Alkene Syn- and Anti-Oxyamination with Malonoyl Peroxides

Jonathan M. Curle, Marina C. Perieteanu, Philip G. Humphreys, Alan R. Kennedy, and Nicholas C. O. Tomkinson*

ABSTRACT: Malonoyl peroxide 6 is an effective reagent for the syn- or anti-oxyamination of alkenes. Reaction of 6 and an alkene in the presence of O-tert-butyl-N-tosylcarbamate (R³ = CO₂Bu) leads to the anti-oxyaminated product in up to 99% yield. Use of O-methyl-N-tosyl carbamate (R³ = CO₂Me) as the nitrogen nucleophile followed by treatment of the product with trifluoroacetic acid leads to the syn-oxyaminated product in up to 77% yield. Mechanisms consistent with the observed selectivities are proposed.

The β-amino alcohol functionality is an important motif present in natural products, agrochemicals, pharmaceuticals, and ligands for catalysis. Many methods exist for the introduction of this functionality with the difunctionalization of alkenes representing a particularly efficient process. In the reaction of an alkene 1, the oxyamination presents significant challenges with regard to regioselectivity and stereoselectivity with up to four possible products 2–5 (Scheme 1).

Considerable attention has been devoted to the intramolecular (tethered) oxyamination of alkenes, which can circumvent regiochemistry issues; however, there are substantially fewer reports of intermolecular procedures which meet the regio- and diastereochromatic challenges of the process.

For the preparation of the syn-products 2 and 3 through an intermolecular oxyamination the osmium catalyzed asymmetric aminohydroxylation developed by Sharpless represents the gold standard within the field. Loss of selectivity for some alkene substrates along with deficiencies in regioselectivity and the desire to prepare the anti-products 4 and 5 have driven further investigation. Important advances have been made with a variety of transition metals including osmium, rhodium, palladium, copper, and iron. Metal-free methods for the intermolecular oxyamination of alkenes have also been developed which include the use of TEMPO or peroxides. Arnold reported a biocatalytic method for anti-oxyamination using a hemoprotein. While these recent developments represent excellent progress, diastereoselectivity in the majority of these transformations is not well explored and provides the impetus for additional research efforts. It is also noteworthy that stereoselective intermolecular methods to access anti-oxyamination product 5 are particularly limited. Within this manuscript, we report the development of an intermolecular metal-free anti-oxyamination through the reaction of an alkene 1, malonoyl peroxide 6 and a nitrogen nucleophile and show how the product can be converted directly into the syn-oxyaminated product by treatment with TFA.

The investigation began with the reaction of trans-stilbene 7 and malonoyl peroxide 6 in the presence of different nitrogen nucleophiles. The aim was to find a nitrogen nucleophile that reacted with dioxonium 8 and not peroxide 6. From a total of 12 nitrogen nucleophiles examined, only saccharin 10 showed the desired activity (see the Supporting Information).

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Reaction of alkene 7 (1.0 equiv), peroxide 6 (1.8 equiv), and saccharin 10 (2.0 equiv) in chloroform at 40 °C for 24 h gave the anti-oxyaminated product 11 (30%) (Scheme 2). Saccharin 10 is an ambident nucleophile which can react through either its nitrogen or oxygen atom. Along with the oxyaminated product 11 the anti-dioxygenated coproduct 12 was also isolated from the reaction mixture in 20% yield. The structures of both 11 and 12 were confirmed by single-crystal X-ray crystallography (see the Supporting Information for full details). In contrast to the related intramolecular oxyamination procedure,2b the product isolated has undergone decarboxylation. It is proposed that the low nucleophilicity of the amine nucleophile allows for decaboxylation of the initial adduct16 to give 8 prior to trapping with saccharin. We believed synthesis of 11 represented a simple and effective anti-oxyamination which proceeded under mild conditions and warranted further investigation.

