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Enantioselective Synthesis of Medium-Sized Lactams Employing Chiral α,β-Unsaturated Acylammonium Salts**

Guowei Kang,[a] Masaki Yamagami,[b] Sreekumar, Vellalath[a] and Daniel Romo*[a]

Abstract: Medium-sized lactams are important structural motifs found in a variety of bioactive compounds and natural products but are challenging to prepare especially in optically active form. A Michael-proton transfer lactamization organocascade process is described that delivers medium-sized lactams including azepanones, benzazepinones, azocanones and benzazocinones in high enantiopurity through the intermediacy of chiral, α, β-unsaturated acylammonium salts. An unexpected indoline synthesis was also uncovered and the benzazocinone skeleton was transformed into other complex heterocyclic derivatives including spiroglutarimides, isoquinolinones and δ- lactones.

Medium-sized nitrogen heterocycles, including seven and eight membered lactams, are structural motifs found in a variety of bioactive compounds and natural products (Figure 1).[1] However, access to these heterocycles is challenging due to unfavorable enthalpic and entropic barriers in transition states leading to medium-sized rings due to developing Pfitzer, Baeyer, and transannular strain.[2]

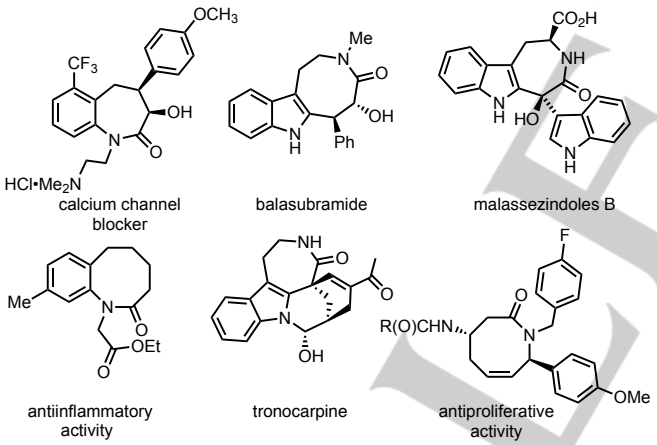
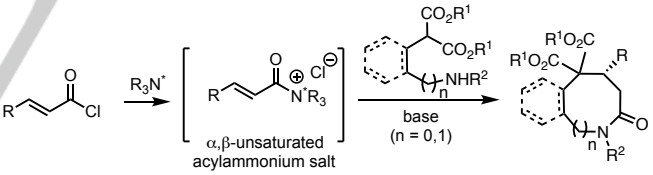


Figure 1. Bioactive compounds including natural products possessing medium-sized nitrogen heterocyclic cores.

While significant efforts have been made toward the synthesis of medium-sized lactams,[3] enantioselective strategies[3b, 3d, 4] lag significantly behind those for 5-and 6-membered lactams despite their presence in natural products and pharmaceuticals.

Recently, chiral α,β-unsaturated acylammonium salts have become versatile intermediates for organocatalysis[5] due to their ready accessibility and their divergent reactivity.[6] The potential of chiral α,β-unsaturated acylammonium salts was first realized by Fu through a described net [3+2] annulation to deliver diquinanes.[7] Following this seminal work, recent reports by Lupton,[8] Rodriguez,[9] Smith,[10] Matsubara[4, 11] Birman[12] and our group[[13] have started to reveal the broad utility of chiral α,β-unsaturated acylammonium salts for accessing numerous optically active products. Toward an enantioselective strategy for medium-sized rings, we considered application of the nucleophile (Lewis base)-catalyzed Michael-proton transfer-lactamization (NCMPL) organocascade previously employed to access optically active γ- and δ- lactams[13e] (Scheme 1). Herein, we describe successful implementation of this strategy for the synthesis of azepanones, benzazepinones, azocanones and benzazocinones in high enantiopurity. Further transformations of the benzazocinone skeleton are also reported along with an unexpected synthesis of an indoline bearing three stereogenic centers.



