Asymmetric allylic oxidation reactions catalyzed by a chiral nonracemic and C_2-symmetric 2,2′-bipyridyl copper(I) complex

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The evaluation of a chiral, nonracemic and C_2-symmetric 2,2′-bipyridyl ligand in copper(I)-catalyzed asymmetric allylic oxidation reactions of a series of cyclic alkenes with *tert*-butyl peroxybenzoate is reported (up to 91% ee, the highest reported enantioselectivity for a bipyridyl ligand copper(I) complex to date).

We have previously reported an efficient synthesis of a chiral nonracemic and C_2-symmetric 2,2′-bipyridyl ligand **1** (Fig. 1).[1,2] In addition, we have demonstrated that this bipyridyl ligand is an outstanding chiral director in asymmetric copper(I)-catalyzed cyclopropanation reactions of a series of alkenes and diazoesters.[1] The corresponding cyclopropanes were isolated in good yield (up to 82%) and in very high enantioselectivities and diastereoselectivities (up to 99% ee and >95 : 5 dr). The application of this bipyridyl ligand in asymmetric copper(II)-catalyzed Friedel–Crafts alkylation reactions of a series of substituted indoles with methyl trifluoropyruvate has also been demonstrated.[2] In this case, the corresponding 3,3,3-trifluoro-2-hydroxy-2-indole-3-yl-propionic acid methyl esters were isolated in good yield (up to 79%) and in high enantiomeric excess (up to 90%).

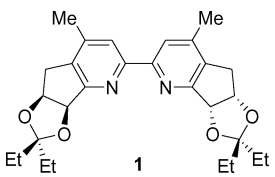

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Fig. 1 Chiral nonracemic and C_2-symmetric 2,2′-bipyridyl ligand **1**.

In this paper and in regard to the further exploration of the versatility of our chiral nonracemic 2,2′-bipyridyl ligand **1** (>99% ee) in catalytic asymmetric synthesis, we report a study of the application of this ligand in copper(I)-catalyzed asymmetric allylic oxidation reactions.[3,4] The specific reaction type we chose to study was first reported in 1959 by Kharasch and Sosnovsky.[5,6] It was shown that alkenes, such as cyclohexene, can be oxidized with a stoichiometric amount of *tert*-butyl peroxybenzoate in the presence of a catalytic amount of copper(I) bromide. This afforded the corresponding racemic allylic ester in good yield (70%). Asymmetric versions of this catalytic allylic oxidation reaction using chiral nonracemic bisoxazoline copper(I)-complexes were first reported independently by Pfaltz and co-workers and Andrus and co-workers in 1995.[7,8] In these cases, enantioselectivities of up to 80% ee were achieved when the reactions were performed in acetonitrile at relatively low temperatures (−20 °C). High enantioselectivities of up to 99% ee have subsequently been achieved for this reaction.[9] However, there still remains a significant problem in that these catalytic asymmetric processes suffer from exceedingly slow reaction rates. In some cases, the reaction has taken up to three weeks to reach a satisfactory level of conversion.[9,10] It has been found that chiral nonracemic and C_2-symmetric 2,2′-bipyridyl copper(I)-complexes are very active catalysts for this reaction in that they provide much faster reaction rates.[11] However, the enantioselectivities obtained, thus far, have been somewhat lower than with bisoxazoline complexes.[12] We also chose to study this asymmetric process because of the inherent usefulness of the reaction products in target-oriented synthesis.[13]

The chiral nonracemic and C_2-symmetric 2,2′-bipyridyl ligand (L*) **1** was evaluated in the copper(I)-catalyzed allylic oxidation reactions of three cyclic alkenes **2a**–**c** (n = 1–3) (Table 1). The active copper(I)-catalyst for these reactions was generated, by a standard method, on reduction of the complex formed between 5 mol% of copper(II) triflate and 5.25 mol% of the bipyridyl ligand **1** with 5.25 mol% of phenylhydrazine in either acetone or acetonitrile.[14,15] These two solvents and reaction conditions were chosen because they have provided the highest enantioselectivities in related catalytic reactions.[6] Following the formation of the catalytic species, the resultant bright red reaction mixtures were treated with the stoichiometric oxidant, *tert*-butyl peroxybenzoate, and an excess (5 equivalents) of the cyclic alkenes **2a**–**c**.

