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Enantioselective, Organocatalyzed, Intramolecular Aldol Lactonizations with Keto Acids Leading to Bi- and Tricyclic β-Lactones and Topology-Morphing Transformations**

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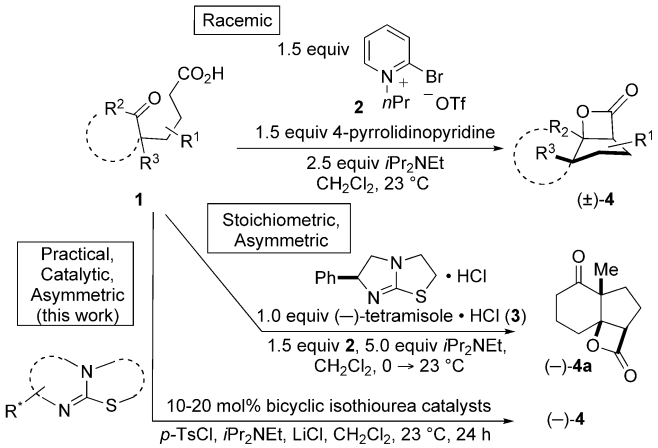
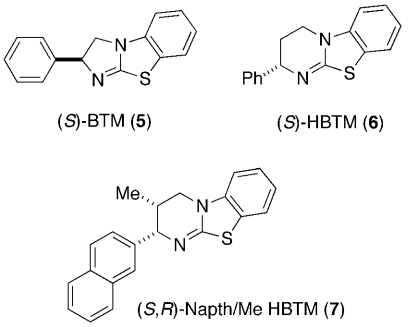
The ability to rapidly assemble complex carbocyclic frameworks in a catalytic, asymmetric manner has garnered great interest in recent years. This type of cascade process, which generates multiple C–C and C–X bonds and stereogenic centers, including quaternary carbon atoms, is highly useful in chemical biology,[1] for example when attempting to synthesize a family of compounds around a natural product lead. We developed intramolecular nucleophile-catalyzed aldol lactonization (NCAL) processes that deliver bicyclic β-lactones[2] from aldehyde acid substrates by using *Cinchona* alkaloid catalysts and modified Mukaiyama activating agents.[3] The NCAL methodology was more recently applied to keto acid substrates by using stoichiometric nucleophiles including 4-pyrrolidinopyridine (4-PPY), which led to a variety of racemic bi- and tricyclic β-lactones,[4] and a nine-step enantioselective synthesis of salinosporamide A from D-serine.[5] Tricyclic-β-lactones (±)-**4** (Scheme 1) were also found to participate in a novel dyotropic process leading to spirocyclic γ-lactones.[6] In the latter report, we described a single example of an enantioselective NCAL process with keto acids leading to β-lactone (−)-**4**, by employing stoichiometric quantities of commercially available tetramisole (Scheme 1).[7]

Herein, we report a significant advance in the NCAL methodology with keto acids involving the use of catalytic homobenzotetramisole (*S*)-HBTM[8] (**6**, Scheme 2) as chiral nucleophile (Lewis base), a tetramisole analogue, and *p*-toluenesulfonyl chloride rather than Mukaiyama's reagent, which led to bi- and tricyclic β-lactones in good yields and excellent enantioselectivities. In addition, we report transformations of these systems that lead to dramatically different topologies. Overall, the reported process provides an expedient route to useful templates for chemical biology through rapid synthesis of carbocyclic frameworks in optically active form. The resident β-lactone is also a versatile handle for further manipulations. Furthermore, the described methodology is the first example of catalytic desymmetrization reactions of cyclic diones by the NCAL process.



Scheme 1. Previous racemic and stoichiometric enantioselective NCAL variants leading to bi- and tricyclic β-lactones, and the described practical, catalytic, asymmetric NCAL process. Tf = trifluoromethanesulfonyl, Ts = toluenesulfonyl.



