Aza-Piancatelli Rearrangement Initiated by Ring Opening of Donor–Acceptor Cyclopropanes

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ABSTRACT

D–A cyclopropanes: a new platform to initiate the aza-Piancatelli reaction

The development of a new platform to initiate the cascade rearrangement of furans for the formation of functionalized cyclopentenone building blocks is reported. This methodology allows the creation of congested vicinal stereogenic centers with high diastereoselectivity through a 4π-electrocyclization process.

Functionalized cyclopentenones are an important structural motif frequently found in natural products and pharmaceutical drugs.1 The 4π-electrocyclization of pentadienyl cation intermediates represents one of the most powerful methods available for constructing cyclopentenones. The quintessential example is the Nazarov cyclization, which relies on a divinyl ketone as the precursor to the requisite pentadienyl cation intermediate.2 Limitations associated with the dienone substitution pattern in the Nazarov cyclization have inspired the search for new approaches to access the requisite pentadienyl cation, and progress in this area has been demonstrated in several elegant reports.3

We were drawn to a conceptually distinct strategy to gain access to the required pentadienyl cation intermediate that is based on the cascade molecular rearrangement of α-furycarbinoins (Scheme 1).4 The overall transformation is highly diastereoselective and believed to proceed through a cascade sequence that terminates in a 4π-electrocyclic ring closure of a pentadienyl cation intermediate D.5

Since the pioneering work by Piancatelli et al. in 1976, the synthesis of functionalized 4-hydroxy- and 4-amino-cyclopentenones through a molecular rearrangement has almost exclusively relied on α-furycarbinoins.6 The classic Piancatelli rearrangement is initiated by activation of

α-furylcarnbinols with a Brønsted or Lewis acid. Despite the success of this strategy, this mode of activation has its limitations. For example, when furylcarnbinols bearing a tertiary carbinol side chain are employed, a competitive dehydration pathway severely decreases the yield of the molecular rearrangement (Scheme 2, eq 1). To permit greater functional group compatibility and to open a new direction for the Piancatelli rearrangement, alternative methods for triggering the reaction are necessary. Here, we describe a novel strategy to initiate the cascade sequence by reporting the first highly stereoselective aza-Piancatelli rearrangement to assemble α-quaternary carbon stereocenters (Scheme 2, eq 2).

Our pursuit of a new trigger for the aza-Piancatelli reaction started by investigating the use of donor-acceptor (D–A) cyclopropanes, as they are proven to be extremely versatile synthetic intermediates. The inherent ring strain (27.5 kcal/mol) and polarization of substituted D–A cyclopropanes make them latent carbocation equivalents upon Lewis acid activation. This work provides a new mode of activation for the molecular rearrangement of a range of furans that complements the traditional Piancatelli rearrangement.

Substituted cyclopropane 3 was selected as a model substrate to test the feasibility of using a D–A cyclopropane to trigger the cascade rearrangement. Lewis acids that were previously known to facilitate ring-opening of D–A cyclopropanes were initially evaluated using p-methoxyaniline as the nucleophile component. Several Lewis acids were found to promote the desired cascade reaction, albeit in a range of conversions and diastereoselectivities (Table 1). To our gratification, the reactions are facile and often complete in <10 min at rt in reagent grade acetonitrile. From the initial screen, Lewis acidic salts of rare earth, Dy(OTf)3, and Sc(OTf)3 were identified to be superior catalysts with respect to diastereoselectivity and conversion. Although less selective, fewer decomposition byproducts were observed by 1H NMR spectroscopy when YbCl3 and ZnBr2 catalysts were used. Interestingly, an increase in both the rate and diastereoselectivity was observed with ZnBr2 at 80°C compared to ZnBr2 at rt (cf. entries 8 and 9). There was no noticeable improvement.

Table 1. Lewis Acid Screen for the Rearrangement

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>time</th>
<th>yield (%)</th>
<th>ratio</th>
<th>a</th>
<th>b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)</td>
<td>48 h</td>
<td>&lt;5</td>
<td>n.d.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Dy(OTf)</td>
<td>5 min</td>
<td>57</td>
<td>6:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>La(OTf)</td>
<td>5 min</td>
<td>77</td>
<td>1:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Sc(OTf)</td>
<td>5 min</td>
<td>50</td>
<td>5:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Sn(OTf)</td>
<td>48 h</td>
<td>&lt;5</td>
<td>n.d.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Yb(OTf)</td>
<td>5 min</td>
<td>58</td>
<td>2:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>YbCl3</td>
<td>24 h</td>
<td>80</td>
<td>1:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>ZnBr2</td>
<td>24 h</td>
<td>84</td>
<td>1:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>ZnBr2</td>
<td>2 h</td>
<td>83</td>
<td>2:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Dy(OTf)</td>
<td>24 h</td>
<td>58</td>
<td>2:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Sc(OTf)</td>
<td>3 h</td>
<td>58</td>
<td>3:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Sn(OTf)</td>
<td>48 h</td>
<td>&lt;5</td>
<td>n.d.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Determined by 1H NMR spectroscopy using dimethyl terephthalate as the internal standard. * Determined by 1H NMR spectroscopy. * 1 equiv of ZnBr2 was used. * Reaction conducted at 80°C. * Reaction conducted in CH2Cl2, n.d. = not determined.

using dichloromethane as the solvent, which is often used in ring-opening reactions of D–A cyclopropanes (entries 10–12). We chose to investigate the scope of this transformation with dysprosium triflate because it gave the best diastereoselectivity and because of our long-term interest in this intriguing Lewis acid. It is important to note that water plays a role in the selectivity of the rearrangement; see Supporting Information for more details.

