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Asymmetric Synthesis of Bicyclic β-Lactones via the Intramolecular, Nucleophile-Catalyzed Aldol Lactonization: Improved Efficiency and Expanded Scope

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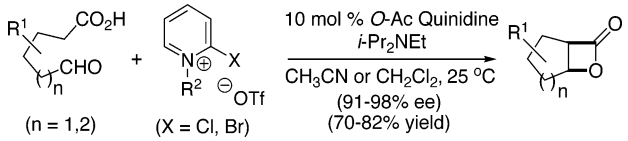
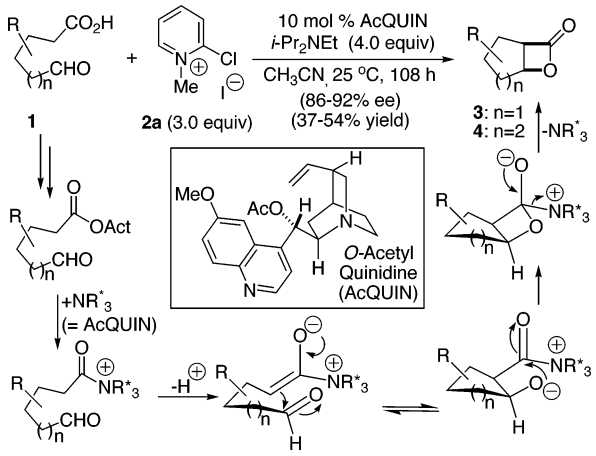
Received January 5, 2005



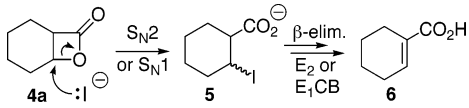
The intramolecular, nucleophile-catalyzed, aldol lactonization (NCAL) process merges catalytic, asymmetric carbocycle synthesis with β-lactone synthesis. The application of modified Mukaiyama reagents to this process led to greatly improved conversion and efficiency (70−82% yield) and shorter reaction times with no diminution of enantioselectivity (91−98% ee). The process was extended to several new aldehyde−acid substrates leading to new bicyclic-β-lactones. This methodology uniquely provides β-lactone-fused cyclopentanes and cyclohexanes readied for further transformations.

A recent resurgence in the exploitation of β-lactones for several applications including natural product total synthesis, biodegradable polymer synthesis, and enzyme inhibitors is leading to great advances in the area.[1] This increased activity parallels the recent development of improved methods for their preparation in optically active form.[2] The Wynberg catalytic, asymmetric β-lactone synthesis from ketenes and aldehydes stands as a benchmark for developments in this area but was limited to highly electrophilic aldehydes (i.e., α-chlorinated substrates).[3] Our group has developed new variants of the Wynberg process leading to the use of *in situ* generated ketene via the Staudinger method[4] and also the first use of non-α-chlorinated aldehydes in an intramolecular nucleophile-catalyzed, aldol-lactonization (NCAL) process.[5] Nelson and co-workers recently found that Lewis acid activation could be employed for intermolecular NCAL variants with non-chlorinated aldehydes.[6]

SCHEME 1. Initial NCAL Process and Proposed Mechanism



SCHEME 2. Possible Decomposition Pathway Leading to Cyclohexene 6



In our initial report of the intramolecular NCAL process, the enantiomeric excess for the examples reported was useful (86−92% ee); however, the efficiency of the catalytic, asymmetric process was moderate (37−54%) due to low conversion (Scheme 1).[5a] Our working mechanism for this process involves carboxylic acid activation, acylammonium formation, deprotonation leading to an ammonium enolate, intramolecular aldol reaction, possible stereochemical and rate-determining oxetane formation, and regeneration of the nucleophilic catalyst.

In our initial studies, Mukaiyama's reagent **2a** was employed. This reagent is widely used for activation of carboxylic acids to provide esters, amides, or lactones[7] and also as a means to generate ketenes *in situ* for subsequent [2 + 2] cycloadditions with alkenes[8] and most recently hydrazones.[9] Two findings made in the course of our studies led us to explore the use of modified Mukaiyama reagents. First, the cyclohexene **6** was isolated in the NCAL process presumably derived from ring opening of bicyclic β-lactone **4a** (Scheme 2). We hypothesize that β-iodo carboxylate **5** is a transient intermediate produced by attack of iodide ion at the β-carbon of the formed β-lactone followed by β-elimina-

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(1) (a) For a review on β-lactones employed in natural product total synthesis, see: Wang, Y.; Tennyson, R. L.; Romo, D. *Heterocycles* **2004**, *64*, 605. (b) For lead references to polymers obtained via β-lactones, see: Rieth, L. R.; Moore, D. R.; Lobkovsky, E. B.; Coates, G. W. *J. Am.* Chem. Soc. **2002**, *124*, 15239. (c) For lead references to their potential as enzyme inhibitors, see: Lall, M. S.; Ramtohul, Y. K.; James, M. N. G.; Vederas, J. C. *J. Org. Chem.* **2002**, *67*, 1536.

