Organocatalytic Stereoselective [8+2] Cycloaddition of Tropones with Azlactones

Jinzhao Li, Yuhao Mo, Liqiao Yan, Xiaoming Feng, Zhishan Su* & Xiaohua Liu*

Key Laboratory of Green Chemistry and Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064

*Corresponding authors: suzhishan@scu.edu.cn; liuxh@scu.edu.cn

Cite this: CCS Chem. 2021, 3, 784–793

Herein, we report an organocatalytic asymmetric [8+2] higher-order cycloaddition of tropones with azlactones employing bifunctional guanidines as hydrogen-bond-mediated catalysts via a 1,8-addition/annulation process. The reaction has a broad scope with respect to both cycloaddition partners and hence offers rapid access to an array of [5.3.0] bicyclic compounds with excellent outcomes [up to 95% yield, >19:1 diastereomeric ratio (dr), and 96% enantiomeric excess (ee)]. Besides, the synthetic utility of the protocol provides rapid transformation into enantioenriched α-amino acid derivatives. Moreover, the isolated [1,5]-H shift isomer, X-ray crystal structure of chiral guanidinium salt, and density functional theory (DFT) calculations provide convincing evidence for the interpretation of diastereo- and enantioselection.

Keywords: asymmetric catalysis, chiral guanidine, higher-order cycloaddition, tropone, azlactone, α-amino acid, DFT calculations

Introduction

Higher-order cycloadditions involve more than 6π electrons and represent efficient strategies to construct complex medium-sized cyclic compounds.1–4 Tropane and related systems, as versatile nonbenzenoid aromatic compounds, can undergo cycloadditions as a 2π,5 4π,6–8 6π,8–15 and 8π16–23 component to afford a variety of natural products and bioactive compounds.24 These competitive reaction pathways make control of periselectivity and stereoselectivity difficult in cycloadditions. To date, only a few enantioselective [8+2] cycloaddition reactions employing tropone or related systems have been successfully developed.25–32 Earlier, our group35,36 utilized a nickel(II) complex of chiral N, N'-dioxide for [8+2] cycloaddition between N-aryl-substituted azaheptafulvenes and electron-deficient olefins (Scheme 1, route 1). Later, various chiral organocatalytic activation strategies were introduced into asymmetric higher-order cycloadditions (Scheme 1, routes 2–6). For instance, the Jørgensen group27 demonstrated that linear dienamines formed from cyclohexenone or cycloheptenone through cinchona-based primary aminocatalytic highest occupied molecular orbital (HOMO)-activation could undergo endo-[8+2] cycloaddition with cyanopehthafulvene (Scheme 1, route 2). Pericàs and co-workers38,29 utilized isothiourea-activated carboxylic acids or N-heterocyclic carbene-activated α,β-unsaturated aldehydes as higher-enophiles, performing [8+2] cycloadditions with N-Tol azaheptafulvenes and tropones to form the...
corresponding bicycles, respectively (routes 3 and 4). As one exception, Albrecht et al. applied prolinol silicon ether-based aminocatalytic lowest unoccupied molecular orbital (LUMO)-activation of α,β-unsaturated aldehydes in the asymmetric [8+2] cycloaddition of electron-rich higherene tropothione (route 5). Nucleophilic chiral phosphine catalysts were also used for enantioselective [8+2] cycloadditions of achiral allenates or racemic allenic amides by Guo et al. and Vicario et al., independently (route 6). Although several examples of racemic thermally allowed higher-order cycloadditions of tropone have been well established, for example trifluoroacetic acid (TFA)- and base-promoted cycloaddition of tropone with azlactones were established by Alemán and co-workers, the stereoselectivity of such transformations remains unresolved. Nevertheless, the exo- or endo-transition states of the cycloadditions, multiple-spatial selection of symmetric tropone, and isomerization of the triene adducts reflect the difficulties in controlling the diastereo- and enantioselectivity.