We sought to understand the ambident reactivity of saccharin 10 to improve the selectivity for N-alkylation over O-alkylation. Literature reports suggest the reactivity of ambident nucleophiles can be altered through changes in solvent and temperature;18 however, despite extensive investigation we were unable to significantly alter the ratio of 11 and 12 obtained. We therefore turned our attention to modifying the structure of saccharin 10. Seven acyl sulfonamide derivatives 13−19 were prepared by altering both the steric and electronic environments of the nitrogen atom, which were then reacted with stilbene 7 in the presence of malonoyl peroxide 6 (CHCl₃, 40 °C, 24 h) (Table 1).

<table>
<thead>
<tr>
<th>entry</th>
<th>nucleophile</th>
<th>A</th>
<th>B</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>20A (19%)</td>
<td>20B (19%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>21A (0%)</td>
<td>21B (60%)</td>
<td></td>
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<tr>
<td>3</td>
<td>22A (0%)</td>
<td>22B (33%)</td>
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</tr>
<tr>
<td>4</td>
<td>23A (0%)</td>
<td>23B (22%)</td>
<td></td>
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<tr>
<td>5</td>
<td>24A (39%)</td>
<td>24B (0%)</td>
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<tr>
<td>6</td>
<td>25A (49%)</td>
<td>25B (0%)</td>
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<tr>
<td>7</td>
<td>26A (45%)</td>
<td>26B (0%)</td>
<td></td>
</tr>
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</table>

Scheme 2. Alkene Oxyamination in the Presence of Saccharin

Table 1. Optimization of Nitrogen Nucleophile

Selectivity. We therefore altered the electronic environment of the nitrogen nucleophile by preparing the N-sulfonyl carbamates 17−19. Under standard reaction conditions, all three nucleophiles were N-selective, providing the anti-oxyaminated products 24A−26A (entries 5−7; 39−49%). This remarkable switch in selectivity by changing the steric or electronic environment of the nitrogen nucleophile represents a powerful observation that presents an intriguing opportunity for further investigation.

O-tert-Butyl-N-tosylcarbamate 18 was selected as the preferred nucleophile. Further optimization of the reaction conditions failed to improve the yield of oxyamination product 25A beyond 49%. However, the conversion of nucleophile 18 to oxyaminated product 25A was an efficient process. Therefore, in examining the substrate scope of the reaction we employed the conditions outlined in Scheme 3 (entry 1, 97%), using the nitrogen nucleophile 18 as the limiting reagent.

Examination of a series of stilbene derivatives showed the reaction to proceed efficiently at room temperature with complete anti-diastereoselectivity (Scheme 3). The reaction was tolerant of substitution in the 2-, 3-, and 4-positions of the stilbene substrate (entries 2−4, 62−92%). In addition, fluorine (entry 6, 71%), chlorine (entry 7, 90%), and bromine (entry 8, 85%) substituents on the aromatic ring also led to the expected products, providing useful handles for further synthetic manipulation. Alternative N- and O-substituted carbamates
were also tolerated under the optimized reaction conditions. For example, O-tert-butyl-N-((4-cyanophenyl)sulfonyl)carbamate 35 (entry 9, 94%) and O-methyl-N-tosylcarbamate 19 (entry 10, 71%) both gave the expected anti-oxyaminated products in excellent yields.

Our attention then turned to styrene substrates (Scheme 4). Reaction of styrene, peroxide 6, and amine nucleophile 18 (CHCl₃, 40 °C, 24 h) gave oxyaminated product 37A along with the regioisomer 37B in a 3.5:1 ratio (Scheme 4, entry 1; 77%). The expected product 37A is a result of the nucleophile 18 adding to the benzylic position A of dioxonium intermediate 36. The minor regioisomer 37B arises through addition of 18 to the more sterically accessible position B. The amount of the major regioisomer A can be increased by the introduction of electron-donating substituents to the aromatic ring. For example, a methyl group can increase the amount of the major isomer to up to 10:1 (Scheme 4, entries 2−4; 76−99%). This ratio increases further using mesityl styrene as the substrate (entry 5, 20:1; 78%). 4-Methoxystyrene provides the expected oxyaminated product 42 with complete selectivity for addition of the nucleophile at position A (entry 6, 47%). Using halogen-substituted styrenes lowers the ratio of products A/B observed as the substituent is moved from para (entries 10−12, up to 5:1) to meta (entry 8, 1:4:1) to ortho positions (entry 7, 1:1). We believe selectivity and reactivity are altered by a combination of lone pair stabilization and the electron-withdrawing nature of the substituents destabilizing any buildup of positive charge at position A of proposed intermediate 36. Introducing substitution at the β-position of the styrene substrate results in complete stereoselectivity in the oxyamination process for addition of the nucleophile at position A (Scheme 4, entries 13−15; 81−92%). This steric factor completely overrides any electronic influence on the regiochemical outcome of the transformation (cf. entries 7 vs 14). The reaction of cis-β-methylstyrene proceeded with complete regioselectivity; however, considerable loss in stereoselectivity was observed, suggesting that cis-alkenes will be poor substrates within this transformation (entry 16).

