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Organocatalytically Generated Donor–Acceptor Cyclopropanes in Domino Reactions. One-Step Enantioselective Synthesis of Pyrrolo[1,2-*a*]quinolines

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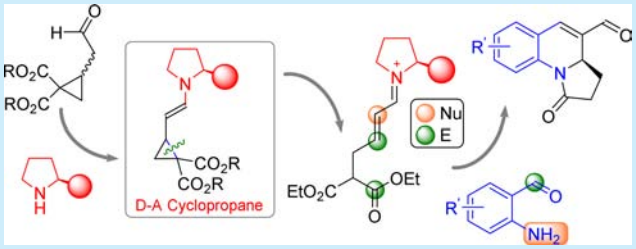
Supporting Information

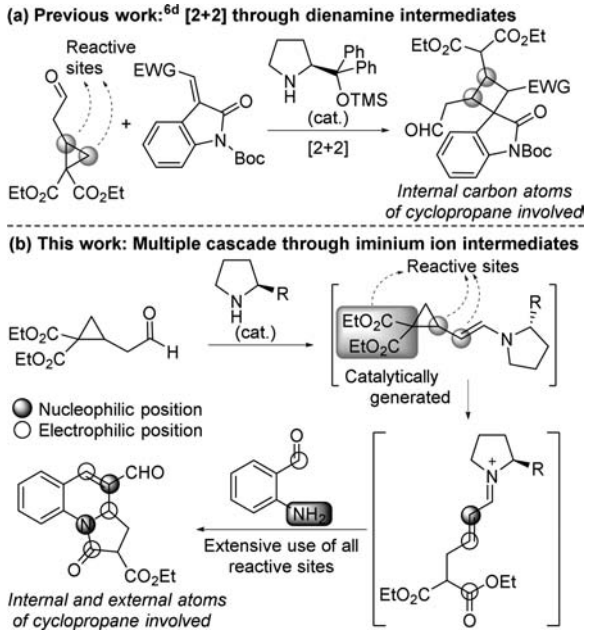
ABSTRACT: An easy and straightforward procedure has been developed for the synthesis of highly enantioenriched pyrrolo-[1,2-*a*]quinolines through a one-pot process that comprises a domino cyclopropane ring opening/aza-Michael/aldol reaction followed by acid-promoted lactamization. The key feature of the synthetic approach relies on the ability of conveniently functionalized cyclopropaneacetaldehydes to undergo organocatalytic activation by a chiral secondary amine that enables the catalytic generation of a donor–acceptor cyclopropane. This intermediate has the potential to undergo a ring opening that generates an electrophilic α,β-unsaturated iminium ion that subsequently reacts through the already mentioned domino sequence and in which stereochemical information is very efficiently transferred from the amine catalyst to the final products. Moreover, one of the alkoxycarbonyl moieties can be easily removed by standard hydrolysis/decarboxylation, providing access to the target adducts as single stereoisomers.



Donor–acceptor cyclopropanes have recently been rediscovered as powerful reagents able to generate polyfunctional reactive intermediates after a strain-driven ring-opening process facilitated by the synergistic effect of the substituents.[1] In particular, the use of donor–acceptor cyclopropanes for the construction of carbocyclic and heterocyclic scaffolds through formal cycloaddition chemistry has experienced a renaissance in the past few years, with many different reactions displayed in which the ring-opening event is promoted by Lewis acids.[2] Organocatalysis has also contributed to the field with some reports in which DABCO is used catalytically to induce nucleophilic ring opening of the cyclopropane.[3] Alternatively, *N*-heterocyclic carbenes used as either Lewis bases[4] or Brønsted bases[5] have also been employed. Despite these advances, most cases have focused in nonenantioselective versions, and only a few examples exist in which a chiral organocatalyst has been employed in order to render the overall process enantioselective.[6] In this particular context, very recently, Jørgensen and co-workers described the enamine activation of cyclopropanes in [2 + 2] cycloaddition reactions with highly electrophilic alkylideneoxindoles with the participation of a *nucleophilic dienamine* intermediate (Scheme 1a).[6d]

In this work, the part of the cyclopropane scaffold containing the electron-withdrawing groups was involved in facilitating the ring-opening event but was not utilized to promote further reactivity, and the reaction resulted in the functionalization of two of the internal carbon atoms of the cyclopropane ring. As an alternative, we propose herein the use of such cyclopropanes as multifunctional reagents able to participate in a complex domino reaction in which all the functional groups of the

Scheme 1. Reaction of in Situ Generated Donor–Acceptor Cyclopropanes through Organocatalytic Activation



