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Double Diastereoselective, Nucleophile-Catalyzed Aldol Lactonizations (NCAL) Leading to β -Lactone Fused Carbocycles and Extensions to β -Lactone Fused Tetrahydrofurans

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Abstract

A double diastereoselective variant of the nucleophile catalyzed aldol-lactonization (NCAL) process is described. This strategy delivers β -lactone-fused carbocycles with good to excellent diastereoselectivities using *cinchona* alkaloid catalysts with enantioenriched aldehyde acids, which gave low diastereoselectivity based on substrate control alone. β -Lactone fused tetrahydrofurans are also prepared for the first time via the NCAL process, however diastereoselectivity was only modestly improved when applying double diastereodifferentiation to these systems.

The significant utility of double diastereodifferentiation¹ has been demonstrated on numerous occasions in the context of natural product total synthesis. Therefore, the importance of this strategy cannot be overstated.² Furthermore, the degree to which a chiral reagent can influence stereochemical outcomes by overcoming inherent substrate bias is revealed through the study of double diastereodifferentiation.

The development of concise enantioselective routes to β -lactones continues to be an active area of research due to their varied reactivity and applications.³ Our recent contributions to this area have focused on intramolecular, nucleophile catalyzed aldol-lactonization (NCAL) processes of aldehyde acids that provide convenient access to bicyclic β -lactones bearing two or more stereogenic centers (Scheme 1a)⁴ building on elegant work by Wynberg and coworkers.⁵ This process was previously rendered enantioselective with the use of *O*-acetyl quinidine (*O*-AcQD) or β -isocupreidine (β -ICPD) as chiral nucleophilic promoters (chiral Lewis bases) to obtain enantioenriched β -lactone fused cyclopentanes.^{4,6} More recently, the NCAL process was extended to ketoacid substrates⁷ (Scheme 1b), and a single example of a

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Supporting Information Available: Experimental procedures and full characterization (including ¹H and ¹³C spectra and stereochemical proofs) for aldehyde acids **9a**, **9c-e** and **11a-e**, carbocyclic β -lactones **10a:10a'**, **10c-e:10c'-e'**, and tetrahydrofuran-fused β -lactones **12a-e:12a'-e'**. X-ray crystallographic data for compounds **10a'** and **12c'** is also provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

stoichiometric, enantioselective reaction made use of tetramisole as a chiral promoter.⁸ In addition, the utility of the NCAL process was demonstrated in a concise, bioinspired, racemic⁹ and subsequently enantioselective¹⁰ total synthesis of salinosporamide A. Herein, we demonstrate the utility and powerful stereochemical influence of *cinchona* alkaloid catalysts in double diastereoselective NCAL reactions for the preparation of variously substituted carbocycle-fused β -lactones. We also report the first examples of tetrahydrofuran-fused β -lactones obtained through the NCAL process.

We previously found that, with respect to the carboxylic acid, β -substituted aldehyde acid and ketoacid substrates provided bicyclic β -lactones (*i.e.* **6**) with high diastereoselectivity (Figure 1). This observation provided evidence for a NCAL process proceeding via ammonium enolate intermediates based on A1:3-strain arguments, since a [2+2] pathway proceeding through a ketene intermediate would be expected to afford low diastereoselectivity. However, substrates bearing substituents at other positions (*i.e.* γ , δ) gave low diastereoselectivities as would be predicted based on the absence of A1:3 strain.⁷ This led us to consider double diastereodifferentiation with chiral nucleophiles, *O*-TMS quinidine (*O*-TMSQD) and *O*-TMS quinine (*O*-TMSQN),¹¹ with enantioenriched substrates to determine if catalyst control could override the low diastereoselectivities obtained with substrate control alone (Figure 2).

We initiated double diastereodifferentiation studies with previously studied carbocyclic substrates. Subjecting enantiomerically enriched aldehyde acid (+)- **9a**¹² (87% ee, chiral HPLC) to standard NCAL conditions with Et₃N as the nucleophile resulted in a 2:1 mixture of *anti/syn* β -lactones **10a:10a'**, respectively (Table 1, entry 1). Use of 10 mol % *O*-TMSQD led to an increased level of diastereoselection and complete reversal in diastereoselection to 1:7 *anti/syn* β -lactones **10**, and both relative and absolute stereochemistry of the major β -lactone **10a'** was confirmed by X-ray analysis (Table 1, entry 2).¹³ Alternatively, diastereomeric β -lactone **10a'** could be obtained with high diastereoselectivity (dr >19:1) employing *O*-TMSQN indicative of the matched case (Table 1, entry 3). Commercially available dimeric catalysts, hydroquinidine 1,4-phthalazinediyl diether ((DHQD)₂PHAL) and hydroquinine 1,4-phthalazinediyl diether ((DHQ)₂PHAL), were also studied and provided similar results (Table 1, entries 4 and 5).