Scheme 2. Birman's chiral cyclic isothiourea catalysts screened in the NCAL process.

To develop a catalytic NCAL process for keto acid substrates premised on our working mechanistic hypothesis,[4] we considered the use of more electron rich nucleophiles (Lewis bases). We postulated that this could lead to increased concentrations of intermediate aldolates, which in turn would increase the rate of the final, presumed rate-limiting ring closure to β-lactone. With this hypothesis in mind and building on initial success with stoichiometric (−)-tetramisole

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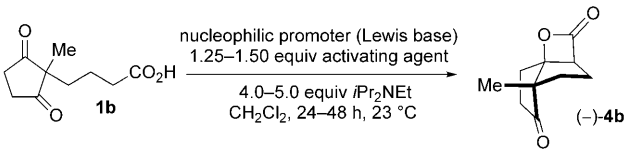
((−)-Tet·HCl, **3**),[6] we considered the use of other chiral, cyclic isothiourea scaffolds developed by Birman and co-workers as powerful acylation catalysts for the kinetic resolution of alcohols (Scheme 2).[9]

Toward a more practical procedure, we were also interested in exploring commercially available, inexpensive carboxylic acid activating agents to improve practicality, since the modified Mukaiyama's reagent **2** must be prepared.[3c] Use of this latter reagent, under previously established conditions for β-lactone **4a**,[6] with as much as 1.5 equivalents of (−)-Tet·HCl (**3**) gave only 35% yield of β-lactone **4b** but with high enantioselectivity (98% *ee*, Table 1, entry 1). Initial

Table 1: Optimization of the NCAL process with dione acid **1b** leading to tricyclic β-lactone (−)-**4b**.



Entry	Activating agent	Nucleophilic promoter (Lewis base)	Yield [%][a,b]	*ee* [%][c]
1	**2**	(−)-Tet·HCl (150 mol%)	35	98
2	*p*-NO_2-$C_6H_4SO_2Cl$	(−)-Tet·HCl (25 mol%)	11	67
3	CDI	(−)-Tet·HCl (25 mol%)	34	1.8
4	3,5-$(NO_2)_2$BzCl	(−)-Tet·HCl (25 mol%)	25	ND
5	*p*-TsCl	(−)-Tet·HCl (25 mol%)	23	53
6	*p*-TsCl	(*S*)-BTM (**5**, 20 mol%)	33	20
7	*p*-TsCl	(*S*)-HBTM (**6**, 20 mol%)	58	96[d]
8	**2**	(*S*,*R*)-Napth/Me-HBTM (**7**, 20 mol%)	40	91[d]

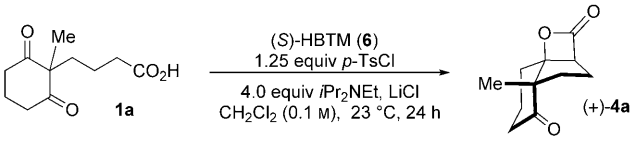
[a] Single diastereomer observed by ^{1}H NMR. [b] Yield of isolated, purified products. [c] Determined by chiral GC analysis. [d] HBTM (**6**) and Napth/Me-HBTM (**7**) provide (+)-**4b**. CDI = carbonyldiimidazole, Bz = benzoyl, Ts = tosyl, Napth = napthyl.

screening of alternative activating agents using 25 mol% (−)-Tet·HCl (**3**) showed that Mukaiyama reagent **2**[3b] could be replaced with *p*-nitrobenzenesulfonyl chloride (*p*-$NO_2C_6H_4SO_2Cl$), carbonyldiimidazole (CDI), 3,5-dinitrobenzoyl chloride (3,5-$(NO_2)_2$BzCl), and *p*-toluenesulfonyl chloride (*p*-TsCl) in conjunction with (−)-Tet·HCl (**3**) to provide tricyclic β-lactone **4** in varying yields and enantioselectivities (Table 1, entries 2–5). However, the maximum yield obtained with these activating agents was 34% using CDI but enantioselectivities were diminished, most likely as a result of the ability of imidazole to serve as an achiral nucleophilic promoter for the NCAL process. Although TsCl gave poor yields and only 53% *ee* (Table 1, entry 5), we decided to pursue this activating agent with other nucleophilic promoters because of its availability and low cost.

