Organocatalysis

Strong and Confined Acids Control Five Stereogenic Centers in Catalytic Asymmetric Diels–Alder Reactions of Cyclohexadienones with Cyclopentadiene

Santanu Ghosh, Sayantani Das, Chandra Kanta De, Diana Yepes, Frank Neese, Giovanni Bistoni, Markus Leutzsch, and Benjamin List*

In memory of Rolf Huisgen

Abstract: We describe a highly enantioselective Diels–Alder reaction of cross-conjugated cyclohexadienones with cyclopentadiene, in which five stereocenters are effectively controlled by a strongly acidic and confined imidodiphosphorimidate catalyst. Our approach provides tricyclic products in excellent stereoselectivity. We also report methods to convert the obtained products into useful intermediates and a computational study that aids in gaining deeper insight into the reaction mechanism and origin of stereoselectivity.

The Diels–Alder reaction is widely appreciated as one of the most powerful methods in chemical synthesis not only for its operational simplicity but also for the construction of molecular complexity and several contiguous stereocenters in a single step.[1,2] Despite the remarkable progress in molecular control the complex stereochemical reaction outcome. We now show that strong and confined imidodiphosphorimidates (IDPi) enable a broadly useful and general catalytic Diels–Alder reaction of cross-conjugated, 4,4-diaryl-substituted cyclohexadienones with cyclopentadiene. Encouraged by our more recent studies on catalytic asymmetric [4+2] cycloadditions, we envisioned that in order to improve the reactivity and selectivity of the targeted reaction, a) a significant LUMO lowering of the diene would be enabled by a strongly acidic catalyst, and b) a catalyst with a confined active site would be required to control the complex stereochemical reaction outcome. We have recently disclosed novel and unique acid catalysts, including imidodiphosphates (IDP), iminoimidodiphosphates (iIDP), and imidodiphosphorimidates (IDPi) that display enzyme-like, highly confined active sites and cover a broad range of acidities, approaching superacidsic pK_a values.[6] Given our recent success in applying such confined acids in both Brønsted and Lewis acid catalysis in various challenging asymmetric carbon–carbon[9] and carbon–heteroatom[10] bond-forming reactions, including diverse enantioselective Diels–Alder reactions and other [4+2] cycloadditions,[9b,11] we hypothesized that our acids might also provide a suitable catalyst platform for the cyclohexadienone Diels–Alder reactions under study here.

At the onset of our studies we chose 4,4-ethyl-methylcyclohexadienone (1a) as a challenging model dieneophile to react with cyclopentadiene in the presence of different chiral Brønsted acid catalysts, including CPA 3a, disulfonimide (DSI) 4a, IDP 5a, and IDPi catalyst 6a (Table 1). While catalysts 3a, 4a, and 5a gave only traces of conversion under the reaction conditions (toluene, −20°C, 24 h; Table 1, entries 1–3), IDPi catalyst 6a gave full conversion and furnished the desired product in promising stereoselectivity and with complete endo selectivity (entry 4). To further improve the selectivity of our reaction, we set out to fine-tune the number of possible isomers to four, two pairs of enantiomers.

Previous catalytic approaches towards challenging cyclohexadienone Diels–Alder reactions have been reported by Takagi and co-workers using a chiral phosphoric acid (CPA) catalyst and by Corey and co-workers, who reported a single example of using a highly activated chiral oxazaborolidine Lewis acid catalyst.[7] However, both of these studies required electronically biased dienones, high catalyst loadings (20–40 mol%), and gave only moderate enantioselectivities. We now show that strong and confined imidodiphosphorimidates (IDPi) enable a broadly useful and general catalytic Diels–Alder reaction of cross-conjugated, 4,4-diaryl-substituted cyclohexadienones with cyclopentadiene.

In memory of Rolf Huisgen

How to cite: Angew. Chem. Int. Ed. 2020, 59, 12347–12351

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
https://doi.org/10.1002/anie.202000307

© 2020 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

[*] Dr. S. Ghosh, Dr. S. Das, Dr. C. K. De, Dr. D. Yepes, Prof. Dr. F. Neese, Dr. G. Bistoni, Dr. M. Leutzsch, Prof. Dr. B. List
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 44470 Mülheim an der Ruhr (Germany)
E-mail: list@kofo.mpg.de

