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Catalytic Enantioselective Cloke-Wilson Rearrangement

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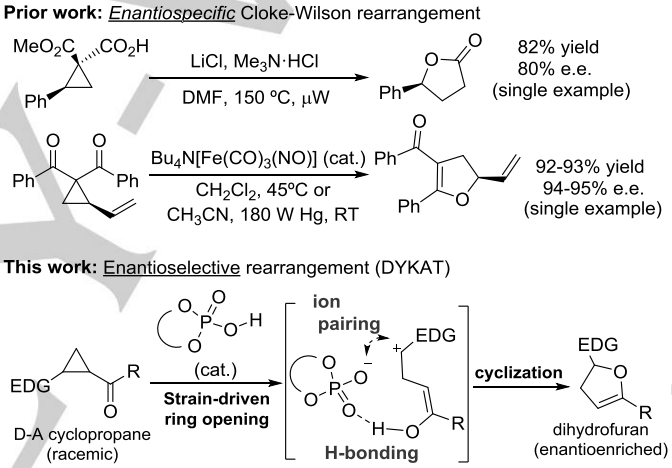
Dedication ((optional))

Abstract: Racemic cyclopropyl ketones undergo enantioselective rearrangement to deliver the corresponding dihydrofurans in the presence of a chiral phosphoric acid as catalyst. The reaction involves activation of the donor-acceptor cyclopropane substrate by the chiral Brønsted acid catalyst that promotes the ring-opening event driven by the release of ring strain, generating a carbocationic intermediate that subsequently undergoes cyclization. Computational studies supported by control experiments support this mechanistic pathway.

Cyclopropanes are inherently reactive compounds because of their thermodynamic tendency to undergo ring-opening driven by the release of ring strain.[1] This feature can be used to unveil unconventional reactivity patterns in transformations in which these molecules are involved. A good example this particular reactivity profile is their ability to undergo rearrangement to form more stable five- six- or seven-membered cyclic compounds,[2] being the so-called Cloke-Wilson rearrangement a remarkable case, in which cyclopropyl ketones form dihydrofurans under thermal conditions.[3] The need for high temperatures has become an important limitation for the synthetic applicability of this reaction,[4] and some very recent attempts have been directed to find milder conditions that enable expanding this transformation to more functionalized substrates.[5] Despite all these efforts, there are no reports regarding catalytic and enantioselective variants of the Cloke-Wilson rearrangement, with only two cases regarding enantiospecific processes (Scheme 1).[6]

With these precedents in mind, we turned our attention to the use of donor-acceptor cyclopropanes[7] such as those shown in Scheme 1 as suitable substrates for Cloke-Wilson rearrangement upon activation by a Brønsted acid. In particular, chiral BINOL-based phosphoric acids[8] were envisioned to be able to protonate the EWG substituent of the D-A cyclopropane, increasing the polarity of the C-C bond and facilitating the ring-opening process that would deliver a carbocation/enol intermediate that, upon ring-closure, would generate the dihydrofuran scaffold in an overall process driven by the release of ring-strain. Moreover, the participation of this intermediate would enable the use of racemic starting materials and their upgrade into enantiopure adducts by the use of a chiral catalyst through a DYKAT process.[9] In this sense, the combination of H-bonding between the phosphate anion and the enol moiety, together with ion-pairing interactions[10] between the phosphate and the stabilized carbocationic moiety were anticipated to provide the required rigid environment for efficient chirality transfer.[11]



Scheme 1. Stereoselective Cloke-Wilson rearrangements.

