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

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ABSTRACT





formation of densely functionalized cyclopentenones (dr up to 60:1)

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 -furylcarbinols (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-aminocyclopentenones through a molecular rearrangement has almost exclusively relied on α -furylcarbinols.⁶ The classic Piancatelli rearrangement is initiated by activation of

⁽¹⁾ For representative reviews, see: (a) Gibson, S. E.; Lewis, S. E.; Mainolfi, N. J. Organomet. Chem. 2004, 689, 3873. (b) Kurteva, V. B.; Afonso, C. A. M. Chem. Rev. 2009, 109, 6809. (c) Roche, S. P.; Aitken, D. J. Eur. J. Org. Chem. 2010, 5339.

⁽²⁾ For reviews on the Nazarov reaction, see: (a) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. (b) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (c) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193. (d) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676. (e) Vaidya, T.; Eisenberg, R.; Frontier, A. J. *ChemCatChem* **2011**, *3*, 1531.

⁽³⁾ For representative examples, see: (a) Prandi, C.; Deagostino, A.; Venturello, P.; Occhiato, E. G. *Org. Lett.* **2005**, *7*, 4345. (b) Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348. (c) Spencer, W. T.; Levin, M. D.; Frontier, A. J. *Org. Lett.* **2010**, *13*, 414. (d) Wu, Y.-K.; West, F. G. *J. Org. Chem.* **2010**, *75*, 5410. (e) Brooks, J. L.; Caruana, P. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 12454.

^{(4) (}a) Veits, G. K.; Wenz, D. R.; Read de Alaniz, J. Angew. Chem., Int. Ed. 2010, 49, 9484. (b) Palmer, L. I.; Read de Alaniz, J. Angew. Chem., Int. Ed. 2011, 50, 7167. (c) Palmer, L. I.; Read de Alaniz, J. Org. Lett. 2013, 15, 476.

⁽⁵⁾ For computational studies on the proposed mechanism, see: (a) Faza, A. N.; Lopez, C. S.; Alvarez, R.; de Lera, I. R. *Chem.*—*Eur. J.* **2004**, *10*, 4324. (b) Davis, L. D.; Tantillo, D. J. *Curr. Org. Chem.* **2010**, *14*, 1561.

^{(6) (}a) Piancatelli, G.; Scettri, A.; Barbadoro, S. *Tetrahedron Lett.* **1976**, *17*, 3555. (b) Piancatelli, G.; Dauria, M.; Donofrio, F. *Synthesis* **1994**, 867. (c) Yin, B.-L.; Wu, Y.-L.; Lai, J.-Q. *Eur. J. Org. Chem.* **2009**, 2695. (d) Ulbrich, K.; Kreitmeier, P.; Reiser, O. *Synlett* **2010**, 2037. (e) Reddy, B.V. S.; Narasimhulu, G.; Lakshumma, P. S.; Reddy, Y. V.; Yadav, J. S. *Tetrahedron Lett.* **2012**, *53*, 1776. (f) Reddy, B.V. S.; Reddy, Y. V.; Lakshumma, P. S.; Narasimhulu, G.; Yadav, J. S.; Sridhar, B.; Reddy, P. P.; Kunwar, A. C. *RSC Adv.* **2012**, *2*, 10661.

Scheme 1. Proposed Mechanism of the Molecular Rearrangement



 α -furylcarbinols with a Brønsted or Lewis acid. Despite the success of this strategy, this mode of activation has its limitations. For example, when furylcarbinols bearing a tertiary carbinol side chain are employed, a competitive dehydration pathway severely decreases the yield of the molecular rearrangement (Scheme 2, eq 1).⁷ 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).

