

Alkene Dihydroxylation with Malonoyl Peroxides: Catalysis Using Fluorinated Alcohols

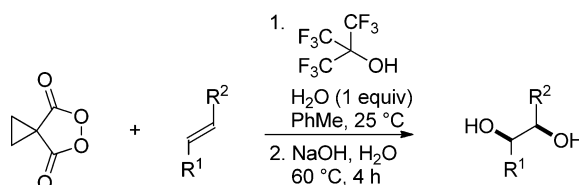
Sylvain Picon,[†] Michael Rawling,[‡] Matthew Campbell,[§] and
Nicholas C. O. Tomkinson^{*,‡}

School of Chemistry, Main Building, Cardiff University, Park Place, Cardiff, CF10
3AT, U.K., GlaxoSmithKline Medicines Research Centre, Stevenage, Hertfordshire,
SG1 2NY, U.K., and WestCHEM, Department of Pure and Applied Chemistry, Thomas
Graham Building, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, U.K.

Nicholas.Tomkinson@strath.ac.uk

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ABSTRACT



The effect of fluorinated alcohols on the dihydroxylation of alkenes using cyclopropyl malonoyl peroxide is described. Addition of perfluoro-*tert*-butyl alcohol to a toluene solution of alkene and peroxide increases the rate of product formation and the stereoselectivity observed, providing a simple and effective method for acceleration of this important class of reaction. Basic hydrolysis of the crude reaction mixture provides access to *syn*-diols in high yield and stereoselectivity.

Alkene dihydroxylation is central in synthetic chemistry. The gold-standard Sharpless asymmetric dihydroxylation represents an outstanding method for performing this reaction, providing the products in excellent yields and high levels of asymmetric induction.¹ Despite the overwhelming acceptance of this reaction, the toxicity and expense of osmium(VIII) has provided an impetus for the development of alternative methods.² Notable success

has been achieved with transition metals including palladium,³ iron,⁴ ruthenium,⁵ manganese,⁶ and copper.⁷ Metal-free methods have also been reported. However, this area is considerably less established than their metal-based counterparts.^{8,9} To date, the development of a catalytic asymmetric, metal-free method for the dihydroxylation of alkenes remains an elusive and attractive target.

We recently described a simple and effective method for the transition-metal free *syn*-dihydroxylation of alkenes

[†] Cardiff University.

[‡] University of Strathclyde.

[§] GlaxoSmithKline.

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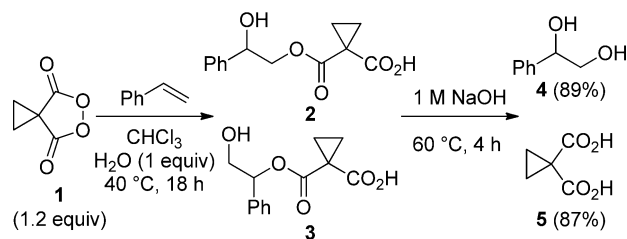
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using cyclic malonoyl peroxides.¹⁰ For example, reaction of cyclopropyl malonoyl peroxide **1** (1.2 equiv) with styrene in the presence of 1 equiv of water leads to intermediate esters **2** and **3**. Removal of the solvent followed by basic hydrolysis of the crude reaction mixture provides diol **4** (89%) and diacid **5** (87%) (Scheme 1). Within this paper we describe successful efforts to catalyze this reaction using fluorinated alcohols.

Scheme 1. Dihydroxylation of Styrene with Cyclopropyl Malonoyl Peroxide **1**



A potential mechanism for the transformation is outlined in Scheme 2. Reaction of alkene and peroxide **1** leads to **6** which undergoes ring closure, forming dioxonium species **7**. Hydrolysis with the molecule of water necessary to bring about reaction gives observed esters **2** and **3**. Interestingly, without water, the overall rate of reaction is considerably reduced (see Supporting Information for details). This suggested water could be playing a dual role within the reaction, hydrolyzing intermediate **7** and activating peroxide **1**, stabilizing a developing negative charge on oxygen (*i.e.*, **6**).

Water has limited solubility in chloroform (mole fraction 0.005),¹¹ such that under the reaction conditions the concentration of water in solution would be less than that of the reagents. Reasoning that alternative H-bond donors which were soluble in chloroform could activate peroxide **1**, and stabilize intermediates **6** and **7**, we examined the effect of alcohols on the reaction rate. Adam has shown di-*n*-butylmalonoyl peroxide reacts with methanol and ethanol.¹² We therefore considered that the less nucleophilic fluorinated alcohols trifluoroethanol (TFE), hexafluoroisopropanol (HFP), and perfluoro-*tert*-butyl alcohol (PFB) might accelerate the reaction (Figure 1).

It is clear from Figure 1 that in the presence of a fluorinated alcohol (1.2 equiv) the rate of product formation in chloroform is enhanced. Increasing the acidity of the alcohol TFE→HFP→PFB¹³ increases the rate. These results are consistent with the alcohol acting as a H-bond donor, activating peroxide **1**.

