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Organocatalytic α-oxybenzoylation of aldehydes

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ABSTRACT

A simple method for the asymmetric α-oxybenzoylation of aldehydes is presented. Treatment of a series of aldehydes with benzoyl peroxide in the presence of a MacMillan imidazolidinone leads directly to the α-oxybenzoylated product with excellent levels of asymmetric induction.

1. Introduction

Dioxygenation of carbon skeletons in a 1,2-manner is ubiquitous in Nature and robust methods for their synthesis are held in high regard. Development of practical techniques to prepare these motifs which proceed at room temperature in the presence of both moisture and air providing products with high levels of asymmetric induction represents a significant chemical challenge that would considerably augment existing methodology. Over the past eight years, organocatalysis has provided a wealth of fundamental bond construction processes of broad applicability which meet these goals,[1] as highlighted by the number of total syntheses of natural products which exploit this methodology.[2]

The current benchmark for organocatalytic α-oxygenation of carbonyl compounds involves proline-derived secondary amine catalysts with nitrosobenzene as the stoichiometric oxidant.[3,4] Although efficient, it is not possible to isolate the oxyaminated products of aldehydes directly. It is therefore necessary to either reduce or functionalise the aldehyde products directly prior to isolation, representing a major drawback.[5] Within this Letter we show it is possible to α-oxybenzoylate and isolate a range of aldehyde substrates with high levels of asymmetric induction as well as manipulate the products into synthetically useful dioxygenated compounds without compromise in ee.

In 1962 Augustine reported that the morpholine-derived enamine of cyclohexanone could be converted to 2-benzoyloxycyclohexanone by treatment with benzoyl peroxide (BPO).[6] Given the number of enamine-catalysed processes reported in recent years,[7] we believed this represented an attractive candidate for development as a novel organocatalytic strategy and designed the catalytic cycle outlined in Figure 1. Condensation of the amine **1** with an aldehyde would give a reactive enamine intermediate **2**, which could react with BPO to give the functionalised iminium ion **3**. Hydrolysis of this iminium ion would give the desired product **4**, releasing the secondary amine **1** back into the catalytic cycle.

Central to successful development of this catalytic cycle was modulating the reactivity of the amine. It is established that secondary amines react with BPO to give either hydroxylamine or amide products,[8] which would terminate the catalytic cycle (e.g., **5** or **6**). Conveniently, the reaction is governed by steric factors.[9] In order to prevent reaction of the catalytic amine with BPO it was therefore necessary to use a hindered nucleophilic amine that would condense with a carbonyl compound at a faster rate than direct nucleophilic attack on BPO. We established rapidly that the MacMillan imidazolidinone **7**[10] was a suitable candidate for the proposed catalytic cycle, with the amine not reacting with the oxidant under the reaction conditions adopted. Significant data on the development of optimal conditions in the reaction between valeraldehyde (**8**) and BPO (**9**) are outlined in Table 1.

In the absence of catalyst **7** no reaction between the aldehyde **8** and BPO (**9**) was observed (entry 1). Without a co-acid the yield obtained for the reaction was low (13%; entry 2), however, the exceptional ee (97%) certainly warranted further investigation. Crucial to successful development was the choice of co-acid. Stronger acids (HCl, TsOH) (entries 3 and 4) provided no product, however, decreasing the strength of the co-acid improved the observed yield (entries

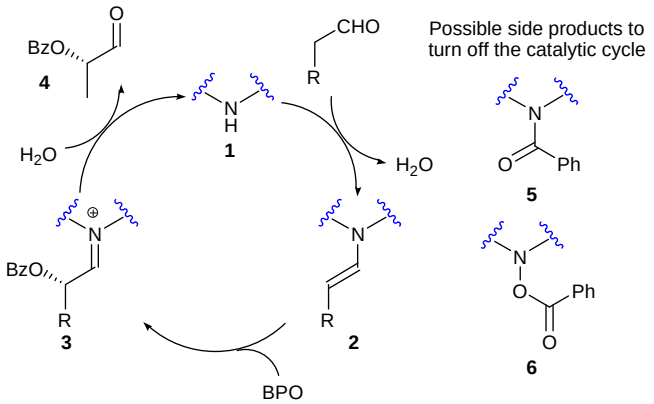

Figure 1.

