Catalytic Enantioselective Cloke–Wilson Rearrangement

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Catalytic Enantioselective Cloke-Wilson Rearrangement

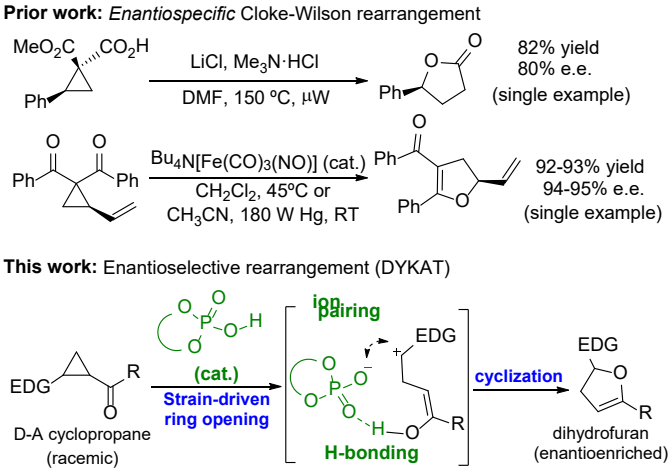
Alesandere Ortega,[a] Rubén Manzano,[a] Uxue Uria, *[a] Luisa Carrillo,[a] Efraim Reyes, [a] Tomas Tejero,[b] Pedro Merino*[c] and Jose L. Vicario*[a]

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 of the particular reactivity profile associated to the cyclopropane scaffold is their ability to undergo rearrangement to form more stable five- six- or seven-membered cyclic compounds.[2] A remarkable case of this type of reactivity is the so-called Cloke-Wilson rearrangement, in which cyclopropyl ketones form dihydrofurans under thermal conditions.[3] The need for high temperatures[4] has become an important limitation for the synthetic applicability of thuis reaction and, for this reason, 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 examples showing the possibility of performing this reaction in a catalytic and enantioselective way with only two cases reported that comprise an enantiospecific Cloke-Wilson rearrangement using enantioenriched starting materials (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 electron-withdrawing 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 final dihydrofuran scaffold in an overall process driven by the release of ring-strain. Moreover, the participation of this carbocationic intermediate would enable the use of racemic starting materials and their upgrade into enantiopure adducts by the use of a chiral phosphoric acid catalyst through a DYKAT process.[9] In this sense, we also anticipated that 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 would provide the required chiral 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 able to undergo 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. With this information in hand, we proceeded next to survey the performance of a family of different chiral Brønsted acids at this temperature (entries 1-8 in Table 1), observing that, while the archetypical BINOL-based 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 in this transformation (entries 2-5). From these different acids tested, 2,2'-bis(9-phenanthryl)-substituted catalyst **3e** was found to be the best performing 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 the spirocyclic phosphoric acid catalyst **3h** also failed to provide high enantiocontrol. Next, the influence of the solvent was evaluated in combination with

[a] A. Ortega, R. Manzano, U. Uria, L. Carrillo, E. Reyes, Prof. Dr. J. L. Vicario
Department of Organic Chemistry II
University of the Basque Country (UPV/EHU)
P.O. Box 644, 48080 Bilbao (Spain)
E-mail: joseluis.vicario@ehu.es; uxue.uria@ehu.es
[b] T. Tejero
Instituto de Síntesis Química y Catálisis Homogénea (ISQH)
Universidad de Zaragoza CSIC
50009 Zaragoza (Spain)
[c] P. Merino
Instituto de Biocomputación y Fisica de Sistemas Complejos (BIFI)
Universidad de Zaragoza
50009 Zaragoza (Spain)
E-mail: pmerino@unizar.es

