Diels–Alder Cycloaddition Strategy for Kinetic Resolution of Chiral Pyrazolidinones

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ABSTRACT

A rare example of the application of a catalytic, enantioselective Diels–Alder cycloaddition to affect a kinetic resolution has been developed. Chiral pyrazolidinones are resolved with high selectivity through a process that utilizes a relay of stereochemical information from a permanent chiral center to a fluxional chiral center to enhance the inherent selectivity of the chiral Lewis acid catalyst.

Enantioselective, metal-catalyzed asymmetric synthesis is among the most powerful means to access enantioenriched compounds. However, many cases exist in which catalyst limitations preclude direct access to a full complement of compounds within a product class. Thus, the kinetic resolution of racemic mixtures remains a prominent and often complementary approach to access enantioenriched compounds. The pyrazolidinones represent a class of heterocycles that highlight the complementarity of direct asymmetric synthesis and kinetic resolution approaches. Furthermore, the pyrazolidinones remain attractive targets due to their bioactivity and the challenges associated with their synthesis in enantioenriched form.


imides as a direct method to synthesize enantioenriched pyrazolidinones. The method allows for the synthesis of C5-substituted pyrazolidinones with good to excellent enantioselectivity when the C5-substituent is of relatively small steric volume. However, the enantioselectivity decreases significantly in reactions that form pyrazolidinones with larger C-5 substituents. Thus, we required an improved strategy to access pyrazolidinones bearing C5-substituents of larger steric volume.

Achiral pyrazolidinones have proven to be exceptionally effective as templates in enantioselective conjugate addition, dipolar cycloaddition, and Diels—Alder (DA) cycloadDITION reactions involving \( \alpha,\beta \)-unsaturated pyrazolidinone imide electrophiles. We hypothesized that the use of racemic 5-substituted pyrazolidinones as the templates in such reactions might lead to a kinetic resolution of the C5-pyrazolidinone stereocenter. We surmised that DA cycloadditions of a diene with racemic, 5-substituted, \( \alpha,\beta \)-unsaturated pyrazolidinone imides were particularly promising as a strategy for kinetic resolution since C5-substituent size exerts a significant influence on the enantioselectivity of chiral Cu(II) Lewis acid-catalyzed DA cycloadditions with achiral pyrazolidinone imides.

Although kinetic resolutions based on DA cycloaddition reactions are known, the majority employ an enantioenriched diene or dienophile as a reagent to accomplish the resolution. In contrast, kinetic resolutions based on catalytic, enantioselective DA cycloadditions are rare. Herein we report a strategy for the resolution of racemic \( \alpha,\beta \)-unsaturated pyrazolidinone imides by catalytic, enantioselective DA cycloadditions.

An initial study of reaction conditions for the kinetic resolution of racemic \( \alpha,\beta \)-unsaturated pyrazolidinone imide 1a led to the identification of Cu(OTf)\(_2\) and aminooindanol-derived bixoxazoline ligand 2 as the most promising catalyst precursors (Scheme 1). When the resolution of 1a was conducted with 10 equiv of cyclopentadiene, 11 mol % of 2, and 10 mol % of Cu(OTf)\(_2\), the enantioenriched \( \alpha,\beta \)-unsaturated pyrazolidinone imide (S)-1a was isolated with 99% ee at 66% conversion (s = 15). This result served to further support our previous observation that pyrazolidinone C5-substitution plays a pivotal role in the enantioselectivity of the chiral Cu(II)-catalyzed DA cycloadditions involving \( \alpha,\beta \)-unsaturated pyrazolidinone imides. Thus, the kinetic resolution of C5-substituted, \( \alpha,\beta \)-unsaturated pyrazolidinone imides based on Cu(OTf)\(_2\)-catalyzed DA cycloadditions was selected for further optimization.

Although pyrazolidinone (S)-1a can be isolated with excellent enantiomeric excess under the reaction conditions presented in Scheme 1, the DA kinetic resolution strategy presented operational challenges not commonly associated with other kinetic resolution strategies. Foremost among the challenges was the use of excess cyclopentadiene as a reactant in the resolving cycloaddition. In contrast to the many kinetic resolution protocols that utilize 0.5–0.6 equiv of a reactive reagent to eliminate the potential for overconversion of the starting material, our kinetic resolution approach based on the DA cycloaddition often led to conversions of greater than 60% due to the presence of excess cyclopentadiene. Unfortunately, the logical solution of adding a limiting quantity of the diene proved impractical due to dimerization of the cyclopentadiene to dicyclopentadiene under the reaction conditions. Furthermore, the use of dienes that are less prone to dimerization led to less selective resolutions.

