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Cross-Coupling of Amines via Photocatalytic Denitrogenation of In Situ-Generated Diazenes

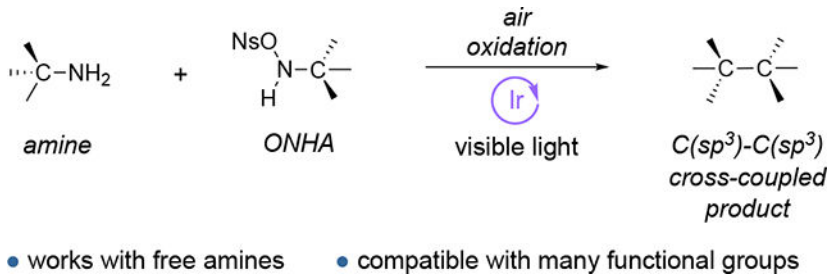
Keri A. Steiniger[†], **Matthew C. Lamb**[†], **Tristan H. Lambert**[†]

[†]Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853, USA.

Abstract

A method for $C(sp^3)$–$C(sp^3)$ cross-coupling of amines is described. Primary amines are converted to 1,2-dialkyldiazenes by treatment with O-nosylhydroxylamines in the presence of atmospheric oxygen. Denitrogenation of the diazenes with an iridium photocatalyst then forges the C–C bond. The substrate scope accommodates a broad latitude of functionality, including heteroaromatics and unprotected alcohols and acids.

Graphical Abstract



Cross-coupling reactions are highly valued for their ability to construct complex carbon frameworks from simple precursors.[1] While conventional cross-couplings utilize coupling partners such as organohalides, organometallics, or boronic acids, recent years have witnessed major efforts to extend the range of functional groups that can be engaged.[2] Of particular interest is the cross-coupling of "native" functionalities, such as alcohols[3] and carboxylic acids,[4] due to their prevalence in natural and synthetic chemical feedstocks. In contrast, amines, which are also broadly available,[5] have less commonly been used as cross-coupling partners. This relative paucity is a reflection of the basicity of the amino nitrogen, which tends to complicate transition metal-based reactions, and the strength of the C–N bond.[6] Nevertheless, several strategies have been developed to cross-couple amines, most notably through their conversion to Katritzky-type pyridinium salts[7] or to redox-active imines,[8] which enables the requisite scission of the C–N bond. While these advancements

Tristan H. Lambert – *Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York, 14853, United States;* tristan.lambert@cornell.edu.

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have enabled impressive transformations of amines, C(sp^3)–C(sp^3) coupling reactions have been limited to radical additions to alkenes,[9] coupling with alkyl metal reagents[10] and radical couplings with specialized substrates.[11] Thus, there remains a strong interest in the development of amine cross-coupling reactions that are simple, versatile, and broadly tolerant of various functional groups for the direct generation of new C(sp^3)–C(sp^3) coupled products. Here, we report such a method involving the photocatalytic denitrogenation of in situ-generated diazenes.[12]

It is well known that diazenes can be induced to expel molecular nitrogen, leaving behind carbon-centered radicals that can combine to form C–C bonds.[13] Indeed, this reactivity has been employed in wide-ranging applications, including for the total synthesis of highly complex natural products.[14] Unfortunately, the current state of the art for this chemistry suffers from several limitations. First, the synthesis of dialkyldiazenes, particularly those with α-C–H bonds, can be challenging because they are prone to isomerize to hydrazones[15] which are inactive for denitrogenation. Second, the denitrogenation step often requires elevated temperatures[16] or UV radiation,[17] which promotes side reactions and limits functional group compatibility. Nevertheless, because the loss of molecular nitrogen provides a powerful driving force that can be leveraged to construct very challenging bond connections, we reasoned that solving the above-mentioned challenges would result in a powerful C–C bond-forming method.

