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# Organocatalyzed enantio- and diastereoselective isomerization of prochiral 1,3-cyclohexanediones into nonalactones bearing distant stereocenters†

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The lactonization of 2-(2-nitrophenyl)-1,3-cyclohexanediones containing an alcohol side chain and up to three distant prochiral elements is reported by isomerization under the mediation of simple organocatalysts such as quinidine. Through a process of ring expansion, strained nonalactones and decalactone are produced with up to three stereocenters in high *er* and *dr* (up to 99 : 1). Distant groups, including alkyl, aryl, carboxylate and carboxamide moieties, were examined.

## Introduction

Desymmetrization of prochiral reagents is an ambitious but rewarding strategy, as the chiral products feature one or more stereocenters, after a single-step reaction in which the catalyst binds in the vicinity of the enantiotopic groups for an effective transfer of the chiral information.<sup>1</sup> Applied to cyclic 2,2-disubstituted-1,3-diketones with enantiotopic carbonyl groups, this strategy was illustrated by Hajos and Parrish with the organocatalyzed enantioselective isomerization reaction of triketone **1** into ketol **2** (Scheme 1).<sup>2</sup> Even though the

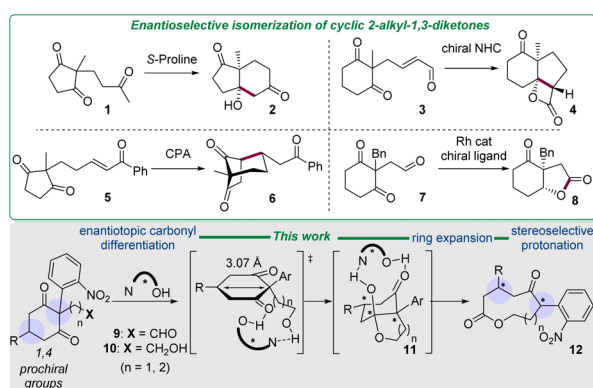
desymmetrization of 2,2-disubstituted-1,3-diones has been richly investigated since then,<sup>3</sup> few reports actually showcase an enantioselective isomerization of these substrates. For example, Scheidt reported the conversion of enal **3**, tethered to 2-methyl-1,3-cyclohexanedione scaffold, to  $\beta$ -lactone **4** in the presence of chiral *N*-heterocyclic carbene (NHC).<sup>4</sup> Through noncovalent interactions, enone **5** was isomerized to bicyclic diketones **6** by exposure to chiral phosphoric acid (CPA), as described by Lam.<sup>5</sup> Later, Dong demonstrated the enantioselective transformation of 2-acetaldehyde-1,3-cyclohexanedione **7** to bicyclic  $\gamma$ -lactone **8** by Rh-catalyzed ketone hydroacylation reactions.<sup>6</sup> Note that the enantioselective isomerization of cyclic 1,3-diones by a process effecting a ring enlargement is unknown.

Nine-membered ring compounds have important applications in medicinal chemistry,<sup>7</sup> but are challenging to synthesise due to ring strain,<sup>8</sup> and their tendency to undergo transannular reactions to form bicyclic products.<sup>9</sup>

Amidst the enantioselective ones leading to medium-sized lactones from racemic or prochiral materials, a general strategy presented itself based on the *in situ* generation of electrophiles, binding to transition metal-chiral ligands or organocatalysts, reacting with enolates or olefins.<sup>10</sup> To our knowledge, though, a single example of enantioselective synthesis of nonalactones from prochiral reagents was reported,<sup>10a</sup> and it is hitherto unknown with distant stereocenters. Herein is reported the distal enantio- and diastereoselective ring expansion of 2-aryl-1,3-cyclohexanediones, into nonalactones with up to three distal stereocenters through an organocatalyzed isomerization.

## Results and discussion

Our interest in the topic stems from our previous report of a domino sequence starting from aldehyde **9** (R = H), containing the motif 2-(2-nitrophenyl)-1,3-cyclohexanedione, which



Scheme 1 Enantioselective isomerization of 2,2-disubstituted-1,3-cyclohexanediones.

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was converted into nonalactones when treated with carbanions (Scheme 1).<sup>11</sup> The resulting alcoholate initiated a series of transformations, eventually affording racemic nonalactones.

