Asymmetric Hydrogen Bonding Catalysis for the Synthesis of Dihydroquinazoline-Containing Antiviral, Letermovir

Cheol K. Chung,* Zhijian Liu,* Katrina W. Lexa, Teresa Andreani, Yingju Xu, Yining Ji, Daniel A. DiRocco, Guy R. Humphrey, and Rebecca T. Ruck

Process Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States

ABSTRACT: A weak Bronsted acid-catalyzed asymmetric guanidine aza-conjugate addition reaction has been developed. C$_2$-symmetric, dual hydrogen-bond donating bis-triflimides are shown to be highly effective in activating a$_\beta$-unsaturated esters toward the intramolecular addition of a pendant guanidinyl nucleophile. Preliminary mechanistic investigation, including density functional theory calculations and kinetics studies, support a conjugate addition pathway as more favorable energetically than an alternative electrocyclization pathway. This methodology has been successfully applied to the synthesis of the 3,4-dihydroquinazoline-containing antiviral, Letermovir, and a series of analogues.

A symmetric Bronsted acid catalysis continues to attract broad interest in organic synthesis as a powerful tool for conducting stereoselective transformations. Recently, it has emerged as a greener, milder alternative to metal-based Lewis acid catalysis in activating imines, carbonyls, and nitro groups in a suite of aldol-type reactions. For conjugate addition reactions, however, the application of Bronsted acid catalysis has been largely limited to neutral or weakly basic nucleophiles as strong bases will interact with known prospective catalysts, reducing their ability to activate the carbonyl group. In addition, the typical electrophiles are a$_\beta$-unsaturated ketones or nitroalkenes, with only a few examples involving esters or amides as Michael acceptors due to the reduced Lewis basicity of the corresponding carbonyl oxygen atoms. Development of a catalytic system capable of incorporating these less reactive substrate classes would represent significant progress in Bronsted acid catalysis.

Recently, we reported an asymmetric synthesis of letermovir (4), an experimental drug currently in phase III clinical trial for the treatment of human cytomegalovirus (CMV) infection (Scheme 1). In this work, the dihydroquinazoline core of 4 is constructed via an aza-conjugate addition reaction by using the bis-quaternary ammonium salt as phase-transfer catalyst (PTC). However, the PTC route suffered from a series of challenges, including the inherent instability of the catalyst under basic conditions and moderate enantioselectivity. Combined with other operational restraints arising from the biphasic nature of the reaction, these concerns rendered the PTC approach less attractive and reliable for inclusion in our manufacturing route. Given the prevalence of the 3,4-dihydroquinazoline core in medicinally important targets, a more robust, efficient asymmetric synthesis of the core was expected to be broadly applicable in medicinal chemistry. To that end, we conducted a survey of alternative chiral promoters, aided by high-throughput experimentation tools. Herein, we report the discovery of a novel asymmetric Bronsted acid catalysis for the intramolecular aza-conjugate addition of a guanidinyl nucleophile to an a$_\beta$-unsaturated ester, that is highly efficient, readily scalable, and broadly applicable to the synthesis of enantioenriched 3,4-dihydroquinazolines.

We began our investigation by screening a variety of metal-based chiral Lewis acids and chiral nucleophilic catalysts to promote the cyclization. Though these attempts were mostly unsuccessful due to the lack of reactivity or enantioselectivity, we observed a significant background cyclization in polar protic solvents. For instance, starting material 1 readily underwent a racemic cyclization in 2,2,2-trifluoroethanol (100%, 15 min), methanol (100%, 1 h), or 2-propanol (78%, 22 h). Conversely, the background reaction was suppressed in aprotic solvents such as toluene and DMSO (<1%, 48 h), suggesting the importance of proton donation in effecting this cyclization. This observation prompted us to postulate that the desired cyclization might be promoted by chiral Bronsted acids or hydrogen bonding catalysts. Regarding potential activation mechanisms, we envisioned a catalytic system that can polarize the enoate acceptor by forming hydrogen bonding complex A with the ester carbonyl group (Figure 1). Given the poor Lewis basicity of the ester group and the presence of a basic guanidine functionality in the substrate, an alternative electrocyclization
pathway could be considered as well.\textsuperscript{10} In this latter pathway, protonation followed by tautomerization of the extended π system of 1 would lead to the aza-equinone methide intermediate B, which is well-positioned to undergo electrocyclicization to yield the new guanidine product 3.\textsuperscript{11}

To probe these hypotheses, we tested the competency of a series of Brønsted acids with different structures and acidity levels, including phosphoric acids, phenols, alcohols, triamides, and thioureas, in catalyzing the desired cyclization. Selected results are summarized in Table 1.

