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Naphthyl-substituted bisoxazoline and pyridylbisoxazoline–copper(I) catalysts for asymmetric allylic oxidation

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ABSTRACT

The synthesis of naphthyl substituted malonyl-derived and pyridine-based bisoxazolines and their applications in the asymmetric allylic oxidation of cyclohexene with *t*-butyl *p*-nitroperbenzoate have been performed with much improved reactivity (75% yield) while maintaining very good enantioselectivity (85% ee). A 1-naphthyl group as the side chain of the oxazoline ligand was found to be optimal. Correlations between the nature of the substituents on the bisoxazolines and the reactivity/selectivity have been established. Tridentate pyridylbisoxazoline ligands with naphthyl groups were also synthesized and employed.

The formation of allylic esters via CH bond oxidation has attracted considerable interest and has emerged as a viable approach for the synthesis of complex targets.[1,2] Among which one of the most notable examples is the asymmetric Kharasch–Sosnovsky allylic oxidation of alkenes.[2] Allylic oxidation offers the advantage of maintaining the alkene functionality in the allylic ester product, which is complementary to epoxidation and dihydroxylation. The utility of this approach is seen in the conversion of cyclohexenyl benzoate into a key intermediate for the synthesis of leukotriene B_4 and brevetoxins.[3] A major advance with regard to enantioselectivity (80% ee level) for allylic oxidation was the development of bisoxazoline–copper(I) catalysts.[2] Since then, a number of bisoxazoline, trioxazoline ligands have been explored that give, in the case of cyclopentene, high selectivity. Pyridyl and bipyridyl bisoxazoline ligands with added phenylhydrazine in acetone[2e,f] show improved reactivity but with modest selectivity. Aminoindanol-derived bisoxazolines[2d] and tridentate pyridine-based bisoxazoline (PyBox),[2e,f] have also been investigated all with moderate selectivities. While a nine-membered chelate ligand, with biaryl bis-*o*-tolyl bisoxazolines shows good selectivity as well as improved reactivity,[2g,h] a more recent class of C_2 symmetric pinene-derived bipyridines displayed excellent 96% yield with cyclohexene but with variable enantioselectivities.[2l] Non-oxazoline-type ligands, bis(imidazolines) and (iminophosphoranyl) ferrocenes,[2o] especially the latter, also showed good enantioselectivity. A mechanistic study of alkene hydroperoxidation with peroxides catalyzed by copper complexes was also reported using a racemic version.[2p] Unique ligand–substrate combinations were identified that for the first time provided excellent selectivities, 94–99% ee, for ester products.[2i] For example, 99% ee was obtained with cyclopentene using *gem*-diethyl-diphenyl-bisoxazoline as ligand. Currently, investigations of asymmetric allylic oxidation of alkenes with bisoxazoline catalysts have been limited, especially from a mechanistic perspective. In this report, we disclose studies on the asymmetric allylic oxidation of cyclohexene using novel naphthyl-substituted Box–Cu(I) complexes, which give considerably improved reactivity together with very good selectivity. Based on previous results with malonyl-derived bisoxazoline–copper(I) catalysts, correlation between the nature of new bisoxazoline substituents and the reactivity/selectivity of the catalyst systems can also be made.

According to our previously reported mechanistic study using ^{13}C NMR,[2i] copper ligand chelation is favored over the formation of a copper–ligand–alkene complex. The selectivity, then, is most likely a consequence of the Cu(II) benzoate intermediate. Attack by the allylic radical at the less hindered quadrant of the Cu(II) complex, away from the flanking *t*-butyl group, leads to a Cu(III) intermediate,[4] which rearranges to give *S*-product and regenerates the Cu(I)–ligand catalyst.

