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Chem. Eur. J. 2018, *24*, 8764

DOI: **10.1002/chem.201801434**

Carboxylates as Nucleophiles in the Enantioselective Ring-Opening of Formylcyclopropanes under Iminium Ion Catalysis

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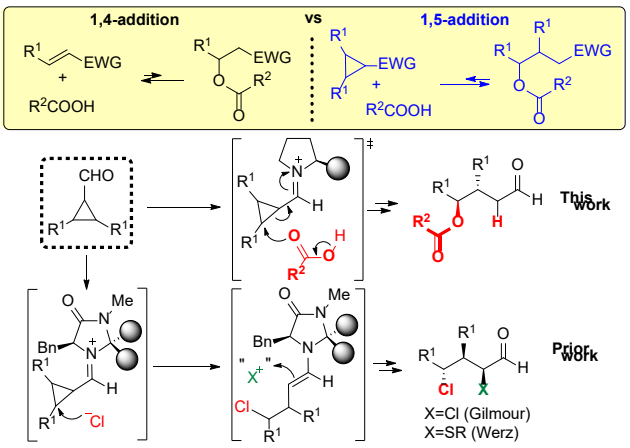
Dedication ((optional))

Abstract: We have demonstrated that carboxylic acids, which are typically regarded as poor nucleophiles, are competent reagents to promote the ring-opening of formylcyclopropanes after activation of the latter through iminium ion formation. Under optimized reaction conditions, a variety of γ-acyloxy-substituted aldehydes can be obtained in high yields and enantioselectivities through the desymmetrization of substituted meso-formylcyclopropanes in the presence of a chiral secondary amine as catalyst.

The ring-strain associated to small-size carbocycles can be utilized to unveil unusual reactivity that enables accessing to chemical architectures that are typically difficult to obtain through conventional methodologies.[1] Donor-acceptor cyclopropanes are a paradigmatic case in which the synergistic nature of the substituents contributes to the polarization of the C-C bond, favoring the ring-opening process.[2] Alternatively, cyclopropanes that only incorporate electron-withdrawing substituents can also be used as substrates to undergo ring-opening with a nucleophile. In terms of synthetic potential, this type of electrophilic cyclopropanes[3] can be considered as Michael acceptor homologues, undergoing 1,5-functionalization upon reaction with a nucleophile in comparison to the standard 1,4-functionalization achieved on Michael-type reactions (see Scheme 1).[4]

On the other hand, carboxylic acids are typically considered as poor oxygen-centered nucleophiles that need to react with potent carbon electrophiles when the corresponding C-O bond formation is desired. Alternatively, they require for an irreversible C-O bond forming process for the reaction to be thermodynamically favored, due to their ability as good leaving groups.[5] This implies that important organic reactions remain elusive when the nucleophilic counterpart is a carboxylate anion like, for example, in the conjugate addition.[6] In this sense, we wish to present herein that carboxylic acids, despite their limited ability as nucleophiles, are competent reagents to initiate the ring-opening of formylcyclopropanes in the presence of a chiral secondary amine as catalyst, which delivers γ-acyloxy-substituted aldehydes in excellent yields, diastereo- and enantioselectivities (Scheme 1).[7] It should be highlighted that a variety of heteronucleophiles have been previously used to promote ring-opening on donor-acceptor cyclopropanes,[8] typically requiring powerful nucleophiles such as amines, azides, halides or indoles.[7,9] Some precedents demonstrate that Lewis acids are efficient promoters of the ring-opening event in electrophilic cyclopropanes,[3] but the ability of organocatalysts to activate these strained substrates[10] has only been recently documented and is exclusively limited to two cases (Scheme 1). Sparr and Gilmour were pioneers in reporting the enantioselective ring-opening of formylcyclopropanes under iminium activation using MacMillan-type imidazolidinones as catalysts in the presence of chloride and *N*-chlorosuccinimine, leading to α,γ-dichlorinated aldehydes.[11] Very recently, Werz extended this reaction to the chlorosulfenylation of formylcyclopropanes with moderate enantiocontrol.[12] These two reports rely on the use of a chloride anion as the nucleophilic species that promote the ring-opening of the cyclopropyliminium ion intermediate[13] and also show the necessity of an external electrophilic sulfur or halogen source to quench the enamine formed after the ring-opening reaction as a common feature, in contrast to the reaction studied herein.[14]