Azmactones, also known as oxazolones, are usually employed in the stereoselective synthesis of quaternary α-amino acid derivatives. A series of amino-acid derived chiral bifunctional guanidine catalysts developed by our laboratory, have succeeded in several asymmetric transformations of azlactones and others. We envisioned that the stereoselective [8+2] cycloaddition could be achieved in the presence of a chiral bifunctional guanidine catalyst (Scheme 1). The guanidine unit as a Brønsted base promotes the enolization of azlactones, whereas the amide unit acts as a hydrogen-bond donor for LUMO-activation of tropone or azaheptafulvenes, which is beneficial to the process of [8+2] cycloaddition in the fixed chiral environment. Herein, we report chiral guanidines catalyze highly efficient diastereo- and enantioselective [8+2] cycloaddition of tropones and azaheptafulvenes with azlactones. This hydrogen-bond-mediated catalytic process provides a new route for asymmetric higher-order cycloaddition of tropones and related higherenes, enabling the generation of a wide range of chiral α-2-tropyl, α-alkyl amino acid derivatives in high yields and enantioselectivities.

**Experimental Methods**

**General procedure for the catalytic cycloadditions**

To a dry reaction tube charged with azlactone (0.12 mmol) and GS8 (10 mol %) was added tropone (0.1 mmol) dissolved in ethyl acetate (EtOAc; 0.5 mL) and another EtOAc (0.5 mL) at −60 °C. The mixture was stirred at −60 °C and monitored by thin-layer chromatography (TLC). After completion, EtOAc was evaporated in vacuo, and then the crude mixture was purified by flash chromatography on silica gel (petroleum ether/EtOAc/dichloromethane (DCM) = 19:1:40) to afford the desired product as white solid. The diastereomeric ratio (dr) was determined by proton nuclear magnetic resonance (1H NMR); and the enantiomeric excess (ee) was determined by supercritical fluid chromatography (SFC) with a chiral column.
Computational details

All calculations were performed using Gaussian 09 program package,50 employing the M062X-D3 density functional with the 6-31G(d,p) basis set. Geometries were optimized in EtOAc solvent and characterized by frequency analysis at 243 K.

Results and Discussion

We initiated our investigation using tropone 1a and phenylalanine-derived azlactone 2i as the model substrates. Reaction of a racemic mixture of 2i in the presence of triethylamine (NEt3) yielded the desired [8+2] cycloaddition adduct 3ai as a mixture of diastereomers. Next, the identification of a suitable chiral guanidine organocatalyst was carried out. It was found that in most cases, nearly only one diastereomer was obtained except for the use of L-pipecolic acid-derived guanidine GS2 (Table 1, entries 1–9). Interestingly, the major diastereomer accessed via base-catalysis is a reversal of the TFA-catalyzed process.33 Bisguanidinium hemisalt BG1·HBArF4 [HBArF4 = tetrakis[3,5-bis(trifluoromethyl)phenyl]boron], which showed excellent

<table>
<thead>
<tr>
<th>Entry</th>
<th>Guanidine</th>
<th>Yield (%)</th>
<th>dr (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BG1·HBArF4</td>
<td>49</td>
<td>&gt;19:1</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>GS1</td>
<td>78</td>
<td>&gt;19:1</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>GS2</td>
<td>69</td>
<td>3.2:1</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>GS3</td>
<td>Trace</td>
<td>&gt;19:1</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>GS4</td>
<td>78</td>
<td>&gt;19:1</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>GS5</td>
<td>78</td>
<td>&gt;19:1</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>GS6</td>
<td>73</td>
<td>&gt;19:1</td>
<td>44</td>
</tr>
<tr>
<td>8</td>
<td>GS7</td>
<td>80</td>
<td>&gt;19:1</td>
<td>71</td>
</tr>
<tr>
<td>9</td>
<td>GS8</td>
<td>82</td>
<td>&gt;19:1</td>
<td>77</td>
</tr>
<tr>
<td>10a</td>
<td>GS8</td>
<td>92</td>
<td>&gt;19:1</td>
<td>87</td>
</tr>
<tr>
<td>11b</td>
<td>GS8</td>
<td>90</td>
<td>&gt;19:1</td>
<td>91</td>
</tr>
<tr>
<td>12c</td>
<td>GS8</td>
<td>41</td>
<td>&gt;19:1</td>
<td>91</td>
</tr>
</tbody>
</table>

* The reactions were carried out with 1a (0.10 mmol), 2i (0.10 mmol), and the catalyst (10 mol %) in DCM (0.1 M) at −30 °C for 12 h.
* Isolated yield.
* dr and ee were determined by SFC with a chiral column.
* EtOAc was used instead of DCM.
* 2i (0.12 mmol) at −60 °C.
* GS8 (5 mol %) was used.