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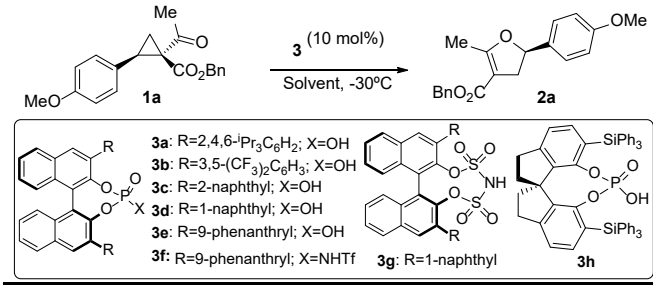
catalyst **3e**, observing that changing to *m*-xylene resulted into a slight improvement in the enantioselectivity of the process but with an inferior yield (entry 9). Remarkably, a much faster reaction was observed when it was carried out in halogenated solvents such as CH_2Cl_2 (entry 10) or 1,2-dichloroethane (entry 11), but with a slightly lower enantioselectivity than that provided by *m*-xylene (entries 10 and 11 *vs* 9). For this reason, binary mixtures of xylene with these chlorinated solvents were evaluated (entries 12 and 13), obtaining an excellent result with the combined use of *m*-xylene and 1,2-dichloroethane (entry 13). Finally, we also evaluated the reaction using a lower catalyst loading, observing a similar performance but requiring for a longer reaction time (entry 14).

Table 1. Screening for best reaction conditions[a]

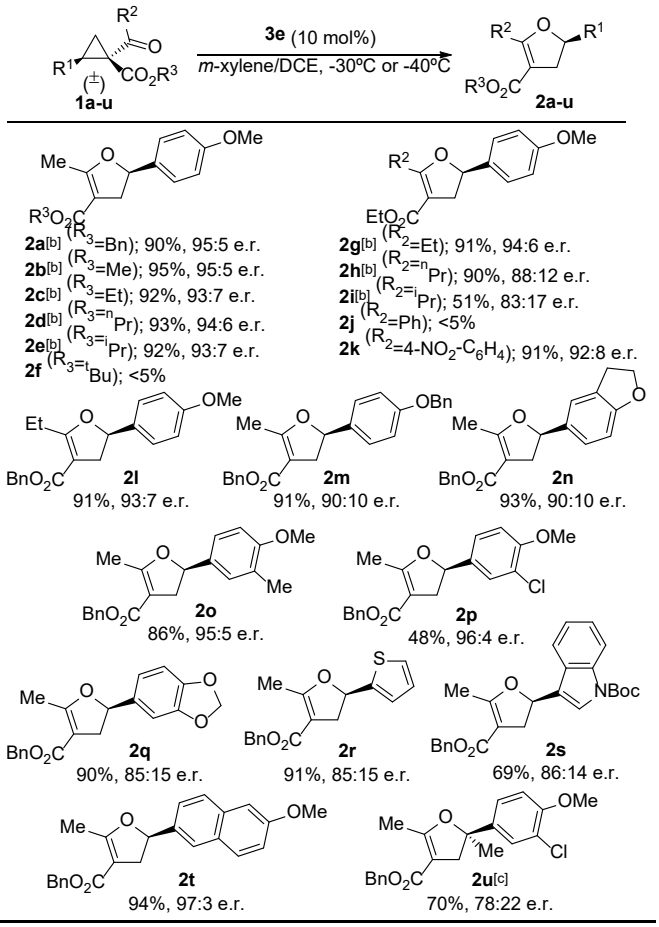


Entry	Catalyst	Solvent	t [h]	Yield [%][b]	e.r.[c]
1	**3a**	Toluene	48	<5	n.d.
2	**3b**	Toluene	48	13	67:33
3	**3c**	Toluene	48	45	75:25
4	**3d**	Toluene	48	72	90:10
5	**3e**	Toluene	48	82	91:9
6	**3f**	Toluene	12	91	50:50
7	**3g**	Toluene	12	83	52:48
8	**3h**	Toluene	72	63	56:44
9	**3e**	m-xylene	48	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 regardless of the nature of the alkoxide substituent at the ester moiety of the cyclopropane reagent (adducts **2b-e)**, although the enantioselectivity decreased slightly when increasing the size of this substituent, requiring for slightly lower temperatures to perform on synthetically useful parameters. Remarkably, the reaction using cyclopropanes **1a-e** as substrates could also be scaled up without any negative effect on the yield and enantioselectivity. The yield was also 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 with cyclopropanes with different alkyl substituents at the ketone moiety, obtaining in general, excellent results with substrates containing linear alkyl substituents (compounds **2g-h** and **2l**) and with a poorer conversion when the steric bulk was increased (compound **2i**) or without observing any reaction when a less reactive phenyl ketone moiety was present (compound **2j**).

