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# Asymmetric peroxidation of $\alpha,\beta$ -unsaturated aldehydes under diarylprolinol ether catalysis

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**Background:** Chiral peroxides, many of which are biologically active, are an attractive target in organic synthesis. Organocatalysts have been used for some time in the asymmetric epoxidation of  $\alpha,\beta$ -unsaturated carbonyls. More recently, cinchona-derived organocatalysts have been adapted to effect the asymmetric peroxidation of unsaturated ketones. We successfully applied this catalyst system to the stereoselective peroxidation of more challenging  $\alpha,\beta$ -unsaturated aldehydes with moderate enantioselectivity observed. Herein we describe our efforts to improve upon the overall stereoselectivity using prolinol-derived organocatalysts.

**Objective:** To determine whether diarylprolinol silyl ethers are effective catalysts in the asymmetric peroxidation of  $\alpha,\beta$ -unsaturated aldehydes.

**Methods:** Using *trans*-2-butenal as the test substrate, peroxidation with *tert*-butyl hydroperoxide was attempted in a range of different solvents. The resulting  $\beta$ -peroxyaldehydes were oxidised *in situ* to afford stable  $\beta$ -peroxyesters. The reaction was further optimised by varying the co-catalyst and by changing the silyl ether group on the prolinol catalyst. A number of short-chain substrates were subjected to peroxidation under optimised conditions.

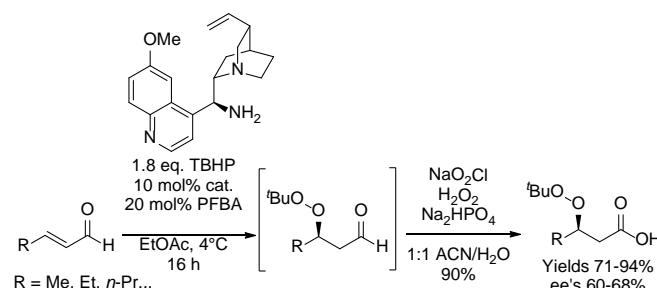
**Results:** Diarylprolinol ethers were found to be effective catalysts for the enantioselective peroxidation of unsaturated aldehydes. The degree of enantioselectivity was influenced both by the choice of solvent and acid co-catalyst. Furthermore, a clear trend emerged where the level of enantioselectivity increased with increasing steric bulk of the silyl group.

**Conclusion:** Diarylprolinol ethers are effective catalysts for the asymmetric peroxidation of  $\alpha,\beta$ -unsaturated aldehydes. Under optimised conditions, short-chain substrates may be converted to the corresponding  $\beta$ -peroxyesters in good yields and excellent enantioselectivities.

**Keywords:** organocatalysis, prolinol, asymmetric, peroxidation, peroxyacid, peroxyesters.

## 1. INTRODUCTION

Chiral peroxides, many of which are biologically active, are an attractive target in organic synthesis. A large number of peroxide-containing natural products display potent biological effects, with artemisinin ranking as one of the most important examples [1, 2]. In spite of this, general methods for the enantioselective preparation of chiral peroxides remain relatively scarce. Organocatalysts have been used for some time in the asymmetric epoxidation of  $\alpha,\beta$ -unsaturated carbonyls using peroxide reagents such as *t*-butyl hydroperoxide (TBHP) [3, 4]. More recently, cinchona-derived organocatalysts have been adapted to effect the asymmetric peroxidation of unsaturated ketones[5]. The stereoselective peroxidation of more challenging  $\alpha,\beta$ -unsaturated aldehydes has also been reported by our group [6] and others [7]. We found that the short-chain, unstable  $\beta$ -peroxyaldehyde intermediates could be readily transformed into stable  $\beta$ -peroxycarboxylic acids in yields of 71% to 94% with ee's ranging from 60% to 68% (Scheme 1).



**Scheme 1.**

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Despite having exhaustively tested a wide range of solvents, additives, and various cinchona-derived catalysts, we were unable to further improve upon the observed enantioselectivity with this system. Accordingly, we sought out an alternative and more effective catalyst. Prolinol ether catalysts have had wide success in the field of organocatalysis [8-10]. Of particular relevance is diarylprolinol ether **1a** which has been successfully

employed by Jørgensen in the asymmetric epoxidation of various  $\alpha,\beta$ -unsaturated aldehydes (Fig. 1) [4].

