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EDGE ARTICLE

Enantio- and diastereoselective addition of cyclohexyl Meldrum's acid to β- and α,β-disubstituted nitroalkenes *via* *N*-sulfinyl urea catalysis†

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Using *N*-sulfinyl urea catalysis, a method has been developed for the asymmetric synthesis of biologically important γ-amino acids with a high level of efficiency, practicality and unprecedented control of multiple stereocenters. This method is based upon the highly enantio- and diastereoselective addition of cyclohexyl Meldrum's acid as an easily deprotectable monocarboxylic acid equivalent. The addition to both β-substituted and α,β-disubstituted nitroalkenes using *N*-sulfinyl urea organocatalyst **8** is described. The utility of this new method toward drug production is demonstrated by the mole scale preparation of a key precursor to the commercial drug Lyrica using catalyst **8** at only 0.2 mol% loading. Moreover, α,β-disubstituted nitroalkene addition products were efficiently converted to γ-amino acid derivatives without epimerization of either stereocenter.

Introduction

γ-Amino acids are present in numerous drugs, drug candidates and bioactive natural products (Fig. 1).[1,2] Moreover, this structure can readily be transformed into pyrrolidinones and pyrrolidines, which are also present in a large number of bioactive compounds.

Consequently, highly effective organocatalytic methods have been developed for the asymmetric addition of malonates to β-substituted nitroalkenes at low catalyst loading to provide efficient and practical access to γ-amino acid derivatives (eqn 1).[3] In contrast, for additions to α,β-disubstituted nitroalkenes only a narrow set of cyclic substrates have been reported.[4] Moreover, despite considerable effort, only moderate enantioselectivity has been achieved for the organocatalytic addition of Meldrum's acid derivatives to nitroalkenes (eqn 2).[5] For each of the reported examples, high catalyst loading was also used.

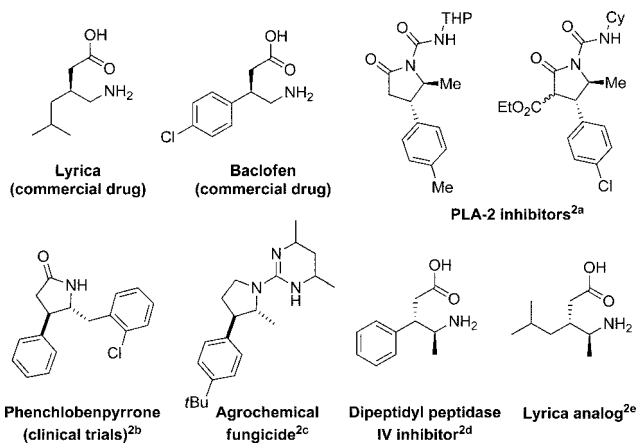
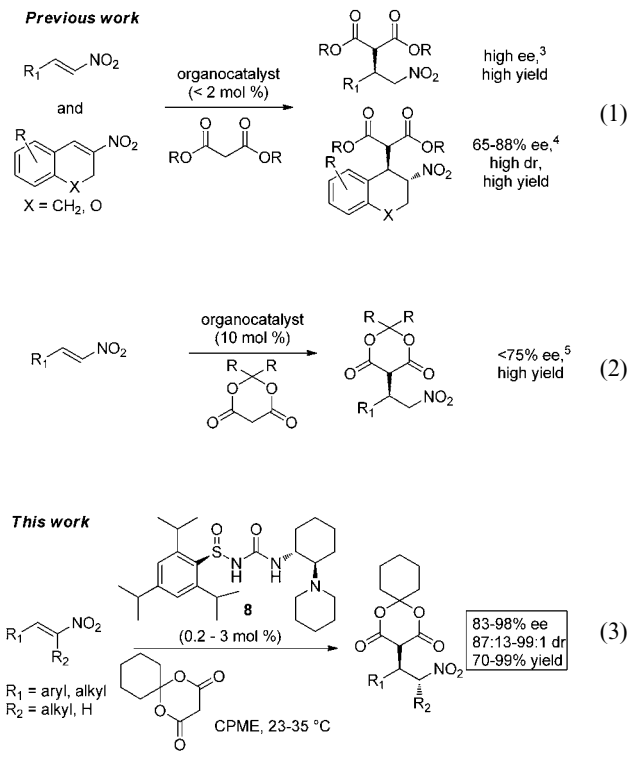


Fig. 1 Representative examples of bioactive γ-amino acid derivatives.



