Unanticipated Silyl Transfer in Enantioselective α,β -Unsaturated Acyl Ammonium Catalysis using Silyl Nitronates

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Supporting Information Placeholder

ABSTRACT: The use of silyl nitronates is reported for the isothioureacatalyzed synthesis of γ -nitro-substituted silyl esters containing up to two contiguous stereocenters in good yield and with excellent enantioselectivity (up to 93% yield, 99:1 er). The serendipitously-discovered formation of silyl ester products in this reaction demonstrates a novel platform for catalyst turnover in α,β -unsaturated acyl ammonium catalysis.

Within the field of Lewis base organocatalysis, the generation and exploitation of α,β -unsaturated acyl ammonium intermediates has been showcased recently in a range of enantioselective catalytic processes.^[1–3] These synthetically versatile intermediates provide new avenues to access stereodefined products through electrophilic reactivity at the C(1) and C(3) positions, as well as latent nucleophilicity at C(2) (Scheme 1). Traditionally, such processes require a reaction partner that contains two nucleophilic sites to perform firstly C(3) conjugate addition and secondly intramolecular turnover of the Lewis base catalyst through addition at C(1) (Scheme 1a).^[1–3] To overcome this limitation, we recently reported the use of α,β -unsaturated aryl esters as α,β -unsaturated acyl ammonium precursors, where catalyst turnover was promoted by the aryloxide counterion released *in situ* during the reaction (Scheme 1b).^[4] While demonstrating successful proof-of-concept, this work was limited by the relatively long reaction times (16 h) and the requirement of using a nitroalkane as both the pronucleophile and the solvent.^[5] In this manuscript, a new protocol in α,β -unsaturated acyl ammonium catalysis is demonstrated. Using silyl nitronates as reactants,^[6] γ -nitro-substituted silyl ester products containing up to two contiguous stereocenters are obtained in good yield and with excellent enantioselectivity (12 examples, up to 95% yield, 99:1 er) (Scheme 1c). The silyl nitronate is therefore not only required for the initial conjugate addition, but also serves an essential role in enabling catalyst turnover. Significantly, the cata-

lytic reactions take ≤ 1 h and require only 1.5–2 equivalents of the silyl nitronate, allowing the application of structurally-diverse nitroalkane substrates in this methodology.

Scheme 1. Catalyst turnover strategies in α,β -unsaturated acyl ammonium catalysis

a) Established reactivity using α,β -unsaturated acyl ammoniums

* 'dinucleophile' required for conjugate addition and catalyst turnover

b) Previous work

✓ aryloxide facilitates catalyst turnover ✓ high enantioselectivity
 ✗ requires pronucleophile as solvent ✗ long reaction times
 ✗ low diastereoselectivity

c) This work

✓ silyl nitronate performs conjugate addition and facilitates catalyst turnover ✓ stoichiometric quantities ✓ high enantioselectivity

Initial studies investigated the application of silyl nitronates in an isothioureacatalyzed Michael addition to α,β -unsaturated aryl ester **1** (Scheme 2a). Using silyl nitronate **2** (1 equiv), HyperBTM **3** as catalyst (20 mol %), and *i*-Pr₂NEt as base (1 equiv) in MeCN gave Michael addition

product **4** in 45% yield and 95:5 er after 5 h at room temperature. Interestingly, a second Michael addition product was also observed (~5%), which was identified as silyl ester **5**. Intrigued by the origin of this unanticipated product, further optimization studies focused on maximizing the yield of silyl ester **5**.^[7] Variation of the α,β -unsaturated acyl ammonium precursor demonstrated that the use of α,β -unsaturated anhydride **6** provided silyl ester **5** in 41% yield and an excellent 99:1 er (Scheme 2b). Significantly, the reaction was complete within just 30 minutes. In addition to silyl ester **5**, an approximately equal quantity of carboxylic acid **7** was identified in the crude reaction product mixture,^[8] indicating that ~80% of the silyl nitronate had been transformed in the desired Michael addition process. Increasing the equivalents of silyl nitronate **2** (to 1.5 equiv) and using anhydrous MeCN^[9] minimized the amount of carboxylic acid **7**, allowing isolation of silyl ester **5** in 92% yield and 99:1 er (Scheme 2c). This methodology therefore represents a significant advance over our previous work using α,β -unsaturated aryl ester **1** and 2-nitropropane as solvent, in which only 46% of Michael addition product **4** was obtained after 16 h.^[4]

Scheme 2. Reaction optimization

Isolated yields given; er determined by CSP-HPLC analysis; TIPS = triisopropylsilyl; ^a er determined following conversion to the corresponding morpholinyl amide;^[4] ^b yield determined by ¹H NMR spectroscopy of the crude product mixture using an internal standard; ^c ND = not determined.

