A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

GDCh

Chemie

www.angewandte.org

Accepted Article

Title: Highly acidic conjugate-base-stabilized carboxylic acids catalyze enantioselective oxa-Pictet–Spengler reactions with ketals

Authors: Zhengbo Zhu, Minami Odagi, Chenfei Zhao, Khalil A. Abboud, Helmi Ulrika Kirm, Jaan Saame, Märt Lõkov, Ivo Leito, and Daniel Seidel

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201912677
Angew. Chem. 10.1002/ange.201912677

Link to VoR: http://dx.doi.org/10.1002/anie.201912677
http://dx.doi.org/10.1002/ange.201912677

WILEY-VCH

10.1002/anie.201912677

COMMUNICATION

WILEY-VCH

Highly acidic conjugate-base-stabilized carboxylic acids catalyze enantioselective oxa-Pictet–Spengler reactions with ketals

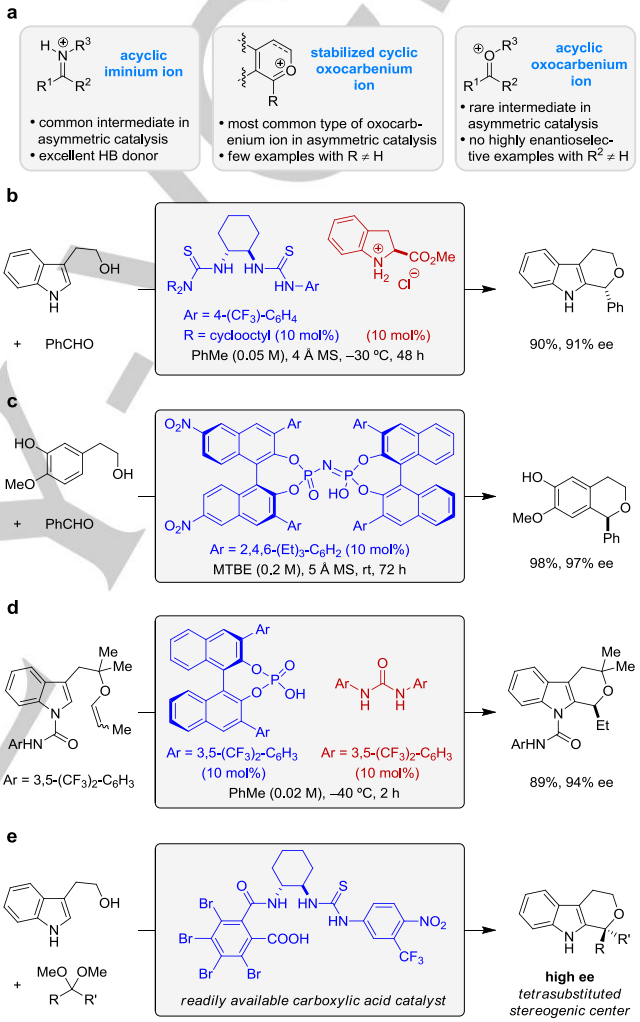
Zhengbo Zhu,[a],+ Minami Odagi, [a],[b],+ Chenfei Zhao,[c] Khalil A. Abboud,[d] Helmi Ulrika Kirm,[e] Jaan Saame,[e] Märt Lõkov,[e] Ivo Leito,[e] and Daniel Seidel[a],*

Abstract: *Acyclic ketone-derived oxocarbenium ions, intermediates that are involved in numerous reactions providing valuable products, have thus far eluded efforts aimed at asymmetric catalysis. We report that a readily accessible chiral carboxylic acid catalyst exerts control over asymmetric cyclizations of acyclic ketone-derived trisubstituted oxocarbenium ions, achieving the synthesis of highly enantioenriched dihydropyran products containing a tetrasubstituted stereogenic center. The high acidity of the carboxylic acid catalyst, exceeding that of the well-known chiral phosphoric acid catalyst TRIP, is largely derived from stabilization of the carboxylate conjugate base via intramolecular anion-binding to a thiourea site.*