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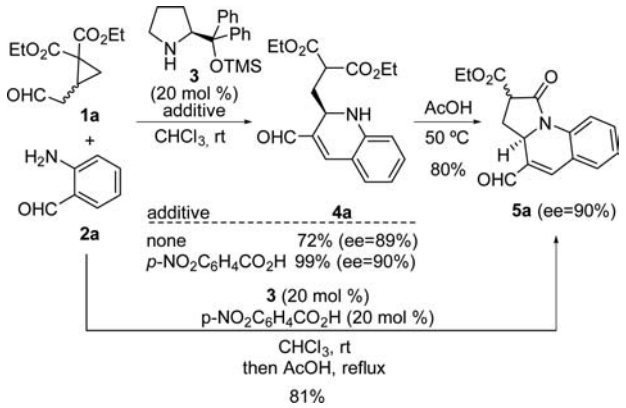
cyclopropane are involved in the overall process, therefore making full use of the potential reactivity of these very interesting molecules. In particular, we have designed an efficient approach to pyrroloquinolines, which is a key structural feature associated with multiple examples of bioactive compounds,[7] by the direct reaction between this type of catalytically generated donor–acceptor cyclopropanes and *o*-aminobenzaldehydes (Scheme 1b), in which in a behavior different from that experienced in the [2 + 2] cycloaddition reaction an *electrophilic iminium ion* intermediate is generated after the ring-opening process. This is afterward engaged in a domino aza-Michael reaction/aldol condensation[8] followed by lactamization. In this way, both the internal atoms of the cyclopropane ring and also additional positions of the lateral substituents of the cyclopropane undergo functionalization, expanding the utility of these highly versatile reagents. Moreover, the mechanistic profile of the projected transformation enables the use of racemic cyclopropanes as starting materials that deliver highly enantioenriched products.

We investigated the viability of the projected reaction using cyclopropane **1a** and *o*-aminobenzaldehyde **2a** as model substrates (Scheme 2). Initially, we subjected these two

Scheme 2. Screening of Reaction Conditions

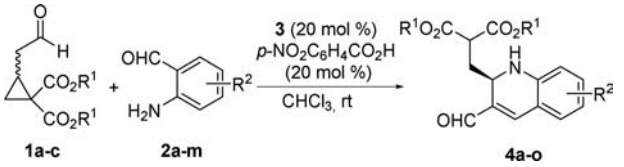


compounds to reaction in the presence of the archetypical *O*-TMS diphenylprolinol catalyst **3**,[9] observing a clean reaction that delivered substituted dihydroquinoline **4a** in good yield and with a promising 89% ee. This product arises from the expected catalytic generation of the donor–acceptor cyclopropane followed by ring-opening that delivers an α,β-unsaturated iminium ion intermediate that next undergoes domino aza-Michael/aldol/dehydration, but this adduct was unable to undergo the projected final lactamization process under these conditions. Conducting the reaction at higher temperatures or during a long time did not lead to formation of the target pyrroloquinoline **5a**, but remarkably, isolated adduct **4a** underwent clean cyclization to **5a** under acidic thermal conditions in 80% yield.

After surveying other catalysts and reaction conditions in order to improve the yield and stereocontrol of the first step of this process,[10] we came to the conclusion the concomitant use of **3** with *p*-nitrobenzoic acid led to a more efficient formation of intermediate **4a** (99% yield, 90% ee). More importantly, the final pyrroloquinoline **5a** could also be easily obtained directly from **1a** and **2a** in a single step with good yield and very high enantiomeric excess.

After all these experiments, we chose a solid experimental protocol to convert aldehydes **1** into either dihydroquinolines **4** or pyrroloquinolines **5** at will using the two optimized different protocols. We therefore proceeded to evaluate the scope of these two transformations, starting first with the organocatalyzed reaction that delivers dihydroquinolines. As can be seen in Table 1, the reaction performed well with a variety of