Reaction of O-methyl-N-tosylcarbamate 19 with stilbene 7 and malonoyl peroxide 6 under the standard reaction conditions provided the oxyaminated product 26A (Scheme 3, entry 10, 71%). Treatment of this adduct with trifluoroacetic acid (12 equiv) in CH₂Cl₂ (40 °C, 5 h) led to the oxazolidinone 53 (77% over two steps), the product of a formal syn-oxyamination of the trans-stilbene substrate (Scheme 5, entry 1). This provides a powerful and particularly useful complementary strategy to the anti-oxyamination procedure described above, allowing access to both diastereomeric oxyaminated products using the same alkene and malonoyl peroxide reagents. This strategy was also effective for styrene (entry 2) and β-substituted styrene derivatives (entries 3 and 4). Consistent with previous observations, 2-fluorostyrene provided the two regioisomeric products 57 and 58 after oxazolidinone formation (entry 5, 72%), the structures of which were confirmed by X-ray crystallography (see the

**Scheme 3. Stilbene Substrate Scope**

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>% yield</th>
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<td>1</td>
<td>Ph</td>
<td>25A</td>
<td>97</td>
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<tr>
<td>2</td>
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<td>3</td>
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<td>4-ClC₆H₄</td>
<td>32</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>4-BrC₆H₄</td>
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</tr>
<tr>
<td>9</td>
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<td>94</td>
</tr>
<tr>
<td>10</td>
<td>Ph</td>
<td>26A</td>
<td>71</td>
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*All reactions conducted in duplicate. bReaction conducted at 0 °C. cO-tert-butyl-N-((4-cyanophenyl)sulfonyl)carbamate 35 was used as nucleophile. dO-Methyl-N-tosylcarbamate 19 was used as nucleophile.

**Scheme 4. Styrene Substrate Scope**

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
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<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>25A</td>
<td>97</td>
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<td>4-MeC₆H₄</td>
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*All reactions were conducted in duplicate, with combined yield of regioisomers quoted. bReaction conducted at 25 °C. ccis-β-β-methylstyrene was used as the alkene substrate.
Supporting Information for full details). The alternative nitrogen nucleophile O-methyl-N-(4-cyanophenyl)sulfonyl)carbamate 60 could also be used effectively within this synthetic sequence (entry 6, 56%).

A mechanism consistent with the observed selectivities is outlined in Scheme 6. Reaction of malonoyl peroxide 6 with the alkene leads to the syn-dioxonium intermediate 8.16 Interception of 8 with the weak nitrogen nucleophile O-methyl-N-(4-cyanophenyl)sulfonyl)carbamate 60 could also be used effectively within this synthetic sequence (entry 6, 56%).

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All reactions conducted in duplicate. b58 corresponds to the regioisomer. 'Methyl ((4-cyanophenyl)sulfonyl)carbamate 60 used as nucleophile.

Scheme 6. Proposed Mechanism for the Anti- and Syn-Oxyamination

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Scheme 6. Proposed Mechanism for the Anti- and Syn-Oxyamination
**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00253.

Analytical data, experimental procedures, and NMR spectra for all compounds reported (PDF)

**Accession Codes**

CCDC 1951983–1951986 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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**Notes**

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