We first optimized the reaction using cyclopropane **1a** as model substrate (see Table 1). Through some preliminary experiments, we initially observed that this compound was undergoing fast rearrangement at r.t. in the presence of diphenylphosphoric acid, to provide dihydrofuran **2a** efficiently. Moreover, we also noticed that the reaction was taking place at temperatures as low as -30ºC. We proceeded next to survey the performance of a family of chiral Brønsted acids (entries 1-8 in Table 1) observing that, while the archetypical TRIP catalyst **3a** was not able to promote the reaction (entry 1), 2,2'-bis(aryl) substituted BINOL-based phosphoric acids **3b-e** turned to be active catalysts (entries 2-5). From these acids tested, **3e** was found to be the best one in terms of both yield and enantiocontrol (entry 5). More acidic *N*-sulfonylphosphoramide **3f** and *N,N*-bis-sulfonimide **3g** promoted a fast reaction but provided almost racemic material (entries 6 and 7) and spirocyclic catalyst **3h** also failed to provide high e.r. Next, the influence of the solvent was evaluated in combination with catalyst **3e**, observing that changing to *m*-xylene resulted into a slight improvement in the e.r. but with an inferior yield (entry 9). Remarkably, a much faster reaction was observed in halogenated solvents such as CH_2Cl_2 or 1,2-dichloroethane (entries 10 and 11),

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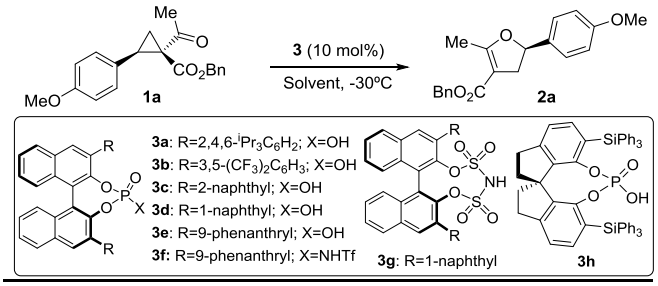
but with a slightly lower enantioselectivity (entries 10 and 11 *vs* 9). For this reason, binary mixtures of xylene with these solvents were evaluated (entries 12 and 13), obtaining an excellent result with *m*-xylene and 1,2-dichloroethane (entry 13). Finally, we also evaluated the reaction with a lower catalyst loading, observing a similar performance but requiring a longer time (entry 14).

Table 1. Screening for best reaction conditions[a]

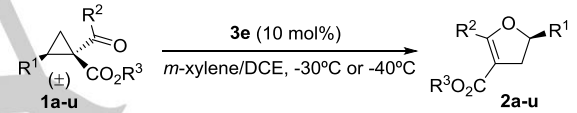


Entry	Catalyst	Solvent	t [h]	Yield [%][b]	e.r.[c]
1	**3a**	Toluene	48	<5	n.d.
2	**3b**	Toluene	48	13	67:33
3	**3c**	Toluene	48	45	75:25
4	**3d**	Toluene	48	72	90:10
5	**3e**	Toluene	48	82	91:9
6	**3f**	Toluene	12	91	50:50
7	**3g**	Toluene	12	83	52:48
8	**3h**	Toluene	72	63	56:44
9	**3e**	m-xylene	48	63	96:4
10	**3e**	CH_2Cl_2	24	80	93:7
11	**3e**	$Cl(CH_2)_2Cl$	24	85	91:9
12	**3e**	m-xylene/CH_2Cl_2	24	76	94:6
13	**3e**	m-xylene/$Cl(CH_2)_2Cl$	24	90	95:5
14[d]	**3e**	m-xylene/$Cl(CH_2)_2Cl$	48	91	95:5

[a] Reaction carried out in a 0.1 mmol scale of **1a**, using 10 mol% of catalyst in the indicated solvent (0.2M) at -30 ºC. [b] Yield of pure product after flash column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase (see Supporting Information). [d] 5 mol% of **3e**.