Oxocarbenium ions, ubiquitous and highly reactive intermediates in numerous synthetically useful transformations generating new stereogenic centers, have long represented a challenge to asymmetric catalysis. Compared to organocatalytic enantioselective reactions involving iminium ions, those proceeding via transient oxocarbenium ions remain significantly less developed (Scheme 1a). Whereas organocatalytic enantioselective transformations of primary-amine-derived iminium ions are typically controlled via hydrogen bonding interactions between the catalyst and the *N*H proton of the iminium ion, oxocarbenium ions lack such obvious binding sites for interaction with a catalyst. Although significant progress has been made in recent years, enabled by the emergence of Brønsted acid,[1] cooperative,[2] and chiral anion/anion-binding catalysis,[3] most organocatalytic enantioselective methods reported to date have been shown to accommodate only cyclic oxocarbenium ions. With few exceptions,[4] most cyclic

[a] Z. Zhu, Dr. M. Odagi, Prof. Dr. D. Seidel
Center for Heterocyclic Compounds, Department of Chemistry
University of Florida, Gainesville, FL 32611 (USA)
E-mail: seidel@chem.ufl.edu
Homepage: http://seidel-group.com/
[b] Dr. M. Odagi
Department of Biotechnology and Life Science, Graduate School of Technology, Tokyo University of Agriculture and Technology, 2-24-16, Naka-cho, Koganei city, 184-8588, Tokyo, Japan
[c] Dr. C. Zhao
Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, NJ 08854 (USA)
[d] Dr. K. A. Abboud
Center for X-ray Crystallography, Department of Chemistry
University of Florida, Gainesville, FL 32611 (USA)
[e] H. U. Kirm, J. Saame, Dr. M. Lõkov, Prof. Dr. I. Leito
Institute of Chemistry, University of Tartu, Tartu, Estonia.
+ These authors contributed equally to this work.

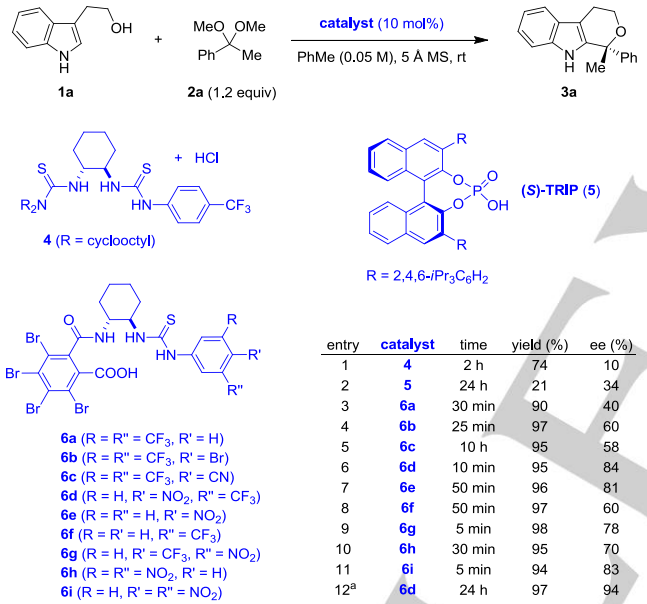
Supporting information for this article is given via a link at the end of the document.



Scheme 1. Oxocarbenium ions in asymmetric catalysis and previous examples of catalytic enantioselective oxa-Pictet–Spengler reactions.

oxocarbenium ion intermediates are of the relatively stabilized pyrylium- or (iso)chroman-type.[5] Of those, the highly enantioselective formation of tetrasubstituted stereogenic centers has been achieved in only two types of transformations.[6] Catalytic enantioselective reactions involving acyclic oxocarbenium ions remain less common,[7] and there appears to be only a single example involving an acyclic trisubstituted oxocarbenium ion in which the corresponding product was obtained with 47% ee.[8] Here, the challenge for the chiral catalyst having to distinguish between two potentially similarly sized carbon-based substituents (vs. distinguishing between a carbon substituent and a hydrogen atom as in reactions of disubstituted oxocarbenium ions), is exacerbated by the fact that, unlike their cyclic counterparts, an acyclic, trisubstituted