In a further step, the reactivity of the alcoholate holds promise for an enantioselective access to nonalactones **12** from alcohol **10** bearing two prochiral groups ( $R \neq H$ ). In the presence of a chiral bidentate organocatalyst, we envisaged that the hydroxyl and the carbonyl moieties of **10** would be engaged in a chiral environment allowing the enantioselective formation of the fused bicyclic lactol **11** preceding the ring expansion by retro-Claisen condensation into **12**.<sup>12</sup> Notably, our blueprint implies a spatial discrimination of prochiral elements through noncovalent interactions.

The desymmetrization of meso cyclic acid anhydrides well illustrates the concept of activation of carbonyl groups for the addition of a nucleophile, effecting thereby the discrimination of vicinal enantiotopic groups. To that end, Oda<sup>13</sup> and Aitken<sup>14</sup> independently identified Cinchona alkaloids as efficient organocatalysts. If it was thus conceivable to promote the enantioselective isomerization of **10** with these alkaloids, whether the process of desymmetrization could establish distant stereocenters was uncertain. For that matter, different strategies were developed requiring catalysts/ligands with large structures.<sup>15</sup>

To test our hypothesis, the alcohols *trans*- and *cis*-**10a** were prepared from the corresponding isomers of the olefins **15a** after a sequence of reactions, without purification, including ozonolysis into aldehydes **16a** followed by a careful reduction (Scheme 2A). Starting from 5-methyl-1,3-cyclohexanedione **14a**, the construction of **15a** began with one-pot *C*-arylation and *O*-allylation steps, preceding a Claisen rearrangement for which the stereochemical outcome, the ratio *trans*/*cis*-**15a** (60/40), is rectifiable under Tsuji-Trost conditions.<sup>16</sup> This is an important aspect as the configuration of alcohol **10a** had an interesting

bearing on the selectivity of the process (see the ESI for the optimization†).<sup>17</sup>

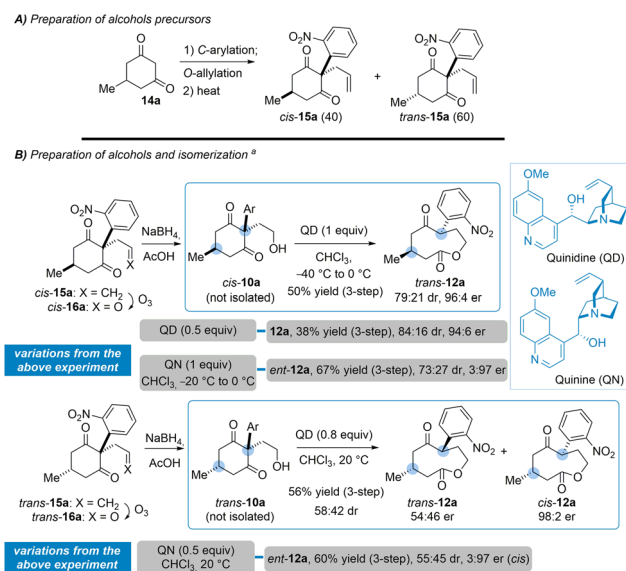
When exposed to quinidine (QD (1 equiv.),  $\text{CHCl}_3$ , 17 h,  $-40$  to  $0^\circ\text{C}$ ), *cis*-**10a** was converted into *trans*-**12a** (79 : 21 diastereoisomers ratio (dr)), the relative configuration being determined by NOESY experiments, with enantioselectivity (96 : 4 enantiomers ratio (er), Scheme 2B) and with a yield of 50% yield over 3-step amounting to a theoretical 85% yield for each step. Note that operating instead with 0.5 equivalent of QD gave *trans*-**12a** with close selectivity (86 : 14 dr, 94 : 6 er) after a longer reaction time (40 h, 38% yield). On the other hand, *trans*-**10a** was lactonized into **12a** (56% yield, 58 : 42 dr, *trans*/*cis*) upon exposure to QD (0.8 equiv.) in  $\text{CHCl}_3$  at room temperature (16 h) and while *trans*-**12a** was formed without enantioselectivity, high enantiopurity (98 : 2 er) was measured for *cis*-**12a**.

