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Catalytic Enantioselective Protonation of Nitronates Utilizing an Organocatalyst Chiral Only at Sulfur

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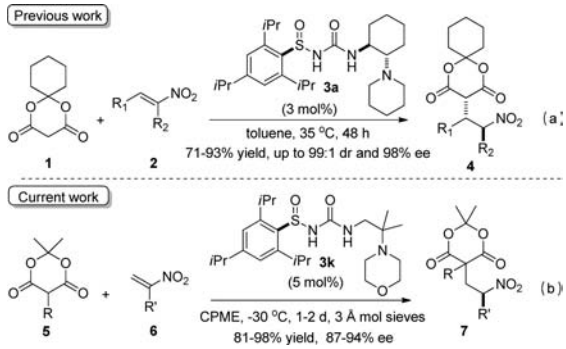
Supporting Information

ABSTRACT: The highly enantioselective protonation of nitronates formed upon the addition of α-substituted Meldrum's acids to terminally unsubstituted nitroalkenes is described. This work represents the first enantioselective catalytic addition of any type of nucleophile to this class of nitroalkenes. Moreover, for the successful implementation of this method, a new type of *N*-sulfinyl urea catalyst with chirality residing only at the sulfinyl group was developed, thereby enabling the incorporation of a diverse range of achiral diamine motifs. Finally, the Meldrum's acid addition products were readily converted to pharmaceutically relevant 3,5-disubstituted pyrrolidinones in high yield.

Recently, we reported the enantio- and diastereoselective addition of cyclohexyl Meldrum's acid to α,β-disubstituted nitroalkenes (Scheme 1a).[1−3] This transformation represented

Scheme 1. Previous and Current Work



the first example in which high enantio- and diastereoselectivity was achieved upon addition of a carbon nucleophile to acyclic α,β-disubstituted nitroalkenes. The key advance enabling this transformation was *kinetic* protonation of the nitronate addition product, which was possible because Meldrum's acid (pK_a = 7−8 in DMSO)[4] is considerably more acidic than the product nitroalkane (pK_a = 16−17 in DMSO),[4] and thus, the newly formed stereocenter was preserved. We hypothesized that *N*-sulfinyl urea-catalyzed[5,6] addition of Meldrum's acid derivatives to α-substituted nitroalkenes lacking β-substituents should also be followed by kinetic protonation, which potentially could proceed by an enantioselective process. However, no examples of catalytic enantioselective addition of any type of nucleophile to terminally unsubstituted nitroalkenes using either transition-metal or organic catalysts had previously been reported.[7,8]

Herein we describe the first example of this type of transformation, in which the addition of α-substituted Meldrum's acids provides **7** in good yields with high enantioselectivities (Scheme 1b). Notably, successful addition was achieved using the versatile new *N*-sulfinyl urea catalyst **3k**, which is chiral solely at sulfur and thus allowed for straightforward exploration of a variety of achiral diamine motifs. Importantly, the Meldrum's acid addition products **7** are readily converted in a convenient and high-yielding two-step process to the therapeutically relevant class of 3,5-disubstituted pyrrolidinones (Figure 1).[9,10]

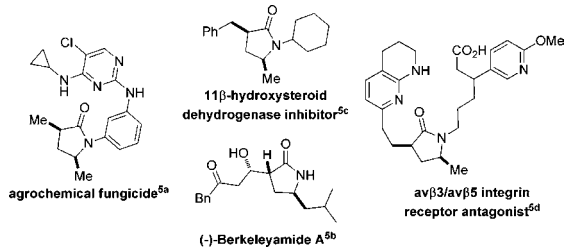


Figure 1. Representative bioactive 3,5-disubstituted pyrrolidinone derivatives.

