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Asymmetric Induction via a Helically Chiral Anion: Enantioselective PCCP Brønsted Acid-Catalyzed Inverse Electron-Demand Diels-Alder Cycloaddition of Oxocarbenium Ions

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Abstract

An enantioselective catalytic inverse electron-demand Diels-Alder reaction of salicylaldehyde acetal-derived oxocarbenium ions and vinyl ethers to generate 2,4-dioxychromanes is described. Chiral PCCP acids are found to be effective for a variety of substrates. Computational and X-ray crystallographic analyses support the unique hypothesis that a point chirality-induced, helically chiral anion dictates the absolute sense of stereochemistry in this reaction.

Graphical Abstract

Oxygenated chromanes form the core architecture of a number of natural products, including the antitumor agent berkelic acid,¹ the antibiotic paecilospirone,² and the anti-HIV agent calanolide A³ (Figure 1a). A particularly attractive strategy to access such structures would be to fuse readily available salicylaldehyde acetals and vinyl ethers via an inverse electron demand Diels-Alder reaction. In theory, a chiral Brønsted acid catalyst⁴ could ionize the acetal substrate to form an activated oxocarbenium ion, and subsequently exert control over absolute stereochemistry in the cycloaddition step, thereby generating enantioenriched 2,4-dioxychromanes. Indeed, related reactions of *o*-quinone methide intermediates generated by the ionization of diaryl methanols or similar species can be achieved with high enantioselectivity.⁵ The production of 2,4-dioxychromanes, on the other hand, requires the

generation and absolute stereocontrol of oxocarbenium ion intermediates, which represents a substantial challenge at the forefront of the field of asymmetric catalysis.⁶ Additionally, a viable catalyst for this process must be sufficiently mild to avoid ionizing the chromane products, which in our design also incorporate acetal functionality.

We recently reported a platform for chiral Brønsted acid catalysis based on pentacarboxycyclopentadienes (PCCPs),⁷ which are strongly acidic and simple to prepare from chiral alcohol precursors (Figure 1b).⁸ In this Communication, we report the development of an enantioselective PCCP-catalyzed inverse electron demand Diels-Alder reaction.

We selected the reaction of salicylaldehyde diethyl acetal (**1**) and ethyl vinyl ether (**2**) to identify a viable catalyst for the Diels-Alder reaction (Table 1). Reactions were conducted with 5 mol% catalyst loading at ambient temperature in benzene. Cycloadduct diastereoselectivity was found to be >20:1 in all cases. The use of the previously reported catalyst **4**, derived from L-menthol, resulted in the production of chromane **3** in 54% yield with an 85:15 er (entry 1). Catalysts **5** and **6**, derived from acyclic alcohols (entries 2 and 3), and catalyst **7**, derived from a five-membered cyclic alcohol (entry 4), also showed promise but could not be sufficiently optimized in terms of enantioselectivity and so were not further pursued. Remarkably, catalyst **8**, derived from *trans*-2-methylcyclohexanol, generated product with a 91:9 er (entry 5), a significant improvement over the structurally related catalyst **4**. In fact, we observed a clear trend of decreasing enantioselectivity with increasing size of the 2-substituent, with *i*-Pr, *i*-Bu, and *c*-hexyl resulting in enantiomeric ratios of 89:11, 82:18, and 59:41 respectively (catalysts **9–11**, entries 6–8). On the other hand, catalyst **12**, derived from *trans*-2-phenylcyclohexanol, furnished the product in 63% yield with 92:8 er (entry 9), which is an essentially identical outcome to catalyst **8**. Once again, however, attempts to increase selectivity with further alkyl substitution led to a major decrease in reactivity (catalysts **13** and **14**, entries 10 and 11), and in the case of **14**, of enantioselectivity as well. In the extreme, catalyst **15**, containing an *o*-methylphenyl substituent, was completely unreactive (entry 12). We next explored the effects of modulating the electronic nature of the phenyl ring. We found that, while a *p*-CF₃ substituent was detrimental to selectivity (**16**, entry 13), *p*-methoxy and *p*-methylthioxy substituents resulted in appreciable increases in both yield and enantioselectivity (**17** and **18**, entries 14 and 15). Catalyst **19**, incorporating a phenylacetylene substituent, was reactive but generated racemic product (entry 16). Based on the combination of performance and accessibility, we selected PCCP **17** as our optimal catalyst. The findings of these catalyst optimization studies were initially perplexing because the catalysts seem to be relatively insensitive to electronic perturbation and to generally follow an inverse steric trend. However, we believe these data can be rationalized via the stereochemical model that we have subsequently developed (*vide infra*).