Scheme 1. Nucleophile (Lewis base)-catalyzed Michael/proton transfer/ lactamization (NCMPL) organocascade for medium-sized lactam synthesis

Our initial studies employed tosyl-protected amino malonate **1a** as a bis-nucleophile and crotonyl chloride (**2a**) as a Michael acceptor (Table 1). Employing reaction conditions previously developed for the NCMPL leading to 5- and 6-membered lactams, namely LiHMDS/DBU as Brönsted base and TMSQD as the Lewis base catalyst with slow addition of acid chloride **1a**[13e] failed to afford any of the targeted benzazocinone (+)-**3a**. This only led to the *N*-acylation product **3a'** (4% yield) along with recovered **1a** (62%) (entry 1). We next studied enolization under thermodynamic conditions employing Hünig's base and LiCl at ambient temperature (23 °C). Under these conditions, the benzazocinone (+)-**3a** was isolated in 55% yield with high enantiomeric purity (98:2 er, entry 2). Solvents were briefly screened and both CH_2Cl_2 and toluene were useful solvents with the latter providing the best yield of (+)-**3a** (74%) without erosion of enantiomeric purity (entries 3,4). A brief evaluation of other Brönsted bases with stoichiometric K_2CO_3[14] did not lead to

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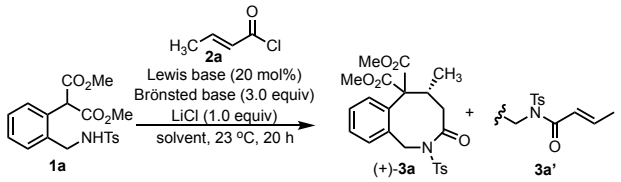
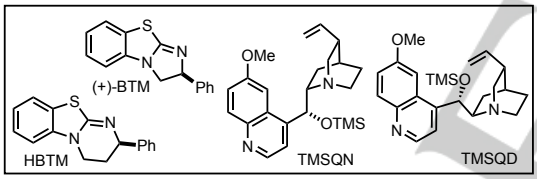
improved results (entries 5, 6). Other chiral Lewis base catalysts, including BTM and HBTM, were examined but only delivered trace quantities of the desired benzazocinone (+)-**3a** (entries 7, 8). Reducing the catalyst loading from 20 to 10 mol % gave slightly reduced yields and enantioselectivity (entry 9). The importance of LiCl in this reaction was revealed by omitting this additive which led to greatly inferior results (entry 10). The enantiomeric benzazocinone (–)-**3a** could be obtained by use of TMSQD (71% yield, 91:9 er).

Table 1: Optimization of the enantioselective Michael-proton transfer-lactamization organocascade toward benzazocinone (+)-**3a**



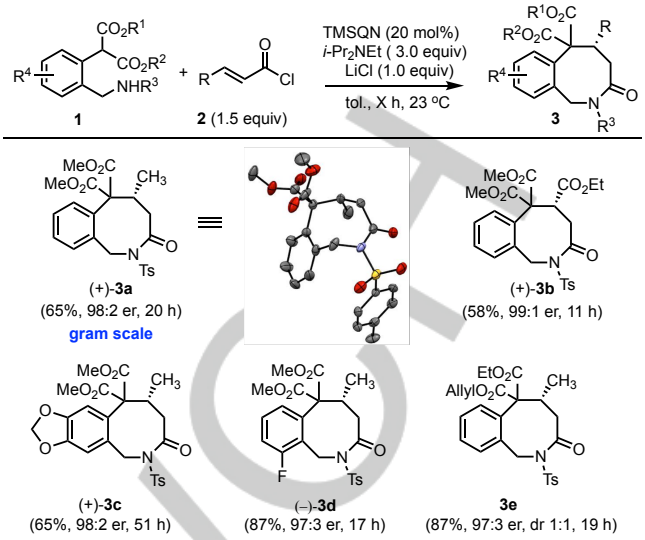
entry[a]	solvent	Lewis base (equiv)	Brönsted base	yield %[b]	er[c]
1[d,e]	THF	TMSQD	LiHMDS with DBU	0	nd
2	THF	TMSQN	*i*-Pr$_2$NEt	55	98:2
3	CH_2Cl_2	TMSQN	*i*-Pr$_2$NEt	60	98:2
4	toluene	TMSQN	*i*-Pr$_2$NEt	74	98:2
5	toluene	TMSQN	DBU	<5	nd
6[f]	toluene	TMSQN	DBU with K_2CO_3	nd	nd
7	toluene	(+)-BTM	*i*-Pr$_2$NEt	<5	nd
8	toluene	HBTM	*i*-Pr$_2$NEt	<5	nd
9	toluene	TMSQN[g]	*i*-Pr$_2$NEt	71	94:6
10[h,i]	toluene	TMSQN	*i*-Pr$_2$NEt	<5	nd
11[ij]	toluene	TMSQD	*i*-Pr$_2$NEt	71	9:91



