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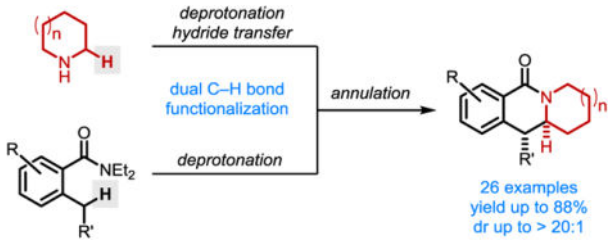
α-C–H/N–H Annulation of Alicyclic Amines via Transient Imines: Preparation of Polycyclic Lactams

Weijie Chen, **Daniel Seidel***
Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida, 32611, United States

Abstract

Polycyclic lactams are prepared in a single operation from *o*-toluamides and cyclic amines in a process that involves transient cyclic imines, species that are conveniently obtained in situ from the corresponding lithium amides and simple ketone oxidants. Imines thus generated, such as 1-pyrroline and 1-piperideine, engage lithiated *o*-toluamides in a facile annulation process. Undesired side reactions such as imine deprotonation and *o*-toluamide dimerization are suppressed through judicious choice of reaction conditions.

Graphical Abstract



The C–H bond functionalization of amines, in particular alicyclic amines, is an attractive strategy for accessing functionalized amines from their parent heterocycles,[1] providing access to valuable pharmacophores.[2] However, despite considerable advances, the vast majority of methods developed to date are incompatible with the presence of an amine N–H bond, limiting their utility to tertiary or protected amines.[3,4] While notable exceptions exist, such as hydroaminoalkylation and electrochemical α-cyanation,[5] these methods are not applicable to direct annulations involving the amine nitrogen atom. Currently, the most general method to achieve the annulation of amines via concomitant N–H and α-C–H bond functionalization appears to be the redox-neutral condensation of amines with aldehydes bearing a covalently linked (pro)nucleophile (e.g., **1** → **2**, Figure 1a).[3j] These transformations are typically facilitated by simple carboxylic acids and have shown to exhibit a rather broad substrate scope.[6] An important limitation of redox-annulations is the

***Corresponding Author**: seidel@chem.ufl.edu.

Supporting Information
Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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need for an activated nucleophilic site on the aldehyde reaction partner. While highly attractive from a synthetic point of view, simple aryl groups and benzylic methyl groups are not sufficiently activated to participate in redox-annulations. In addition, redox-annulations of aldehyde substrates on the lower end of the reactivity scale are typically limited to relatively activated amines such as 1,2,3,4-tetrahydroisoquinoline. Here we report a new method for the α-C–H/N–H annulation of alicyclic amines to provide products that are inaccessible via redox-annulation approaches.

Inspired by seminal studies by Wittig and coworkers published about half a century ago,[7] we recently developed a new method for the α-C–H bond functionalization of secondary amines that utilizes the ability of lithiated amines to act as hydride donors (Figure 1b).[8] Readily available ketones such as benzophenone act as hydride acceptors, facilitating the formation of transient cyclic imine **3** and a lithium alkoxide. Imine **3** subsequently engages an organolithium reagent, resulting in lithium amide intermediate **4**, providing amine **5** upon workup.[8a] In the presence of appropriate Lewis acids, other organometallic species such as Grignard reagents and enolates can also be added to **3**.[8b,8e] While some imines of type **3** (e.g., 1-pyrroline and 1-piperideine) are well-known and have been prepared by other means, their propensity to trimerize[9] has previously limited their broader use in reactions that involve strong nucleophiles.[10] We hypothesized that the hydride transfer strategy to access imine monomers in situ could potentially be applied to an annulation process that further harnesses the reactivity of intermediate **4** without the need for an additional reagent. Specifically, an organolithium nucleophile containing a strategically placed electrophile/leaving group (e.g. **6**), upon reacting with imine **3**, would form lithium amide intermediate **7** (Figure 1c). The latter could subsequently undergo ring-closure to form annulation product **8**. A particularly attractive variant of this strategy would be the synthesis of polycyclic lactams **10** from *o*-toluamides **9**. It should be noted that this processes is significantly more challenging than our previously reported transformations.[8] Due to the increased bulk of the nucleophile, deprotonation of the enolizable imine might become competitive with the desired nucleophilic addition. In addition, the reduced nucleophilicity of the annulation partner can likely not be compensated for by the addition of Lewis acid additives, which are expected to be incompatible with the desired transformations.