Under the optimized reaction conditions (10 mol % Dy(OTf)$_3$, MeCN, rt), we investigated the scope of this transformation with various aniline nucleophiles (Scheme 3). A variety of cyclopentenones were synthesized in excellent yield with diastereoselectivities that range from 6:1 to 60:1. Nuclear Overhauser effect spectroscopy (NOESY) of the major diastereomer and X-ray crystal structure analysis of 10 indicated a cis-relationship between the C4 hydrogen atom and C5 tethered dimethyl malonate group. In general, the use of anilines substituted with an electron-withdrawing group resulted in the highest diastereoselectivity (11–13). Secondary anilines were also well tolerated, but a drop in diastereoselectivity was observed for tetrahydroquinoline 15 compared to N-methylaniline 14.

Encouraged by these results, we subsequently investigated a series of reactions to evaluate if other aryl substituted D–A cyclopropanes would be compatible with the new mode of activation. Specifically, we studied the electronic effects by varying the R$^1$ substituents on the aryl ring attached to cyclopropane starting material 6 (Scheme 3). The reaction proceeded exceptionally well when R$^1$ was an electron rich p-methoxyphenyl group (16–18). In these cases, excellent diastereoselectivities were obtained with anilines possessing either an electron-donating group (16) or an electron-withdrawing group (18). This is a notable distinction compared to cascade rearrangements with 3 (Ar = Ph; compare substrates 4 and 16 to 11 and 18, respectively). It appears that the electron-rich aryl substituent plays a more significant role in controlling the diastereoselectivity compared to anilines and can override the wide variations previously observed.

To our surprise, we discovered that it was difficult to study the cascade rearrangement when an electron-deficient group was placed at the R$^1$ position because the products derived from these substrates were less stable and frequently underwent an intramolecular Michael addition to afford a bicyclic compound. X-ray crystal structure analysis of bicycle 22 helped establish the configuration of the three contiguous stereocenters and confirmed that only the cyclopentenone derived from the major diastereomer led to bicycle formation (Figure 1). Unfortunately, all attempts to suppress bicycle formation were unsuccessful and isolation of the desired cyclopentenone product was further complicated by bicycle formation during column chromatography. Although cyclopentenone product isolation was difficult, $^1$H NMR spectroscopy was successfully utilized to study the diastereoselectivity resulting from the cascade rearrangement. Treatment of a cyclopropane bearing an electron-withdrawing benzonitrile group with a variety of anilines resulted in products with low diastereoselectivity, ranging from 1:1 to 5:1 (19–21). Under the current reaction conditions, the incorporation of an electron-deficient aryl ring decreases product stability and erodes diastereoselectivity. Despite this, we were pleased to find that all reactions in Table 2 could be initiated at ambient temperature and pressure, regardless of the electronic nature of the aryl ring attached to the D–A

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(12) See Supporting Information. CCDC 916408.
(13) p-Benzonitrile and p-trifluoromethyl benzene were tested.
(14) See Supporting Information. CCDC 901791.
cyclopropane starting material. High temperatures or pressures are often required to help facilitate the Piancatelli reaction when furylcarbinols are employed.\textsuperscript{6b}

We next turned our attention toward increasing the diastereoselectivity of reactions that proceeded with moderate levels of selectivity (below 12:1). Early experiments indicated that temperature influenced the diastereoselectivity of the cascade rearrangement (Table 1, entry 9). Generally, increasing the reaction temperature leads to decreased levels of stereocontrol; however, there have been reports in the literature illustrating an inverse relationship between temperature and stereoselectivity.\textsuperscript{15} To our delight, increasing the reaction temperature to 80 °C led to a significant increase in the levels of diastereoselectivity (Scheme 4). The diastereoselectivity increased from 6:1 to 16:1 (4) when \( p \)-methoxyaniline was employed and from 13:1 to 30:1 (9) when aniline was used. Importantly, the efficiency of these reactions also improved. We observed a similar pattern of higher temperatures leading to increased levels of diastereoselectivity for the series of cyclopropane starting materials bearing an electron-withdrawing aryl group (19, 20, and 21).\textsuperscript{16} The most notable example was with \( p \)-trifluoromethylaniline where the selectivity went from 5:1 to 22:1.

The results in Schemes 3 and 4 revealed that both the temperature and electronic nature of the substituents at the termini of the pentadienyl cation intermediate, either C1 or C5, influence the diastereoselectivity of the transformation. To gain insight into the mechanistic implications of the increased diastereoselectivity with heat, we carried out reversibility studies. Resubjection of 4, 11, 12, and 19 to the reaction conditions at 80 °C did not provide any support for a reversible reaction. The minor diastereomer remained unchanged, and some of the major diastereomer was converted into a bicyclic compound via an intramolecular Michael addition, analogous to the formation of 22. These results suggest that the \( 4\pi \)-electrocyclization is not reversible under the reaction conditions and that there is an inverse temperature dependence on the diastereoselectivity.\textsuperscript{15} Further studies are underway to help elucidate the mechanism and the diastereodetermining event of this cascade transformation.

In conclusion, we have developed a method for the construction of densely functionalized cyclopentenones based on a new cascade rearrangement. Electron-donating groups at the C5 position, electron-withdrawing groups on the aniline, and heat all increase the diastereoselectivity of the transformation. Utilizing uniquely reactive donor–acceptor cyclopropanes as a trigger for the aza-Piancatelli provides efficient access to all-carbon quaternary stereogenic centers and provides a novel platform to initiate the cascade rearrangement. We believe this new approach holds promise to develop other novel transformations.

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Supporting Information Available. Full experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.