© 2020 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

Angew. Chem. Int. Ed. 2020, 59, 12347–12351 © 2020 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Wiley Online Library 12347
the active site of the catalyst. First, we varied the aryl substituents at the 3,3'-positions of the binaphthyl backbone (catalysts 6b and 6c; entries 5 and 6). Indeed, a beneficial effect on the enantiomeric ratio of the major diastereomer was observed upon incorporating the 3-Ph-C6H4 substituent in catalyst 6c. Subsequent effort to modify the inner core of the catalyst led to the replacement of the CF3SO2 substituent on the nitrogen atom of catalyst 6c by a C6F5SO2 group in catalyst 6d, and, as a consequence, led to significantly enhanced enantiomeric ratios for both two diastereomers (entry 7). Gratifyingly, decreasing the temperature from 0°C to −80°C with this catalyst improved both the diastereoselectivity and the enantioselectivity (entry 8). Further lowering of the reaction temperature to −95°C led to significantly diminished reactivity (entry 9). Hence, the reaction conditions shown in entry 8 were chosen for further investigations.

The scope of the reaction was explored under these optimized reaction conditions (Table 2). The reaction tolerates a variety of dienones (1) that contain different aliphatic, allylic, or aromatic substituents next to the methyl group in the 4-position. Generally, the cycloaddition adducts were obtained with good to excellent yields, enantioselectivities, and diastereoselectivities. As expected, increasingly sterically demanding and branched 4-substituents such as isopropyl in dienone 1d led to significantly higher diastereoselectivity (>20:1 dr). The enantioselectivities remained high to excellent in essentially all studied cases. Notably, in comparison to earlier studies,[7a] functionalized substrates 1j, 1k, and 1l furnished the cycloaddition products with excellent er of up to 96:4 and diastereoselectivities of up to >20:1, demonstrating a significant improvement. Additionally, dienones 1i–1l gave the other diastereomer 2 (Tables S4–S6 in the Supporting Information). The absolute stereochemistry of Diels–Alder product 2g was determined by NMR spectroscopy of Mosher ester derivatives (see the Supporting Information); the

Table 1: Reaction development.[a]

| Entry | Catalyst | Conv. [%][b] | dr[bf] | er[bf] (2a) | er[bf] (2a') |
|-------|----------|-------------|-------|------------|------------|
| 1     | 3a       | trace       | –     | –          | –          |
| 2     | 4a       | trace       | –     | –          | –          |
| 3     | 5a       | trace       | –     | –          | –          |
| 4     | 6a       | 100         | 3:1   | 65:35      | 74:26      |
| 5     | 6b       | 65          | 3:1   | 49:51      | 47:53      |
| 6     | 6c       | 100         | 3:1   | 67:33      | 71:29      |
| 7     | 6d       | 100         | 4:1   | 82:18      | 84:16      |
| 8[a]  | 6d       | 100         | 5:1   | 92.8       | 94.6       |
| 9[a]  | 6d       | 38          | 5:1   | 93.5:6.5   | 96:4       |

[a] 0.05 mmol scale. The product formed exclusively (>99:1) from the endo approach as determined by NMR analysis of the products (see the Supporting Information for details). [b] The conversion and dr values were determined by 1H NMR analysis of the crude reaction mixture. The er values were determined by HPLC analysis on a chiral stationary phase. [c] Reaction at −80°C for 4 d. [d] Reaction at −95°C for 4 d.
relative configuration of products 2a–h was assigned accordingly. In addition, the absolute configuration of ketone 2b was assigned by derivatization (Figure 2) to a known product (see below). The absolute configuration of product 2l was confirmed by an NMR study and by comparing the specific rotation with a literature report,[7a] the relative configurations of 2i', 2j', and 2k' were assigned by analogy.

In order to gain deeper insight into the reaction mechanism and to understand the origin of enantio- and diastereoselectivity of the process, we performed computational modeling using dienones 1a and 1j, cyclopentadiene, and catalyst ([S,S]-6d). Mechanistic studies were carried out at the M06-2X/def2-TZVP + C-PCM-(toluene)//PBE-D3(BJ)/def2-SVP level of theory. [12] For transition states, a thorough conformational sampling [13] was performed (177 structures were optimized at the PBE-D3 level), and single-point energies were refined using high-level domain-based local pair natural orbital coupled cluster calculations (DLPNO-CCSD(T)/def2-TZVP; see the Supporting Information for details.)

