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O-Benzoylhydroxylamines as Alkyl Nitrene Precursors: Synthesis of Saturated N-Heterocycles from Primary Amines

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02842 Read Online

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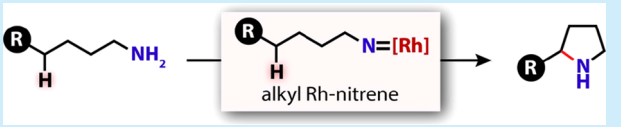
ABSTRACT: We introduce *O*-benzoylhydroxylamines as competent alkyl nitrene precursors. The combination of readily available, stable substrates and a proficient rhodium catalyst provides a straightforward means for the construction of various pyrrolidine rings from the corresponding primary amines. Preliminary mechanistic investigation suggests that the structure of the nitrene precursor plays a role in determining the nature of the resulting reactive intermediate.



Saturated N-heterocycles have attracted increasing attention in drug discovery programs.[1] Among various available methods for constructing the nitrogen-containing cyclic framework,[2] nondirected, intramolecular C−H functionalization involving a metalated nitrene is attractive because it does not require the installation of a directing group in the molecule of interest that is often difficult to remove. Since Breslow and Gellman first disclosed that a manganese− or iron−porphyrin complex catalyzes intramolecular C(sp^3)−H insertion using a sulfonamide as a nitrene precursor,[3] the synthetic utility of metallonitrenes has significantly expanded through contributions from many laboratories,[4] including those from the Du Bois group (Scheme 1a).[5] Rh-nitrenes generated in situ from carbamates or sulfamates under oxidative conditions are now considered to be reliable intermediates for the preparation of aminoalcohol moieties, having been shown to be suitable even in the context of complex natural product synthesis.[6] Despite their tremendous utility, the limitation lies in the structure of nitrene precursors; the requirement for the activating group adjacent to the nitrogen does not allow for the synthesis of saturated N-heterocycles such as pyrrolidines (Scheme 1b). Indeed, alkyl nitrenes suitable for the synthesis of N-heterocycles are known to be unstable because of their facile isomerization to the corresponding imines.[7] Betley first reported that an iron−dipyrrin complex promotes the formation of alkyl nitrenes from aliphatic azides that undergo intramolecular cyclization to afford N-heterocycles with various ring sizes in the presence of Boc_2O, which facilitates catalyst turnover.[8] Following this report, Fe-,[9] Co-,[10] Ni-,[11] Pd-[12] and Ru-based[13] catalysts were reported to promote similar transformations, some of which rendered the

Scheme 1. Prior Art in the Nitrene Chemistry and Current Work

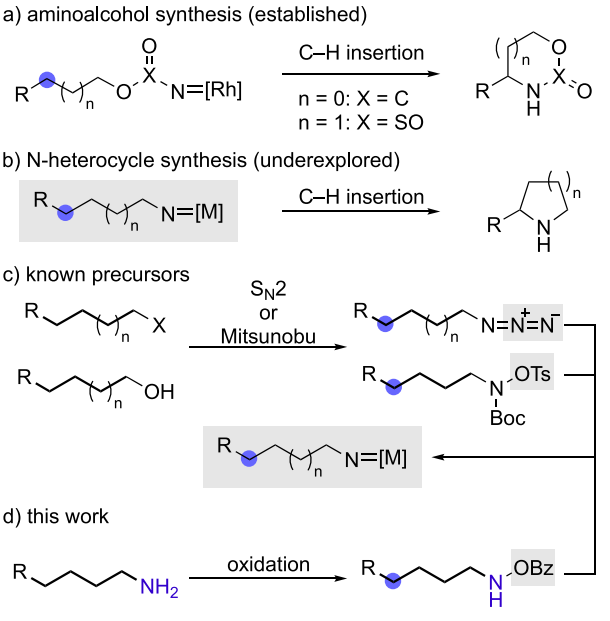
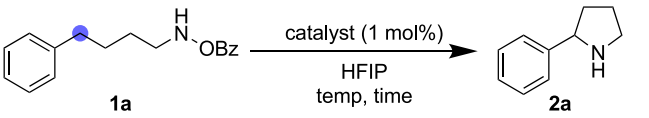


Table 1. Conditions Screened for Pyrrolidine Synthesis



1a 2a

entry	catalyst	temp (°C)	time (h)	yield (%)[a]
1	$Rh_2(esp)_2$	23	1	>90
2	$Rh_2(esp)_2$	0	24	<5
3	none	40	48	0

[a]Yields were determined by ^{1}H NMR analysis of the unpurified reaction mixture.