## 2.1. Catalyst screening and optimisation

Using conditions similar to those for our cinchona system, initial peroxidation of *trans*-2-butenal with TBHP in the presence of **1a** and benzoic acid as co-catalyst was followed by Pinnick oxidation to the stable  $\beta$ -peroxycarboxylic acid. In order to determine the level of enantioselectivity, the  $\beta$ -peroxycarboxylic acids were directly coupled with methyl D-mandelate allowing for the resulting diastereomeric esters to be separated by chiral HPLC. An ee of 59% and an overall yield of 69% was recorded in ethyl acetate (Table 1, entry 1). The absolute configuration was determined based on our previous work whereby the fortuitous crystallisation of the minor diastereomer of mandelate ester **3a**, namely (*S,R*)-**3a**, allowed for the confirmation of the stereochemical configuration *via* X-ray crystallography. Comparison of the retention times with our earlier sample confirmed that formation of the (*R*)-enantiomer was preferred as was the case with the cinchona system. A solvent screen was next undertaken to identify the optimal reaction medium. The choice of solvent was found to have a major impact on the reaction outcome. In general, higher enantioselectivities were recorded in more polar solvents, with 1,4-dioxane and THF proving especially effective (entries 2 and 3). In contrast to Jørgensen's study, non-polar solvents proved to be a poor match for this system, with both toluene and hexane returning ee's of only 30% (entries 6 and 7).

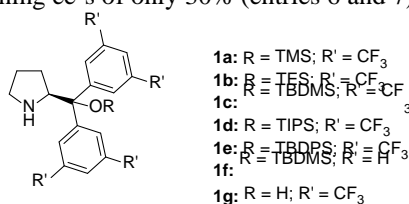
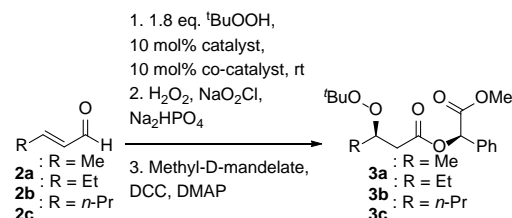


Fig. (1). Prolinol ether catalysts used in this study.

As we had previously found that additives played an important role in our cinchona-based system, we also conducted a screen of acid co-catalysts. Replacing benzoic acid with less acidic acetic acid led to fall in stereoselectivity (entry 8). 4-Trifluoromethylbenzoic acid gave ee's broadly comparable with benzoic acid (entry 9), while further increases in the acidity of the co-catalyst led to a more significant reduction in enantioselectivity with 4-nitrobenzoic acid affording an ee of only 70% (entry 10). Asymmetric counteranion-directed catalysis (ACDC) has a proven track record in many organocatalysed reactions [11-13]. We observed an interesting matched/mismatched effect when D- and L-proline were tested as co-catalysts in this system. While the use of L-proline had a negative impact on stereoselectivity (11% ee, entry 11), D-proline proved to be considerably more effective affording an ee of 76% (entry 12).

Table 1. Optimisation of asymmetric peroxidation under diarylprolinol ether catalysis