The allylic oxidation reaction of cyclopentene **2a** (n = 1) in acetone at room temperature for 24 h afforded the desired reaction product **3a** (n = 1) in good yield (64%) and in relatively low enantioselectivity (32% ee) (Table 1, entry 1). On repeating this reaction in acetonitrile for 16 h, the reaction product **3a** was isolated in similar yield and enantioselectivity (69% and 34% ee, respectively) (Table 1, entry 2). The allylic oxidation reaction of cyclohexene **2b** (n = 2) in acetone at room temperature for 16 h afforded the corresponding reaction product **3b** (n = 2) in good yield (67%) and in higher enantiomeric excess (65%) (Table 1, entry 3). Moreover, the enantioselectivity of this reaction was substantially increased (84% ee) on employing acetonitrile as the solvent at room temperature (Table 1, entry 4). In this instance, however, the reaction rate was slower and the reaction product **3b** was isolated in slightly lower yield (56%) after 72 h. In view of these encouraging results, we attempted to increase the enantioselectivity of this reaction by repeating it at a lower temperature. The product **3b** was isolated in moderate yield (51%) and good enantiomeric excess (81%) when the allylic oxidation reaction was performed at 0 °C for 48 h (Table 1, entry 5). Moreover, a further enhancement of enantioselectivity was observed when the reaction

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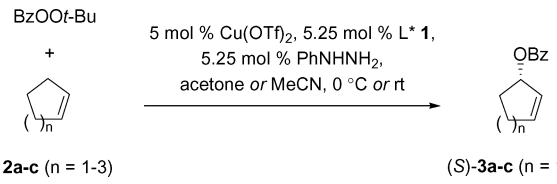
Table 1 Asymmetric allylic oxidation reactions of cyclic alkenes **2a**–**c**



Entry	Substrate	*n*	Solvent	Reaction temperature	Reaction time/h	Yield (%)[a]	Ee (%)[b]
1	**2a**	1	Acetone	rt	24	64	32
2	**2a**	1	MeCN	rt	16	69	34
3	**2b**	2	Acetone	rt	16	67	65
4	**2b**	2	MeCN	rt	72	56	84
5	**2b**	2	Acetone	0 °C	48	51	81
6	**2b**	2	MeCN	0 °C	96	45	91
7	**2c**	3	Acetone	rt	16	72	36
8	**2c**	3	MeCN	rt	16	76	40

[a] Isolated yield, based on the amount of *tert*-butyl peroxybenzoate employed, after purification by flash chromatography. [b] Determined by analytical chiral HPLC (Daicel Chiralcel OD column).

was performed in acetonitrile at 0 °C for 96 h (91% ee). However, the yield was again somewhat compromised (45%) (Table 1, entry 6). To the best of our knowledge, this is the highest reported enantioselectivity for an asymmetric allylic oxidation reaction with a chiral nonracemic 2,2′-bipyridyl ligand. In addition, the rate of this reaction was significantly greater than has been achieved with several bisoxazoline ligands which have been shown to be highly enantioselective.[9] The allylic oxidation reaction of cycloheptene **2c** ($n = 3$) in acetone for 16 h afforded the reaction product **3c** ($n = 3$) in good yield (72%) but only in relatively low enantiomeric excess (36%) (Table 1, entry 7). When the corresponding reaction was performed in acetonitrile for 16 h, the reaction product **3c** was formed in similar yield and enantioselectivity (72% and 40% ee, respectively) (Table 1, entry 8). Collectively, the results of these asymmetric catalytic reactions indicate that the process is highly substrate-dependent. The absolute stereochemistry of each of the above reaction products **3a**–**c** ($n = 1$–3) was assigned as (*S*) on comparison of the optical rotations with literature values.[10]

A rationalization of the stereochemical outcome of the copper(I)-catalyzed asymmetric allylic oxidation reactions of the cyclic alkenes **2a**–**c** (shown for cyclohexene **2b**) is illustrated below (Fig. 2).

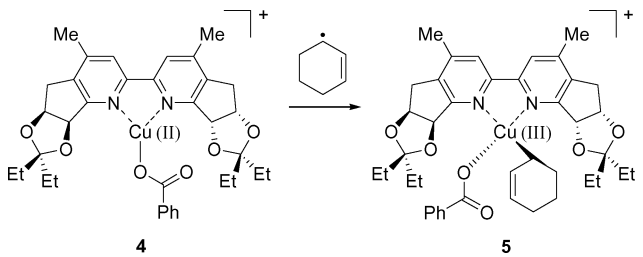


Fig. 2 Rationalization of the stereochemical outcome of the asymmetric allylic oxidation reactions.