oxocarbenium ion can exist as a mixture of *E*/*Z* isomers. Among reactions proceeding via acyclic oxocarbenium ions, a particularly attractive method for the formation of chiral dihydropyrans is the oxa-Pictet–Spengler reaction.[9] Only three examples of highly enantioselective oxa-Pictet–Spengler reactions have been reported.[10] Some of us achieved enantioselective oxa-Pictet–Spengler reactions with tryptophol and aldehydes via a dual catalysis approach involving an amine HCl salt (the chirality of which is irrelevant) and a chiral bisthiourea compound (Scheme 1b).[10a] Simultaneously, the List group reported catalytic enantioselective oxa-Pictet–Spengler reactions with β-phenylethanols and aldehydes, employing an imidodiphosphoric acid catalyst (Scheme 1c).[10b] Scheidt and coworkers recently disclosed enantioselective oxa-Pictet–Spengler cyclizations with preformed enol ethers containing a protected indole moiety, applying a cooperative catalysis concept that utilizes a combination of a chiral phosphoric acid and an achiral urea catalyst (Scheme 1d).[10c] Here we report the first examples of highly enantioselective oxa-Pictet–Spengler reactions that provide dihydropyran products containing a tetrasubstituted stereogenic center (Scheme 1e).



entry	catalyst	time	yield (%)	ee (%)
1	4	2 h	74	10
2	5	24 h	21	34
3	6a	30 min	90	40
4	6b	25 min	97	60
5	6c	10 h	95	58
6	6d	10 min	95	84
7	6e	50 min	96	81
8	6f	50 min	97	60
9	6g	5 min	98	78
10	6h	30 min	95	70
11	6i	5 min	94	83
12[a]	6d	24 h	97	94

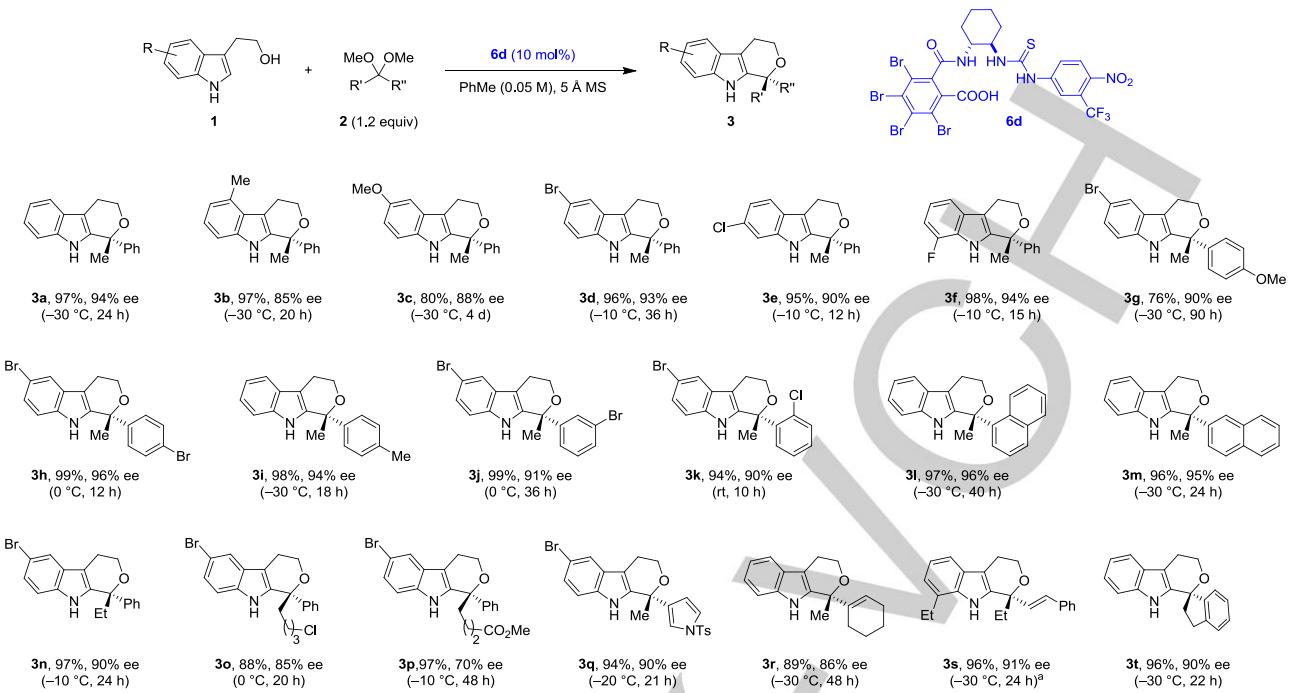
Scheme 2. Reaction development. Reactions were performed with 0.1 mmol of **1a** and 1.2 equiv of **2a**. All yields correspond to isolated yields. The ee values were determined by SFC analysis. [a] Reaction was performed at –30 °C.

