Heterocycle Synthesis

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Entry to Heterocycles Based on Indium-Catalyzed Conia-Ene Reactions: Asymmetric Synthesis of (−)-Salinosporamide A**

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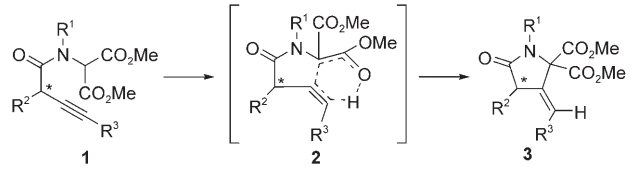
The importance of nitrogen-containing heterocycles as drugs and other chemical entities continue to inspire the development of tactical methods for their synthesis. In connection with a project directed towards the synthesis of intriguing natural products[1] having a highly functionalized pyrrolidinone core, such as salinosporamide A, lactacyctin,[2] and oxazolomycins,[3] we became interested in developing a novel approach which relied upon the Conia-ene reaction of amidomalonate **1** to give pyrrolidinone **3** via **2** (Scheme 1).



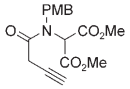
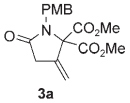
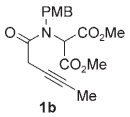
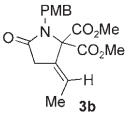
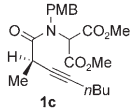
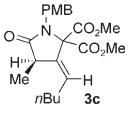
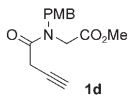
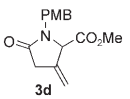
Scheme 1. An approach to preparation of pyrrolidinones by the Conia-ene reaction.

Recently, in place of the original thermal Conia-ene reaction,[4] a number of metal-catalyzed reactions that are carried out under mild conditions have been devised for the preparation of carbocycles[5,6] and heterocycles,[7,8] although the latter are largely limited to 3-methylene pyrrolidines and tetrahydrofurans. However, it was unknown whether metal-catalyzed versions of the Conia-ene reaction would be applicable to our envisaged transformation (Scheme 1). Herein, we report a new route to pyrrolidinones and other heterocycles based on the indium-catalyzed Conia-ene-type cyclization of nitrogen- and oxygen-tethered acetylenic malonic esters. We also demonstrate the utility of this reaction by its application to the synthesis of (−)-salinosporamide A, a highly potent 20S proteasome inhibitor produced by the marine actinomycete *Salinispora tropi*ca.[9–12]

We examined Au^{I}-,[5a] Ni^{II}-,[5c] and In^{III}-catalyzed[5f,6] reactions of **1a** (Table 1). $In(OTf)_3$ was found to most effectively catalyze the cyclization reaction to give **3a** in 97% yield (Table 1, entries 1–3). The $In(OTf)_3$-catalyzed reaction was also applicable to nonterminal alkynes (Table 1, entries 5–8). It should be highlighted that the cyclization proceeded with complete *E* selectivity and without racemization, even at higher temperatures. Addition of an equimolecular amount of DBU relative to $In(OTf)_3$ markedly accelerated the reaction, (Table 1, entries 3–8) and in particular resulted in better yields for the reactions of nonterminal alkynes **1b** and **1c**. Importantly, no *endo* cyclization and no isomerization of the olefinic double bond (from the β,γ- to the α,β-position) were observed. Treatment of **1d** with $In(OTf)_3$ or $In(OTf)_3$/DBU did not promote the cyclization at all (Table 1, entries 9 and 10), thus suggesting that a malonyl functionality is vital for this cyclization to occur. This structural requirement and the *E* selectivity observed for **1b** and **1c** lead us to propose a catalytic cycle involving carbometalation of indium enolate **4** and proton exchange between alkenylindium **5** and **1** to produce (*E*)-**3** and regenerate **4** (Scheme 2).[13]

Table 2 shows the substrate scope for the $In(OTf)_3$/DBU method. Gratifyingly, this method was found to be applicable

Table 1: Cyclization of amidomalonates **1** to give pyrrolidinones **3**.

