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Intramolecular C(sp³)–N Coupling by Oxidation of Benzylic C,N-Dianions

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The ability to effect direct, carbon–nitrogen (C–N) bond formation between an N–H group and a C(sp³)–H group by the formal loss of H₂ 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 serve as a complement to processes such as reductive amination and would obviate the requirement of a preoxidized coupling partner (e.g., a carbonyl group). Although the Hoffman–Löffler–Freitag (HLF) reactionⁱ and its associated modern variantsⁱⁱ 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, while five-membered rings are readily formed using the HLF reaction, 6- and 7-membered rings are more difficult to obtain. Thus, a general, one-pot, C(sp³)–N coupling reaction would be highly desirable.^{iii, iv, v}

Despite notable recent advances in oxidative C–C bond formation between two C(sp³)–H groups,^{vi, vii} the corresponding C(sp³)–N coupling remains under-developed. In 2008, during the total synthesis of the *Lycopodium* alkaloid lyconadin A (**3**, Scheme 1),^{viii} we demonstrated the efficient, one-pot, conversion of amine **1** to caged pentacycle **2**. Subsequently, we showed that the oxidation of the C,N-dianion with iodine likely occurs by a single electron transfer process.^{viii b} This net oxidative C(sp³)–N coupling represented a first step toward the more ambitious goal of a general C(sp³)–N coupling. The cyclization of amine **1** to caged pentacycle **2** required the deprotonation of a moderately acidic, pseudobenzylic methylene group (see **1**; p*K*_a ~34 in THF)^{ix} in a rigid, caged system.

As such, several outstanding challenges for this one-pot coupling method remained, including whether (a) conformationally unbiased substrates could participate in this reaction, (b) significantly less acidic C–H bonds (e.g., a benzylic methyl group; p*K*_a ~41)^{x, xi} could be employed and (c) if less nucleophilic Li-amides, for example Li-*N*-acyl amides, could serve competently in the reaction. In this Communication, we report the successful realization of these goals.

To begin addressing the challenge of the direct C(sp³)–N coupling between benzylic carbon groups and amines, we selected tolylamine **4** (Table 1) for our studies.^{xii} In contrast to **1**, tolylamine **4** lacks any conformational bias that could enforce a complex-induced proximity

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effect^{xiii} on the subsequent C–N bond formation following generation of the C,N-dianion. Not surprisingly, under the conditions that led to the successful conversion of **1** to **2**, the starting material (**4**) was recovered unchanged. Increasing the reaction temperature to 0 °C (see Table 1, entry 1) also led to the recovery of starting material. We hypothesized that a Lewis acid additive could promote *in situ* templation of the dianion generated from **4** (by analogy to the probable proximity effect for the dianion generated from **1**)^{xiv} and furthermore, could facilitate deprotonation of the benzylic methyl group by breaking down organolithium aggregate structures.^{xv} 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 (see entries 2–4). However, trimethyl borate (see entry 5), which we investigated as an additive on the basis of the oxidative C–N bond forming success of Shenvi,^{xvi} led mostly to decomposition but gave an encouraging 9% yield of the product, along with starting amine **4** (16% yield). Pleasingly, ZnCl₂ proved to be effective as an additive and led to the formation of isoindoline **5** in 54% yield (as determined by ¹H NMR analysis)^{xvii} along with some recovered **4** (8% yield). 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 non-specific decomposition, trace amounts of imine and iodinated byproducts were formed as well. Generally, the isolated yield of **5** was low because of the instability of the isoindoline moiety.

As illustrated in Figure 1 (only products are shown), the optimal conditions identified in Table 1, entry 6, using ZnCl₂ 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 encumbrance 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 (**12**), which could undergo lateral deprotonation, and a methoxy group (**13**), which could promote *ortho*-lithiation. Under the current conditions, C(sp³)–N coupling involving a methylene group proceeds in reduced yield (**15**). This result likely points to the associated kinetic challenge in deprotonating methylene groups relative to methyl groups using alkylolithium bases.^{xviii,xix,xx} *N*-Aryl substrates yield only small amounts of the corresponding isoindolines (see **16**) indicating a deleterious effect of *N*-aryl substitution on the reaction.

Overall, the formation of isoindolines using the C,N-dianion oxidation protocol proceeds in modest to good yield, which is partly attributable to the stated inherent instability of alkylated isoindolines.^{xxi} To our knowledge, these C(sp³)–N couplings cannot be effected using any other established methods.