Table 1. Scope of the Reaction. Synthesis of Dihydroquinolines 4a–o[a]



entry	**1**, R^1	**2**, R^2	**4**	yield[b] (%)	ee[c] (%)
1	**1a**, Et	**2a**, H	**4a**	99	90
2	**1a**, Et	**2b**, 4-F	**4b**	86	95
3	**1a**, Et	**2c**, 4-Cl	**4c**	97	96
4	**1a**, Et	**2d**, 4-Br	**4d**	87	95
5	**1a**, Et	**2e**, 4-CF_3	**4e**	90	96
6	**1a**, Et	**2f**, 4-Me	**4f**	91	85
7	**1a**, Et	**2g**, 4-MeO	**4g**	81	80
8	**1a**, Et	**2h**, 5-Cl	**4h**	93	95
9	**1a**, Et	**2i**, 5-Br	**4i**	89	94
10	**1a**, Et	**2j**, 5-Me	**4j**	80	81
11	**1a**, Et	**2k**, 3-Me	**4k**	64	97
12	**1a**, Et	**2l**, 3-MeO	**4l**	64	79
13	**1a**, Et	**2m**, benzo[*d*]	**4m**	93	85
14	**1b**, Me	**2a**, H	**4n**	86	91
15	**1c**, Bn	**2a**, H	**4o**	69	88

[a]Reaction performed with **1a–c** (0.1 mmol) and **2a–m** (0.1 mmol) in the presence of catalyst **3** and *p*-nitrobenzoic acid (0.02 mmol each) in $CHCl_3$ at rt for 16 h. [b]Yield of pure product after flash column chromatography. [c]Determined by HPLC analysis on the chiral stationary phase (see the Supporting Information).

aminobenzaldehydes, in which either electron-donating or electron-withdrawing substituents at the 4-position with respect to the formyl group were well tolerated (Table 1, entries 2–7).

In all cases, high yields and enantioselectivities were obtained, although the latter parameter was slightly affected with electron-donating groups (Table 1, entries 6 and 7). Changing the position of the substituents in the aromatic ring was also compatible with the reaction, observing a very similar behavior in all cases, regardless of the relative situation of the substituent (Table 1, entries 8–12). 3-Amino-2-naphthaldehyde **2m** also performed very well in the reaction, providing 1,2-dihydrobenzo[*g*]quinoline **4m** in excellent yield and enantioselectivity.[11] Finally, we could also demonstrate that the reaction proceeded with the same level of efficiency regardless of the nature of the alkoxide moiety of the ester substituents at cyclopropane **1** (entries 14 and 15).

At this point, we evaluated the scope of the reaction with respect to direct access to the final pyrroloquinolines from a variety of cyclopropanes **1** and aminobenzaldehydes **2** through the one-pot procedure already optimized in Scheme 2. In this sense, this one-pot reaction performed equally well, furnishing the final adducts with excellent yields and stereoselectivities. In general, the reaction behaved in a comparable way to what it had been previously observed for the synthesis of quinolines **4**

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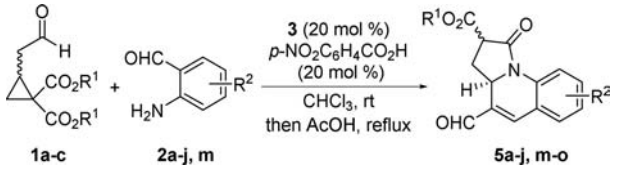
in Table 1 for the same combination of reagents (Table 2). This indicates that the acid-promoted lactamization can be

Table 2. One-Pot Catalytic and Enantioselective Synthesis of Pyrroloquinolines 5. Scope of the Reaction[a]



1a-c 2a-j, m 5a-j, m-o

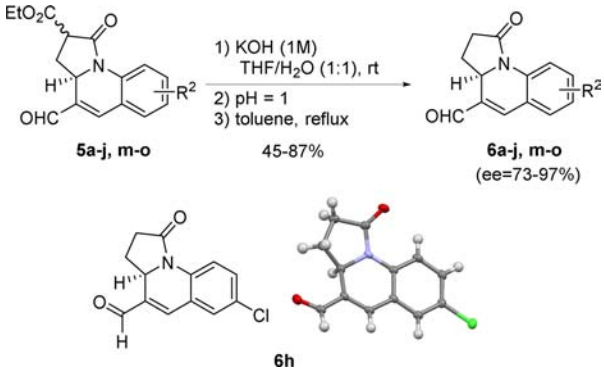
entry	1, R^1	2, R^2	5	yield[b] (%)	ee[c] (%)
1	**1a**, Et	**2a**, H	**5a**	81	91/87
2	**1a**, Et	**2b**, 4-F	**5b**	77	95/95
3	**1a**, Et	**2c**, 4-Cl	**5c**	83	97/97
4	**1a**, Et	**2d**, 4-Br	**5d**	86	96/96
5	**1a**, Et	**2e**, 4-CF_3	**5e**	74	94/96
6	**1a**, Et	**2f**, 4-Me	**5f**	69	85/87
7	**1a**, Et	**2g**, 4-MeO	**5g**	48	75/78
8	**1a**, Et	**2h**, 5-Cl	**5h**	75	94/91
9	**1a**, Et	**2i**, 5-Br	**5i**	79	96/94
10	**1a**, Et	**2j**, 5-Me	**5j**	81	84/87
11	**1a**, Et	**2m**, benzo[*g*]	**5m**	69	84/85
12	**1b**, Me	**2a**, H	**5n**	81	91/89
13	**1c**, Bn	**2a**, H	**5o**	60	90/89

