

## Enantioselective Organocatalytic Singly Occupied Molecular Orbital Activation: The Enantioselective $\alpha$ -Enolation of Aldehydes

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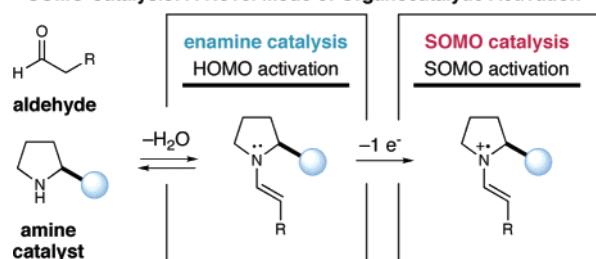
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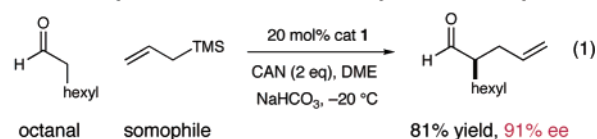
Over the last 40 years, thousands of asymmetric catalytic reactions have been invented in accord with the increasing need for enantiopure medicinal agents and the rapid advancement of the field of chemical synthesis.<sup>1</sup> Remarkably, however, the vast majority of these enantioselective processes are derived from a small number of long-established activation modes (e.g., Lewis acid catalysis,<sup>2</sup>  $\sigma$ -bond insertion,<sup>3</sup>  $\pi$ -bond insertion,<sup>4</sup> atom-transfer catalysis,<sup>5</sup> and hydrogen-bonding catalysis<sup>6</sup>). A critical objective, therefore, for the continued advancement of the field of asymmetric catalysis is the design and implementation of novel activation modes that enable the invention of unprecedented transformations. Recently, our laboratory introduced a new mode of organocatalytic activation, termed singly occupied molecular orbital (SOMO) catalysis,<sup>7–9</sup> that is founded upon the mechanistic hypothesis that one-electron oxidation of a transient enamine intermediate (derived from aldehydes and chiral amine catalysts) will render a  $3\pi$ -electron SOMO-activated species that can readily participate in a range of unique asymmetric bond constructions.<sup>10</sup> In our original SOMO studies,<sup>7</sup> we documented the first direct and enantioselective allylic alkylation of aldehydes (eq 1). In this Communication, we further advance this activation concept to describe the first asymmetric aldehyde  $\alpha$ -enolation, a protocol that allows direct access to enantioenriched  $\gamma$ -ketoaldehydes from simple aldehydes, enolsilanes and a commercial catalyst (eq 2).

form a SOMO-activated cation (DFT-2) that projects the  $3\pi$ -electron system away from the bulky *tert*-butyl group, while the carbon-centered radical will selectively populate an (*E*)-configuration to minimize nonbonding interactions with the imidazolidinone ring. In terms of enantiofacial discrimination, the calculated structure of DFT-2 reveals that the benzyl group on the catalyst system will effectively shield the *Re*-face of the radical cation, leaving the *Si*-face exposed to enolsilane addition.

### SOMO Catalysis: A Novel Mode of Organocatalytic Activation

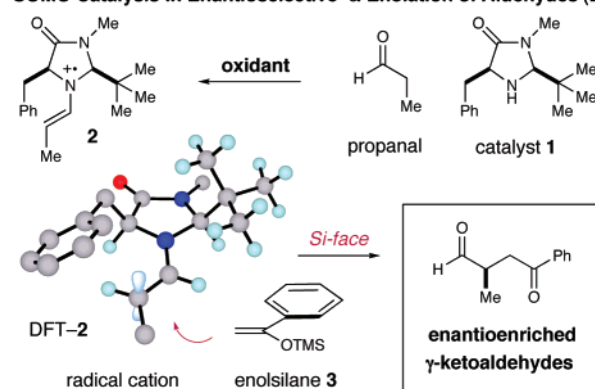


### SOMO Catalysis I: Enantioselective $\alpha$ -Allylation of Aldehydes<sup>7</sup>



**Design Plan.** We proposed that condensation of imidazolidinone catalyst **1** with a simple aldehyde (e.g., propanal) in the presence of a suitable oxidant should provide the putative radical cation **2**. Addition of an accompanying enolsilane to the  $\alpha$ -position of **2** would then render an  $\alpha$ -OTMS carbon-centered radical that should rapidly participate in a second oxidation event<sup>11</sup> to generate an oxocarbenium ion that, upon hydrolysis of the silyl group, will furnish the requisite  $\alpha$ -substituted- $\gamma$ -ketoaldehyde. On the basis of DFT calculations<sup>12</sup> we proposed that catalyst **1** should selectively

### SOMO Catalysis II: Enantioselective $\alpha$ -Enolation of Aldehydes (2)



Our enantioselective organocatalytic SOMO enolation was first evaluated using enolsilane **3**, imidazolidinone catalyst **1**, and a series of  $\alpha$ -substituted aldehydes (Table 1, eq 3). Initial investigations revealed that the introduction of 2 equiv of the oxidant ceric

**Table 1.** Organocatalytic Enolation: Scope of the Aldehyde Substrate

entry	product	% ee, <sup>a</sup> yield,	entry	product	% ee, <sup>a</sup> yield,
1		90% ee 85% yield	4		91% ee 77% yield
2		92% ee 92% yield	5		90% ee 71% yield
3		93% ee 74% yield	6		95% ee 84% yield

<sup>a</sup> Enantiomeric excess determined by chiral SFC analysis.