The proposed lactam-forming annulation process was evaluated with pyrrolidine and *N,N*-diethyl-*o*-toluamide (**9a**) as the model substrates (Table 1). Motivation for utilizing this substrate combination was provided by the fact that benzoindolizidinones, benzoquinolizidinones, and other compounds related to structure **10** represent important structural motifs found in a range of natural products and synthetic bioactive materials.[11] Methods for the synthesis of such polycyclic compounds remain limited and typically require the multistep construction of the fused rings with a series of functional group interconversions, ultimately limiting the utility of these compounds as a platform for synthesis and drug discovery. While it has been shown that lithiated *N,N*-diethyl-*o*-toluamides undergo the corresponding reaction with acyclic imines and stable, non-enolizable dihydroisoquinolines,[12] the enolizable nature of alicyclic imines and their propensity to rapidly undergo transformation to unreactive imine trimers represent significant challenges (vide supra). Conditions for the deprotonation of **9a** previously

developed by Clark and coworkers were tested first.[12a] Accordingly, **9a** was treated with LDA (1.5 equiv) in THF solution at −78 °C for 30 min, followed by addition of an ether solution of 1-pyrroline. The latter was prepared in a separate flask from pyrrolidine, *n*-BuLi, and benzophenone (2 equiv each). Desired product **10a** was obtained in 34% yield (Table 1, entry 1). In addition, side product **11** was isolated in 15% yield, resulting from the undesired dimerization of **9a**. A moderate improvement in the yield of **10a** was observed with three equiv of imine, with concurrent reduction of the amount of dimer **11** (entry 2). An increase in the amount of LDA used to deprotonate **9a** resulted in a further increase in yield (entry 3). Based on precedent, *s*-butyllithium (*s*-BuLi) was also tested in the lithiation of *o*-toluamide. However, a lower yield of product **10a** was obtained, despite of no obvious formation of **11** (entry 4). Given their known propensity to impart a strong influence on the aggregation state and the reactivity of organolithium reagents,[13] various additives were then evaluated. Strongly coordinating ligands such as TMEDA, HMPA and DMPU all provided improved yields regardless of the base (entries 5–9). In all cases, LDA proved superior to *s*-BuLi. The sterically more demanding base lithium 2,2,6,6-tetramethylpiperidide (LiTMP) provided results similar to LDA (entry 10). Interestingly, product **10a** was obtained in 72% yield upon the addition of LiCl (entry 11).[14] A brief evaluation of the hydride acceptor utilized in the preparation of 1-pyrroline revealed that trifluoroacetophenone performed slightly worse than benzophenone (entry 12). Reduced amounts of starting materials (1.5 equiv of base and 2 equiv of 1-pyrroline) were then tested in combination with the two most effective additives (HMPA and LiCl) (entries 13–16). No obvious negative effects on the yield of **10a** were observed. Under these more favorable conditions, trifluoroacetophenone was superior to benzophenone as the hydride acceptor. Notably, at most trace amounts of dimer **11** were observed in the presence of any additive tested. Finally, the amount of LiCl was varied. With catalytic amounts of LiCl and no LiCl the yield of the annulation product decreased to 61% and 42%, respectively (entries 17, 18).

The scope of the annulation was then examined as summarized in Scheme 1. *o*-Toluamides bearing various substituents on the phenyl ring readily participated in the reaction. Generally, electron-deficient *o*-toluamides provided higher yields of the lactam products than those with electron-donating substituents. Multiple factors, acting individually or in concert, could potentially account for this: 1) the increased acidity of protons in the benzylic *ortho*-position enables a more efficient deprotonation to generate lithiated *o*-toluamide; 2) better stabilization of the benzylic anion; 3) the cyclization step is facilitated due to the increased electrophilicity of the amide group. Substrates with a substituent in the other *ortho* position of the amide group required elevated temperatures for the lithiation and provided lower product yields. Most likely, the additional *ortho*-substituent prevents the amide from being coplanar with the methyl group, a requirement for achieving optimal results in the directed lithiation. The lithiation of the electron-rich *o*-toluamide required to prepare product **10n** was found to be inefficient with LDA. In this case *s*-BuLi/TMEDA provided superior results. Heteroaromatic amides also participated in this annulation chemistry and provided the corresponding pyridine and furan-containing products **10p** and **10q** in acceptable yields. The annulation process tolerates a wide scope of cyclic imines. Cyclic imines with expanded ring sizes, bicyclic imines, cyclic imines with remote substituents, and *N*-alkyl piperazine-derived imines were all viable substrates and produced the corresponding lactams in

moderate to good yields and excellent diastereoselectivities. The imine derived from 2-methylpiperidine provided the corresponding product **10v** in low yield, presumably due to unfavorable steric interactions in the course of the reaction. The *o*-ethyl benzamide starting material required for the synthesis of product **10y** was a challenging substrate to be lithiated, requiring two equiv of *s*-BuLi/TMEDA. However, the addition/ring closure steps proceeded smoothly at −78 °C and provided **10y** in 56% yield as a 2:1 mixture of diastereomers. An *o*-benzyl group facilitated the lithiation of the corresponding benzamide. Given the reduced nucleophilicity of the resulting organolithiate, the addition/ring-closure steps required an increase in reaction temperature. Regardless, product **10z** was obtained in good yield and excellent diastereoselectivity.