Scheme 2. Cascade Rearrangements of Activated Furans

Previous work: Piancatelli rearrangement of a furans with a tertiary



This work: Aza-Piancatelli rearrangement of furans with donoracceptor cyclopropane side chain



Donor-acceptor cyclopropanes: new trigger to initiate the aza-Piancatelli
 No competitive dehydration product observed
 Evacilized directoracelesticity

- Excellent diastereoselectivity

Our pursuit of a new trigger for the aza-Piancatelli reaction started by investigating the use of donoracceptor (D-A) cyclopropanes, as they are proven to be extremely versatile synthetic intermediates.⁸ The inherent Table 1. Lewis Acid Screen for the Rearrangement



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

ring strain $(27.5 \text{ kcal/mol})^9$ and polarization of substituted D–A cyclopropanes make them latent carbocation equivalents upon Lewis acid activation.¹⁰ 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.⁸ 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

⁽⁷⁾ D'Auria, M.; D'Onofrio, F.; Piancatelli, G.; Scettri, A. *Gazz. Chim. Ital.* **1986**, *116*, 173.

⁽⁸⁾ For representative reviews on D-A cyclopropanes, see: (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (c) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051. (d) Campbell, M. J.; Johnson, J. S.; Parsons, A. T.; Pohlhaus, P. D.; Sanders, S. D. J. Org. Chem. **2010**, *75*, 6317.

⁽⁹⁾ Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. Chem. Rev. **1989**, 89, 165.

⁽¹⁰⁾ For representative examples using cyclopropanes in the homo-Nazarov cyclization, see: (a) Yadav, V. K.; Kumar, N. V. *Chem. Commun.* **2008**, 0, 3774. (b) De Simone, F.; Andrès, J.; Torosantucci, R.; Waser, J. *Org. Lett.* **2009**, *11*, 1023. (c) De Simone, F.; Gertsch, J.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5767. (d) Patil, D. V.; Phun, L. H.; France, S. *Org. Lett.* **2010**, *12*, 5684. (e) Phun, L. H.; Patil, D. V.; Cavitt, M. A.; France, S. *Org. Lett.* **2011**, *13*, 195.

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.¹¹ 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.¹² 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 \mathbf{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 electrondeficient group was placed at the R¹ position because the products derived from these substrates were less stable and frequently underwent an intramolecular Michael addition to afford a bicyclic compound.¹³ 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).¹⁴ 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, ¹H NMR spectroscopy was successfully utilized to study the diastereoselectivity resulting from

Scheme 3. Substrate Scope for the Cascade Rearrangement^a



^{*a*} Diastereoselectivity and yield determined by ¹H NMR spectroscopy using dimethyl terephthalate as the internal standard. ^{*b*}See Supporting Information for details.

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

⁽¹¹⁾ Veits, G. K.; Read de Alaniz, J. Tetrahedron 2012, 68, 2015.

⁽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.^{6b}



Figure 1. ORTEP drawing of bicyclic compound **22** (left) shown with 50% thermal ellipsoids. Hydrogen atoms have been omitted for clarity.

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.¹⁵ To our delight, increasing the reaction temperature to 80 °C lead 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).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



^{*a*} Diastereoselectivity and yield determined by ¹H NMR spectroscopy using dimethyl terephthalate as the internal standard.

Michael addition, analogous to the formation of **22**. These results suggest that the 4π -electrocyclization is not reversible under the reaction conditions and that there is an inverse temperature dependence on the diastereoselectivity.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.

^{(15) (}a) Landis, C. R.; Halpern, J. J. Am. Chem. Soc. 1987, 109, 1746.
(b) Markó, I. E.; Chesney, A.; Hollinshead, D. M. Tetrahedron: Asymmetry 1994, 5, 569. (c) Stone, G. B. Tetrahedron: Asymmetry 1994, 5, 465. (d) Muzart, J.; Hénin, F.; Aboulhoda, S. J. Tetrahedron: Asymmetry 1997, 8, 381. (e) Sibi, M. P.; Rheault, T. R. J. Am. Chem. Soc. 2000, 122, 8873.

⁽¹⁶⁾ As observed previously with substrates bearing an electrondeficient aryl ring, the same difficulties in product isolation were encountered.

The authors declare no competing financial interest.