sharp contrast, oxocarbenium ions lack a Lewis basic site for coordination to a chiral Lewis acidic catalyst, thereby requiring alternative strategies for controlling facial selectivity in reactions of these defiant electrophiles.

In addition to the inherent challenge of these substrates to asymmetric catalysis, the utility of the chiral ether products has provoked several research groups, including ours, to develop new strategies to enable highly enantioselective additions to prochiral oxocarbenium ions.² Before our work in this area, the methods reported for enantioselective additions of carbon nucleophiles to prochiral oxocarbenium ions had relied on either chiral Lewis acids or organocatalysts.^{2a–e, 2g–i} We have now shown that a method employing a chiral transition metal catalyst and proceeding through organometallic intermediates also provides high enantioselectivity in additions to prochiral oxocarbenium ions (Scheme 1).^{2f} Due to the importance of α -substituted oxygen heterocycles as biologically active molecules and

natural products (Figure 2),³ we and others in this area have focused on additions to cyclic oxocarbenium ions.

Three highly innovative approaches towards enantioselective additions to prochiral cyclic oxocarbenium ions had been demonstrated before our work.^{2a-c} Collectively, these methods showed that enantioselectivity can be achieved via catalytic generation of either a chiral electrophile or a chiral nucleophile. The first method was published in 2004, when Braun reported a single example of enantioselective allylation of racemic tetrahydropyranyl acetal **3** (Scheme 2).^{2a} Braun proposes that this reaction proceeds via dynamic kinetic resolution of the Lewis acid-bound acetal; interconversion of the diastomeric catalyst-acetal complexes occurs via a prochiral oxocarbenium ion. By coordination of the titanium catalyst to the methoxy group, Braun catalytically generates a chiral electrophile. Despite the necessity for stoichiometric Ti(IV) for catalytic turnover, this reaction is notable as a first demonstration that catalytic generation of a chiral electrophile is possible in additions that proceed via oxocarbenium ion intermediates.

The Jacobsen group demonstrated an impressive alternative approach to catalytic generation of a chiral electrophile using a thiourea catalyst (Scheme 3).^{2b} In this addition of silyl ketene acetals to isochroman acetals, the chiral thiourea is proposed to bind the chloride ion upon ionization of the α -chloro ether intermediate. Via electrostatic attraction (and other noncovalent interactions), the chiral thiourea is thus associated with the oxocarbenium ion and controls facial selectivity in the C–C bond formation.

In an elegant and fundamentally distinct approach, Schaus et al. showed that catalytic generation of a chiral nucleophile can also enable highly enantioselective additions of vinyl and aryl nucleophiles to chromene acetals (Scheme 4).^{2c} As shown, the tartrate-derived diol catalyst, in concert with a Lewis acid co-catalyst, transforms the boronic ester into a chiral boronate nucleophile.

In our research, we have focused on a new approach to enantioselective additions to prochiral cyclic oxocarbenium ions, specifically one that relies on catalytic generation of chiral organometallic intermediates. This approach is inspired by metal-catalyzed enantioselective additions of terminal alkynes to aldehydes, pioneered by Carreira's group (Scheme 5),⁴ and bears resemblance to enantioselective alkynylations of pyridinium ions.⁵ By exploiting these well-developed methods for catalytic generation of chiral carbon nucleophiles, we have developed a highly enantioselective alkynylation of isochroman acetals (Scheme 1).

The successful development of the enantioselective alkynylation depended on several factors. First, we needed to determine whether or not metal acetylide formation is compatible with oxocarbenium ion formation. Encouraged by Downey's report that trimethylsilyl triflate (TMSOTf) enables catalytic turnover of Zn-catalyzed aldehyde alkynylations,⁶ we optimized our reaction conditions around the use of TMSOTf to form prochiral oxocarbenium ions in situ from racemic isochroman acetals. Secondly, although the use of both Zn(II) and Cu(I) catalysts enable alkynylation in the absence of a chiral ligand, only Cu(I) catalysts with non-coordinating counterions are effective in the presence of chiral

ligands. Finally, we found that the use of bis(oxazoline) ligands delivers highly enantioenriched products with Bn-BOX proving optimal.

