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

Kay A. Morris, Kevin M. Arendt, Seong Ho Oh,[†] and Daniel Romo*

Department of Chemistry, Texas A&M University, P.O. Box 30012, College Station, Texas 77842-3012

romo@tamu.edu

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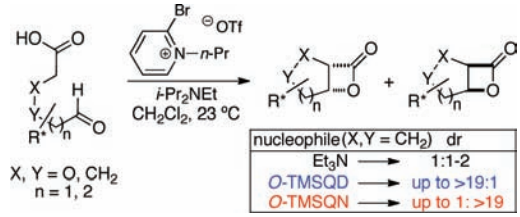
ABSTRACT



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 diastereodifferentiation[1] 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 because of 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 co-

[†] Present address: Codexis Laboratories Singapore Pte Ltd, 61 Science Park Rd, Singapore, Singapore 117525.

(1) (a) Sharpless, K. B. *Chem. Scr.* **1985**, *25*, 71. (b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1.

(2) For some examples, see: (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263. (c) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (d) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (e) For applications in aldol reactions, see: Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65.

(3) For reviews describing enantioselective β-lactone synthesis, see: (a) Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403. (b) Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545. (c) Paull, D. H.; Weatherwax, A.; Letcka, T. *Tetrahedron* **2009**, *65*, 6771. (d) Purohit, V. C.; Matla, A. S.; Romo, D. *Heterocycles* **2008**, *76*, 949. (e) For recent publications not included in these reviews, see: Chidara, S.; Lin, Y.-M. *Synlett* **2009**, 1675. (f) Wang, X.-N.; Shao, P.-L.; Lv, H.; Ye, S. *Org. Lett.* **2009**, *11*, 4029. (g) Phillips, E. M.; Wadamoto, M.; Scheidt, K. A. *Synthesis* **2009**, 687.

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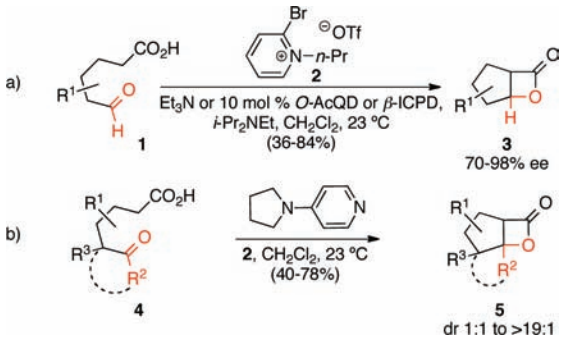
Scheme 1. Formation of Bicyclic and Tricyclic β-Lactones via the NCAL Process from (a) Aldehyde Acids (**1**) and (b) Ketoacids (**4**)



workers.[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 substrates[7] (Scheme 1b), and a single example of a 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, racemic,[9] and subsequently enantioselective[10] 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 $A^{1,3}$-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 on the basis of the absence of $A^{1,3}$ 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

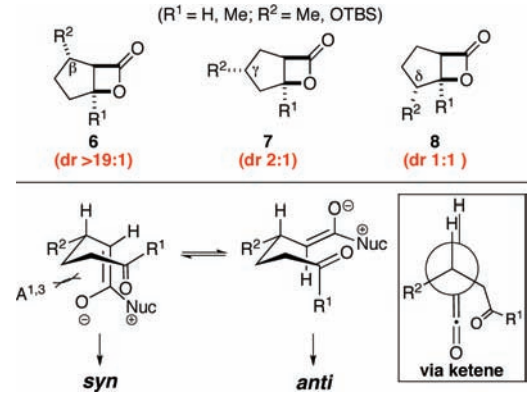


Figure 1. Observed diastereoselectivites for NCAL reactions leading to β-lactone fused carbocycles **6**−**8** and proposed selectivity models.

substrates to determine if catalyst control could override the low diastereoselectivities obtained with substrate control alone (Figure 2).

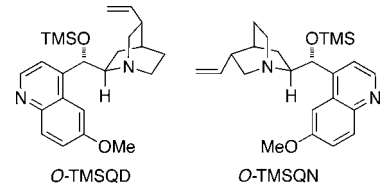


Figure 2. Optically active nucleophiles (Lewis bases) employed in the NCAL process.

