Aryloxide-Facilitated Catalyst Turnover in Enantioselective α,β-Unsaturated Acyl Ammonium Catalysis

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Abstract: A new general concept for α,β-unsaturated acyl ammonium catalysis is reported that uses p-nitrophenoxide release from an α,β-unsaturated p-nitrophenyl ester substrate to facilitate catalyst turnover. This method was used for the enantioselective isothiourea-catalyzed Michael addition of nitroalkanes to α,β-unsaturated p-nitrophenyl esters in generally good yield and with excellent enantioselectivity (27 examples, up to 79% yield, 99:1 er). Mechanistic studies identified rapid and reversible catalyst acylation by the α,β-unsaturated p-nitrophenyl ester, and a recently reported variable-time normalization kinetic analysis method was used to delineate the complex reaction kinetics.

Lewis base organocatalysis is a widely studied field due to the diverse range of molecular frameworks that can be produced with high levels of regio-, chemo- and stereocontrol.[1] At the carboxylic acid oxidation level a variety of ammonium intermediates with differing reactivity can be accessed from readily available substrates using tertiary amine Lewis bases (Scheme 1a). Acyl ammonium and ammonium enolate intermediates have been extensively studied and applied in enantioselective acyl transfer processes and formal cycloadditions, respectively.[2,3] A less studied but equally powerful reactivity mode is that of α,β-unsaturated acyl ammonium intermediates.[4] These species contain electrophilic centres at the C1 and C3 positions, and a latent nucleophilic centre at C2, providing new opportunities for reaction design to target previously inaccessible product architectures.[5]

Seminal work by Fu first demonstrated the feasibility of this concept in a formal [3+2] cycloaddition using α,β-unsaturated acyl fluorides as the α,β-unsaturated acyl ammonium precursor (Scheme 1b).[4] Recent studies from ourselves, Romo, and Matsubara, has built on this precedent to achieve highly enantioselective Michael addition-annulation, formal cycloaddition and complex cascade methodologies.[7]

These examples used α,β-unsaturated acyl anhydrides or halides as the α,β-unsaturated acyl ammonium precursors. In addition, these methodologies require the reactive partner to contain two distinct nucleophilic functionalities to 1) undergo conjugate addition to the α,β-unsaturated acyl ammonium intermediate, and 2) enable turnover of the Lewis base catalyst (Scheme 1b). This requirement inherently limits α,β-unsaturated acyl ammonium catalysis and must be overcome to allow more diverse processes. In addition only preliminary experimental mechanistic work has been undertaken, with no kinetic analysis reported to date.[9]

Here we report the development of a new general concept for α,β-unsaturated acyl ammonium catalysis. Catalyst turnover is not facilitated by the nucleophilic reaction partner, but by an aryloxide counterion released in situ during the reaction by using an α,β-unsaturated aryl ester as the α,β-unsaturated acyl ammonium precursor (Scheme 1c).[8] This allows the use of simple nucleophiles as reaction partners, providing enhanced potential for further advancement of the field. Mechanistic work including kinetic analysis, catalyst labeling and crossover studies are also reported to deliver a fundamental understanding of this process.

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As initial proof of concept, the Michael addition of nitroalkanes to α,β-unsaturated aryl esters using a Lewis basic isothiourea catalyst was investigated. Although the organocatalytic enantioselective Michael addition of nitroalkanes to enones or enals is well precedented, Lewis base catalysis of this process has not been demonstrated at the carboxylic acid oxidation level.

Initial investigations focused on the reaction of a range of α,β-unsaturated aryl esters 1–4, bearing different aryl groups, with excess nitromethane using HyperBTM 5 as catalyst (Table 1, entries 1–4). The Michael addition products 6–9 were formed in each case in moderate to excellent yield (48–81%) but with uniformly high enantioselectivity (up to 96:4 er) and with complete regioselectivity. The highest yields were obtained using p-nitrophenyl (PNP) and 3,5-bis(trifluoromethyl)phenyl esters 1 and 4, with PNP ester 1 chosen for further studies due to the higher enantioselectivity obtained. Mixed solvent systems proved ineffective, with lower yields obtained in the presence of both THF and MeCN (entries 5 and 6). The addition of a base (2,6-lutidine) did not prove beneficial (entry 7), whilst heating the reaction at 70 °C resulted in complete decomposition (entry 8). Alternative isothiourea catalysts did not provide improved results, and lower catalyst loadings resulted in incomplete conversion, which complicated product isolation.

The scope and limitations of the method was then investigated. Given the moderate isolated yields of PNP ester products, the addition of a suitable nucleophile at the end of the reaction was used to give a range of readily isolable functionalized products (Table 2). The use of primary and secondary amines gave secondary and tertiary amides 10–14 in good yield, whilst addition of methanol gave methyl ester 15. All amide and ester products were obtained with high enantioselectivity indicating no significant loss in enantiopurity during the derivatization process. The scope of β-substituted α,β-unsaturated aryl esters amenable to the process was then investigated. Methyl-, isopropyl- and benzyl esters gave the addition products 16–18 in good yield and with excellent enantioselectivity. The incorporation of amides at the β-position was also well tolerated, giving unsymmetrical succinamide derivatives 19 and 20 in equally high yield and levels of enantiocontrol. The absolute configuration of 19 was confirmed by single crystal X-ray analysis, with all other examples assigned by analogy. Limitations of this methodology include incompatibility of substrates such as γ-keto ester derivative 22, which gave a complex mixture of products, and cinnamic acid derivative 23, which was completely unreactive. A derivative bearing β-alkyl substitution however gave product 21 with excellent enantiocontrol, albeit in low yield. The synthesis of a quaternary stereogenic carbon centre was also attempted, however application of β,β-disubstituted derivative 24 failed to give the desired Michael addition product.