Table 1. Survey of Chiral Bronsted Acids for Aza-conjugate Addition\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent\textsuperscript{a}</th>
<th>conversion (%)\textsuperscript{f}</th>
<th>e.r.\textsuperscript{f}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>toluene</td>
<td>16</td>
<td>79:21</td>
</tr>
<tr>
<td>2\textsuperscript{g}</td>
<td>6</td>
<td>TFT</td>
<td>96</td>
<td>90:10</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>toluene</td>
<td>23</td>
<td>95:5</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>toluene</td>
<td>92</td>
<td>64:36</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>EtOAc</td>
<td>71</td>
<td>94:6</td>
</tr>
<tr>
<td>6</td>
<td>10\textsuperscript{a}</td>
<td>CPME</td>
<td>53</td>
<td>87:13</td>
</tr>
<tr>
<td>7</td>
<td>10\textsuperscript{b}</td>
<td>CPME</td>
<td>5</td>
<td>70:30</td>
</tr>
<tr>
<td>8</td>
<td>10\textsuperscript{c}</td>
<td>CPME</td>
<td>65</td>
<td>71:29</td>
</tr>
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<td>9</td>
<td>10\textsuperscript{d}</td>
<td>anisole</td>
<td>100</td>
<td>69:31</td>
</tr>
<tr>
<td>10</td>
<td>10\textsuperscript{e}</td>
<td>CPME</td>
<td>100</td>
<td>92:8</td>
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<tr>
<td>11</td>
<td>10\textsuperscript{f}</td>
<td>CPME</td>
<td>100</td>
<td>92:8</td>
</tr>
<tr>
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<td>CPME</td>
<td>100</td>
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<tr>
<td>13</td>
<td>10\textsuperscript{h}</td>
<td>CPME</td>
<td>100</td>
<td>95:5</td>
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<td>14</td>
<td>10\textsuperscript{i}</td>
<td>CPME</td>
<td>100</td>
<td>96:4</td>
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<tr>
<td>15\textsuperscript{h}</td>
<td>10\textsuperscript{j}</td>
<td>CPME</td>
<td>100</td>
<td>97:3</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Conditions: 10 mol % catalyst, 50 °C, 15–24 h. \textsuperscript{b}Ar = 2,4,6-trisopropylphenyl. \textsuperscript{c}Ar = 3,5-bis(trifluoromethyl)phenyl. \textsuperscript{d}DCE = 1,2-dichloroethane, TFT = α,α,α-trifluorotoluene, CPME = cyclopentyl methyl ether. \textsuperscript{e}Conversion was measured by HPLC using an internal standard. \textsuperscript{f}e.r. was measured by chiral HPLC (Chiralpak IC-3). \textsuperscript{g}The reaction was run at 60 °C for 24 h. \textsuperscript{h}The reaction was run at 35 °C for 24 h.

Chiral phosphoric acids have been shown to promote conjugate addition via simultaneous activation of both nucleophiles and Michael acceptors.\textsuperscript{12} Unfortunately, in our system, poor reactivity with modest enantiocontrol was observed (entry 1). Postulating that a strong acid—base interaction between the guanidine moiety in the substrate and phosphoric acid might have caused the poor reactivity, we turned our attention to weaker Brønsted acids such as BINOL and TADDOL. This application was particularly intriguing because, although these diols are extraordinarily useful as chiral ligands, their employment as organocatalysts has been limited.\textsuperscript{13} To our gratification, chiral binaphthol 6 provided the desired cyclized product in 90:10 e.r., with excellent reactivity at a slightly more elevated temperature (entry 2).

Encouraged by these initial results, we expanded our screening to include a range of hydrogen bond donors with a variety of frameworks and range of pK\textsubscript{a} values, which revealed additional requirements for efficient cyclization.\textsuperscript{14} For instance, using a dual hydrogen bond donating thiourea catalyst 7 was beneficial for obtaining high enantioselectivity, albeit with poor reactivity (entry 3). Though other variants of dual hydrogen bond donors, such as squaramides, and more elaborated ureas containing secondary functionality proved unproductive, chiral bistriamides provided greatly improved reactivity with high conversion and high enantioselectivity (entry 5). The ethylene-1,2-bistriamide system was particularly attractive for further catalyst optimization, as its simple C\textsubscript{2}-symmetric framework was amenable to modular structural modifications.\textsuperscript{15} Our initial efforts to understand catalyst SAR revealed that the presence of a hydrogen bond acceptor (entry 6), bulky aryl group (entry 7), or alkyl substituents (entry 8 and 9) on the backbone provide the product in lower ee. Notably, the bistriamides possessing ortho-substituted aryl groups on the backbone offered excellent catalytic activity, promoting the cyclization in high ee’s with full conversion (entries 12–15). On the other hand, replacing N-trifluorosulfonyl groups with other sulfonyl or acyl groups was not well-tolerated, resulting in poor reactivity.\textsuperscript{16} Considering the dearth of examples in which αβ-unsaturated esters are used as electrophiles in Bronsted acid catalysis, it is remarkable that these structurally simple bistriamides are so efficient in promoting the desired cyclization.\textsuperscript{17}

The generality of this process was next examined, and the results are summarized in Table 2. Encouragingly, the bistriamide catalysis tolerated a variety of functional groups providing the cyclized products in high yield and good to excellent enantioselectivity (3b to 3i).