Using catalyst **17**, we next probed the impact of structural changes to the substrates (Table 2). In terms of the salicylaldehyde acetal moiety, we found that ethyl and isopropyl acetals led to products **3** and **20** with essentially equal enantioselectivities (entries 1 and 2), while the reaction with the methyl acetal substrate was somewhat less selective in producing **21** (entry 3). Methyl substitution on the aromatic ring was well tolerated as long as it was not

ortho to the phenol group (entries 4–6). A significant effect of halide substitution was also observed. Thus, while a fluoro substituent was innocuous relative to hydrogen (entry 7), a switch to chloro (entry 8) and especially bromo (entry 9) resulted in dramatic decreases in enantioselectivity.

With regard to the vinyl ether, we found that β -substitution was possible, leading to the production of **28** or **29** bearing three stereogenic centers (entries 10 and 11). Notably, α -substitution on the vinyl ether reduced both the yield and the enantioselectivity (entry 12). Alteration of the ether substituent to an *i*-butyl group was also feasible (entry 13). With the current catalyst, a cyclic vinyl ether participated with only poor enantiocontrol (entry 14). However, there is cause for optimism in the fact that the use of a different catalyst (i.e. **4**) had a noticeable impact on the stereoselectivity of the reaction (entry 15).

In order to gain insight into the structure of this catalyst, we subjected the conjugate base of **17** (as the $^+\text{NMe}_4$ salt) to single crystal X-ray analysis (Figure 2a). Notably, the five carboxyl groups appear strongly geared to one another, existing in an (*M*) helically chiral arrangement. Each carboxyl exists at an angle of between 28 and 57 degrees relative to the plane of the cyclopentadienyl ring, with the carbonyl oxygens on one face and the 2-arylcyclohexyl substituents on the other.

This type of helical arrangement might be presumed to be a result of crystal packing energetics. However, when we calculated the corresponding transition structures using catalyst **17**,⁹ the lowest energy transition structures had precisely the same helically-geared conformation of the carboxyl groups (Figure 2b). These closely matching structures suggest that the helical conformation has an inherently strong energetic bias, which we attribute to conformational A(1,3)-minimization of each chiral ester group along with gearing of all five carboxyls to accommodate the steric demands of the chiral substituents. It thus appears that the point chirality of the ester substituents induces helical chirality of the PCCP anion as a whole, which in turn leads to biasing of the enantiodetermining transition state.

This view offers a rationale for the results obtained in the catalyst SAR study (Table 1). Specifically, chiral substituents (e.g. **17**, entry 14) that reinforce the helical organization result in high enantioselectivities, while those that destabilize the helix, either due to excessive steric volume (e.g. **11**, **14**, and **15**, entries 8, 11, and 12) or length (e.g. **19**, entry 16) are less effective.

To investigate how this helically chiral anion achieves asymmetric induction, we modeled the cycloaddition transition state involving the putative oxocarbenium ion intermediate and vinyl ether (**2**) catalyzed by the PCCP catalyst **17** using B3LYP¹⁰/6-31G* calculations as implemented in Gaussian 09 (Figure 2b).¹¹ We chose catalyst **8** for our initial computational study since it had 55 atoms fewer than the optimal catalyst **17**, thus allowing for a more rigorous conformational analysis. The lowest energy structures for each enantiomer that emerged from these initial calculations were recalculated using catalyst **17**. A detailed description of the computational methodology along with cartesian coordinates for all relevant structures located using both catalyst **8** and **17** are in the Supporting Information. The energies reported in Figure 2b are extrapolated relative Gibbs free energies obtained

from single point energy calculations performed using the B3LYP-GD3 method¹² with a 6-31+G* basis set and the PCM solvent model¹³ for benzene. This dispersion-corrected DFT method provides a reasonable description of the energetics of non-covalent interactions present at the transition state.

The lowest energy transition state **TS**_(S,S) leading to the major (S,S)-enantiomer of the cycloaddition product is described as a concerted but highly asynchronous [4+2] transition structure with C–C bond formation being more advanced (2.42 Å) than C–O bond formation (3.11 Å). Three key non-covalent interactions that stabilize this transition state are: (a) a strong H-bonding interaction (1.58 Å) between the phenolic hydrogen and a carbonyl oxygen atom of **17**; (b) a weak C–H...O interaction (2.34 Å) between the oxocarbenium C–H and second carbonyl oxygen atom of **17**; and (c) a strong C–H- π interaction between the polarized internal vinylic C–H of **2** and the cyclopentadienyl anion.¹⁴

