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Heterocycle Synthesis

Intramolecular C(sp^3)–N Coupling by Oxidation of Benzylic C,N-Dianions**

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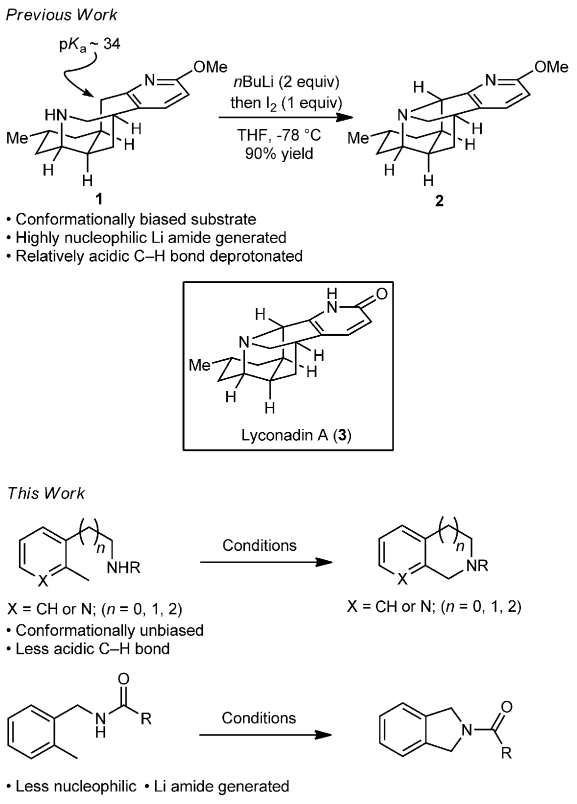
The ability to effect direct, carbon–nitrogen bond formation between an N–H group and a C(sp^3)–H group by the formal loss of H_2 would significantly enhance the existing toolbox of synthetic methods to build complex nitrogen-containing molecules. Such a transformation, particularly involving *N,N*-dialkyl secondary amines, would complement processes such as reductive amination and would obviate the requirement of a preoxidized coupling partner (e.g., a carbonyl group). Although the Hofmann–Löffler–Freytag (HLF) reaction[1] and its associated modern variants[2] offer one such alternative, preoxidation of the nitrogen partner is usually required and success remains limited to the formation of specific ring sizes. For example, although five-membered rings are readily formed using the HLF reaction, six- and seven-membered rings are more difficult to obtain. Thus, a general, one-pot, C(sp^3)–N coupling reaction would be highly desirable.[3–5]

Despite notable recent advances in oxidative C–C bond formation between two C(sp^3)–H groups,[6,7] the corresponding C(sp^3)–N coupling remains underdeveloped. In 2008, during the total synthesis of the Lycopodium alkaloid lyconadin A (**3**; Scheme 1),[8] we demonstrated the efficient, one-pot, conversion of amine **1** into caged pentacycle **2**. Subsequently, we showed that the oxidation of the C,N-dianion with iodine likely occurs by a single-electron transfer.[8b] This net oxidative C(sp^3)–N coupling represented a first step toward the more ambitious goal of a general C(sp^3)–N coupling. The cyclization of amine **1** to caged pentacycle **2** required the deprotonation of a moderately acidic, pseudo benzylic methylene group (see **1**; pK_a = ca. 34 in THF)[9] in a rigid, caged system.

As such, several challenges for this one-pot coupling method remained, including whether 1) conformationally unbiased substrates could participate in this reaction, 2) significantly less-acidic C–H bonds (e.g., a benzylic methyl group; pK_a of ca. 41)[10,11] could be employed, and 3) if less-nucleophilic Li amides, for example Li *N*-acyl amides, could serve competently in the reaction. Herein, we report the successful realization of these goals.



Scheme 1. One-pot C(sp^3)–N bond formation.

To begin addressing the challenge of the direct C(sp^3)–N coupling between benzylic carbon groups and amines, we selected tolylamine **4** (Table 1) for our studies.[12] In contrast to **1**, tolylamine **4** lacks any conformational bias that could enforce a complex-induced proximity effect[13] on the C–N bond formation subsequent to the generation of the C,N-dianion. Not surprisingly, under the reaction conditions that led to the successful conversion of **1** into **2**, the starting material (**4**) was recovered unchanged. Starting material was also recovered from the reaction carried out at an increased reaction temperature of 0 °C (Table 1, entry 1). We hypothesized that a Lewis acid additive could act as a template to control the conformation of the dianion generated from **4** (by analogy to the probable proximity effect for the dianion