Various secondary alkyl amines, including indole, isindo-line, diethylamine, pyrroline and morpholine, have all successfully been employed in this process, affording good enantioselectivities in the corresponding dihydroquinazoline products (3j to 3o). Interestingly, the substituent adjacent to the guanidine had a significant impact, and the des-fluoro substrate yielded much lower enantioselectivity (3q) compared with its parent 3. Similarly, the 7-Cl substituent (3r) afforded lower enantioselectivity than the 8-Cl substituent (3s). It is also noteworthy that the naphthyl substrate provided the corresponding product in good selectivity (3p).

To gain an understanding of the mechanism, we probed the essential features of the catalyst by making a variety of structural modifications (Figure 2). Catalytic activity was essentially lost when a conformationally restricted backbone was used (10k) or when one of the protons was removed by methylation (10l), whereas monotriamide 10m partly retained the reactivity.

Figure 1. Two potential cyclization mechanisms.
Intriguingly, the bistriﬂamide derived from meso-diamine 10n was much less reactive than its C2-symmetric analogue. On the other hand, bistriﬂamide 10o was highly active as a catalyst, suggesting C2-symmetry was not required. Taken together, these results showed that both hydrogen atoms were needed for eﬃcient cyclization and the backbone must be ﬂexible enough to allow the two hydrogens to adopt a productive conformation. This ﬁnding was consistent with the hypothesis of dual hydrogen bond donation from the catalyst as the key driving force for the cyclization.18

To further clarify the reaction mechanism, we conducted a quantum mechanical study of both proposed reaction pathways. Ground and transition state energies were obtained at the M06-2X-D3/6-311G(d,p)-SMD(toluene)//B3LYP-D2/6-31G(d,p) level of theory using Gaussian09.19 The calculations showed ring closure via electrocyclization was quite facile from the aza o-quinone methide intermediate formed by tautomerization of the protonated guanidine starting material 1 (Intt1)20. However, the barrier to undergo tautomerization initially was substantial; therefore overall, the electrocyclization pathway required a higher energy relative to the conjugate addition pathway (∆∆G‡ = 25.9 kcal/mol) (Figure 3).

Although these preliminary density functional theory (DFT) calculations do not completely rule out the potential involvement of the electrocyclization pathway, two subsequent kinetic experiments corroborated the computational results identifying the conjugate addition as the more plausible mechanism (Scheme 2). First, the primary kinetic isotope eﬀect observed with the deuterated catalyst 10j-d and substrate 1-d (kH/kD = ca. 4.1) aligned well with conjugate addition,20 because the transition state for the electrocyclization pathway (TSEC) does not involve dissociation of a hydrogen atom.21 Second, in a competition experiment suggested by computational predictions made from mapping the reaction pathway with various substrates, there was no diﬀerence in reaction rate between 1 and the naphthyl substrate 11 (k11/k1 ∼ 1.0),21 which indicated the mechanism was not likely to involve partially dearomatized intermediates such as those in the electrocyclization pathway.22

Because of this structure-based mechanistic understanding, we are currently exploring further improvements to the catalyst structure by employing computational tools.23

In summary, we have developed the ﬁrst enantioselective bistriﬂamide-catalyzed 3,4-dihydroquinazoline synthesis. This transformation represents a rare case of Brønsted acid catalysis in which a dual hydrogen bond donating catalyst activates an ester functional group toward the conjugate addition of a strongly basic nucleophile. The newly developed hydrogen bonding catalyst has emerged as the cornerstone of the Letermovir commercial process and been applied and demonstrated for the large-scale synthesis, improving the overall eﬃciency while obviating the operational constraints from which the original PTC-catalyzed transformation suﬀered.24

The details of the chemical process development focusing on improved sustainability, and our continuing eﬀorts to optimize the catalyst structure using QSAR will be the subject of a future communication.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b05806.
Full experimental and computational details for DFT calculation (PDF)

**AUTHOR INFORMATION**

**Corresponding Authors**

*cheol_chung@merck.com*

*zhijian_liu@merck.com*

**ORCID**

Zhijian Liu: 0000-0002-5750-9890

Rebecca T. Ruck: 0000-0001-9980-9675

**Notes**

The authors declare no competing financial interest.

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**REFERENCES**