[a] The reactions were performed with 1.0 equiv of **1a**, 1.5 equiv of **2a** and 1.0 equiv of LiCl and acid chloride **2a** was added over 5 h via syringe pump. [b] Yields of isolated product. [c] Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. [d] The reaction was conducted at -30 °C with 1.05 equiv of LiHMDS and 1.0 equiv of DBU. [e] 4% of **3a'** was isolated and 62% of **1a** was recovered. [f] 0.2 equiv of DBU and 3.0 equiv of K_2CO_3 were used. [g] 10 mo% of TMSQN was employed. [h] LiCl was not added. [i] **3a'** (9%) was isolated along with recovered **1a** (44%). [j] Use of TMSQD gave the enantiomeric benzazocinone (−)-**3a**.Ts = 4-toluenesulfonyl, THF = tetrahydrofuran, DIPEA = *N,N*-Diisopropylethylamine, DBU = 1,8-Diazabicyclo[5.4.0] undec-7-ene, TMS = trimethylsilyl, BTM = benzotetramisole, HBTM = homobenzo tetramisole

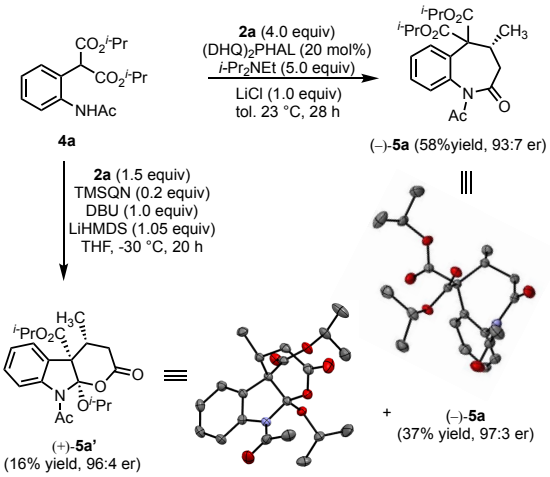
The substrate scope with other acid chlorides and variously substituted-aryl malonates toward benzazocinones was briefly explored. Both electron donating and withdrawing substituents on the aromatic ring of the benzo malonates were tolerated affording the corresponding benzazocinones (+)-**3c** and (-)-**3d** (Table 2). The allyl, ethyl malonate **1e** was studied with an eye towards subsequent Pd-catalyzed transformations (*vide infra*) delivering benzazocinone **3e** in 87% yield (97:3 er) as the expected mixture of diastereomers (dr 1:1). The synthesis of benzazocinone (+)-**3a** was repeated on gram scale and led to comparable yields and enantioselectivity (65%, 98:2 er). In addition, this crystalline benzazocinone enabled absolute configuration assignment by anomalous dispersion effects in single crystal X-ray crystallographic analysis (inset, Table 2). The absolute configuration of other medium-sized rings obtained with TMSQN as Lewis base were assigned by analogy.

Table 2: NCMPL organocascade for the synthesis of benzazocinones **3**



[a] The reactions were performed with 1.0 equiv of malonates **1a-d,** 1.5 equiv of acid chlorides **2a-b** and the latter was added over 5 h via syringe pump and then the reactions were stirred for times indicated in parentheses. [b] Yields are provided for isolated, purified product. [c] Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. [d] Inset is the ORTEP representation of the single-crystal X-ray structure of (+)-(*R*)-**3a**; thermal ellipsoids shown at 50% probability.

Several benzazepinones are modulators of γ-secretase[1a] and serve as longer acting and more potent antihypertensive agents than the often prescribed diltiazem bearing a benzothiazepine core.[1c] We therefore targeted a representative benzo-fused lactam (–)-**5a** (Scheme 2). After a brief study of substrates including variations of the malonate and the aniline *N*-protecting group (see SI), the desired benzazepinone (–)-**5a** was obtained in 58% yield and 93:7 er from malonate **2a** using (DHQ)$_2$PHAL (20 mol%). A more sterically incumbered malonate, namely diisopropyl diester **4a**, was required to slow intramolecular γ-lactamization of the substrate. Unexpectedly, under kinetic conditions, the complex indoline (+)-**5a'** was obtained (16%, 96:4 er) along with lactam (–)-**5a** (37% yield, 97:3 er). The structure of these adducts was confirmed by X-ray analysis (inset, Scheme 2).