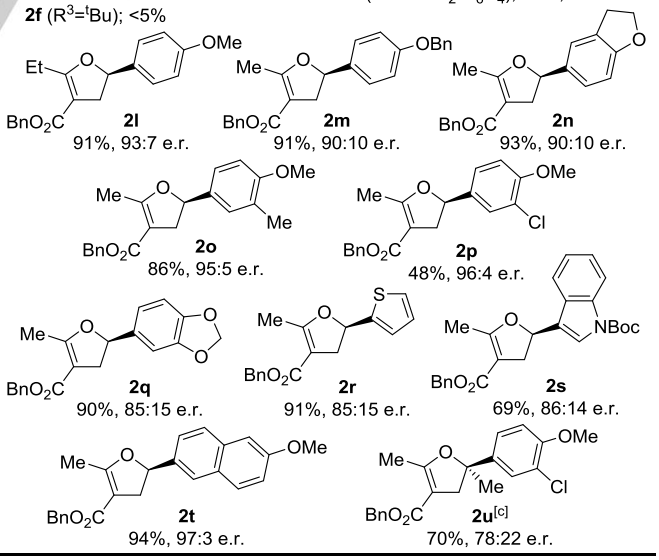
With an optimal experimental procedure in hands, we proceeded to evaluate the scope of the reaction. As it can be seen in Table 2, the reaction was found to proceed excellently with a variety of substrates with different alkoxide substituents at the ester moiety (adducts **2b-e)**, although the e.r. decreased slightly when increasing the size of this substituent, requiring for slightly lower temperatures to perform on synthetically useful parameters. Remarkably, the reaction could also be scaled up without any negative effect. The yield was significantly affected by the size of this substituent, observing that the reaction did not take place with the most sterically demanding *tert*-butyl ester substrate (see compound **2f**). A similar behavior was observed using cyclopropanes with different alkyl substituents at the ketone moiety, obtaining in general, excellent results with those containing linear alkyl substituents (**2g-h** and **2l**) and with a poorer conversion when the steric bulk was increased (**2i**): Aroyl-substituted cyclopropanes were also examined, observing that compound **1j** with a simple phenyl group was found to be inert to the ring-opening process. In contrast, 4-nitrobenzoyl derivative **1k** in which the polarization of the cyclopropane C-C bond is increased, provided **2k** in high yield and with good e.r. Cyclopropanes with a variety of substituents as the donor group were successfully tested, obtaining in general good results (compounds **2m-q**). If electron-withdrawing groups that decreased the ability of this substituent to stabilize the carbocationic intermediate were incorporated, the yield was affected (compound **2p**) but still maintaining an excellent enantiocontrol. Heteroaryl- and electron-rich naphthyl substituents were also well tolerated (compounds **2r-t**).[12] Interestingly, a cyclopropane such as **1u** underwent clean rearrangement under slightly modified conditions, leading to **2u** with a quaternary stereocentre, although with modest e.r.

Table 2. Scope of the reaction.[a]



2a[b] (R^3=Bn); 90%, 95:5 e.r.
2b[b] (R^3=Me); 95%, 95:5 e.r.
2c[b] (R^3=Et); 92%, 93:7 e.r.
2d[b] (R^3=^{n}Pr); 93%, 94:6 e.r.
2e[b] (R^3=^{i}Pr); 92%, 93:7 e.r.
2f (R^3=^{t}Bu); <5%

2g[b] (R^2=Et); 91%, 94:6 e.r.
2h[b] (R^2=^{n}Pr); 90%, 88:12 e.r.
2i[b] (R^2=^{i}Pr); 51%, 83:17 e.r.
2j (R^2=Ph); <5%
2k (R^2=4-NO_2-C_6H_4); 91%, 92:8 e.r.



[a] Reaction carried out in a 0.05 mmol scale of **1a-u** with 10 mol% of **3e** in m-xylene/DCE (3:1, 0.2M) at -30 ºC. Enantiomeric ratio (e.r.) was determined by HPLC analysis (see Supporting Information). [b] Reaction carried out at 0.4 mmol scale. [c] Reaction carried out in toluene at -60 ºC