In regard to the denitrogenation problem, we recently reported the electrophotocatalytic decomposition of diazenes to form olefin products (e.g. **2** → **1**, Figure 1), using a trisaminocyclopropenium catalyst **4** that enabled the formation of distonic radical cation intermediates.[18] As part of that work, we demonstrated that iridium photocatalyst **5** resulted instead in the generation of a diradical intermediate, leading to exclusive C–C bond formation, i.e. **2** → **3**. This latter denitrogenation is believed to occur via energy transfer from the photoexcited iridium complex to the diazene group,[19] a process that has been employed to great effect for the related decomposition of diazirines to form carbenes.[20] In brief, the photocatalyst [Ir] can absorb a photon to access the singlet excited state ^{1}[Ir]*, which can undergo intersystem crossing to the triplet state ^{3}[Ir]* (see Figure 1). Energy transfer from this triplet state to the diazene can then generate the triplet excited state of the diazene. Expulsion of nitrogen from this triplet excited state gives rise to two radical fragments that can recombine to form a new C–C bond. We recognized that this photocatalytic denitrogenation of 1,2-dialkyldiazenes[21] could enable an attractive means to cross-couple amines if 1) the process was generally applicable to acyclic diazenes, and 2) a simple synthesis of dialkydiazenes could be developed.

In regard to the second question, although several methods to prepare dialkyldiazenes are known, they tend to be inefficient,[22] and in our hands proved unserviceable for the development of a useful cross-coupling procedure. We envisioned making use of the facile autooxidation of hydrazines[23] as a way to prepare diazenes under mild conditions; our goal thus became to convert a primary amine substrate to a hydrazine intermediate. While it is known that treatment of an amine with an *N*-chloroamine can forge the requisite N–N bond to form diaziridines,[24] *N*-chloroamines are problematic and did not suit our purposes. Inspired by the diaziridine work and limited examples utilizing tosyl-substituted

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hydroxylamines,[25] we found that reaction with *O*-nosylhydroxyamines (ONHAs) provided the desired efficiency.

The optimized amine cross-couping conditions we identified involved treatment of a primary amine substrate, such as leelamine, with one equivalent of the isopropyl ONHA•TFA[26] salt **6** and 2,6-lutidine in MeCN at room temperature with exposure to air (Table 1). After 12 h, 2 mol% $[Ir(dFCF_3ppy)_2(dtbbpy)]PF_6$ was added, and the mixture was irradiated by blue LEDs for 24 h. This procedure resulted in an 85% isolated yield of the cross-coupled product **7**.[27] In addition to this example, products derived from *t*-Bu glycinate **8** and leucine *p*-nitroanilide **9** were generated in high yields. Reactions to form products **7** and **8** were also conducted on a preparative scale (1 mmol) with reasonable yields. Meanwhile, we found that unprotected 1,2-aminoalcohols were viable substrates, with aminoindanol furnishing **10** and threonine benzyl ester giving rise to **11**, both as single diastereomers. In the case of **10**, both cis and trans aminoindanol substrates led to the same trans product. Unprotected amino acids could also be directly coupled, as with products **12**-**14** derived from asparagine, methionine, and methyldopa respectively. Peptide starting materials aspartame and lisinopril were converted to adducts **15** and **16** in good and modest yields, respectively. The benzazapinone derivative **17** was prepared in 76% yield, and reaction of aminoethyl biotinamide led to **18** in 75% yield.

To further explore the applicability of this reaction to complex molecular settings, we examined the cross-coupling of several amine-containing drug molecules. For example, the reactions of fingolimod, oseltamivir, saxagliptin, dehydroamlopidine, sitagliptin, amoxicillin, and linagliptin to furnish adducts **19**-**25** in good yields highlight the compatibility of this procedure with a range of functionality and complex architectures. Due to the nature of the radical intermediates, stereoselectivity for these reactions relies exclusively on substrate control. Thus, while **20** was formed as a single diastereomer; **21** and **24**, derived from substrates with more isolated amino groups, were generated as mixtures of diastereomers.