As summarized in Scheme 2, tryptophol (**1a**) and acetophenone-derived ketal **2a** were utilized as the model substrates in the development of the proposed oxa-Pictet–Spengler reaction. The bisthiourea-HCl catalyst combination (**4**), previously utilized in asymmetric oxa-Pictet–Spengler reactions with acetals,[10a] exhibited favorable reaction rates and provided product **3a** in good yield but negligible ee (entry 1). The widely utilized phosphoric acid catalyst **(*S*)-TRIP** (**5**)[11] was found to be relatively inactive, furnishing **3a** with slightly improved ee (entry 2). We then turned our attention to carboxylic-acid-thiourea **6a**, a catalyst that was designed with the notion that its thiourea functionality would stabilize the carboxylate conjugate base via intramolecular anion-binding, thus resulting in a highly acidic carboxylic acid catalyst.[1i],[12] Catalyst **6a** was previously shown to facilitate catalytic enantioselective Pictet–Spengler reactions[13] and other processes that proceed via the intermediacy of iminium ions.[14] However, **6a** had never been employed successfully in reactions involving oxocarbenium ions. Gratifyingly, **6a** was found to be a highly active catalyst in the title reaction, providing product **3a** in excellent yield and notable ee after a reaction time of only 30 min (entry 3). Introduction of an additional bromine substituent on the thiourea aryl group resulted in the presumably more acidic catalyst **6b**, which displayed higher reactivity and selectivity than **6a** (entry 4). This trend did not hold for catalyst **6c** containing a cyano substituent instead of bromine (entry 5). Here, the significantly lower reactivity is likely the result of **6c**'s low solubility (a heterogeneous reaction mixture was observed). Relatively minor structural variations of the thiourea aryl group led to the identification of more active and selective catalysts (entries 6–11). A dramatically improved reaction outcome was observed with catalyst **6d**, which provided product **3a** in 95% yield and 84% ee following a reaction time of just 10 min at room temperature (entry 6). At –30 °C, a significantly slower but still reasonable reaction rate was maintained that allowed for the isolation of **3a** in 97% yield and 94% ee (entry 12).[15]

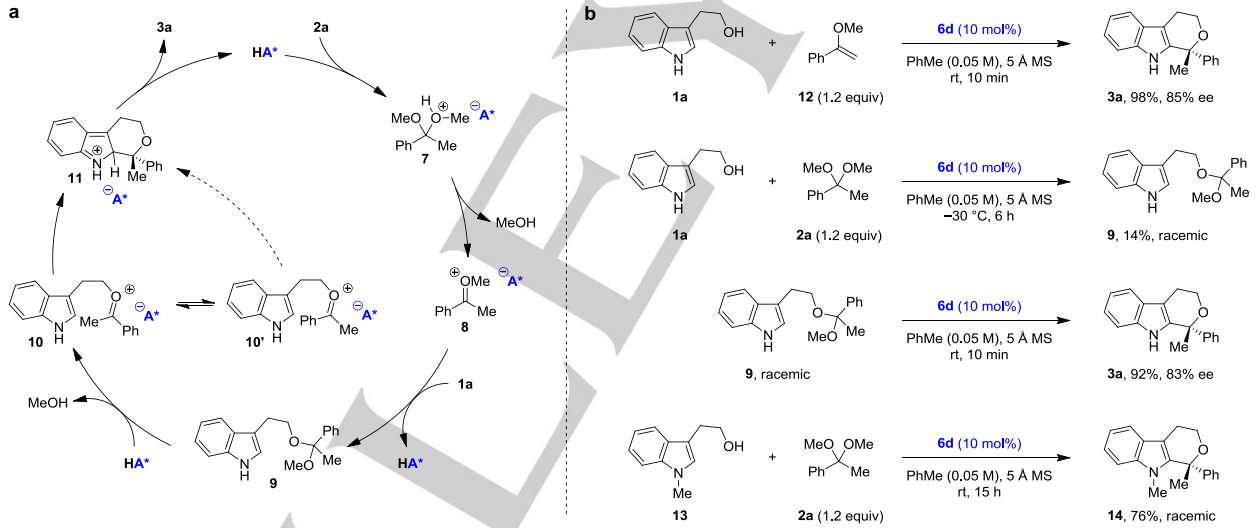
The scope of the catalytic enantioselective oxa-Pictet–Spengler reaction with ketals is depicted in Scheme 3. Substitution of the tryptophol indole ring with electronically diverse groups on the 4-, 5-, 6-, and 7-positions was well tolerated (products **3a–f**). Different aryl groups on the ketal reaction partner were also accommodated (products **3g–m**). High enantioselectivity was maintained with the dimethoxyketal derived from propiophenone (product **3n**). Other aliphatic substituents containing terminal functional groups were also tolerated (products **3o**, **3p**). Pyrrole-containing ketal provided product **3q** with good ee, and alkyl-alkenyl ketals were also found to be viable reaction partners (products **3r**, **3s**). Furthermore, spirocyclic product **3t** was obtained in good enantioselectivity.