The lowest energy transition state leading to the minor (R,R)-enantiomer of the cycloaddition product **TS**_(R,R) differs from **TS**_(S,S) in terms of the mode of stabilization of the three acidic hydrogen atoms. While the phenolic hydrogen is stabilized by a strong H-bonding interaction (1.62 Å) similar to **TS**_(S,S), the mode of stabilization of the oxocarbenium C–H and the polarized internal vinyl C–H is switched compared to **TS**_(S,S) – the oxocarbenium C–H is now stabilized by a moderate C–H- π interaction with the aromatic ring and the internal vinylic C–H is engaged in a strong H-bonding interaction (2.12 Å) with a carbonyl oxygen atom of **17**.

The C–C and C–O bond-forming distances in **TS**_(R,R) are 2.24 Å and 2.81 Å respectively; a significantly ‘later’ transition structure compared to **TS**_(S,S) (*vide supra*). The difference in the Gibbs free energy barrier for these two transition structures ($\Delta G^\ddagger$) is 2.8 kcal/mol in favor of **TS**_(S,S); this corresponds to a predicted enantioselectivity of 99% ee at room temperature. Considering the size of the model system (220 atoms) and the limitations of the DFT methods used, this value is in reasonable agreement with the experimental 87% ee observed for catalyst **17** (Table 1, entry 14). The steric portion of the PCCP catalyst does not directly interact with the organization of either of the transition structures shown in Figure 2b. In the absence of any notable steric bias, the energetic preference for **TS**_(S,S) over **TS**_(R,R) is likely a result of superior transition state stabilization achieved by the non-covalent interactions present in **TS**_(S,S) compared to those present in **TS**_(R,R).

Based on this insight, we propose the mechanistic rationale for this reaction shown in Figure 3. Thus, acid catalyst **17** induces ionization of acetal **1** to generate oxocarbenium–PCCP salt **33**. Cycloaddition of this oxocarbenium with ethyl vinyl ether (**2**) then proceeds through transition state **34**, in which the absolute stereochemistry of the product is dictated by the helical chirality of the anion transmitted via a collection of H-bonding, C–H...O interactions and C–H-aryl interactions. Finally, deprotonation of the resulting intermediate **35** by the PCCP anion furnishes the chromane product **3** and regenerates the catalyst. As an alternative to this final “proton return” step, we note that it may be that intermediate **35** serves as the acid to directly ionize another molecule of substrate in a “proton propagation” pathway.