Scheme 1. Electrophilic cyclopropanes as homologous Michael acceptor equivalents reacting with carboxylates.

The optimization of the reaction conditions was carried out using formylcyclopropane **1a** as model substrate and benzoic acid **2a** as nucleophile (Table 1). We initially surveyed the performance of MacMillan-type imidazolidinone **3a**, which was found to perform best in the other two examples mentioned earlier.[11,12] However, the formation of **4a** was observed in very low amount (entry 1). As an alternative, we tested *O*-TMS-protected diphenylprolinol **3b**,

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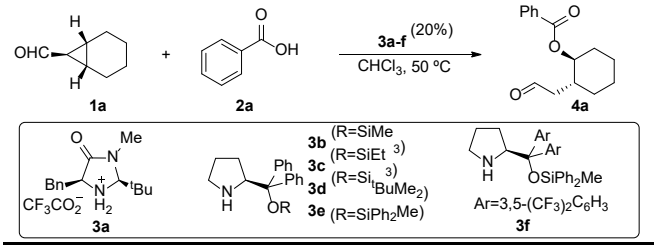
which is the other archetypical catalyst employed in iminium activation chemistry.[15] In this case, the desired product was obtained in moderate yield and low enantiocontrol (entry 2). The fact that the reaction required a relatively high temperature could possibly induce desilylation of the catalyst and, for this reason, other analogues of **3b** were surveyed (entries 3-5). All these derivatives performed similarly in terms of yield but provided increased enantioselectivity when a bulkier $SiPh_2Me$ group was incorporated (catalysts **3e** and **3f**, entries 6 and 7). Once a catalyst providing optimal stereocontrol was identified (catalyst **3f**, entry 7), we moved to modify the conditions with the aim to increase the yield (entries 7-10). In this sense, while changing the solvent did not end up in any major improvement (entries 7-9), using an excess of **2a** had a very positive effect (entry 10).

Table 1. Screening for best reaction conditions[a]