The proposed catalytic cycle for the oxa-Pictet–Spengler cyclization is shown in Scheme 4a. Accordingly, the reaction is initiated by protonation of ketal **2a** by the acid catalyst **HA*** (e.g., **6d**) to provide ion pair **7**, followed by elimination of methanol and concomitant formation of oxocarbenium intermediate **8**. The latter then reacts with tryptophol (**1a**) to form mixed ketal **9**. Protonation of **9** by **HA*** followed by loss of methanol can give rise to two stereoisomeric oxocarbenium ions (**10** and **10'**). Presumably, only one of these isomers is a competent intermediate for the subsequent cyclization to form ion pair **11**. Deprotonation/rearomatization furnishes product **3a** and releases **HA***. Several experiments provide support for this scenario (Scheme 4b). The intermediacy of **8** is highly likely, given that the use of enolether **12** as an alternative starting material to ketal **2a** provided nearly identical results in the catalytic reaction. Mixed ketal intermediate **9** could be isolated in low yield under carefully controlled conditions. Exposure of ketal **9** to the standard reaction conditions provided **3a** with very similar levels of efficiency. This seemingly rules out a scenario in which tryptophol (**1a**) first engages **8** via the indole C2-carbon with concomitant C–C bond formation (not shown). Another insight was obtained in a reaction with *N*-methyltryptophol (**13**). In addition to a drastically reduced reaction rate, the corresponding product **14** was obtained in racemic fashion, consistent with related studies.[10a,13b,16] This strongly suggests that an interaction of the indole *N*H proton with the catalyst is a key feature of at least one critical intermediate in the catalytic cycle.

10.1002/anie.201912677



Scheme 3. Reaction scope. Reactions were performed with 0.25 mmol of **1** and 1.2 equiv of **2**. All yields correspond to isolated yields. The ee values were determined by SFC analysis. The absolute configuration of product **3d** was assigned by X-ray crystallography. All other compounds were assigned by analogy. [a] Catalyst **6i** was used.



Scheme 4. Proposed catalytic cycle (a) and mechanistic studies (b).

In order to identify a possible correlation between catalyst activity and acidity, and to determine the impact of conjugate-base-stabilization on the pK_a values of our chiral carboxylic acid catalysts, detailed acidity measurements were conducted for several catalysts and control compounds. Due to the multiple advantages of acetonitrile,[17] all acidity measurements were conducted in this solvent. The results of this study are summarized in Figure 1, along with literature values of several known acids for comparative purposes. Catalyst **6a** was determined to have a pK_a of 12.4 in acetonitrile, whereas the more active and selective catalyst **6d** was found to be slightly less acidic with a pK_a of 12.7. To put these values into perspective, **6a** and **6d** are about as acidic as trifluoroacetic acid,[18] and thus one order of magnitude more acidic than the widely used chiral phosphoric acid catalyst **(*S*)-TRIP** (**5**).[19] The pK_a of the truncated carboxylic acid **15** lacking the thiourea moiety is 19.2 while the pK_a of the truncated thiourea **16** lacking the carboxylic acid moiety is 24.3. Remarkably, these findings imply that conjugate-base-stabilization by the weakly acidic thiourea is responsible for an increase in carboxylic acid acidity of nearly 7 orders of magnitude! Moreover, dual hydrogen bonding interactions of the carboxylate anion with both thiourea *N*H protons appear to be crucial, as judged by the fact that trifluoroacetamide derivative **17** (pK_a = 18.1), possessing only one hydrogen bond donor site, is only one order of magnitude more acidic than **15**.