It is possible at this point to address the correlation between the nature of the substituent on the ligand and the reactivity as well as selectivity. According to studies of bisoxazoline–Cu(II) complexes by Jørgensen[2k] and Evans,[2j] a distorted square planar geometry is adopted by *gem*-dimethyl di-*t*-butyl and diphenyl Box–copper complexes, with a higher degree of distortion with the di-*t*-butyl Box complex. *t*-Butyl substituents tend to adopt pseudo-axial

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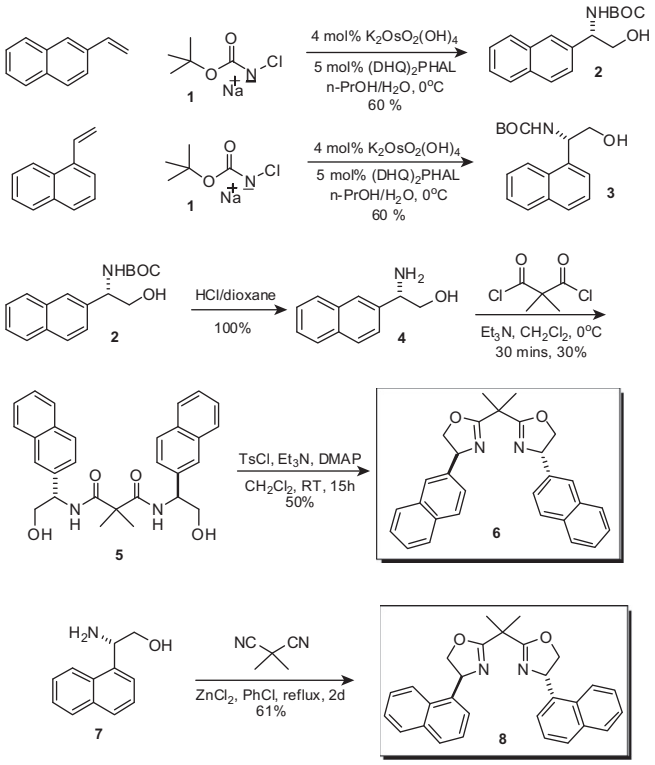
positions, while one phenyl group is pseudo-axial and the other assumes a pseudo-equatorial position.

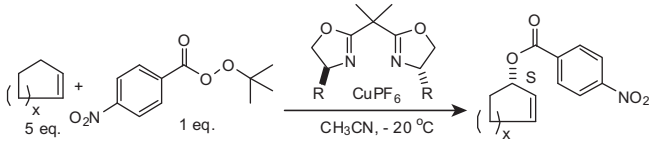
In perester based allylic oxidation, attack of the intermediate allyl radical on the Cu(II)–ligand–benzoate should be faster with the *gem*-dimethyl di-*t*-butyl than with the corresponding diphenyl ligand. This is due to the phenyl group occupying a more relaxed pseudo-equatorial position with less distortion from the square planar geometry. A disfavored steric interaction between the phenyl groups and the incoming allyl radical is consistent with lower yields obtained with both cyclopentene and cyclohexene (49% and 44% in Table 1). In addition, this disfavored interaction could also contribute to a certain degree of reversibility for the allyl–Cu(III) intermediate formation, causing lower catalyst turnover. On the other hand, this type of interaction presumably produces stronger enantio-differentiation of the Cu(III) intermediate which leads to higher enantioselectivity. With an incoming relaxed allyl radical of larger steric size, interaction with a bulky *t*-butyl is expected to be stronger, causing slower Cu(III) formation, thus leading to lower yields for cycloheptene and 1,5-cyclooctadiene (3% and 13%). On the other hand, interaction between a larger allyl radical and a more rigid Cu(II)–ligand framework with a bulky *t*-butyl may contribute to higher enantio-differentiation of the Cu(III) intermediate, which irreversibly affords higher selectivity for medium-sized ring substrates (95% ee and 94% ee). Among the malonyl-derived bisoxazoline ligands used in the reactions discussed above, the phenyl substituted oxazoline ligands generally produce higher selectivities for a range of substrates. In addition, phenyl oxazoline complexes are more flexible compared to the corresponding *t*-butyl ligands.[5] Therefore by introducing a larger aryl group, with naphthyl in place of phenyl, it was envisioned that a stronger directing effect than the previous phenyl based ligands could be imposed with enhanced reactivity while maintaining high enantioselectivity. In addition, naphthyl based catalysts may provide additional mechanistic insight. Therefore, the synthesis of naphthyl bisoxazolines is reported together with their application for catalytic cyclohexene oxidation using *t*-butyl *p*-nitroperbenzoate as oxidant.