| Entry           | R            | Cat.      | Co-cat.   | Solvent           | Overall Yield (%) | ee (%) <sup>a</sup> |
|-----------------|--------------|-----------|---|-------------------|-------------------|---------------------|
| 1               | Me           | <b>1a</b> | PhCO <sub>2</sub> H   | EtOAc             | 69                | 59                  |
| 2               | Me           | <b>1a</b> | PhCO <sub>2</sub> H   | Dioxane           | 75                | 78                  |
| 3               | Me           | <b>1a</b> | PhCO <sub>2</sub> H   | THF               | 78                | 82                  |
| 4               | Me           | <b>1a</b> | PhCO <sub>2</sub> H   | Et <sub>2</sub> O | 75                | 66                  |
| 6               | Me           | <b>1a</b> | PhCO <sub>2</sub> H   | Toluene           | 71                | 30                  |
| 7               | Me           | <b>1a</b> | PhCO <sub>2</sub> H   | Hexane            | 68                | 30                  |
| 8               | Me           | <b>1a</b> | AcOH  | THF               | 65                | 38                  |
| 9               | Me           | <b>1a</b> | 4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H | THF               | 74                | 79                  |
| 10              | Me           | <b>1a</b> | 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H | THF               | 70                | 70                  |
| 11              | Me           | <b>1a</b> | L-Proline   | THF               | 56                | 11                  |
| 12              | Me           | <b>1a</b> | D-Proline   | THF               | 59                | 76                  |
| 13              | Me           | <b>1b</b> | PhCO <sub>2</sub> H   | THF               | 66                | 81                  |
| 14              | Me           | <b>1c</b> | PhCO <sub>2</sub> H   | THF               | 78                | 89                  |
| 15              | Me           | <b>1d</b> | PhCO <sub>2</sub> H   | THF               | 70                | 90                  |
| 16              | Me           | <b>1e</b> | PhCO <sub>2</sub> H   | THF               | 78                | 69                  |
| 17              | Me           | <b>1f</b> | PhCO <sub>2</sub> H   | THF               | -                 | -                   |
| 18              | Me           | <b>1g</b> | PhCO <sub>2</sub> H   | THF               | 54                | 11                  |
| 19 <sup>b</sup> | Me           | <b>1c</b> | PhCO <sub>2</sub> H   | THF               | 78                | 94                  |
| 20 <sup>b</sup> | Et           | <b>1c</b> | PhCO <sub>2</sub> H   | THF               | 59                | 97                  |
| 21 <sup>b</sup> | <i>n</i> -Pr | <b>1c</b> | PhCO <sub>2</sub> H   | THF               | 53                | 96                  |

<sup>a</sup>As determined by derivatisation to the mandelate esters

<sup>b</sup>0.9 mmol aldehyde in 0.1 mL THF, -15 °C.

We next turned our attention to modification of the prolinol catalyst itself. It has been observed that the incorporation of bulkier silyl protecting groups can provide higher selectivities [14]. Computational studies have further demonstrated that steric shielding of the iminium ion intermediate in diarylprolinol-catalysed reactions is primarily owed to the silyl group rather than the aryl moieties [15]. With this in mind, we prepared a series of diarylprolinol catalysts with silyl groups of increasing steric bulk (Fig. 1). A clear trend emerges from this data where the level of enantioselectivity increases with increasing steric bulk of the silyl group (entries 13-16) with the highest ee of 90% obtained with the triisopropylsilyl-protected catalyst **1d** (entry 15). However, this high enantioselectivity comes at the cost of lower reactivity with reduced yields and considerably longer reaction times recorded for peroxidations catalysed by **1d**. Overall, TBDMS-protected **1c** was found to be the best compromise between reactivity and selectivity. Further modification of **1c** demonstrated that the presence of the trifluoromethyl substituents on the aryl ring was critical for catalytic activity (entry 17) while the TBDMS-group was crucial for stereoselectivity (entry 18).

From these results, it appeared that a combination of catalyst **1c** with benzoic acid as co-catalyst in THF offered the highest overall yields and ee's. In an attempt to further improve the enantioselectivity, the reaction temperature was reduced to -15°C, which saw an increase in ee to above 90% but at the cost of lower conversions and a yield of only 15%. Following further optimisation, it was discovered that the reduced reactivity caused by the lower reaction temperature could be offset by increasing the reaction concentration from 0.6M to 9M. Under these conditions, the asymmetric peroxidation of *trans*-2-butenal proceeded with excellent enantioselectivity and in high yields (entry 17) [16]. Longer chain substrates, such as *trans*-2-pentenal (entry 18) and *trans*-2-hexenal (entry 19), were also amenable to these conditions affording the  $\beta$ -peroxyesters in ee's of 97% and 96% respectively, albeit in lower yields. Work on the extension of this approach is on-going, and will be reported at a future date.

## CONCLUSION

In conclusion, we have demonstrated that diarylprolinol ethers are effective catalysts for the asymmetric peroxidation of  $\alpha,\beta$ -unsaturated aldehydes. Under optimised conditions, short-chain substrates were converted to the corresponding  $\beta$ -peroxyesters with excellent enantioselectivities and good yields. We hope to report on the full scope of this methodology in due course.

## CONFLICT OF INTEREST

Declared none.

## ACKNOWLEDGEMENTS

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## SUPPLEMENTARY MATERIAL

A typical experimental procedure is outlined in Supplementary Material.

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