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Enantioselective Aldehyde α-Nitroalkylation via Oxidative Organocatalysis

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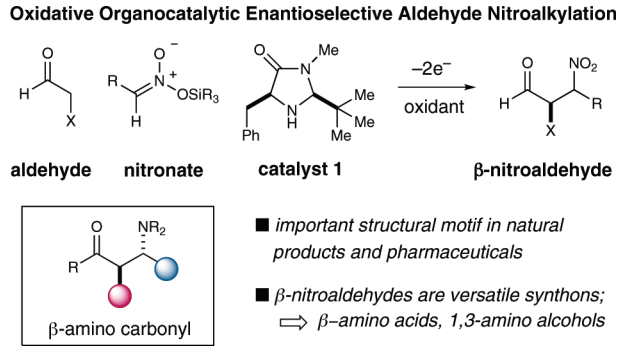
Over the last 70 years, β-aminocarbonyl-containing compounds have had a profound impact on the fields of chemistry (natural products such as Taxol), biology (β-peptides), and medicine (β-lactam antibiotics). As a result, significant synthetic efforts have been directed toward the invention of new chemical technologies that allow rapid and generic access to β-aminocarbonyl moieties.[1] To date, enantioselective catalytic routes to this synthon have been accomplished via a variety of strategies, including Mannich couplings,[2] enamine hydrogenation,[3] conjugate additions,[4] and Staudinger reactions.[5] Recently, our laboratory implemented a new mode of organocatalytic activation termed singly occupied molecular orbital (SOMO) catalysis, wherein a transiently generated three-π-electron radical cation species can undergo enantioselective bond formation with a variety of π-SOMOphiles to furnish a range of α-functionalized aldehyde adducts.[6] Recently, we became interested in the possibility of using silyl nitronates as suitable SOMOphiles within this manifold,[7] a pathway that would provide enantioselective access to β-nitroaldehydes. Herein, we describe the successful execution of these ideas to provide a fundamentally new approach to β-aminocarbonyl synthesis using oxidative organocatalysis.[8] This versatile new strategy allows enantioselective access to either syn or anti diastereomers of β-amino acids or 1,3-aminoalcohols.



From the outset, we anticipated that the proposed aldehyde nitroalkylation might follow one of two possible oxidation-addition pathways. In accord with our previous SOMO catalysis studies, we hypothesized that a transiently generated enamine intermediate **2** might undergo oxidation to form a radical cation **3** that is suitably disposed to intercept a silyl nitronate species (Scheme 1, SOMO pathway). Conversely, in view of the low oxidation potentials of silyl nitronates, we were aware that an alternative but equally productive pathway might involve nitronate oxidation to forge a nitronate radical cation that could rapidly trap the enamine species **2** (Scheme 1, SOMOphile pathway).[9] At this stage, a second oxidation event in each pathway (with either the resulting N-centered radical or the α-amino radical) would render a common iminium intermediate that upon hydrolysis and subsequent Si−O bond cleavage would lead to the desired β-nitroaldehyde adduct. As a central design criterion, we reasoned that both of these mechanistic scenarios should be highly enantioselective, given the structural similarities of the enamine, DFT-**2**, and the enamine radical cation, DFT-**3** (Figure 1).[10] More specifically, catalyst **1** should selectively form an enamine intermediate **2** (DFT-**2**) or a radical cation **3** (DFT-**3**) that projects the bond-forming site away from the bulky *tert*-butyl group, while the benzyl group effectively shields the *Re* face of the two-carbon π-system, leaving the *Si* face exposed.