Table 2. Scope of the reaction.[a]



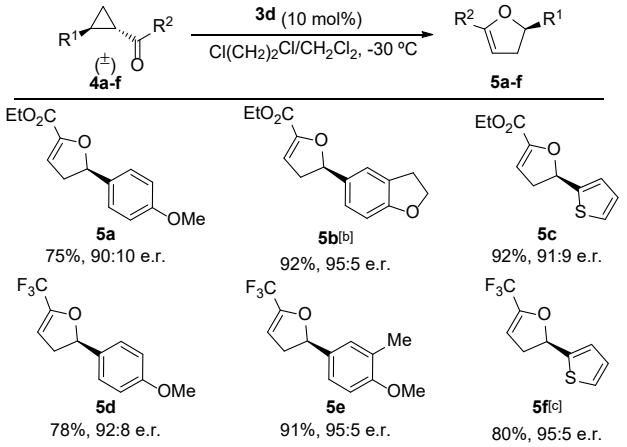
[a] Reaction carried out in a 0.05 mmol scale of **1a-u** with 10 mol% of **3e** in m-xylene/DCE (3:1, 0.2M) at -30 ºC. Enantiomeric ratio (e.r.) was determined by HPLC analysis (see Supporting Information). [b] Reaction carried out at 0.4 mmol scale. [c] Reaction carried out in toluene at -60 ºC

In contrast, 4-nitrophenyl ketone derivative **1k** provided dihydrofuran **2k** in high yield with good e.r. Other cyclopropanes with a variety of electron-rich substituents as the donor group were successfully tested, obtaining in general good results when

substituents of different nature were incorporated at the aryl ring (compounds **2m-q**). If electron-withdrawing groups that decreased the ability of this substituent to stabilize the carbocationic intermediate were incorporated, the yield of the reaction was affected (see compound **2p**) but still maintaining an excellent performance with respect to enantiocontrol. Heteroaryl- and electron-rich naphthyl substituents were also well tolerated (see compounds **2r-t**).[12] Interestingly, a cyclopropane such as **1u** was also found to undergo clean rearrangement under slightly modified conditions, leading to the formation of dihydrofuran **2u** with a quaternary stereocentre, although with modest enantioselectivity.

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 in the reaction (Table 3). In this case, the structure of the catalyst had to be slightly modified, observing that **3d** was the best one for the reaction. A series of representative examples of donor-acceptor cyclopropanes incorporating an α-ketoester or a trifluoroacetyl group as the electron-withdrawing substituent reacted efficiently under the optimized reaction conditions, 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 directed to a better understanding of the reaction pathway, using BINOL-derived phosphoric acid (**3i**, R=H) as a simplified catalyst. The reaction starts through coordination of the catalyst to **1b** (Figure 1, top) and, 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 course of 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** (point 121), 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.

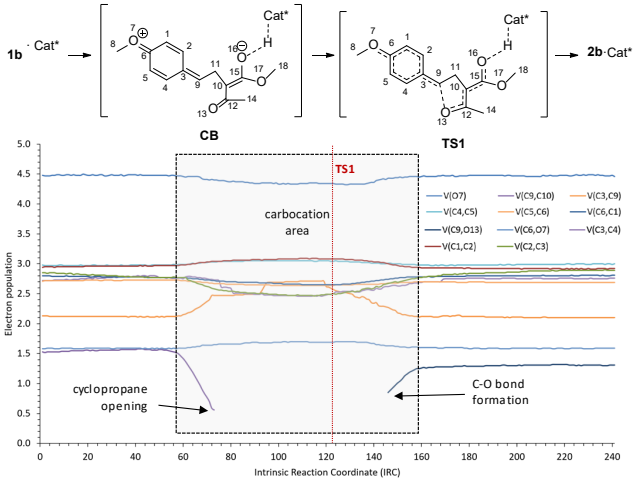


Figure 1. Mechanism of the reaction and evidences for the formation of a carbocationic hidden intermediate.