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**Table 2.** Organocatalytic Enolation: Scope of the Enolsilane Substrate

entry	enolsilane	product	% yield	% ee <sup>a,b</sup>
1 <sup>c</sup>			85	90
2 <sup>d</sup>			77	92
3 <sup>d</sup>			70	93
4			61	90
5			71	92
6			74	96
7			67	86
8			55	92

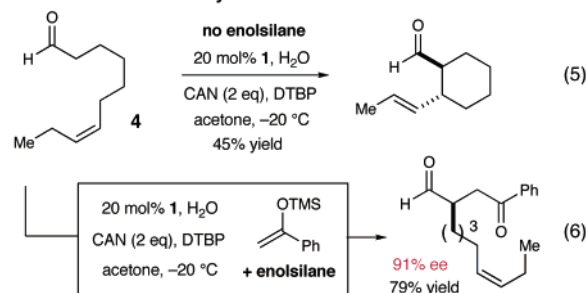
<sup>a</sup> Enantioselectivity determined by GLC or SFC analysis. <sup>b</sup> Stereochemistry assigned by chemical correlation or by analogy. <sup>c</sup> Performed in acetone. <sup>d</sup> Performed at  $-50\text{ }^{\circ}\text{C}$ .

ammonium nitrate (CAN), 2 equiv of  $\text{H}_2\text{O}$  and 2 equiv of 2,6-di-*tert*-butyl pyridine (DTBP) is necessary to achieve high levels of enantioselectivity and reaction efficiency.<sup>13</sup> As revealed in Table 1, variation in the steric contribution of the radical cation substituent ( $\text{R} = \text{hexyl}$ , *cyc*-hexyl, 4-piperdyl entries 1, 3, and 6) is possible without substantial loss in yield or enantiocontrol (74–85% yield, 90–95% ee). Moreover, a variety of chemical functionalities appear to be inert to these mild oxidative conditions including olefins, aryl rings, and carbamates (entries 2, 4, and 6, 77–92% yield, 91–95% ee).

As highlighted in Table 2, a wide array of  $\pi$ -rich enolsilanes will readily participate as somophiles in this new catalytic enolation protocol (entries 1–8). For example, alkyl, vinyl, and aryl substituted silyl enolethers can be tolerated without loss in reaction efficiency or enantiocontrol (entries 1–8, 55–85% yield, 86–96% ee). Moreover, significant latitude in the steric demand of the somophilic substituent can be accommodated (entry 7,  $\text{R} = \text{Me}$ , 67% yield, 86% ee; entry 8,  $\text{R} = t\text{-Bu}$ , 55% yield, 92% ee). Interestingly, the incorporation of bulky silyl groups to prevent substrate hydrolysis (in the case of alkyl substituted enolsilanes) provides slightly higher enantioselectivities.<sup>14</sup> Perhaps most striking, electron rich heteroaromatic systems that are often susceptible to mild oxidants are compatible with these organocatalytic conditions (entries 2–3, 70–77% yield,  $\geq 92\%$  ee). It is important to note that the sense of

asymmetric induction observed in all cases (Tables 1 and 2) is consistent with addition of the enolsilane to the *Si*-face of the radical cation **2**, in complete accord with the calculated structure DFT-2.

#### Intramolecular Radical Cyclization versus Intermolecular Enolation



Last, we have observed that the capacity of the putative radical cation species to undergo intermolecular enolation is dramatically superior to that of intramolecular cyclohexyl ring formation with  $\pi$ -neutral olefins (cf. eqs 5 and 6). This finding again demonstrates the remarkable ability of electron deficient radical cations to participate in highly chemoselective transformations, a mechanistic feature not traditionally associated with radical activation.

In summary, the first enantioselective organocatalytic  $\alpha$ -enolation of aldehydes has been accomplished using SOMO catalysis. Further applications of this new organocatalytic activation mode will be reported shortly.

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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>.

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- (12) DFT calculations performed using B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d).
- (13) The use of alternative bases ( $\text{NaHCO}_3$ ,  $\text{Na}_2\text{CO}_3$ , pyridine) or lower equivalents of oxidant or  $\text{H}_2\text{O}$  resulted in useful levels of enantioselectivity ( $\geq 90\%$  ee) but diminished yields (25–68% yield). Products arising from enamine-aldehyde aldol were not observed in this study.
- (14) The use of TMS enolethers in Table 2, entries 7 and 8, provides the corresponding products in 39% yield, 73% ee and  $\leq 10\%$  yield, 0% ee. JA0719428