DOI: 10.31635/ccschem.021.202000664
CCS Chem. 2021, 3, 784–793
catalytic activity and enantio-inducing ability in several asymmetric transformations of azlactones, promoted the current reaction to furnish the desired product 3ai with moderate yield but poor enantioselectivity (Table 1, entry 1). Gratifyingly, we found that another type of bifunctional guanidine (GS1–GS5) with an additional sulfonamide functional group was beneficial to the enantio-induction of this reaction (48–72% ee, entries 2–6), while the distinct chiral amino acid backbone had obvious influences on reactivity and stereoselectivity. A poor yield was obtained when GS3 derived from L-ramipril was used as the catalyst (entry 4). Neither the guanidine GS1 derived from L-proline nor GS4 derived from L-perindopril was superior to L-tetrahydroisoquinoline-based GS5 in terms of enantioselectivity (entry 6 vs entries 2 and 5). As a result, the L-tetrahydroisoquinoline-based guanidine-sulfonamides were chosen to be the advanced chiral amino acid precursors. Next, our optimization shifted to adjusting the sulfonamide substituents, and the catalyst GS8 containing the 2,6-difluorobenzenesulfonamide group afforded slightly better yield and enantioselectivity (82% yield, 77% ee; entry 9 vs entries 6–8), while the sterically hindered GS6 decreased the enantioselectivity (entry 7). With catalyst GS8 in EtOAc as the solvent instead of DCM, the yield and enantioselectivity of the corresponding product 3ai greatly increased to 92% and 87% ee (entry 10). When the reaction was performed at −60 °C with 1.2 equiv of azlactone 2i, the enantioselectivity obviously improved to 91% ee with a slightly decreased isolated yield of 90% (entry 11).

Scheme 2 | (a–c) Substrate scope of azlactones and tropones. The reactions were carried out with 1 (0.10 mmol), 2 (0.12 mmol), and GS8 (10 mol %) in EtOAc (0.1 M). Yields from isolated material; dr was determined by 1H NMR (> 19:1); and ee was determined by SFC. aAt −30 °C. bAt −60 °C. cAt 0 °C.
catalyst loading was reduced to 5 mol%, the isolated yield of 3ai sharply decreased to 41% albeit the stereoselectivity was nearly maintained (entry 12).

With the optimized catalytic system established, we set out to explore the substrate scope of the catalytic [8+2] reaction between pristine tropone 1a and azlactones (Schemes 2a and 2b). A number of 4-alkyl-substituted azlactones (2a–2h) were first explored, which showed good compatibility in this catalytic reaction system regardless of the steric hindrance. The azlactones synthesized from α-amino acids, containing the methyl (2a), ethyl (2b), n-propyl (2c), iso-propyl (2d), iso-butyl (2e), 2-(methylthio)ethyl (2f), cyclohexyl (2g), and cyclohexymethyl (2h) group, underwent the reactions smoothly to afford the corresponding products (3aa–3ah) in moderate to high yields (66–92%) and good to excellent enantioselectivities (84–96% ee). Subsequently, the azlactones 2i–2k derived from phenylalanine, 2-ami-

do-4-phenylbutanoic acid, and tryptophan also tolerated the azlactones was investigated, and the cycloaddition reaction well in the presence of 10 mol % of the catalyst GS8. The corresponding dihydro-2H-cyclohepta[b]furran derivatives 3ai–3ak were obtained in high yields (84–92%) and satisfying ee values (91–95% ee). The electronic property of the 4-halo substituent on the aromatic ring of phenylalanine-derived azlactones 2i–2n hardly affected the enantioselectivity (92–94% ee) but had a significant effect on the reactivity (51–78% yield). Moreover (Scheme 2b), it was found that azlactones 2o–2r with various substituents at the C-2 position underwent the reaction smoothly, resulting in moderate to high yields (74–90%) with excellent enantioselectivities (92–94% ee). Notably, almost only one diastereomer of the products 3 was detected under the catalysis of chiral guanidine GS8. The absolute configuration of the major enantiomer 3ag was confirmed to be (3R, 3aS) by single-crystal X-ray diffraction analysis.*

As outlined in Scheme 2c, the scope of substituted tropones was investigated, and the cycloaddition reaction occurred at the less substituted position when 2-substituted tropones were used. For example, 2-chlorotropane 1b reacted with azlactone 2a, affording the bicyclic product 3ba in 91% yield with 85% ee. The bulky 2-aryl-substituted tropones were also employed as good substrates for this cycloaddition, and the electron property of the substituents had a slight influence on its behavior (3ca–3ea; 86–94% yield and 88–92% ee). Also, the azlactone 2q reacted with 2-chlorotropane 1b, affording the corresponding product 3bq in 95% yield with 92% ee.

