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Asymmetric Synthesis of Cyclic Ethers by Rearrangement of Oxonium Ylides Generated from Chiral Copper Carbenoids

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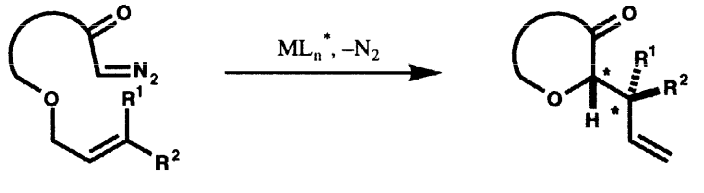
Abstract: Tetrahydrofuran-3-ones and tetrahydropyran-3-ones can be prepared enantioselectively by rearrangement of the ylide-type intermediates generated by the reaction of a chiral copper carbenoid with the oxygen atom of a pendant allylic ether. Cyclic ethers with enantiomeric excesses of up to 57% have been obtained using a copper complex of the enantiomerically pure diimine **1a** for carbenoid generation.

The rearrangement of oxonium ylides generated from metal carbenoids constitutes a versatile approach to the synthesis of cyclic ethers.[1] In previous studies,[2] we have shown that tetrahydrofuran-3-ones and tetrahydropyran-3-ones can be prepared diastereoselectively by the [2,3]-rearrangement of oxonium ylides generated upon reaction of metal carbenoids with allylic ethers. In the course of these studies, we discovered that copper carbenoids derived from α-diazo ketones are particularly effective for ylide generation and are generally superior to rhodium carbenoids for this transformation.[2,3] We also found that the nature of the metal complex employed for carbenoid generation has a profound influence on the level of diastereocontrol achieved, a finding which suggests either that the carbenoid reacts selectively with one of the diastereotopic ether-oxygen lone pairs to produce a configurationally stable ylide, or that the metal complex influences the stereochemical outcome of the reaction because it is intimately involved in the rearrangement step of the reaction.

We have recently embarked on a study to explore the use of chiral copper complexes as catalysts for carbenoid generation in order to prepare substituted cyclic ethers enantioselectively from achiral α-diazo ketones (eq. 1). Prior to our work, Nozaki had reported that it was possible to prepare tetrahydrofurans with low ee by [1,2]-rearrangement of oxonium ylides generated in an *intermolecular* fashion by reaction of racemic oxetanes with carbenoids generated from the reaction of ethyl diazoacetate with chiral non-racemic copper complexes.[4] Recently, Katsuki has extended this work and reported that tetrahydrofurans can be prepared with high enantiomeric purity when copper bipyrindine complexes are employed as catalysts for this reaction.[5] While our studies were in progress, McKervey reported the enantioselective synthesis of a limited range of cyclic ethers with modest ee by intramolecular cyclisation of chiral rhodium carbenoids generated from α-diazo β-keto esters[6] and Doyle demonstrated that it is possible to perform highly enantioselective tandem oxonium ylide formation and [1,2]-rearrangement reactions using chiral rhodium carbenoids.[7] These recent reports have prompted us to disclose some of our preliminary results at this time.



(1)

A wide range of chiral copper complexes was screened in order to find the most suitable chiral catalyst for carbenoid generation.[1a,1b,8] Preliminary experiments focused on chiral catalysts that had been used for analogous asymmetric carbenoid reactions such as cyclopropanation.[9] Initial results revealed that C_2-symmetric diimines (**1**) prepared by reaction of commercially available (*S*,*S*)-1,2-cyclohexane diamine with aryl aldehydes