Next, we examined the scope of the ONHA component, using threonine benzyl ester **26** as the amine coupling partner (Table 2). Carbocycles of various sizes could be engaged to furnish adducts **27**-**29** with complete diastereoselectivity for the trans product. We also found that products incorporating tetrahydropyran **30** and piperidine **31** rings could be formed in good yields and as single stereoisomers. When non-α-branched ONHA partners were employed, products **32**-**34** were obtained, albeit as 1:1 mixtures of diastereomers. In the case of product **35**, some measure of stereocontrol was exerted by the existing stereocenter on the ONHA coupling partner.

Under the assumption that the hydrazine formation step proceeds by nucleophilic attack of the amine on the nitrogen of the ONHA, we anticipated that selective cross-coupling of only one amino group of a diamine substrate based on steric differences might be possible. Indeed, treatment of lysine (**36**) with one equivalent of ONHA **6** under the standard conditions led to the selective formation of **37** in 68% yield (Figure 2, eq 1). No products derived from reaction of the α-amino group were detected. Finally, we examined the applicability of this amine cross-coupling to forge C–C bonds in the context

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of a highly complex natural product, namely the antibiotic natamycin (**38**, Figure 2, eq 2). This macrocyclic compound bears a dense array of potentially sensitive functionality, including multiple hydroxyl groups, an allylic epoxide, a carboxylic acid, and a conjugated tetraene, in addition to the aminoglycan appendage. Even within this formidable setting, this coupling method enabled the formation of isopropyl derivative **39** in 48% yield as a single diastereomer, highlighting the potential for late-stage editing of complex molecules.

In summary, we have developed a new method to convert primary amines to $C(sp^3)$–$C(sp^3)$ cross-coupled products by employing a simple yet effective 1,2-dialkyldiazene synthesis followed by the use of visible light photocatalysis to trigger their in situ denitrogenation. Because of the mild nature of these conditions, a wide range of functional groups were found to be compatible, including unprotected alcohols, carboxylic acids, and even other amino groups. This work thus expands the ability to utilize widely available amines as building blocks for the construction of complex carbon frameworks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

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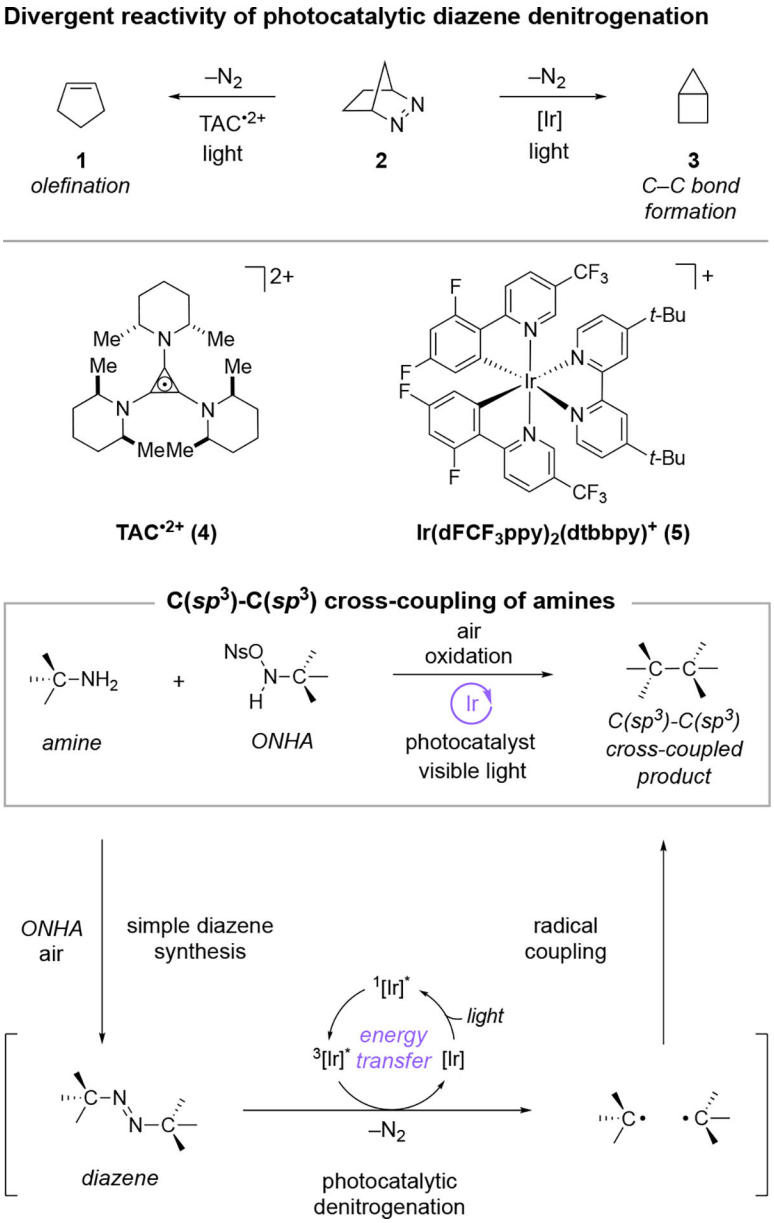