Entry	Substrate	Method[a]	*t* [h]	Product[b,c]	Yield [%][d]
1	 **1a**	A	24	 **3a**	0
2		B	0.8		19
3		C	1		97
4		D	0.5		90
5	 **1b**	C	2.5	 **3b**	70
6		D	1		80
7	 **1c** 100% *ee*	C	4	 **3c** 100% *ee*	48
8		D	1		69
9	 **1d**	C	5	 **3d**	0[e]
10		D	4		0[f]

[a] Method A: [AuCl(PPh$_3$)] (5 mol%), AgOTf (5 mol%), CH_2Cl_2, RT. Method B: [Ni(acac)$_2$] (10 mol%), Yb(OTf)$_3$ (7 mol%), 1,4-dioxane, 50°C. Method C: In(OTf)$_3$ (5 mol%), toluene, reflux. Method D: In(OTf)$_3$ (5 mol%), DBU (5 mol%), toluene, reflux. acac = acetylacetonate, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, PMB = *para*-methoxybenzyl, Tf = trifluoromethanesulfonyl. [b] The configurations of **3b** and **3c** were determined by NOESY spectroscopy. [c] The enantiomeric purities of **1c** and **3c** were determined by HPLC on a chiral stationary phase. [d] Yield of isolated products. [e] The corresponding allene was obtained in 15% yield. [f] Decomposed.

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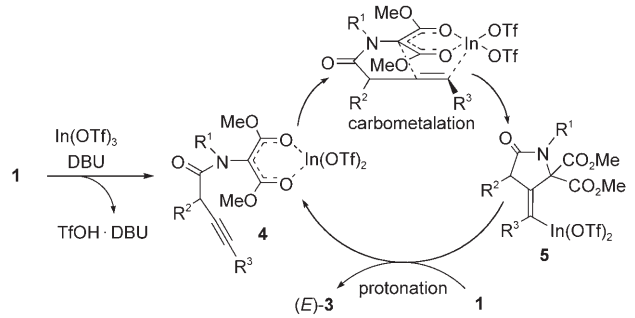
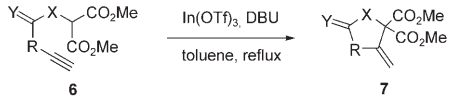
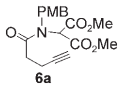
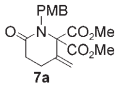
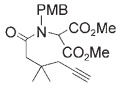
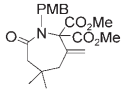
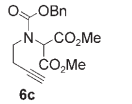
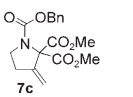
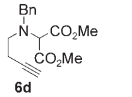
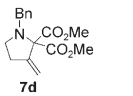
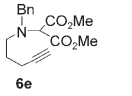
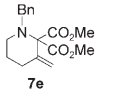
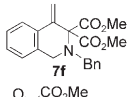
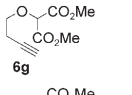
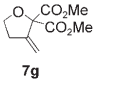
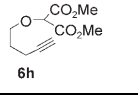
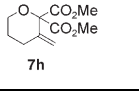


Scheme 2. A plausible reaction mechanism.

to the synthesis of other five- to seven-membered heterocycles such as piperidinone **7a**, azepanone **7b**, pyrrolidines **7c** and **7d**, piperidine **7e**, tetrahydroisoquinoline **7f**, tetrahydrofuran **7g**, and tetrahydropyran **7h** in moderate to excellent yields. In the case of carbamate **6c** (Table 2, entry 3), the reaction was rather sluggish possibly because of the tight coordination of indium(III) to the benzyloxycarbonyl and the ester groups. It should be stressed that even basic amines cleanly underwent the cyclization (Table 2, entries 4–6).