(2) Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *51*, 6403.

(3) (a) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc*. **1982**, *104*, 166. (b) Wynberg, H. *Top. Stereochem*. **1986**, *16*, 87.

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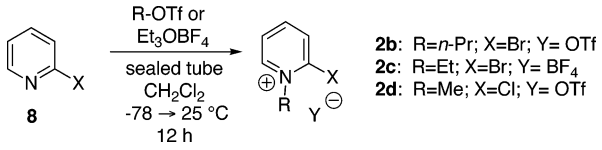
(9) Diez, E.; Fernandez, R.; Marques-Lopez, E.; Martin-Zamora, E.; Lassaletta, J. M. *Org. Lett.* **2004**, *6*, 2749.

10.1021/jo050024u CCC: $30.25
Published on Web 02/26/2005

SCHEME 3. Inactivation Pathway for Mukaiyama's Reagent 2a

SCHEME 4. Synthesis of Modified Mukaiyama Reagents 2b–d



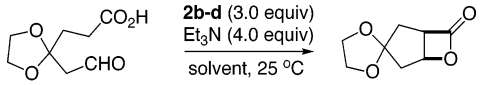
tion. Related ring-opening processes with halides are known to occur with β-lactones[10] and the polar solvent employed in the NCAL process to solubilize Mukaiyama's reagent may facilitate this side reaction.

Second, Rappaport demonstrated that cyclizations of β-amino acids to β-lactams proceed with greater efficiency using modified Mukaiyama's reagents.[11] The study of these reagents was premised on the known inactivation of Mukaiyama's reagent due to halogen exchange and the known unreactivity of *N*-methyl-2-iodopyridinium chloride (**7**) as an activating agent for carboxylic acids (Scheme 3).[12]

This led us to the use of modified Mukaiyama reagents possessing non-nucleophilic counterions such as triflate and tetrafluoroborate which may preclude undesired ring-opening of the product β-lactone by iodide and also avoid inactivation of these reagents by the process described above. Another advantage to the use of these modified reagents is their increased solubility allowing the use of less polar solvents that may further minimize ring-opening reactions accelerated by polar media. Herein, we report the application of these reagents to the NCAL process leading to greatly improved yields and extensions of this process for accessing optically active, functionalized, β-lactone-fused cyclopentanes and cyclohexanes. The new pyridinium salt **2b** and known pyridinium salts **2c**,**d** and were synthesized by *N*-alkylation of the corresponding 2-halopyridines (**8**) with the corresponding alkyl triflate[11] or triethyloxonium tetrafluoroborate[13] in nearly quantitative yield as colorless crystals by literature procedures (Scheme 4).

To compare the efficiency of the various pyridinium salts **2a**–**d**, a racemic NCAL process employing aldehyde acid **1a** was explored and aliquot NMR was used to monitor reaction progress (Table 1).[14] In general, the aldehyde acid substrates employed in these studies were prepared by either ozonolysis of the corresponding cyclic enol ethers or hydrolysis and ozonolysis of the corresponding alkene esters.[15] Initially, when triflate salt **2b** was employed under previously reported NCAL conditions, β-lactone **3a** was produced in 79% yield (entry 2); an improvement over the use of Mukaiyama's reagent (**2a**) under otherwise identical conditions (entry 1).[5a]

TABLE 1. Optimization of the Intramolecular NCAL Process Employing 2-Halopyridinium Activating Agents 2b–d



entry	activ. agent	solvent	addn. time[a] (h)	total reaction time (h)	% yield[b]
1[c]	**2a**	CH_3CN	10	24	66
2	**2b**	CH_3CN	10	24	79
3	**2b**	CH_3CN	1	11	72
4	**2c**	CH_3CN	1	11	71
5	**2d**	CH_3CN	1	11	68
6	**2a**	CH_3CN	1	11	28
7	**2b**	THF	1	11	70
8	**2b**	CH_2Cl_2	1	11	88
9	**2b**	CH_2Cl_2	<10 min	12	~10[d]

[a] A syringe pump was used for addition of aldehyde acid **1a**. [b] Yields of isolated product after chromatography on silica gel. [c] Initial conditions previously reported (see ref 5). [d] Yield estimated by ^{1}H NMR analysis of the crude reaction mixture.