Substrate activation is an exergonic process (ΔG° = −11.5 kcal mol⁻¹) that occurs immediately by protonation of dienone 1a. The resulting cationic product forms a strongly directional hydrogen bond with an oxygen atom of the -SO₂C₆F₅ group of the counteranion (CIP-1a in Figure 3). The strong catalyst interaction in CIP-1a renders C-4 stereogenic, and thus the computed early diastereoselectivity of 3.7:1 is in good agreement with the experimental value of 5:1. Afterwards, CIP-1a forms a reactant complex (RC-1a) with cyclopentadiene, which then leads to product complex P-2a by an endo attack. In the stereodetermining transition state TS-2a, cyclopentadiene interacts with the catalyst through a network of non-conventional C/H···O and C/H···N hydrogen bonds. [14] Finally, product 2a is released upon exchange with 1a, thus forming CIP-1a and concomitantly restoring the catalytic cycle (Figure 3B).

It is noteworthy that the hydrogen bond established as the early molecular recognition between the activated substrate and the counteranion is conserved along the entire reaction path. It is also worth emphasizing that the R and Me substituents of 1 are oriented away from the chiral pocket of 6d, which is consistent with the high stereoselectivities obtained with different R groups (Table 2). Accurate dr and er values (Figure 3D) were calculated as the relative free energies of the corresponding TSs (according to the Curtin–Hammett principle) at the DLPNO-CCSD(T)/def2-TZVP level of theory.[15] For 2a, the experimentally determined 5:1 dr (ΔDG° = 0.58 kcal mol⁻¹) and 92:8 er (ΔDG° = 0.94 kcal mol⁻¹) are in good agreement with the computed dr and er values of 3.7:1 (ΔDG° = 0.5 kcal mol⁻¹) and 83:17 (ΔDG° = 0.6 kcal mol⁻¹), respectively.

To shed light on the physical factors responsible for the diastereoselectivity in the formation of 2a (5:1 dr), especially in comparison to the methoxy derivative 2j (> 20:1 dr), we conducted a local energy decomposition analysis (LED) of the DLPNO-CCSD(T) interaction energy between the CIP and cyclopentadiene at the TS geometries. For 2a, the calculated energies indicate that the trajectory of cyclopentadiene is mainly controlled by steric factors, leading to favorable attack from the less congested face, which corre-

---

**Table 2:** Scope of the reaction.[a,b]

| Reaction | dr | er |
|----------|----|----|
| 1a (major) | >20:1 dr | >98:2 er |
| 1b (major) | >20:1 dr | >98:2 er |
| 2a (major) | >20:1 dr | >98:2 er |
| 2b (major) | >20:1 dr | >98:2 er |
| 2c (major) | >20:1 dr | >98:2 er |
| 2d (major) | >20:1 dr | >98:2 er |
| 2e (major) | >20:1 dr | >98:2 er |
| 2f (major) | >20:1 dr | >98:2 er |

[a] Reactions on 0.2 mmol scale; the er values were determined by HPLC analysis on a chiral stationary phase (see the Supporting Information).

[b] The dr values were determined by ¹H NMR analysis after isolation of the desired product. [c] Reaction performed at ~95 °C. [d] Reaction time 8 d.

---

**Figure 2.** Derivatizations of Diels–Alder products (see the Supporting Information for details).
sponds to that with the small group closer to the π-system of cyclopentadiene. On the contrary, the inversion of the stereogenic center at C-4 for 2j is evident from the stability of the TS-2j' over TS-2j (ΔAG* = 3.2 kcal mol⁻¹; see the Supporting Information for details). This preference arises from the lower steric repulsion between the π-system of cyclopentadiene and the methoxy oxygen atom (DEel(TS-ent-2j) = 362.7 kcal mol⁻¹) compared to that induced by the methylene group (DEel(TS-2j) = 369.7 kcal mol⁻¹; see the Supporting Information for more details).

To illustrate the synthetic utility of our method several highly stereoselective derivatizations of products 2b and 2g were performed without loss of enantiopurity of the functionalized products (Figure 2). For example, a conjugate addition of an in situ generated cuprate to 2b proceeded with an excellent dr of >20:1, giving highly enantoienriched product 7. A [2+2] photocycloaddition reaction of enone 2b furnished product 8 in excellent yield, without any deterioration of enantioselectivity. Along the same lines, a potentially attractive route to alkyl-substituted Robinson-annulation-type products such as enone 9b was also developed. Accordingly, a conjugate reduction of enone 2b with t-selectride followed by a thermal retro-Diels–Alder cycloaddition provided the desired ketone 9b in good yield and with preservation of enantiopurity. The absolute configuration of 9b was confirmed by comparing its specific rotation with a literature value (see the Supporting Information).