[a]Reaction performed using **1a–c** (0.1 mmol) and **2a–j,m** (0.1 mmol) in the presence of catalyst **3** and *p*-nitrobenzoic acid (0.02 mmol each) in $CHCl_3$ at rt for 16 h, and then AcOH (3.0 mL) was added and the mixture was refluxed until full conversion. [b]Yield of pure product after flash column chromatography. [c]Determined by HPLC analysis on chiral stationary phase under conditions optimized for a mixture containing both diastereoisomers in racemic form (see the Supporting Information). The ee of each diastereoisomer is given.

carried out in situ on the crude reaction mixtures obtained in the cyclopropane ring opening/aza-Michael/aldol condensation domino process and that it proceeds in an almost quantitative form and without affecting the stereochemical integrity of the stereocenters generated in the aminocatalytic reaction.

The final adducts **5** were isolated as mixtures of diastereoisomers due to the configurational lability of the stereocenter of the α-ketolactam moiety. For this reason, and for better characterization purposes, these adducts **5** were subjected to a one-pot hydrolysis/decarboxylation process that cleanly delivered pyrroloquinolines **6** in excellent yields and high optical purities (Scheme 3). In fact, we could verify that

Scheme 3. One-Pot Hydrolysis/Decarboxylation of Adducts 5 and X-ray Structure of Compound 6h



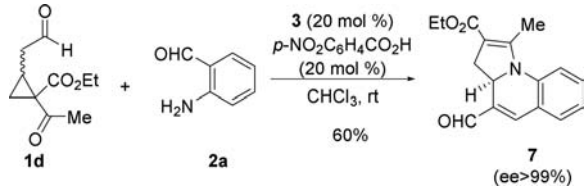
5a-j, m-o 45-87% 6a-j, m-o (ee=73-97%)

6h

the enantiomeric excess of each adduct **6** was perfectly correlated (within experimental error) to the corresponding dihydroquinoline **4** and pyrroloquinolines **5** (both diastereoisomers) obtained in the reaction shown in Tables 1 and 2, respectively. This also indicates that the hydrolysis/decarboxylation process took place without racemization. We could also grow a crystal of compound **6h** suitable for X-ray analysis, which allowed us to establish unambiguously the absolute configuration of all products **4–6**.

We have also surveyed the possibility of using aldehydes **1** with two different electron-withdrawing groups. In particular, when we employed aldehyde **1d** incorporating an alkoxycarbonyl and an acyl moieties at the cyclopropane ring, the reaction behave similarly, indicating that the initial aza-Michael/aldol condensation cascade was taking place very efficiently (Scheme 4). Remarkably, a subsequent intra-

Scheme 4. Reactivity of Aldehyde 1d. Direct Access to Pyrroloquinolines



1d 2a 7 (ee>99%)

molecular hemiaminal formation followed by dehydration also took place, leading to the clean formation of pyrroloquinoline **7**, in moderate yield, and with excellent enantiomeric excess.

In conclusion, we have demonstrated that donor–acceptor cyclopropanes, catalytically generated from aldehydes **1**, undergo ring opening and the intermediate formed can also show iminium-type reactivity, undergoing a domino aza-Michael/aldol/dehydration reaction that generates highly enantioenriched dihydroquinolines. Moreover, the full use of all of the functionalities present at this particular type of cyclopropanes has been demonstrated through a one-pot process that combines the initial aza-Michael/aldol domino reaction with an acid-promoted lactamization that delivers directly pyrroloquinolines in a single step and also in excellent overall yield and high enantiocontrol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00173.

X-ray crystallographic data for compound **6h** (CIF)
Experimental procedures and characterization data (^{1}H and ^{13}C NMR spectra and HPLC traces) for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(10) See the Supporting Information for details.

(11) Following the suggestions by one reviewer, we also tested some *o*-formylheteroarylamines such as 3-aminoisonicotinaldehyde and 2-aminonicotinaldehyde. However, we did not observe any reaction using these reagents, most likely because of their poor solubility in the reaction solvent.

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