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Enantioselective Aldehyde α -Nitroalkylation via Oxidative Organocatalysis

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Abstract

Oxidative Organocatalytic Enantioselective Aldehyde Nitroalkylation

- **SOMO Catalysis or Enamine Catalysis**
- **Mechanism Controlled by Silyl Group**

The first enantioselective organocatalytic α -nitroalkylation of aldehydes has been accomplished. The aforementioned process involves the oxidative coupling of an enamine intermediate, generated transiently via condensation of an amine catalyst with an aldehyde, with a silyl nitronate to produce a β -nitroaldehyde. Two methods, one which furnishes the *syn*-isomer and a second which provides access to the *anti*- β -nitroaldehyde, have been developed. Data is presented to support a hypothesis to explain this phenomenon that centers upon a silyl group controlled change in mechanism. Finally, a three-step procedure for the synthesis of both *syn*- and *anti*- α,β -disubstituted- β -amino acids is presented.

Over the last 70 years, β -amino carbonyl 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 towards the invention of new chemical technologies that allow rapid and generic access to β -amino carbonyl 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 SOMO catalysis (singly occupied molecular orbital), wherein a transiently generated 3π -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 a suitable SOMophile within this manifold,⁷ a pathway that would provide enantioselective access to β -nitroaldehydes. Herein, we describe the successful execution of these ideals to provide a fundamentally new approach to β -amino carbonyl 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-amino alcohols.

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Supporting Information Available. Experimental procedures, and spectral data are provided (xx pages) (PDF).

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Design Plan 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, given 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 both pathways (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 criteria, we reasoned that both of these mechanistic scenarios should be highly enantioselective given the structural similarities of the enamine, DFT-**2**, and 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.

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 mildly basic additives such as NaO₂CCF₃ or NaHCO₃. 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, provide the *syn* diastereomer preferentially (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 reproducibly accomplished via the use of THF as the reaction medium and NaHCO₃ as base (Table 1, entry 7).¹²

Having developed optimal reaction conditions for both *syn* and *anti* nitroalkylation couplings, we next turned our attention to 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 NaO₂CCF₃ routinely provide the α,β -*syn*-alkylation products (Table 2, even number entries), while the use of the corresponding TIPS-nitronate (with NaHCO₃ and THF) leads selectively to the α,β -nitroaldehyde system (Table 2, odd number entries).

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 nitro alkane 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).

To highlight its chemical utility, we have applied this new catalytic alkylation reaction to the enantioselective construction of β -amino acids. As revealed in Scheme 2, implementation of our organoSOMO coupling prior to Pinnick oxidation and then Raney nickel reduction allows the 3-step conversion of propanal to α -methyl β -amino hexanoic 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.

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 that undergoes rapid oxidation to generate a nitronate radical cation **6**. In this case, we presume that the catalyst derived enamine now functions as a SOMOphile to intercept this highly electrophilic radical (Scheme 3, SOMOphile pathway). Experimental evidence for the participation of both an *anti*-selective SOMO and a *syn*-selective SOMOphile pathway has been accumulated. First, we have discovered that NaO_2CCF_3 desilylates the TBS-nitronate at -40°C , while the TIPS-nitronate is inert to these conditions.¹³ Second, we have 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 homo-coupling. 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 not likely involved during the *syn* diastereomer bond-forming event (Table 1, entries 1–3).

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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10. Performed using B3LYP/6-311+G(2d,p)// B3LYP/6-31G (d). See ref 6a.
11. Relative stabilities of silyl ethers towards base hydrolysis: TMS (1) < TES (10–100) < TBDMS~TBDPS (20,000) < TIPS (100,000). These values have been taken from: Greene TW, Wuts PGM. *Protective Groups in Organic Synthesis* (3rd Ed.). 1999 New York John Wiley & Sons
12. We have observed that the use of THF as solvent or NaHCO_3 as base generally increases the amount of *anti*- β -nitroaldehyde whereas the use of acetone as solvent and/or NaO_2CCF_3 as base generally increases the amount of *syn*- β -nitroaldehyde produced.
13. 12% of the TBS-nitronate 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 remains unchanged under identical conditions.
14. TMS-allylsilane will readily function as a SOMOphile to react with radical cations (see ref 5a) however it will not undergo oxidation itself to form a radical cation under these conditions.
15. See the Supporting Information for further details.

SOMO activated intermediate **Enamine intermediate***structurally similar*

Figure 1.
Structural Similarity of SOMO and Enamine Intermediate.

Scheme 1.
Possible Mechanistic Scenarios for Nitroalkylation.

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

Scheme 3.
Proposed Divergence of Mechanistic Pathways.

Scheme 4.
Distinguishing Divergent Mechanistic Pathways.

Table 1

Effect of Reaction Conditions on Diastereoselectivity.

entry	SiR ₃	base	solvent	yield (%) ^a	ee (%) ^b	anti:syn ^b
1	TBS	NaO ₂ CCF ₃	acetone	68	94	1:6
2	TMS	NaO ₂ CCF ₃	acetone	70	94	1:7
3	TES	NaO ₂ CCF ₃	acetone	71	94	1:7
4	TBDPS	NaO ₂ CCF ₃	acetone	77	91	3:1
5	TIPS	NaO ₂ CCF ₃	acetone	81	86	3:1
6	TIPS	NaO ₂ CCF ₃	THF	82	89	4:1
7	TIPS	NaHCO ₃	THF	84	90	5:1

^aThe yield was determined by GC analysis relative to an internal standard.

^bThe ee of major isomer and diastereoselectivity were determined by GC analysis and the absolute and relative stereochemistry were assigned by analogy.

Table 2

Asymmetric Aldehyde Nitroalkylation: Aldehyde Scope.

entry	X (aldehyde)	SiR ₃	yield (%) ^b	ee (%) ^c	anti:syn
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: NaHCO₃ (2 equiv), THF (0.13 M) at -40 °C, 24–48 h. For TBS-nitronates: NaO₂CCF₃ (3 equiv), acetone (0.13 M) at -40 or -50 °C, 4–16 h.

^b Isolated yield.

^c Ee of major isomer and diastereoselectivity were determined by chiral GC, HPLC, or SFC analysis and the absolute and relative stereochemistry were assigned by analogy.

Table 3

Asymmetric Aldehyde Nitroalkylation: Nitronate Scope.

entry	R	X (nitronate)	SiR ₃	yield (%) ^b	ee (%) ^c <i>anti:syn</i> ^d
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 –

^aSee Table 2 footnote *a*.^bIsolated yield.^cEe of major isomer determined by chiral GC, HPLC, or SFC analysis; absolute and relative stereochemistry were assigned by analogy.^dYield was determined by GC analysis.