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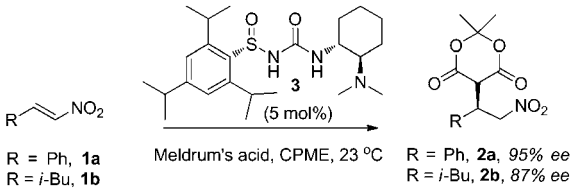
The successful asymmetric addition of Meldrum's acid with high selectivity and catalyst efficiency is a worthwhile and important goal due to two distinctive properties of the Meldrum's acid structure. First, Meldrum's acid derivatives are more acid labile than malonates due to their acetal framework, thereby enabling a mild and convenient single step, acid-catalyzed process for tandem deprotection/decarboxylation to form the corresponding γ-amino acid derivatives.[6] Second, Meldrum's acid derivatives (pK_a in DMSO = 7–8)[7] are considerably more acidic than malonates (pK_a in DMSO = 16–17),[7] resulting in new opportunities for reactivity and selectivity. In particular, the previously reported addition of malonates to cyclic nitroalkenes (eqn 1), presumably provides the more stable *trans*-disubstituted products through thermodynamic control as a consequence of the comparable acidity of the malonate nucleophile and the nitroalkane product (pK_a in DMSO = 16–17).[7] Unfortunately, only a very modest thermodynamic ratio of *trans*-/*cis*-isomers for acyclic nitroalkene addition products with α- and β-stereocenters is likely to be observed (see below). The much greater acidity of Meldrum's acids relative to both malonates and nitroalkanes should enable efficient kinetic control and potentially high selectivity for additions to α,β-disubstituted nitroalkenes.[8]

Herein, we report that *N*-sulfinyl urea[9,10] catalyst **8** at low catalyst loadings (0.2–3 mol%) provides the first highly enantio- and diastereoselective organocatalytic addition of Meldrum's acid derivatives to nitroalkenes (eqn 3). This work also provides the first example of the organocatalytic addition of any carbon nucleophile to acyclic α,β-disubstituted nitroalkenes to set both the α- and β-stereocenters in acyclic products with high enantio- and diastereoselectivity.[11] Significantly, the Meldrum's acid addition products undergo facile hydrolysis and decarboxylation under acidic conditions followed by reduction to directly afford enantioenriched γ-amino acids without epimerization. A representative addition product of Meldrum's acid to an α,β-disubstituted nitroalkene has also been converted to useful γ-amino acid-derivatives without epimerization. The practicality of our method is further demonstrated by the mole scale addition of cyclohexyl Meldrum's acid to nitroalkene **1b** at only 0.2 mol% organocatalyst loading followed by one-step hydrolysis/decarboxylation to provide a known precursor to the drug *S*-Pregabalin (Lyrica),[12] which is used extensively for the treatment of neuropathic pain, as well as other disorders.[1b,c]

Results

Reaction development

N-Sulfinyl ureas have emerged as promising enantioselective organocatalysts with the sulfinyl group serving as both a chiral directing group and electron withdrawing substituent[10a] and have proven to be particularly effective for the addition of the acidic thioacetic acid pronucleophile.[10b] The previously reported *N*-sulfinyl urea catalyst **3**[10b] (see Fig. 2) was used for initial screening in the enantioselective addition of Meldrum's acid to nitroalkenes **1**. In cyclopentyl methyl ether (CPME), which has seen increasing use as solvent for large scale industrial applications,[13] the addition to *trans*-β-nitrostyrene **1a** proceeded at rt with 95% ee, while the alkyl nitroalkene **1b**, which notably leads to the drug Lyrica,[12] provided the addition product **2b** in 87% ee (eqn 4). With the goal of ultimately applying the method to the synthesis of Lyrica, we focused subsequent optimization studies on substrate **1b**.



(4)

Recent reports for other urea catalysts have shown dramatic differences in the selectivity and activity arising from different tertiary amine moieties.[14] On this basis, several new sulfinyl ureas were synthesized and tested in the enantioselective addition of Meldrum's acid to aliphatic nitroalkene **1b** (Table 1). Catalysts **4–6**, all bearing acyclic tertiary amines, uniformly reduced the enantioselectivity (entries 2–4). Cyclic tertiary amine catalysts, such as pyrrolidine **7** and piperidine **8**, showed more promise, with catalyst **8** propelling the reaction to 91% conversion and 92% ee (entry 6). Free amine catalyst **9** exhibited poor solubility and poor conversion (entry 7). Interestingly, diastereomeric catalyst **10** gave drastically reduced selectivity, indicating a substantial matched–mismatched effect arising from the relative configurations of the sulfinyl and 1,2-diamine stereocenters (entry 8). *tert*-Butanesulfinyl urea **11** was also tested, but was found to be less selective than the corresponding trisyl sulfinyl urea **3** (entry 9).[15]