The tricyclic lactams obtained from the annulation of *o*-toluamides and cyclic imines could be readily utilized to access other structurally diverse compounds. For instance, reduction of compound **10g** with lithium aluminum hydride ($LiAlH_4$) furnished benzoindolizidine **12** in 80% yield. Suzuki-Miyaura coupling[15] of **10g** with phenyl boronic acid resulted in the formation of product **13** in 93% yield. Buchwald-Hartwig coupling[16] involving **10g** provided **14** in 77% yield. These products would likely be difficult to prepare via direct annulation reactions due to the inaccessibility or unfavorable electronic characteristics of the corresponding starting materials.

In conclusion, we have achieved annulation reactions of lithiated *o*-toluamides with enolizable cyclic imines, elusive species that were prepared in situ via the intermolecular hydride transfer of the corresponding lithiated amines onto a simple ketone acceptor. This methodology allows for the facile construction of structurally diverse polycyclic lactams in a single operation, dramatically simplifying access to these materials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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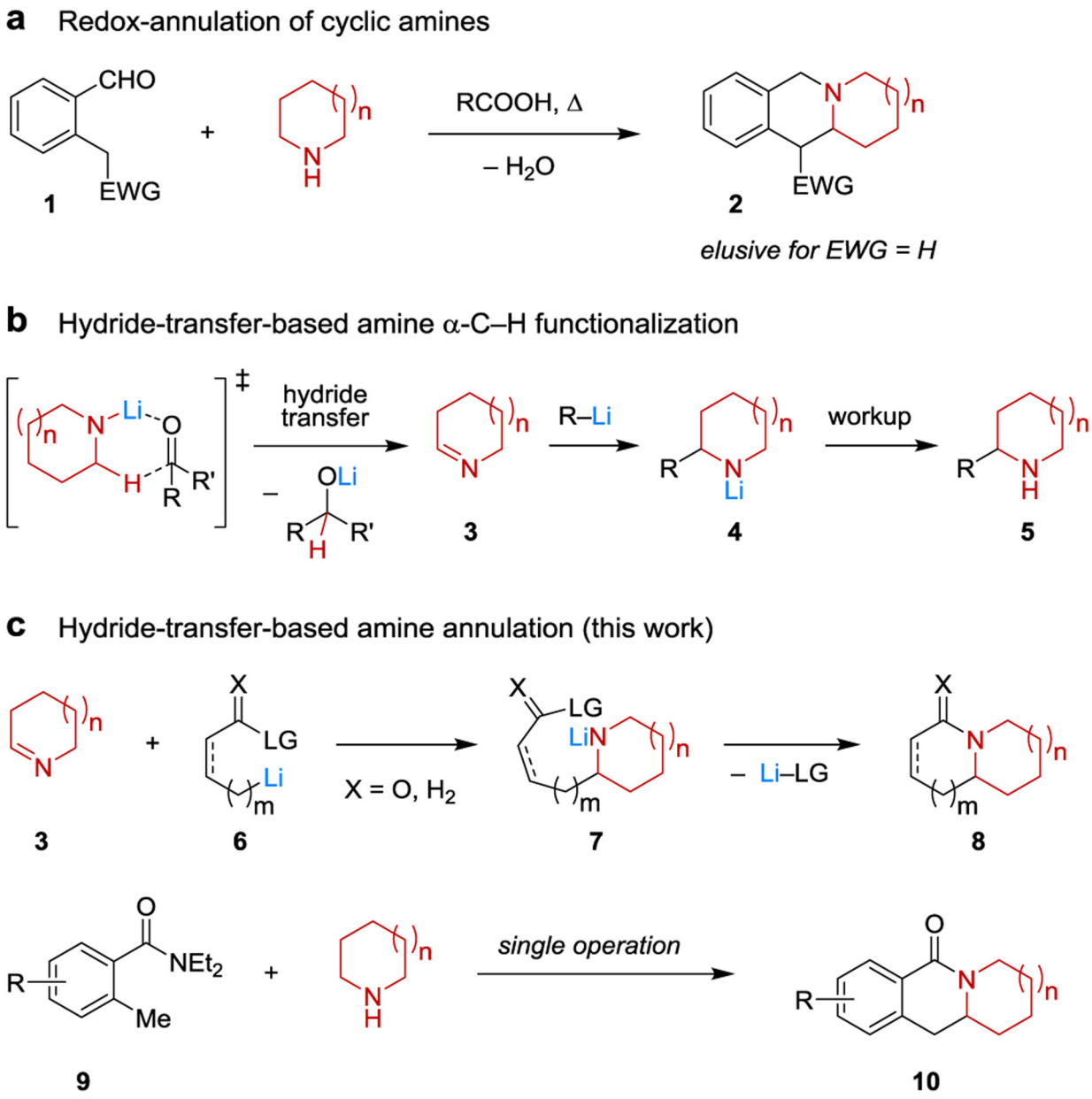
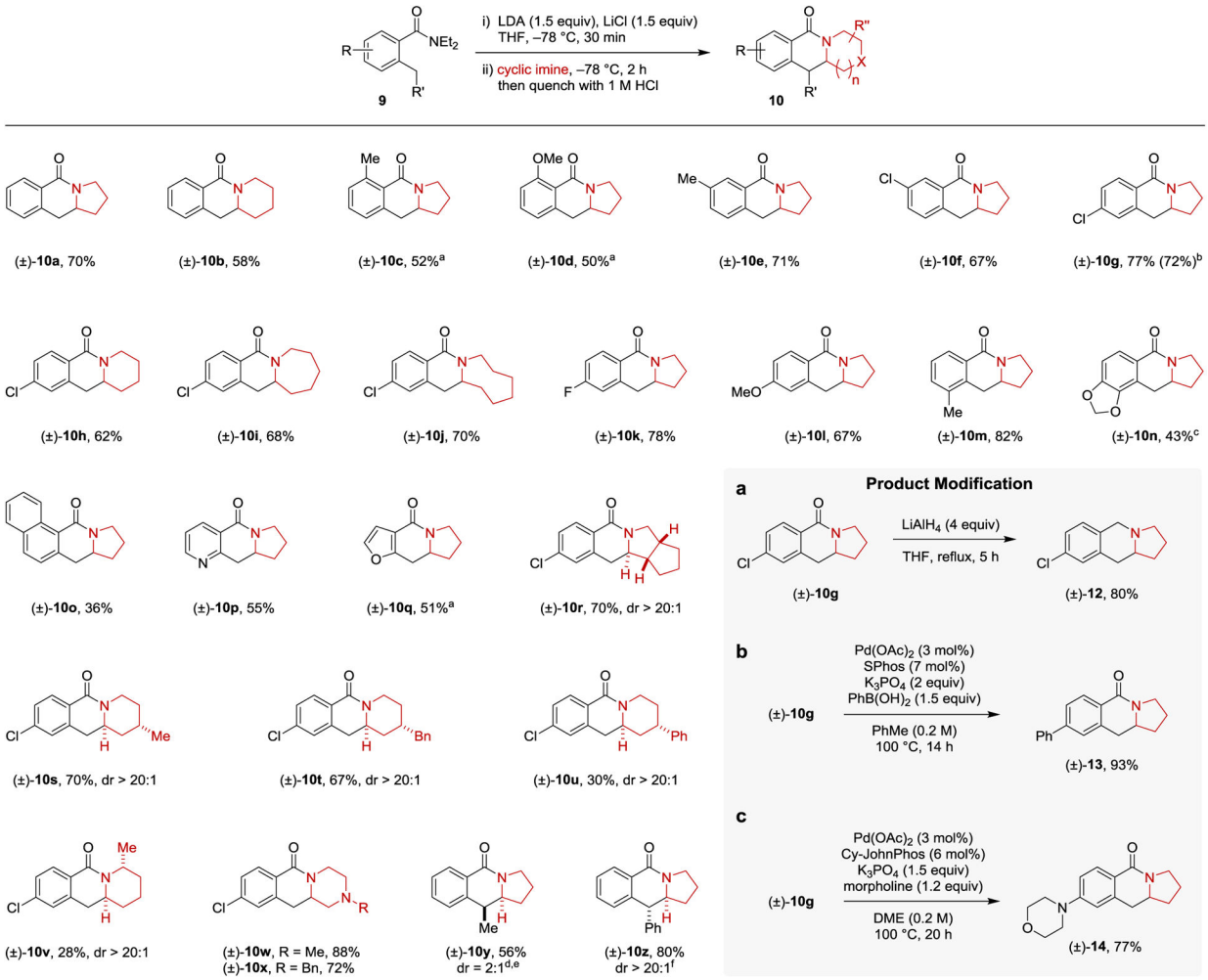


Figure 1.
Selected Precedent and New Concept for Amine Annulation.