When cycloadditions between azahetafulvenes and azlactone were attempted, the desired product 7ap from chiral guanidine-amide or -sulfonamide catalysis of N-tosyl azahetafulvene 6a and azlactone 2p could not be obtained with satisfying results (screening and optimizing results are given in Supporting Information Tables S5–S8). However, with 5 mol % of bisguanidinium hemi-salt BG1·HBArF in chloroform at −60 °C, the formal [8+2] cycloadduct 7ap was readily formed in good yield with acceptable stereoselectivity (86% yield, 3.2:1 dr, and 78% ee). As shown in Scheme 3, the steric hindrance on the N-sulfonylamide protecting group of azahetafulvene has a significant impact on the yield, diastereo- and enantioselectivity. 2-Nitrobenzensulfonyl-substituted 6c was sluggish in this system, affording the [8+2] cycloadduct 7cp in moderate yield with poor stereoselectivities. When the N-methylsulfonyl group was installed into the azahetafulvene, the ee value of the desired product decreased to 63%. The best result (7bp; 90% yield, 4.6:1 dr, and 86% ee) was obtained when N-nosyl azahetafulvene 6b was used. The relative configuration of the major diastereomer 7dp was confirmed by Nuclear Overhauser Effect Spectroscopy (NOESY)
correlations to be in accordance with the adduct 3ag. At this point, we assume that the existence of Z/E-selectivity and steric hindrance of the N-protecting group of azahetapfulvene increase the difficulty of controlling stereoselectivity.

To further evaluate the synthetic potential of the catalytic system, a gram-scale synthesis of 3bq was carried out (Scheme 2c). Under optimized conditions, the formal cycloaddition between 2-chlorotropone 1b (0.422 g, 3 mmol) and azlactone 2q (0.755 g, 3.6 mmol) proceeded smoothly. Notably, we also observed a self-disproportionation of enantiomers (SDE) effect of the adduct 3bq during the flash chromatography separation (Supporting Information Page S54). The hydrogenation of 3bq furnished hexahydrocycloheptafuranone derivative 4 in 48% yield with 99% ee. Single-crystal X-ray diffraction analysis of 4 confirmed that the configuration of the major isomer is consistent with the product of the pristine tropone 1a. Moreover, optically active \(\alpha\)-(2-tropyl) \(\alpha\)-amino acetate 5 was readily available in 91% yield with 96% ee by treatment with K₂CO₃ (Scheme 4a).

Keen on understanding the underlying mechanism of our obtained high diastereoselectivity, we performed several control experiments (Scheme 4b). Product 3ai with approximately a 1:1 dr value was subjected to diverse basic conditions. Although complete epimerization did happen after treating the isomers with chiral guanidine GS2 in DCM at 30 °C for 12 h, it was found that slight epimerization occurred in the asymmetric catalytic conditions with GS8. The reversal of diastereoselectivity was also possible with excessive amount of NEt₃, which might undergo a double [1,5]-H shift isomerization process via the formation of isomer 8, delivering the relative thermally stable product 3ai. In view of the slow epimerization process, we think that the generation of the major product 3 is directly caused by the cycloaddition step rather than the isomerization process in the optimized asymmetric catalytic version.

The X-ray crystal structure of chiral guanidinium salt GS8-HCl exhibits that three syntropic hydrogens are distributed among the protonated imine and two amide units, and the amides of the catalyst could seize the chlorine ion via dual hydrogen bonding. It indicates that such an arrangement produces a type of noncovalent hydrogen-bond-mediated bifunctional organocatalyst. Initially, the basic guanidine unit promotes the enolization of azlactone 1, forming a hydrogen-bond-associated...
intermediate, and at the same time, the two amide hydrogens fix the oxygen of tropone 2. The corresponding enolate intermediate is ready to attack tropone, performing the desymmetrization of tropone via intermolecular 1,8-conjugate addition, which is the stereodetermining step. Subsequently, the newly formed oxygen anion of tropone attacks the carbonyl group of azlactone, accomplishing lactonization to afford the corresponding product 3.

