Enantioselective Organo-Singly Occupied Molecular Orbital Catalysis: The Carbo-oxidation of Styrenes

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A critical objective for the continued advancement of the field of asymmetric catalysis is the design and implementation of novel activation modes that allow the invention of unprecedented transformations.1 Recently, our laboratory introduced a new mode of organocatalytic activation, termed (singly occupied molecular orbital) SOMO catalysis,2 that is founded upon the transient production of a 3π-electron radical-cation3 species that can function as a generic platform of induction and reactivity. As part of these studies, we documented the first direct and enantioselective allylic alkylation,2 enolation,4 and vinylation5 of aldehydes, three protocols that were not previously known in a chiral or achiral format. Continuing this theme, we recently questioned whether feedstock olefins, such as styrenes, might be exploited in this SOMO pathway to allow the enantioselective α-homobenzylzation of aldehydes, a new C–C bond-forming reaction between functional groups that are generally inert to chemical combination. In this context, we disclose the first asymmetric SOMO-catalyzed carbo-oxidation of styrenes to provide γ-nitrate-α-alkyl aldehydes, a valuable synthon for the production of enantioenriched butyrolactones, pyrrolidines, and α-formyl homobenzylzation adducts. Most important, this new organo-SOMO reaction allows simple styrenes to function as α-alkylation partners for aldehydes, a transformation that to our knowledge is without precedent.6

**Table 1.** Organocatalytic Carbo-oxidation: Aldehyde Scope

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde</th>
<th>styrene</th>
<th>20 mol% 1-TFA CAN (2.5 eq), H2O NaH2PO4, DME, 0 °C</th>
<th>γ-oxoaldehydes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>hexyl</td>
<td></td>
<td>91</td>
<td>3:1</td>
</tr>
<tr>
<td>2</td>
<td>cyc-hexyl</td>
<td></td>
<td>68</td>
<td>3:1</td>
</tr>
<tr>
<td>3</td>
<td>(CH2)5C==CEt</td>
<td></td>
<td>90</td>
<td>3:1</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td></td>
<td>81</td>
<td>3:1</td>
</tr>
<tr>
<td>5</td>
<td>(CH2)4OBn</td>
<td></td>
<td>90</td>
<td>3:1</td>
</tr>
<tr>
<td>6</td>
<td>4-N-BOC piperidinyl</td>
<td></td>
<td>82</td>
<td>3:1</td>
</tr>
</tbody>
</table>

5π-electron system away from the bulky tert-butyl group, while the carbon-centered radical will selectively populate an (E)-configuration to avoid nonbonding interactions with the catalyst framework. Moreover, the calculated structure of DFT-2 reveals that the methyl group on the catalyst system will effectively shield the Si-face of the SOMO-activated π-system, leaving the Re-face exposed to styrene addition.

The proposed enantioselective α-formyl homobenzylzation was first examined using octanal and styrene, with imidazolidinone 1 as the SOMO catalyst and ceric ammonium nitrate (CAN)8 as the stoichiometric oxidant (Table 1, entry 1). Notably, the desired aldehyde α-alkylation was successful along with intermolecular trapping of the putative cation 4 by the nitrate anion arising from reduction of the Ce(IV) oxidant. Indeed, the resulting homosaldol-type product was formed in excellent yield and enantioselectivity, while diastereorecontrol...
The benzylic stereocenter was formed in all cases with 3:1 α,γ-anti
diastereocentro. Values of ee determined by SFC or HPLC analysis.
Stereochemistry assigned by X-ray analysis or by analogy.

For the cation trapping step was moderate (~75:25 anti:syn). As
revealed in Table 1, substantial variation in the steric contribution
of the aldehyde component is possible (entries 1, 2 and 6, R = n-hexyl,
cyclohexyl, 4-piperidinyl, 3-methyl, 96% ee). Moreover, a
variety of functionalities appear to be inert to these mild oxidative
conditions including alkynes, aryl rings, ethers, and carbamates (entries
3–6, 81–94% yield, 94–96% ee).

As highlighted in Table 2, a wide array of styrenes readily participate
as SOMOphiles in this new catalytic carbo-oxidation (entries 1–10).
For example, electron-rich and electron-deficient styrenes are readily
tolerated (entries 1–8, 88–95% yield, 92–97% ee). Notably, the
implementation of β-substituted styrenes in this coupling reaction
allows the stereospecific formation of carbo-oxidation products that
incorporate three stereogenic centers. As exemplified in Table 2,
the use of trans-β-methyl styrene allows selective formation of the
syn-anti stereochemical triad (entry 9, 6:1 dr, 94% ee), while the cis-
β-methyl styrene leads to the corresponding anti-syn isomer (entry
10, 4:1 dr, 89% ee).

The utility of this new enantioselective carbo-oxidation and the
accompanying γ-nitrate-α-alkyl aldehyde products is highlighted in
eqs 2–6. First, we have found that the crude product of our SOMO
catalysis step can be subjected to hydrogenation to selectively cleave
the benzylic nitrate ester without reduction of the aldehyde moiety or
loss in enantiopurity (eq 2). This mild two-stage protocol allows the
enantioselective α-homobenzylation of aldehydes using a variety of
styrenyl substrates (eq 2, 82–92% yield, ≥91% ee). Second, the nitrate
ester products can be utilized for the rapid construction of enantioen-
riched heterocyclic rings (eqs 3–6). For example, in situ treatment
with sodium borohydride leads directly to tetrahydrofuran products,
while a reductive amination sequence using allylamine provides rapid
access to optically active pyrrolidines. While direct oxidation of the
aldehyde moiety provides the corresponding trans-γ-lactone, the
enantioenriched cis-γ-lactone can be accessed via zinc reduction to the
corresponding lactol and subsequent oxidation. Notably, the
stereochemical purity of the carbo-oxidation adducts is retained in all
of these ring forming steps and the resulting heterocycles are readily
isolated in isomerically pure form.

Table 2. Organocatalytic Carbo-oxidation: Scope of the Styrene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product* (%)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93% yield, 96% ee</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>90% yield, 96% ee</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>92% yield, 96% ee</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>88% yield, 96% ee</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>92% yield, 96% ee</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>86% yield, 94% ee</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>83% yield, 92% ee</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>89% yield, 94% ee</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>91% yield, 94% ee</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>92% yield, 94% ee</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

* The benzylic stereocenter was formed in all cases with 3:1 α,γ-anti
diastereocentro. Values of ee determined by SFC or HPLC analysis.
Stereochemistry assigned by X-ray analysis or by analogy.

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Supporting Information Available: Experimental procedures and
spectral data. This material is available free of charge via the Internet at
http://pubs.acs.org.

References
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(6) It is important to note that a noncatalytic, non-enantioselective intermo-
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(9) (a) Auricchio, S.; Racca, A. Tetrahedron 2007, 63, 3983. (b) Baldwin, S. W.;
(11) Cailleti, G.; Maneschi, F.; Martelli, G.; Panunzio, M.; Plessi, L.
(12) We were unable to separate the nitrate ester diastereomeric adducts prior
to heterocyclic ring formation.
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