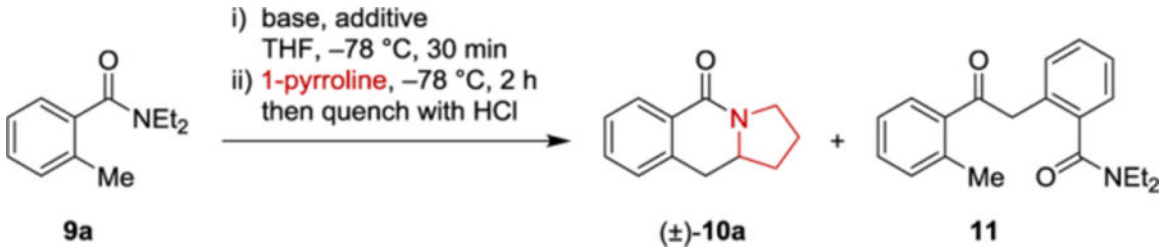


Scheme 1. Scope of the Annulation of *N,N*-Diethyl-o-Toluamides with Cyclic Imines Generated in Situ and Applications.

Reactions were performed with 0.5 mmol of **9**. Yields correspond to isolated yields. THF (2.5 mL) was used for the lithiation of **9**. Cyclic imines were prepared in situ by adding *n*-BuLi (2 equiv) to a solution of the corresponding cyclic amine (2 equiv) in ether (1 mL) at −78 °C, followed by the addition of trifluoroacetophenone (2 equiv). [a] *o*-Toluamide lithiation was performed at −40 °C. [b] Yield in parenthesis corresponds to reaction conducted on a 2 mmol scale. [c] o-Toluamide lithiation was performed using *s*-BuLi/TMEDA (1.5 equiv each) at −78 °C for 30 min. [d] *o*-Toluamide lithiation was performed using *s*-BuLi/TMEDA (2 equiv each) at −78°C for 1 h. [e] 3 Equiv of 1-pyrroline was used. [f] Reaction was warmed up to room temperature over 30 min after 1-pyrroline was added. **Product Modification** a, Reduction of lactam to amine. b, Suzuki-Miyaura coupling. c, Buchwald-Hartwig coupling.

Table 1.

Evaluation of Reaction Parameters for the Annulation of *N,N*-Diethyl-*o*-Toluamide with 1-Pyrroline.[a]



entry	base (equiv)	additive (equiv)	hydride acceptor	yield of 10a (%)	yield of 11 (%)
1[b]	LDA (1.5)	–	Ph_2CO	34	15
2	LDA (1.5)	–	Ph_2CO	41	8
3	LDA (2)	–	Ph_2CO	54	6
4	*s*-BuLi (2)	–	Ph_2CO	45	ND
5	LDA (2)	TMEDA (2)	Ph_2CO	58	ND
6	*s*-BuLi (2)	TMEDA (2)	Ph_2CO	51	ND
7	LDA (2)	HMPA (4)	Ph_2CO	68	ND
8	*s*-BuLi (2)	HMPA (4)	Ph_2CO	55	ND
9	LDA (2)	DMPU (4)	Ph_2CO	66	ND
10	LiTMP (2)	DMPU (4)	Ph_2CO	64	ND
11	LDA (2)	LiCl (2)	Ph_2CO	72	ND
12	LDA (2)	LiCl (2)	$PhCOCF_3$	66	ND
13[b]	LDA (1.5)	HMPA (3)	Ph_2CO	59	ND
14[b]	LDA (1.5)	HMPA (3)	$PhCOCF_3$	65	ND
15[b]	LDA (1.5)	LiCl (1.5)	Ph_2CO	56	ND
16[b]	**LDA (1.5)**	**LiCl (1.5)**	**$PhCOCF_3$**	**70**	ND
17[b]	LDA (1.5)	LiCl (0.3)	$PhCOCF_3$	61	ND
18[b]	LDA (1.5)	–	$PhCOCF_3$	42	7

[a]Yields correspond to isolated yields. Reactions were performed with 0.5 mmol of **9a**. THF (2.5 mL) was used for the lithiation of **9a**. 1-Pyrroline was prepared in situ by adding *n*-BuLi (3 equiv) to a solution of pyrrolidine (3 equiv) in ether (1 mL) at −78 °C, followed by the addition of the hydride acceptor (3 equiv).

[b]2 equiv of pyrrolidine, *n*-BuLi and the hydride acceptor were used for the preparation of 1-pyrroline.