With this result in hand, we then explored the possibility of shortening the addition and reaction times. After some experimentation, we found that comparable yields of β-lactone **3a** were obtained by adding aldehyde acid **1a** over 1 h (syringe pump) to the mixture of pyridinium salt **2b** and Et_3N, followed by stirring for an additional 11 h (Table 1, entry 3). Use of modified Mukaiyama reagents **2c**,**d** also led to comparable yields of 68–72% (entries 3 and 4) with shortened reaction times. Use of the original Mukaiyama's reagent **2a** under these optimized conditions gave low yields (28%) of β-lactone **3a** (entry 6).[5a] Importantly, with the more soluble pyridinium salt **2b**, these reactions could also be conducted in THF or CH_2Cl_2 in yields up to 88% (entries 7 and 8). Attempts to further reduce the time of addition of substrate to <10 min followed by stirring for 10 h gave very low conversion (entry 9). Similarly, addition times of 30 min gave about 45% isolated yield (not shown).

Several racemic bicyclic β-lactones prepared previously[5a] and new bicylic systems were prepared in improved yields (up to 23% increase) employing these new conditions (methods B–D) compared to prior conditions (method A) (Table 2). The lowered polarity of the medium may lower the potential of undesired side-reactions of the product β-lactone. In line with this hypothesis, the byproduct cyclohex-2-ene carboxylic acid (**6**) was not detected using pyridinium salt **2b** in the NCAL reaction leading to the volatile β-lactone **4a**. This may be due to the non-nucleophilic character of the triflate counterion or the lowered potential of secondary carbocation formation in the less polar solvents. However, monitoring the reaction by aliquot NMR revealed that the reaction reached a plateau at about 80% conversion and ultimately led to only 40% isolated yield of this volatile

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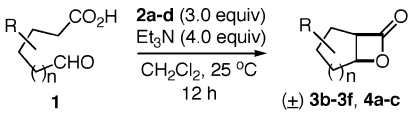
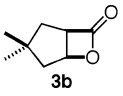
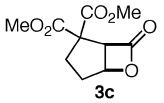
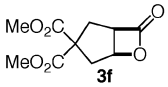
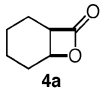
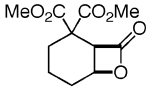
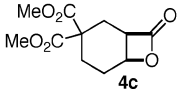
(13) Xu, J.-C.; Li, P. *Tetrahedron* **2000**, *56*, 8119.
(14) For aliquot NMR, a sample of the reaction mixture was removed by syringe, evaporated under vacuum, and added directly to a NMR tube using $CDCl_3$ for the transfer.
(15) For optimal yields in the NCAL process, it is imperative to have the aldehyde acid of high purity. See the Supporting Information for details on the synthesis and purification of the aldehyde acid substrates employed.

TABLE 2. Synthesis of Racemic Carbocycle-Fused *β*-Lactones Employing the Optimized Conditions

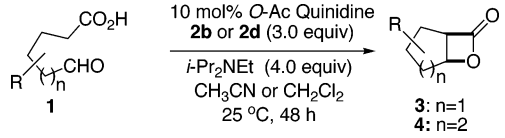


entry	bicyclic β-lactone	method[a]	% yield[b]
1	 3b	***A***	*68*
		B	75
		C	76
2	 3c	***A***	*62*
		B	75
		C	72
3	 3d	***A***	*55*
		D	78
4	 3e	***A***	*62*
		C	60
5	 3f	**C**	84
6	 4a	***A***	*36*[c]
		C	40
7	 4b	***A***	*57*
		B	74
		C	65
8	 4c	**C**	84

[a] In all reactions, substrates were added by syringe pump. Method A (original procedure in italics): 3.0 equiv of activating reagent **2a** was used and substrate was added over 10 h in CH_3CN (ref 5a). Method B: 3.0 equiv of activating agent **2b** was used and substrate was added over 1 h. Method C: 2.0 equiv of activating agent **2b** was used and substrate was added over 1 h. Method D: 3.0 equiv of activating reagent **2c** was used and substrate was added over 10 h. [b] Yields shown are for purified products (Fluorosil or SiO_2 with 1% Et_3N). [c] Cyclohex-2-ene carboxylic acid was also isolated in 5% yield.