Received: August 25, 2020

https://dx.doi.org/10.1021/acs.orglett.0c02842
Org. Lett. XXXX, XXX, XXX−XXX

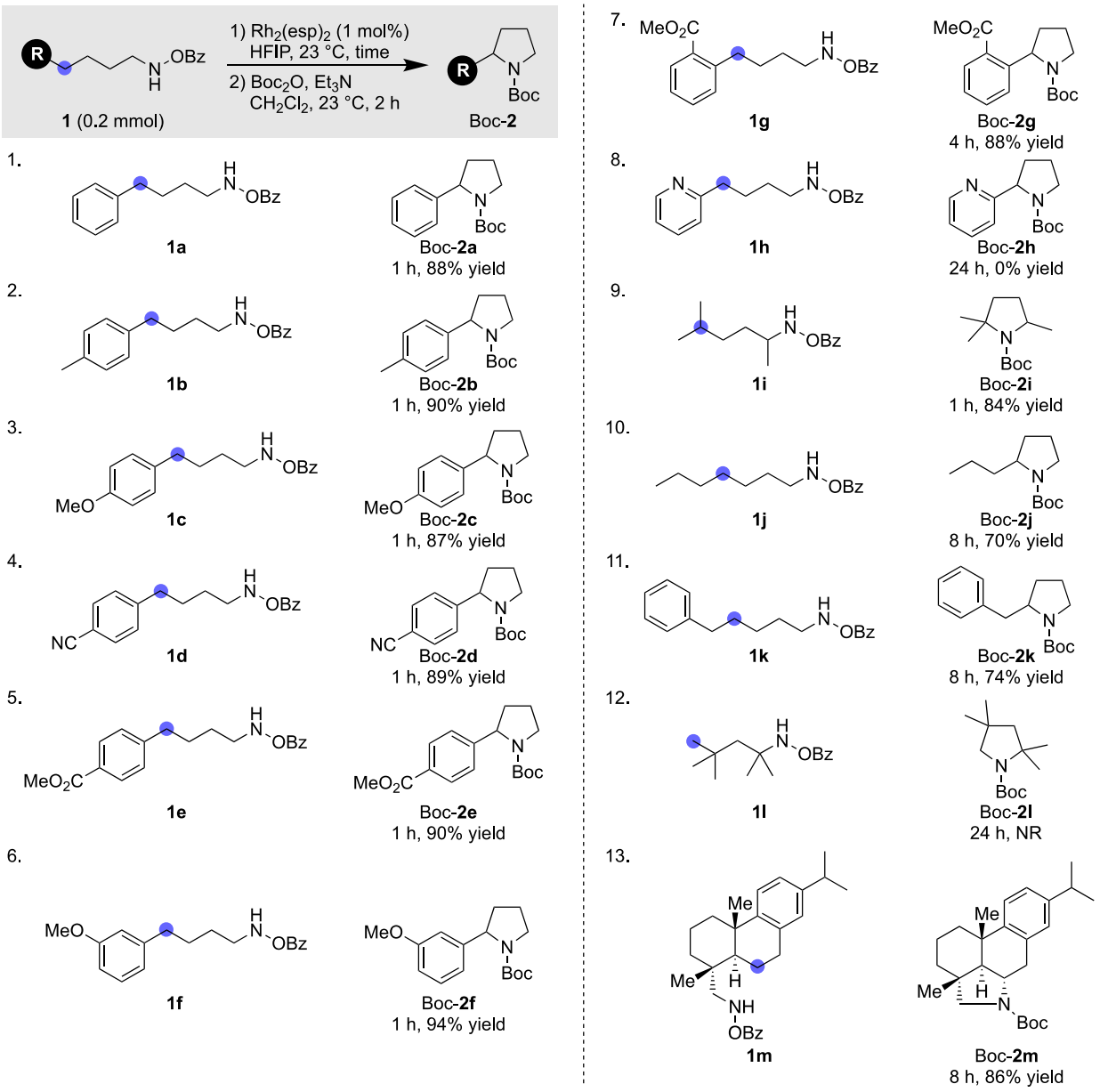
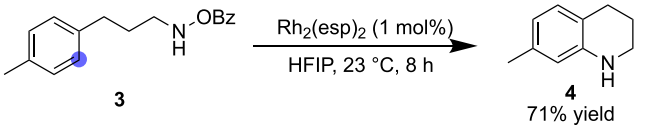
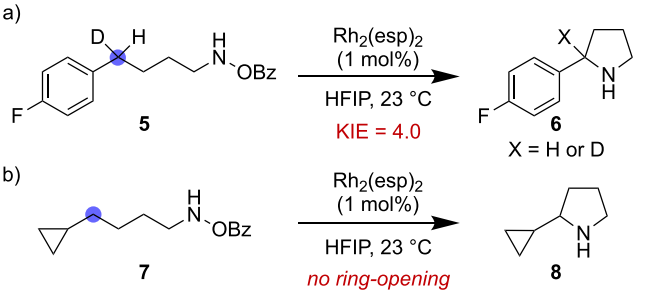