Since double diastereoselectivity was possible with γ -substituted aldehyde acid substrates, we next studied other enantiomerically enriched substrates with alternate substitution patterns. As previously reported and to serve as a reference point, both enantiomers of the unsubstituted bicyclic β -lactone **10b:10b'** were obtained with good enantioselectivity employing the pseudoenantiomeric catalysts, *O*-AcQD and β -ICPD, in 92% and 90% ee, respectively.^{4a} This example demonstrates the potential for significant catalyst control in the NCAL process of aldehyde acids. As expected, *anti*-silyloxy- β -lactone **10c'** derived from aldehyde acid **9c** was obtained with high diastereoselectivity (dr >19:1) with Et₃N as the nucleophilic promoter due to the β -substituent (Table 2, entry 2). This substrate also provided excellent efficiency. However, not surprisingly, diastereoselectivity could not be altered with either *O*-TMSQD or *O*-TMSQN due to the strong conformational bias exerted by allylic 1,3-strain (see Figure 1) but rather led only to greatly reduced conversion. Use of Et₃N with the γ,δ -substituted aldehyde acid **9d** gave low diastereoselectivity leading to a 2:1 mixture of β -lactones **10d:10d'** (Table 2, entry 3). Reversed diastereoselectivity (dr 1:3) was obtained with *O*-TMSQD providing β -lactone **10d'** as the major diastereomer but gave low yield (32%). However, use of *O*-TMSQN gave both improved yields and diastereoselectivity (dr 10:1) with β -lactone **10d** as the major diastereomer suggestive of a matched case. Double diastereodifferentiation was also possible with cyclohexyl-fused β -lactones **10e:10e'**, which improved a 2:1 diastereomeric ratio obtained with Et₃N to complete catalyst control with *O*-

TMSQN leading to high diastereoselectivity (>19:1); however, conversions were low (Table 2, entry 4).

In the context of a total synthesis effort, we explored the NCAL process for the synthesis of tetrahydrofuran-fused β -lactones **14** (e.g. **12**). Initial studies toward these bicycles provided access to racemic tetrahydrofuran- and tetrahydropyran-fused β -lactones **12a-d:12a'-d'** (Table 3). However, after extensive optimization studies, only low yields were obtained using Et₃N leading to γ - or δ -substituted tetrahydrofurans along with attendant low diastereoselectivities as expected in analogy to cyclopentyl systems (Table 3, entries 1, 2). More tractable ketoacid substrates (e.g. **11**, R = Me) delivered the highest yields with the use of 4-pyrrolidinopyridine (PPY) leading to β -lactones **12c:12c'** as a 1:1 mixture of diastereomers (Table 3, entry 3). The relative stereochemistry of β -lactone **12c'** was confirmed by single crystal X-ray analysis (Figure 3). In the case of tetrahydropyran-fused β -lactone **12d**, high diastereoselectivity was observed, however, in low yield (Table 3, entry 4). The presence of an oxygen atom in the tether likely alters reactive rotamer populations and a change in mechanism is possible, especially with α -oxygenated acid substrates leading to ketene intermediates e.g. [2+2] cycloadditions, which may account for lower yields in these reactions.

While *cinchona* alkaloid catalysts proved useful for double diastereodifferentiation leading to carbocyclic systems, they were less successful when applied to aldehyde acids bearing oxo-linkages (Scheme 2). For example, racemic aldehyde acid **11e** provided 47% yield of a 1:1 mixture of diastereomeric tetrahydrofuran-fused β -lactones **12e:12e'** employing Et₃N.¹⁵ Attempted double diastereodifferentiation with *O*-TMSQD and racemic gave low enantioselectivity for both diastereomers 2:1 indicating that effective catalyst control did not occur with this substrate and thus diastereoselectivity would not be expected to improve when employing enantioenriched substrate. Similar results were obtained with *O*-TMSQN (not shown). These initial results obtained with *cinchona* alkaloid catalysts along with the consistently low yields of tetrahydrofuran-fused β -lactones obtained via the NCAL process, despite extensive optimization studies, precluded further investigations of double diastereodifferentiation with this class of substrates.