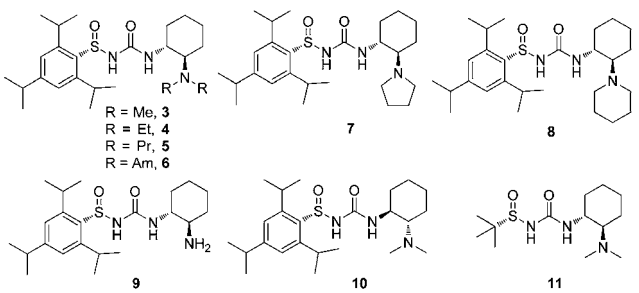


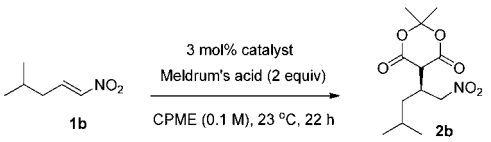
Fig. 2 Catalysts tested in the addition of Meldrum's acid to nitroalkenes.

Low catalyst loading was sought to enhance the practical utility of this transformation. However, the reaction rate was limited by the low solubility of Meldrum's acid in CPME and other nonpolar solvents (more polar solvents result in diminished enantioselectivities). We postulated that using a more hydrophobic Meldrum's acid derivative might circumvent this problem. Indeed, cyclohexyl Meldrum's acid exhibited enhanced (~4-fold at 23 °C) solubility in CPME. The resulting increase in the effective concentration allowed the catalyst loading to be reduced to 1 mol% at room temperature. Additionally, a slight increase in enantioselectivity was observed upon switching to cyclohexyl Meldrum's acid (Table 2, entry 2).

Synthetic scope

The substrate scope was explored for the addition of cyclohexyl Meldrum's acid to various aromatic and aliphatic nitroalkenes

Table 1 Identification of optimal catalyst

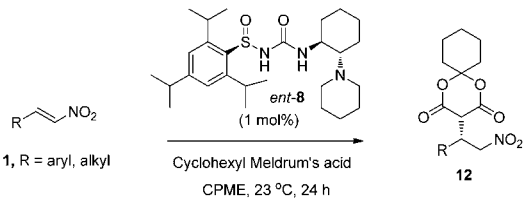


Entry	Catalyst	Conversion[a] (%)	ee[b,c] (%)
1	**3**	76	87
2	**4**	62	80
3	**5**	71	77
4	**6**	82	81
5	**7**	83	91
6	**8**	91	92
7	**9**	29	70
8	**10**	73	−64
9	**11**	70	79

[a] Conversion was determined by ^{1}H NMR from the ratio of the product to starting material. [b] Enantiomeric excess was determined by chiral HPLC. [c] Absolute stereochemistry was determined by the correlation of the optical rotation of product **2b** to the literature value.[5b]

1 using 1 mol% of catalyst ent-**8** (the enantiomer of catalyst **8**) (Table 2). *trans*-β-Nitrostyrene **1a** underwent addition in 95% yield and 98% ee (entry 1) and the aliphatic Lyrica precursor **1b** gave the product **12b** in 90% yield and 94% ee (entry 2). Substitution around the aromatic ring was well tolerated, giving up to 99% yield and 98% ee over a range of aromatic substrates (entries 3–7). The enantioselectivity was also excellent for both electron-deficient and -rich derivatives (entries 5 and 6, respectively). 2,4-Dichlorophenyl substrate **1g** reacted more slowly, but increasing

Table 2 Catalytic enantioselective addition of cyclohexyl Meldrum's acid to β-substituted nitroalkenes



Entry	R	Product[a]	Yield[b] (%)	ee[c] (%)
1	C_6H_5	**12a**	95	98
2	*i*-Bu	**12b**	90	94
3	*o*-MeC_6H_4	**12c**	94	96
4	*p*-MeC_6H_4	**12d**	99	98
5	*p*-$CF_3C_6H_4$	**12e**	82	98
6	*p*-$MeOC_6H_4$	**12f**	99	96
7	*o*,*p*-$Cl_2C_6H_3$	**12g**[d]	95	96
8	*n*-Pr	**12h**	94	94
9	*c*-Hex	**12i**	73	96

[a] Reactions were performed with 1.0 mol% catalyst loading at 0.3 M concentration of substrate with 1.5 equiv. of cyclohexyl Meldrum's acid. [b] Isolated yield of analytically pure material after chromatography. [c] Enantiomeric excess was determined by chiral HPLC. [d] Reaction was run using 3.0 equiv. of cyclohexyl Meldrum's acid.

the amount of cyclohexyl Meldrum's acid afforded the product in 95% yield and 96% ee (entry 7). Moreover, both linear (entry 8) and branched (entries 2 and 9) β-alkyl substituted nitroalkenes provided addition products in good yields and with high selectivities (≥94% ee).