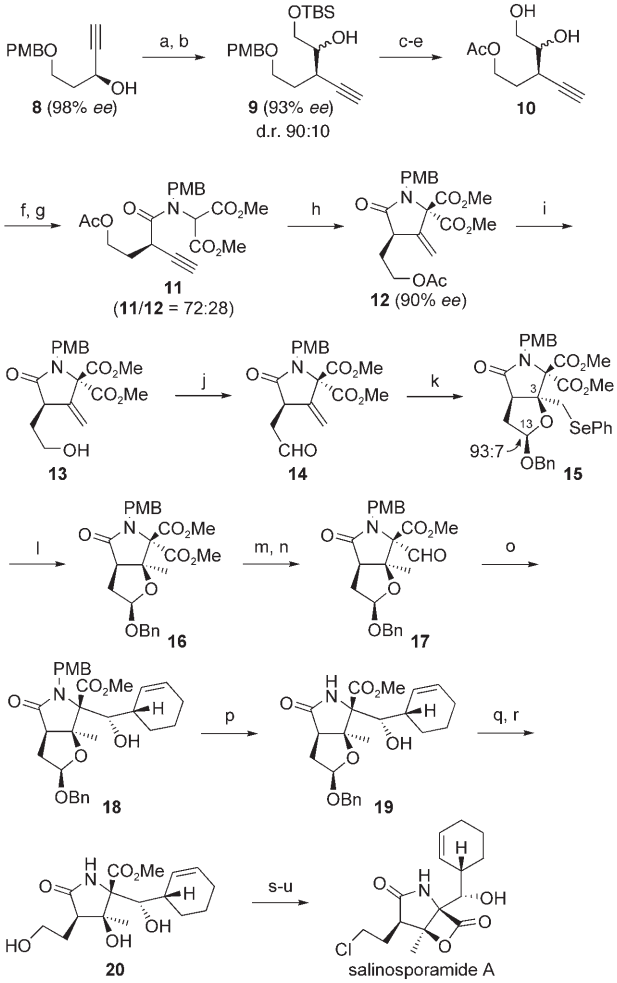
Table 2: In(OTf)$_3$-catalyzed cyclization of **6** to give **7**.



Entry	Substrate	Reaction conditions[a]	Product	Yield [%][b]
1	 **6a**	5 mol% cat., 1 h	 **7a**	84
2	 **6b**	15 mol% cat., 4 h	 **7b**	41
3	 **6c**	10 mol% cat., 3 h	 **7c**	55 (74)[c]
4	 **6d**	5 mol% cat., 5 h	 **7d**	93
5	 **6e**	5 mol% cat., 3 h	 **7e**	93
6	 **6f**	10 mol% cat., 14 h	 **7f**	71
7	 **6g**	5 mol% cat., 2.5 h	 **7g**	74
8	 **6h**	5 mol% cat., 6 h	 **7h**	75

[a] The reactions were carried out in toluene at reflux using In(OTf)$_3$/DBU (1:1) as the catalyst. [b] Yield of isolated products. [c] Yield was calculated based on the consumed starting material.

Scheme 3 illustrates the synthesis of salinosporamide A and shows the synthetic utility of the above-mentioned methodology. Our synthesis began with the preparation of amide **11**, a precursor of the key In(OTf)$_3$-catalyzed cyclization, from the chiral propargyl alcohol **8**.[14] According to the procedure developed by Marshall,[15] **8** was converted into the mesylate, which was then treated with (*tert*-butyldimethylsilyloxy)acetaldehyde via the allenylzinc species to give **9** as a



