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Asymmetric organocatalytic Michael addition of Meldrum’s acid to nitroalkenes: probing the mechanism of bifunctional thiourea organocatalysts

Antti O. Kataja and Ari M. P. Koskenen*

Department of Chemistry, Aalto University School of Science and Technology,
PO Box 16100, FI-00076 Aalto, Finland
E-mail: Ari.Koskenen@tkk.fi

Abstract
The asymmetric Michael addition of Meldrum’s acid to nitroalkenes was studied using a novel type of Cinchona alkaloid-based bifunctional thiourea organocatalyst. The functionality of the thiourea catalysts was also probed by preparing and testing thiourea-N-methylated analogues of the well-known bis-(3,5-trifluoromethyl)phenyl-substituted catalyst.

Keywords: Organocatalysis, Michael addition, bifunctional thiourea catalysts, Cinchona alkaloids, Meldrum’s acid

Introduction
Enantioselective carbon-carbon bond formation is one of the lasting challenges in organic chemistry. Though well-established methods and strategies for stereocontrolled bond formation have been developed, the modern chemist should also consider ‘green’ values and hence avoid metal-based catalysis when possible. Thus asymmetric organocatalysis is in high demand and the subject of rigorous study.1 A relatively recent addition to the library of organocatalysts is the family of thiourea-based bifunctional catalysts that combine a hydrogen bond-donor with a tertiary amine attached to a chiral scaffold. Thiourea-based bifunctional catalysis has indeed been extensively studied in recent years, with a great number of reports showing its applicability to a wide range of reactions.2,3 The stereochemical potential of Cinchona alkaloids has also been successfully exploited in the elaboration of thiourea-based organocatalysts.4 Other recently reported Cinchona-based H-bond donor catalysts include squaramide5 and sulfonamide derivatives.6

We recently developed a concise, enantioselective synthesis for (S)-pregabalin (Lyrica®).7 The key stereoselective Michael addition of Meldrum’s acid 1 to the nitroalkene precursor 2a was performed with a novel 9-amino-(9-deoxy)-epi-quinidine thiourea catalyst 3, which contains
the sterically bulky trityl group as a thiourea substituent, instead of the widely used 3,5-bis(trifluoromethyl)phenyl group. Moreover, the original *Cinchona*-derived catalyst 4, described independently and in rapid succession along with its close analogues by the groups of Chen, Sóos, Connon and Dixon, was found to be severely lacking in stereoinduction in the key step of the synthesis, in spite of complete conversion and a reasonable reaction time (eight hours in model studies). The Michael adduct 5a was attained using 3 with an enantiomeric excess of 75%, whereas 4 gave an ee of only 32% (Scheme 1). In this present study we set out to elaborate further the behavior of 3 in Michael addition reactions of Meldrum’s acid to nitroalkenes. We also attempted to probe the general reactivity of thiourea-type catalysts by perturbing the bicoordinating ability of the thiourea moiety.

![Scheme 1. The key step in the synthesis of (S)-Pregabalin.](image)

**Results and Discussion**

We began our study on the activity of 3 by performing solvent and substrate screening. The results for the solvent screen are shown in Table 1. There is little significant difference in enantioselectivity between CH2Cl2, Et2O and THF. MeCN gave a slightly lower selectivity,
whereas with DMF asymmetric induction was nearly completely suppressed. This is more or less expected for a solvent that is a good hydrogen bond acceptor, as it would conceivably compete for the donor sites on the catalyst. Chlorobenzene was found to give a slightly higher enantioselectivity, but the incomplete and slow solubility of Meldrum’s acid to chlorobenzene led us to complete the substrate screening using CH$_2$Cl$_2$.

**Table 1. Solvent screening for 3**

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>ee (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_2$Cl$_2$</td>
<td>10</td>
<td>&gt;95</td>
<td>72$^c$</td>
</tr>
<tr>
<td>2</td>
<td>Et$_2$O</td>
<td>21</td>
<td>&gt;95</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>18</td>
<td>&gt;95</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>17</td>
<td>&gt;95</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>PhCl</td>
<td>16</td>
<td>&gt;95</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>18</td>
<td>&gt;95</td>
<td>16</td>
</tr>
</tbody>
</table>

Reaction conditions: 100 mg (0.8 mmol) of nitroalkene, 200 mol% of Meldrum’s acid, 10 mol% of 3, 0.5 mL solvent, rt. $^a$ Determined by $^1$H NMR; $^b$ Determined by chiral HPLC of the anilide derivative 6a.$^9$ $^c$Result of model studies, actual synthesis of Ref. 7 gave 75% ee.

Meldrum’s acid functions as a protected enol equivalent of acetic acid. Easy deprotection and further functionalization makes it an interesting nucleophile.$^{10}$ However, examples of asymmetric reactions with Meldrum’s acid as a nucleophile are scarce, and furthermore the reports have not been encouraging, as was previously shown by Kleczkowska and Sas.$^{11}$ They reported poor enantioselectivities in the Michael addition of Meldrum’s acid to β-nitrostyrene 2b, when catalyzed by *Cinchona* alkaloids or other chiral amines such as (-)-sparteine or (-)-brucine. Takemoto also reported mediocre enantioselectivity for the well-known Takemoto’s catalyst in this reaction.$^{12}$ In a control experiment, we measured an ee of 31% when catalyst 4 was used.

For catalyst 3, we likewise found that the reaction between Meldrum’s acid and aromatic and heteroaromatic nitroalkenes uniformly gave mediocre enantioselectivities with no clear trends based on electronic properties of the aromatic ring, as shown in Table 2. Surprisingly, aliphatic substrates turned out to give slightly higher selectivities, though with ample room for further improvement. This seems to be a reversal of the common tendency of aliphatic nitroalkenes to give poorer stereoselectivity in thiourea-catalyzed nitro-Michael additions.$^{8c,d}$ Thus Meldrum’s
acid does not seem to function well with chiral bifunctional catalysts, and a different solution to establishing its use as a nucleophile in asymmetric synthesis awaits discovery (see Ref. 7 for a screening of different thiourea catalysts).

Table 2. Substrate screening for 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>( Ee ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph (2b)</td>
<td>8</td>
<td>&gt;95</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>4-MeOC₆H₄ (2c)</td>
<td>9</td>
<td>&gt;95</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>3-MeOC₆H₄ (2d)</td>
<td>12</td>
<td>&gt;95</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>4-BrC₆H₄ (2e)</td>
<td>17</td>
<td>&gt;95</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>3-BrC₆H₄ (2f)</td>
<td>8</td>
<td>&gt;95</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>2-furyl (2g)</td>
<td>9</td>
<td>&gt;95</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td>3-furyl (2h)</td>
<td>9</td>
<td>&gt;95</td>
<td>48</td>
</tr>
<tr>
<td>8</td>
<td>Cy (2i)</td>
<td>49</td>
<td>91</td>
<td>59</td>
</tr>
<tr>
<td>9</td>
<td>( n )-C₅H₁₁ (2j)</td>
<td>19</td>
<td>&gt;95</td>
<td>68</td>
</tr>
<tr>
<td>10</td>
<td>BnOCH₂ (2k)</td>
<td>7</td>
<td>&gt;95</td>
<td>62</td>
</tr>
</tbody>
</table>

Reaction conditions: 0.8 mmol nitroalkene, 1.6 mmol of Meldrum’s acid, 10 mol% of 1, 0.5 mL CH₂Cl₂, rt. \(^{a}\) Determined by \(^1\)H NMR; \(^b\) Determined by chiral HPLC of the anilide derivatives 6b-k.