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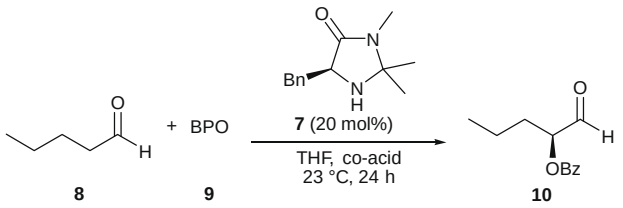
Table 1
Development of the catalytic asymmetric oxygenation procedure



8 9 10

Entry[a]	Co-acid[b]	% Yield of **10**[c]	% ee[d]
1[e]	None	0	—
2	None	13	97
3	HCl	0	—
4	TsOH	0	—
5	TFA	5	—
6	TCA	25	92
7	DCA	35	92
8	3-$NO_2C_6H_4CO_2H$	54	90
9	4-$NO_2C_6H_4CO_2H$	72	93
10	3-$ClC_6H_4CO_2H$	22	94
11	BzOH	<20%	—

TCA—trichloroacetic acid; DCA—dichloroacetic acid.
[a] All reactions carried out at 23 °C in THF with 1 equiv of aldehyde **8**, 1 equiv of BPO (**9**) and imidazolidinone (**7**) (20 mol %), unless otherwise stated.
[b] 20 mol % co-acid added.
[c] Isolated yield.
[d] Determined by reduction of the aldehyde ($NaBH_4$) followed by HPLC analysis; chiracel OJ, 0.5% IPA/hexane, 0.5 mL min^{-1}, 254 nm (t_1 = 40.5 min; t_2 = 46.2 min).
[e] Reaction performed in the absence of catalyst **7**.

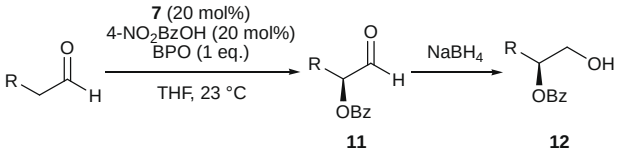
5–8), with the most efficient co-acid being 4-nitrobenzoic acid (72% yield; 93% ee) (entry 9). Further reduction in the co-acid strength was detrimental to the efficiency of the reaction (entries 10 and 11).

A precise explanation for these observations, which mirror the findings of others,[11] is not immediately apparent. Addition of the acids given in Table 1 to the imidazolidinone **7** would clearly form the corresponding salt. Therefore, it would be expected that acid strength would not significantly affect reactivity. However, the data clearly indicate a remarkable influence on reactivity by the co-acid and a better understanding of the origins of this effect would have important implications in the field.

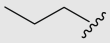
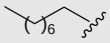
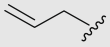
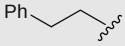
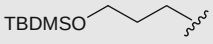
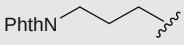
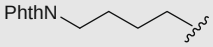
Having established effective reaction conditions for the α-oxybenzoylation reaction, a series of alternative substrates were examined (Table 2). In the majority of cases excellent levels of asymmetric induction were observed, apart from the functionalisation of benzylic centres (entry 7; 60% ee). The reaction worked well for unfunctionalised alkanes (entries 1–3; 93–95% ee). Yields were reduced when steric hindrance was increased around the reactive centre, however, this did not affect the ee's observed (entry 4; 40% yield; 93% ee). Alkene and aromatic functionalities tolerated the reaction conditions (entries 5 and 6; 90–94% ee) along with protected oxygen and nitrogen groups (entries 8–10; 94–95% ee). As well as providing direct access to α-oxybenzoylated aldehydes, addition of sodium borohydride directly to the crude reaction mixture efficiently provided the corresponding mono-protected diol **12**, without compromise of ee. Of interest is the fact that with each of these reduced products, the protecting group resides on the more hindered secondary alcohol, a non-trivial overall transformation.

The ability to isolate the α-functionalised aldehyde products from the reaction mixture represents a considerable benefit to the chemistry described with the products being ripe for further synthetic manipulation. In preliminary investigations we were able to alter the oxidation level of these compounds without affecting the ee (Scheme 1). For example, reduction of **10** with sodium borohydride provides the 1,2-diol **13** (98% yield; 92% ee). Oxidation to either the acid **14** (87% yield; 91% ee)[12] or the ester **15** (75% yield;

Table 2
Scope of the α-oxybenzoylation reaction

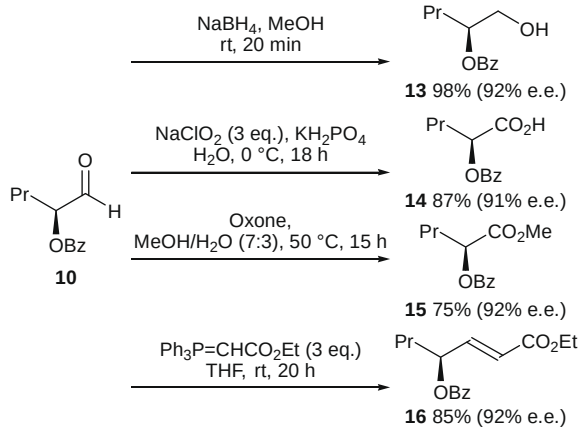


11 12

Entry	R	% Yield **11**[a]	% Yield **12**[a]	% ee[b]
1		72	72	93
2		55	50	93
3		71	66	95
4[c]		42	40	93
5		50	50	94
6		57	54	90
7		47	42	60
8		55	51	95
9		—	55	94
10		—	55	94

[a] Isolated yield of either aldehyde **11** or diol **12**.
[b] Determined by HPLC; chiracel OJ.
[c] Two equivalents of aldehyde used.