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 Et_3N 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

(4) (a) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945. (b) Cortez, G. S.; Oh, S. H.; Romo, D. *Synthesis* **2001**, 1731. (c) Oh, S. H.; Cortez, G. S.; Romo, D. *J. Org. Chem.* **2005**, *70*, 2835.

(5) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166.

(6) For a review on cinchona organocatalysts, see: Marcelli, T.; Van Maarseveen, J. J.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496.

(7) Henry-Riyad, H.; Lee, C.; Purohit, V. C.; Romo, D. *Org. Lett.* **2006**, *8*, 4363.

(8) Purohit, V. C.; Matla, A. S.; Romo, D. *J. Am. Chem. Soc.* **2008**, *130*, 10478.

(9) Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.* **2007**, *9*, 2143.

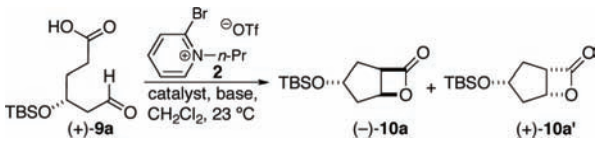
(10) Nguyen, H.; Ma, G.; Romo, D. *Chem. Commun.* **2010**, *46*, 4803.

(11) Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006.

(12) For the preparation of optically active aldehyde acid substrates used in this study and determination of enantiomeric purity, see Supporting Information.

(13) See Supporting Information for further details.

Table 1. Catalyst Screening for Double Diastereodifferentiation with Aldehyde Acid (+)-**9a**



entry	nucleophile (mol %)	base	% yield[a]	dr (**10a**:**10a'**)[b]
1	Et_3N (100)[c]	Et_3N	58	2:1
2	*O*-TMSQD (10)[d]	*i*-Pr_2NEt	73	1:7
3	*O*-TMSQN (10)[d]	*i*-Pr_2NEt	60	>19:1
4	$(DHQD)_2PHAL$ (10)[d]	*i*-Pr_2NEt	59	1:4
5	$(DHQ)_2PHAL$ (10)[d]	*i*-Pr_2NEt	53	>19:1

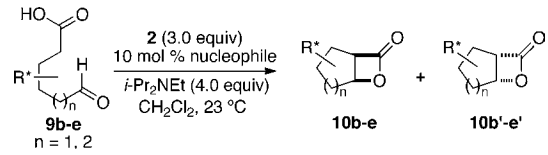
[a] Isolated yield. [b] Diastereomeric ratio determined by ^1H NMR (500 MHz) of the crude reaction mixture. [c] Reaction was run for 48 h at 0.05 M. [d] Reaction was run for 72 h at 0.2 M.

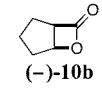
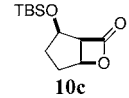
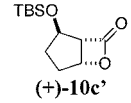
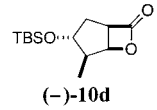
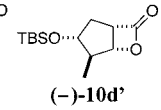
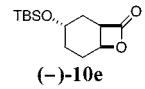
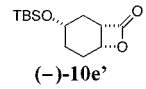
enantiomerically enriched substrates with alternate substitution patterns. As previously reported and to serve as a reference point, both enantiomers of the unsubstituted bicyclic β-lactone **10b**:**10b′** were obtained with good enantioselectivity employing the pseudoenantiomeric catalysts, *O*-AcQD 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 Et_3N as the nucleophilic promoter as a result of 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 because of the strong conformational bias exerted by allylic 1,3-strain (see Figure 1) but rather led only to greatly reduced conversion. Use of Et_3N 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 with 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 Et_3N 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,

(14) For previous reports of tetrahydrofuran-fused β-lactones obtained via (a) lactonization of β-hydroxy acids, see: Crich, D.; Hao, X. *J. Org. Chem.* **1999**, *64*, 4016. (b) Presumed [2 + 2] cycloadditions, see: Brady, W. T.; Giang, Y. F.; Marchand, A. P.; Wu, A. *J. Org. Chem.* **1987**, *52*, 3457.