However, the real surprise was the complete inactivity of 3 in the reaction between dimethyl malonate (7) and \( \beta \)-nitrostyrene. After 48 hours, racemic 8 was isolated in 14% yield, presumably the result of a slow background reaction (Scheme 2). With acetylacetone 9 as the nucleophile, a comparable reaction gave 10 in 45% yield with an \( ee \) slightly below 50%. For comparison, when catalyzed by 4 the reaction gave complete conversion in eight hours and an \( ee \) of 85%.
Scheme 2. Activity of 3 with common 1,3-dicarbonyl nucleophiles.

Before addressing the question of this inactivity, the mechanism of bifunctional thiourea catalysts should be discussed briefly. The widely accepted qualitative rationalization presented e.g. by Takemoto et al. assumes the electrophile to be activated via H-bond assisted coordination of the nitro group to the thiourea (Scheme 3).\textsuperscript{12b} The protonated tertiary amine then directs the nucleophile to attack from the less hindered face. In a theoretical study, Pápai and Sóos showed\textsuperscript{13} that while calculations do support this, and also explain the preferred stereochemistry of the product, an opposite coordination scheme is not only possible, but in fact energetically slightly more favorable.

Scheme 3. Possible coordination schemes of the catalyst-nucleophile-electrophile ternary complex according to Takemoto (left), Soós (middle), and nucleophile deprotonation (right).

Takemoto\textsuperscript{11b} and Jacobsen\textsuperscript{14} have also recently published X-ray structures of their respective thiourea catalysts. In both cases the thiourea N–H protons are found in a \textit{trans}-conformation with respect to the sulfur atom across the N–C\textsubscript{sp2} bond. Conversely, in our earlier study the thiourea moiety was found to be in \textit{trans/cis}-form for a phenylfluorenyl-substituted \textit{Cinchona}-thiourea catalyst.\textsuperscript{7} A general survey of published thiourea crystal structures revealed that the \textit{trans/cis} form is by far preferred in solid state, with less than 20% of published compounds showing
trans/trans-conformation.\textsuperscript{15} Though solid state structures obviously do not directly correlate with solvated structures, it is possible that the additional demand of energy for finding the optimal conformation would pose problems for catalysts with substituents that force the thiourea moiety to retain its trans/cis-conformation.

The unusually high acidity of Meldrum’s acid (p\textit{K}_a 4.97 in H\textsubscript{2}O, 7.32 in DMSO)\textsuperscript{16} shows that it can be deprotonated by an amine alone, as shown by the use of e.g. (-)-sparteine as a chiral base in the Michael addition (see above). The tertiary amine (p\textit{K}_a 11/9.8 in H\textsubscript{2}O/DMSO) of the Cinchona-type thiourea catalysts might not be basic enough for the deprotonation of less acidic nucleophiles. Coordination to the thiourea H-bond donor sites is required to acidify the \(\alpha\)-proton sufficiently for deprotonation to take place. In the case of 3, either insufficient acidity of the thiourea N-H protons and thus their poorer ability to act as H-bond donors, or steric clashes from the bulky trityl substituent could account for the inactivity of the catalyst with regard to dimethyl malonate.

To investigate this, the ‘Southern’ substituent of the thiourea moiety was changed from trityl to cyclohexyl to give catalyst 11, which (like 3) has a significantly less acidic thiourea moiety than 4, and is sterically less demanding than 3. Catalyzed by 11, the reaction of dimethyl malonate and nitrostyrene gave 8 in 73\% yield after 24 hours, with an \textit{ee} of 73\% (Scheme 4). Thus it seems that neither the acidity of thiourea N–Hs nor of the dimethyl malonate \(\alpha\)-proton is a main factor for the inactivity of 3.

\[
\begin{align*}
2b & \quad + \quad \begin{array}{c} \text{MeO} \quad \text{O} \\ \text{O} \quad \text{OMe} \end{array} \quad \text{11 (10 mol\%)} \quad \text{CH\textsubscript{2}Cl\textsubscript{2}, rt, 24 h} \quad 8 & \quad \text{73\%, ee 73}\% \\
& \quad \text{11}
\end{align*}
\]

\textbf{Scheme 4.} Reaction of dimethyl malonate and nitrostyrene catalyzed by 11.

The general mechanistic assumptions of bifunctional thiourea catalysts are based on the 1,3-dicarbonyl nucleophile deprotonation taking place on the more acidic enol form. There are practically no reports on the enolization constants of malonate diesters, and they are usually found to contain no enol form in solution (an NMR evaluation in CD\textsubscript{2}Cl\textsubscript{2} confirmed this). Hence the tentative conclusion is that the steric bulk of the trityl group disrupts crucial H-bond
coordination and α proton acidification between dimethyl malonate and 3, thus strongly suppressing the deprotonation step. On the other hand, acetylacetone is normally enolized to a considerable extent, especially in nonpolar solvents, stabilized by the formation of an intramolecular H-bond. This, together with the difference of several pK\text{a} units in the respective acidities of acetylacetone and dimethyl malonate α protons (9/13.3 vs. 13/15.9 H\text{2}O/DMSO) makes the former significantly easier to deprotonate, which most likely accounts for the difference in activities.

A recent report suggested that the bicoordinating ability of the H-bond donor site is not completely essential; according to a study by Lu, the sulfonamide analogues of Cinchona-derived thiourea catalysts are quite able to catalyze the Michael reaction of β-ketoesters and nitroalkenes. We set out to test how the perturbation of the bicoordinating ability of the thiourea affects the activity of the catalyst. Based on the results of Lu, our tentative hypothesis was that perhaps one site would be enough, and this site should be closer to the Cinchona backbone to allow for interaction with the tertiary amine. This was examined by modifying the structure of 4 in order to prepare derivatives 12 and 13, in which both H-bond donors of the thiourea group are in turn substituted with methyl groups.

The catalysts were prepared by condensation of the corresponding isothiocyanate and methylated amine (Scheme 5). The free amine 14 was prepared according to a slightly modified method of Brunner. The methylated catalyst 12 was prepared by first forming the corresponding ethyl carbamate 15 from 14. The carbamate was subjected to LiAlH\text{4} reduction to attain the amine 16, which was subsequently condensed with 3,5-bis(trifluoromethyl)phenyl isothiocyanate. Catalyst 13 was prepared via reversing the original route. The free amine 14 was converted into the corresponding isothiocyanate 17 in good yield. The methylated aniline 18 was easily prepared from the commercially available 3,5-bis(trifluoromethyl)aniline via trifluoroacetylation, methylation and hydrolysis, giving a practically pure product in excellent yield. The condensation step was found to be somewhat problematic, since 18 is an extremely electron-poor nucleophile. Catalyst 13 was obtained by deprotonating 18 with n-BuLi at −78 °C and then adding the isothiocyanate dissolved in DMF.
We found that, for both compounds 12 and 13, the catalytic activity was strongly diminished. After 48 hours the product was isolated in 36% and 45% yields, respectively, with practically no asymmetric induction. Hence this would seem to confirm that the bicoordinating ability is crucial for the functioning of thiourea-based catalysts (Scheme 6).

Scheme 5. Synthesis of thiourea-N-methylated catalysts. Reagents and conditions: i) EtOCOCl, Et$_3$N, CH$_2$Cl$_2$, rt (53%) ii) LiAlH$_4$, THF, 0 °C to rt (51%). iii) 3,5-bis(trifluoromethyl)phenyl isothiocyanate, THF, rt (71%). iv) CS$_2$, DCC, THF, –15 °C to rt (74%). v) n-BuLi, 18, THF, DMF, –78 °C to rt (49%). vi) TFAA, CH$_2$Cl$_2$, 0 °C to rt. vii) MeI, acetone, rfx. viii) MeOH:H$_2$O (5:1), K$_2$CO$_3$, rt (90% over 3 steps).