In conclusion, we have developed an enantioselective Brønsted acid-catalyzed Diels-Alder reaction of salicylaldehyde acetals and vinyl ethers. This protocol enables enantioenriched 2,4-dioxochromanes to be prepared in straightforward fashion. Through a combined effort of SAR investigation, X-ray analysis, and computational study, we have developed a unique stereochemical rationale for this process involving a point-chirality induced, helically chiral anion. This model offers insight into the operation of PCCP catalysts with weakly interacting intermediates and will inform further catalyst development studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. (a) Stierle AA, Stierle DB, Kelly K. *J Org Chem.* 2006; 71:5357. [PubMed: 16808526] (b) Razzak M, De Brabander JK. *Nature Chem Biol.* 2011; 7:865. [PubMed: 22086288]
2. (a) Namikoshi M, Kobayashi H, Yoshimoto T, Meguro S. *Chem Lett.* 2000:308.(b) Yuen TY, Yang SH, Brimble MA. *Angew Chem Int Ed.* 2011; 50:8350.
3. (a) Kashman Y, Gustafson KR, Fuller RW, Cardellina JH II, McMahon JB, Currens MJ, Buckheit RW Jr, Hughes SH, Cragg GM, Boyd MR. *J Med Chem.* 1992; 35:2735. [PubMed: 1379639] (b) Flavin MT, Rizzo JD, Khilevich A, Kucherenko A, Sheinkman AK, Vilaychack V, Lin L, Chen W, Greendwood EM, Pengsuparp T, Pezzuto JM, Hughes SH, Flavin TM, Cibulski M, Boulanger WA, Shone RL, Xu ZQ. *J Med Chem.* 1996; 39:1303. [PubMed: 8632437]
4. For reviews on enantioselective Brønsted acid catalysis, see: Parmar D, Sugiono E, Raja S, Rueping M. *Chem Rev.* 2014; 114:9047. [PubMed: 25203602] Akiyama T, Mori K. *Chem Rev.* 2015; 115:9277. [PubMed: 26182163] Akiyama T. *Acid Catalysis in Modern Organic Synthesis.* Yamamoto H, Ishihara K. Wiley-VCH Weinheim 2008:62–107. Kampen D, Reisinger C, List B. *Top Curr Chem.* 2010; 291:395–456. [PubMed: 21494945] Akiyama T. *Chem Rev.* 2007; 107:5744. [PubMed: 17983247] Akiyama T, Itoh J, Fuchibe K. *Adv Synth Catal.* 2006; 348:999. Doyle AG, Jacobsen EN. *Chem Rev.* 2007; 107:5713. [PubMed: 18072808] Terada M. *Chem Commun.* 2008:4097. Adair G, Mukherjee S, List B. *Aldrichimica Acta.* 2008; 41:31. Zamfir A, Schenker S, Freund M, Tsogoeva SB. *Org Biomol Chem.* 2010; 8:5262. [PubMed: 20820680] Terada M. *Synthesis.* 2010:1929. Terada M. *Bull Chem Soc Jpn.* 2010; 83:101. Terada M. *Curr Org Chem.* 2011; 15:2227. Zhu C, Saito K, Yamanaka M, Akiyama T. *Acc Chem Res.* 2015; 48:388. [PubMed: 25611073] Min C, Seidel D. *Chem Soc Rev.* 2017; 46:5889. [PubMed: 28730207]
5. For selected examples, see: Wu Q, Zhao J, Sun S, Tu M, Shi F. *Acta Chim Sin.* 2016; 74:576. Zhang YC, Zhu QN, Yang X, Zhou LJ, Shi F. *J Org Chem.* 2016; 81:1681. [PubMed: 26800116] Hsiao CC, Raja S, Liao HH, Atodiresei I, Rueping M. *Angew Chem Int Ed.* 2015; 54:5762. Zhao JJ, Sun SB, He SH, Wu Q, Shi F. *Angew Chem Int Ed.* 2015; 54:5460. Alden-Danforth E, Scerba MT, Lectka T. *Org Lett.* 2008; 10:4951. [PubMed: 18850717] Marsini MA, Huang Y, Lindsey CC, Wu KL, Pettus TRR. *Org Lett.* 2008; 10:1477. [PubMed: 18336038]
6. (a) Braun M, Kotter W. *Angew Chem Int Ed.* 2004; 43:514.(b) Reisman SE, Doyle AG, Jacobsen EN. *J Am Chem Soc.* 2008; 130:7198. [PubMed: 18479086] (c) Benfatti F, Benedetto E, Cozzi PG. *Chem Asian J.* 2010; 5:2047. [PubMed: 20607780] (d) Moquist PN, Kodama T, Schaus SE. *Angew Chem Int Ed.* 2010; 49:7096.(e) Burns NZ, Witten MR, Jacobsen EN. *J Am Chem Soc.* 2011; 133:14578. [PubMed: 21848300] (f) Maity P, Srinivas HD, Watson MP. *J Am Chem Soc.* 2011; 133:17142. [PubMed: 21988178] (g) Rueping M, Volla CMR, Atodiresei I. *Org Lett.* 2012; 14:4642. [PubMed: 22913599] (h) Cui Y, Villafane LA, Clausen DJ, Floreancig PE. *Tetrahedron.* 2013; 69:7618. [PubMed: 23913987] (i) Terada M, Li F, Toda Y. *Angew Chem Int Ed.* 2014;