The one-pot oxidative C(sp³)–N coupling illustrated in Figure 1 spurred an investigation of the dianion formation/oxidation in a more challenging system using amide substrates that would generate less nucleophilic lithium-amides.^{xxii} Using our established conditions, *N*-acylated isoindolines **17** and **18** (Figure 2) were formed in good *isolated* yields. Unlike the alkylated isoindoline compounds (Figure 1), these acylated variants could be purified without event. Furthermore, isoindolinones (**19** – **23a**) were also formed in modest to good isolated 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 2), which is not possible using the HLF or Suárez reactions, participate in the oxidative C(sp³)-N coupling. For example, *N,N*-dialkyl amine **24a** yields seven-membered azacycle **25a** in 51% isolated yield under our standard conditions, whereas amide **24b** affords **25b** in 46% yield (as determined by NMR).^{xxiii} Notably, an attempted HLF reaction with the *N*-chloro derivative of **24a** or a Suárez reaction with **24b** led only to non-specific decomposition.^{xvii}

In a significant development, 5,6,7,8-tetrahydro-1,7-naphthyridine (THN) derivative **27** is formed in 64% yield from **26**.^{xxiv} THNs have attracted considerable attention from the synthetic and medicinal chemistry communities because of their emergence as constrained analogs of the established pharmacophore 2-(3-pyridyl)ethylamine,^{xxv} which has led to their investigation in combating, for example, Alzheimer's disease.^{xxvi} As shown in Scheme 2C, pyrido-azepine **29** is formed in 74% yield from the conformationally flexible substrate **28** using our standard conditions. Additionally, methoxypicoline derivative **30** yields benzo[*f*] [1,7]naphthyridine **31** following sequential oxidative C(sp³)-N coupling and a manganese(IV) oxide oxidation.^{xxvii} This overall transformation presents a novel entry to naphthyridines, which also have interesting documented biological properties.^{xxviii}

Finally, in addition to C(sp³)-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 3). Thus, subjecting pivalamide **32** to 2.2 equivalents of *n*-BuLi presumably yields dilithio-*N,O* intermediate **33**. A standard acidic workup affords imine **34** (following dehydration) in 86% yield. Alternatively, oxidative workup by the addition of 1 equiv of molecular iodine yields amide **36** in 55% yield.^{xxix} Amide **36** likely forms via the intermediacy of *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 form the basis for future studies in our laboratory.

In conclusion, we report a single-pot, C(sp³)-N coupling between the anions of *benzylic* carbon groups (pK_a ~ 41) and nitrogen-based anions to yield various azacycles, including isoindolines and isoindolinones. Our optimal conditions for C(sp³)-N coupling are readily applied to: (A) tolyl substrates, which are significantly less acidic than our one prior example with a picoline substrate (i.e., **1**), (B) conformationally unbiased substrates to effectively form six- and seven-membered azacycles, and (C) 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 ZnCl₂ additive in these reactions, as well as expanding the scope of C(sp³)-N bond formation to include substrates that possess sterically congested C-H bonds (e.g., methine groups).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

^a Isoindolines prepared. Conditions: Substrate in THF (0.3 M), *n*-BuLi (2.2 equiv), 0 °C, 2 h, then ZnCl₂ (1.1 equiv), 1 h, then, I₂ (1.3 equiv); warm to 23 °C over 2 h. ^a Yields determined by ¹H NMR analysis using hexamethylenetetramine (HMTA) as an internal standard because of the inherent instability of the isoindoline products. ^b The amine precursor to isoindoline **8** was found to be volatile, which may account for the reduced yield of **8**. THF = tetrahydrofuran.

Figure 2.

N-Acyl isoindolines and isoindolinones prepared. All yields shown are isolated yields unless otherwise stated. Conditions: Substrate in THF (0.3 M), *n*-BuLi (2.2 equiv), 0 °C, 2 h, then ZnCl₂ (1.1 equiv), 1 h, then, I₂ (1.3 equiv); warm to 23 °C over 2 h. ^a Yield of **23b** determined by ¹H NMR analysis using HMTA as an internal standard. THF = tetrahydrofuran.

Previous Work **This Work** **Scheme 1. One-pot C(sp³)-N bond formation**

Scheme 2.

Oxidative C–N bond formation to form six- and seven-membered rings. ^a Yield of **25b** determined by ¹H NMR analysis using HMTA as an internal standard.

Scheme 3.

A divergent C–C bond forming reaction of C,N-dianions

Table 1
Optimization studies of the C–N bond formation

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 byproducts
6	ZnCl ₂	5 (54%) + 4 (8%)

^a All reactions were conducted at a concentration of 0.3 M of **4** in THF.

^b Yield determined by ¹H NMR analysis using an internal standard. THF = tetrahydrofuran.