92% ee)[13] also proceeds under standard reaction conditions. Finally, we found it was also possible to undertake standard Wittig chemistry to provide the α,β-unsaturated ester **16** (85% yield;



Scheme 1.

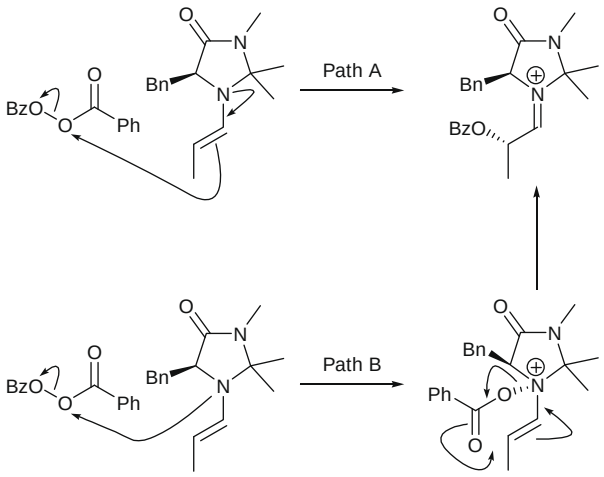


Figure 2.

92% ee). This suggests that the stereogenic centre in the α-oxybenzoylated aldehydes should be stable to a variety of acidic and basic reaction conditions allowing the potential of the products to be revealed.

Two plausible ionic mechanisms can be proposed for the key C–O bond-forming process (Fig. 2). Direct attack of the enamine carbon on the peroxide (path A) or N-oxybenzoylation of the enamine followed by [3,3]-sigmatropic rearrangement[14] (Path B). Current work is focussed on determining the precise pathway this reaction follows.

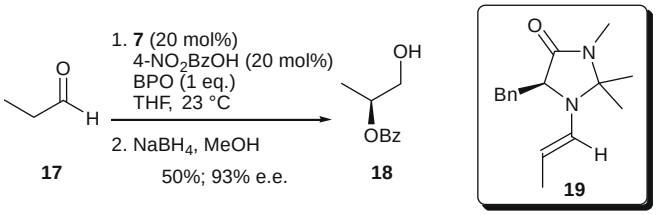
Confirmation of the proposed sense of asymmetric induction observed within these transformations came from the reaction of propanal (**17**) with BPO (**9**) followed by in situ reduction to give the known mono-protected propane diol **18**[15] (Table 2, entry 2) (50% yield; 93% ee). The observed (*S*)-stereochemistry of the product is consistent with formation of the *E*-enamine **19** and approach of the oxidant from the less hindered *Si*-face, directed by the benzyl arm of the catalyst (Scheme 2). This proposal is in line with previous observations.[16]

In summary, we have described a simple and effective method for the α-oxybenzoylation of aldehydes using a commercially available catalyst and reagent which proceeds with excellent levels of asymmetric induction. The products are stable, isolable compounds that can be exploited in a series of further transformations. Of note is the one-pot preparation of the mono-protected 1,2-diol functionality, with the protecting group on the more sterically encumbered alcohol. The stereochemical course of these reactions is consistent with formation of an *E*-enamine followed by direction of the approach of peroxide by the benzyl arm of the catalyst structure.

2. Typical experimental procedure

2.1. 2-Oxybenzoylvaleraldehyde 10

To a solution of valeraldehyde (62 μl, 0.58 mmol) in tetrahydrofuran (1 mL) were added imidazolidinone **7** (20 mol %, 25 mg, 0.12 mmol), 4-nitrobenzoic acid (20 mol %, 19 mg, 0.12 mmol) and benzoyl peroxide (70% w/w, 201 mg, 0.58 mmol). The reaction mixture was stirred at 23 °C for 48 h before dilution with aq saturated $NaHCO_3$ solution (5 mL) and extraction of the aqueous phase with EtOAc (3 × 20 mL). The organic layer was collected and dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure and purified by flash column chromatography eluting with light petroleum–EtOAc (9:1) to give 2-oxybenzoylvaleraldehyde **10** as a colourless oil (86 mg, 72%): $[\alpha]_D$ −37.4 (*c* 1.0; $CHCl_3$); IR (thin film) 2955, 1716, 1267, 1111, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 0.67 Hz, 1H), 8.18–8.16 (m, 2H), 7.69–7.65 (m, 1H), 7.56–7.53 (m, 2H), 5.31–5.28 (m, 1H), 2.00–1.94 (m, 2H), 1.65–1.59 (m, 2H), 1.06 (t, *J* = 7.37 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 166.2, 133.5, 129.9, 129.3, 128.5, 78.6, 30.1, 18.4, 13.8; *m/z* (ES) 207 $[M+H]^+$; HRMS (ES) calculated for $C_{12}H_{15}O_3$ 207.1016 $[M+H]^+$, found 207.1015.



Scheme 2.

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