Figure 1.

Cross-coupling of amines via photocatalytic denitrogenation of in situ-generated diazenes.

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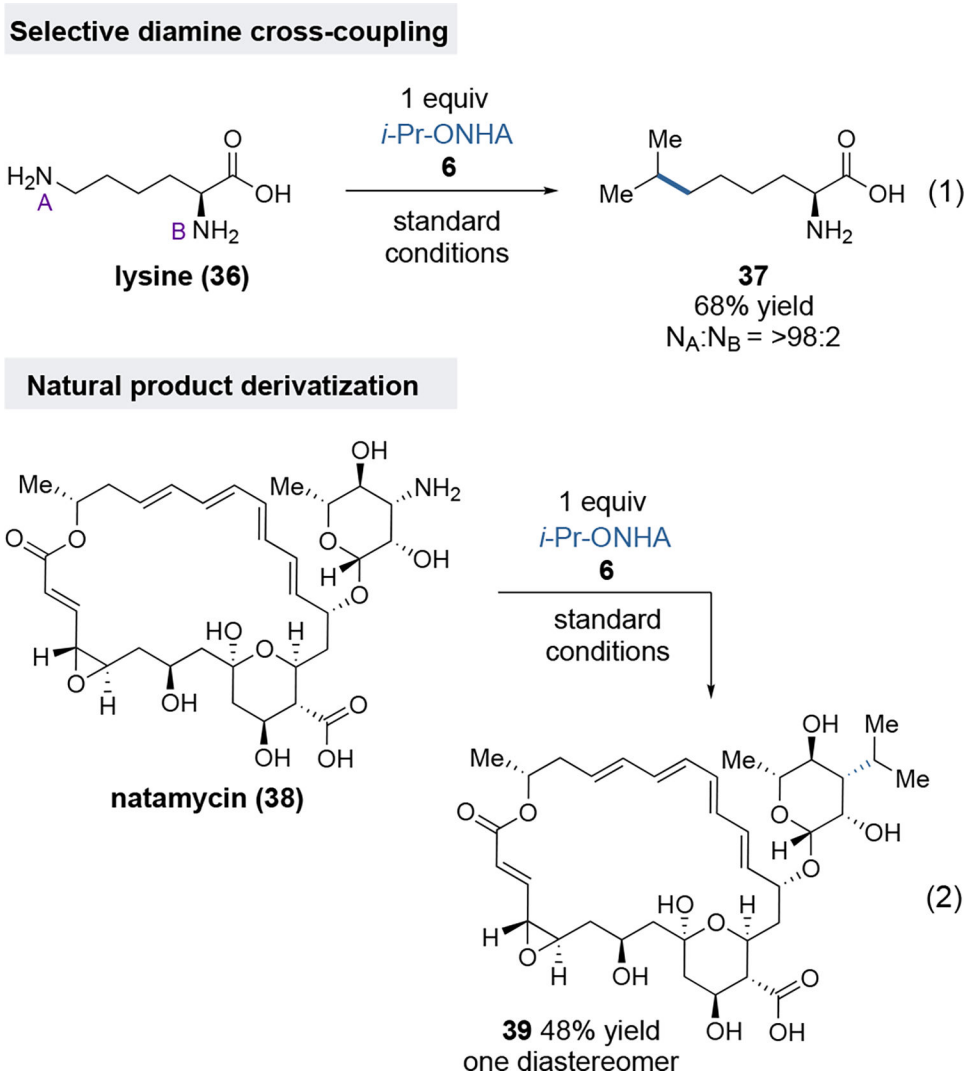