Moreover, the treatment of *cis*-**10a** with quinine QN (1 equiv.,  $-40$  to  $0^\circ\text{C}$ )—a natural pseudo enantiomer of QD—led to *trans*-**12a** (67% yield, 73 : 27 dr) having the attendant opposite enantioselectivity (3 : 97 er). Similarly, exposure of *trans*-**10a** to QN (0.5 equiv., rt) led to **12a** (70% yield, 55 : 45 dr) and, while the formation of *trans*-**12a** occurred without enantioselectivity, the enantiopurity of *cis*-**12a** was excellent (3 : 97 er).

To sum up, both alcohols *trans*-**10a** and *cis*-**10a** were simply lactonized into **12a** by an enantioselective ring expansion process upon exposure to readily available organocatalysts, that are easily recovered.

We then sought to identify the catalyst functions influencing the selectivity and, among them, the secondary benzylic alcohol appeared crucial for the enantioselectivity (Fig. 1). Bearing instead an alkyl ether or the acidic 2-nitroaniline, the corresponding catalysts induced the formation of *rac*-**12a** or were inactive.<sup>18</sup>

While no improvement was noted with cupreidine **17a** (*trans*-**12a**: 75 : 25 er), increasing the steric hindrance of the quinolin-6-ol scaffold was rewarding. Simply obtained by *O*-alkylation of **17a** with *i*-butyl bromide (47% yield), **17b** isomerized *cis*-**10a** to *trans*-**12a** (70 h, 51% yield) with better selectivity (90 : 10 dr, 96 : 4 er). Prepared by *O*-alkylation of **17a** with bromocyclohexane (15% yield), **17c** induced the formation of *trans*-**12a** (120 h, 63% yield) with high values of 95 : 5 dr and 96 : 4 er. For a slight modification of the ether appendage, **17d** was synthesized by *O*-alkylation of **17a** with (bromomethyl)cyclohexane in excellent



**Scheme 2** (A and B) Preparation and enantioselective isomerization of *trans*-**10a** and *cis*-**10a**. (a) dr was measured by  $^1\text{H}$  NMR spectroscopy of the crude reaction mixture and HPLC analysis, er was determined by HPLC analysis.

| Substitution at C <sup>6</sup> | <i>trans</i> - <b>12a</b> <sup>a</sup><br>dr <sup>b</sup> | er <sup>b</sup> |
|--------------------------------|---|-----------------|
| QD:                            | 79:21   | 96:4            |
| 17a:                           | 75:25   | 75:25           |
| 17b:                           | 90:10   | 96:4            |
| 17c:                           | 95:5  | 96:4            |
| 17d:                           | 93:7  | 96:4            |
| 17e:                           | 92:8  | 90:10           |

**Legend:**  
  
 X = OH is key for enantioselectivity  
 X = Oalkyl → *rac*-**12a**  
 X = NH(2-NO<sub>2</sub>Ph) → no reaction

**Fig. 1** Tuning the catalyst. (a) Reaction conditions: *cis*-**10a** and **17a**–**17e** in  $\text{CHCl}_3$ , 40 h,  $-40^\circ\text{C}$ , then  $0^\circ\text{C}$  over 6 h; (b) dr was measured by  $^1\text{H}$  NMR spectroscopy of the crude reaction mixture and HPLC analysis, er was determined by HPLC analysis.



yield (92%). Gratifyingly, the lactonization of *cis*-**10a** catalyzed by **17d** was completed within a shorter timeframe (96 h, 60% yield) and with excellent selectivity (93 : 7 dr, 96 : 4 er). As noted with **17e**, a bulkier group at this position was detrimental to *trans*-**12a** enantiopurity (90 : 10 er).