Table 2. Double Diastereoselective NCAL Reactions with Enantioenriched Aldehyde Acids **9b**−**e**



entry	carbocycle fused bicyclic β-lactones		NEt_3 % yield (dr)[a,b]	*O*-TMSQD % yield (dr)[b,c]	*O*-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 was run for 12−24 h at 0.05 M. [b] Yields refer to isolated, purified products; diastereomeric ratios were determined by ^1H NMR (500 MHz) analysis (integration) of the crude reaction mixtures. [c] Reaction was run for 48−72 h at 0.20 M. [d] Previously described (see refs 4b and 4c) enantioselective NCAL process with an achiral substrate shown for comparison. [e] Reaction was run with *O*-AcQD. [f] Reaction was run with β-ICPD.

after extensive optimization studies, only low yields were obtained using Et_3N leading to γ- or δ-substituted tetrahydrofurans along with attendant low diastereoselectivies 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

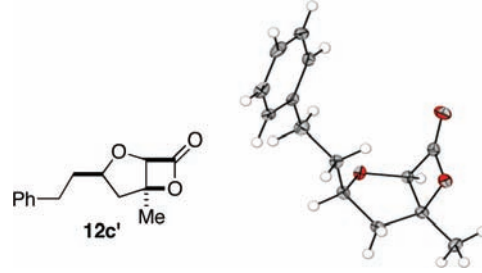
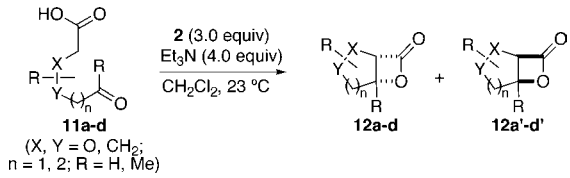
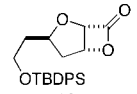
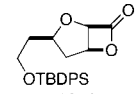
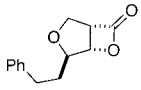
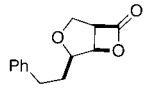
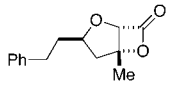
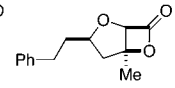
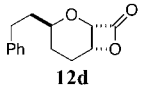
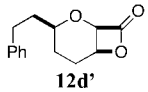


Figure 3. Single crystal X-ray structure (ORTEP representation) of tetrahydrofuran-fused β-lactone **12c′**.

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



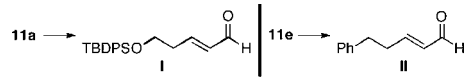
entry	tetrahydrofuran bicyclic β-lactones	% yield (dr)[a]
1	 **12a**  **12a'**	25 (1:1)
2	 **12b**  **12b'**	31[b] (2:1)
3	 **12c**  **12c'**	54[c,d] (1:1)
4[b]	 **12d**  **12d'**	26 (>19:1)

[a] Yields refer to isolated, purified products; diastereomeric ratios were determined by ^{1}H NMR analysis (integration) of the crude reaction mixtures. [b] Reaction was run at −30 °C. [c] PPY (1.5 equiv) was used as nucleophile and *i*-Pr$_2$NEt (2.0 equiv) as base. [d] Reaction was run at 0 °C.

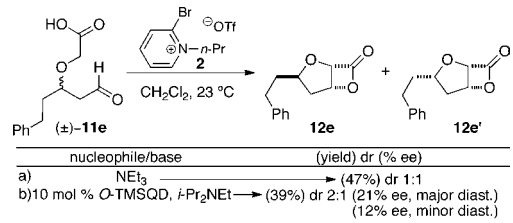
β-lactone **12d**, high diastereoselectivity was observed, however, in low yield (Table 3, entry 4). The presence of an oxygen atom in the tether likely alters reactive rotamer populations, and a change in mechanism is possible, especially with α-oxygenated acid substrates leading to ketene intermediates, e.g., [2 + 2] cycloadditions, which may account for lower yields in these reactions.

While cinchona alkaloid catalysts proved useful for double diastereodifferentation 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 Et$_3$N.[15] Attempted double diastereodifferentation with *O*-TMSQD and racemic **11e** gave low enantioselectivity for both diastereomers (dr 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.

(15) α,β-Unsaturated aldehydes **I** and **II** were isolated as byproducts as a result of competitive β-elimination of the corresponding aldehyde acid starting material.



Scheme 2. Attempted Double Diastereoselective Synthesis of Tetrahydrofuran-Fused β-Lactones **12e**/**12e′**



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 to be obtained with high diastereoselectivity. Tetrahydrofuran-fused β-lactones were accessed for the first time via the NCAL process; however, prospects for double diastereodifferentiation were precluded because of 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.

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Supporting Information Available: Experimental procedures and full characterization (including ^{1}H and ^{13}C 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′** are also provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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