We next explored more nucleophilic chiral catalysts and modified the conditions in an attempt to render this process catalytic. Initial screening of several chiral isothiourea acylation catalysts developed by Birman gave very promising results. Use of 20 mol% (*S*)-HBTM (**6**)[8] provided up to 58% yield and 96% *ee* of the desired tricyclic β-lactone (+)-**4b** with *p*-TsCl as an activating agent (Table 1, entry 7); this was superior to the use of Mukaiyama reagent **2** as an activating agent and stoichiometric (−)-Tet·HCl (**3**) in terms of conversion (cf. Table 1, entry 1). Other related catalysts, such as benzotetramisole ((*S*)-BTM, **5**)[7] or (*S*,*R*)-Napth/Me-HBTM (**7**),[10] led to lower yields and enantioselectivities compared to (*S*)-HBTM (Table 1, entries 6 and 8). Various substrate concentrations (0.05–0.15 M) and reaction times (21–72 h) were also studied with dione keto acid **1b**, and optimal conversion and enantioselectivity were observed at a concentration of 0.10 M after 24 hours.

Although yields for the catalytic process were now comparable to those of the stoichiometric reaction, we sought to further improve conversion. We turned our attention to the use of mild Lewis acids as co-catalysts, as previously demonstrated by Nelson et al.[11] and Calter et al.[12] for intermolecular β-lactone synthesis. We began our studies with LiCl, an inexpensive, commercially available Lewis acid, which was previously reported to serve a bifunctional role to both stabilize metal enolates and assist in ring opening of aziridines.[13] Addition of 25 mol% of LiCl with substrate **1a** (Table 2, entry 2) did indeed lead to a meas-

Table 2: Optimization of the NCAL reaction using LiCl as co-catalyst leading to β-lactone (+)-**4a**.



Entry	(*S*)-HBTM (**6**) [Equiv]	LiCl [Equiv]	Yield [%][a,b]	*ee* [%][c]
1	0.2	none	59	97
2	0.2	0.25	72	93
3	0.2	0.5	80	91
4	0.2	1.0	93	90
5	0.2	2.0	71	93
6	0.1	1.0	82	90

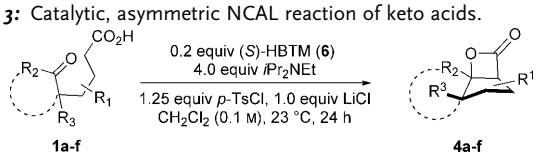
[a] Single diastereomer (d.r. > 19:1) observed by ^{1}H NMR spectroscopy. [b] Yield of isolated, purified products. [c] Determined by chiral GC analysis.

urable increase in yield from 59% without LiCl (Table 2, entry 1) to 72% with only a slight decrease in enantiopurity (97→93% *ee*). Increasing the amount of LiCl to 1.0 equivalent provided further increases in yield to 93% (90% *ee*, Table 2, entry 4). However, addition of more than 1.0 equivalent of LiCl did not offer further improvements (Table 2, entry 5). Employing 1.0 equivalent of LiCl also allowed decreased catalyst loading of (*S*)-HBTM to 10 mol% to provide an 82% yield (90% *ee*) of the desired tricyclic β-lactone **4b** (Table 2, entry 6). In general, we found the use of 0.2 equivalents of catalyst and 1.0 equivalent of LiCl to be an ideal compromise between yield and optical purity of the β-lactone product.