Our investigation began with the addition of α-methyl Meldrum's acid derivative **8a** to 2-nitropropene (**6a**)[11] (Scheme 2). While *N*-sulfinyl urea catalyst **3a**, which had previously been successfully employed for additions to α,β-disubstituted nitroalkenes,[1] resulted in an encouraging 50% ee, a screen of various *N*-sulfinyl urea catalysts incorporating different chiral diamines did not result in improved selectivity. However, this screen did establish that catalysts **3a** and **3b** incorporating enantiomeric (1*S*,2*S*)- and (1*R*,2*R*)-1,2-cyclohexanediamine, respectively, gave equivalent selectivities with the *same* sense of stereoinduction. This result suggested that the *N*-sulfinyl group is the dominant stereocontrolling element for this transformation, in contrast to previously successful *N*-sulfinyl urea catalysts that relied upon the cooperative effect of an additional chiral controlling element along with the sulfinyl stereocenter.[6a−c] The potential ramifications of exclusive *N*-sulfinyl stereocontrol include (1) a simplified catalyst without multiple stereocenters and (2) a greater degree of structural versatility in catalyst optimization.

To probe whether a catalyst possessing only a sulfur stereocenter could be used, catalyst **3c** with a simplified

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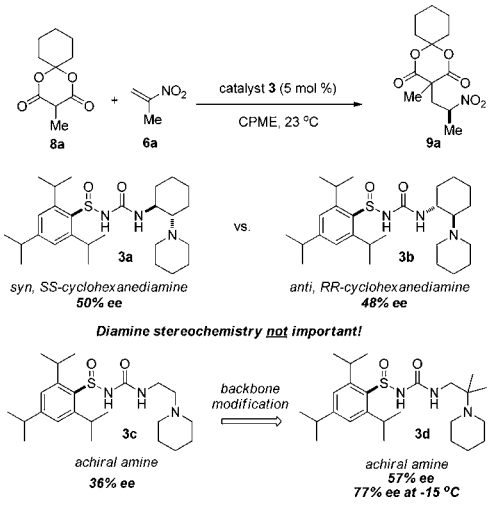
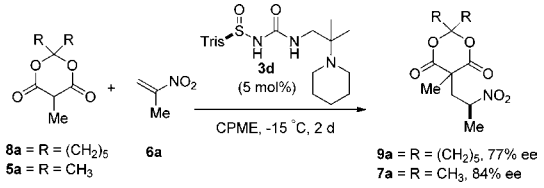
Scheme 2. Discovery of Dominant Sulfinyl Stereocontrol



ethylenediamine backbone was synthesized and evaluated; it provided addition product **9a** with 36% ee (Scheme 2). The enantioselectivity was only marginally diminished, thereby demonstrating that the chiral cyclohexanediamine backbone was not an essential stereodetermining element. Furthermore, placement of geminal dimethyl substitution on the ethylenediamine linker (catalyst **3d**) provided **9a** with 57% ee, indicating that this type of *N*-sulfinyl urea catalyst could indeed be further modified to increase the selectivity. Importantly, catalyst **3d** displayed a significant temperature effect. Cooling the reaction solution from room temperature to −15 °C provided the product with 77% ee.[12] Encouraged by this result, we sought to optimize this transformation by using catalysts prepared from *achiral* diamines.

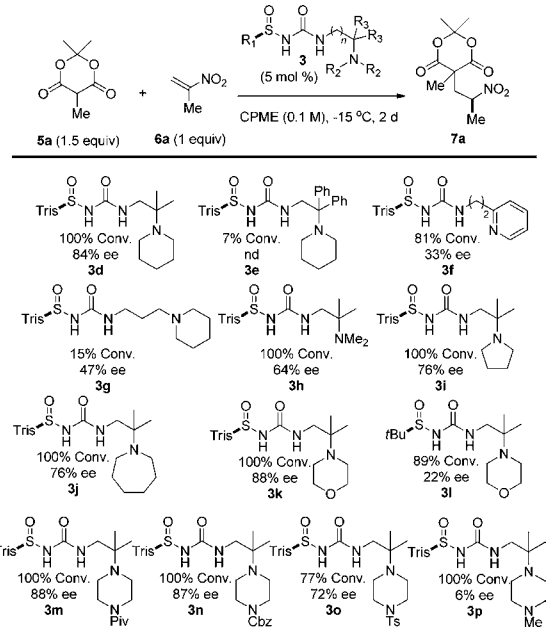
Prior to the full exploration of the diamine component of the catalyst, Meldrum's acid derivatives incorporating different acetal substituents (R) were evaluated [Scheme 3; see the Supporting Information (SI) for full details]. The simplest derivative, **5a** (R = Me), gave the highest selectivity and was employed in all subsequent studies. Meldrum's acid **5a** is preferable to derivatives with other R groups because of its low cost and the fact that hydrolysis of its addition products produces volatile and easily removed acetone as the byproduct (see below).