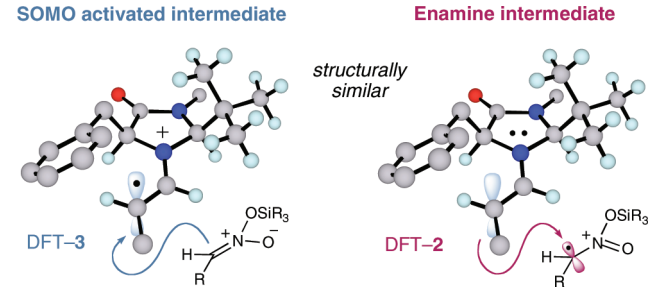
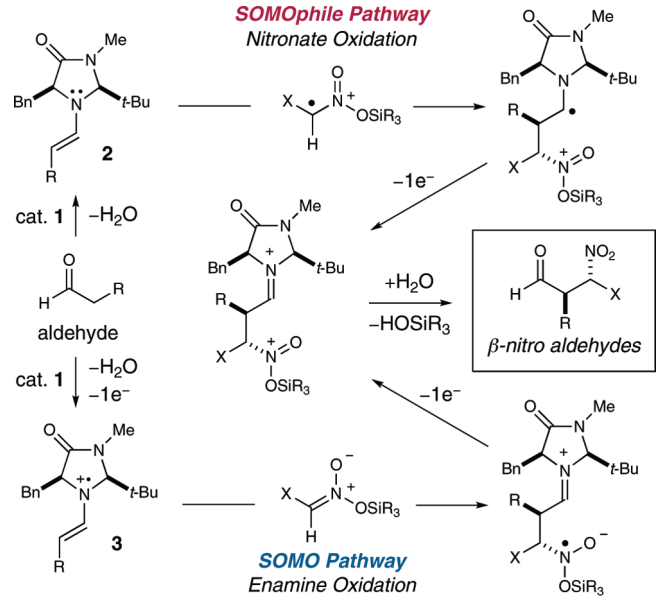


Figure 1. Structural similarity of the SOMO and enamine intermediates.

Scheme 1. Possible Mechanistic Scenarios for Nitroalkylation



The proposed nitroalkylation was first examined using hexanal, imidazolidinone catalyst **1**, ceric ammonium nitrate (CAN) as the stoichiometric oxidant, and a series of silyl nitronates derived from nitropropane. As revealed in Table 1, high levels of enantioselectivity and reaction efficiency could be accomplished using a variety of coupling partners in the presence of a mildly basic additive such as NaO_2CCF_3 or $NaHCO_3$. Most striking, however, was the apparent relationship between reaction diastereocontrol and the inherent lability of the silyl nitronate system employed. For example, relatively labile silyl species such as TBS, TMS, and TES preferentially provide the syn diastereomer (Table 1, entries 1−3) while TBDPS and TIPS nitronates enjoy anti diastereocontrol (Table 1, entries 4 and 5).[11] Moreover, useful levels of anti-selective couplings could be repro-

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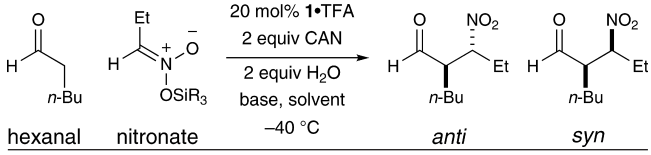
Table 1. Effect of Reaction Conditions on Diastereoselectivity



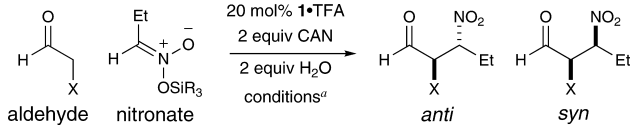
entry	SiR_3	base	solvent	yield (%)[a]	ee (%)[b]	anti/syn[b]
1	TBS	NaO_2CCF_3	acetone	68	94	1:6
2	TMS	NaO_2CCF_3	acetone	70	94	1:7
3	TES	NaO_2CCF_3	acetone	71	94	1:7
4	TBDPS	NaO_2CCF_3	acetone	77	91	3:1
5	TIPS	NaO_2CCF_3	acetone	81	86	3:1
6	TIPS	NaO_2CCF_3	THF	82	89	4:1
7	TIPS	$NaHCO_3$	THF	84	90	5:1

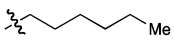
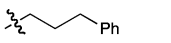
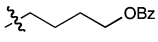
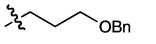
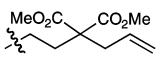
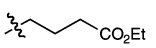
[a] Determined by GC analysis relative to an internal standard. [b] The ee of the major isomer and the diastereoselectivity were determined by GC analysis, and the absolute and relative stereochemistries were assigned by analogy.

ducibly accomplished via the use of THF as the reaction medium and $NaHCO_3$ as the base (Table 1, entry 7).[12]