There are other reports probing the activity of bifunctional thiourea catalysts by adding, blocking or removing additional hydrogen bond donor sites. Wang reported that catalyst activity in nitro-Michael addition is significantly boosted by addition of H-bond donor sites (19, 20), giving improved yields and enantioselectivities. Conversely, the enantioselectivity is significantly eroded when the additional coordination sites around the thiourea moiety are blocked or removed. In another study, Liang and Ye tested a hybrid Cinchona-thiourea catalyst 21 in which chiral 1,2-diaminocyclohexane was used as the other thiourea substituent, thus incorporating an additional primary amine in the catalyst structure. The catalyst was found to be effective in Michael addition of diethyl malonate to both cyclic and open chain enones. Dimethylation of the free amino group completely suppressed the catalytic activity, but the authors did not further address the mechanistic questions this raises.

Scheme 7. Catalysts with additional H-bond donor sites.

Conclusions

Chiral bifunctional thiourea organocatalysts are a new and effective way to conduct asymmetric C–C-bond formation. Among the several promising examples are Cinchona-alkaloid derived thiourea catalysts that have been found to be effective in a wide range of reactions. In this study we have elaborated the activity of a novel trityl-substituted 9-amino-(9-deoxy)epi-quinidine thiourea catalyst and the properties of Meldrum’s acid as a nucleophile in asymmetric Michael addition. Furthermore, we have probed the functionality of Cinchona-derived thiourea catalysts in general by preparing and testing N-methylated thiourea analogues. Blocking the thiourea N–H-sites with methyl groups led to severe lack of catalytic activity in the Michael-addition of dimethyl malonate to β-nitrostyrene, thus underlining the importance of the bicoordinating H-bond donor functionality for bifunctional thiourea-tertiary amine catalysts.
Experimental Section

General. Reagents were used as purchased from suppliers, unless otherwise indicated. Dry solvents (CH₂Cl₂, THF, Et₂O, MeCN) were obtained with MBraun MB-SPS 800 solvent drying system. Chlorobenzene was distilled from P₂O₅ on 4 Å molecular sieves. Reactions requiring inert conditions were performed in flame-dried glassware under a positive pressure of argon. The nitroalkenes were synthesized from corresponding aldehyde and nitromethane by Henry reactions (2b-c, 2f-k), followed by elimination in case of aliphatic substrates, or by Knoevenagel condensation (2d-e). Compounds 3, 4, 5a, 6a, 14 and 17 were synthesized according to published methods⁷,⁸ and spectral data was found to correspond with literature. Spectral data for 5b and 5c,²² 8,²³ and 10²⁴ was found to correspond with literature data. Reactions were monitored by thin layer chromatography using SiO₂ (silica gel 60 F₂₅₄, Merck, coated aluminum plates), and visualizing by UV light or by aqueous KMnO₄ or ninhydrin solutions. Flash chromatography was carried out on SiO₂ (silica gel 60 F₂₅₄, 230-400 mesh ASTM, Merck). ¹H and ¹³C NMR spectra were recorded with a Bruker Avance 400 (¹H: 399.98 MHz; ¹³C: 100.59 MHz) spectrometer. Chemical shifts are reported in ppm relative to TMS internal standard (δ = 0.00) in CDCl₃, or residual solvent signal in MeOD-d₄ (δ = 3.31) for ¹H NMR spectra. For ¹³C NMR spectra, solvent residual peaks (δ = 77.0 ppm for CDCl₃, δ = 49.0 ppm for MeOD-d₄) were used as internal standards. Abbreviation of multiplicities is as follows: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet). The prefix br is used when the signal is broadened, and app when the signal resolution is not good enough to determine the true multiplicity (e.g. dd becomes t). High-resolution mass spectrometric data was recorded with Waters LCT Premier-spectrometer at Helsinki University of Technology. IR spectra were recorded with Perkin-Elmer Spectrum One FTIR instrument. Optical rotations were obtained with a Perkin-Elmer 343 polarimeter (λ = 589 nm) using a 1 dm cell. Chiral HPLC analysis was performed with Waters 501 pump and Waters UV 2487 dual absorbance detector. The exact conditions are reported in connection with each analyzed substance. HPLC analyses were performed before crystallization steps to exclude possible additional enantioreichment. Elemental analyses were performed with Perkin-Elmer (PE) 2400 Series II CHNS/O Analyzer. Melting points were recorded with Stuart SMP3 melting point apparatus in open capillary tubes.

General procedure for screening reactions
Nitroalkene (0.8 mmol, 100 mol%) was loaded in a small vial equipped with a magnetic stirrer. Compound 1 (230 mg, 1.6 mmol, 200 mol%) was added, and the mixture was dissolved in CH₂Cl₂ (0.5 mL). Catalyst 3 (50 mg, 0.08 mmol, 10 mol%) was added, the vial was capped and the mixture was stirred at room temperature until completion. The solvents were evaporated and the crude mixture analyzed by ¹H NMR and used as such in the derivatization step.

5-(1-(3-Methoxyphenyl)-2-nitroethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione  (5d). Prepared according to the general procedure. Purification of a small sample for analytical purposes by
flash chromatography (10% MeOH in EtOAc) gave 5d as a yellowish oil. Rf = 0.21 (EtOAc); IR (neat): 2997, 2941, 1734, 1572, 1435, 1375, 1261 cm⁻¹; ¹H NMR (MeOD-d₄, 400 MHz): NB! Dicarbonyl α proton not visible. Compounds 5b-k are completely enolized in MeOD-d₄. δ 7.12 (t, J = 7.9 Hz, 1H), 7.03 (s, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.69 (dd, J = 8.1, 2.0 Hz, 1H), 5.21 (dd, J = 12.0, 8.7 Hz, 1H), 5.07 (dd, J = 11.9, 7.5 Hz, 1H), 4.74 (t, J = 8.1 Hz, 1H), 3.74 (s, 3H), 1.54 (s, 6H); ¹³C NMR (MeOD-d₄, 100 MHz): δ 169.2, 160.9, 145.3, 129.9, 121.2, 114.4, 112.8, 102.8, 79.2, 76.5, 55.5, 41.3, 25.8; HRMS m/z 346.0906 [C₁₅H₁₇NO₇ (M+Na)⁺ requires 346.0903].

5-(1-(4-Bromophenyl)-2-nitroethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (5e). Prepared according to the general procedure. Purification of a small sample for analytical purposes by flash chromatography (10% MeOH in EtOAc) gave 5e as a yellow oil. Rf = IR (neat): 2997, 2941, 1734, 1572, 1435, 1375, 1261 cm⁻¹; ¹H NMR (MeOD-d₄, 400 MHz): NB! Dicarbonyl α proton not visible. Compounds 5b-k are completely enolized in MeOD-d₄. δ 7.12 (t, J = 7.9 Hz, 1H), 7.03 (s, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.69 (dd, J = 8.1, 2.0 Hz, 1H), 5.21 (dd, J = 12.0, 8.7 Hz, 1H), 5.07 (dd, J = 11.9, 7.5 Hz, 1H), 4.74 (t, J = 8.1 Hz, 1H), 3.74 (s, 3H), 1.54 (s, 6H); ¹³C NMR (MeOD-d₄, 100 MHz): δ 169.2, 160.9, 145.3, 129.9, 121.2, 114.4, 112.8, 102.8, 79.2, 76.5, 55.5, 41.3, 25.8; HRMS m/z 415.9742/417.9731 [C₁₄H₁₄BrNO₆ (M-H+2Na)⁺ requires 415.9722/417.9702].