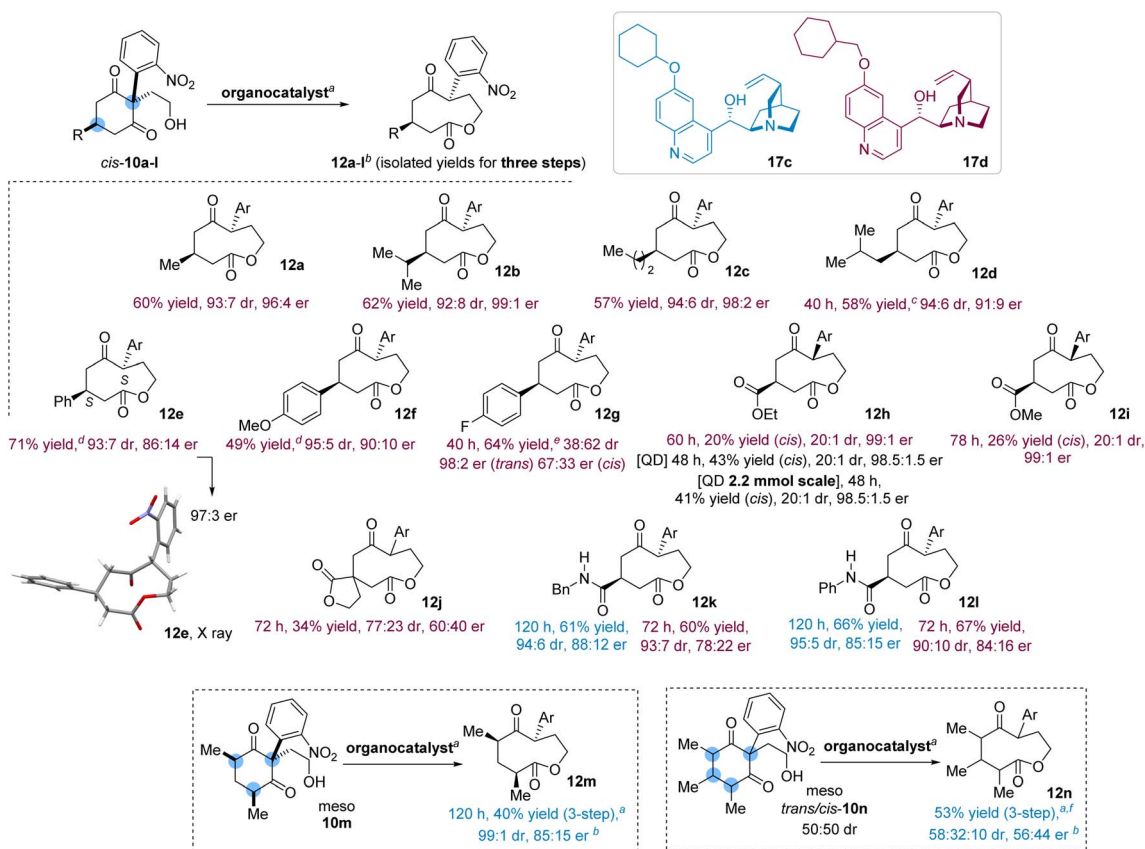
Selecting catalysts **17c** and **17d**, the scope of the process was first examined with prochiral 5-alkyl-2-(2-nitrophenyl)-1,3-cyclohexanediones (Scheme 3). Substituted with *i*-propyl group, *trans*-**12b** was isolated (62% yield—over three steps as every other given yields) with 92 : 8 dr and 99 : 1 er after exposure of *cis*-**10b** to **17d** (results obtained with **17c** are provided in the ESI†). Substituted with the *n*-propyl group, *cis*-**10c** was lactonized with excellent selectivity (*trans*-**12c**: 94 : 6 dr, 98 : 2 er). The *i*-butyl derivative *cis*-**10d** was transformed into *trans*-**12d** with 94 : 6 dr and 91 : 9 er, values obtained at −10 °C due to a solubility issue.

We then investigated the desymmetrization of 5-aryl-2-(2-nitrophenyl)-1,3-cyclohexanediones. Starting with the lactonization of phenyl derivative *cis*-**10e**, *trans*-**12e** (71% yield, 93 : 7 dr) was isolated with moderate enantiopurity (86 : 14 er). A suitable crystal for X-ray crystallography was obtained with enhanced values (99 : 1 dr, 97 : 3 er) allowing the determination of the absolute (*S*, *S*)-configuration of the major isomer. The isomerization of the 4-methoxyphenyl derivative *cis*-**10f** led to

*trans*-**12f** (49% yield) with high selectivity (95 : 5 dr, 90 : 10 er). Lactonization of the 4-fluorophenyl derivative *cis*-**10g** into **12g** (64% yield, 40 h) occurred with an intriguing switch of diastereoselectivity. While the *cis*-lactone was so far formed in traces, *cis*-**12g** became slightly predominant (38 : 62 dr, *trans*/*cis*), the relative configuration being determined by NOESY experiments, and although the enantiopurity of *cis*-**12g** was low (67 : 33 er), *trans*-**12g** was enantioenriched (98 : 2 er).