Having developed optimal reaction conditions for both syn and anti nitroalkylation couplings, we next turned our attention to the substrate scope. As revealed in Table 2, a diverse range of aldehydes (long-chain alkyl, β-branched, and functionalized) react to furnish the desired enantioenriched β-nitroaldehyde products. Importantly, the nature of the aldehyde substituent has little impact on the observed silyl-dependent diastereocontrol, as TBS nitronates with NaO_2CCF_3 routinely provide the syn α,β-alkylation products (Table 2, even-numbered entries) while use of the corresponding TIPS nitronates (with $NaHCO_3$ and THF) leads selectively to the anti α,β-nitroaldehyde products (Table 2, odd-numbered entries).

Table 2. Asymmetric Aldehyde Nitroalkylation: Aldehyde Scope

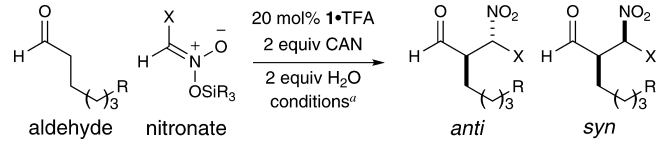


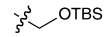
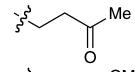
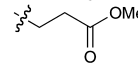
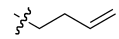
entry	X (aldehyde)	SiR_3	yield (%)[b]	ee (%)[c]	*anti:syn*[c]
1		TIPS	84	91	5:1
2		TBS	78	94	1:7
3		TIPS	65	97	3:1
4		TBS	55	96	1:4
5		TIPS	86	86	4:1
6		TBS	76	94	1:5
7		TIPS	78	90	4:1
8		TBS	74	94	1:6
9		TIPS	77	87	4:1
10		TBS	80	95	1:6
11		TIPS	71	95	9:1
12		TBS	67	94	1:5
13		TBS	82	94	1:6

[a] For TIPS nitronates: $NaHCO_3$ (2 equiv), THF (0.13 M), −40 °C, 24−48 h. For TBS nitronates: NaO_2CCF_3 (3 equiv), acetone (0.13 M), −40 or −50 °C, 4−16 h. [b] Isolated yield. [c] The ee of the major isomer and the diastereoselectivity were determined by chiral GC, HPLC, or SFC analysis, and the absolute and relative stereochemistries were assigned by analogy.

Significant latitude in the nitronate coupling partner can also be accommodated in this alkylation reaction. As shown in Table 3, alkyl, sterically hindered, and functionalized nitroalkane derivatives are suitable substrates for both the syn- and anti-selective bond formations. Moreover, nitromethane-derived nitronates can also be employed (using the triisopropylsilyl derivative) to provide β-nitroaldehyde adducts with high levels of enantiocontrol (Table 3, entry 12).

Table 3. Asymmetric Aldehyde Nitroalkylation: Nitronate Scope

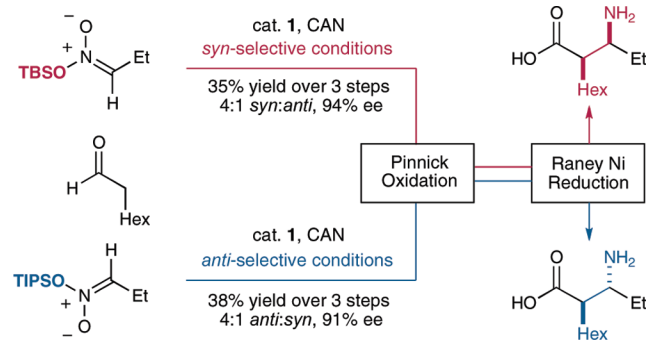


entry	R	X (nitronate)	SiR_3	yield (%)[b]	ee (%)[c]	*anti:syn*[c]
1	OBz		TIPS	73	87	6:1
2	OBn		TBS	74	94	1:4
3	OBz		TIPS	53	90	1:1
4	OBn		TBS	86	90	1:8
5	OBn		TBS	65	92	1:3
6	OBz		TIPS	65	91	6:1
7	OBz		TIPS	79	91	6:1
8	OBz		TBS	68	91	1:6
9	OBz		TIPS	73	80	2:1
10	OBn		TBS	91	91	1:5
11	Et		TIPS	95[d]	84	–

[a] See footnote [a] of Table 2. [b] Isolated yield. [c] The ee of the major isomer was determined by chiral GC, HPLC, or SFC analysis; the absolute and relative stereochemistries were assigned by analogy. [d] Determined by GC analysis.