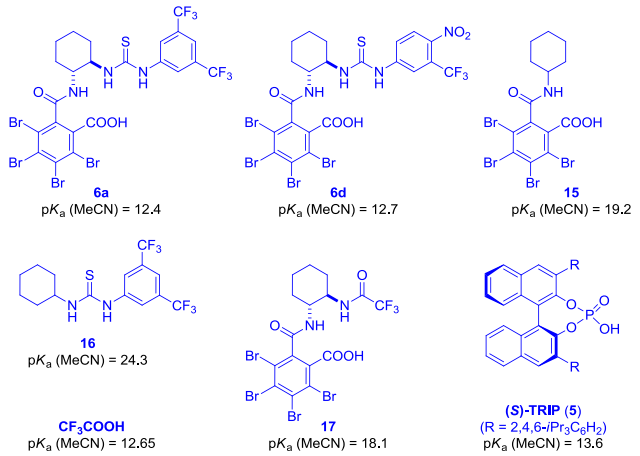


Figure 1. Impact of conjugate-base-stabilization on carboxylic acid pK_a and comparison to other acids.

In conclusion, we have achieved the first highly enantioselective reactions of acyclic trisubstituted oxocarbenium ions. The unique carboxylic acid catalysts employed in this study derive their unusually high acidity (exceeding that of the chiral phosphoric acid **(*S*)-TRIP** by one order of magnitude) from conjugate-base-stabilization via intramolecular anion binding to a thiourea receptor, an interaction that is responsible for an increase in acidity of nearly 7 orders of magnitude.

Acknowledgements

This material is based upon work supported by the National Science Foundation under CHE–1856613 (grant to D.S.). M.O. thanks the Program for Advancing Strategic International Networks to Accelerate the Circulation of Talented Researchers (R2801) from the Japan Society for the Promotion of Science (JSPS). We further acknowledge the National Science Foundation (grant# 1828064 to K.A.A.) and the University of Florida for funding the purchase of the X-ray equipment. The work at Tartu was supported by the EU through the European Regional Development Fund (TK141 “Advanced materials and high-technology devices for energy recuperation systems”) and by the institutional research grant IUT20-14 from the Estonian Research Council.

Keywords: Asymmetric catalysis • Brønsted acid catalysis• oxocarbenium ions • oxa-Pictet–Spengler reaction • pK_a determination

[1] Selected reviews on Brønsted acid catalysis: a) H. Yamamoto, K. Futatsugi, *Angew. Chem. Int. Ed.* **2005**, *44*, 1924; b) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744; c) M. Terada, *Synthesis* **2010**, 1929; d) M. Rueping, B. J. Nachtsheim, W. Ieawsuwan, I. Atodiresei, *Angew. Chem. Int. Ed.* **2011**, *50*, 6706; e) J. Yu, F. Shi, L. Z. Gong, *Acc. Chem. Res.* **2011**, *44*, 1156; f) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047; g) T. Akiyama, K. Mori, *Chem. Rev.* **2015**, *115*, 9277; h) M. Rueping, D. Parmar, E. Sugiono, *Asymmetric Brønsted Acid Catalysis*, Wiley-VCH, Weinheim, **2015**; i) C. Min, D. Seidel, *Chem. Soc. Rev.* **2017**, *46*, 5889; j) R. Mitra, J. Niemeyer, *ChemCatChem* **2018**, *10*, 1221.

[2] Selected reviews on asymmetric ion pairing and cooperative catalysis: a) S. Piovesana, D. M. Scarpino Schietroma, M. Bella, *Angew. Chem., Int. Ed.* **2011**, *50*, 6216; b) A. E. Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, *3*, 633; c) J.-F. Brière, S. Oudeyer, V. Dalla, V. Levacher, *Chem. Soc. Rev.* **2012**, *41*, 1696; d) R. Peters, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2015**, p 427. See also references [3].