Figure 1. Scope and limitations of the Rh-catalyzed C(sp^3)−H insertion reaction for the synthesis of substituted pyrrolidines.

Scheme 2. Rh-Catalyzed C(sp^2)−H Amination



Scheme 3. Mechanistic Investigations



reaction diastereo- or enantioselective. In addition to alkyl azides, Falck introduced *N*-Boc-protected *O*-Ts hydroxylamines as precursors for alkyl Rh-nitrenes, which were generated after the in situ removal of the Boc group and preferentially formed pyrrolidines through intramolecular C(sp^3)−H insertion.[14] Both alkyl azides and bis-protected hydroxylamines were readily prepared from the corresponding alkyl halides by nucleophilic substitution or from alcohols by the Mitsunobu reaction (Scheme 1c). Given the importance of saturated N-heterocycles, the availability of an alternate alkyl nitrene precursor is desirable, in particular, one that can be directly produced from a primary amine, as a wide range of primary amines are commercially available. Herein, we disclose that *O*-Bz hydroxylamines meet this criterion (Scheme 1d). They serve as alkyl nitrene precursors under rhodium catalysis, thereby providing straightforward access to substituted pyrrolidines. Our results also suggest that the structure of the precursor controls the nature of the underexplored reactive intermediate.

https://dx.doi.org/10.1021/acs.orglett.0c02842
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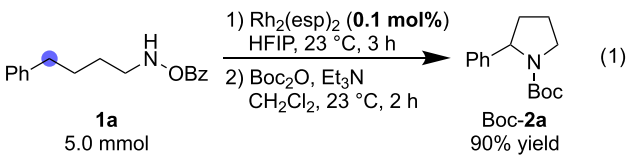
At the outset, we focused on the use of halogenating agents, as *N*-haloamines are readily prepared from the corresponding primary amines and have been used in various transformations.[15] Our preliminary investigations revealed that the halogen acts as a strong activating group; consequently, the addition of various transition metals led to complex mixtures that were difficult to analyze (see the Supporting Information for details). Motivated by our recent identification that 4-substituted isoxazolidin-5-ones,[16] cyclic variants of *O*-acylhydroxylamines, serve as alkyl nitrene precursors suitable for Rh-catalyzed C(sp^3)−H insertions,[17] we then turned our attention to *O*-benzoylhydroxylamines: *O*-Bz hydroxylamines can also be prepared from amines using benzoyl peroxide, a commercial oxidant.[18,19] Treatment of **1a**, which was synthesized from 4-phenylbutylamine, with 1 mol % $Rh_2(esp)_2$ in HFIP at an ambient temperature led to the full consumption of the substrate to afford pyrrolidine **2a** in good yield (entry 1, Table 1). The transformation was sluggish at lower temperature, and no reaction occurred without the added catalyst, even at higher temperature (entries 2, 3).