Additions to α,β-disubstituted nitroalkenes **13** would generate products **14** (Table 3) with two stereocenters, which are desirable for the preparation of bioactive compounds (*e.g.*, see Fig. 1). However, these more highly substituted nitroalkenes present several additional challenges. Firstly, under basic conditions, the acidity of the proton α to the nitro group of **14** can cause epimerization of that stereocenter, leading to a thermodynamic ratio of diastereomers. Secondly, for acyclic nitroalkane products **14**, the thermodynamic product ratio is very modest.[16] Finally, the more substituted nitroalkenes **13** were expected to undergo addition at much slower rates. Nevertheless, we were pleased to find that using catalyst ent-**8**, α,β-disubstituted nitroalkene **13a** afforded addition product **14a** with almost perfect diastereoselectivity (Table 3, entry 1). An X-ray crystal structure of product **14a** revealed that the relative stereochemistry is consistent with delivery of the nucleophile and proton to the same face of the nitroalkene.

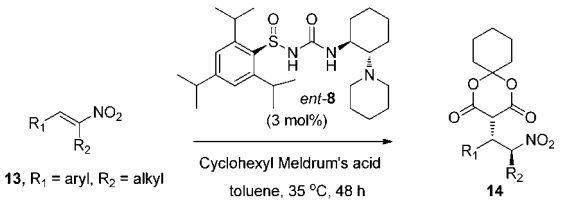
We investigated the substrate scope for the enantioselective addition of cyclohexyl Meldrum's acid to a number of cyclic and acyclic α,β-disubstituted nitroalkenes **13** (Table 3). Despite the lower reactivity of these more challenging substrates, only 3 mol % of catalyst ent-**8** was necessary for efficient conversion to addition products **14**. Parent substrate **13a** afforded the product in 97 : 3 dr, 93% ee, and after chromatography, a 90% isolated yield of a single diastereomer. Variation of the aromatic ring shows a high tolerance for both electron-rich and electron-poor derivatives, as well as various *para*-substituents (entries 2–5). The substituent alpha to the nitro group can also be varied from a simple methyl group to other groups such as benzyl (entry 6) and butyl (entry 7) groups. The less challenging cyclic α,β-disubstituted nitroalkenes are also effective substrates, affording products **14h–14j** with high selectivities and yields. In fact, these cyclic substrates required only 1 mol% catalyst loading.

Applications to the synthesis of γ-amino acid derivatives

We then sought to demonstrate the utility of these addition products for the construction of biologically relevant γ-amino acid derivatives. Importantly, adduct **14a** with two stereocenters can be readily converted to γ-amino acid derivatives[2] with retention of the stereochemical information (Scheme 1). The TsOH-catalyzed one-pot hydrolysis/decarboxylation[12] of **14a** affords monoacid **16** in 93% yield and in a diastereomerically and analytically pure form after simple extractive isolation. Monacid **16** can then be reduced either using Zn dust and HCl to give diastereomerically pure γ-amino acid **17**[2d] in 97% yield or by $SnCl_2$ reduction/esterification conditions to provide the amino ethyl ester **18** in 61% overall yield, also in diastereomerically pure form.

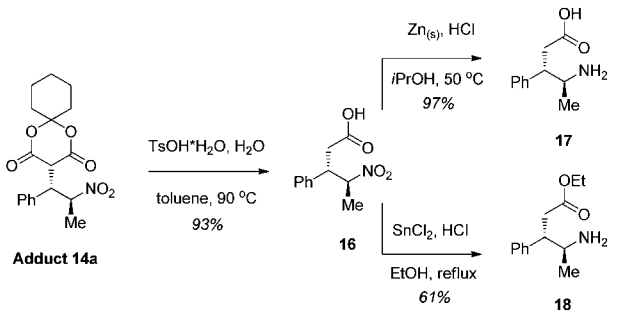
Finally, we sought to demonstrate the utility of our method for drug production with the mole scale synthesis of Lyrica precursor **15** (Scheme 2). Although 1 mol% catalyst loading is sufficient for laboratory scale chemistry, further reduction of the catalyst loading is desirable for large scale drug production. With