Scheme 3. Influence of the Meldrum's Acid Substituents



We next synthesized a range of *N*-sulfinyl urea catalysts to explore several different aspects of the achiral diamine structure, including the tether length, geminal substituents, and modulation of the steric environment and basicity of the tertiary amine base (Scheme 4). In evaluating the different catalysts, a slight excess of Meldrum's acid (1.5 equiv) was employed to buffer the reaction solution, thereby ensuring that no postreaction racemization would occur. Changing the geminal substituents from methyl to phenyl (**3e**) caused the reaction to become too sluggish to be considered. Interestingly, the pyridine catalyst **3f** gave relatively high conversion, although with decreased selectivity, suggesting that the catalyst structure was not necessarily limited to alkylamine bases. Catalyst **3g** possessing an increased tether length relative to **3c** (Scheme 2) provided the product with reduced conversion but comparable selectivity, indicating that a three-carbon linker could be a viable alternative to a two-carbon linker.[13] Comparison of catalysts **3d** and **3h−j** suggested that the six-membered piperidine ring provides the optimal amine geometry. The high conversion observed with the less basic pyridine catalyst **3f** prompted us to explore less basic analogues of the optimal piperidine catalyst **3d**. To our delight, catalyst **3k** possessing a morpholine unit[14] increased the enantioselectivity to 88% ee. Notably, the corresponding *tert*-butylsulfinamide-derived catalyst incorporating the morpholine base, **3l**, gave poor selectivity, further defining the importance of the trisylsulfinyl group. Piperazine derivatives **3m** and **3n** with *N*-pivaloyl and carbobenzyloxy groups, respectively, also performed well. In contrast, piperazine catalyst **3o** with an *N*-tosyl group was much less efficient and less selective. Not surprisingly, piperazine **3p** with an additional basic site did not perform well. The possibility of adding an exogenous base to a simple trisylsulfinyl urea lacking amine functionality was also explored, but all of the bases evaluated, including *N*-methylmorpholine, pyridine, and inorganic bases, gave <10% ee (see the SI for full details). Morpholine catalyst **3k** was thus selected for further experiments because of its high selectivity and ease of preparation in a single step from commercially available components.[15]

Scheme 4. Identification of the Optimal Catalyst



With catalyst **3k**, the reaction conditions were further optimized for yield and enantioenrichment. The commercially available nitroalkene was used in excess (2−3 equiv), and the concentration was increased from 0.1 to 0.2 M. With these changes, the reaction solution could be further cooled from −15 to −30 °C, which provided a substantial increase in the enantioselectivity while maintaining high conversion at convenient reaction times (15−48 h). Finally, the addition of

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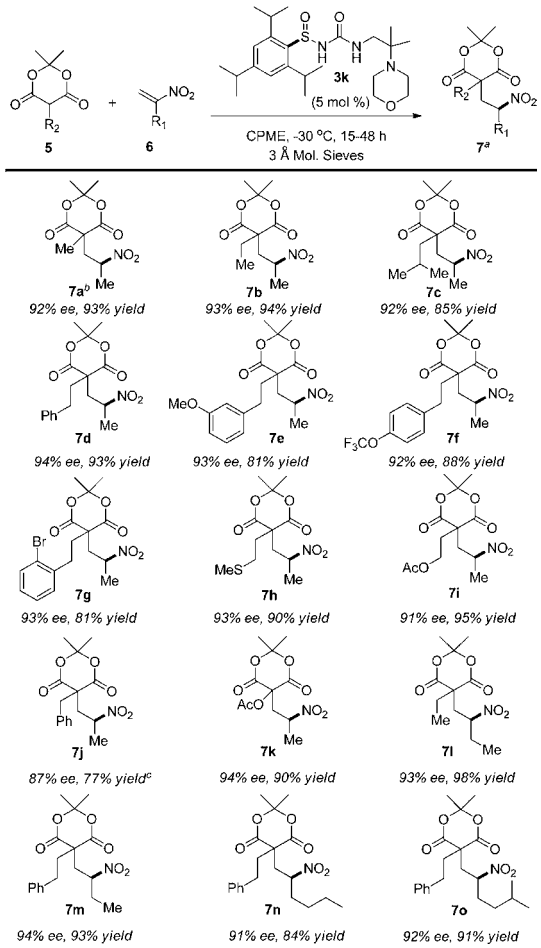
3 Å molecular sieves was found to improve the consistency from run to run (see the SI for complete data).[16]