Scheme 2. Synthesis of benzazepinone (–)-**5a** and an unexpected indoline (+)-**5a'**

Proposed reaction pathways leading to the indoline (–)-**5a** and benzazepinone (+)-**5a'** (and by analogy, benzazocinones **3**) are provided (Scheme 3). Kinetic enolate **II** undergoes Michael addition with the unsaturated acylammonium salt **I** generating ammonium enolate **III**. Proton transfer leads to acylammonium

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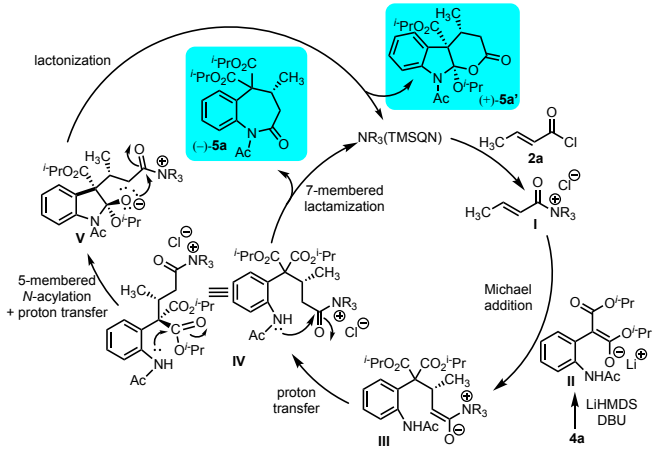
salt **IV** enabling subsequent 7-membered lactamization affording benzazepinone (–)-**5a**. Alternatively, the aniline nitrogen can engage the pro-(*S*) isopropyl ester, guided by the adjacent stereocenter, generating tetrahedral intermediate **V**, which undergoes lactonization to form tricyclic indoline (+)-**5a'**.



Scheme 3. Proposed reaction pathways leading to benzazepinone (–)-**5a** and indoline (+)-**5a'**

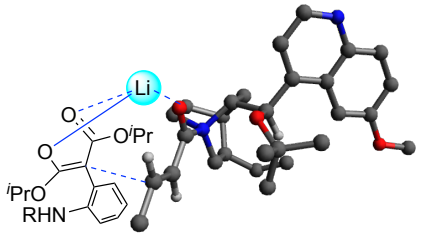
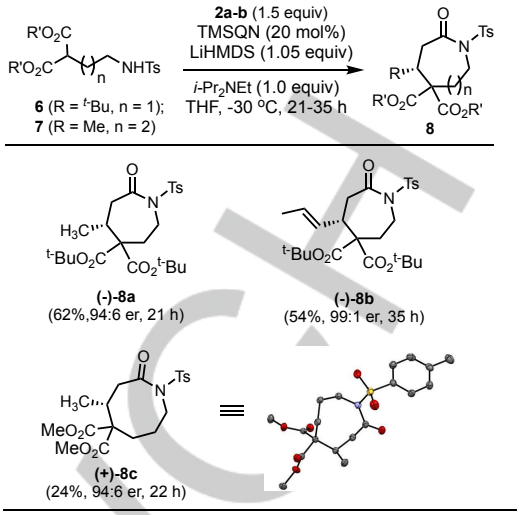


Figure 2. Proposed transition state arrangement for the Michael addition showing potential role of the Li cation in organizing the transition state

Based on our previous studies[13e] and those of Lectka,[15] we propose the transition state arrangement shown for the stereochemical-setting Michael addition of the NCMPL process (Figure 2). The TMS group of TMSQN effectively blocks the *Re* face of the unsaturated acylammonium salt which in concert with the extended *s*-trans conformation enforces addition of the malonate anion to the *Si* face. Coordination of the Li cation with both the enolate and the acylammonium carbonyl leads to an ordered transition state and thus greater enantioselectivity.

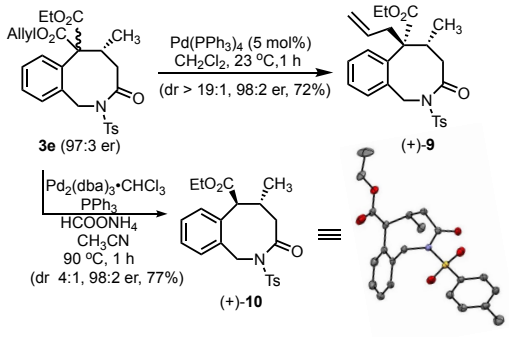
We also investigated the synthesis of monocyclic lactams through this Michael-initiated organocascade process. Use of a kinetic, strong base worked best for these substrates and enabled synthesis of azepanones (–)-**8a** (62% yield, 94:6 er) and (–)-**8b** (54% yield, 99:1 er) from tosyl-protected di-*tert*-butyl amino malonates **6** as bis-nucleophiles and crotonyl and sorbic chlorides, respectively. Additionally, azocanone (+)-**8c** could be accessed with good optical purity (94:6 er) albeit in modest yield (24%). Use of ethyl fumaroyl chloride as a Michael acceptor led to a racemic δ-lactam **8'** in 46% yield (confirmed by X-ray analysis) presumably formed through an *N*-acylation pathway (see SI for details).