Thus, a more controllable set of reaction conditions was necessary to minimize the conversion of the dienophile past 50% in the presence of excess cyclopentadiene. Two parameters were evaluated to accomplish this goal. First, the loading of the chiral Lewis acid catalyst was reduced to 5 mol % (Table 1, entry 1). This modification led to a more controllable reaction of cyclopentadiene with pyrazolidinone crotonimide 1a (56% conversion over 9 h, 98% ee for the remaining (S)-1a. Second, the effect of substitution at the \( \beta \)-position of the enoyl fragment of the dienophile was studied. Not surprisingly, the cycloaddition of pyrazolidinone acrylimide 1b was essentially uncontrollable (entry 2). The Cu(OTf)\(_2\)-catalyzed cycloaddition of 1b with cyclopentadiene proceeded to 100% conversion in less than 1 h at room temperature. In contrast, the corresponding resolution of pyrazolidinone cinnamimide 1c was extremely slow (entry 3). The cycloaddition of 1c with cyclopentadiene occurred to only 36% conversion after 54 h and with reduced selectivity (s = 8). Given these results, we chose to proceed

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**Scheme 1.** Cu(OTf)\(_2\)-Catalyzed Kinetic Resolution of \( \alpha,\beta \)-Unsaturated Pyrazolidinone Imide 1a

[Diagram of Scheme 1]

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with further studies on the scope of the kinetic resolution with pyrazolidinone crotonimide dienophiles.

### Table 1. Effect of Enoyl β-Substitution on the Kinetic Resolution

<table>
<thead>
<tr>
<th>entry</th>
<th>R (1)</th>
<th>time (h)</th>
<th>conversion (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (S)-1a (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>s&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me (1a)</td>
<td>9</td>
<td>56</td>
<td>98</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>H (1b)</td>
<td>1</td>
<td>100</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>Ph (1c)</td>
<td>54</td>
<td>36</td>
<td>39</td>
<td>8</td>
</tr>
</tbody>
</table>

<sup>a</sup> For experimental details, see the Supporting Information. <sup>b</sup> Determined by 1H NMR spectroscopy of the crude reaction mixture with triphenyl-methane as the internal standard. <sup>c</sup> Determined by chiral HPLC. Selectivity factor (s) = ln[(1 - c)(1 - ee)]/ln[(1 - c)(1 + ee)] where c is the conversion and ee is the enantiomeric excess of remaining 1.

We next set out to determine whether the reaction conditions for the kinetic resolution of pyrazolidinone crotonimide 1a would also be effective for the resolutions of additional pyrazolidinones bearing a chiral center at the 5-position of the pyrazolidinone ring (Table 2). As previously illustrated, the resolution of pyrazolidinone crotonimide 1a occurred with high selectivity (entry 1, s = 34). We were further pleased to observe that the resolutions of pyrazolidinone crotonimides 1d (R<sub>1</sub> = t-Bu, R<sub>2</sub> = Ph) and 1e (R<sub>1</sub> = Ph, R<sub>2</sub> = Ph) occurred with high selectivities (entries 2 and 3; s = 19 and 30, respectively). Entries 1–3 in Table 2 clearly demonstrate the feasibility of using our DA strategy for highly selective kinetic resolutions of pyrazolidinone crotonimides, but these results provide minimal insight into the origin of the observed selectivity.

We next synthesized pyrazolidinone crotonimides 1f (R<sub>1</sub> = i-Pr, R<sub>2</sub> = 1-naphthyl) and 1g (R<sub>1</sub> = i-Pr, R<sub>2</sub> = Me) to evaluate whether the size of the substituent on the fluxional N1 nitrogen impacts the selectivity of the resolution. Pyrazolidinone crotonimide 1f (R<sub>2</sub> = 1-naphthyl) was resolved efficiently and controllably (entry 4, s = 35). The nearly identical selectivity factors observed for the resolutions of 1a (R<sub>1</sub> = Ph) and 1f (R<sub>1</sub> = 1-naphthyl, compare entries 1 and 4) led us to initially conclude that the selectivity of the kinetic resolution was primarily controlled by the catalyst and the identity of the C5 substitution. However, the resolution of an additional pyrazolidinone crotonimide 1g bearing a relatively small N1 substituent (R<sub>2</sub> = Me) was markedly less selective. The selectivity factor for resolution of 1g (R<sub>2</sub> = Me) was 8, and enantiomerically enriched (S)-1g was isolated in only 86% ee (entry 5). The lower selectivity observed for the resolution of 1g compared with 1a and 1f (compare entry 5 with entries 1 and 4) suggests that a relay of stereochemical information from the fixed chirality of the pyrazolidinone to the fluxional chirality of the N1 nitrogen plays a prominent role in the selectivity of the resolution.