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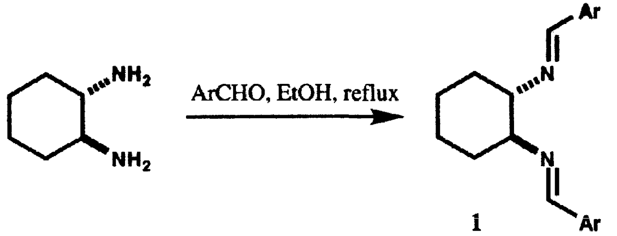
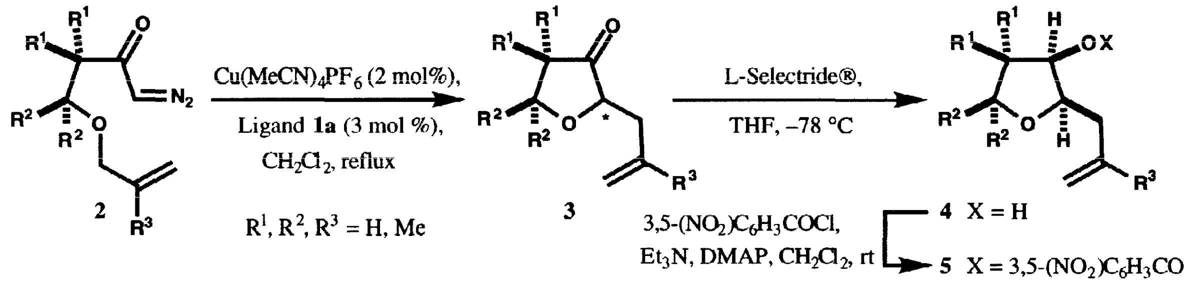
were the most satisfactory ligands for our purpose, and so a wide range of these compounds was prepared (eq. 2). Ligands based on chiral C_2-symmetric diamines are becoming increasingly important in asymmetric synthesis, and Jacobsen has used copper complexes of analogous diimine ligands to catalyse asymmetric cyclopropanation and aziridination reactions.[10]



a Ar = 2,6-$Cl_2C_6H_3$
b Ar = 3,4-$Cl_2C_6H_3$
c Ar = 3,5-$F_2C_6H_3$
d Ar = 3,5-$(MeO)_2C_6H_3$
e Ar = 3,5-$(CF_3)C_6H_3$
f Ar = 4-$(MeO)C_6H_4$
g Ar = 4-NCC_6H_4
h Ar = 4-MeC_6H_4
i Ar = 2,4,6-$Me_3C_6H_2$
j Ar = 2-$(Ph_2P)C_6H_4$
(2)

We first investigated the asymmetric cyclisation of some simple achiral α-diazo ketones (**2**) to give tetrahydrofuran-2-ones (**3**) (**Scheme 1**). Copper complexes of a wide variety of diimine ligands (**1a–j**) were evaluated as catalysts for the reaction of the substrate **2a**. Although significant levels of asymmetric induction were obtained in most cases,[11] the copper complex obtained by *in situ* reaction of the ligand **1a** with $Cu(MeCN)_4PF_6$ gave the best results.[10] In each case, the enantiomeric purity was determined by chiral HPLC analysis of the alcohol **4** or the 3,5-dinitrobenzoyl ester **5** resulting from esterification of this alcohol (**Scheme 1**). We found that the substituent pattern had a profound effect on level of enantiocontrol (**Table**). Cyclisation of the parent substrate **2a** provided the product ketone **3a** in 57% ee. Introduction of methyl substituents adjacent to the carbonyl group (substrate **2b**) had little effect on the level of asymmetric induction. However, when methyl substituents were placed adjacent to the ether-oxygen (substrate **2c**), the level of asymmetric induction was substantially reduced. The presence of a methyl substituent at the 2-position of the allyl group (substrate **2d**) resulted in a dramatic reduction in the level of asymmetric induction. Interestingly, this drop in ee could be largely counteracted by the introduction of methyl substituents adjacent to the ketone (substrate **2e**).