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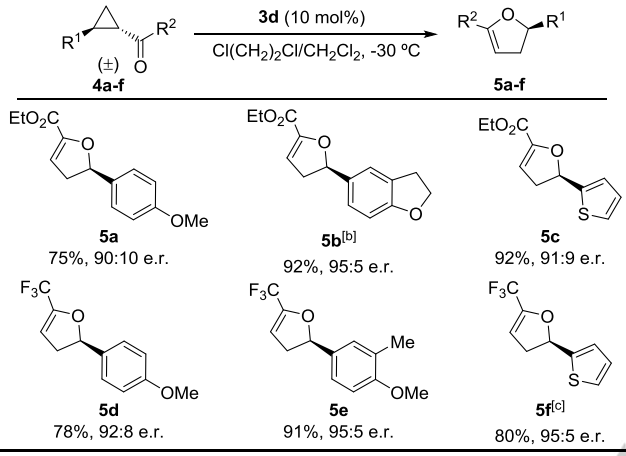
In addition, cyclopropyl ketones **4a-f** that do not incorporate the electron-withdrawing alkoxycarbonyl substituent together with the acyl moiety were also found to perform excellently (Table 3). In this case, the catalyst had to be changed to **3d**. Some representative examples of donor-acceptor cyclopropanes incorporating an α-ketoester or a trifluoroacetyl group as the EWG substituent reacted efficiently, providing the corresponding 1,2-dihydrofurans with high yield and e.r.[13]

Table 3. Enantioselective Cloke-Wilson rearrangement with ketones **4a-f**.[a]



[a] Reaction carried out in a 0.05 mmol scale of **4a-f** using 10 mol% of **3d** in DCE/DCM (1:1, 0.2M) at -30 ºC. Enantiomeric ratio (e.r.) was determined by HPLC analysis (see Supporting Information). [b] Reaction carried out at -60 ºC. [c] Reaction carried out in DCE.

We also carried out a computational study using BINOL-phosphoric acid **3i** (R=H) as a simplified catalyst. The reaction starts through coordination of **3i** to **1b** (Figure 1, top). At this point, any attempt to locate an intermediate carbocation failed and only transition structure **TS1** was located. The IRC analysis clearly showed that **TS1** connects **1b** with **2b** along a concerted but highly asynchronous pathway. Indeed, the IRC showed a shoulder, suggesting the presence of a hidden intermediate, a situation often found when carbocations that are not stable enough to be characterized as minima are involved.[14] A geometrical analysis of C9 environment during the reaction (see SI) revealed the planarity (as expected for a sp^2-hybridization) of that center. The formation of a carbocationic species **CB** was confirmed by a topological analysis of the electron localization function (ELF),[15] which was used for monitoring the evolution of the electron population along the reaction coordinate (Figure 1, bottom). After point 60 of the IRC bonds C1-C2 and C4-C5 increased their population whereas bonds C2-C3, C3-C4, C5-C6 and C6-C1 decreased their population.[16] This situation continues until several points after **TS1**, clearly illustrating the formation of a quinoid form for the aryl moiety compatible with the expected delocalization of the positive charge. At the start (before point 60) and the end (after point 160) of the reaction, a degenerated situation for all the aromatic bonds was observed indicating the aromatic character of the ring. The ELF analysis also confirms the early cyclopropane ring opening and the late C-O bond formation providing enough time for the "virtual existence" of a carbocation.

