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Enantio- and Diastereoselective Organocatalytic Conjugate Additions of Nitroalkanes to Enone Diesters

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Abstract

Enantio- and diastereoselective conjugate addition reactions between nitroethane or nitropropane and enone diesters are reported. A bifunctional triaryliminophosphorane catalyzed the addition reaction with consistently excellent stereoselectivities and yields across a wide range of substrates. By the use of the *gem*-diester functional handle present in the adducts, local desymmetrization via diastereotopic group discrimination was demonstrated, and a polyfunctionalized lactam with three contiguous stereocenters was synthesized.

Graphical Abstract

The prevalence of nitrogen-containing acyclic and heterocyclic scaffolds in bioactive molecules provides ongoing opportunities for the development of methodologies for their efficient construction. Asymmetric organocatalytic conjugate additions of nitroalkanes have enabled the rapid construction of small polyads possessing numerous functional handles for downstream transformations. Previous approaches utilizing Brønsted base organocatalysis have accomplished this transformation in a stereoselective manner.¹ Although methods have been developed for the enantioselective addition of nitromethane, diastereocontrol with homologues has proven challenging in many contexts because of prochirality in both

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Notes

The authors declare no competing financial interest.

Supporting Information

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Crystallographic data for **2d** (CIF)

Experimental procedures, characterization, and spectral data for all compounds (PDF)

reaction partners.² Furthermore, substrates bearing both acrylate and enone moieties have been found to undergo regioselective addition exclusively at the enone Michael acceptor (Scheme 1a), which limits the scope of products accessible through this reaction. We sought to meet the challenges of regioselectivity and stereoselectivity by using a bifunctional organocatalyst to orient and unite extended nitroalkanes with acylidene malonates. In this paper, we report the enantio- and diastereoselective conjugate addition of nitroethane and nitropropane to enone diester electrophiles (Scheme 1b).

With the aim of exploiting these highly activated substrates and delivering useful functionality in the derived products, we initiated conjugate addition reaction studies with enone diesters **1**. The preparation of the latter was achieved by a one-pot reaction wherein di-*tert*-butyl 2-diazomalonate was subjected to oxo transfer under the action of Rh(II)/propylene oxide and the resulting ketone underwent Wittig olefination³ with a stabilized ylide (Scheme 2).^{4–6} The telescoped sequence avoided the problematic hydration issues associated with isolation of ketomalonates.⁷ Using this reaction sequence, we synthesized a variety of enone diesters in moderate to good yields.

Having established a synthetic path to access enone diesters **1**, we began optimization of the stereoselective addition of nitroalkanes. By screening chiral Brønsted bases known to enable this transformation, we identified triaryliminophosphorane **C3**, a bifunctional compound pioneered in the Dixon laboratory, as a suitable catalyst (see the Supporting Information for additional details).⁸ Evaluating the effect of the solvent and the identity of the diester present in **1a** ($R^1 = \text{Ph}$) allowed us to maximize the stereoselectivity and yield.

When the optimized conditions were applied to the parent substrate **1a**, the reaction proceeded with >20:1 diastereoselection and 97:3 er in 88% isolated yield (Figure 1). We observed similar reaction outcomes with halogen-substituted arenes **2b–d**. X-ray diffraction analysis of **2d** allowed us to determine the absolute stereochemical outcome of the reaction.⁹ We observed that placing the bromo substituent at the *ortho* position resulted in the formation of an undesired and inseparable byproduct. Other electron-deficient enone diesters **1e–g** provided the desired products in high stereoselectivity and yield. When we turned our attention to the electron-donating substituents present in **1h–j** (4-methoxy, 3-methoxy, piperonyl), we found similar results regardless of the specific substitution pattern. A study of furan (**1k**), thiophene (**1l**), and pyridine (**1m**) heterocycles also provided products with nearly perfect stereoselectivities and high yields. Aliphatic enones **1n** and **1o** performed well in the reaction, giving >20:1 dr with high enantioselectivities and good yields. Finally, we investigated whether homologous nitroalkanes could be employed. A nitropropane addition product was prepared with high stereoselectivity and chemical yield (**2p**). On a 1 g scale, the reaction of enone diester **1a** provided the adduct **2a** with nearly perfect stereoselectivity in 86% isolated yield (Scheme 3).

Seeking to take advantage of the diastereotopic ester groups, we developed a three-step local desymmetrization¹⁰ protocol that enables the formation of a new stereocenter with concomitant lactamization (Scheme 4). It was necessary to transform the di-*tert*-butyl malonate substructure into a dimethyl malonate to achieve ring closure during the nitro group reduction. The final lactam **5a** was obtained with 9.1:1 dr in 45% yield over three

steps while maintaining the same level of enantiopurity as the starting material **2a**. On the basis of the absence of a H²–H³ NOE, the three-bond coupling constant of 7.5 Hz in CD₃OD (or 8.2 Hz in CDCl₃), and strong literature precedent,¹¹ the benzoyl group and methyl ester were assigned as *trans* on the γ -butyrolactam ring.

In summary, we have developed asymmetric organocatalytic conjugate additions of extended nitroalkanes to enone diester electrophiles. A chiral bifunctional iminophosphorane enabled the creation of two adjacent stereocenters with high levels of enantio- and diastereoselectivity. Through subsequent diastereotopic group selection, the establishment of a third stereocenter during the formation of a polyfunctional lactam was demonstrated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Asymmetric conjugate addition of nitroalkanes. All of the reactions were conducted on a 0.1 mmol scale using 21.0 equiv of $EtNO_2$ or 20.2 equiv of $n\text{-}PrNO_2$. Isolated yields are shown. All yields and dr and er values are the averages of two trials. The er of **2a** was determined by derivatization to dimethyl malonate **4a**.

(a) Prior art (Xiao, 2009): conjugate addition with 4-oxo-enoates

(b) Current work: conjugate addition with functionalized enone diesters

Scheme 1.
Asymmetric Conjugate Additions of Nitroalkanes

Scheme 3.
Gram-Scale Asymmetric Conjugate Addition Reaction

Scheme 4.

Local Desymmetrization via Transesterification and Diastereoselective Lactamization