With derivatives of 5-alkylcarboxylate-2-(2-nitrophenyl)-1,3-cyclohexanedione such as **10h**, the selectivity of the process was worth examining. Unlike the previous pattern, *cis*-**12h** was isolated enantiopure (20% yield, 99 : 1 er) while *trans*-**12h** was obtained with lower enantiopurity (57% yield, 61 : 39 er), the relative configuration being determined by NOESY experiments. As noted at the beginning of the study, QD induced the lactonization of *cis*-**10a** with high enantioselectivity but with moderate diastereoselectivity. This proved to be advantageous, though, in this context as the treatment of *cis*-**10h** with QD led to an equal amount of *trans*- and *cis*-**12h**, the latter being isolated with an exquisite enantiopurity (43% yield, 98.5 : 1.5 er), values that remain consistent on a larger scale experiment (2.2 mmol, 41% yield, 98.5 : 1.5 er).<sup>19</sup>

Decreasing the steric hindrance of the ester, as with *cis*-**10i**, was slightly beneficial since **17d** catalyzed the formation of *cis*-



**Scheme 3** Enantioselective lactonization of prochiral 2-(2-hydroxyethyl)-2-(2-nitrophenyl)-1,3-cyclohexanediones. (a) Reaction conditions: **17c**, **17d** or QD (1 equiv.) in CHCl<sub>3</sub> at −40 °C then 0 °C over 6 h, C = 0.12 M, 96 h. (b) dr was measured by both <sup>1</sup>H NMR spectroscopy of the crude reaction mixture and HPLC analysis, er was determined by HPLC analysis. (c) −10 °C then 0 °C over 6 h. (d) −20 °C then 0 °C over 6 h. (e) CH<sub>2</sub>Cl<sub>2</sub> as co-solvent (1 : 1, v/v). (f) −40 °C to 0 °C.

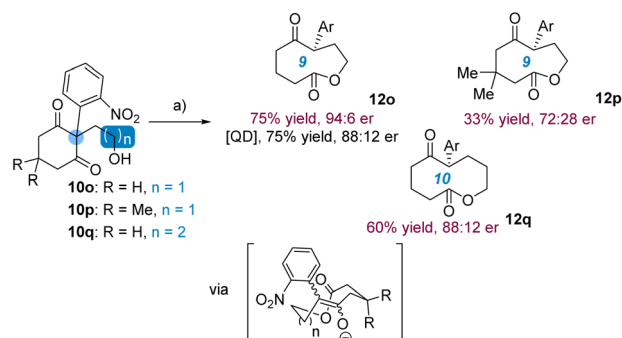


**12i** in 26% yield and 99:1 er, *trans*-**12i** (40% yield) being isolated with 65:35 er values. The treatment of the hindered **10j** (unknown relative configuration), bearing a spiro  $\gamma$ -lactone moiety, afforded **12j** (34% yield) with modest selectivity (77:23 dr, 60:40 er).

After examining hydrogen bond acceptors, the isomerization of scaffolds bearing also hydrogen bond donors was evaluated with the secondary benzylcarboxamide derivative *cis*-**10k**. In this setting, **17c** performed best the lactonization into *trans*-**12k** (120 h, 61% yield) and, in contrast with the carboxylate esters, the *trans*-isomer was prevalent (94:6 dr) and enantioenriched (88:12 er). On the other hand, **17d** enabled the formation of *trans*-**12k** in shorter reaction time (72 h, 60% yield, 93:7 dr) but with lower selectivity (78:22 er). Embedding a more acidic N-H bond, the anilinecarboxamide *cis*-**10l** was isomerized into *trans*-**12l** (120 h, 66% yield, 95:5 dr) by **17c** without enhancement of the enantiopurity (85:15 er). But this structural modification had more consequences when exposed to **17d**, as the reaction of *cis*-**10l** (72 h, *trans*-**12l**: 67% yield, 90:10 dr) proceeded with higher enantioselectivity (84:16 er) than with *cis*-**10k** (78:22 er). When comparing the influence of alkyl carboxylate and secondary carboxamide functions on the selectivity, the latter steers the reaction pathway toward the enantioselective production of the *trans*-isomer.