To highlight its chemical utility, we applied this new catalytic alkylation reaction to the enantioselective construction of β-amino acids. As revealed in Scheme 2, implementation of our organoSOMO coupling followed by Pinnick oxidation and then Raney nickel reduction allows the three-step conversion of octanal to 2-(1-aminopropyl)octanoic acid. Notably, this sequence allows selective access to all of the possible β-amino acid stereoisomers via the judicious choice of catalyst and silyl nitronate partner.

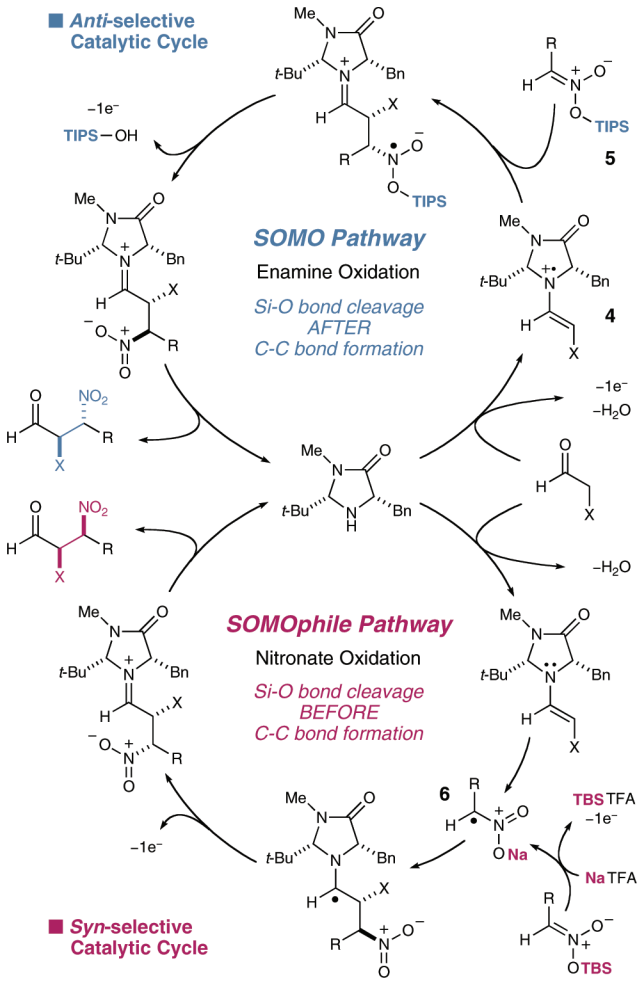
Scheme 2. Three-Step Diastereoselective β-Amino Acid Synthesis



In an effort to rationalize the remarkable turnover in diastereoselectivity as a function of the nitronate silyl group (Tables 1−3), we propose the participation of two distinct reaction pathways (along with two modes of catalytic activation) that separately lead to the observed syn and anti selectivities. Specifically, we believe that for anti-selective couplings, the primary pathway involves enamine oxidation (in accord with our previous organoSOMO catalysis studies) and coupling of the resulting radical cation **4** with the TIPS nitronate substrate **5** (Scheme