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Scheme 2. Possible Mechanism for the Reaction of Styrene with Cyclopropyl Malonoyl Peroxide **1**

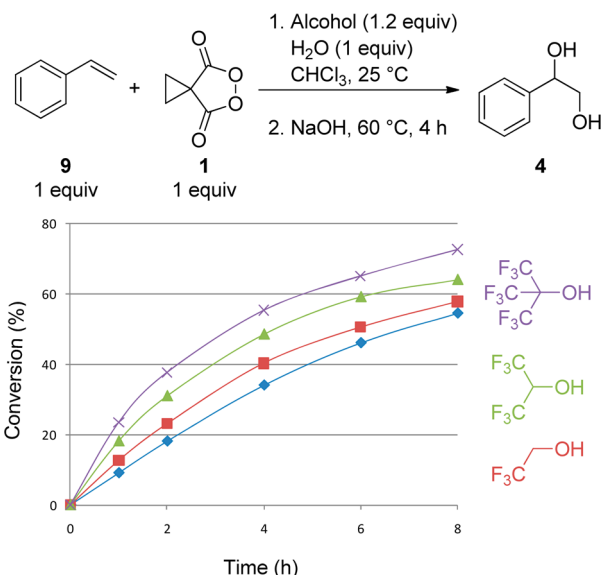
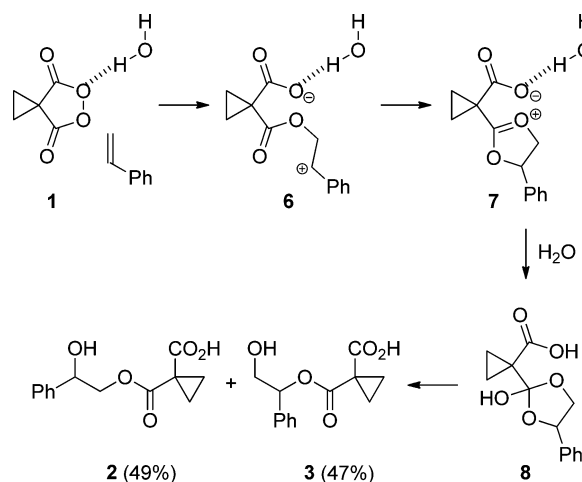


Figure 1. Relative rates of product formation for the reaction of **1** with styrene in the presence of fluorinated alcohols. All reactions performed in CHCl₃ [0.65 M] at 25 °C in the presence of H₂O (1.0 equiv) and fluorinated alcohol (1.2 equiv). (♦) No alcohol; (■) trifluoroethanol (TFE); (▲) hexafluoroisopropanol (HFP); (×) perfluoro-*tert*-butyl alcohol (PFB).

In developing the reaction,¹⁰ a number of solvents were examined with chloroform emerging as the most effective with respect to rate and yield. We were unable to rationalize this finding at the time. Based upon the results above (Figure 1), it is possible that chloroform may also act as a H-bond donor in a similar manner to the fluorinated alcohols.^{14,15}

(14) Similar reaction rate profiles for “bench” chloroform and base washed chloroform were observed; see Supporting Information for full details.

In an effort to slow down the background reaction we examined toluene as the reaction medium (Figure 2). Consistent with the hypothesis that chloroform was acting as a H-bond donor, the rate of reaction in toluene was substantially reduced. It is also noteworthy that water is less soluble in toluene (mole fraction 0.0025)¹¹ when compared to chloroform, which can also account for the reduced rate. Importantly, the use of PFB (×; 1.2 equiv) led to a significantly enhanced rate of product formation. Reducing the loading of PFB (▲; 0.2 equiv) also showed an improved reaction rate.

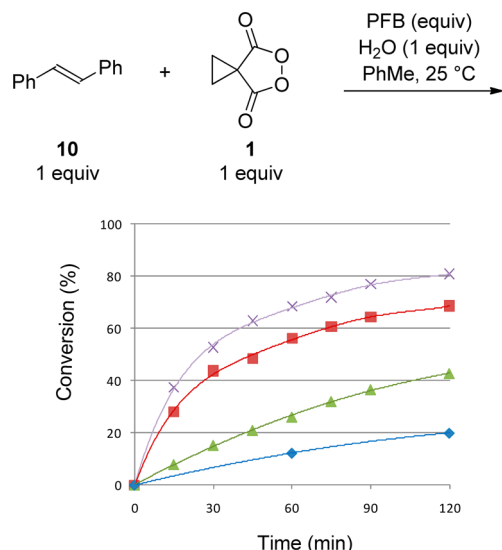


Figure 2. Acceleration of reaction of stilbene and **1** in the presence of PFB. Average of two runs in PhMe [0.6 M] at 25 °C in the presence of H₂O (1.0 equiv). (◆) No alcohol; (×) 1.2 equiv of PFB; (■) 1.0 equiv of PFB; (▲) 0.2 equiv of PFB.

