A Highly Diastereoselective and Enantioselective Synthesis of Polysubstituted Pyrrolidines via an Organocatalytic Dynamic Kinetic Resolution Cascade

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ABSTRACT

Highly functionalized pyrrolidine and piperidine analogues, with up to three stereogenic centers, were synthesized in good yield (50–95%), excellent dr (single isomer), and high ee (>90%) using a Cinchona alkaloid-derived carbamate organocatalyst. High stereoselective synergy was achieved by combining a reversible aza-Henry reaction with a dynamic kinetic resolution (DKR)-driven aza-Michael cyclization. Whereas both reactions proceed with moderate enantioselectivities (50–60% for each step), high enantioselectivities are obtained for the overall products devoid of dr sacrifice.

Dynamic kinetic asymmetric transformations (DYKATs) have now emerged as powerful tools for the construction of stereogenic centers.1 Using this strategy, products of high optical purity can be synthesized via reaction cascades that no longer necessitate overwhelmingly selective steps. In addition, ee enrichment of the overall products does not come at the cost of sacrificing either yields or diastereoselectivities. Since the discovery of organocatalytic cascade reactions,2 DYKAT has enjoyed remarkable advances that have led to a number of efficient organocatalytic domino processes3 and synergistic catalysis cascades, a process in which two distinct catalytic mechanisms are merged into a single reaction.20 In particular, cascades that take advantage of a first reversible step and a second dynamic kinetic resolution step (DKR) have led to one-pot syntheses of chiral cyclic compounds with particularly high ee and dr in excellent yield. For example, Wang reported a cascade featuring a reversible thio-Michael and a DKR Michael reaction for his synthesis of substituted thiochromans.4 Córdova, Jørgensen, Wang and others

disclosed a series of “organo-metal cooperative catalysis” utilizing reversible Michael reactions and transition metal catalyzed diastereoselective carbocyclization to access five-membered carbo- and heterocycles. Very recently, Zhao reported a chiral cyclohexane synthesis that combined a reversible Henry reaction and a subsequent selective Michael cyclization. In this report, we describe the highly diastereone- and enantioselective synthesis of polysubstituted pyrrolidines using a parallel DYKAT strategy. In this cascade, a reversible aza-Henry reaction was combined with an aza-Michael cyclization to yield N-containing heterocycles. Most recently, Zhao catalyzed diastereoselective carbocyclization to access five-membered carbo- and heterocycles. Noteworthy, most strategies only permit access to pyrrolidines with specific substitution patterns, as restricted by their individual reaction mechanisms. Our aza-Henry/aza-Michael cascade (Table 1) offers a solution to the 2,3,5-trisubstituted pyrrolidine scaffold. One advantage of this method is that it does not require the common usage of a gem-diester like substrates.

The NO$_2$ substrate 1a was readily available in two steps following literature procedures. The racemic reaction proceeded smoothly at rt with DBU as the catalyst, yielding the desired trisubstituted pyrrolidine in quantitative yield. In order for the second step aza-Michael cyclization to proceed, the N—H acidity of the aza-Henry product had to be strong enough to be deprotonated by DBU. Aldimines other than Ts-N=C stalled at the initial aza-Henry stage, with no heterocyclization typically observed, as documented previously. A single diastereomer (trans-4aa) was isolated. NMR experiments revealed that the initial aza-Henry reaction was modestly diastereoselective, giving a mixture of trans/cis products in a ca. 2:1 ratio. It was observed that only the trans aza-Henry adduct trans-3aa underwent subsequent cyclization.

The need to employ NTs aldilimes posed a challenging task for the development of an asymmetric synthesis. There is no successful organocatalytic aza-Henry reaction involving this quite reactive imine functionality. Dual functional H-bond/base catalysts were examined for asymmetric induction. Moderate yields and enantioselectivities were observed with the popularly used Takemoto–Jacobsen amine/thiourea. Attempts to improve ee through thiourea modification were fruitless. The corresponding amine/squaramide, developed by Rawal et al., afforded a nearly racemic product (Figure 1).

Table 1. Cascade Design and Initial Condition Screening

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>additive</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCM</td>
<td>0.1 M.S.</td>
<td>50</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>0.1 M.S.</td>
<td>33</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>0.1 M.S.</td>
<td>23</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>Et$_2$O</td>
<td>0.1 M.S.</td>
<td>46</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>CH$_3$CN</td>
<td>0.1 M.S.</td>
<td>26</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>toluene</td>
<td>0.1 M.S.</td>
<td>&gt;99</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>toluene</td>
<td>0.1 M.S.</td>
<td>&gt;99</td>
<td>80</td>
</tr>
</tbody>
</table>

* Reactions were carried out on a 0.1 mmol scale using 10 mol % catalyst at rt; 1a 2a = 1:1.5 at 0.2 M. $^b$ Isolated yields after flash column chromatography. $^c$ Ec’s were determined by chiral HPLC analysis.


(11) For detailed catalyst and condition screening, see Supporting Information for details.