[3] Selected reviews on asymmetric anion-binding catalysis: a) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187; b) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nature Chem.* **2012**, *4*, 603; c) M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 518; d) K. Brak, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2013**, *52*, 534; e) D. Seidel, *Synlett* **2014**, *25*, 783; f) N. Busschaert, C. Caltagirone, W. Van Rossom, P. A. Gale, *Chem. Rev.* **2015**, *115*, 8038; g) J. W. Attard, K. Osawa, Y. Guan, J. Hatt, S.-i. Kondo, A. Mattson, *Synthesis* **2019**, *51*, 2107.

[4] a) M. Braun, W. Kotter, *Angew. Chem. Int. Ed.* **2004**, *43*, 514; b) I. Čorić, B. List, *Nature* **2012**, *483*, 315; c) S. Lee, P. S. J. Kaib, B. List, *J. Am. Chem. Soc.* **2017**, *139*, 2156; d) Z. Sun, G. A. Winschel, A. Borovika, P. Nagorny, *J. Am. Chem. Soc.* **2012**, *134*, 8074.

[5] a) S. E. Reisman, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 7198; b) P. N. Moquist, T. Kodama, S. E. Schaus, *Angew. Chem. Int. Ed.* **2010**, *49*, 7096; c) P. Maity, H. D. Srinivas, M. P. Watson, *J. Am. Chem. Soc.* **2011**, *133*, 17142; d) M. Rueping, C. M. R. Volla, I. Atodiresei, *Org. Lett.* **2012**, *14*, 4642; e) Z. Meng, S. Sun, H. Yuan, H. Lou, L. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 543; f) H. Qian, W. Zhao, Z. Wang, J. Sun, *J. Am. Chem. Soc.* **2015**, *137*, 560.

[6] a) N. Z. Burns, M. R. Witten, E. N. Jacobsen, *J. Am. Chem. Soc.* **2011**, *133*, 14578; b) M. R. Witten, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2014**, *53*, 5912; c) S. Dasgupta, T. Rivas, M. P. Watson, *Angew. Chem. Int. Ed.* **2015**, *54*, 14154.

[7] a) N. Umebayashi, Y. Hamashima, D. Hashizume, M. Sodeoka, *Angew. Chem. Int. Ed.* **2008**, *47*, 4196; b) M. Terada, H. Tanaka, K. Sorimachi, *J. Am. Chem. Soc.* **2009**, *131*, 3430; c) I. Čorić, S. Vellalath, B. List, *J. Am. Chem. Soc.* **2010**, *132*, 8536; d) J. H. Kim, I. Čorić, S. Vellalath, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 4474; e) C. D. Gheewala, B. E. Collins, T. H. Lambert, *Science* **2016**, *351*, 961; f) L. Liu, P. S. J. Kaib, A. Tap, B. List, *J. Am. Chem. Soc.* **2016**, *138*, 10822; g) H. Wu, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2017**, *56*, 5858.

[8] E. Ascic, R. G. Ohm, R. Petersen, M. R. Hansen, C. L. Hansen, D. Madsen, D. Tanner, T. E. Nielsen, *Chem. Eur. J.* **2014**, *20*, 3297.

[9] General reviews on the oxa-Pictet–Spengler reaction: a) E. L. Larghi, T. S. Kaufman, *Synthesis* **2006**, 187; b) E. L. Larghi, T. S. Kaufman, *Eur. J. Org. Chem.* **2011**, *2011*, 5195; c) A. Moyano, R. Rios, *Chem. Rev.* **2011**, *111*, 4703. Review on catalytic enantioselective oxa-Pictet–Spengler reactions: d) Z. Zhu, A. Adili, C. Zhao, D. Seidel, *SynOpen* **2019**, *03*, 77.

[10] a) C. Zhao, S. B. Chen, D. Seidel, *J. Am. Chem. Soc.* **2016**, *138*, 9053; b) S. Das, L. Liu, Y. Zheng, M. W. Alachraf, W. Thiel, C. K. De, B. List, *J. Am. Chem. Soc.* **2016**, *138*, 9429; c) M. A. Maskeri, M. J. O'Connor, A. A. Jaworski, A. V. Davies, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2018**, *57*, 17225.

