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Asymmetric allylic oxidation of bridged-bicyclic alkenes using a copper-catalysed symmetrising–desymmetrising Kharasch–Sosnovsky reaction

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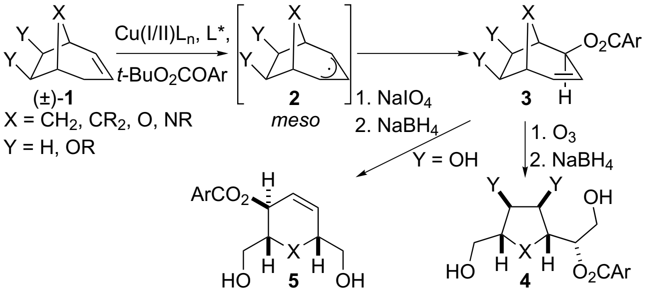
Abstract—Enantioselective symmetrising–desymmetrising allylic oxidation of racemic bridged bicyclic alkenes using an asymmetric copper-catalysed Kharasch–Sosnovsky reaction has been explored. Good yields and reasonable levels of induction (up to 70% ee) have been obtained using carbocyclic systems as substrates.

The discovery of new catalytic asymmetric allylic oxidation reactions has been the objective of much research over the past decade.[1,2] In 1995, independent reports from the groups of Pfaltz and Andrus showed that it is possible to perform enantioselective allylic oxidation of cyclic alkenes using an asymmetric copper-catalysed version of the Kharasch–Sosnovsky reaction in which a perester acts as the stoichiometric oxidant.[3,4] Several other groups have since reported similar asymmetric reactions, employing various chiral copper complexes as catalysts.[5,6] However, these reactions have largely been restricted to the enantioselective oxidation of simple substrates and the levels of asymmetric induction have been modest in most cases.

The asymmetric Kharasch–Sosnovsky reaction has seldom been applied to systems other than simple cyclic alkenes, but in a recent landmark study, Kohmura and Katsuki showed that it was possible to use the reaction to oxidise *racemic* dicyclopentadiene and derivatives to give the corresponding allylic oxidation products in *non-racemic* form.[6] Subsequent applications of the asymmetric symmetrisation–desymmetrisation concept to the oxidation of other substrates have not appeared. We now report that the asymmetric copper-catalysed Kharasch–Sosnovsky reaction can be used to prepare bridged bicyclic allylic alcohol derivatives from the corresponding *racemic* alkenes in good yield and with reasonable levels of asymmetric induction.

The application of the asymmetric symmetrising–desymmetrising allylic oxidation reaction to more complex substrates is highly attractive. Bicyclo[3.2.1]oct-2-enes and the *O*-bridged analogues are particularly attractive substrates because of the obvious synthetic potential of the oxidised products. At the outset, our plan was to perform copper-catalysed asymmetric allylic oxidation of a variety of racemic substrates **1** to give the products **3** in non-racemic form (Scheme 1). The success of the reaction would depend on symmetrisation of the racemic



Scheme 1.

Keywords: Alkene; Catalytic; Enantioselective; Oxidation.

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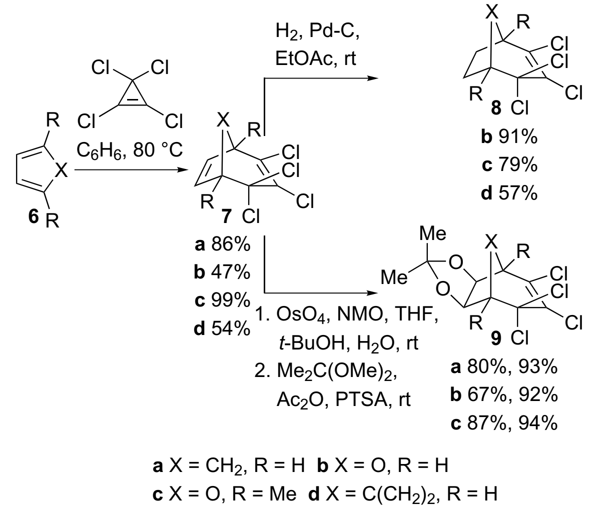
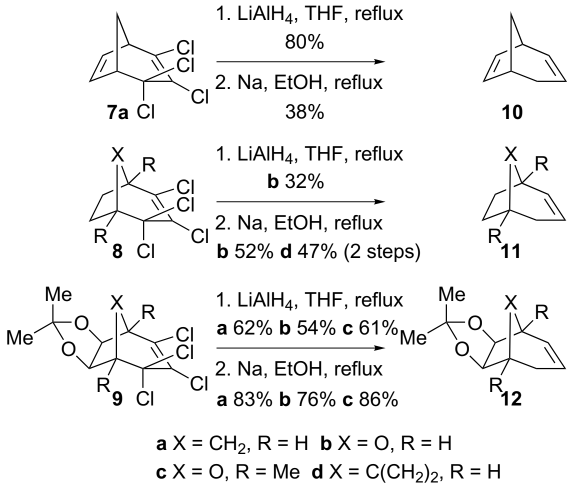
substrate **1** by generation of the putative *meso* allylic radical **2** followed by highly enantioselective desymmetrisation of this transient intermediate to give the allylic alcohol derivative **3**. In principle, the reaction should accommodate diverse functionality Y and a variety of carbon or heteroatom bridging groups X. The non-racemic bicyclic products **3** could be subjected to ring scission by simple oxidative cleavage of the alkene or diol, giving the highly functionalised five- and six-membered carbocycles/heterocycles **4** and **5** (Scheme 1).