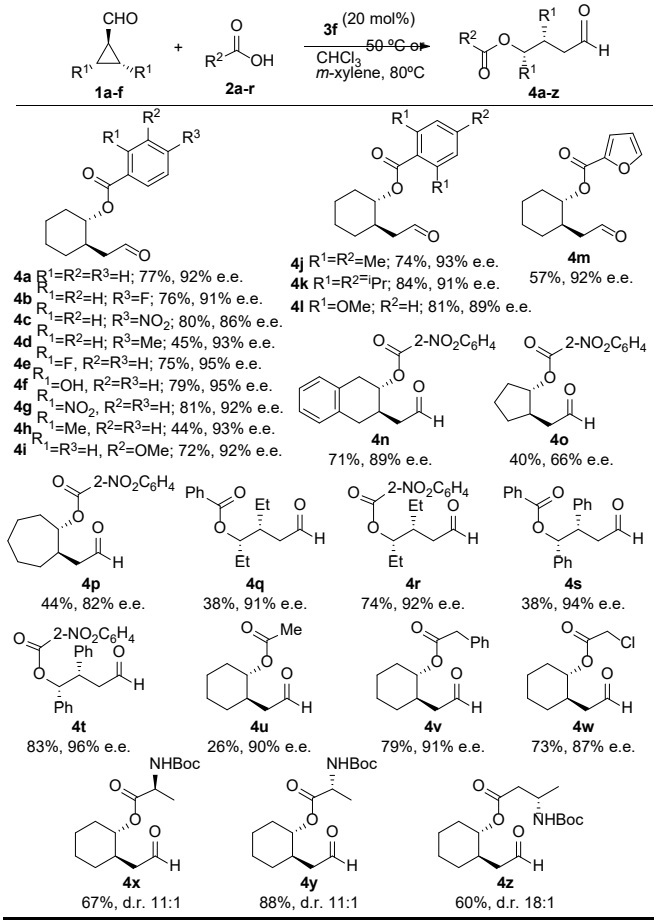


Entry	Catalyst	Solvent	Yield [%][b]	d.r.[c]	e.e. [%][b]
1	**3a**	$CHCl_3$	8	>20:1	31
2	**3b**	$CHCl_3$	43	>20:1	51
3	**3c**	$CHCl_3$	33	>20:1	61
4	**3d**	$CHCl_3$	41	>20:1	13
5	**3e**	$CHCl_3$	40	>20:1	70
6	**3f**	$CHCl_3$	40	>20:1	92
7	**3f**	Toluene	28	>20:1	90
8	**3f**	THF	<5	>20:1	n.d.
9	**3f**	$ClCH_2CH_2Cl$	32	>20:1	89
10[e]	**3f**	$CHCl_3$	77	>20:1	92

[a] Reaction carried out in a 0.25 mmol scale of **1a**, using 1 eq. of **2a** and 20 mol% of catalyst.. [b] Yield of pure product after column chromatography. [c] Determined by NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis of the corresponding primary alcohol obtained after reduction (see Supporting Information). [e] Reaction carried out using 3 equiv. of **2a**.

With optimized conditions in hand, we next evaluated the scope of this transformation. As it can be seen in Table 2, the reaction performed well with a variety of benzoic acid derivatives (compounds **4a** to **4l**), providing better results when electron-withdrawing substituents were placed at the aryl moiety and also furnishing the desired adduct efficiently regardless the position of the substituent at the aryl ring. Moreover, when a heteroaromatic substrate such as 2-furanecarboxylic acid was employed, adduct **4m** was obtained as highly enantiopure material, although the yield was slightly lower. Other formylcyclopropanes were also surveyed, observing that, in general, good results were obtained for related benzocyclohexane- cyclopentane- and cycloheptane-fused substrates (adducts **4n**-**4p**),[16] although the latter two cases provided the final ring-opening product in somewhat lower amount, which also provides interesting insights into reaction mechanism, as it will be discussed afterwards. In addition, simpler *meso*-2,3-disubstituted formylcyclopropanes also reacted efficiently under the optimized conditions (adducts **4q**-**4t**). Remarkably, the reaction is not only limited to the use of benzoic acids as nucleophiles, also performing well with other aliphatic carboxylic acids (adducts **4v** and **4w**), with the only exception of acetic acid, for which **4u** was obtained in lower yield because of isolation/purification issues. α-Aminoacids are also able to undergo this reaction in a clean way and under exclusive catalyst control with respect to stereocontrol (see **4x** and **4y**) and even a β-aminoacid provided the corresponding adduct with good yield and as a single diastereoisomer (compound **4z**).

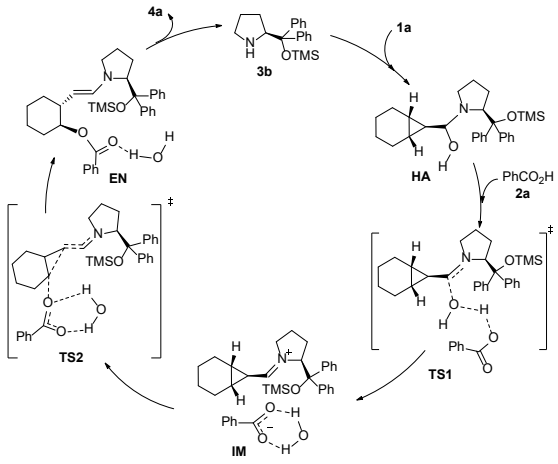
Table 2. Scope of the reaction.[a]



[a] Reaction carried out in a 0.25 mmol scale of **1a-f**, using 1.5-3.0 eq. of **2a-r** and 20 mol% of **3f.** e.e. was determined by HPLC analysis of the corresponding primary alcohol obtained after reduction.