5-(1-(3-Bromophenyl)-2-nitroethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (5f). Prepared according to the general procedure. Purification of a small sample for analytical purposes by flash chromatography (10% MeOH in EtOAc) gave 5f as a yellow oil. Rf = IR (neat): 2997, 2941, 1734, 1572, 1435, 1375, 1261 cm⁻¹; ¹H NMR (MeOD-d₄, 400 MHz): NB! Dicarbonyl α proton not visible. Compounds 5b-k are completely enolized in MeOD-d₄. δ 7.12 (t, J = 7.9 Hz, 1H), 7.03 (s, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.69 (dd, J = 8.1, 2.0 Hz, 1H), 5.21 (dd, J = 12.0, 8.7 Hz, 1H), 5.07 (dd, J = 11.9, 7.5 Hz, 1H), 4.74 (t, J = 8.1 Hz, 1H), 3.74 (s, 3H), 1.54 (s, 6H); ¹³C NMR (MeOD-d₄, 100 MHz): δ 169.2, 160.9, 145.3, 129.9, 121.2, 114.4, 112.8, 102.8, 79.2, 76.5, 55.5, 41.3, 25.8; HRMS m/z 415.9742/417.9731 [C₁₄H₁₄BrNO₆ (M-H+2Na)⁺ requires 415.9722/417.9702].
Compounds 5b-k are completely enolized in MeOD-d₄. δ 7.32 (m, 2H), 6.46 (s, 1H), 5.05 (dd, J = 11.6, 8.7 Hz, 1H), 4.94 (dd, J = 11.6, 7.6 Hz, 1H), 4.66 (t, J = 8.1 Hz, 1H), 1.55 (s, 6H); 13C NMR (MeOD-d₄, 100 MHz): δ 169.0, 161.2, 143.3, 140.5, 126.9, 111.7, 102.8, 79.1, 75.6, 33.0, 25.8; HRMS m/z 306.0601 [C₁₂H₁₃NO₇ (M+Na)+ requires 306.0590].

5-(1-Cyclohexyl-2-nitroethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (5i). Prepared according to the general procedure. Purification of a small sample for analytical purposes by flash chromatography (10% MeOH in EtOAc) gave 5i as a clear oil. Rf = 0.13 (50% EtOAc in hexane); IR (neat): 2994, 2926, 2852, 1731, 1575, 1406, 1373, 1260 cm⁻¹; ¹H NMR (MeOD-d₄, 400 MHz): δ 4.90 (app. t, J = 10.8 Hz, 1H), 4.62 (dd, J = 10.8, 5.0 Hz, 1H), 3.25-3.17 (m, 1H), 1.84-1.66 (m, 5H), 1.65-1.60 (m, 1H), 1.55 (s, 6H), 1.31-1.10 (m, 3H), 1.10-0.90 (m, 2H); 13C NMR (MeOD-d₄, 100 MHz): δ 169.5, 102.6, 78.2, 74.0, 42.6, 39.9, 32.1, 27.6, 27.6, 27.5, 25.9; HRMS m/z 322.1254 [C₁₄H₂₁NO₆ (M+Na)+ requires 322.1266].

2,2-Dimethyl-5-(1-nitrohexan-2-yl)-1,3-dioxane-4,6-dione (5j). Prepared according to the general procedure. Purification of a small sample for analytical purposes by flash chromatography (10% MeOH in EtOAc) gave 5j as a clear oil. Rf = 0.13 (50% EtOAc in hexane); IR (neat): 2956, 2930, 2863, 1782, 1741, 1718, 1553, 1383, 1206 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 4.98 (dd, J = 13.3, 10.2 Hz, 1H), 4.57 (dd, J = 13.4, 4.4 Hz, 1H), 3.89 (d, 2.4 Hz, 1H), 3.31-3.22 (m, 1H), 1.81 (s, 3H), 1.79 (s, 3H), 1.64-1.53 (m, 1H), 1.51-1.41 (m, 1H), 1.40-1.27 (m, 4H), 0.94-0.87 (m, 3H); 13C NMR (CDCl₃, 100 MHz): δ 164.0, 105.5, 75.8, 46.9, 36.4, 29.5, 29.0, 28.2, 26.9, 22.4, 13.8; HRMS m/z 296.1106 [C₁₂H₁₉NO₆ (M+Na)+ requires 296.1110].

5-(1-(Benzyloxy)-3-nitropropan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (5k). Prepared according to the general procedure. Purification of a small sample for analytical purposes by flash chromatography (10% MeOH in EtOAc) gave 5k as a yellowish oil. Rf = IR (neat): 2865, 1709, 1579, 1551, 1412, 1376, 1260 cm⁻¹; ¹H NMR (MeOD-d₄, 400 MHz): δ 7.35-7.21 (m, 5H), 4.93 (dd, J = 11.3, 9.2 Hz, 1H), 4.74 (dd, J = 11.3, 5.5 Hz, 1H), 4.50 (q, J = 11.6 Hz, 2H), 3.91-3.76 (m, 2H, overlapping signals), 3.55 (dd, J = 9.1, 4.8 Hz, 1H), 1.55 (s, 6H); 13C NMR (MeOD-d₄, 100 MHz): δ 169.3, 139.9, 129.3, 128.8, 128.5, 102.9, 77.4, 73.7, 72.5, 71.5, 37.1, 25.7; HRMS m/z 360.1064 [C₁₀H₁₉NO₇ (M+Na)+ requires 360.1059].

General procedure for derivatization

The crude product (100 mg) was loaded in a 5 mL flask and dissolved in dry DMF (2.5 mL). Distilled aniline (0.25 mL) was added and the mixture was heated to 100 °C for 3 hours. The mixture was partitioned between 10 mL EtOAc and 10 mL 1 M HCl, and washed further 3 times with 1 M HCl (à 10 mL). The organic phase was dried over MgSO₄, filtered and evaporated. The residue was purified by flash chromatography (EtOAc in hexane)
4-Nitro-N,3-diphenylbutanamide (6b). Prepared according to the general procedure, purified by flash chromatography (50% EtOAc in hexane) and crystallized from EtOAc:hexane to give 6b as white crystals (10 mg): R_f = 0.45 (50% EtOAc in hexane); mp 107-109 °C; IR (neat): 3302, 3138, 3063, 3032, 1661, 1599, 1551, 1498, 1443 cm^{-1}; 1H NMR (CDCl_3, 400 MHz): δ 7.40-7.23 (m, 9H), 7.15-7.06 (m, 2H), 4.85 (dd, J = 12.6, 6.4 Hz, 1H), 4.73 (dd, J = 12.6, 7.9 Hz, 1H), 4.07 (app d, J = 7.1 Hz, 1H), 2.83 (dd, J = 15.0, 7.3 Hz, 1H), 2.75 (dd, J = 15.0, 7.1 Hz, 1H); 13C NMR (CDCl_3, 100 MHz): δ 167.9, 138.4, 137.2, 129.2, 129.0, 128.1, 127.9, 127.3, 124.7, 120.1, 79.3, 40.7, 40.6; HPLC: Chiralcel OD column (0.46 cm × 25 cm), 25% i-PrOH in hexane, 1.0 mL/min, λ = 254 nm, t_R(major) 17.9 min, t_R(minor) 23.8 min; Anal. Calcd. for C_{16}H_{16}N_2O_3: C, 67.59; H, 5.67; N, 9.85% Found: C, 67.50; H, 5.74; N, 9.85%