The effect of olefin configuration was investigated using maleate PNP ester derivative 25 (Scheme 2). Interestingly,
the Michael addition product 12 was obtained in the same enantiomeric form (93:7 er) as when using the isomeric fumarate PNP ester 1 (95:5 er). Monitoring reaction progress by $^1$H NMR spectroscopy revealed rapid isomerization of maleate 25 to fumarate PNP ester 1 on a faster timescale than formation of product, with control reactions in [D$_6$]DMSO indicating reversible aryloxide conjugate addition as a possible mechanism for this isomerization process.$^{[16,18]}$

Attention was next turned to the use of alternative nitroalkanes and subsequent derivatization of the products. Nitroethane and nitropropane were suitable nucleophiles giving addition products 26 and 27 in good yield. Although only minimal diasterecontrol was observed, both diastereoisomers were obtained with excellent enantioselectivity (99:1 er, Table 3). Pleasingly, the use of 2-nitropropane and nitrocyclopentane was also successful, giving amide and ester products 28–31 in moderate yield but with excellent enantiocontrol.

Reduction of $\gamma$-nitro methyl esters 15, 29 and 31 and subsequent cyclization was achieved with no loss in enantiopurity to give pyrrolidinone derivatives 32–34 in excellent yield and highly enantioenriched form (Table 4).$^{[19]}$ The biological importance of pyrrolidonones, and $\gamma$-aminobutyric acid (GABA) derivatives in general, is well precedented.$^{[20]}$

To provide greater insight into this methodology, the reaction mechanism and kinetics were investigated to identify reaction intermediates and determine the reaction order with respect to each component. Quantitative reaction monitoring was achieved by in situ $^{19}$F[$^1$H] NMR spectroscopy using $^{19}$F-labeled PNP ester 35 and (2$R$,3$S$)-8F-HyperBTM 36 in MeNO$_2$ using PhF as internal standard and a C$_6$D$_6$-filled capillary reference (Figure 1 a,b). Attempts to interrogate the kinetic data revealed a substantial reduction in reaction rate over the course of the reaction, suggesting deactivation of the catalyst. During the reaction, the $^{19}$F chemical shift ($\delta_F$) of

<table>
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<th>Table 3: Reaction scope: Nitroalkane variation.[a]</th>
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<td><img src="image1.png" alt="Reaction Scheme" /></td>
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$^{[a]}$ Isolated yields given; dr of crude product determined by $^1$H NMR spectroscopic analysis (relative configurations not confirmed); er determined by chiral HPLC analysis. $^{[b]}$ Isolated as a mixture of diastereoisomers. $^{[c]}$ er of both diastereoisomers. $^{[d]}$ Diastereoisomers separated by column chromatography [41% (major); 32% (minor)]. $^{[e]}$ Excess MeOH and DMAP (20 mol%) used in step i.)
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Conflict of interest

The authors declare no conflict of interest.

Keywords: aryloxides · isothiourea · kinetic analysis · Lewis base catalysis · α,β-unsaturated ammonium compounds

9 For a review on aryloxide-assisted catalyst turnover in Lewis base catalysis see: W. C. Hartley, T. J. C. O’Riordan, A. D. Smith, Synthesis 2017, 3303 – 3310.
14 Yields determined by 1H NMR spectroscopy using an internal standard. Isolated yields were 13 – 33% lower, which was
attributed to hydrolysis of the PNP ester upon purification by flash silica column chromatography.

[15] Romo has reported a beneficial effect of using 2,6-lutidine in Diels–Alder/lactonization organocascades, see Refs [7d,8b].

[16] See the Supporting Information for full details.

[17] CCDC 1554262 (19) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.


[19] CCDC 1554261 (34) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.


[22] α,β-Unsaturated acyl isothiouronium chloride 38 (where X = Cl) was unreactive in MeNO₂, however upon addition of tetrabutylammonium p-nitrophenoxide (1 equiv), product 37 and starting material 35 were formed rapidly (< 120 s), with subsequent full conversion to product 37 over time (≈ 600 s). See the Supporting Information for full details.


[24] Michael addition products 44 – 47 were independently synthesised to allow identification.

[25] In the crossover experiment between reaction products (Scheme 3b), the formation of α,β-unsaturated esters 40 – 43 was not observed. In addition, whilst reaction of (2R,3S)-8F-HyperBTM 36 with Michael addition product 37 gave post-Michael addition acyl isothiouronium 39, the formation of α,β-unsaturated acyl isothiouronium 38 or PNP ester 35 was not observed. Both of these experiments suggest that one or both steps in the catalytic cycle between 49 and 51 may be essentially irreversible under the reaction conditions (Scheme 4).


[28] The research data underpinning this publication can be found at DOI: [https://doi.org/10.17630/421487e5-d537-4fc8-b067-b6dd664c20d3](https://doi.org/10.17630/421487e5-d537-4fc8-b067-b6dd664c20d3).

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Aryloxide-Facilitated Catalyst Turnover in Enantioselective α,β-Unsaturated Acyl Ammonium Catalysis

**Turnover a new leaf:** A new concept in α,β-unsaturated acyl ammonium catalysis uses aryloxide release from an α,β-unsaturated aryl ester substrate to facilitate catalyst turnover. Enantioselective isothiourea-catalyzed Michael addition of nitroalkanes to α,β-unsaturated p-nitrophenyl esters was achieved in good yield and with excellent enantioselectivity. Kinetic analysis was used to probe the reaction mechanism.