The potential existed for the fluorinated alcohol to increase the solubility (and hence concentration) of water in the reaction solvent, and it was this factor which was responsible for rate enhancement. In order to examine this, we monitored the consumption of peroxide in the presence and absence of both water and PFB (Figure 3). Without PFB present similar rates for peroxide consumption were observed, in both the absence (◆) and presence (■) of water, suggesting that water has little effect on the rate in toluene. In the presence of PFB and water (●) the rate of peroxide consumption was significantly increased. This rate increased further in the presence of PFB and absence of water (▲). If the origin of rate enhancement by PFB addition was due to an increased concentration of water in the reaction medium it would be expected that under anhydrous reaction conditions (▲) the rate of peroxide consumption would be slower. This is not the case. It is thought that the rate of peroxide consumption is greater

under anhydrous reaction conditions (▲) as both the peroxide **1** and water would compete to H-bond with the fluorinated alcohol when water is present (●).

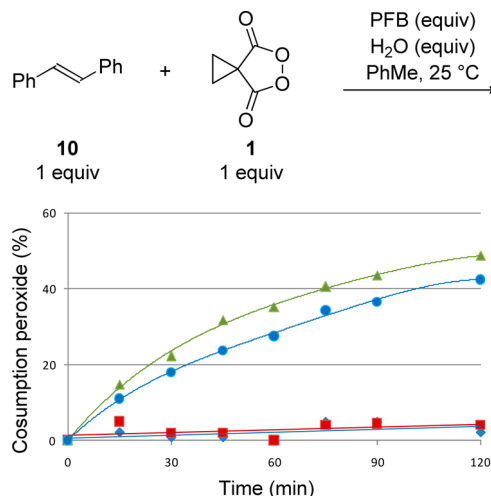


Figure 3. Effect on rate of water and PFB in toluene. All reactions performed in PhMe [0.3 M] at 25 °C. (◆) No water and no PFB; (■) 1 equiv of water and no PFB; (●) 1 equiv of water and 1 equiv of PFB; (▲) no water and 1 equiv of PFB.

Table 1. Effect of Fluorinated Alcohols on Stereoselectivity in the Reaction of **1** with β -Substituted Alkenes^a

entry	alcohol	R ¹	R ²	<i>syn/anti</i> ^b	% yield ^c
1	none	Ph	Me	13:1	78
2	TFE	Ph	Me	17:1	84
3	HFP	Ph	Me	17:1	81
4	PFB	Ph	Me	19:1	85
5	none	Ph	Ph	31:1	76
6	PFB	Ph	Ph	49:1	79
7 ^d	none	Ph	Ph	4:1	77
8 ^d	PFB	Ph	Ph	4:1	78
9	none	4-BrC ₆ H ₄	Me	10:1	74
10	PFB	4-BrC ₆ H ₄	Me	15:1	74

^a All reactions performed in PhMe [0.6 M] at 25 °C in the presence of H₂O (1.0 equiv) and fluorinated alcohol (1.2 equiv). ^b Determined by ¹H NMR spectroscopy of crude reaction mixture. ^c Isolated yield. ^d *cis*-Stilbene used as substrate.

Finally, further evidence for the intimate involvement of the H-bond donor within the transition state came from examining the effect of fluorinated alcohols on the

(15) For a discussion of chloroform as a H-bond donor, see: Kwak, K.; Rosenfeld, D. E.; Chung, J. K.; Fayer, M. D. *J. Phys. Chem. B* **2008**, *112*, 13906.

stereoselectivity of dihydroxylation (Table 1). In the absence of an alcohol additive, reaction of *trans*- β -methylstyrene was slow, providing the product in a respectable 78% yield and a *syn/anti* ratio of 13:1 (entry 1). Addition of TFE, HFB, and PFB (1.2 equiv) consistently gave the product in higher yield and a higher *syn/anti* ratio (entries 2–4). This observation also held true for the reaction of *trans*-stilbene **10** (entries 5 and 6) and 4-bromo- β -methylstyrene (entries 9 and 10). With more challenging substrates such as *cis*-stilbene (entries 7 and 8), reactions were faster but levels of selectivity still did not reach those required by contemporary standards. The precise origin of this remarkable effect is not apparent. However, the ability to significantly affect the stereoselectivity of the reaction by addition of a fluorinated alcohol further increases the power of this simple and effective dihydroxylation process.

In summary, we have shown that fluorinated alcohols accelerate the reaction between alkenes and cyclopropyl malonoyl peroxide providing a catalytic transition-metal-free *syn*-dihydroxylation procedure. In addition,

fluorinated alcohols can significantly enhance the stereoselectivity of the reaction with 1,2-disubstituted alkenes. This highly practical *syn*-dihydroxylation procedure, which proceeds at room temperature in the presence of moisture and air, provides a powerful and robust method to carry out this important class of transformation. Current efforts focus on the use of chiral H-bond donors to provide a catalytic asymmetric protocol.

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Supporting Information Available. Analytical data, experimental procedures, and NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.