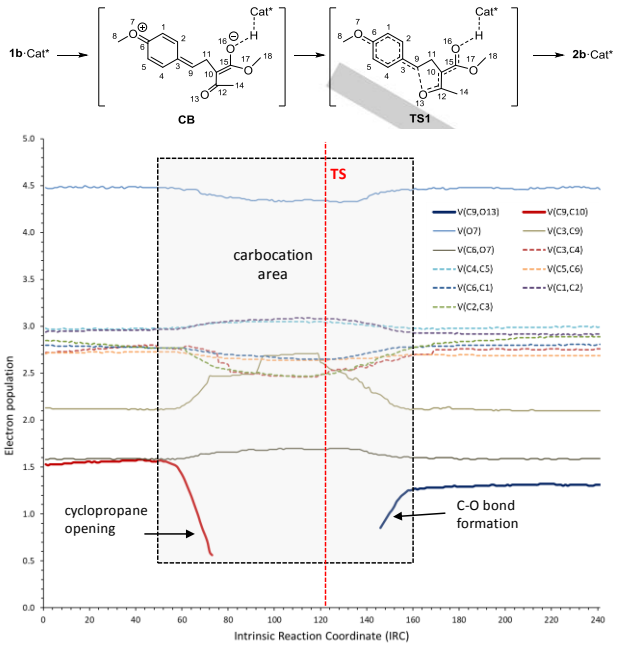


Figure 1. Mechanism of the reaction and evidences for the formation of a carbocationic hidden intermediate. The different traces correspond to the evolution of electronic populations of the indicated bonds along the reaction coordinate. Bolded lines correspond to breaking (red) and forming (blue) bonds. Dotted lines correspond to aromatic bonds.

The development of a planar arrangement capable of surviving along the reaction has dramatic consequences for the stereochemical outcome. Any initial chiral information of the starting substrate is lost during the reaction and four possible interconnected approaches are possible (See SI). When the real catalyst **3e** was considered the lowest energy transition state structure corresponded to that leading to the (*R*)-isomer (Figure 2) in agreement with experimental results. The driving force ultimately responsible for the high selectivity is the presence of attractive London interactions between the phenanthryl moiety and the aromatic ring responsible of stabilizing the carbocation, that are not present in the transition structure leading to the (*S*)-enantiomer. These London interactions are π-stacking interactions that during the carbocation phase become cation π-interactions. The presence of such favorable interactions was corroborated by NCI analysis,[17] which revealed the expected surface between the two aromatic systems.

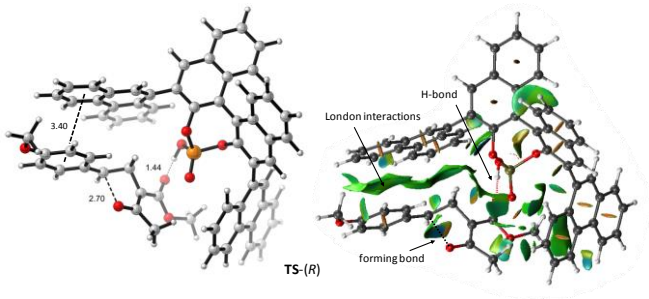


Figure 2. Preferred transition state structure for the reaction (right: NCI analysis).

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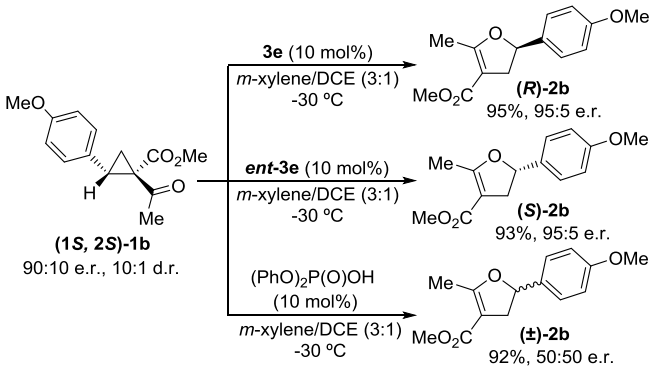
To confirm this proposal, we carried out some experiments using an enantioenriched sample of **1b** as starting material (Scheme 2). When this compound was subjected to reaction with catalyst **3e**, adduct **(*R*)-2b** was isolated in comparable yield and e.r. as observed when the racemic material was used (see Table 1). Remarkably, when using the enantiomer of **3e** as catalyst, **(*S*)-2b** was isolated with a similar yield and e.r. Finally, the reaction of **(1*S*,2*S*)-1b** promoted by an achiral catalyst provided racemic **2b**. In all cases, all reactions took place at a comparable rate, indicating the absence of any matched/mismatched effect at the catalyst/substrate interaction stage.



Scheme 2. Experiments using enantioenriched cyclopropane **(1*S*,2*S*)-1b**.

