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

Eduardo Sanchez-Diez, Diana L. Vesga, EfRAIN Reyes,∗ Uxue Uria, Luisa Carrillo, and Jose L. Vicario∗

Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología, Universidad del País Vasco (UPV/EHU), P.O. Box 644, E-48080 Bilbao, Spain

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 cyclopropylacetaldehydes to undergo organo-catalytic 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. 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. Organocatalysis has also contributed to the field with some reports in which DABCO is used catalytically to induce nucleophilic ring opening of the cyclopropane. Alternatively, N-heterocyclic carbenes used as either Lewis bases or Brønsted bases 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. 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). 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

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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, by the direct reaction between this type of catalytically generated donor—acceptor cyclopropanes and o-aminobenzaldehydes (Scheme 1b), in which 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 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 compounds to reaction in the presence of the archetypical O-TMS diphenylprolinol catalyst 3, 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-unsubstituted 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, 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 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[e]quinoline 4m in excellent yield and enantiomeric selectivity. Finally, we could also demonstrate that the reaction proceeded with the same level of efficiency regardless of the nature of the alkoxy 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 stereochemistries. 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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**Scheme 2. Screening of Reaction Conditions**

After surveying other catalysts and reaction conditions in order to improve the yield and stereocontrol of the first step of this process, 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.

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

<table>
<thead>
<tr>
<th>entry</th>
<th>1, R1</th>
<th>2, R2</th>
<th>4 yield (%)</th>
<th>ee (%)</th>
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<tr>
<td>1</td>
<td>1a, Et</td>
<td>2a, H</td>
<td>4a 99 90</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1a, Et</td>
<td>2b, 4-F</td>
<td>4b 86 95</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1a, Et</td>
<td>2c, 4-Cl</td>
<td>4c 97 96</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1a, Et</td>
<td>2d, 4-Br</td>
<td>4d 87 95</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1a, Et</td>
<td>2e, 4-CF3</td>
<td>4e 90 96</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1a, Et</td>
<td>2f, 4-Me</td>
<td>4f 91 85</td>
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<tr>
<td>7</td>
<td>1a, Et</td>
<td>2g, 4-MeO</td>
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<tr>
<td>8</td>
<td>1a, Et</td>
<td>2h, 5-Cl</td>
<td>4h 93 95</td>
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<td>2a, H</td>
<td>4n 86 91</td>
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<tr>
<td>15</td>
<td>1c, Bn</td>
<td>2a, H</td>
<td>4o 69 88</td>
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</tbody>
</table>

*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 CHCl3 at rt for 16 h. Yield of pure product after flash column chromatography. Determined by HPLC analysis on the chiral stationary phase (see the Supporting Information).
in Table 1 for the same combination of reagents (Table 2). This indicates that the acid-promoted lactamization can be

done selectively in good yields and high enantiocontrol. 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 alkoxy

methyl 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-

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 enantiocntrol.

**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 (1H and 13C NMR spectra and HPLC traces) for all new compounds (PDF)

**AUTHOR INFORMATION**

Corresponding Authors

*E-mail: efraim.reyes@ehu.es.

*E-mail: joseluis.vicario@ehu.es.

**Notes**

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**ACKNOWLEDGMENTS**

REFERENCES


(10) See the Supporting Information for details.

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