Figure 2.
Selective cross-coupling of lysine (eq. 1) and cross-coupling of natamycin (eq. 2).

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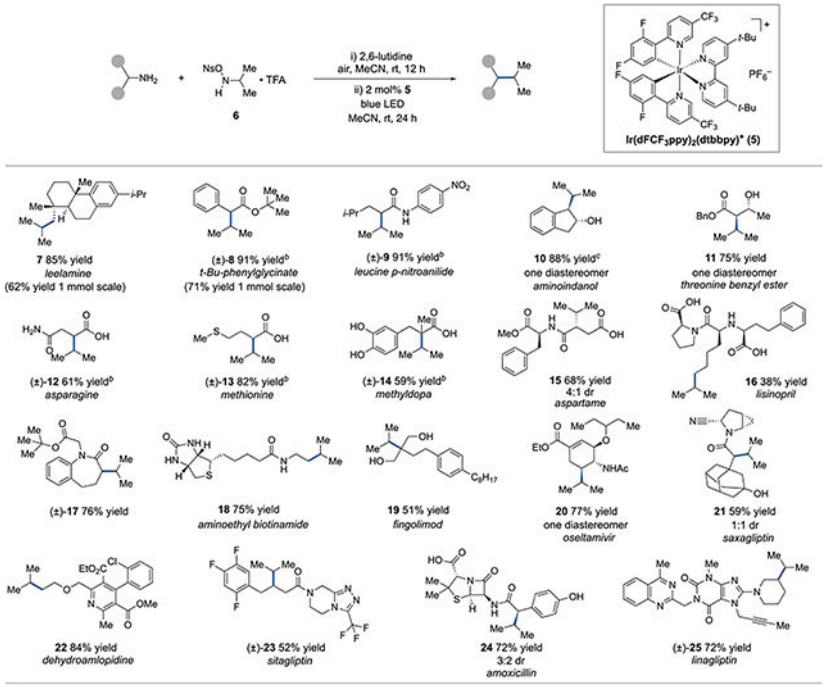
Table 1.

Scope of photocatalytic cross-coupling of amines with *N*-isopropyl-*O*-nosylhydroxylamine[a]



[a]See SI for detailed procedures. Reaction Conditions: Amine (1.0 equiv), **6** (1.0 equiv), 2,6-lutidine (2.0 equiv) under ambient air in dry MeCN at room temperature for 12 h, followed by addition of **5** (2 mol%) and irradiation with blue LEDs under N_2 at room temperature for 24 h. Yields determined on purified products. Diastereomeric ratios (dr) determined by 1H NMR spectroscopy.

[b]Enantiopure starting materials were used. Products were obtained in racemic form.