We also developed a 1,2-addition of methylithium to enone 2g, giving the corresponding tertiary alcohol 10 in excellent yield and diastereoselectivity (>20:1). Epoxidation of the electron-rich olefinic double bond of enone 2g was performed using mCPBA as the oxidant and gave epoxide 11 (>20:1 dr) in 82% yield. A carbonyl reduction of enone 2g under Luche conditions proceeded with high diastereoselectivity (>20:1 dr) and provided the corresponding enantioenriched alcohol 12.

In summary, we have developed an efficient Brønsted acid catalyzed asymmetric intermolecular Diels–Alder reaction of cross-conjugated dienones containing electronically unbiased quaternary centers with cyclopentadiene that furnishes previously inaccessible products. The high acidity and confined structure of our IDPi catalyst directs the cycloaddition and provides the corresponding adducts with up to five stereocenters in excellent yields, enantio-, and diastereoselectivities. Further studies of our IDPi catalysts as privileged motifs for Diels–Alder reactions are ongoing.
Acknowledgements

Generous support from the Max Planck Society, the Deutsche Forschungsgemeinschaft (Leibniz Award to B.L. and Cluster of Excellence Ruhr Explores Solvation, RESOLV), and the European Research Council (ERC, European Union’s Horizon 2020 research and innovation program, “C-H Acids for Organic Synthesis, CHAOS” Advanced Grant agreement No. 694228) is gratefully acknowledged. We thank Benjamin Mitschke for his help during the preparation of this manuscript and several members of the group for crowd reviewing. We also thank the technicians of our group and the members of our NMR, MS, and chromatography groups for their excellent service.

Conflict of interest

The authors declare no conflict of interest.

Keywords: Brønsted acids · cyclohexadienones · Diels–Alder reaction · imidodiphosphorimidates · organocatalysis