Scheme 3. Synthesis of (−)-salinosporamide A: a) MsCl, Et_3N, DMAP, CH_2Cl_2, 0°C, 95%; b) $Pd(OAc)_2$, PPh_3, Et_2Zn; then $TBSOCH_2CHO$, THF, −78 to −20°C, 63%; c) DDQ, CH_2Cl_2/H_2O (10:1), 0°C, 87%; d) AcCl, 2,4,6-collidine, CH_2Cl_2, −78°C, quant.; e) TBAF, THF, 0°C, 92%; f) CrO_3, HIO_4, acetone, H_2O, 0°C; g) $(COCl)_2$, DMF, CH_2Cl_2, 0°C; then $PMBNHCH(CO_2Me)_2$, toluene, 75%; h) In(OTf)$_3$ (5 mol%), toluene, 110°C, 96%; i) Lipase PS, phosphate buffer, acetone, 35°C, 89%; j) Dess–Martin periodinane, CH_2Cl_2, 88%; k) PhSeBr, $AgBF_4$, $PhCH_2OH$, CH_2Cl_2, −20 to 0°C, 85%; l) AIBN, $(n\text{Bu})_3SnH$, toluene, 100°C, 83%; m) $NaBH_4$, THF/EtOH, 88%; n) Dess–Martin periodinane, CH_2Cl_2, 94%; o) cyclohex-2-enylzinc chloride, THF, −78°C, 88%; p) CAN, aq MeCN, 0°C, 83%; q) Na, liq. NH_3, THF, −78°C; r) $NaBH_4$, aq THF, 71% (over 2 steps); s) $(Me_2AlTeMe)_2$, toluene; t) BOP-Cl, pyridine, CH_2Cl_2, 54% (over 2 steps); u) Ph_3PCl_2, pyridine, 77%. AIBN = 2,2′-azobisisobutyronitrile, Bn = benzyl, BOP-Cl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride, CAN = ceric ammonium nitrate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-dimethylaminopyridine, Ms = methanesulfonyl, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl.

90:10 mixture of epimers.[16] Upon removal of the PMB group, selective acetylation,[17] and desilylation, **9** afforded **10**. Exposure of **10** to CrO_3 and HIO_4[18] in aqueous acetone gave the corresponding carboxylic acid, which was then condensed with dimethyl 2-(4-methoxybenzylamino)malonate[19] via the acid chloride. Surprisingly during purification by column chromatography on silica gel amide **11** partially underwent cyclization to give an inseparable 72:28 mixture of **11** and **12**.[20] Treatment of this mixture with a catalytic amount of $In(OTf)_3$ in toluene at reflux led to complete conversion of **11** into **12** to give an almost quantitative yield. Notably in this particular case, significant loss of enantiomeric purity of the substrate was not observed. As **12** was very labile under basic conditions, the acetoxy group was hydrolyzed under mild lipase-catalyzed reaction conditions to give alcohol **13**, which was then oxidized to aldehyde **14**. For the assembly of the C3 quaternary center, **14** was subjected to acetal-mediated cationic cyclization as reported by Danishefsky and Endo.[10c] Thus, **14** was treated with phenylselenenyl bromide and $AgBF_4$ in the presence of benzyl alcohol to give **15** (d.r. 93:7 at C13) which, upon radical deselenenylation, afforded **16**. Reduction of **16** with $NaBH_4$ resulted in excellent discrimination of the geminal esters, and aldehyde **17** was obtained as the sole product after oxidation with Dess–Martin periodinane. Reaction of **17** with cyclohex-2-enylzinc chloride under the protocol developed by Corey et al.[10a] yielded **18** as a single stereoisomer. Removal of the PMB group of **18** afforded **19**, which was subjected to reductive ring-opening of the cyclic acetal to give known intermediate **20**.[10a] Finally, upon dealkylative cleavage of the methyl ester promoted by $(Me_2AlTeMe)_2$,[11a,21] β-lactonization, and chlorination, **20** furnished (−)-salinosporamide A. The specific rotation, melting point, and spectroscopic properties of the synthesized natural product were in full accordance with the reported data.[9]

In conclusion, the work presented here provides a new entry to pyrrolidinones and other heterocycles. The key $In(OTf)_3$-catalyzed reaction features broad applicability, atom-economical efficiency, and operational simplicity. The synthesis of (−)-salinosporamide A illustrates the power of this newly developed methodology for natural product synthesis.

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Keywords: Conia-ene reaction · cyclization · heterocycles · indium · synthetic methods

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