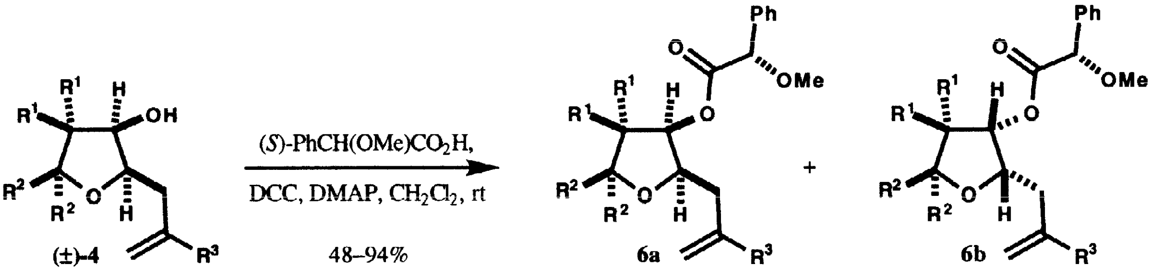
Scheme 1

Substrate	R^1	R^2	R^3	Yield 3 (%)[a]	ee (%)[b]	Configuration[c]
2a	H	H	H	62	57	*R*
2b	Me	H	H	57	56	—[d]
2c	H	Me	H	54	23	—[d]
2d	H	H	Me	62	6	*R*
2e	Me	H	Me	92	42	*R*

a Yield of isolated material after purification by column chromatography. *b* Enantiomeric excess determined by HPLC analysis of the alcohol **4** or the 3,5-dinitrobenzoyl ester **5** (**Scheme 1**). *c* Configuration determined by NMR analysis of derivatives of the alcohol **4** (see text). *d* Absolute configuration was not determined.

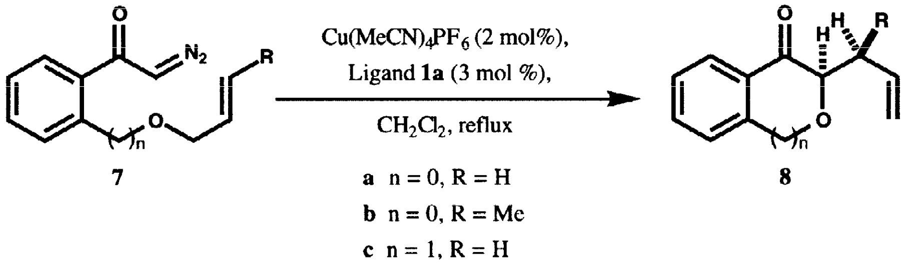
Table

In those cases where the absolute configuration could be determined, the configuration at the new stereogenic centre in the product **3** was found to be *R*. The absolute configuration was determined by conversion of the racemic alcohols (±)-**4** into the corresponding diastereomeric derivatives **6a** and **6b** and subsequent analysis of these derivatives by ^{1}H NMR as described by Trost (eq. 3).[12] In those cases where separation of diastereoisomers was possible, the diastereomeric esters were distinguishable by chemical shift differences caused by the shielding effects of the phenyl group of the auxiliary and hence the relative configuration was established.[13] Removal of the auxiliary permitted correlation with the non-racemic alcohols **4** obtained by reduction of the ketones **3** isolated from the enantioselective reactions (**Scheme 1**).



(3)

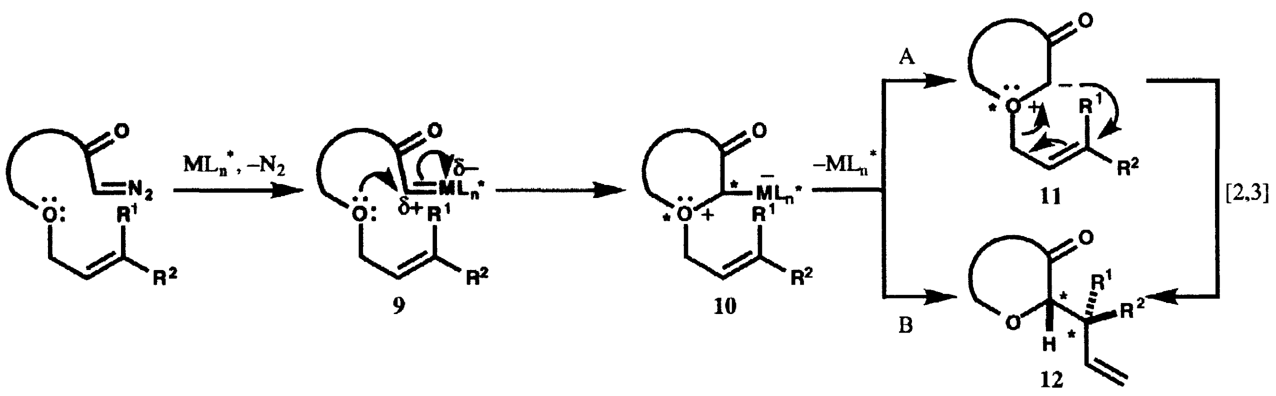
We also examined the enantioselective cyclisation reactions of the aromatic substrates **7** (eq. 4). Cyclisation of the substrate **7a** under optimum conditions afforded the ketone **8a** with an ee of 37%. However, we observed a gradual decline in the ee of the product when reaction times were extended (>10–15 min),[14] indicating that this product is prone to racemisation. Therefore, it is conceivable that racemisation may be occurring during the reduction and derivatisation sequence (analogous to **Scheme 1**) and that the ketone obtained directly after cyclisation may have a significantly greater ee than that indicated. Cyclisation of the diazo ketone **7b** afforded the product **8b** with a high level of diastereocontrol. Erosion of ee by racemisation was not an issue in this case because loss of stereochemical integrity at the stereogenic centre α to ketone would have manifested itself by the formation of the other diastereoisomer. Cyclisation of substrate **7c**, in which tether length was increased, afforded the ketone **8c** with low ee.