Using 1.5 equiv of silyl nitronate, 1 equiv of *i*-Pr₂NEt and 20 mol % of HyperBTM **3** in anhydrous MeCN at room temperature for 30 minutes as standard, the scope and limitations of the method were investigated (Schemes 3 and 4). Variation of the β -substituent of the anhydride showed that methyl ester and morpholinyl amide substituents were tolerated, giving products **8** and **9** in excellent yield and with high enantioselectivity (Scheme 3). The absolute configuration of **9** was confirmed by single crystal X-ray analysis. The use of cinnamic anhydride did not provide the expected Michael addition product, but in-

stead gave the isolable nitroso cinnamate ester derivative **10** in 55% yield.^[10] Based on literature precedent, this side-product **10** is proposed to form through *O*-acylation of the silyl nitronate followed by a formal [2,3]-sigmatropic rearrangement (Scheme 3, grey box).^[11] This result indicates that conjugate addition was disfavored in this case, and is consistent with previous examples of α,β -unsaturated acyl ammonium catalysis where the presence of a β -electron-withdrawing group is often beneficial for activity.

Scheme 3. Reaction scope: Variation of α,β -unsaturated anhydride

Isolated yields given; er determined by CSP-HPLC analysis; TIPS = triisopropylsilyl; majority of hydrogen atoms omitted for clarity from representation of X-ray crystal structure of **9**.

The potential to apply this method to access more structurally-complex products was next probed through the use of a diverse set of silyl nitronate reactants (Scheme 4). The use of a cyclic silyl nitronate provided cyclohexyl-substituted derivative **11** in 60% yield and with excellent enantioselectivity (98:2 er), again in just 30 minutes. Notably, in our previous methodology,^[4] the use of nitrocyclohexane as the solvent provided no Michael addition product, emphasizing the vastly improved reactivity obtained by using silyl nitronates. The application of unsymmetrically-substituted silyl nitronates, leading to products containing two contiguous stereocenters, was investigated next. The use of a dialkyl-substituted nitronate allowed a single diastereoisomer of **12** to be isolated in 26% yield with >99:1 er. The relative and absolute configuration of **12** was confirmed by single crystal X-ray analysis following conversion to the benzylamide derivative **13**. Signals corresponding to the other diastereoisomer could not be identified in the ¹H NMR spectra of the crude reaction mixture; however ~ 50% of a nitroso fumarate ester product (analogous to **10**) was also isolated,^[7] contributing to the low yield of **12**. The nitroso ester product was presumably also formed following *O*-acylation of the silyl nitronate, and may be a consequence of the increased steric demands of this nitronate retarding the rate of the desired Michael addition. Next, a selec-

tion of (hetero)aryl-alkyl-substituted nitronates was investigated. Michael addition products **14**, **16** and **17** were obtained in moderate to good yield and with high enantioselectivity (94:6 to 96:4 er). The diastereoselectivity in each case was ~70:30; however the diastereoisomers were readily separable by column chromatography. The relative and absolute configuration of the major diastereoisomer within this series was confirmed by single crystal X-ray analysis following conversion of silyl ester **14** to the morpholinyl amide derivative **15**. The protocol was further extended to monoaryl-substituted nitronates,^[12,13] with additional optimization showing that 2 equivalents of silyl nitronate and the absence of base was optimal for these substrates.^[7] Variation of the aryl group within this series provided Michael addition products **18–21** in good yield, ~75:25 dr and consistently excellent er (up to >99:1). The relative and absolute configuration of the major diastereoisomer within this series was confirmed by single crystal X-ray analysis following conversion of silyl ester **21** to the morpholinyl amide derivative **22**.