DFT calculations were carried out in order to gain further insight into the mechanism of the reaction and on the origin of stereocontrol. The proposal follows the iminium activation concept, i.e. condensation of **1a** with the catalyst involves

activation of the former towards ring-opening through an increment on the C-C bond polarity. The reaction would therefore start with the formation of hemiaminal **HA** and generation of iminium ion would take place promoted by benzoic acid that participates in the abstraction of hydroxyl group (**TS1**), leading to the formation of an encounter pair **IM** in which a water molecule that stabilizes the ion pair is present.[17] From the two carbon atoms of the cyclopropane moiety that can be attacked by benzoate anion leading to the two possible enantiomers (through **TS2**, the rate-limiting step) calculations showed a clear preference (4.0 kcal/mol) for the pathway leading to the experimentally observed enantiomer.



Scheme 2. Proposed catalytic cycle for the reaction.

The formation of the intermediate **EN** might be considered as a S_N2-type reaction but a close inspection of **TS2** and the associated IRC showed a slight asynchronicity in the process (see SI). We carried out a topological analysis of the electron localization function,[18] recently evidenced as a useful tool for assessing the synchronicity of organic reactions.[19] Figure 1 shows the evolution of electronic populations along the reaction coordinate from ion pair **IM** into **EN** through **TS2** for selected bonds and atoms (for the full topological analysis see SI). When the cyclopropane C1-C3 bond is broken (point 56), both N5 and C3-C4 bond increase their electronic population. Simultaneously, population of C4-N5 bond decreases to single bond values, indicating the opening of the cyclopropane ring and concomitant evolution of the iminium ion towards the enamine. However, O12 remains with the same electron population and it is only at point 72 when it decreases as a consequence of the C1-O6 bond formation, revealed by the electron density appearing between those atoms. The observed gap between C1-C3 breaking (point 62) and C1-O6 formation (point 72) reveals the formal existence of a carbocation (not stable enough to be located as a minimum) forming an intimate ion pair and thus consisting of an inverting-S_N1 process rather a typical S_N2 mechanism. Since there are no intermediates, the reaction proceeds through a single kinetic step and it should be considered a concerted asynchronous process since two events are identified along the reaction coordinate. The formation of a contact ion pair[20] explains the inversion of configuration and also the observed differences in reactivity between **2a** and cyclopentane- and cycloheptane-fused formylcyclopropanes, for which their lower reactivity is attributed to the lower stability of the incipient carbocation. This observation is in agreement with the observed differences in the stability of cyclohexyl, cyclopentyl and cycloheptyl carbocations calculated through solvolysis of the corresponding 1-arylcycloalkanols.[21]