3-(4-Methoxyphenyl)-4-nitro-N-phenylbutanamide (6c). Prepared according to the general procedure. Purified by flash chromatography (50% EtOAc in hexane) and crystallized from EtOAc:hexane to give 6c as white crystals (12 mg). R_f = 0.38 (50% EtOAc in hexane); mp 97-99 °C; IR (neat): 3309, 3199, 3138, 3061, 3038, 2969, 2837, 1664, 1600, 1551, 1514, 1499, 1443, 1379, 1303, 1251 cm^{-1}; 1H NMR (CDCl_3, 400 MHz): δ 7.37 (d, J = 7.6 Hz, 2H), 7.28 (t, J = 7.9 Hz, 2H), 7.19 (br s, 1H), 7.16 (d, J = 8.5 Hz, 2H), 7.10 (t, J = 7.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 4.80 (dd, J = 12.5, 6.5 Hz, 1H), 4.67 (dd, J = 12.5, 7.9 Hz, 1H), 4.06-3.97 (m, 1H), 3.77 (s, 3H), 2.79 (dd, J = 15.0, 7.2 Hz, 1H), 2.71 (dd, J = 15.0, 7.2 Hz, 1H); 13C NMR (CDCl_3, 100 MHz): δ 168.0, 159.2, 137.2, 130.2, 129.0, 124.7, 120.1, 114.5, 79.6, 55.2, 40.8, 39.9; HPLC: Chiralcel OD column (0.46 cm × 25 cm), 25% i-PrOH in hexane, 1.0 mL/min, λ = 254 nm, t_R(major) 26.1 min, t_R(minor) 46.7 min; Anal. Calcd. for C_{17}H_{18}N_2O_4: C, 64.96; H, 5.77; N, 8.91% Found: C, 64.81; H, 5.63; N, 8.86%

3-(3-Methoxyphenyl)-4-nitro-N-phenylbutanamide (6d). Prepared according to the general procedure. Purified by flash chromatography (50% EtOAc in hexane) and crystallized from EtOAc:hexane to give 6d as white crystals (16 mg). R_f = 0.39 (50% EtOAc in hexane); mp 101-103 °C; IR (neat): 3303, 3139, 3059, 2919, 2837, 1661, 1600, 1551, 1498, 1443, 1378, 1303, 1251 cm^{-1}; 1H NMR (CDCl_3, 400 MHz): δ 7.41-7.34 (m, 2H), 7.32-7.23 (m, 3H), 7.14-7.07 (m, 2H), 6.86-6.76 (m, 3H), 4.84 (dd, J = 12.6, 6.4 Hz, 1H), 4.72 (dd, J = 12.6, 7.9 Hz, 1H), 4.09-4.00 (m, 1H), 3.77 (s, 3H), 2.81 (dd, J = 15.1, 7.2 Hz, 1H), 2.75 (dd, J = 15.0, 7.0 Hz); 13C NMR (CDCl_3, 100 MHz): δ 167.8, 160.1, 140.0, 137.2, 130.3, 129.0, 124.7, 120.0, 119.4, 113.5, 113.2, 79.2, 55.2, 40.7, 40.6; HPLC: Chiralcel OD column (0.46 cm × 25 cm), 25% i-PrOH in hexane, 1.0 mL/min, λ = 254 nm, t_R(major) 16.6 min, t_R(minor) 21.3 min; Anal. Calcd. for C_{17}H_{18}N_2O_4: C, 64.96; H, 5.77; N, 8.91% Found: C, 64.80; H, 5.50; N, 8.88%

3-(4-Bromophenyl)-4-nitro-N-phenylbutanamide (6e). Prepared according to the general procedure. Purified by flash chromatography (40% EtOAc in hexane) and crystallized from EtOH:H_2O to give 6e as white crystals (10 mg). R_f = 0.42 (50% EtOAc in hexane); mp 127-130 °C; IR (neat): 3302, 3139, 3062, 2918, 1662, 1599, 1551, 1498, 1443, 1377 cm^{-1}; 1H NMR (CDCl_3, 400 MHz): δ 7.47 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 7.7 Hz, 2H), 7.31 (t, J = 7.9 Hz, 2H), 7.18-7.08 (m, 4H), 4.84 (dd, J = 12.8, 6.3 Hz, 1H), 4.71 (dd, J = 12.8, 8.0 Hz, 1H), 4.11-4.01 (m, 1H), 2.82 (dd, J = 15.3, 7.3 Hz, 1H), 2.73 (dd, J = 15.3, 6.9 Hz, 1H); 13C NMR (CDCl_3, 100
MHz): $\delta$ 167.5, 137.5, 137.1, 132.3, 129.1, 124.9, 122.1, 120.1, 79.0, 40.3, 39.9; HPLC: Chiralcel OD column (0.46 cm $\times$ 25 cm), 25% $i$-PrOH in hexane, 1.0 mL/min, $\lambda$ = 254 nm, $t_R$(major) 14.5 min, $t_R$(minor) 17.7 min; Anal. Calcd. for C$_{16}$H$_{15}$BrN$_2$O$_3$: C, 52.91; H, 4.16; N, 7.71% Found: C, 52.93; H, 3.84; N, 7.55%

3-(3-Bromophenyl)-4-nitro-N-phenylbutanamide (6f). Prepared according to the general procedure. Purified by flash chromatography (40% EtOAc in hexane) and crystallized from EtOAc:hexane to give 6f as white crystals (13 mg). $R_f$ = 0.45 (50% EtOAc in hexane); mp 110-111 °C; IR (neat): 3302, 3199, 3139, 3061, 2918, 1661, 1598, 1551, 1498, 1443, 1376 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.45-7.36 (m, 4H), 7.30 (t, $J$ = 7.9 Hz, 2H), 7.24-7.16 (m, 3H), 7.12 (t, $J$ = 7.3 Hz, 1H), 4.84 (dd, $J$ = 12.8, 6.3 Hz, 1H), 4.71 (dd, $J$ = 12.8, 8.0 Hz, 1H), 4.10-4.01 (m, 1H), 2.81 (dd, $J$ = 15.4, 7.5 Hz, 1H), 2.73 (dd, $J$ = 15.4, 6.9 Hz, 1H); 13C NMR (CDCl$_3$, 100 MHz): $\delta$ 167.5, 137.1, 131.3, 130.7, 130.4, 129.1, 126.2, 124.9, 123.1, 120.1, 78.9, 40.2, 40.0; HPLC: Chiralcel OD column (0.46 cm $\times$ 25 cm), 25% $i$-PrOH in hexane, 1.0 mL/min, $\lambda$ = 254 nm, $t_R$(major) 16.3 min, $t_R$(minor) 18.8 min; Anal. Calcd. for C$_{16}$H$_{15}$BrN$_2$O$_3$: C, 52.91; H, 4.16; N, 7.71% Found: C, 52.99; H, 3.82; N, 7.71%

3-(Furan-2-yl)-4-nitro-N-phenylbutanamide (6g). Prepared according to the general procedure. Purified by flash chromatography (40% EtOAc in hexane) and crystallized from EtOAc:hexane to give 6g as white crystals (10 mg). $R_f$ = 0.48 (50% EtOAc in hexane); mp 111-124 °C; IR (neat): 3304, 3141, 2918, 1662, 1600, 1552, 1499, 1444, 1376 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.43 (d, $J$ = 8.1 Hz, 2H), 7.37 (d, $J$ = 1.1 Hz, 1H), 7.31 (t, $J$ = 7.9 Hz, 2H), 7.22 (br. s, 1H), 7.12 (t, $J$ = 7.3 Hz, 1H), 6.31 (dd, $J$ = 3.1, 1.8 Hz, 1H), 6.21 (d, $J$ = 3.3 Hz, 1H), 4.84 (dd, $J$ = 12.6, 5.9 Hz, 1H), 4.76 (dd, $J$ = 12.6, 7.1 Hz, 1H), 4.23-4.15 (m, 1H), 2.87 (dd, $J$ = 15.0, 6.6 Hz, 1H), 2.82 (dd, $J$ = 15.1, 7.4 Hz, 1H), 13C NMR (CDCl$_3$, 100 MHz): $\delta$ 167.6, 151.3, 142.5, 137.2, 129.1, 124.8, 120.1, 110.6, 107.5, 77.1, 38.1, 34.5; HPLC: Chiralcel OD column (0.46 cm $\times$ 25 cm), 25% $i$-PrOH in hexane, 1.0 mL/min, $\lambda$ = 254 nm, $t_R$(major) 12.0 min, $t_R$(minor) 15.1 min; Anal. Calcd. for C$_{14}$H$_{14}$N$_2$O$_4$: C, 61.31; H, 5.14; N, 10.21% Found: C, 61.26; H, 4.98; N, 10.16%