With the optimized conditions in hand, we explored the reaction scope (Table 1). A range of α-alkyl-substituted

Table 1. Catalytic Conjugate Addition/Enantioselective Protonation of Nitroalkenes with α-Substituted Meldrum's Acids

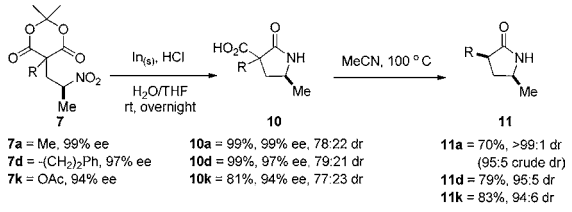


[a]Yields are of isolated products after chromatography. Enantiomeric excess was determined using chiral HPLC analysis. [b]The absolute stereochemistry of **7a** was determined by X-ray analysis, and those of **7b–o** were assigned by analogy to **7a**. [c]The yield and ee correspond to a reaction run at −50 °C for 90 h. The standard conditions provided **7j** in 87% yield with 83% ee.

Meldrum's acids served as effective coupling partners, with methyl, ethyl, isobutyl, and phenethyl substituents, providing the addition products **7a–d** in good yields with >92% ee. Importantly, the reaction was tolerant of a number of functional groups, including aryl ethers, aryl bromides, thioethers, and esters (adducts **7e–i** and **7k**). In view of the scope of the Meldrum's acid component and the straightforward introduction of diverse alkyl substituents, this method should serve as an excellent means of incorporating functionality into more complex molecules. While α-benzyl Meldrum's acid provided the product with somewhat lower selectivity (83% ee) at −30 °C, decreasing the temperature to −50 °C and extending the reaction time increased the selectivity to 87% ee (adduct **7j**). Notably, the substituent of the Meldrum's acid derivative was not limited to an α-alkyl group. Despite being significantly more acidic, α-acetoxy Meldrum's acid was also an excellent substrate, providing product **7k** in 90% yield with 94% ee. While 2-nitropropene proved to be an excellent substrate for the reaction, a number of other nitroalkenes performed equally well. Specifically, comparable yields and selectivities were observed for additions to 2-nitrobutene (adducts **7l** and **7m**) as well as other linear (**7n**) and branched (**7o**) terminal nitroalkenes.

We envisioned that addition products **7** would be versatile intermediates for the asymmetric synthesis of γ-amino acid derivatives and in particular for pharmaceutically relevant 3,5-disubstituted pyrrolidinones. This transformation would require reduction of the nitro group in adducts **7** without epimerization, followed by lactamization with extrusion of acetone and subsequent diastereoselective decarboxylative protonation (Scheme 5). However, we could not find relevant

Scheme 5. Rapid Synthesis of α,γ-Disubstituted γ-Lactams



precedent for racemization-free reduction and cyclization of α-substituted nitroalkanes. Although many reducing conditions gave incomplete conversion, racemization, or multiple products, clean reduction and cyclization occurred in nearly quantitative yield upon treatment of **7a** with metallic indium and HCl in H_2O/THF (Scheme 5).[17,18] Only a single literature report was available for diastereoselective decarboxylative protonation of α-substituted α-carboxypyrrolidinones, and the transformations proceeded with only modest selectivities.[19] We therefore explored thermal decarboxylation of lactam **10a** using a range of aprotic solvents and reaction temperatures. We were pleased to find that decarboxylative protonation in acetonitrile at 100 °C proceeded with 95:5 dr,[20] providing **11a** as single diastereomer in 70% yield after column chromatography. Furthermore, the optimized two-step process for reduction, cyclization, and decarboxylative protonation provided high yields and comparably high diastereoselectivities for phenethyl-substituted adduct **11d** and α-acetoxy derivative **11k**.