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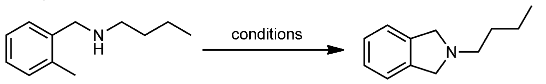
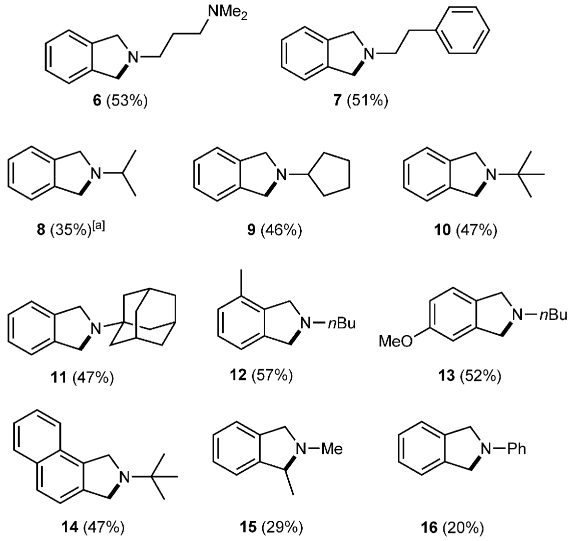
Table 1: Optimization studies of the C–N bond formation.[a]



4 **5**

Entry	Additive	Result[b]
1	none	**4** recovered
2	$SnCl_2$	**4** recovered
3	$CuCl_2$	**5** (trace) + **4** (major)
4	CuCl	**5** (trace) + **4** (major)
5	$B(OMe)_3$	**5** (9%) + **4** (16%) + unidentified by-products
6	$ZnCl_2$	**5** (54%) + **4** (8%)

[a] Reaction conditions: *n*BuLi (2.2 equiv), THF, 0 °C, 2 h, then additive (1.1 equiv) 1 h, then I_2 (1.3 equiv), 0 °C→23 °C, 2 h. All reactions were conducted at a concentration of 0.3 M of **4** in THF. [b] Yield determined by ^1H NMR analysis using hexamethylenetetramine (HMTA) as an internal standard. THF = tetrahydrofuran.



Scheme 2. The prepared isoindolines. Reaction conditions: Substrate in THF (0.075 M), *n*BuLi (2.2 equiv), 0 °C, 2 h, then $ZnCl_2$ (1.1 equiv), 1 h, then, I_2 (1.3 equiv); warm to 23 °C over 2 h. Because of the inherent instability of the isoindoline products, the yields were determined by ^1H NMR analysis using HMTA as an internal standard. [a] The amine precursor to isoindoline **8** was found to be volatile, which may account for the reduced yield of **8**. THF = tetrahydrofuran.

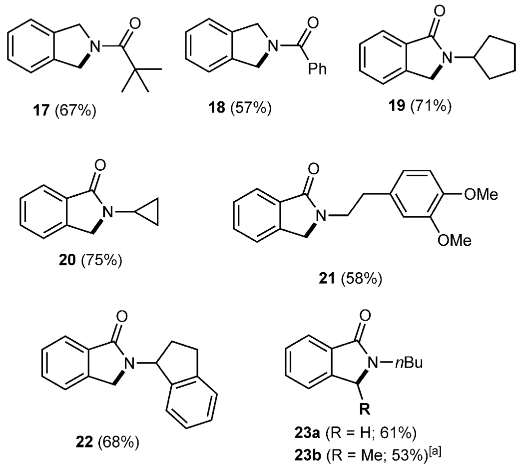
generated from **1**)[14] and furthermore, could facilitate deprotonation of the benzylic methyl group by breaking down organolithium aggregates.[15] To that end, we investigated several additives. Stannous chloride, cupric chloride, and cuprous chloride were ineffective and led mostly to the recovery of the starting material (entries 2–4). However, trimethyl borate (see entry 5), which we investigated as an additive on the basis of the successful oxidative C–N bond-forming reaction reported by Shenvi and co-workers,[16] led mostly to decomposition but gave an encouraging 9% yield of the product, along with the starting amine **4** (16% recovery). Pleasingly, $ZnCl_2$ proved to be effective as an additive and led to the formation of isoindoline **5** in 54% yield (as determined by ^1H NMR analysis)[17] along with some recovered **4** (8%). A slight improvement in the yield of **5** (59% yield; 68% yield based on remaining starting material) could be obtained by conducting the reaction at a lower concentration of 0.075 M in THF. Although the balance of the material was mostly accounted for by nonspecific decomposition, trace amounts of imine and iodinated by-products were formed as well. Generally, the yield of isolated **5** was low because of the instability of the isoindoline moiety.