3-(Furan-3-yl)-4-nitro-N-phenylbutanamide (6h). Prepared according to the general procedure. Purified by flash chromatography (40% EtOAc in hexane) and crystallized from EtOAc:hexane to give 6h as white crystals (10 mg). $R_f$ = 0.42 (50% EtOAc in hexane); mp 101-107 °C; IR (neat): 3304, 3136, 2918, 1664, 1599, 1551, 1499, 1443, 1377 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.44 (d, $J$ = 7.7 Hz, 2H), 7.40 (t, $J$ = 1.6 Hz, 1H), 7.37 (br s, 1H), 7.32 (app t, $J$ = 7.9 Hz, 2H), 7.19 (br s, 1H), 7.12 (app t, $J$ = 7.4 Hz, 1H), 6.34 (br s, 1H), 4.80 (dd, $J$ = 12.5, 6.0 Hz, 1H), 4.67 (dd, $J$ = 12.5, 7.3 Hz, 1H), 4.02 (app d, $J$ = 6.8 Hz, 1H), 2.79 (dd, $J$ = 15.2, 7.3 Hz, 1H), 2.72 (dd, $J$ = 15.1, 6.7 Hz, 1H), 13C NMR (CDCl$_3$, 100 MHz): $\delta$ 167.8, 143.9, 139.8, 137.2, 129.1, 124.8, 122.7, 120.0, 108.8, 78.8, 40.1, 31.8; HPLC: Chiralcel OD column (0.46 cm $\times$ 25 cm), 25% $i$-PrOH in hexane, 1.0 mL/min, $\lambda$ = 254 nm, $t_R$(major) 13.0 min, $t_R$(minor) 16.0 min; Anal. Calcd. for C$_{14}$H$_{14}$N$_2$O$_4$: C, 61.31; H, 5.14; N, 10.21% Found: C, 61.07; H, 5.10; N, 10.18%
3-Cyclohexyl-4-nitro-\(N\)-phenylbutanamide (6i). Prepared according to the general procedure. Purified by CombiFlash (0 to 15% EtOAc in hexane) to give 6i as a yellow oil in quite poor yield. \(R_f = 0.61\) (50% EtOAc in hexane); IR (neat): 3302, 3139, 3061, 2958, 2931, 2861, 1661, 1600, 1548, 1499, 1443, 1380 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.50 (d, \(J = 7.7\) Hz, 2H), 7.33 (t, \(J = 7.9\) Hz, 2H), 7.28-7.23 (br. s, 1H), 4.62 (dd, \(J = 12.4, 6.3\) Hz, 1H), 4.53 (dd, \(J = 12.3, 5.1\) Hz, 1H), 2.65-2.56 (m, 2H), 2.43 (dd, \(J = 16.5, 9.5\) Hz, 1H), 1.85-1.73 (m, 4H), 1.72-1.65 (m, 1H), 1.55-1.46 (m, 1H), 1.32-1.19 (m, 2H), 1.19-1.10 (m, 1H), 1.09-0.96 (m, 2H); 13C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 169.2, 137.5, 129.1, 124.6, 119.9, 76.8, 40.0, 38.9, 36.5, 30.3, 29.9, 26.2, 26.2; HPLC: Chiralcel OD column (0.46 cm \(\times\) 25 cm), 10% \(i\)-PrOH in hexane, 0.7 mL/min, \(\lambda = 254\) nm, \(t_R\) (major) 22.9 min, \(t_R\) (minor) 26.8 min; HRMS \(m/z\) 313.1540 [C\(_{16}\)H\(_{22}\)N\(_2\)O\(_3\) (M+Na)\(^+\) requires 313.1528].

3-(Nitromethyl)-\(N\)-phenylheptanamide (6j). Prepared according to the general procedure. Purified by CombiFlash (0 to 15% EtOAc in hexane) and crystallized from EtOAc:hexane to give 6j as white crystals (9 mg). \(R_f = 0.59\) (50% EtOAc in hexane); mp 75-76 °C; IR (neat): 3307, 3200, 3139, 3061, 2926, 2854, 1711, 1661, 1600, 1549, 1499, 1443, 1379 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.51 (d, \(J = 7.7\) Hz, 2H), 7.36-7.28 (m, 3H), 7.13 (t, \(J = 7.4\) Hz, 1H), 4.60 (dd, \(J = 12.1, 5.9\) Hz, 1H), 4.53 (dd, \(J = 12.0, 5.0\) Hz, 1H), 2.74-2.63 (m, 1H), 2.52 (dd, \(J = 15.2, 7.7\) Hz, 1H), 1.53-1.45 (m, 2H), 1.42-1.29 (m, 4H), 0.91 (t, \(J = 7.0\) Hz, 3H); 13C NMR (CDCl\(_3\), 100 MHz): partial, anilide quaternary C not seen, \(\delta\) 168.8, 129.1, 124.6, 119.9, 78.4, 39.1, 34.9, 31.1, 28.8, 22.5, 13.9; HPLC: Chiralcel OD column (0.46 cm \(\times\) 25 cm), 15% \(i\)-PrOH in hexane, 1.0 mL/min, \(\lambda = 254\) nm, \(t_R\) (major) 18.6 min, \(t_R\) (minor) 23.0 min; Anal. Calcd. for C\(_{14}\)H\(_{20}\)N\(_2\)O\(_3\): C, 63.62; H, 7.63; N, 10.60%; Found: C, 63.59; H, 8.06; N, 10.60%.

4-(Benzyloxy)-3-(nitromethyl)-\(N\)-phenylbutanamide (6k). Prepared according to the general procedure. Purified by flash chromatography (40% EtOAc in hexane) and crystallized from EtOAc:hexane to give 6k as white crystals (17 mg). \(R_f = 0.51\) (50% EtOAc in hexane); mp 82-85 °C; IR (neat): 3310, 3138, 3062, 3031, 2864, 1663, 1600, 1550, 1498, 1443, 1380 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.43 (d, \(J = 7.7\) Hz, 2H), 7.37-7.27 (m, 3H), 7.13 (t, \(J = 7.4\) Hz, 1H), 4.60 (dd, \(J = 12.1, 5.9\) Hz, 1H), 4.53 (dd, \(J = 12.0, 5.0\) Hz, 1H), 2.74-2.63 (m, 1H), 2.52 (dd, \(J = 15.2, 5.9\) Hz, 1H), 2.48 (dd, \(J = 15.2, 7.7\) Hz, 1H), 1.53-1.45 (m, 2H), 1.42-1.29 (m, 4H), 0.91 (t, \(J = 7.0\) Hz, 3H); \(^1\)C NMR (CDCl\(_3\), 100 MHz): partial, anilide quaternary C not seen, \(\delta\) 168.3, 137.5, 137.4, 129.0, 128.5, 128.0, 127.8, 124.6, 119.9, 76.3, 73.5, 69.4, 36.4, 35.3; HPLC: Chiralpak AS column (0.46 cm \(\times\) 25 cm), 10% \(i\)-PrOH in hexane, 1.0 mL/min, \(\lambda = 254\) nm, \(t_R\) (major) 86.3 min, \(t_R\) (minor) 23.0 min; Anal. Calcd. for C\(_{18}\)H\(_{20}\)N\(_2\)O\(_4\): C, 65.84; H, 6.14; N, 8.53%; Found: C, 65.79; H, 6.35; N, 8.53%.