Table 3 Catalytic enantio- and diastereoselective addition of cyclohexyl Meldrum's acid to α,β-disubstituted nitroalkenes



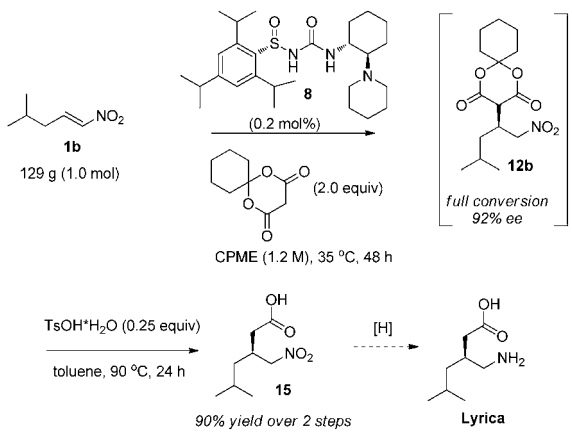
Entry	R_1	R_2	Product[a]	Yield[b] (%)	Crude d.r.[c]	ee[d] (%)
1	C_6H_5	Me	**14a**[e]	90	97 : 3	93
2	*p*-$CF_3C_6H_4$	Me	**14b**	71	95 : 5	94
3	*p*-$MeOC_6H_4$	Me	**14c**	91	96 : 4	92
4	*p*-ClC_6H_4	Me	**14d**	77	96 : 4	91
5	*p*-MeC_6H_4	Me	**14e**	91	97 : 3	92
6	C_6H_5	Bn	**14f**	74	98 : 2	90
7	C_6H_5	*n*-Bu	**14g**	70	99 : 1	83
8	$-(CH_2)_4-$	$-(CH_2)_4-$	**14h**[f,g]	78	87 : 13	91
9	$-(CH_2)_3-$	$-(CH_2)_3-$	**14i**[f,g]	93	98 : 2	97
10	$-(CH_2)_5-$	$-(CH_2)_5-$	**14j**[f,h]	92	>99 : 1	98

[a] Reactions were performed with 3.0 mol% catalyst loading at 0.6 M concentration of substrate and with 3.0 equiv. of cyclohexyl Meldrum's acid. [b] Isolated yield of analytically pure single diastereomers after chromatography. [c] Crude diastereomeric ratios were determined by ^{1}H NMR. [d] Enantiomeric excess was determined by chiral HPLC. [e] Absolute and relative stereochemistry was determined from an X-ray crystal structure. [f] Reaction was performed using 1.0 mol% catalyst. [g] Reaction was performed at 0.05 M concentration. [h] Reaction was performed at 0.3 M concentration using 1.5 equiv. of cyclohexyl Meldrum's acid.



Scheme 1 The synthesis of γ-amino acid scaffolds from adduct **14a**.

mild heating to 35 °C, complete conversion can be achieved with only 0.2 mol% of catalyst **8** and with only a very slight reduction in enantioselectivity. The crude addition product can be taken on directly to a one-pot hydrolysis/decarboxylation step, allowing for a telescoped overall process. Key Lyrica intermediate **15** was synthesized by this route on a one mole scale in 90% overall yield from nitroalkene **1b**. A one-step conversion of intermediate **15** to Lyrica *via* hydrogenation has been reported in the literature.[12]



Scheme 2 Large-scale production of the key Lyrica intermediate.

Conclusion

In summary, we have introduced a practical method for constructing optically active γ-amino acids that utilizes cyclohexyl Meldrum's acid as a versatile monocarboxylic acid equivalent and piperidinyl sulfinyl urea **8** as a highly selective and efficient organocatalyst. Decarboxylation and nitro reduction can be performed to provide γ-amino acid derivatives without any loss of stereochemistry even for α,β-disubstituted nitroalkene inputs. The viability of this method toward drug production was demonstrated with the mole scale synthesis of Lyrica precursor **15** using only 0.2 mol% of catalyst **8**. This method is not only the first example of the highly enantioselective addition of Meldrum's acid derivatives to nitroalkenes, but also provides the first example of the organocatalytic addition of any type of carbon nucleophile to acyclic α,β-disubstituted nitroalkenes to set both the α- and β-stereocenters in acyclic products with high enantio- and diastereoselectivity. The key to obtaining high diastereoselectivity is the acidic nature of Meldrum's acid *vs.* the more traditional malonate esters. We believe that Meldrum's acid will be similarly advantageous for a variety of transformations that are currently under investigation.

Acknowledgements

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and Steve Han for providing trisyl sulfinamide at the early project stage.

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