The key step for the naphthyl oxazoline ligand synthesis was the preparation of the naphthyl-substituted amino alcohols. The reported approach of Sharpless for naphthyl-substituted amino alcohol synthesis[6] using asymmetric aminohydroxylation[6a–d] of vinylnaphthalenes was found to be the most efficient and reliable. *t*-Butylhypochlorite was made according to a reported procedure[6g] using *t*-butyl alcohol and commercial bleach. The *t*-butylhypochlorite obtained was dried over anhydrous $CaCl_2$ prior to use. As shown in Scheme 1, BOC-protected chiral amino alcohols (**2** and **3**) were obtained by treating 1-vinylnaphthalene and 2-vinylnaphthalene with a mixture of *t*-butyl carbamate and *tert*-butylhypochlorite in basic alcoholic solution (**1** is formed in situ), followed by the addition of catalytic (4 mol %) $K_2OsO_2(OH)_4$ along with 5 mol % of phthalazine dihydroquinine $(DHQ)_2PHAL$ ligand in *n*-$PrOH/H_2O$ at 0 °C. Reasonable yields were acquired with subsequent BOC deprotection of **2** and **3** using 4 N HCl in dioxane at room temperature, giving the corresponding amino alcohols in quantitative yields with high purity (Scheme 1). The crude amino alcohols were subsequently coupled with 2,2-dimethylmalonyl dichloride. Compound **4** gave the desired bis-hydroxymalonodiamide **5** in only 30 min, with low yield. Treatment of the bis-hydroxy malonodiamide **5** under standard cyclization conditions using *p*-toluenesulfonyl chloride and triethylamine in the presence of catalytic DMAP afforded the bis-(2-naphthyl)-substituted *gem*-dimethyl bisoxazoline (Box) **6** in moderate yield. Low yield (37%) of bis-hydroxymalonodiamide was also observed when amino alcohol **7** was reacted with 2,2-dimethylmalonyl dichloride in the presence of triethylamine at low temperature, −20 °C. This problem of producing the bis-hydroxymalonodiamide in low yield was addressed by an alternative approach using 2,2-dimethylmalononitrile to couple with the amino alcohol **7**. In the presence of excess anhydrous zinc chloride[7] in refluxing chlorobenzene for two days the corresponding bisoxazoline (Box) **8** was afforded in 61% yield (Scheme 1). In addition, this new bis-nitrile route is able to give the target ligands in only three steps from the vinylnaphthlenes, which is superior to previous literature approaches.



Scheme 1. Synthesis of naphthyl-substituted bisoxazoline ligands.

Table 1
Allylic oxidation of cycloalkenes using *gem*-dimethyl bisoxazolines copper(I) complex[2i]



Entry	Cycloalkenes	R	Time[a] (d)	Yield[b] (%)	% ee[c]
1	Cyclohexene	Ph	17	44	96
2	Cyclopentene	Ph	10	49	82
3	Cycloheptene	*t*-Bu	10	3	95
4	1,5-Cyclooctadiene	*t*-Bu	10	13	94

[a] Time in days, using a sealed vial placed in the freezer with stirring.
[b] Yields are for isolated, chromatographed materials based on the perester.
[c] Enantiomeric excess determined by chiral phase HPLC.

The pyridine-based naphthyl-substituted bisoxazolines (PyBox **11a** and **11b**) have not been reported previously. The goal for our synthesis is to extend the scope of bisoxazoline ligands applied in asymmetric allylic oxidation of alkenes. The same synthetic strategy for the preparation of known bisoxazolines was employed for the preparation of these compounds. The naphthyl-substituted amino alcohols (**4** and **7**) were prepared and coupled with commercially available 2,6-pyridine-dicarbonyldichloride to give the corresponding bis-hydroxy pyridinediamide products (**9** and **10**, Scheme 2).