product (entry 6). On the other hand, good yields of nonvolatile cyclohexyl *β*-lactones **4b** and **4c** were achieved (entries 7 and 8). The addition times of substrates and overall reaction time were decreased significantly using these modified Mukaiyama's reagents and we attribute this primarily to their increased solubility. The potential utility of low molecular weight *β*-lactones is compromised due to the volatility of these products despite the high conversion as determined by aliquot ^{1}H NMR (entries 1, 4, and 5). The use of only 2.0 equiv of activating agent resulted in a reduction in yield of 1−9%. In most cases, the mass balance is accounted for by unreacted starting material since reaction progress appears to plateau at ∼90% conversion as determined by aliquot ^{1}H NMR. As noted previously, the presence and placement of geminal

TABLE 3. Catalytic, Asymmetric Intramolecular NCAL Reactions Employing the Optimized Conditions



entry	*β*-lactone	method[a]	% yield	% ee[b]	config.
1	***3a***	***A***	*37*	*92*	*3R,4S*[c]
		B	74	92	3*R*,4*S*[c]
2	**3c**	**B**	70	70	1*R*,2*S*[d]
3	***3d***	***A***	*54*	*92*	*1R,2S*[c]
		C	82	92	1*R*,2*S*[c]
4	**3f**	**B**	74	91	1*R*,2*S*[d]
5	**4c**	**B**	76	98	1*R*,2*S*[d]

[a] Method A (original procedure in italics): pyridinium salt **2a** in CH_3CN for 108 h (ref 5a). Method B: pyridinium salt **2b** was employed in CH_2Cl_2 for 48 h. Method C: pyridinium salt **2d** in CH_3CN for 108 h. [b] Enantiomeric excess was determined by chiral GC analysis. [c] Absolute configuration was determined previously (see ref 5a). [d] Predicted based on analogy to that determined for *β*-lactones **3a** and **3d**.

substitution had minimal effect on reaction efficiency (cf. entries 1−4).

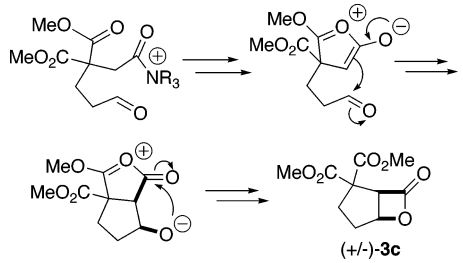
The most dramatic improvements in reaction efficiency were observed for the asymmetric variant of the NCAL process. As summarized in Table 3, use of activating agents **2b**−**d** greatly improved the efficiency of bicyclic-*β*-lactone formation (28−37% yield increases) with similar optical purities to those reported previously using Mukaiyama's reagent (e.g., entry 1; methods A vs B). As expected, asymmetric NCAL variants have slower rates as only 10 mol % of nucleophilic catalyst is employed compared to a full equivalent of Et_3N in the racemic series. However, shorter substrate addition time (from 10 to 1 h) and total reaction time (from 108 to 48 h) were possible when CH_2Cl_2 was employed as solvent (Method B) with no erosion in reaction efficiency as shown for *β*-lactone **3d** (entry 3). Similarly, two new bicyclic *β*-lactones **3f** and **4c** were prepared employing improved conditions (entries 4 and 5). The latter *β*-lactone was obtained in good yield (76%) and excellent enantioselectivity (98% ee); the highest enantioselectivity obtained for the NCAL process to date.

An exception to the results described above was *β*-lactone **3c**, which was obtained in only 70% ee (Table 3, entry 2). A possible rationalization for this discrepancy is the involvement of a competing, nonenantioselective background process due to neighboring-group participation of an adjacent ester group. Thus, following activation of the carboxylic acid and generation of an acylammonium species, cyclization followed by deprotonation leads to an oxyfuran species, which ultimately delivers racemic bicyclic *β*-lactone **3c** (Scheme 5). In line with this mechanistic hypothesis, use of various cinchona alkaloids did not alter the enantioselectivity.[16]

In conclusion, several pyridinium salts **2b**−**d** are superior activating agents for the intramolecular NCAL reaction process compared to the original Mukaiyama reagent **2a**. Use of these pyridinium salts led to marked

(16) Low enantioselectivity was also obtained using the caged-QND[5b] (81% ee, 76% yield) and 9-*O*-trimethylsilylquinine (78% ee, 78% yield) as nucleophilic catalysts (10 mol %).

SCHEME 5. Possible Nonenantioselective, Background Process Leading to Racemic *β*-Lactone 3c



improvements in efficiency (28−37% yield increase) for the catalytic, asymmetric process while maintaining high enantioselectivity (91−98% ee). Furthermore, the improved solubility profile of these reagents enables the use of THF and CH_2Cl_2 as solvents. The NCAL process, which effectively merges catalytic, asymmetric carbocycle synthesis with β-lactone synthesis, now allows practical access to several versatile bicyclic β-lactones readied for further chemistry. The application of the NCAL process to the total synthesis of natural products and derivatives constitute our current efforts in this area.