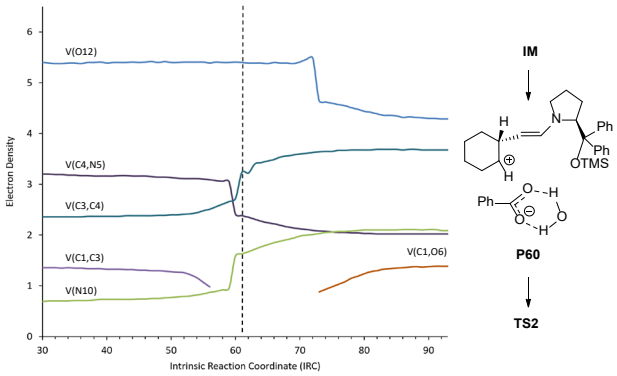
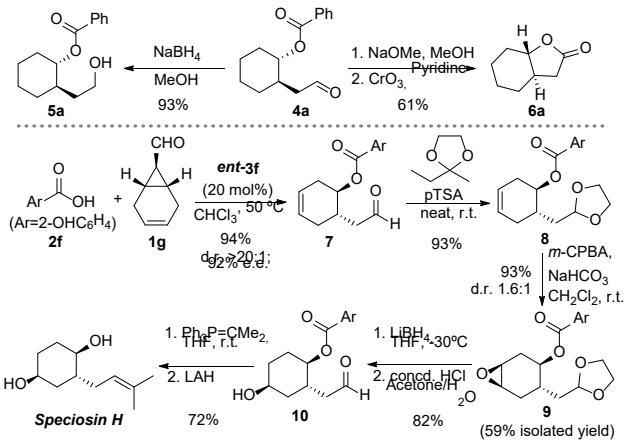


Figure 1. ELF analysis for the formation of 4a.

Finally, the synthetic applicability of the reaction was demonstrated by the different chemical manipulations that can be carried out o substrate **4a** as model. In particular, reduction of the aldehyde is straightforward to the corresponding primary alcohol **5a** and hydrolysis of **4a** delivered the corresponding γ-hydroxyaldehyde as an equilibrating mixture of closed and open-chain isomers that, after oxidation, led to γ-lactone **6a**. Moreover, the synthetic potential of this reaction as a tool in synthesis was demonstrated with the preparation of *speciosin H* (Scheme 3), which is a metabolite isolated from the basidiomycete fungus *Hexagonia speciosa* that grows in subtropical areas of China.[22]



Scheme 3. Synthetic manipulations carried out on **4a** and total synthesis of *Speciosin H*.

In conclusion, carboxylic acids are proficient pronucleophiles for inducing the ring-opening of formylcyclopropanes under iminium activation. In the presence of chiral catalyst **3f** the reaction proceeds with excellent yields and stereoselectivities, providing γ-acyloxy-substituted aldehydes after the ring-opening process.

The reaction is wide in scope and includes the possibility of using α- and β-aminoacids as pronucleophiles, which could open the possibility of applying this approach to the bioconjugation to peptide-type molecules. Mechanistic studies also indicate that the reaction proceeds through an S_N2-type process in which the catalyst is involved in the stereodifferentiation of the two chemically equivalent electrophilic carbon atoms of the *meso*-cyclopropane reagent.

Acknowledgements

This research was supported by Spanish MINECO (FEDER-CTQ2017-83633-P and FEDER-CTQ2016-76155-R), Basque Government (IT908-16), UPV/EHU (fellowship to E. D.) and Government of Aragon. The authors acknowledge resources from the supercomputers "Memento" and “Cierzo”, technical assistance provided by BIFI-ZCAM (UZ, Spain)"

Keywords: Asymmetric catalysis · Carboxylic acids · Cyclopropanes · Strained molecules · Organocatalysis

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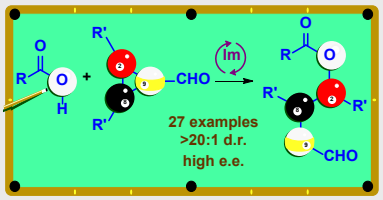

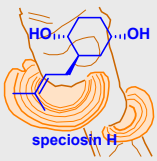

Open up!: Carboxylic acids, which are typically regarded as poor nucleophiles, are competent reagents to promote the ring-opening of formylcyclopropanes after activation of the latter through iminium ion formation. In this way, stereodefined γ-acyloxy-substituted aldehydes are obtained through the desymmetrization of *meso*-formylcyclopropanes catalysed by a chiral secondary amine.

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Carboxylates as Nucleophiles in the Enantioselective Ring-Opening of Formylcyclopropanes under Iminium Ion Catalysis