- 53:235.(j) Meng Z, Sun S, Yuan H, Lou H, Liu L. *Angew Chem Int Ed*. 2014; 53:543.(k) Dasgupta S, Rivas T, Watson MP. *Angew Chem Int Ed*. 2015; 54:14154.(l) Srinivas HD, Maity P, Yap GPA, Watson MP. *J Org Chem*. 2015; 80:4003. [PubMed: 25847687] (m) Hardman-Baldwin AM, Visco MD, Wieting JM, Stern C, Kondo S-i, Mattson AE. *Org Lett*. 2016; 18:3766. [PubMed: 27453257] (n) Yang Z, He Y, Toste FD. *J Am Chem Soc*. 2016; 138:9775. [PubMed: 27472195] (o) Kennedy CR, Lehnher D, Rajapaksa NS, Ford DD, Park Y, Jacobsen EN. *J Am Chem Soc*. 2016; 138:13525. (p) Lee S, Kaib PSJ, List B. *J Am Chem Soc*. 2017; 139:2156. [PubMed: 28169541] (q) Banik SM, Levina A, Hyde AM, Jacobsen EN. *Science*. 2017; 358:761. [PubMed: 29123063]
7. Gheewala CD, Collins BE, Lambert TH. *Science*. 2016; 351:961. [PubMed: 26917768]
8. Gheewala CD, Radtke AM, Hui J, Hon AB, Lambert TH. *Org Lett*. 2017; 19:4227. [PubMed: 28771371]
9. This structure was computed based on the lowest energy transition structures for 17 (Figure 2). The coordinates and pdb files for the two transition structures located for catalyst 17 are in the Supporting Information.
10. Becke AD. *J Chem Phys*. 1993; 98:5648.
11. Frisch, MJ., Trucks, GW., Schlegel, HB., Scuseria, GE., Robb, MA., Cheeseman, JR., Scalmani, G., Barone, V., Mennucci, B., Petersson, GA., Nakatsuji, H., Caricato, M., Li, X., Hratchian, HP., Izmaylov, AF., Bloino, J., Zheng, G., Sonnenberg, JL., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montgomery, JA., Jr, Peralta, JE., Ogliaro, F., Bearpark, M., Heyd, JJ., Brothers, E., Kudin, KN., Staroverov, VN., Keith, T., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, JC., Iyengar, SS., Tomasi, J., Cossi, M., Rega, N., Millam, JM., Klene, M., Knox, JE., Cross, JB., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, RE., Yazyev, O., Austin, AJ., Cammi, R., Pomelli, C., Ochterski, JW., Martin, RL., Morokuma, K., Zakrzewski, VG., Voth, GA., Salvador, P., Dannenberg, JJ., Dapprich, S., Daniels, AD., Farkas, O., Foresman, JB., Ortiz, V., Cioslowski, J., Fox, DJ. *Gaussian 09, Revision D.01*. Gaussian, Inc; Wallingford CT: 2013.
12. Grimme S, Antony J, Ehrlich S, Krieg H. *J Chem Phys*. 2010; 132:154104. [PubMed: 20423165]
13. Tomasi J, Mennucci B, Cammi R. *Chem Rev*. 2005; 105:2999–3093. [PubMed: 16092826]
14. This interaction is characterized by a 2.69 Å and 2.73 Å distance between the internal vinylic CH of 2 and two of the aromatic carbon atoms of 17.

Figure 1.

(a) Inverse electron-demand Diels-Alder reaction of salicylaldehyde acetals and vinyl ethers to yield 2,4-dioxychromanes, and several biologically active natural products that incorporate this architecture. (b) PCCP Brønsted acids.

Figure 2.

(a) X-ray structure of **17**·NMe₄. Only a portion of the crystal unit is shown. There are four independent PCCP anions and ammonium cations in the crystal unit, along with two molecules of chloroform. The anions and cations pack alternately in columnar arrays, meaning that each anion is closely associated with two cations; only one cation is shown. In addition, there was disorder in the cations, but only one orientation is shown for clarity. (b) Lowest energy transition structures leading to the major (*S,S*) and minor (*R,R*) enantiomer of the [4+2] cycloaddition product of the reaction of **1** and **2** catalyzed by **17** computed using B3LYP/6-31G*. The two forming bonds are highlight in pink and the aromatic ring of the catalyst is highlighted in green. All distances are in angstroms.

Figure 3.
Mechanistic rationale for PCCP-catalyzed inverse electron-demand Diels-Alder reaction.

Table 1

Catalyst optimization studies for inverse electron demand Diels-Alder reaction.^{a,b}

Catalyst -OR Group			
(1) 4 69% yield 85:15 er	(2) 5 79% yield 67:33 er	(3) 6 58% yield 89:11 er	(4) 7 69% yield 59:41 er
(5) 8 60% yield 91:9 er	(6) 9 70% yield 89:11 er	(7) 10 65% yield 82:18 er	(8) 11 81% yield 59:41 er
(9) 12 63% yield 92:8 er	(10) 13 11% yield 93:7 er	(11) 14 10% yield 84:16 er	(12) 15 no reaction
(13) 16 78% yield 83:17 er	(14) 17 78% yield 94:6 er	(15) 18 78% yield 94:6 er	(16) 19 90% yield ~50:50 er

^aYields were determined on purified product.

Enantiomeric ratios were determined by HPLC analysis.

^bThe catalysts depicted in entries 2, 4, 5, 11–13, and 15 are the opposite enantiomer to the ones used, but are drawn as the same series to minimize confusion.The major product obtained in these cases was thus also the opposite enantiomer (*ent*-3).

Table 2

Scope studies for inverse electron demand Diels-Alder reaction.^a ^aYields were determined on purified product.

Enantiomeric ratios were determined by HPLC analysis.