Scheme 4. Reaction scope: Variation of silyl nitronate

Isolated yields given; dr determined by ¹H NMR spectroscopy of the crude product mixture; er determined by CSP-HPLC analysis; TIPS = triisopropylsilyl; majority of hydrogen atoms omitted for clarity from representations of X-ray crystal structures of **13**, **15** and **22**. ^a Product isolated as a single diastereoisomer; ^b ND = not determined; ^c reaction performed at 0 °C; ^d each diastereoisomer isolated separately, yield given is the sum of both diastereoisomers; ^e 2 equiv silyl nitronate and no *i*-Pr₂NEt used; ^f isolated yield is of a mixture of diastereoisomers.

Epimerization studies were performed to provide insight into the origin of diastereoselectivity for each series of silyl nitronate (Scheme 5). Applying a single diastereoisomer of **14** under the standard reaction conditions resulted in no change in diastereo- or enantiopurity (Scheme 5a), indicating that the ~70:30 dr obtained in the catalytic reaction arises from kinetic control. In contrast, when a single diastereoisomer of **21** was treated with HyperBTM (20 mol %) in MeCN, the dr readjusted to 78:22 within 30 minutes (Scheme 5b). This result can be rationalized by epimerization at the C(1') stereocenter (α to the NO₂ group), indicating that the diastereoselectivity observed in the catalytic reaction most likely reflects the relative thermodynamic stability of the two diastereoisomers.

Scheme 5. Epimerization studies

dr determined by ¹H NMR spectroscopy of the crude product mixture; er determined by CSP-HPLC analysis; TIPS = triisopropylsilyl.

Based on previous work,^[1–4] the following reaction mechanism is tentatively outlined (Scheme 6a). *N*-Acylation of HyperBTM **3** by α,β-unsaturated anhydride **23** gives the key α,β-unsaturated acyl isothiuronium intermediate **24**, to which the silyl nitronate **25** undergoes stereoselective Michael addition. The α,β-unsaturated acyl isothiuronium **24** is believed to adopt an *s*-cis conformation, with a *syn*-coplanar non-covalent 1,5-O⋯S interaction providing a conformational lock.^[2c,3a,14,15] The stereochemical outcome of the reaction can be rationalized by the stereodirecting phenyl substituent of the isothioureia catalyst controlling Michael addition of the silyl nitronate to the *Si*-face of α,β-unsaturated acyl isothiuronium **24** to give ammonium enolate **26**.^[16] To release silyl ester product **27** and regenerate HyperBTM **3**, three events are required: (i) protonation at C(2), (ii) incorporation of an oxygen atom, and (iii) silyl transfer. A variety of reasonable mechanisms can be postulated in which these steps can take place in any order. One of the simplest possibilities is desilylation of alkyl nitronium ion **26** by adventitious water to generate silanol **29**, which is then responsible for catalyst turnover; however, control experiments suggest that direct *O*-acylation of silanol **29** is unlikely (Scheme 6b). Although alternative mechanisms for catalyst turnover can be spec-

ulated,^[7] differentiation between these possibilities is the subject of on-going investigations and is beyond the scope of this communication.

Scheme 6. Mechanistic outline and control studies

^a Followed by *in situ* ¹H NMR spectroscopy through comparison to authentic samples of expected reaction products.

In conclusion, a new approach for isothiourea catalyst turnover in α,β -unsaturated acyl ammonium catalysis has been demonstrated. The use of a silyl nitronate in this Michael addition was essential to promote catalyst turnover, giving γ -nitro-substituted silyl esters with up to two

contiguous stereocenters in good yield and with excellent enantioselectivity (12 examples, up to 93% yield, >99:1 er). The catalytic reactions are complete within 1 h, and require only 1.5–2 equivalents of the silyl nitronate. This methodological advance therefore allows significantly more valuable, bespoke and structurally-diverse nitroalkane substrates to be applied in α,β -unsaturated acyl ammonium conjugate additions for the first time. Further investigation and exploitation of the synthetic potential and mechanistic aspects of this catalyst turnover approach is currently underway in our laboratory.^[17]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, compound characterization, NMR spectra, HPLC traces (PDF).

Accession Codes

CCDC 1962792–1962795 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

The authors declare no competing financial interest.

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17. Research data underpinning this publication can be found at: <https://doi.org/10.17630/987798e4-e872-4007-bc92-931c73232a6b>