In conclusion, we have shown that cyclopropyl ketones are excellent substrates for enantioselective Cloke-Wilson rearrangement catalyzed by a chiral phosphoric acid. Under the optimized conditions, the corresponding dihydrofurans are obtained in high yield and enantioselectivity. Computational and experimental studies demonstrate that the reaction proceeds through the formation of a transient carbocationic intermediate that enables the use of racemic cyclopropanes as starting materials through a Dynamic Kinetic Asymmetric Transformation (DYKAT) process.

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Keywords: Asymmetric catalysis · Rearrangement · Carbocations · Strained molecules · Organocatalysis

[1] For some selected reviews see: a) A. Nikolaev, A. Orellana, *Synthesis* **2016**, *48*, 1741. b) P. Tang, Y. Qin, *Synthesis* **2012**, *44*, 2969. c) V. Ganesh, S. Chandrasekaran *Synthesis*, **2016**, *48*, 4347. d) J. R. Green, V. Snieckus, *Synlett* **2014**, *25*, 2258. e) F. De Simone, J. Waser, *Synthesis* **2009**, 3353. f) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev*. **2009**, *38*, 3051. g) M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev*. **2007**, *107*, 3117. h) H. N. C. Wong, M. Y. Hon, C. W. Tse, Y. C. Yip, J. Tanko, T. Hudlicky, *Chem. Rev.* **1989**, *89*, 165.

[2] a) V. A. Rassadin, Y. Six, *Tetrahedron* **2016**, *72*, 4701. b) D. J. Mack, J. T. Njardson, *ACS Catal.* **2013**, 3, 272. c) J. E. Baldwin, *Chem. Rev.* **2003**, *103*, 1197. See also d) W. R. Dolbier Jr., *Acc. Chem. Res.* **1981**, *14*, 195. e) S. Sarel, *Acc. Chem. Res.* **1978**, *11*, 204. f) S. Sarel, J. Yovell, M. Sarel-Imber, *Angew. Chem. Int. Ed. Engl*. **1968**, *7*, 577.

[3] a) J. B. Cloke, *J. Am. Chem. Soc*. **1929**, *51*, 1174. b) C. L. Wilson, *J. Am. Chem. Soc*. **1947**, *69*, 3002.

[4] T. F. Schneider, D. B. Werz, *Org. Lett*. **2011**, *13*, 1848.

[5] a) J. Zhang, Y. Tang, W. Wei, Y. Wu, Y. Li, J. Zhang, Y. Zheng, S. Xu, *Org. Lett.* **2017**, *19*, 3043. b) Y. Wang, J. Han, J. Chen, W. Cao, *Chem. Commun*. **2016**, *52*, 6817. c) J. E. M. N. Klein, G. Knizia, B. Miehlich, J. Kastner, B. Plietker, *Chem. Eur. J*. **2014**, *20*, 7254. d) E. Gopi, I. N. N. Namboothiri, *J. Org. Chem*. **2013**, *78*, 910. e) J. Kaschel, T. F. Schneider, P. Schirmer, C. Maaß, D. Stalke, D. B. Werz, *Eur. J. Org. Chem*. **2013**, 4539. f) M. Li, S. Lin, Z. Dong, X. Zhang, F. Liang, J. Zhang, *Org. Lett.* **2013**, *15*, 3978. g) P. Huang, N. Zhang, R. Zhang, D. Dong, *Org. Lett*. **2012**, *14*, 370. h) Z. Zhang, Q. Zhang, S. Sun, T. Xiong, Q. Liu, *Angew. Chem., Int. Ed.* **2007**, *46*, 1726. i) R. K. Bowman, J. S. Johnson, *Org. Lett.* **2006**, *8*, 573. j) M. Honda, T. Naitou, H. Hoshino, S. Takagi, M. Segi, T. Nakajima, *Tetrahedron Lett*. **2005**, *46*, 7345. k) V. K. Yadav, R. Balamurugan, *Org. Lett.* **2001**, *3*, 2717. l) P. D. Pohlhaus, J. S. Johnson, *J. Org. Chem.* **2005**, *70*, 1057.