[11] S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem. Int. Ed.* **2005**, *44*, 7424.

[12] Selected examples of other types of chiral carboxylic acids acting as Brønsted acid catalysts: (a) H. Tohma, S. Takizawa, H. Watanabe, Y. Fukuoka, T. Maegawa, Y. Kita, *J. Org. Chem*. **1999**, *64*, 3519; b) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc*. **2005**, *127*, 1080; c) T. Hashimoto, K. Maruoka, *J. Am. Chem. Soc.* **2007**, *129*, 10054; d) T. Hashimoto, M. Hirose, K. Maruoka, *J. Am. Chem. Soc*. **2008**, *130*, 7556; e) H. Ube, S. Fukuchi, M. Terada, *Tetrahedron: Asymmetry* **2010**, *21*, 1203; f) T. Hashimoto, H. Kimura, Y. Kawamata, K. Maruoka, *Nat. Chem*. **2011**, *3*, 642; g) T. Hashimoto, H. Kimura, Y. Kawamata, K. Maruoka, *Angew. Chem., Int. Ed.* **2012**, *51*, 7279; h) T. Hashimoto, A. O. Gálvez, K. Maruoka, *J. Am. Chem. Soc*. **2013**, *135*, 17667.

[13] a) N. Mittal, D. X. Sun, D. Seidel, *Org. Lett.* **2014**, *16*, 1012; b) M. Odagi, H. Araki, C. Min, E. Yamamoto, T. J. Emge, M. Yamanaka, D. Seidel, *Eur. J. Org. Chem.* **2019**, *2019*, 486.

[14] a) C. Min, N. Mittal, D. X. Sun, D. Seidel, *Angew. Chem. Int. Ed.* **2013**, *52*, 14084; b) C. Min, C.-T. Lin, D. Seidel, *Angew. Chem. Int. Ed.* **2015**, *54*, 6608.

[15] Catalyst **6d** is readily prepared on multi-gram scale without the need for chromatography. See the Supporting Information for details.

[16] R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem. Int. Ed.* **2005**, *44*, 6576.

[17] A. Kütt, S. Selberg, I. Kaljurand, S. Tshepelevitsh, A. Heering, A. Darnell, K. Kaupmees, M. Piirsalu, I. Leito, *Tetrahedron Lett.* **2018**, *59*, 3738.

[18] F. Eckert, I. Leito, I. Kaljurand, A. Kütt, A. Klamt, M. Diedenhofen, *J. Comput. Chem.* **2009**, *30*, 799.

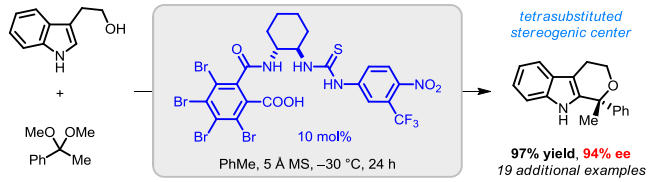
[19] K. Kaupmees, N. Tolstoluzhsky, S. Raja, M. Rueping, I. Leito, *Angew. Chem. Int. Ed.* **2013**, *52*, 11569.

10.1002/anie.201912677

WILEY-VCH

Entry for the Table of Contents

COMMUNICATION



A chiral carboxylic acid catalyst exerts control over asymmetric cyclizations of acyclic ketone-derived trisubstituted oxocarbenium ions, achieving the synthesis of highly enantioenriched dihydropyran products containing a tetrasubstituted stereogenic center. The high acidity of the carboxylic acid catalyst, exceeding that of the well-known chiral phosphoric acid catalyst TRIP, is largely derived from stabilization of the carboxylate conjugate base via intramolecular anion-binding to a thiourea site.

Zhengbo Zhu, Minami Odagi, Chenfei Zhao, Khalil A. Abboud, Helmi Ulrika Kirm, Jaan Saame, Märt Lõkov, Ivo Leito, and Daniel Seidel

Page No. – Page No.

Highly acidic conjugate-base-stabilized carboxylic acids catalyze enantioselective oxa-Pictet–Spengler reactions with ketals