The formation of a trisubstituted lactone was next studied from a meso reagent. Advantageously synthesized as a single isomer, *cis*-**10m** was converted by **17c** into the trisubstituted lactone **12m** (40% yield), isolated as a single diastereoisomer (99:1 dr) and with appreciable enantioselectivity (85:15 er). In contrast, exposure of *cis*-**10m** to **17d** gave **12m** (99:1 dr, 55:45 er) with low enantioselectivity, demonstrating thus the superior affinity of **17c** for the topography of meso compounds. A step further, we sought to prepare the persubstituted lactone **12n** from *cis*/*trans*-**10n** (50:50 dr). In this complex scenario however, **12n** (53% yield, 58:32:10 dr) was obtained without enantioselectivity (56:44 er).

Subsequent to the isomerization of substrates with at least two prochiral elements, the strategy was applied to **10o** bearing a single prochiral group (Scheme 4). Note that it was not part of our initial plan devised in Scheme 1 since it was unclear



**Scheme 4** Enantioselective formation of **12o–q** via the corresponding enolate. Reaction conditions: (a) **17d** or QD (1 equiv.) in  $\text{CHCl}_3$  at  $-40^\circ\text{C}$ , 40 h then  $0^\circ\text{C}$  over 6 h. The yields are given for three steps.

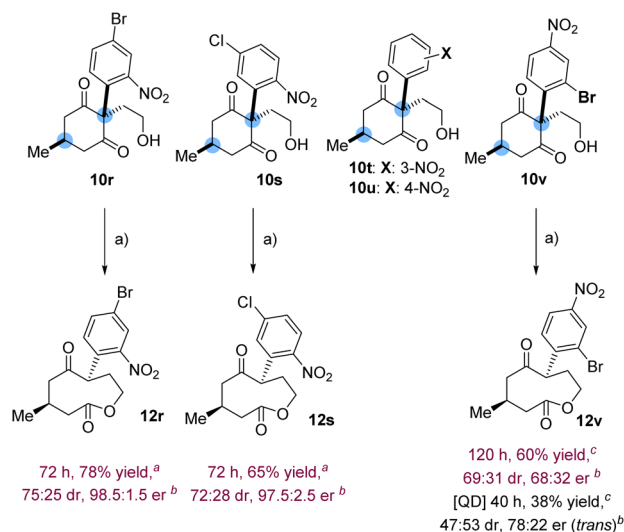
whether the chiral information of lactol **11o** would be preserved during the ring expansion into enolate (**12o**)<sup>–</sup>.

We were therefore surprised to measure the high enantioselectivity of **12o** (75% yield, 94:6 er) obtained by treatment of **10o** with **17d**, which dropped to 88:12 er when QD was instead employed. Indicative that a quaternary carbon within the 1,3-cyclohexanedione ring remains moderately compatible with the chemistry, **10p** was converted into **12p** (33% yield) with 72:28 er value. Pleasingly, bearing a longer alcohol appendage, **10q** was converted into decalactone **12q** with significant enantioselectivity (60% yield, 88:12 er).<sup>20</sup>

Amidst all the structural modulations examined within the study, the aromatic substitution of the prochiral scaffold was left to explore. To that end, alcohols *cis*-**10r,s** were synthesized, each one embedding a different halo-substituted 2-nitrophenyl ring (Fig. 2).

Compared to the case of *cis*-**10a**, 4-bromo-2-nitrophenyl derivative *cis*-**10r** was isomerized with less diastereoselectivity (**12r**: 78% yield, 75:25 dr) but enhanced enantioselectivity (98.5:1.5 er) when exposed to **17d**. With a different pattern of substitution, 5-chloro-2-nitrophenyl derivative *cis*-**10s** was converted by **17d** into **12s** (65% yield, 72:28 dr) with excellent enantioselectivity (97.5:2.5 er).