This Cu(I)-catalyzed alkynylation is effective for preparing a wide range of 1-alkynylisochromans in high enantioselectivity (typically 85–94% ee). As shown in Scheme 6, the highest enantioselectivity is observed with the more extended π -system of benzoisochroman. Various substituents are also tolerated on the acetal, including halides. Further, a wide range of aryl-substituted alkynes can be used in this reaction, including electron-rich and electron-poor systems. The reaction proceeds in good yields and selectivities in the presence of functional groups such as trifluoromethyls, ethers, and chlorides. As the alkyne can be easily reduced with little to no loss of enantioenrichment (Equation 1), this method also enables preparation of 1-alkyl isochromans via a straightforward alkynylation/hydrogenation sequence.

Based on analysis of the C–C bond forming step of this reaction, we proposed a preliminary model for enantioselectivity (Figure 3). Examination of the approach of the oxocarbenium ion from above the N–Cu–N plane suggests that steric hindrance between the benzene ring of the oxocarbenium ion and the benzyl substituent of the catalyst may disfavor approach from the *Re* face, which leads to the minor enantiomer observed. Although this model is in agreement with the observed stereochemistry, this simple steric argument does not account for the poor enantioselectivities observed with larger ligand substituents, such as *i*-propyl and *t*-butyl. However, there is no clear evidence for π – π or cation– π interactions between the catalyst and oxocarbenium ion. These lingering questions suggest that there is an opportunity to understand more deeply how this chiral metal catalyst controls facial selectivity in additions to oxocarbenium ion intermediates. Such understanding would be powerful in the development of additions to other oxocarbenium ion intermediates.

With our development of an enantioselective Cu-catalyzed alkynylation of isochromanacetals, we have established that a new class of catalytically generated chiral nucleophiles can be used in additions to prochiral cyclic oxocarbenium ions. This method efficiently transforms readily available racemic isochromanacetals into 1-alkynylisochromans in high enantioselectivity. However, challenges remain in controlling enantioselectivity to prochiraloxocarbenium ions. Perhaps the most notable gap is the lack of substrate generality of the methods published to date, all of which only address a single class of acetal (tetrahydropyran, isochroman, chromene or acyclic). At present, it is unclear whether a single strategy can be applied to various oxocarbenium ion structures. Our current research is focused on investigating the Cu-catalyzed alkynylation with a wide variety of cyclic oxocarbenium ions. To date, we have promising enantioselectivities in the alkynylation of chromeneacetals (Scheme 7) and are working to optimize the selectivity of this reaction to synthetically useful levels. The development of enantioselective additions to a wide range of oxocarbenium ions will not only enable efficient syntheses of these important oxygen-containing heterocycles, but will also provide a platform for mechanistic discoveries of how chiral catalysts interact with cationic intermediates.

Acknowledgments

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Biography

Mary Watson grew up in Tampa, FL, USA. She earned her A.B. degree in chemistry from Harvard University in 2000 and her Ph.D. in chemistry from the University of California, Irvine, in 2006 under the mentorship of Prof. Larry Overman. After an NIH postdoctoral fellowship with Prof. Eric Jacobsen at Harvard University, she joined the faculty at the University of Delaware as an assistant professor in 2009.

Prantik Maity was born in Padumkhana near Tamluk, West Bengal, India. He received his B.Sc. degree in chemistry from the University of Calcutta in 2002, his M.Sc. in chemistry from the Indian Institute of Technology, Madras, in 2004, and his Ph.D. from the University of Regensburg in 2008 under the mentorship of Prof. Burkhard König. He was a postdoctoral fellow with Prof. Bernhard Breit at the University of Freiburg from 2008–2009 and is now a postdoctoral fellow at the University of Delaware.

Figure 1.
Electrophiles for asymmetric catalysis

Figure 2.
Bioactive and natural cyclic ethers

Figure 3.
Working stereochemical model

Scheme 1.

Enantioselective Cu-catalyzed alkylation of oxocarbenium ion intermediates

Scheme 2.

Braun's allylation via dynamic kinetic resolution

Scheme 3.

Jacobsen's thiourea-catalyzed additions to isochromanacetals

Scheme 4.

Schaus' diol-catalyzed vinylations of chromeneacetals

Scheme 5.
Carreira's Zn-catalyzed alkynylation of aldehydes

Scheme 6.
Representative scope of Cu-catalyzed alkynylation

Scheme 7.

Preliminary result in alkynylation of chromeneacetals

Equation 1.
Facile hydrogenation of 1-alkynyl isochroman