Table 3: NCMPL for the synthesis of azepanones and azocanones



[a] The reactions were performed with 1.0 equiv of **6** or **7** and acid chlorides **2a-b** were added over 5 h via syringe pump with total reaction time provided in parentheses. [b] Yields refer to isolated and purified adducts. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [d] Inset is the ORTEP representation of the single-crystal X-ray structure of (+)-**8c**, thermal ellipsoids shown at 50% probability.

We next studied transformations of the allyl, ethyl malonate bearing benzazocinone (+)-**3e**. Subjecting to the decarboxylative allylation conditions reported by Ohta[16] led to allylated benzazocinone (+)-**9** with high diastereoselectivity in 72% yield bearing a new quaternary carbon center (dr > 19:1) directed by the adjacent stereocenter. Employing reductive conditions with $HCOONH_4$,[17] delivered ester (+)-**10** in 77% yield with moderate diastereoselectivity (dr 4:1) and the relative stereochemistry of the major diastereomer was confirmed as *anti* by X-ray analysis (Scheme 4).



Scheme 4. Decarboxylative allylation and deallylative decarboxylation of benzazocinone **3e**

Benzazocinone (+)-**3a** was detosylated with Mg° in MeOH to afford lactam (–)-**11** (74% yield, Scheme 5).[18] Reduction of (+)-**3a** using a bulky hydride donor, $LiAlH[OC(CH_3)_3]_3$, did not afford diastereoselectivity by selective reduction of one of the prochiral esters (dr 1:1), but gave ring-opened ester aldehyde **12** in which the liberated methoxide led to ring opening of the tosyl lactam. Further reduction of aldehyde **12** with $NaBH_4$ led to δ-lactones **13** (74% yield, dr 1:1) through lactonization of the derived alcohol.

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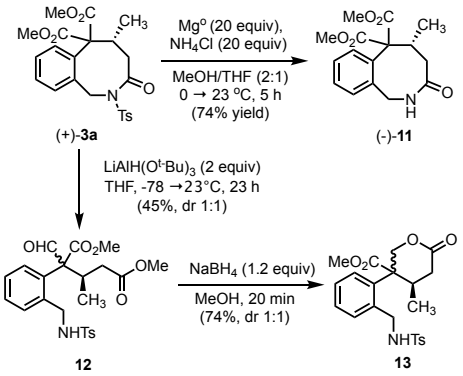
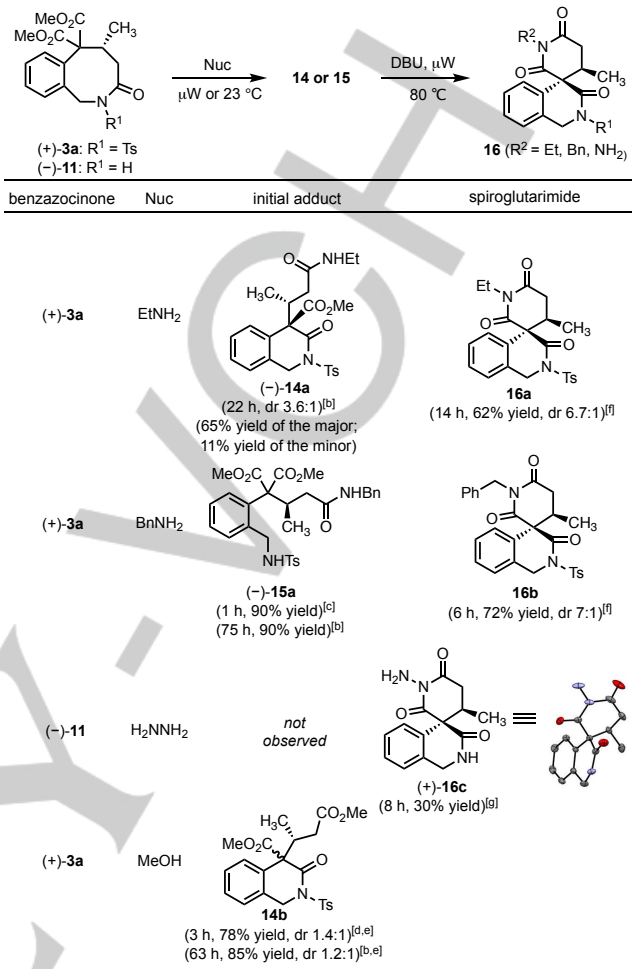