1-Cyclohexyl-3-(((\(R\))-((6-methoxyquinolin-4-yl)((2\(R\),4\(S\),5\(R\))-5-vinylquinuclidin-2-yl)methyl)-thiourea (11). To a solution of 14 (180 mg, 0.56 mmol, 100 mol%) in dry THF (2 mL) was added freshly distilled cyclohexyl isothiocyanate (90 µL, 0.63 mmol, 110 mol%). Mixture was stirred under Ar overnight. Solvents were evaporated, and purification by flash chromatography (8% to 10% MeOH in CH\(_2\)Cl\(_2\)) gave 11 as white foam (124 mg, 48%). \(R_f = 0.30\) (10% MeOH in
CH₂Cl₂); [α]²⁰_D = +218.5 (c = 1.0, CHCl₃); IR (neat): 3247 (broad), 3067, 2933, 2856, 2669, 2212, 1622, 1589, 1542, 1509, 1474, 1452, 1364, 1337, 1321, 1227 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 8.75 (d, J = 4.6 Hz, 1H), 8.03 (d, J = 9.1 Hz, 1H), 7.63 (d, J = 1.8 Hz, 1H), 7.50-7.45 (br s, 1H), 7.45 (d, J = 4.6 Hz, 1H), 7.41 (dd, J = 9.2, 2.7 Hz, 1H), 5.89 (ddd, J = 17.2, 10.7, 6.3 Hz), 5.24-5.15 (m, 2H), 3.99 (s, 3H), 3.34-3.20 (m, 1H), 3.20-2.90 (m, 5H), 2.45-2.34 (m, 1H), 1.99-1.87 (m, 1H), 1.83-1.70 (m, 2H), 1.70-1.46 (m, 1H), 1.37-1.16 (m, 4H), 1.16-0.97 (m, 3H), 0.97-0.79 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 180.9, 158.1, 147.6, 144.8, 139.3, 131.8, 127.6, 122.4, 120.1, 115.4, 101.3, 61.1, 55.7, 53.3, 48.8, 46.8, 38.5, 34.5, 32.3, 27.1, 25.8, 25.3, 24.8, 24.3; HRMS m/z 487.2510 [C₂₇H₃₆N₄OS (M+H)⁺ requires 487.2508].

Ethyl (R)-(6-methoxyquinolin-4-yl)((2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl carbamate (15). To a solution of 14 (715 mg, 2.2 mmol, 100 mol%) in dry THF (10 mL) was added Et₃N (330 µL, 2.4 mmol, 110 mol%), followed by slow addition of ethyl chloroformate (230 µL, 2.4 mmol, 110 mol%). The mixture was stirred at room temperature under Ar for 2 hours. The solvent was partly evaporated, and the mixture was partitioned between H₂O (30 mL) and Et₂O (30 mL). The aqueous phase was washed with Et₂O (3 × 20 mL). The organic phases were combined and washed with brine, then dried over MgSO₄, filtered and evaporated. Purification by flash chromatography gave 16 as a white foam (463 mg, 53%). R_f = 0.23 (10% MeOH in CH₂Cl₂); [α]²⁰_D = +176.6 (c = 1.0, CHCl₃); IR (neat): 3185, 3075, 2936, 2870, 1709, 1622, 1590, 1508, 1474, 1433, 1365, 1298, 1252, 1227 cm⁻¹; ¹H NMR (C₂D₂Cl₄, 400 MHz, 85°C): δ 8.74 (d, J = 4.6 Hz, 1H), 8.06 (d, J = 9.3 Hz, 1H), 7.62 (d, J = 2.7 Hz, 1H), 7.41 (dd, J = 11.9, 2.7 Hz, 1H), 7.40 (br s, 1H), 6.09 (br s, 1H), 6.01-5.91 (m, 1H), 5.18 (d, J = 1.5 Hz, 1H), 5.11 (dt, J = 6.3, 1.5 Hz, 1H), 5.10 (dd, J = 10.5, 3.0 Hz, 1H), 4.00 (s, 3H), 3.99 (q, J = 7.1 Hz, 2H), 3.09-2.90 (m, 5H), 2.39-2.31 (m, 1H), 1.73-1.68 (m, 1H), 1.65-1.48 (m, 2H), 1.39-1.31 (m, 1H), 1.10 (t, J = 7.1 Hz, 3H), 1.07-0.98 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz, 60°C): δ 180.9, 158.1, 147.6, 145.8, 145.0, 140.5, 131.9, 128.4, 121.7, 119.5, 114.7, 101.7, 60.8, 60.4, 55.5, 49.4, 47.3, 39.3, 27.6, 26.8, 25.5, 14.3; HRMS m/z 396.2293 [C₂₃H₃₀N₃O₃ (M+H)⁺ requires 396.2287].

9-N-Methylamino-(9-deoxy)-epi-quinidine (16). Lithium aluminum hydride (100 mg, 2.6 mmol, 260 mol%) was suspended in dry THF (4 mL) at 0°C under Ar. Compound 15 (390 mg, 1.0 mmol, 100 mol%) was added as a solution in dry THF (8 mL). The reaction was stirred at 0°C for 6 hours, then allowed to warm to room temperature and stirred overnight. LiAlH₄ added as THF suspension (1 mmol, 100 mol%) to drive the reaction to completion. The reaction was quenched by adding H₂O (1.4 mL), 10 M NaOH (0.15 mL) and H₂O 0.6 mL sequentially to give a yellow mixture. The organic phase was dried over MgSO₄, filtered and evaporated to give a yellow foam. Purification by flash chromatography (9% MeOH in CH₂Cl₂); [α]²⁰_D = +56.6 (c = 1.0, CHCl₃); IR (neat): 3317, 3075, 2937, 2870, 2787, 1666, 1621, 1588, 1508, 1473, 1454, 1432, 1357, 1257, 1240, 1226 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, partial spectra, probably due to heavy rotamerism): δ 8.77 (br s, 1H), 8.03 (d, J = 9.5 Hz, 1H), 7.77-7.41 (m, 2H), 7.38 (dd, J = 9.2, 2.7 Hz, 1H), 5.92 (ddd, J = 17.5, 10.1, 6.6 Hz, 1H), 5.12-5.05 (m, 2H), 4.36 (br s, 1H), 3.97
(s, 3H), 3.08-2.80 (m, 5H), 2.32-2.23 (m, 1H), 2.20 (s, 3H), 1.62-1.46 (m, 3H), 1.24-1.15 (m, 1H), 0.89-0.73 (m, 1H); 13C NMR (CDCl3, 100 MHz, 55°C, partial spectra, probably due to heavy rotamerism): δ 157.5, 147.8 (broad, possibly 2 signals), 144.9, 140.9, 131.8, 129.6, 121.3, 114.4, 102.1, 55.5, 49.6, 47.8, 39.7, 34.3, 27.7, 26.8, 25.0; HRMS m/z 338.2227 [C21H28N3O (M+H)+ requires 338.2232].