Surprisingly, switching to a single point amine/amide catalyst allowed excellent cascade stereoselectivity. Interestingly, stronger H-bond analogues, such as sulphonamides, were much less selective, which indicated that the H-bond strength of the catalyst ought to be finely tuned within a narrow range for optimal results. The enantioselectivity of this cascade was in direct inverse proportion to the polarity of solvents. In order to improve the overall conversion of this cascade, several additives were screened and 5 Å molecular sieves were found to significantly accelerate the aza-Michael cyclization without eroding the product ee. The desired trans-4aa was isolated in 72% yield with 91% ee. Heating to 100 °C accelerated the cyclization, and a quantitative yield of trans-4aa could be achieved with 80% ee. Both the relative and absolute configuration of trans-4aa was unambiguously determined by single-crystal X-ray diffraction.

The substrate scope was examined, and the results are summarized in Table 2. The substrate tolerance for aldimines was particularly broad. Both aromatic and aliphatic aldimines with various substitutions were well suited to this cascade, and high enantioselectivities (>90%) were obtained uniformly, regardless of electronics and the substitution pattern. Heterocyclic aldimines derived from pyridines were particularly selective (>99% ee). The rate of the aza-Michael cyclization for this substrate, on the other hand, proved very slow, and only a 30% isolated yield was obtained after 2 days at rt. The overall yield could be improved by heating at 100 °C upon completion of the initial step, while still maintaining 90% enantioselectivity. This observation is worth noting, as relatively loose H-bonding catalysis rarely shows high selectivity at such elevated temperatures. This might be the result of amplified rate differences between the rate of reversibility of the aza-Henry adduct could be accelerated by the addition of organic bases.

Nitroalkenes bearing various esters and ketones readily engaged in the cyclization cascade. Both pyrrolidines and piperidines were synthesized in good-to-excellent yields and selectivities. It was evident that, for groups which allowed faster cyclization, lower ee’s were observed. This is in consistent with our reversible-DKR cascade model.

The DKR aza-Michael cyclization step was confirmed by an independent experiment using racemic trans-3aa (Scheme 1). Trans-3aa did not cyclize in the absence of a base. Pyrrolidine trans-4aa was isolated in 50% ee in 80% yield after 24 h, revealing a modestly selective kinetic resolution. With aza-Henry reversibility omitted, this result correlated to an S factor of 3. Standing pure cis-3aa in DCM solution led to the emergence of starting materials, a process which could be accelerated by the addition of organic bases.

Real time NMR experiments showed that the first aza-Henry reaction proceeded rather quickly (completed within 4 h), generating a 2.3:1 mixture of trans-3aa and cis-3aa (Table 3). The rate determining step was evidently the cyclization step, as the primary aza-Henry adduct could be isolated by column chromatography on SiO2. Under standard reaction conditions, the trans/cis ratio of the thermodynamic equilibrium of the aza-Henry adduct was

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2.3:1 (trans-3aa vs cis-3aa). A stand alone aza-Henry experiment between nitropropane and N-Ts benzaldimine using catalyst 5 yielded similar levels of dr and ee. While trans-3aa was formed with modest ee (65%), the optical purity of the cis isomer was merely 20% ee initially. Ee's of trans-3aa, cis-3aa, and the product were monitored over time. Ee's of both intermediate isomers gradually decreased over time, accompanied by a steady accumulation of the cascade product trans-4aa of constantly high optical purity. Eventually, both cis-3aa and trans-3aa became racemic. Factoring a 3:1 kinetic resolution efficiency (S = 3), the initial moderate 65% enantioselectivity for trans-3aa (er = 6.6:1) was enhanced by the subsequent DKR step to a theoretical enantiomeric ratio of 6.6 x 3 = 19.8/1, compared to the 91% observed ee, for the pyrrolidine product trans-4aa. Based on the above analysis, the low ee of cis-3aa is direct evidence that the cis-to-trans isomerization is primarily due to reaction reversibility (C—C bond cleavage), not NO2 group epimerization under basic conditions. Due to the modest selectivity of the kinetic resolution step, direct epimerization of cis-3aa of 20% ee would result in a theoretical ee of 83% (er = 3.7 x 3 = 11.1) for the final product.

The rich functionalities surrounding this scaffold could be engaged in additional cyclization reactions with the pyrrolidine nitrogen. Interestingly, attempts to tether the aromatic ring and pyrrolidine via dehydrogenative annulation resulted in a fully aromatized compound due to in situ oxidation.16

The appending side chain could be engaged in additional cyclization reactions with the pyrrolidine nitrogen. Interestingly, attempts to tether the aromatic ring and pyrrolidine via dehydrogenative annulation resulted in a fully aromatized compound due to in situ oxidation.16

Table 3. Real Time Conversion, dr, and ee for the Intermediates and Product

<table>
<thead>
<tr>
<th>entry</th>
<th>time (h)</th>
<th>trans/cis (3aa)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>2.3</td>
<td>10</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>2.5</td>
<td>24</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>2.7</td>
<td>40</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>3.1</td>
<td>72</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>2.3</td>
<td>quant.</td>
<td>80</td>
</tr>
</tbody>
</table>

*The aza-Michael cyclization was carried at 100 °C.

In summary, we have developed a highly diastereo- and enantioselective organocatalytic cascade that provides heavily substituted pyrrolidines with up to three stereogenic centers. This domino reaction relies on a reversible aza-Henry reaction and a subsequent DKR aza-Michael cyclization, both catalyzed by an amine/amide Cinchona alkaloid derivative, to ensure overall stereoselectivity. The unique features of this reaction and the further utility of amide derived H-bond catalysts are being investigated in detail and will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for all new compounds, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.


The authors declare no competing financial interest.