To modulate the position of the nitro group, we set about preparing 2-(3-nitrophenyl)-1,3-cyclohexanedione derivative **10t**. But the instability of the precursor aldehyde **9t** thwarted our plan and a similar outcome was noted with the 4-nitrophenyl analogue **9u**. We surmised that a steric effect, induced by the ortho substitution of the aromatic ring, could prevent the degradation of the aldehyde. Lending credence to this hypothesis, 2-(2-bromo-4-nitrophenyl) derivative **9v** was successfully obtained and converted into alcohol *cis*-**10v**. In the presence of



**Fig. 2** Enantioselective isomerization of *cis*-**10r,s,v** into nonalactones *trans*-**12r,s,v**. Reaction conditions: (a) **17d** or QD (1 equiv.) in  $\text{CHCl}_3$  at  $-40^\circ\text{C}$ , then  $0^\circ\text{C}$  over 6 h. (b) dr was measured by  $^1\text{H}$  NMR spectroscopy of the crude reaction mixture and HPLC analysis, er was determined by HPLC analysis. (c)  $-10^\circ\text{C}$ . The yields are given for three steps.



**17d**, the formation of *trans*-**12v** occurred slowly at  $-10\text{ }^{\circ}\text{C}$  (120 h, 60% yield) with modest selectivity (69 : 31 dr, 68 : 32 er). A slight enhancement was noted upon the catalysis of QD (40 h,  $-10\text{ }^{\circ}\text{C}$ , 38% yield), *trans*-**12v** being formed with higher enantiopurity (78 : 22 er) but at the expense of the diastereoselectivity (47 : 53 dr). The nitro group in the ortho-position of the aromatic ring seems therefore favorable to achieve high stereoselectivity.

However, as illustrated in Scheme 5, this structural requirement advantageously paves the way to the synthesis of enantioriched alkaloids and derivatives. For instance, the indole **18a** was prepared from **12a** by reduction of the nitro group (Zn, AcOH, >95% yield) and the regioselective halogenation occurred in 6-position (**19**, 72% yield), offering a synthetic handle for the decoration of the aromatic ring. Underscoring the strain of the indolononolactone, the spontaneous air oxidation of the aromatic ring of **18a** into hydroxylindolenine was noted ( $\sim 20\%$  after two months of storage at rt, see the ESI† for the details†). For that matter, we purposely performed the consecutive ring-expansion reaction of **18a** by oxidative cleavage ( $\text{NaIO}_4$ )<sup>21a</sup> delivering the 12-membered ring **20** (56% yield). Not only this demonstrated a short route to enantioenriched 12-membered ring from 6-membered ring **10a** *via* **12a**,<sup>21b</sup> but **20** provides a platform for further ring expansion, as illustrated by Unsworth, to access macrocycles.<sup>21c</sup>

Palladium-catalyzed alkylative dearomatization of the indole **18a** led to *trans*-allylic indolenine **21** (53% yield, non-optimized) after the distal diastereoselective formation of a quaternary carbon (97 : 3 dr).<sup>22</sup> Bearing an additional reactive function, the aldehyde **22** was smoothly obtained after oxidative cleavage of the allylic appendage (>95% yield). Prepared from **12h** by hydrogenation (>95% yield), the indolic ethyl ester **18h** was treated with NaOH (1 equiv., 1,4-dioxane,  $\text{H}_2\text{O}$ ) to give the carboxylic acid lactone **18ha** (56% yield, 68% brsm), demonstrating thus the robustness of the strained but sterically hindered ring.<sup>23</sup> To access new scaffolds, **12a** (80 : 20 dr) was deconstructed with  $\text{LiAlH}_4$  into triol **23** (42% yield, 75 : 25 dr) and next converted into  $\delta$ -lactone **24** ( $\text{PhI}(\text{OAc})_2/\text{TEMPO}$ , 59%