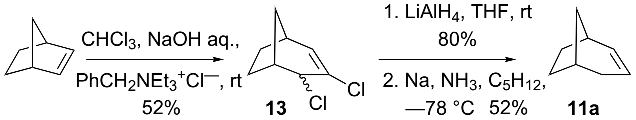
The bridged bicyclic alkenes required for our study were prepared by the routes shown in Schemes 2–4. The bicyclo[3.2.1]oct-2-ene framework was constructed by the Diels–Alder cycloaddition of tetrachlorocyclopropene with a simple cyclopentadiene or furan, following a procedure reported by Law and Tobey in 1968 (Scheme 2).[7] Heating tetrachlorocyclopropene with the cyclopentadienes **6a**,**d** and the furans **6b**,**c** resulted in Diels–Alder cycloaddition followed by presumed ionisation and electrocyclic ring opening to afford the chlorinated bicyclic dienes **7a**–**d** directly.[7,8] The dienes **7b**–**d** underwent partial catalytic hydrogenation to give the alkenes **8b**–**d**, and the dienes **7a**–**c** were subjected to sequential dihydroxylation and acetonide formation to give the acetals **9a**–**c** in excellent yield.



Scheme 2.



Scheme 3.



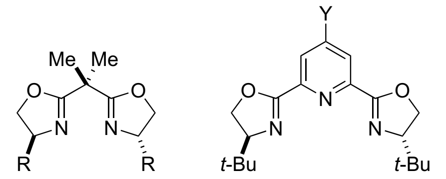
Scheme 4.

The chlorinated alkenes **8b**–**d** and **9a**–**c** were then dechlorinated to give the alkene oxidation precursors. Methods for direct and complete dechlorination were explored, but they proved to be unreliable and delivered mixtures of partially dechlorinated products or destroyed the bridged bicyclic compounds. After extensive experimentation, we discovered a reliable two-stage procedure for the complete dechlorination of the compounds **7a**, **8b**, **8d** and **9a**–**c** in which removal of chlorine at the 2- and 4-positions was achieved using an excess of lithium aluminium hydride and the remaining 3-chloro substituent was removed by treatment with sodium in ethanol (Scheme 3).[9,10] Reasonable yields of the dechlorinated alkenes **10**, **11b**, **11d** and **12a**–**c** were obtained by this simple two-step route.[8]

The simplest substrate of those prepared, bicyclo[3.2.1]oct-2-ene (**11a**), was synthesised using a straightforward route developed by Kraus et al. (Scheme 4).[11] Addition of dichlorocarbene to norbornene afforded the dichloride **13** in 52% yield, and complete dechlorination was then performed by successive reaction of this intermediate with lithium aluminium hydride and sodium in liquid ammonia to give bicyclo[3.2.1]oct-2-ene (**11a**).[11]

The successful synthesis of the bridged bicyclic alkenes **10**, **11a**, **11b**, **11d** and **12a**–**c** permitted exploration of the asymmetric copper-catalysed symmetrising–desymmetrising Kharasch–Sosnovsky allylic oxidation of these substrates. We had already explored the enantioselective allylic oxidation of simple alkenes such as cyclopentene and cyclohexene, and had identified a subset of the bis-oxazoline (*box*) and pyridyl-bisoxazoline (*pybox*) systems as potential ligands for the copper-catalysed reaction (Fig. 1).[5e] The *box* ligands **14a**,**b** and the *pybox* ligands **15a**–**d** were selected for the study; the sterics and electronics of the *pybox* ligands were varied by placing appropriate substituents at the 4-position of the pyridine.