In summary, we have developed a catalytic enantioselective addition of α-substituted Meldrum's acids to α-substituted nitroalkenes. This reaction is the first example of nucleophilic addition to a terminally unsubstituted nitroalkene followed by enantioselective protonation, and it demonstrates the viability of this disconnection in asymmetric synthesis. In the development of this transformation, a new type of *N*-sulfinyl urea catalyst with chirality residing only at the sulfinyl group was also identified, thereby allowing modifications to the diamine portion of the catalyst structure that previously were not possible. Finally, we have demonstrated that the addition products can readily be converted with high diastereoselectivity to the important class of 3,5-disubstituted pyrrolidinones, which are present in a number of bioactive compounds and serve as convenient intermediates to substituted γ-amino acids and pyrrolidines.

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■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, product characterization, HPLC traces, and a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) Use of unsubstituted Meldrum's acid led to overalkylation.

(12) Catalyst **3d** provided **9a** with 57% ee at 23 °C and 77% ee at −15 °C, whereas **3a** provided **9a** with 50% ee at 23 °C and 62% ee at −15 °C. The greater temperature effect may result from the increased amount of rotational freedom in **3d**, which upon cooling increasingly reacts through a more selective conformer.

(13) For a nice example of the design of an innovative four-carbon chiral diamine linker, see: Palacio, C.; Connon, S. J. *Chem. Commun.* **2012**, *48*, 2849.

(14) Morpholine is ∼2 pK_a units less basic than piperidine.[4]

(15) Catalyst **3k** was made via 1,1'-carbonyldiimidazole coupling of commercially available trisylsulfinamide and 2-methyl-2-morpholinopropan-1-amine in ∼80% yield on a 1 mmol scale. The synthesis of the piperazine catalysts (**3m**−**p**) was lengthier. See the SI for full details.

(16) The racemic β-hydroxynitroalkane generated by hydration of the nitroalkene starting material reduced the enantioselectivity of the reaction. Molecular sieves prevented formation of this product and consequently resulted in improved reproducibility.

(17) For indium-mediated nitro reduction, see: Singh, V.; Kanojiya, S.; Batra, S. *Tetrahedron* **2006**, *62*, 10100.

(18) Reduction occurred with preservation of the α-nitro stereocenter under the indium/HCl conditions. Enantiomeric purities were determined by chiral HPLC analysis.

(19) (a) Diastereoselective decarboxylative protonation of 3-substituted pyrrolidinones has been reported only for an *N*-H pyrrolidinone (with ∼3:1 dr) and an *N*-pivaloyl pyrrolidinone (with 55:45 dr). See: Hook, D.; Thomas, R.; Bernhard, R.; Wietfeld, B.; Sedelmeier, G.; Napp, M.; Baenziger, M.; Hawker, S.; Ciszewski, L.; Waykole, L. M. New Process. WO2008083967 (A2). (b) In analogy with Meyers' alkylations of enolates of simple *N*-methyl-5-methylpyrrolidinone, it was expected that the decarboxylative protonation should also take place from the face opposite the 5-substituent and that the magnitude of the diastereoselectivity would be greater for *N*-H than *N*-carbamoyl pyrrolidinones. For an excellent explanation of this phenomenon, see: Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 4565.

(20) The relative configuration of decarboxylated lactam **9a** was determined to be cis by correlation with literature ^{1}H NMR data. See: Crich, D.; Ranganathan, K. *J. Am. Chem. Soc.* **2005**, *127*, 9924.