In summary, double diastereodifferentiation via the NCAL process is possible with *cinchona* alkaloid catalysts and enantioenriched aldehyde acids. In particular, carbocycle-fused β -lactones were highly amenable to double diastereodifferentiation leading to improvements in diastereoselectivities from 1:1-2 to >19:1 in several cases. This process thus enables access to highly functionalized carbocycles with existing stereocenters with high diastereoselectivity. Tetrahydrofuran-fused β -lactones were accessed for the first time via the NCAL process; however, prospects for double diastereodifferentiation were precluded due to low reaction yields. These studies reveal the exquisite stereochemical control exerted by the *cinchona* alkaloids in the NCAL process given the ability of these catalysts to override inherent substrate bias and in some cases reverse diastereoselectivity obtained from substrate control alone.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Observed diastereoselectivities for NCAL reactions leading to β -lactone fused carbocycles **6-8** and proposed selectivity models.

Figure 2.
Optically active nucleophiles (Lewis Bases) employed in the NCAL process.

Figure 3. Single crystal X-ray structure (ORTEP representation) of tetrahydrofuran-fused β -lactone **12c'**.

Scheme 1.

Formation of Bicyclic and Tricyclic β -Lactones via the NCAL Process From (a) Aldehyde Acids (**1**) and (b) Ketoacids (**4**)

Scheme 2.

Attempted Double Diastereoselective Synthesis of Tetrahydrofuran-Fused β -Lactones **12e**/**12e'**

Table 1

Catalyst Screening for Double Diastereodifferentiation with Aldehyde Acid (+)-9a

entry	nucleophile (mol %)	base	% yield ^a	dr (10a:10a') ^b
1	Et ₃ N (100) ^c	Et ₃ N	58	2:1
2	OTMSQD (10) ^d	<i>i</i> -Pr ₂ NEt	73	1:7
3	OTMSQN (10) ^d	<i>i</i> -Pr ₂ NEt	60	>19:1
4	(DHQD) ₂ PHAL (10) ^d	<i>i</i> -Pr ₂ NEt	59	1:4
5	(DHQ) ₂ PHAL (10) ^d	<i>i</i> -Pr ₂ NEt	53	>19:1

^a Isolated yield.^b Diastereomeric ratio determined by ¹H NMR (500 MHz) of the crude reaction mixture.^c Reaction was run for 48 h at 0.05 M.^d Reaction was run for 72 h at 0.2 M.

Table 2

Double Diastereoselective NCAL Reactions with Enantioenriched Aldehyde Acids **9b-e**

entry	carbocycle fused bicyclic β -lactones	NEt ₃ % yield (dr) ^{a,b}	<i>O</i> -TMSQD % yield (dr) ^{b,c}	<i>O</i> -TMSQN % yield (dr) ^{b,c}
1 ^d	(-)- 10b (+)- 10b'	55	82, 92% ee ^e	42, 90% ee ^f
2	10c (+)- 10c'	84 (1:>19)	33 (1:>19)	23 (1:>19)
3	(-)- 10d (-)- 10d'	45 (2:1)	32 (1:3)	55 (10:1)
4	(-)- 10e (-)- 10e'	38 (2:1)	31 (1:>19)	10 (>19:1)

^a Reaction run for 12-24 h at 0.05 M.^b Yields refer to isolated, purified products and diastereomeric ratios were determined by ¹H NMR (500 MHz) analysis (integration) of the crude reaction mixtures.^c Reaction run for 48-72 h at 0.20 M.^d Previously described (see refs. 4b,c) enantioselective NCAL process with an achiral substrate shown for comparison.^e Reaction run with *O*-AcQD.^f Reaction run with β -ICPD.

Table 3Tetrahydrofuran- and Tetrahydropyran-fused β -Lactones **12** via the NCAL Process

(X, Y = O, CH₂;
n = 1, 2; R = H, Me)

entry	tetrahydrofuran bicyclic β -lactones	% yield (dr) ^a
1	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> 12a </div> <div style="text-align: center;"> 12a' </div> </div>	25 (1:1)
2	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> 12b </div> <div style="text-align: center;"> 12b' </div> </div>	31 ^b (2:1)
3	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> 12c </div> <div style="text-align: center;"> 12c' </div> </div>	54 ^{c,d} (1:1)
4 ^b	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> 12d </div> <div style="text-align: center;"> 12d' </div> </div>	26 (>19:1)

^aYields refer to isolated, purified products and diastereomeric ratios were determined by ¹H NMR analysis (integration) of the crude reaction mixtures.

^bReaction was run at -30 °C.

^cPPY (1.5 equiv) was used as nucleophile and *i*-Pr₂NEt (2.0 equiv) as base.

^dReaction run at 0 °C.