The enantioselective copper-catalysed allylic oxidation reactions of bicyclo[3.2.1]oct-2-ene (**11a**) and the cyclopropyl homologue **11d** were explored first (Eq. 1, Table 1). Asymmetric Kharasch–Sosnovsky oxidation of bicyclo[3.2.1]oct-2-ene (**11a**) proceeded to give the *endo*-bicyclo[3.2.1]oct-3-en-2-ol benzoate (**16**) in yields of up to 70% and with ee levels of up to 66% using copper complexes of the *pybox* ligands **15** as catalysts.[12] The substit-



14a R = Ph
14b R = *t*-Bu

15a Y = H
15b Y = Cl
15c Y = OMe
15d Y = 2,6-$Me_2C_6H_3$

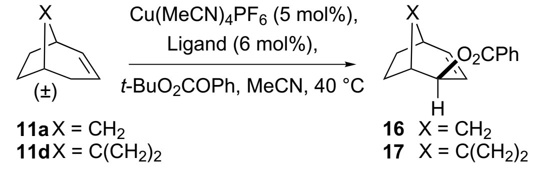
Figure 1.

Table 1. Asymmetric copper-catalysed symmetrising–desymmetrising allylic oxidation of racemic bicyclo[3.2.1]oct-2-enes **11a** and **11d**

Entry	Substrate	Ligand	Time (d)	Product	Yield[a] (%)	Ee[b] (%)
1	**11a**	**15a**	10	**16**	70	58 (−)
2	**11a**	**15b**	10	**16**	70	50 (−)
3	**11a**	**15c**	10	**16**	36	66 (−)
4	**11a**	**15d**	8	**16**	63	62 (−)
5	**11d**	**14a**	6	**17**	48	60 (−)
6	**11d**	(*R*,*R*)-**14a**	5	*ent*-**17**	38	54 (+)

[a] Yield of purified product.
[b] The ee was determined using chiral HPLC.

uent at the 4-position of the pyridine unit in the *pybox* ligand was found to have a marginal influence on the level of asymmetric induction. Interestingly, the copper complex of the ligand **15c** delivered the lowest yield of the product **16** but with the highest ee (entry 3). The cyclopropyl substrate **11d** also underwent asymmetric copper-catalysed Kharasch–Sosnovsky allylic oxidation (entries 5 and 6), but in this case the conventional *box* ligand **14a** proved to be superior to the *pybox* ligands **15**. The ester **17** was obtained with ee levels of up to 60% but the yields were modest.



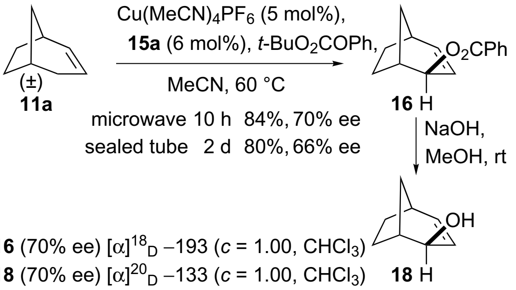
11a $X = CH_2$
11d $X = C(CH_2)_2$

16 $X = CH_2$
17 $X = C(CH_2)_2$

(1)

Copper complexes of the *S*,*S* configured *box* and *pybox* ligands delivered the allylic benzoate (−)-**16**, which was found to have the absolute configuration 1*R*,2*S*,5*S* by comparison of optical rotation data for the alcohol (−)-**18** with literature data (Scheme 5).[13] Tentative stereochemical assignments for the benzoate **17** were made by analogy with those of the benzoate (−)-**16**.

It was possible to improve the yield and level of asymmetric induction whilst dramatically reducing the reaction time by performing the allylic oxidation reaction of bicyclo[3.2.1]oct-2-ene (**11a**) under microwave irradiation or in a sealed tube at 60 °C (Scheme 5).[14] Microwave irradiation gave the best result; the allylic oxidation product (−)-**16** was obtained in 84% yield with an ee of 70% when the copper complex of the *pybox* ligand **15a** was employed as the catalyst.



Scheme 5.

Attempted allylic oxidation of the bicyclic diene **10** resulted in complete decomposition of the starting material, and none of the expected oxidation product was obtained. Surprisingly, the oxygen-containing substrates **11b**, **11c** and **12a–c** did not deliver the expected products under the usual Kharasch–Sosnovsky conditions using either copper *box* or *pybox* complexes as catalysts, and a significant amount of unreacted starting material was recovered in each case. The lack of reactivity of the oxygen-containing alkenes **11b**, **11c**, and **12a–c** is difficult to explain and further studies will be required to reveal why these substrates do not react under conditions that result in efficient allylic oxidation of the carbocyclic substrates **11a** and **11d**.

In summary, we have shown that it is possible to perform enantioselective symmetrising–desymmetrising allylic oxidation of racemic bridged bicyclic alkenes using an asymmetric Kharasch–Sosnovsky reaction catalysed by a chiral copper *box* or *pybox* complex. Yields of up to 84% and levels of induction up to 70% ee have been obtained upon oxidation of the alkenes **11a** and **11d**. The reaction should be applicable to a variety of other simple racemic bridged bicyclic compounds.

Acknowledgements

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