As illustrated in Scheme 2 (only products are shown), the optimal conditions identified in Table 1, entry 6, with $ZnCl_2$ as the additive, are applicable to a range of tolyl substrates and give the corresponding isoindoline products. In the case of **6**, a tertiary amine group, which could lead to competing lithiation elsewhere, is tolerated. In addition, lithiation of the pendant phenyl group present in **7** does not appear to significantly compete with the desired reaction. Steric bulk proximal to the secondary amine group does not adversely affect the efficiency of the reaction (compare yields of **5**–**7** and **8**–**11**). Additionally, substituents on the benzenoid portion of the substrates are tolerated, including an alkyl group (see **12**), which could undergo lateral deprotonation, and a methoxy group (see **13**), which could promote *ortho* lithiation. Under the current conditions,
C(sp^3)–N coupling involving a methylene group proceeds in reduced yield (see **15**). This result likely points to the associated kinetic challenge in deprotonating methylene groups relative to methyl groups by using alkyllithium bases.[18–20] *N*-Aryl substrates yield only small amounts of the corresponding isoindolines (see **16**), thus indicating a deleterious effect of *N*-aryl substitution on the reaction.

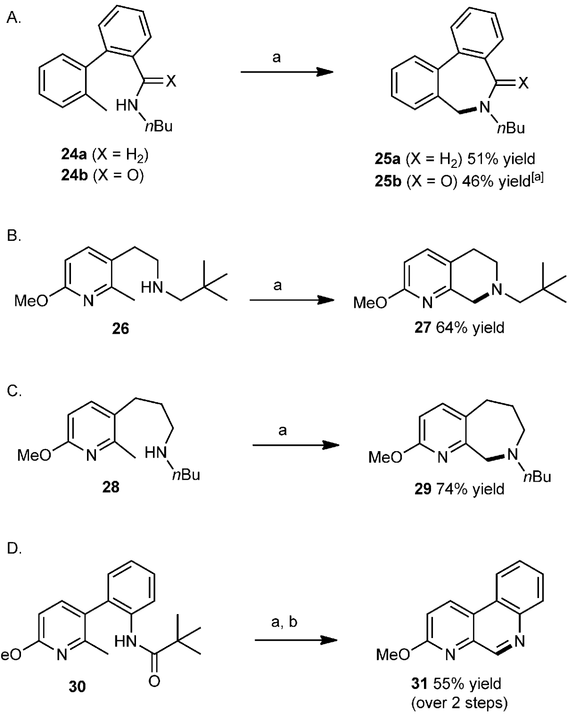
Overall, the formation of isoindolines by the C,N-dianion oxidation protocol proceeds in modest to good yield, which is partly attributable to the stated inherent instability of alkylated isoindolines.[21] To our knowledge, these C(sp^3)–N couplings cannot be effected using any other established methods.

The one-pot oxidative C(sp^3)–N coupling illustrated in Scheme 2 spurred an investigation of the dianion formation/oxidation in a more challenging system involving amide substrates that would generate less nucleophilic lithium amides.[22] With our established reaction conditions, *N*-acylated isoindolines **17** and **18** (Scheme 3) were formed in good yields. Unlike the alkylated isoindoline compounds (Scheme 2), these acylated variants could be purified without substantial loss of material. Furthermore, isoindolinones (**19**–**23a**) were also formed in modest to good yield. Notably, products such as **21** were formed without competing *ortho* lithiation of the dimethoxybenzene moiety and a methylene C–H bond could be functionalized with good fidelity (see isoindolinone **23b**).

Using our protocol, even substrates that form six- and seven-membered rings (Scheme 4), the formation of which is not possible using the HLF or Suárez reactions, participate in the oxidative C(sp^3)–N coupling. For example, *N*,*N*-dialkyl amine **24a** yields seven-membered azacycle **25a** in 51% yield under our standard reaction conditions, whereas amide **24b** affords **25b** in 46% yield (as determined by NMR spectroscopy).[23] Notably, an attempted HLF reaction with the *N*-



Scheme 3. The prepared *N*-acyl isoindolines and isoindolinones. All yields shown are of the isolated products unless otherwise stated. Reaction conditions: Substrate in THF (0.075 M), *n*BuLi (2.2 equiv), 0 °C, 2 h, then $ZnCl_2$ (1.1 equiv), 1 h, then, I_2 (1.3 equiv); warm to 23 °C over 2 h. [a] Yield of **23b** was determined by ^1H NMR analysis using HMTA as an internal standard. THF = tetrahydrofuran.