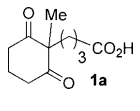
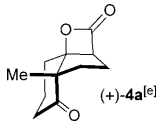
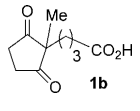
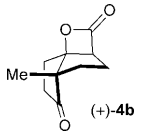
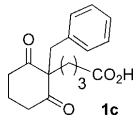
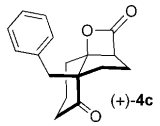
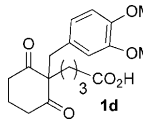
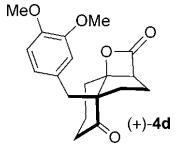
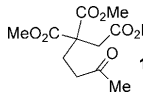
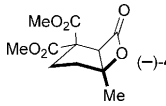
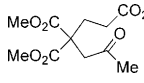
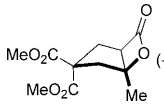
The LiCl-assisted variant of the NCAL process was then applied to a variety of keto acids[14] under optimized conditions with TsCl as activating agent, which provided good to high yields and typically high enantioselectivities for

both bi- and tricyclic β-lactones (Table 3). Comparisons were made to reactions without added LiCl and in general higher yields (18–34% increase) were observed with only slight reductions in enantiopurity (0–8% *ee* decrease). Thus, if higher enantiopurities of β-lactone adducts are desired, then LiCl can be omitted at the expense of yield. The NCAL process was readily run on the gram scale with keto acid **1b** without loss in optical purity but with some erosion of yield (65 vs. 77%, Table 3, entry 2).

Table 3: Catalytic, asymmetric NCAL reaction of keto acids.

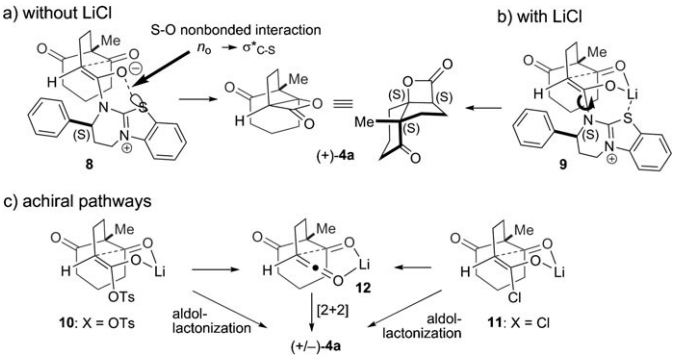


1a-f **4a-f**

Entry	Keto acid	β-Lactone[a]	Yield [%][b,c]	*ee* [%][c,d]
1	 **1a**	 (+)-**4a**[e]	93 (59)	90 (97)
2	 **1b**	 (+)-**4b**	77 (59) 65[f]	96 (96) 96[f]
3	 **1c**	 (+)-**4c**	70 (36)	87 (95)
4	 **1d**	 (+)-**4d**	73 (48)	84 (92)
5	 **1e**	 (−)-**4e**	85[g] (68)	98[g] (94)
6	 **1f**	 (+)-**4f**	71 (47)	>98[h] (>98)[h]

[a] Single diastereomers were observed by crude ^{1}H NMR spectroscopy (d.r. > 19:1) in all cases. [b] Yield of isolated, purified products. [c] Yields and optical purities in parentheses are from reactions without LiCl. [d] All optical purities were determined by chiral GC analysis, except for **4d**, which was analyzed by chiral HPLC. [e] The absolute configuration of the known β-lactone **4a** was assigned by comparison of optical rotations to published data.[18] The absolute configurations of other β-lactones were assigned by analogy. [f] Yield and optical purity refer to a 1 gram scale reaction. [g] 0.5 equiv of LiCl was used in this reaction. [h] The minor enantiomer was not detected by chiral GC.