[c](*1R,2R*)-1-aminoindan-2-ol used as substrate. The (*1S,2R*) substrate furnished the same product diastereomer. Ns = 4-nitrobenzenesulfonyl.

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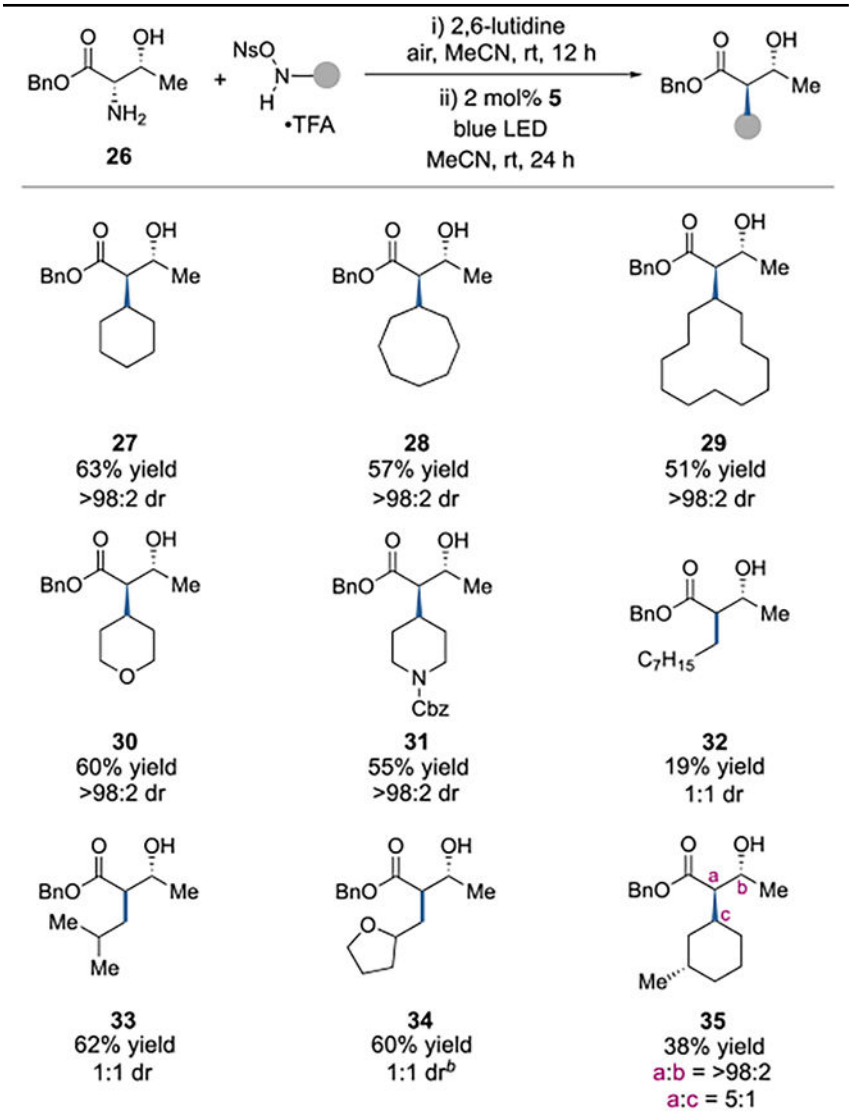
Table 2.

Scope studies for the ONHA coupling partner.[a]



[a]See SI for detailed procedures. Reaction Conditions: **26** (1.0 equiv), ONHA (1.0 equiv), 2,6-lutidine (2.0 equiv) under ambient air in MeCN at room temperature for 12 h, followed by addition of **5** (2 mol%) and irradiation with blue LEDs under N_2 at room temperature for 24 h. Yields determined on purified products. Diastereomeric ratios (dr) determined by ^{1}H NMR spectroscopy.

[b]Diastereomeric ratio refers to the α and β stereocenters. Racemic ONHA was used, so all diastereomers were obtained.