To reveal the mechanism and origin of diastereo- and enantioselectivity of the [8 + 2] cycloaddition of tropone (1a) with azlactone (2g) catalyzed by guanidine catalyst, preliminary density functional theory (DFT) calculations were performed at the M062X-D3/6-31G(d,p) theoretical level. Starting from two enolate intermediates (GS8-2g-Re and GS8-2g-Si), four transition states (TS1, TS2, TS1*, and TS2*) in the stereodetermining C–C bond formation step were generated, affording the stereoisomers with (3R,3aS), (3R,3aR), (3S,3aR), and (3S,3aS) configurations, respectively (Figures 1a and 1b). The relative Gibbs free energy of TS1 was the lowest among the four transition states, indicating that the cycloadduct with (3R,3aS)-3ag configuration predominantly forms, which is consistent with the experiment result.

Then, a distortion/interaction activation strain (D/IAS) analysis52 was performed at the same theoretical level (Figure 2). The geometry of transition state was decomposed into the guanidine-azlactone fragment (GS8-2g).

![Calculated stereomodels of transition states and intermediates for GS8. (a) The relative Gibbs free energy of GS8-2g-Re was set to 0 kcal/mol. (b) The relative Gibbs free energy of TS1 was set to 0 kcal/mol.](image)
and tropone fragment (1a). Suffering from the steric repulsion of the N-Cy group in the guanidine catalyst, the distortion energy $\Delta E_{\text{dist}}$ of TS1* was more destabilizing than TS1 by 1.1 kcal mol$^{-1}$. Moreover, the interaction energy $\Delta E_{\text{int}}$ of TS1* was less stabilizing. As a result, the $\Delta E$ of TS1* was 2.3 kcal mol$^{-1}$ higher than TS1, leading to high ee. For TS2 and TS2*, the bulky C4-Cy substituent in azlactone was placed alongside the aromatic ring of tropone. This unfavorable conformation weakened the interaction of the two reactants. Accordingly, their $\Delta E_{\text{int}}$ ($-8.5$ and $-10.3$ kcal/mol) were less stabilizing than TS1 ($-14.0$ kcal/mol). Compared with TS2, TS2* was less stable by 2.8 kcal/mol due to the much more destabilizing $\Delta E_{\text{dist}}$ (25.6 kcal/mol). We assumed that the repulsion between tropone and the C4-substituent in azlactone reduced the stabilizing interaction energy of the two reacting fragments in the transition-state TS2, contributing to high diastereoselectivity. This calculated result was in good agreement with the experimental observations.

**Conclusion**

We have developed the organocatalytic asymmetric [8+2] higher-order cycloaddition reactions of tropones or azaheptafulvenes with azlactones through a stepwise 1,8-addition/annulation process. The reactions proceed with excellent diastereo- and enantioselectivity (up to $>19:1$ dr and 96% ee) for tropones that reacted with various azlactones in the presence of a chiral guanidine-sulfonamide bifunctional catalyst. This set of reactions provided a range of bicyclic lactones, which could be readily transformed into optically active 2-tropyl, $\alpha$-alkyl amino acid derivatives. In addition, chiral bisguanidinium salt organocatalyst enabled the reaction of azaheptafulvenes to access bicyclic lactams. Further application of hydrogen-bond activation via guanidine catalysts in asymmetric organocatalysis and others are underway in our laboratory.

**Footnote**

* CCDC 1977871 (3ag), CCDC 2006510 (4), and CCDC 2002610 (GS8·HCl) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

**Supporting Information**

Supporting Information is available and includes general information, substrates synthesis, experimental procedures, optimization details, X-ray crystallographic data, product characterization data, synthesis transformations, computational details, and copies of SFC and NMR spectra.

**Conflict of Interest**

There is no conflict of interest to report.

**Funding Information**

The authors appreciate the National Natural Science Foundation of China (nos. 21625205 and U19A2014) for financial support.

**Acknowledgments**

The authors wish to acknowledge Dr. Yuqiao Zhou (Sichuan University) for his assistance in single-crystal X-ray diffraction analysis.

**References**


DOI: 10.31635/ccschem.021.202000664
CCS Chem. 2021, 3, 784–793

DOI: 10.31635/ccschem.021.202000664
CCS Chem. 2021, 3, 784–793