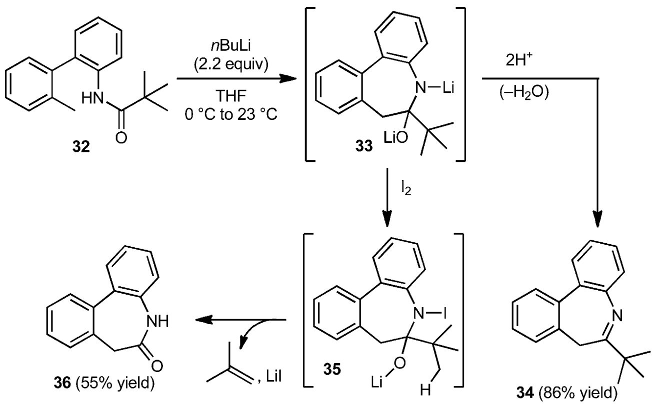


Scheme 4. Oxidative C−N bond formation to form six- and seven-membered rings. Reaction conditions: a) *n*BuLi (2.2 equiv), THF, 0 °C, 2 h; then $ZnCl_2$ (1.1 equiv), 1 h; then I_2 (1 equiv), 0 °C→23 °C, 2 h. b) MnO_2 (excess), CH_2Cl_2, 23 °C, 12 h [a] Yield of **25b** determined by ^1H NMR analysis using HMTA as an internal standard.

chloro derivative of **24a** or a Suárez reaction with **24b** led only to nonspecific decomposition.[17]

In a significant development, 5,6,7,8-tetrahydro-1,7-naphthyridine (THN) derivative **27** is formed in 64 % yield from **26**.[24] THNs have attracted considerable attention from the synthetic and medicinal chemistry communities. They are constrained analogues of the established pharmacophore 2-(3-pyridyl)ethylamine,[25] which has led to their investigation in combating, for example, Alzheimer's disease.[26] As shown in Scheme 4C, under our standard reaction conditions, pyridoazepine **29** is formed in 74 % yield from the conformationally flexible substrate **28**. Additionally, methoxypicoline derivative **30** yields benzo[*f*][1,7]naphthyridine **31** subsequent to sequential oxidative C(sp^3)−N coupling and manganese(IV) oxide oxidation.[27] This overall transformation presents a novel entry to naphthyridines, which also have interesting documented biological properties.[28]

Finally, in addition to C(sp^3)−N coupling of C,N-dianions under oxidative conditions, we have observed an interesting C−C bond-forming reaction where the course of the reaction can be diverted to a different outcome (Scheme 5). Thus, treating pivalamide **32** with 2.2 equivalents of *n*BuLi presumably yields *N*,*O*-dilithio intermediate **33**. A standard acidic workup affords imine **34** (following dehydration) in 86 % yield. Alternatively, oxidative workup by the addition of 1 equivalent of molecular iodine yields amide **36** in 55 % yield.[29] Amide **36** likely forms via *N*-iodo intermediate **35** (or the corresponding *O*-iodo compound), which undergoes a loss of isobutylene and LiI. These unusual C−C bond-forming reactions offer new opportunities for the synthesis of nitrogen heterocycles and will form the basis for future studies in our laboratory.



Scheme 5. A divergent C−C bond-forming reaction of C,N-dianions.

In conclusion, we report a one-pot, C(sp^3)−N coupling between the anions of benzylic carbon groups (pK_a of ca. 41) and nitrogen-based anions to yield various azacycles, including isoindolines and isoindolinones. Our optimal reaction conditions for C(sp^3)−N coupling are readily applied to: 1) tolyl substrates, which are significantly less acidic than our one prior example with a picoline substrate (i.e., **1**), 2) conformationally unbiased substrates to effectively form six- and seven-membered azacycles, and 3) amide substrates that give rise to less-reactive nitrogen nucleophiles. The scope of the transformations that we can now achieve sets the stage for myriad applications, including complex molecule synthesis. Current efforts are focused on gaining insight into the role of the $ZnCl_2$ additive in these reactions, as well as expanding the scope of C(sp^3)−N bond formation to include substrates that possess sterically congested C−H bonds (e.g., methine groups).

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Keywords: carbanions · C−N coupling · dianions · nitrogen heterocycles · oxidative coupling

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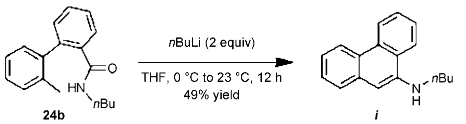
[23] In the absence of $ZnCl_2$ and iodine, **24b** is converted into phenanthrylamine ***i*** in 49 % yield.



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Communications

Heterocycle Synthesis

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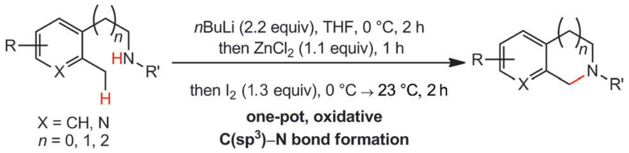
Intramolecular C(sp^3)–N Coupling by Oxidation of Benzylic C,N-Dianions



What a couple! An intramolecular, C-(sp^3)–N coupling to afford azacycles is reported. This reaction proceeds through the oxidation of benzylic C,N-dianions with iodine and builds on an earlier discovery during the synthesis of the natural product lyconadin A. The current study employs conformationally unbiased substrates with less acidic C–H bonds and less reactive nitrogen nucleophiles. $ZnCl_2$ was identified as an important additive.