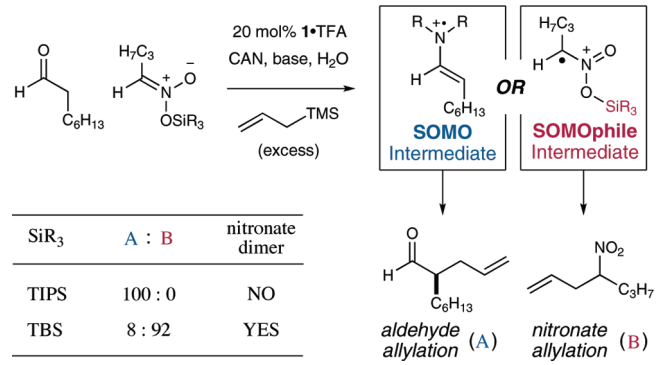
3, SOMO pathway). In contrast, for syn-selective reactions, we believe that the TBS nitronate is desilylated to form a sodium nitronate, which undergoes rapid oxidation to generate a nitronate radical cation **6**. In this case, we presume that the catalyst-derived enamine functions as a SOMOphile to intercept this highly electrophilic radical (Scheme 3, SOMOphile pathway). Experimental evidence for the participation of both anti-selective SOMO and syn-selective SOMOphile pathways was accumulated. First, we discovered that NaO_2CCF_3 desilylates a TBS nitronate at −40 °C, while the corresponding TIPS nitronate is inert under these conditions.[13] Second, we observed substantial amounts of nitronate dimerization in syn couplings but only trace amounts in the anti variant. It should be noted that a nitronate dimerization pathway necessitates the formation of a nitronate-derived radical cation prior to homocoupling. Third, for the anti couplings, the nature of the silyl group affects the enantioselectivity of the reaction (Table 1, entry 4 vs entry 5), while for syn-selective reactions, the enantioinduction remains constant across a range of silyl nitronates. This suggests that the silyl group is likely not involved during the syn diastereomer bond-forming event (Table 1, entries 1−3).

Scheme 3. Proposed Divergence of Mechanistic Pathways



Further support for our mechanistic proposal was gained from a series of experiments employing an internal SOMOphilic probe (Scheme 4). More specifically, incorporation of excess allyl trimethylsilane[14] during the anti-selective protocol resulted only in the formation of aldehyde allylation and aldehyde nitroalkylation products. However, when allyl trimethylsilane was included in a syn-selective experiment, nitronate allylation was predominat while *aldehyde allylation was minimal*. These results lend strong support to a mechanistic divergence wherein nitronate oxidation is operative for syn couplings and enamine oxidation is central to the anti-selective mechanism.[15]

Scheme 4. Distinguishing the Divergent Mechanistic Pathways



SiR_3	A : B	nitronate dimer
TIPS	100 : 0	NO
TBS	8 : 92	YES

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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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(7) For nonenantioselective couplings of nitronates with π nucleophiles, see: (a) Arai, N.; Narasaka, K. *Chem. Lett.* **1995**, *24*, 987. (b) Arai, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2525.
(8) Notably, silyl nitronates can be employed in enantioselective Henry reactions with aldehydes under nonoxidative conditions. See: (a) Risgaard, T.; Gothelf, K. V.; Jørgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 153. (b) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054. (c) For a review, see: Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561.
(9) (a) We measured the oxidation potentials of the standard silyl nitronates used in our studies and found them to be slightly lower than the values reported for enamines (see ref 9b): for *tert*-butyldimethylsilyl propylideneazinate, $E^\circ = 0.45$ V vs SCE; for triisopropylsilyl propylideneazinate, $E^\circ = 0.47$ V vs SCE. However, because these potentials are thermodynamic in nature and there is a strong overpotential when CAN is employed, it is impossible to predict a priori whether the enamine or the silyl nitronate will be kinetically more prone to oxidation by CAN using these values. (b) Schoeller, W. W.; Niemann, J.; Rademacher, P. *J. Chem. Soc., Perkin Trans. 2* **1988**, 369.
(10) Performed at the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) level (see ref 6a).
(11) Relative stabilities of silyl ethers toward base hydrolysis: TMS (1) < TES (10−100) < TBDMS ≈ TBDPS (20 000) < TIPS (100 000). These values were taken from: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.
(12) We observed that the use of THF as the solvent or $NaHCO_3$ as the base generally increases the amount of anti β-nitroaldehyde, whereas the use of acetone as the solvent and/or NaO_2CCF_3 as the base generally increases the amount of syn β-nitroaldehyde produced.
(13) 12% of the TBS nitronate was converted to 1-nitropropane via desilylation by NaO_2CCF_3 (1 equiv) at−40 °C in acetone-d_6 after 3 h, while TIPS nitronate remained unchanged under identical conditions.
(14) Allyl trimethylsilane readily functions as a SOMOphile to react with radical cations (see ref 6a), but it does not itself undergo oxidation to form a radical cation under these conditions.
(15) See the Supporting Information for further details.

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