a	85%	37% ee
b	73%	24% ee
c	57%	15% ee

(4)

The results presented above can be accounted for by two alternative mechanistic pathways (A and B, **Scheme 2**). In both mechanisms, treatment of the achiral α-diazo ketone substrate affords a chiral carbenoid (**9**) which is then attacked by the ether oxygen to give the metal-bound ylide **10** with the creation of two stereogenic centres (denoted by *). In mechanism A, loss of the metal affords the free oxonium ylide **11** which possesses a stereogenic oxonium centre (*). Rearrangement then occurs with efficient transfer of chirality to afford the cyclic ether **12**.[15] For this mechanism to be operative, the energy barrier to inversion of configuration at the sp^3 oxonium centre of the ylide must be significantly greater than the transition state energy for the rearrangement reaction. In mechanism B, rearrangement occurs directly (i.e. without formation of a free oxonium ylide) from the metal bound intermediate **10** to give the cyclic ether **12** by an as yet undefined process. In this case the stereochemical outcome of the reaction is dictated by the stereogenic centres (*) established during initial attack on the carbenoid, and the environment created by the chiral ligand(s) attached to copper.



Scheme 2

The results described above demonstrate that it is possible to prepare five- and six-membered cyclic ethers enantioselectively with modest to reasonable levels of asymmetric induction from achiral diazo ketones using chiral copper complexes as catalysts. The results obtained upon cyclisation of the substrates **7** suggest that the presence of a phenyl ring in the tether connecting the diazo ketone to the allylic ether has a deleterious effect on the level of asymmetric induction obtained upon cyclisation.

Molecular modelling and further synthetic work to elucidate the detailed reaction mechanism are in progress. The results of these studies will be reported in due course.

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9. Other classes of ligands that were screened included bisoxazolines, chiral 1,3-diketones derived from camphor and diimines produced by condensation of 2,2'-diamino-1,1'-binaphthalene with various aldehydes.
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11. Use of copper complexes of diimines **1b-j** (eq. 2) as pre-catalysts for the cyclisation of the α-diazo ketone **2a** afforded samples of the cyclic ether **3a** with enantiomeric excesses of less than 32% (**Scheme 1**).
12. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.
13. For diastereoisomer **6a**, shielding of the 5-pro-*S* substituent (H or Me) compared to the corresponding substituent in the diastereoisomer **6b** was evident in the ^{1}H NMR spectrum. For diastereoisomer **6b**, shielding of the protons in the side-chain compared to the corresponding protons in the side-chain of diastereoisomer **6a** was evident in the ^{1}H NMR spectrum.
14. The optimum reaction time was found to be approximately 10 minutes. Prolonging the reaction time to 1–2 hours resulted in a 15–30% (relative) erosion in enantiomeric purity of the product.
15. For a review of 'chirality transfer' during sigmatropic rearrangements, see: Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D. Ed.; Academic Press: 1983; Vol. 3, Chapter 8, pp 503–572.