yield, relative configuration determined by NOESY experiments).<sup>24</sup>

## Conclusions

While they are among the most difficult cyclic scaffolds to prepare for kinetic and thermodynamic reasons,<sup>8b</sup> nonalactones and decalactone with up to three non-vicinal stereocenters were prepared by ring expansion of prochiral alcohols (21 examples). Modulation of the configuration and substitution patterns of the prochiral material allowed the exploration of various steric and electronic scenarios (alkyl, aryl, carboxylate and carboxamide), picturing the perimeter and potential of the strategy with high values of dr and er (up to 99 : 1) owing to the 2-nitrophenyl function. Whether other electron-withdrawing groups may enable the enantioselective desymmetrization of the corresponding alcohol remains to be determined. However, this current limitation is counterbalanced by the enantio- and diastereoselective access to indoles, indolenines and derivatives thus provided, structural motifs notably encountered in many alkaloids (natural products or pharmaceuticals). From this investigation emerges a tool box in which readily available organocatalysts—QD or QN, **17c**, **17d**—effectively synthesized isomers of lactones **12** from *cis*-**10** or *trans*-**10**. Bearing a quinolin-6-ol substituted with a methylenecyclohexyl ether, which increased the volume of the appendage, **17d** offered a good balance between reactivity and stereoselectivity in most cases. Quinidine and quinine being commercially available, the two other derivatives are prepared in one step from cupreidine and are easily recovered after reaction, offsetting the catalytic load used to perform the energy-demanding ring expansion step. For that matter, the process of ring expansion of *trans*-**10a** into *cis*-**12a** required higher temperature to occur, without inducing lower enantioselectivity.

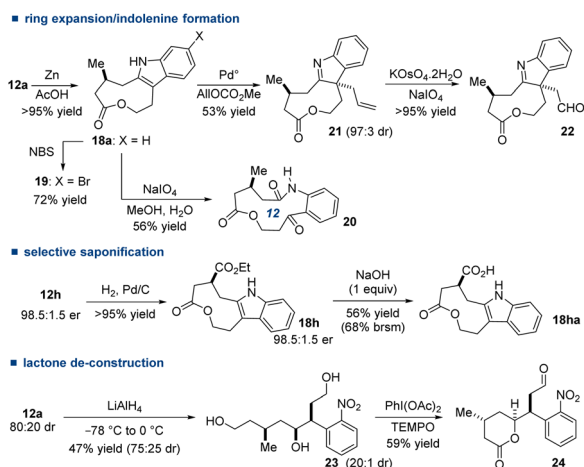
Futures studies will be focused on some features and implications of this complex and yet simple to implement process, such as the inversion of selectivity observed with fluorophenyl and carboxylate ester derivatives, or the origins of the stereoselectivity induced by the alkyl ether of the quinolin-6-ol appendage of the catalyst.

## Data availability

All experimental and characterization data including HPLC traces and NMR spectra are available in the ESI.† Crystallographic data for compound **12e** has been deposited in the Cambridge Crystallographic Data Centre under accession number CCDC 2162117.

## Author contributions

A. A. and O. G. conducted the investigation and prepared the ESI.† C. F. conducted the DFT calculations. L. B. and E. P. contributed to the formal analysis of the results. J. M. reviewed the manuscript. M. D. P. conceptualized and supervised the research, wrote the manuscript.



Scheme 5 Synthetic manipulations.



## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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- 17 In the absence of a catalyst, no formation of **12a** was noted at a low temperature. Likely by acidic activation, the slow conversion of *cis*-10a into *rac*-12a occurred at room temperature in CDCl<sub>3</sub> (after 1 h) or on silica gel, making a full conversion mandatory to achieve high enantioselectivity. Otherwise, oxidation of the unreacted alcohol into aldehyde was performed by addition of Dess-Martin periodinane.
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- 19 We sought to confirm the absolute configuration of **12h,i**, to no avail. While the absolute configuration of **12e** was used as a basis of extrapolation to the other cases, the peculiar selectivity noted with **12h,i** suggests a different mechanism with potential implication on this point. Moreover, performing the experiment at room temperature (4 h, 70% yield) revealed that the enantiopurity of *cis*-**12h** (18% yield) was only marginally decreased (96 : 4 er), the stereoselectivity being more impacted (75 : 25 dr) with *trans*-**12h** isolated in 70 : 30 er. Incidentally, *trans*-**12h** was measured with reversed and higher, though still modest, enantiopurity when the reaction was conducted at room temperature than at –40 °C (45 : 55 er), probably due to the epimerization of enantioenriched *cis*-**12h** into *trans*-**12h** occurring at room temperature.
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