[6] a) H. K. Grover, M. R. Emmet, M. A. Kerr, *Org. Lett.* **2013**, *15*, 4838. b) C.-H. Lin, D. Pursley, J. E. M. N. Klein, J. Teske, J. A. Allen, F. Rami, A. Kohn, B. Plietker, *Chem. Sci*. **2015**, *6*, 7034.

[7] For selected reviews on the chemistry of donor-acceptor cyclopropanes, see: a) S. J. Gharpure, L. N. Nanda, *Tetrahedron Lett*. **2017**, *58*, 711. b) H. K. Grover, M. R. Emmett, M. A. Kerr, *Org. Biomol. Chem*. **2015**, *13*, 655. c) R. A. Novikov, Y. V. Tomilov, *Mendeleev Commun*. **2015**, *25*, 1. d) M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev*. **2014**, *43*, 804. e) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem., Int. Ed*. **2014**, *53*, 5504. f) S. J. Gharpure, L. N. Nanda, F. de Nanteuil, F. De Simone, R. Frei, F. Benfatti, E. Serrano, J. Waser, *Chem. Commun*. **2014**, *50*, 10912. g) M. YaMel’nikov, E. M. Budynina, O. A. Ivanova, I. V. Trushkov, *Mendeleev Commun*. **2011**, *21*, 293.

[8] For some selected reviews see: a) M. R. Monaco, G. Pupo, B. List, *Synlett* **2016**, *27*, 1027. b) T. Akiyama, *Chem. Rev*. **2015**, *115*, 9277. c) T. James, M. van Gemmeren, B. List, *Chem. Rev.* **2015**, *115*, 9388. d) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev*. **2014**, *114*, 9047. e) M. Terada, *Synthesis*. **2010**, 1929. f) M. Rueping, B. J. Nachtsheim, W. Leawsuwan, I. Atodiresei, *Angew. Chem. Int. Ed.* **2011**, *50*, 6706. g) M. Terada, *Curr. Org. Chem*. **2011**, *15*, 2227. h) M. Rueping, A. Kuenkel, I. Atodiresei, *Chem. Soc. Rev.* **2011**, *40*, 4539. i) M. Terada, *Bull. Chem. Soc. Jpn.* **2010**, *83*, 101. j) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.* **2010**, *291*, 395. k) A. Zamfir, S. Schenker, M. Freund, S. B. Tsogoeva, *Org. Biomol. Chem.* **2010**, *8*, 5262. l) M. Terada, *Chem. Commun.* **2008**, *35*, 4097. m) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744. n) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2017**, *117*, 10608.

[9] For some selected examples of enantioselective reactions using racemic donor-acceptor cyclopropanes see: a) A. T. Parsons, J. S. Johnson, *J. Am. Chem. Soc.* **2009**, *131*, 3122. b) A. T. Parsons, A. G. Smith, A. J. Neel, J. S. Johnson, *J. Am. Chem. Soc*. **2010**, *132*, 9688. c) B. M. Trost, P. J. Morris, *Angew. Chem., Int. Ed*. **2011**, *50*, 6167. d) H. Xiong, H. Xu, S. Liao, Z. Xie, Y. Tang, *J. Am. Chem. Soc*. **2013**, *135*, 7851. e) T. Hashimoto, Y. Kawamata, K. Maruoka, *Nat. Chem*. **2014**, *6*, 702. f) A. G. Amador, E. M. Sherbrook, T. P. Yoon, *J. Am. Chem. Soc.* **2016**, *138*, 4722. g) Y. Y. Zhou, L. J. Wang, J. Li, X. L. Sun, Y. Tang, *J. Am. Chem. Soc.* **2012**, *134*, 9066. h) Y. Xia, X. Liu, H. Zheng, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* **2015**, *54*, 227. i) Y. Xia, L. Lin, F. Chang, X. Liu, X. Feng, *Angew. Chem. Int. Ed.* **2015**, *54*, 13748. j) H. Xu, J.-P. Qu, S. Liao, H. Xiong, Y. Tang, *Angew. Chem. Int. Ed.* **2013**, *52*, 4004. k) S. M. Wales, M. M. Walker, J. S. Johnson, *Org. Lett.* **2013**, *15*, 2558.