Scheme 2 presents an explanation for the influence of N1 substituent size on the selectivity of the kinetic resolution reactions reported in Table 2. Initial coordination of the chiral Cu(II) Lewis acid to the racemic starting material establishes an equilibrium population of complexes 4 and 5. Complex 4, which is formed from the (S)-enantiomer of the pyrazolidinone crotonimide, likely leads to a dissonant stereochemical interaction between the ligand chirality and the chirality of the fluxional nitrogen configuration at C5. Such a situation would result in both faces of the dienophile being blocked from approach of the diene and a relatively slow rate of reaction through complex 4. Complex 5, which is formed from the (R)-enantiomer of the pyrazolidinone crotonimide, would lead to a consonant interaction between the ligand chirality and the chirality of the fluxional nitrogen center. Thus, the ligand chirality and the chirality of the fluxional nitrogen center reinforce each other and effectively shield the bottom face of the dienophile, leaving the top face open to approach of the diene and a relatively fast rate of reaction for complex 5 relative to complex 4. The poor selectivity for the kinetic resolution of pyrazolidinone crotonimide 1g (R<sub>2</sub> = Me) compared with those for pyrazolidinone crotonimides 1a (R<sub>2</sub> = Ph) and 1f (R<sub>2</sub> = 1-naphthyl) offers support for the hypothesis presented in Scheme 2. The small size of the fluxional N1 substituent in 1g prevents efficient shielding of the top face of the dienophile by the fluxional group, rendering the cycloaddition with complex 4 competitive with the corresponding cycloaddition with complex 5.

### Table 2. Effect of Substitution on the Selectivity of the Kinetic Resolution Reactions<sup>a</sup>

<table>
<thead>
<tr>
<th>entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>1</th>
<th>time (h)</th>
<th>conv (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (S)-1 (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>yield</th>
<th>1 (%)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>s&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
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<td>1a</td>
<td>8</td>
<td>56</td>
<td>98</td>
<td>40</td>
<td>34</td>
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</tr>
<tr>
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<td>t-Bu</td>
<td>Ph</td>
<td>1d</td>
<td>18</td>
<td>60</td>
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<td>39</td>
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</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>Ph</td>
<td>1e</td>
<td>2</td>
<td>57</td>
<td>98</td>
<td>34</td>
<td>30</td>
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</tr>
<tr>
<td>4</td>
<td>i-Pr</td>
<td>1-Naph</td>
<td>1f</td>
<td>20</td>
<td>57</td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td>i-Pr</td>
<td>Me</td>
<td>1g</td>
<td>7</td>
<td>63</td>
<td>86</td>
<td>40</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> For experimental details, see the Supporting Information. <sup>b</sup> Determined by 1H NMR spectroscopy of the crude reaction mixture with triphenyl-methane as the internal standard. <sup>c</sup> Determined by chiral HPLC. <sup>d</sup> Isolated yield of (S)-1. <sup>e</sup> Selectivity factor (s) = ln[(1 - c)(1 - ee)]/ln[(1 - c)(1 + ee)] where c is the conversion and ee is the enantiomeric excess of remaining 1.
With an efficient method to access enantiomerically enriched, N2 acylated pyrazolidinones in hand, it remained to develop conditions that would provide access to both enantiomers of the N–H pyrazolidinones 6 (Scheme 3).\(^{10}\)

After separation of the enantiomerically enriched starting material and the DA cycloadduct, the (S)-N–H pyrazolidinones 6a and 6f are liberated by reaction of 1a and 1f with the lithium alkoxide of p-methoxybenzyl alcohol (Scheme 3). The parent pyrazolidinones (S)-6a and (S)-6f were isolated in moderate to good yields with minimal erosion of the enantiomeric excess (eq 1). The enantiomeric (R)-N–H pyrazolidinones (R)-6a and (R)-6f could also be isolated in good yields, albeit with lower enantiomeric purity from the reaction of the DA adducts 3a and 3f with the lithium alkoxide of p-methoxybenzyl alcohol (eq 2).

In conclusion, we have developed a practical DA cycloaddition strategy for the kinetic resolution of chiral pyrazolidinones that could not be obtained in high enantiomeric excess from direct methods. Our approach represents a rare example of a catalytic, enantioselective DA cycloaddition reaction as a means to effect a kinetic resolution. Furthermore, this strategy highlights the role that fluxional chirality at nitrogen centers may play in influencing stereochemical outcomes, and further demonstrates the potential to relay stereochemical information from a remote stereocenter to a fluxional nitrogen center near the site of reaction. The extension of the present strategy to access enantiomerically enriched 4-substituted, 4,5-disubstituted, and 4,4-disubstituted pyrazolidinones is currently underway.

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**Supporting Information Available:** Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For procedures and additional data on the cleavage of \( \alpha,\beta \)-unsaturated pyrazolidinone imides 1a, 1d–g, and Diels–Alder adducts 3a and 3d–g with the lithium alkoxide of p-methoxybenzyl alcohol, see Table 1 and Table 2 in the Supporting Information.