We propose the transition state arrangements shown in Scheme 3, which build on models by Birman and which are also consistent with the absolute stereochemical outcome of the NCAL process. Without added LiCl, a transition state arrangement that invokes the $n_O \rightarrow \sigma^*_{C-S}$ nonbonded interaction previously invoked by Birman[15] leads to a preferred

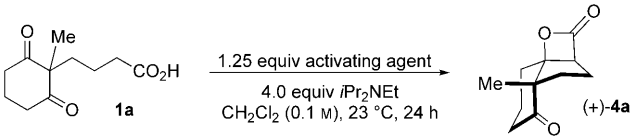


Scheme 3. Proposed transition states for the NCAL reaction of dione acid **1a**: a) without LiCl, b) with LiCl, and c) possible achiral pathways.

approach of the ammonium enolate to the ketone of the cyclohexanedione, which minimizes interactions with the phenyl ring of the catalyst (see **8**, Scheme 3a). In the presence of LiCl, a similar transition-state arrangement is possible; however, in this case, this arrangement may be further enforced by replacement of the $n_O \rightarrow \sigma^*_{C-S}$ interaction with Li–S chelation, thus leading to a bicyclic chairlike transition-state arrangement **9** that includes activation of the ketone possibly leading to increased conversion (Scheme 3b).[16] However, if the Li–S chelation is absent, the loss of the $n_O \rightarrow \sigma^*_{C-S}$ interaction with added LiCl would be expected to provide lower enantioselectivity as observed, because of greater freedom of rotation around the indicated C–N bond of the ammonium enolate **9** (Scheme 3b). Furthermore, LiCl may also lead to the tosyl ester enolate **10** or promote further conversion to an acid chloride and the corresponding enolate **11**, and both could undergo aldol lactonization in an achiral manner leading to lower enantioselectivity, as generally observed with added LiCl (Scheme 3c). Generation of an acid chloride may also promote ketene formation leading to an achiral [2+2] cycloaddition pathway (cf. **12**→(±)-**4a**).[17]

To investigate putative, competitive achiral pathways, the NCAL reaction was run without (*S*)-HBTM (**6**) and this gave β-lactone **4a** in 18% yield (Table 4, entry 1), which indicated

Table 4: Exploring the role of Lewis acid co-catalyst and activating agents in the NCAL reaction with keto acid **1a**.

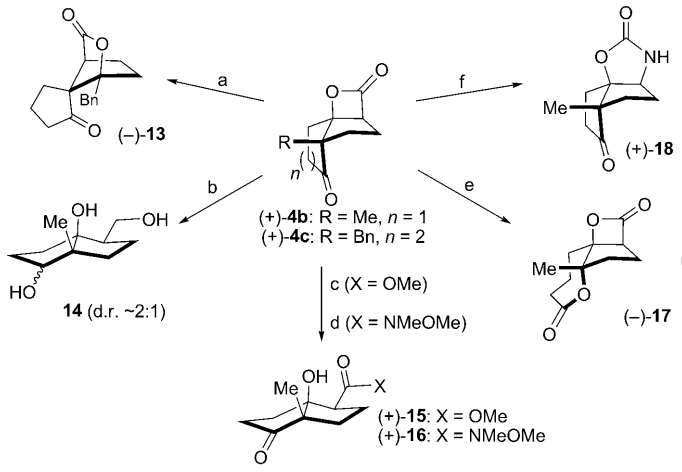


1a (+)-**4a**

Entry	Lewis base	Activating agent	Lewis acid (equiv)	Yield [%][a]	*ee* [%][b]
1	none	TsCl	LiCl (1.0)	18	–
2	none	TsCl	none	7	–
3	none	TsOTs	$LiClO_4$ (1.0)	≈16[c]	–
4	none	TsOTs	none	≈20[c]	–
5	0.2 equiv (*S*)-HBTM (**6**)	TsOTs	$LiClO_4$ (1.0)	21	91

[a] Yield of isolated, purified products. [b] Determined by chiral GC analysis. [c] Approximate yield due to inseparable minor impurity.