[10] For reviews on the concept of asymmetric counterion-directed catalysis see: a) M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 518. b) E. P. Avila, G. W. Amarante, *ChemCatChem* **2012**, *4*, 1713. c) S. Mayer, B. List, *Angew. Chem. Int. Ed.* **2006**, *45*, 4193. See also d) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nat. Chem.* **2012**, *4*, 603. e) K. Brak, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2013**, *52*, 534.

[11] For a previous example from our group on the use of the cooperative H-bonding and ion-pairing interactions in a (4+3) cycloaddition catalyzed by chiral BINOL-based phosphoric acid derivatives see: a) L. Villar, U. Uria, J. I. Martinez, L. Prieto, E. Reyes, L. Carrillo, J. L. Vicario, Angew. *Chem. Int. Ed*. **2017**, *56*, 10535. For some selected examples on the use of this strategy in the enantioselective functionalization of benzylic cations see:. b) M. Rueping, U. Uria, M.-Y. Lin, I. Atodiresei, *J. Am. Chem. Soc.* **2011**, *133*, 3732. c) P.-S. Wang, X.-L. Zhou, L.-Z. Gong, *Org. Lett.* **2014**, *16*, 976. d) M. Zhuang, H. Du, *Org. Biomol. Chem.* **2014**, *12*, 4590. e) J. Zhou, H. Xie, *Org. Biomol. Chem.* **2018**, *16*, 380. f) D. Qian, L. Wu, Z. Lin, J. Sun, *Nat. Commun.* **2017**, *8*, 567.

[12] The absolute configuration of compound **2t** was determined by X-ray analysis of the corresponding *p*-bromophenyl ester (See SI for details). CCDC 1838380 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] The absolute configuration of compound **5a** was determined by X-ray analysis of the corresponding *p*-bromophenyl ester (See SI for details). CCDC 1838379 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

[14] a) R. P. Pemberton, D. J. Tantillo, *Chem. Sci.* **2014**, *5*, 3301. b) M. A. Chiacchio, L. Legnani, P. Caramella, T. Tejero, P. Merino, *Eur. J. Org. Chem.* **2017**, 1952.

[15] A. Savin, R. Nesper, S. Wengert, T. F. Fässler, *Angew. Chem. Int. Ed.* **1997**, *36*, 1808.

[16] The analysis of the electron population is based on the population of the corresponding basins according to ELF analysis; for details see SI.

[17] E. R. Johnson, S. Keinan, P. Mori-Sanchez, J. Contreras-Garcia, A. J. Cohen, W. Yang, *J. Am. Chem. Soc.* **2010**, *132*, 6498.

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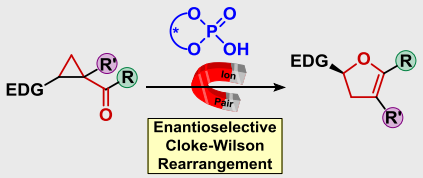

A paired rearrangement: Racemic cyclopropyl ketones undergo enantioselective rearrangement to deliver dihydrofurans in the presence of a chiral phosphoric acid as catalyst. The reaction involves activation of the D-A cyclopropane substrate by the Brønsted acid catalyst that promotes the ring-opening event driven by the release of ring strain, generating a carbocationic intermediate that subsequently undergoes cyclization.

Alesandere Ortega, Rubén Manzano, Uxue Uria, Luisa Carrillo, Efraim Reyes, Tomas Tejero, Pedro Merino* and Jose L. Vicario**

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Catalytic Enantioselective Cloke-Wilson Rearrangement