N-Methyl-3,5-bis(trifluoromethyl)aniline (19). 3,5-Bis(trifluoromethyl)aniline (1.0 mL, 6.4 mmol, 100 mol%) was dissolved in CH2Cl2 (14 mL) and cooled to 0 °C. Trifluoroacetic anhydride (2.7 mL, 19 mmol, 300 mol%) was added, and the mixture was stirred at 0 °C for 20 minutes. The solvents were evaporated, and the residue was dissolved in acetone (15 mL). Anhydrous K2CO3 (1.77 g, 12.8 mmol, 200 mol%) and iodomethane (1.2 mL, 19 mmol, 300 mol%) were added, and the mixture was heated to mild reflux for 2 hours. The mixture was filtered and evaporated, the residue was dissolved in H2O:MeOH (5 mL : 25 mL), and anhydrous K2CO3 (880 mg, 6.4 mmol, 100 mol%) was added. The mixture was stirred at room temperature for one hour. The solvents were partly evaporated, and the residue partitioned between H2O (25 mL) and CH2Cl2 (30 mL). The aqueous phase was extracted with CH2Cl2 (30 mL). The combined organic phases were dried over MgSO4, filtered and evaporated to give 19 as a yellowish oil (1.41 g, 90%). The product was practically pure with some solvent residues present. No further purification was done since the compound was somewhat volatile at reduced pressures and could be lost in rigorous drying. RF = 0.23 (5% EtOAc in hexane); IR (neat): 3465, 2927, 1623, 1523, 1485, 1385, 1273, 1168, 1116, 1100, 1072 cm-1; 1H NMR (CDCl3, 400 MHz): δ 7.15 (s, 1H), 6.92 (s, 2H), 4.16 (br s, 1H), 2.91 (s, 3H); 13C NMR (CDCl3, 100 MHz): δ 150.1, 132.8 (q, 2JCF = 33.0 Hz), 124.0 (q, 1JCF = 272.0 Hz), 111.8, 110.4, 30.7; HRMS m/z 244.0557 [C9H7F6N (M+H)+ requires 244.0561].

3-(3,5-Bis(trifluoromethyl)phenyl)-1-((R)-(6-methoxyquinolin-4-yl)((2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)-1-methylthiourea (12). To a solution of 16 (140 mg, 0.42 mmol, 100 mol%) in dry THF (3 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (90 µL, 0.49 mmol, 110 mol%). The mixture was stirred overnight at room temperature under Ar. The solvents were evaporated and the residue purified by flash chromatography (5% to 10% MeOH in CH2Cl2) to give 12 as a whitish foam (181 mg, 71%). RF = 0.39 (10% MeOH in CH2Cl2); [α]20D = −3.8 (c = 1.0, CHCl3); IR (neat): 3237 (broad), 3070, 2938, 2872, 1622, 1510, 1474, 1370, 1311, 1278, 1242, 1175, 1134 cm-1; 1H NMR (MeOD-d4, 400 MHz): δ 8.72 (d, 1H, J = 4.8 Hz), 8.53 (d, 1H, J = 1.8 Hz), 7.98 (s, 2H), 7.93 (d, 1H, J = 9.3 Hz), 7.74 (d, 1H, J = 4.8 Hz), 7.67 (s, 1H), 7.41 (dd, 1H, J = 9.1, 2.7 Hz), 7.36 (d, 1H, J = 11.0 Hz), 5.84 (ddd, 1H, J = 17.2, 10.7, 6.4 Hz), 5.22 (dt, 1H, J = 17.3, 1.6 Hz), 5.03 (dt, 1H, J = 10.6, 1.5 Hz), 4.09-4.00 (m, 1H), 4.00-3.90 (m, 1H), 3.98 (s, 3H), 3.19-3.11 (m, 1H), 3.05 (s, 3H), 3.05-2.91 (m, 2H), 2.36 (q, 1H, J = 7.8 Hz), 1.89-1.79 (m, 1H), 1.77-1.66 (m, 2H), 1.59-1.49 (m, 1H), 1.10-1.01 (m, 1H); 13C NMR (MeOD-d4, 100 MHz): δ 184.4, 160.2, 147.7, 145.7, 144.4, 143.4, 141.3, 132.2 (q, 2JCF = 33.3 Hz), 131.3, 131.1, 127.2, 124.8 (q, 1JCF = 271 Hz), 124.3, 123.0, 118.7, 115.2, 105.7, 61.0,
57.7, 56.4, 54.8, 50.8, 50.0, 40.3, 32.8, 28.9, 27.6, 27.2. HRMS m/z 609.2133 [C_{30}H_{31}F_6N_4OS (M+H)^+] requires 609.2123.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-(R)-(6-methoxyquinolin-4-yl)((2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)-1-methylthiourea (13). Compound 18 (130 mg, 0.5 mmol, 100 mol%) was dissolved in dry THF (2 mL) under Ar and cooled to -78 °C. n-BuLi (2.2 M, 230 µL, 0.5 mmol, 100 mol%) was added and the resulting yellow mixture was stirred for 15 minutes. Isothiocyanate 17 (180 mg, 0.5 mmol, 100 mol%) dissolved in DMF (3 mL) was added, and the mixture was stirred at -78 °C for 40 minutes, then allowed to warm to room temperature and stirred for further one hour. The reaction was quenched by adding sat. NH_4Cl (1.0 mL), and the mixture was partitioned between H_2O (15 mL) and EtOAc (15 mL). The organic layer was washed with H_2O (3 x 10 mL), dried over MgSO_4, filtered and evaporated. The residue was purified by flash chromatography (3% to 10% MeOH in CH_2Cl_2) to give 13 as an amorphous solid (158 mg, 52%). Another product was also isolated (50 mg) which had identical HRMS spectra and highly similar NMR spectra. The correct product was assigned by comparison with NMR data reported by Soós (Ref. 8b). R_f = 0.34 (10% MeOH in CH_2Cl_2); [α]^{D}_{20} = +220.7 (c = 1.0, CHCl_3); IR (neat): 3241 (broad), 3076, 2939, 2876, 1622, 1590, 1474, 1382, 1278, 1226, 1180, 1138 cm^{-1}; ^1H NMR (CDCl_3, 400 MHz, 40°C): δ 8.62 (d, J = 4.7 Hz, 1H), 8.02 (d, J = 2.2 Hz, 1H), 7.93 (d, J = 9.2 Hz, 1H), 7.87 (br s, 1H), 7.81 (br s, 2H), 7.47 (d, J = 4.7 Hz, 1H), 7.42 (dd, J = 9.2, 2.7 Hz, 1H), 6.35 (br d, J = 10.7 Hz), 5.95 (ddd, J = 17.3, 10.6, 6.1 Hz, 1H), 5.21 (dt, J = 17.4, 1.6 Hz, 1H), 5.13 (dt, J = 10.6, 1.5 Hz, 1H), 4.01 (s, 3H), 3.56 (s, 3H), 3.36-3.21 (m, 2H, overlapping signals), 2.99 (dd, J = 14.0, 10.6 Hz, 1H), 2.95-2.85 (m, 2H), 2.40-2.30 (m, 1H), 1.64-1.49 (m, 3H), 1.26-1.17 (m, 1H), 1.04-0.94 (m, 1H); ^13C NMR (MeOD-d_4, 100 MHz): δ 184.5, 159.6, 148.5, 148.2, 148.0, 145.2, 141.7, 134.0 (q, J_CF = 34.0 Hz), 131.2, 130.2, 129.3, 124.4, (q, J_CF = 272.7 Hz), 123.7, 121.7, 121.1, 121.1, 115.2, 104.3, 61.2, 56.5, 50.0, 42.6, 40.2, 28.7, 27.4, 26.5; HRMS m/z 609.2137 [C_{30}H_{31}F_6N_4OS (M+H)^+] requires 609.2123.

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References


4. For a review, see e.g.: Connon, S. J. *Chem. Commun.* 2008, 2499.


15. The survey contained all thiourea structures containing the –HNC(S)NH-moiety similar to the catalysts (numbering over 700) published in the Cambridge Structural Database by September 2009. For an example of trans/trans-structure see CCDC-275454 (Ref. 14), and for a trans/cis-structure, CCDC-685194 (Ref. 7), respectively.