[1] a) O. Diels, K. Alder, Liebigs Ann. Chem. 1926, 450, 237–254; b) O. Diels, K. Alder, Liebigs Ann. Chem. 1928, 460, 98–122; c) J. A. Norton, Chem. Rev. 1942, 31, 519–523.
[2] a) G. Desimoni, G. Tacconi, A. Bario, G. P. Pollini, ACS Monograph 189, American Chemical Society, Washington, 1984; b) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, Angew. Chem. Int. Ed. 2002, 41, 1668–1698; Angew. Chem. 2002, 114, 1742–1773; c) K.-i. Takao, R. Munakata, K.-i. Tadano, Chem. Rev. 2005, 105, 4779–4807; d) F. E. Held, S. B. Tsogoeva, Catal. Sci. Technol. 2016, 6, 645–667; e) B. Yang, S. Gao, Chem. Soc. Rev. 2018, 47, 7926–7953.
[3] a) H. B. Kagan, O. Riant, Chem. Rev. 1992, 92, 1007–1019; b) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, J. Am. Chem. Soc. 2000, 122, 4243–4244; c) H. Kim, G. Gerosa, J. Aronow, P. Kasaplar, J. Ouyang, J. B. Lingnau, P. Guerry, C. Farès, B. List, Nat. Commun. 2019, 10, 770.
[4] a) A. B. Northrup, D. W. C. MacMillan, J. Am. Chem. Soc. 2002, 124, 2458–2460; b) J. M. Hawkins, M. Nambu, S. Loren, Org. Lett. 2003, 5, 4293–4295; c) D. Nakashima, H. Yamamoto, J. Am. Chem. Soc. 2006, 128, 9626–9627; d) R. P. Singh, K. Bartelson, Y. Wang, H. Su, X. Lu, L. Deng, J. Am. Chem. Soc. 2008, 130, 2422–2423; e) J. N. Payette, H. Yamamoto, Angew. Chem. Int. Ed. 2009, 48, 8060–8062; Angew. Chem. 2009, 121, 8204–8206.
[5] a) M. Breuning, E. J. Corey, Org. Lett. 2001, 3, 1559–1562; b) D. A. Evans, J. Wu, J. Am. Chem. Soc. 2003, 125, 10162–10163; c) D. H. Ryu, G. Zhou, E. J. Corey, J. Am. Chem. Soc. 2004, 126, 4800–4802; d) E. P. Balasuk, E. N. Jacobsen, Science 2007, 317, 1736; e) E. J. Corey, Angew. Chem. Int. Ed. 2009, 48, 2100–2117; Angew. Chem. 2009, 121, 2134–2151; f) K. M. Reddy, E. Bhimireddy, B. Thirupathi, S. Breitler, S. Yu, E. J. Corey, J. Am. Chem. Soc. 2016, 138, 2443–2453.
[6] a) H.-J. Liu, Y. Han, Tetrahedron Lett. 1993, 34, 423–426; b) K. A. Kalstabakken, A. M. Harned, Tetrahedron 2014, 70, 9571–9585; c) X.-P. Zeng, Z.-Y. Cao, Y.-H. Wang, F. Zhou, J. Zhou, Chem. Rev. 2016, 116, 7330–7396.
[7] a) R. Takagi, T. Nishi, Org. Biomol. Chem. 2015, 13, 11039–11045; b) Y. Han, S. Breitler, S.-L. Zheng, E. J. Corey, Org. Lett. 2016, 18, 6172–6175.
[8] a) I. Coric, B. List, Nat. Chem. 2012, 4, 315–319; b) L. Liu, M. Leutzsch, Y. Zheng, M. W. Alachraf, W. Thiel, B. List, J. Am. Chem. Soc. 2015, 137, 13268–13271; c) L. Liu, P. S. J. Kaib, A. Tap, B. List, J. Am. Chem. Soc. 2016, 138, 10822–10825; d) P. S. J. Kaib, L. Schreyer, S. Lee, R. Properzi, B. List, Angew. Chem. Int. Ed. 2016, 55, 13200–13203; Angew. Chem. 2016, 128, 13394–13397.
[9] a) H. Y. Bae, D. Höfler, P. S. J. Kaib, P. Kasaplar, C. K. De, A. Döhring, S. Lee, K. Kaupmees, I. Leito, B. List, Nat. Chem. 2018, 10, 888–894; b) L. Schreyer, P. S. J. Kaib, V. N. Wackhaure, C. Obradors, R. Properzi, S. Lee, B. List, Science 2018, 362, 216–219; c) L. Schreyer, R. Properzi, B. List, Angew. Chem. Int. Ed. 2019, 58, 12761–12777; Angew. Chem. 2019, 131, 12891–12908.
[10] N. Tsuji, J. L. Kennemur, T. Buyck, S. Lee, S. Prévost, P. S. J. Kaib, D. Bykov, C. Farès, B. List, Science 2018, 359, 1501–1505.
[11] a) T. Gatzenmeier, M. van Gemmeren, Y. Xie, D. Höfler, M. Leutzsch, B. List, Science 2016, 351, 949–952; b) L. Liu, H. Kim, Y. Xie, C. Farès, P. S. J. Kaib, R. Goddard, B. List, J. Am. Chem. Soc. 2017, 139, 13656–13659; c) Y. Xie, B. List, Angew. Chem. Int. Ed. 2017, 56, 4936–4940; Angew. Chem. 2017, 129, 5018–5022; d) T. Gatzenmeier, M. Turberg, D. Yepes, Y. Xie, F. Neese, G. Bistoni, B. List, J. Am. Chem. Soc. 2018, 140, 12671–12676.
[12] Y. Zhao, D. G. Truhlar, Theor. Chem. Acc. 2008, 120, 215–241.
[13] a) xtb v6.1. xtb@thch.uni-bonn.de, University Bonn, 2019; b) D. Yepes, F. Neese, B. List, G. Bistoni, J. Am. Chem. Soc. 2020, 142, 3613–3625.
[14] a) Y. Gu, T. Kar, S. Scheiner, J. Am. Chem. Soc. 1999, 121, 9411–9422; b) C. E. Cannizzaro, K. N. Houk, J. Am. Chem. Soc. 2002, 124, 7163–7169; c) R. C. Johnston, P.-H.-Y. Cheong, Org. Biomol. Chem. 2013, 11, 5057–5064.
[15] a) F. Neese, Wires Comput. Mol. Sci. 2012, 2, 73–78; b) C. Riplinger, P. Pinski, U. Becker, E. F. Valeev, F. Neese, J. Chem. Phys. 2016, 144, 024109.
[16] W. B. Schneider, G. Bistoni, M. Sparta, M. Saitow, C. Riplinger, A. A. Auer, F. Neese, J. Chem. Theory Comput. 2016, 12, 4778–4792.