Scheme 5. Detosylation and δ-lactone formation from benzazocinone (+)-**3a**

We next explored addition of various nucleophiles to both the tosylated and detosylated benzazocinones, (+)-**3a** and (–)-**11**. Ring opening of benzazocinone (+)-**3a** with $EtNH_2$ afforded isoquinolinone analogue **14a** (65%) proceeding through presumed ring-cleavage of the benzazocinone ring followed by intramolecular lactamization with moderate diastereoselectivity (dr. 3.6:1). On the other hand, addition of benzyl amine delivered only the ring-opened amide (–)-**15a** in 90% yield, without lactamization, when conducted at room temperature (75 h) or with microwave heating (1 h). Subsequent treatment of the amides **14a** and **15a** with DBU afforded spiroglutarimides **16a** and **16b** (62% and 72% respectively) with some degree of diastereotopic group (methyl ester) selectivity (6.7:1 and 7:1, respectively). Addition of hydrazine to the detosylated benzazocinone (–)-**11** directly afforded the spiroglutarimide (+)-**16c** (30% yield) and confirmed by X-ray analysis. Finally, treatment of benzazocinone with MeOH, in a similar manner to reaction with ethylamine, led to ring cleavage and lactamization delivering esters **14b** (dr 1:1).

In conclusion, we developed a direct, organocatalytic method for the asymmetric synthesis of medium-sized heterocycles including azepanones, benzazepinones, azocanones and benzazocinones. These are prepared from commodity acid chlorides and readily available amino malonates through the intermediacy of chiral α,β-unsaturated acylammonium salts. The organocascade involves a Michael addition-proton transfer-medium-sized ring lactamization. An unexpected tricyclic indoline (+)-**5a'** was prepared through interception of a tetrahedral intermediate during the organocascade process. Addition of various nucleophiles to the derived benzazocinone led to simple cleavage of the medium sized-ring but also subsequent δ-lactam formation delivering isoquinolinones and spirolactamization leading to spiroglutarimides. An additional stereocenter, including a quaternary carbon center, was introduced onto the benzazocinone ring through a deallylative decarboxylation or decarboxylative allylation, respectively. The described methodology expands the utility of unsaturated acylammonium salts to the synthesis of medium-sized nitrogen heterocycles.

Table 4: Transformations of benzazocinones (+)-**3a** and (–)-**11**[a]



[a] Isolated yields are indicated for all reactions and relative stereochemistry was assigned by comparison with the structure of (+)-**16c** which was confirmed by X-ray analysis (inset, ORTEP representation of single-crystal X-ray structure; thermal ellipsoids are shown at 50% probability.). [b] The reaction was performed at 23 °C without microwave irradiation [c] The reaction was performed using microwave irradiation at 100 °C. [d] The reaction was performed using microwave irradiation at 70 °C. [e] DBU was added to this reaction. [f] 4 Å MS were added. [g] The reaction was performed at 105 °C in the absence of DBU.

Keywords: medium-ring compounds •Michael addition • organocatalysis•enantioselectivity• medicinal chemistry

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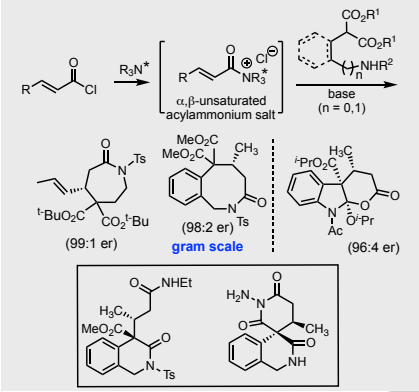
Mid-sized, no problem. A Michael-proton transfer-lactamization organocascade delivers medium-sized lactams including azepanones, benzazepinones, azocanones and benzazocinones via α, β-unsaturated acylammonium salt intermediates with high enantioselectivity. The benzazocinones are converted to spiroglutarimides and isoquinolines. An unexpected indoline is also prepared from capture of a tetrahedral intermediate in this organocascade.



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Enantioselective Synthesis of Medium-Sized Lactams Employing Chiral α,β-Unsaturated Acylammonium Salts