The asymmetry of the process is most likely the result of the approach of the cyclohexenyl radical (generated by abstraction of a hydrogen atom from cyclohexene by a *tert*-butoxy radical which in turn was generated by a copper(I)-mediated homolytic cleavage reaction of the oxygen–oxygen bond of *tert*-butyl peroxybenzoate) to one of the less hindered quadrants of the intermediate C_2-symmetric copper(II) benzoate complex **4**. The resultant copper(III) species **5** then would undergo a pericyclic rearrangement (or direct reductive elimination) to afford the observed product (1*S*)-cyclohex-2-enyl benzoate **3b** and regenerate the initial catalytic copper(I) complex.[16]

In conclusion, we have evaluated our new chiral nonracemic and C_2-symmetric 2,2′-bipyridyl ligand **1** in copper(I)-catalyzed asymmetric allylic oxidation reactions of the cyclic alkenes **2a**–**c** ($n = 1$–3) with *tert*-butyl peroxybenzoate. On performing the reaction of cyclohexene **2b** ($n = 2$) in acetonitrile at 0 °C for 96 h, the corresponding product, (1*S*)-cyclohex-2-enyl benzoate **3b** ($n = 2$), was isolated in 45% yield and in high enantiomeric excess (91%). The yields and enantioselectivities of these copper(I)-catalyzed processes were found to be dependent on the substrate, solvent and reaction temperature.

Studies are currently underway to improve the enantioselectivities that can be obtained with this new type of exceptionally promising chiral nonracemic 2,2′-bipyridyl ligand, in various metal-catalyzed asymmetric processes, by modification of the substituents of the cyclic acetal moieties of the 2,2′-bipyridine.

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11 A pinene-derived bipyridyl ligand has been shown to be particularly effective for copper(I)-catalyzed asymmetric allylic oxidation reactions (reaction times of *ca.* 30 min and up to 75% ee), see: (*a*) A. V. Malkov, M. Bella, V. Langer and P. Kočovský, *Org. Lett.*, 2000, **2**, 3047. This research group has also reported the evaluation of a closely related carene-derived ligand in which the maximum enantioselectivity reached 82% ee. However, the reaction time required was 96 h and the isolated yield of the reaction product [(1*R*)-cyclohept-2-enyl benzoate] was only 35%, see: (*b*) A. V. Malkov, D. Pernazza, M. Bell, M. Bella, A. Massa, F. Teplý, P. Meghani and P. Kočovský, *J. Org. Chem.*, 2003, **68**, 4727.
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14 For discussion and experimental procedures regarding the use of phenylhydrazine in the generation of copper(I) complexes from copper(II) species, see: ref. 10 and citations therein.
15 General procedure for copper(I)-catalyzed asymmetric allylic oxidation reactions: To a screw-cap vial was added copper(II) trifluoromethanesulfonate (6.3 mg, 17 μmol), the chiral nonracemic C_2-symmetric bipyridyl ligand **1** (8.5 mg, 18 μmol) and the reaction solvent (acetone or acetonitrile, 2.5 mL). The resultant solution was stirred at room temperature for 1 h. Phenylhydrazine (2.0 μL, 20 μmol) was added and the reaction mixture was stirred for an additional 5 min at room temperature. The reaction mixture was then cooled to 0 °C in certain instances (see: Table 1). One of the cyclic alkenes **2a**–**c** (n = 1–3, 1.8 mmol) and *tert*-butyl peroxybenzoate (67 μL, 0.35 mmol) were added. The reaction was monitored by thin-layer chromatography (diethyl ether–hexanes, 1 : 1) until the oxidant, *tert*-butyl peroxybenzoate, had beenconsumed. The reaction mixture was concentrated *in vacuo* to afford the crude product. The benzoates (*S*)-**3a**–**c** were isolated in pure form as colourless oils by flash chromatography using hexanes–diethyl ether (5 : 1) as the eluant. (1*S*)-Cyclohex-2-enyl benzoate (*S*)-**3b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65–1.76 (1H, m), 1.78–2.21 (5H, m), 5.49–5.55 (1H, m), 5.80–5.87 (1H, m), 5.98–6.04 (1H, m), 7.40–7.66 (4H, m), 8.06 (1H, d, J = 7.3 Hz), 8.13 (1H, d, J = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.1, 25.1, 28.5, 68.8, 125.8, 128.4, 128.6, 129.7, 130.4, 132.9, 133.0, 133.9, 166.4; IR (neat) ν_{max} 2941, 1713, 1602, 1584, 1453, 1428, 1326, 1271, 1178, 1112, 1070, 1026, 918 cm^{-1}; MS (CI) m/z (rel. intensity) 203 (M + H, 14), 181 (87), 159 (24), 91 (55). Analytical chiral HPLC analysis using a Daicel Chiralcel OD column [hexanes–isopropanol (250 : 1), flow rate at 0.50 mL min^{-1}, detection at λ = 220 nm, t_{MAJOR} = 26.1 min, t_{MINOR} = 29.0 min]. (1*S*)-Cyclopent-2-enyl benzoate (*S*)-**3a**: Analytical chiral HPLC as above [t_{MAJOR} = 32.4 min, t_{MINOR} = 43.6 min]. (1*S*)-Cyclohept-2-enyl benzoate (*S*)-**3c**: analytical chiral HPLC as above [t_{MAJOR} = 19.2 min, t_{MINOR} = 23.5 min].
16 A related mechanistic interpretation has been reported by Andrus and Zhou (ref. 9).