Experimental Section

Representative Procedure for the Ozonolysis of Silyl Enol Ethers as Described for Aldehyde Acid 1a.

Hazard Warning: Ozonides are produced in this procedure. To ensure complete reduction of the ozonides, excess dimethyl sulfide should be used and stirring should be continued for at least 10 h at 25 °C prior to further handling.

8-(Trimethylsilyloxy)-1,4-dioxaspiro[4,5]dec-7-ene[17] (7.3 g, 32 mmol) was dissolved in 200 mL of dichloromethane and cooled to −78 °C, and a stream of ozone was bubbled through the solution for 5 min beyond when the solution turned pale blue. The stream of ozone was stopped, and excess ozone was removed by bubbling nitrogen through the solution for 30 min. The ozonide was quenched by addition of dimethyl sulfide (5.2 mL, 154.0 mmol, 4.8 equiv), and the reaction mixture was allowed to warm to 25 °C and stirred for at least 10 h to ensure reduction of ozonides. The solvent was removed under reduced pressure, and the resulting residue was purified by MPLC (2:1 hexanes/EtOAc) to afford aldehyde acid **1a** (5.25 g, 72%) as a colorless oil: R_f 0.31 (3:2 hexanes/EtOAc); IR (thin film) 1794, 1731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.75 (t, J = 2.7 Hz, 1H), 4.00 (s, 4H), 2.72 (d, J = 3.0 Hz, 2H), 2.47 (t, J = 1.5 Hz, 2H), 2.13 (t, J = 1.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.1, 179.2, 108.6, 65.5, 50.9, 33.3, 28.5; LRMS (ESI) calcd for $C_8H_{11}O_5$ [M − H] 187.0, found 187.0.

Representative Procedure for the Catalytic, Asymmetric NCAL Reaction as Described for Bicyclic *β*-Lactone (+)-3f (Method B). To a solution of pyridinium salt **2b** (525 mg, 1.5 mmol, 3.0 equiv), *O*-acetyl quinidine (17 mg, 0.05 mmol, 10 mol %), and diisopropylethylamine (282 μL, 2.0 mmol, 4.0 equiv) in 6 mL of CH_2Cl_2 was added, via syringe pump, a solution of aldehyde acid **1f** (123 mg, 0.5 mmol, 1.0 equiv) in 4 mL of CH_2Cl_2 with stirring over 1 h. The resulting dark yellow solution was stirred for another 47 h, at which point the volatiles were removed under reduced pressure to give a dark red residue. The crude reaction mixture was then portioned between ethyl acetate and satd NH_4Cl solution (50 mL each). The phases were separated, and the organic phase was washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated to afford a light red residue that was purified by flash chromatography on SiO_2 (CH_2Cl_2 with 1% triethylamine) to afford β-lactone (+)-**3f** (84 mg, 74%) as a light yellow oil: R_f 0.41 (3:2 hexanes/EtOAc); IR (thin film) 1829, 1743 cm^{-1}; $[\alpha]^{25}_D$ +67.0 (c 0.0201, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.07 (app t, J = 4.0 Hz, 1H), 4.03 (dd, J = 8.0, 4.0 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.21 (d, J = 14.5 Hz, 1H), 3.06 (d, J = 11.0 Hz, 1H), 2.50 (dd, J = 15.5, 4.5 Hz, 1H), 2.14 (dd, J = 14.5, 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 170.7, 169.2, 77.1, 59.9, 56.2, 53.7, 53.5, 39.4, 34.3; LRMS (APCI) calcd for $C_{10}H_{13}O_6$ [M + H] 229.0, found 229.0; enantiomeric excess was determined to be 91% by chiral GC analysis using a 2,3-di-OAc-6-TBS β-CD column (140 °C, 11psi); $t_{(1S,2R)}$ = 6.44 min (major), $t_{(1R,2S)}$ = 6.58 min (minor).

Acknowledgment. We thank the NSF (CHE-0416260), the Robert A. Welch Foundation (A-1280), and Pfizer for support of these investigations. D.R. is an Alfred P. Sloan Fellow and a Camille and Henry Dreyfus Teacher−Scholar. The NSF (CHE-0077917) also provided funds for purchase of NMR instrumentation.

Supporting Information Available: Experimental details and characterization data (including ^1H and ^{13}C NMR spectra) for pyridinium salt **2b**, aldehyde acid **1a**, and bicyclic β-lactones **3f** and **4c** obtained via the intramolecular NCAL reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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