The development of a planar arrangement capable of surviving during a period along the reaction course has dramatic consequences for the stereochemical outcome of the reaction. 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 for analyzing the stereochemical preferences the lowest transition structure corresponded to that leading to the (*R*)-isomer (Figure 2) in a good agreement with experimental results. The driving force ultimately responsible for the high selectivity observed with **3e** 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. The presence of such favorable interactions was corroborated by NCI analysis,[17] which revealed the expected surface between the two aromatic systems.

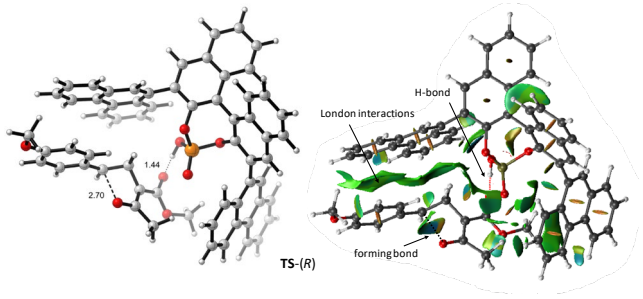
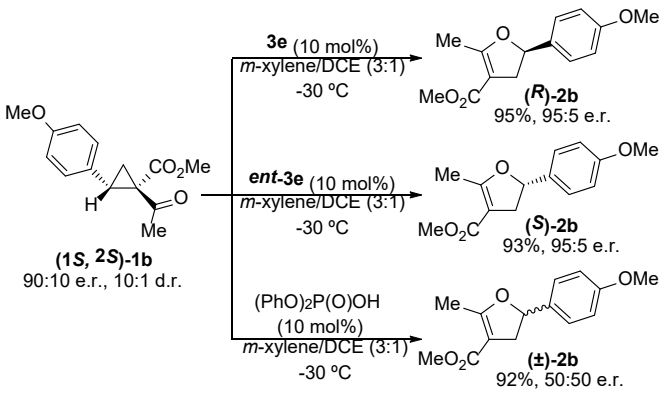


Figure 2. Preferred transition state structure for the reaction (left: NCI analysis).

To confirm this mechanistic proposal, we carried out a series of experiments using an enantioenriched sample of **1b** as starting material (Scheme 2).[18] When this compound was subjected to the Cloke-Wilson rearrangement under the optimized conditions with catalyst **3e**, adduct **(*R*)-2b** was isolated in comparable yield and e.r. as observed when the racemic material had been used before (see Table 1). Remarkably, using the opposite enantiomer of **3e** as catalyst, the opposite enantiomer **(*S*)-2b** was isolated, also with a similar yield and e.r. Finally, the reaction of **(1*S*,2*S*)-1b** promoted by an achiral catalyst provided **2b** as racemic product. 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. Enantioselective Cloke-Wilson rearrangement using enantioenriched cyclopropane **(1*S*,2*S*)-1b**.

In conclusion, we have demonstrated that cyclopropyl ketones are excellent substrates to undergo enantioselective Cloke-Wilson rearrangement catalyzed by a chiral phosphoric acid. Under the optimized conditions, the corresponding dihydrofuranes are obtained in high yield and enantioselectivity, with this transformation showing a wide substrate scope. Computational and experimental studies demonstrates that the reaction proceeds through the formation of a transient carbocationic intermediate that enables the use of racemic cyclopropanes as starting materials through a DYKAT process.

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

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[12] The absolute configuration of compound **2t** was determined by X-ray analysis of the corresponding *p*-bromophenyl ester, which was obtained as crystalline material after hydrolysis/esterification following standard procedures (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

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[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.

[18] Enantioenriched cyclopropane **1b** was synthesized by resolution. For full experimental details see SI.

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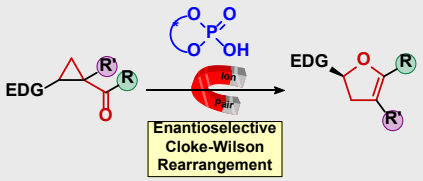

A paired rearrangement: Racemic cyclopropyl ketones undergo enantioselective rearrangement to deliver dihydrofurans in the presence of a chiral phosphoric acid as catalyst. The reaction involves activation of the D-A cyclopropane substrate by the Brønsted acid catalyst that promotes the ring-opening 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