the availability of an achiral pathway leading to a racemic product. When performed in the absence of both nucleophile and LiCl, the yield of β-lactone was reduced to 7%, which suggested an achiral pathway promoted to some extent by LiCl (Table 4, entry 2). This prompted us to study the use of tosic anhydride as activating agent, both with and without $LiClO_4$, in an effort to remove all chloride counterion.[11,12] Even under these conditions, without added Lewis base, a considerable amount of β-lactone was formed (≈16–20%, Table 4, entries 3 and 4). In the presence of (*S*)-HBTM (**6**) under these latter conditions, enantioselectivities were similar (91% *ee*) but yields were greatly reduced (21%, Table 4, entry 5). This suggests that the chloride ion is not detrimental to enantioselectivity and may in fact promote the rate of the NCAL process, possibly through formation of acid chloride and/or ketene intermediates leading to an increased rate for generation of the required acyl ammonium intermediate (Scheme 4). Further mechanistic studies are underway to gain a better understanding of this process.



Scheme 4. Reagents and conditions: a) $ZnCl_2$ (2.2 equiv), CH_2Cl_2, 23 °C, 48 h, 78%; b) DIBAl-H (6.0 equiv), CH_2Cl_2, 0 °C, 3 h, 60% (d.r. ≈ 2:1); c) MeOH, K_2CO_3 (1.3 equiv), 23 °C, 3 h, 83%; d) HNMeOMe·HCl (1.4 equiv), iPr_2NEt, 2-hydroxypyridine, CH_2Cl_2, 23 °C, 20 h, 78%; e) *m*-CPBA (3.0 equiv), Na_2HPO_4 (8.0 equiv), CH_2Cl_2, 23 °C, 5 days, 23% (68% rec SM); f) i) NaOH (5.4 equiv), THF/H_2O, 23 °C, 3.5 h; ii) DPPA (1.1 equiv), Et_3N, $PhCH_3$, reflux, 36 h, 36% (2 steps). Bn = benzyl, DIBAl-H = diisobutylaluminum hydride, *m*-CPBA = *meta*-chloroperbenzoic acid, DPPA = diphenylphosphoryl azide.

To demonstrate the utility of these tricyclic β-lactones for accessing structural diversity through the inherent reactivity of the β-lactone moiety, we explored several transformations that significantly alter the topology of these compounds (Scheme 4). A dyotropic process delivers the tricyclic bridged γ-lactone **13** under modified conditions with $ZnCl_2$ compared to that reported previously.[19] Simple reduction and nucleophilic addition under mild conditions delivers the triol **14** and hydroxy ester **15** and amide **16**, respectively. Mild Baeyer–Villiger oxidation under buffered conditions delivers the ring-expanded bis-lactone **17** without consequence to the β-lactone. Finally, hydrolysis followed by Curtius rearrangement/intramolecular trapping delivers the tricyclic oxazolidinone **18**.

In conclusion, a practical, catalytic, asymmetric NCAL process of keto acids was developed that highlights a novel utility of Birman's homobenzotetramisole derivative (HBTM, **6**). The optimized process, which makes use of inexpensive TsCl as an activating agent and LiCl as mild Lewis acid co-catalyst, provides bi- and tricyclic β-lactones in excellent enantioselectivities and good to excellent yields, and demonstrates the first catalytic desymmetrization through the NCAL process. The use of LiCl as a Lewis acid co-catalyst substantially increased yields of a variety of β-lactone systems with only slight reduction in enantioselectivity in some cases. The process has added value for structural diversity given the inherent reactivity of the β-lactone nucleus, as demonstrated by subsequent dyotropic rearrangement, ring expansions to oxazolidinones, and simple reductions and ring openings. Moreover, Baeyer–Villiger oxidations can be performed with the resident ketone without detriment to the β-lactone. The enantioselective NCAL process with keto acids represents a mild, versatile, and highly practical strategy for rapid construction of complexity leading to optically active carbocyclic frameworks, which should find great utility in natural product and diversity-oriented synthesis. Studies along these lines continue in our laboratory.

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