As *O*-Bz hydroxylamines were identified as suitable substrates for the synthesis of pyrrolidines, the scope and limitations of the current C(sp^3)−H insertion reaction were investigated (Figure 1). In this study, products were isolated in their Boc-protected forms for ease of purification. Depending on precursor availability, *O*-Bz hydroxylamines **1** were synthesized directly from the corresponding primary amines or the corresponding alcohols by the Mitsunobu reaction with BocNHOBz, followed by the removal of the Boc group. A wide range of 4-arylbutylamine derivatives underwent C−H insertion at their benzylic positions to afford pyrrolidines in good yields, regardless of the electronic nature and position of the substituent on the aromatic ring (**2a**−**2g**). The slower reaction observed for *ortho*-substituted substrate **1g** is likely due to an unfavorable conformation for C−H insertion. In stark contrast, heteroaryl-containing substrates were found to be unsuitable in the current system (**2h**; also see the Supporting Information). Not only does insertion into benzylic C−H bonds occur rapidly, but also methine C−H bonds proved to be reactive, forming **2i** in good yield. Furthermore, unactivated methylene C−H bonds underwent the rhodium-catalyzed pyrrolidine-forming reaction, albeit with a slower rate (**2j**). Although the benzylic position appears to be the preferred reaction site, its higher reactivity cannot overcome the innate tendency of the current catalyst system to form five-membered rings, as exemplified by the exclusive formation of **2k**. Moreover, the C−H bonds in a terminal methyl group did not exhibit any reactivity under the optimized conditions (**2l**). The successful cyclization of hydroxylamine **1m** derived from leelamine, a diterpene amine, suggests the potential utility of the current protocol for the derivatization of natural products and pharmaceuticals. The scalability of the Rh-catalyzed C(sp^3)−H amination was demonstrated on a larger scale: The cyclization proceeded with as little as a 0.1 mol % catalyst loading without compromising the efficiency (eq 1).



(1)

When truncated *O*-Bz hydroxylamine **3** was employed as a substrate, tetrahydroquinoline **4** was obtained in good yield through C(sp^2)−H functionalization (Scheme 2). While similar transformations have also been reported for more reactive *O*-Ts hydroxylamines with[20] or without[21] rhodium catalysis, *O*-Bz hydroxylamines did not react in the absence of the catalyst, establishing the importance of generating the reactive electrophilic nitrogen species in this system. Given the lack of regioisomer formation, the cyclization likely proceeds from the *ortho* carbon rather than the *ipso* carbon, followed by skeletal rearrangement.[22] The distinctive product distribution from structurally related substrates, isoxazolin-5-ones and *O*-Bz hydroxylamines, underscores the importance of leaving group structures to determine the reactivity of resulting active species.

The observed higher reactivity at benzylic and methine C−H bonds suggests a buildup of positive charge or the formation of a radical at the reaction site. To better obtain mechanistic insight, two experiments were conducted (Scheme 3). When monodeuterated substrate **5** was subjected to the optimized conditions, a kinetic isotope effect (KIE) value of 4.0 was measured (Scheme 3a); this value lies between that reported for the reaction of an *O*-Ts hydroxylamines and $Rh_2(esp)_2$ (5.3), which likely proceeds in a stepwise mechanism,[14] and that observed for sulfamate esters using similar Rh catalysts (1.9−2.9), which likely proceeds in a concerted mechanism.[23] Furthermore, a radical clock experiment did not produce any cyclopropyl-opening products, which indicates that the reaction proceeds in either a concerted or stepwise manner in which five-membered ring formation involving radical recombination is kinetically faster than cyclopropane ring opening ($k^{25\ °C}$ 1.3 × 10^8 s^{-1}).[24] While further evidence is required to draw a conclusion, these divergent data may suggest that both the singlet and triplet pathways are operative during the catalytic cycle depending on the substrate structure.[25]

In conclusion, we have demonstrated that *O*-Bz hydroxylamines serve as proficient alkyl nitrene precursors in the presence of a rhodium catalyst. From a retrosynthetic perspective, the current protocol offers an alternate route to those involving other known alkylnitrene precursors, azides and *O*-Ts hydroxylamines. The generated rhodium-nitrenes undergo intramolecular C−H insertions without decomposition to form various substituted pyrrolidines. Our experimental data indicate that the structure of the nitrene precursor plays a role in determining the nature of the underexplored reactive intermediate. Development of asymmetric catalysts for the synthesis of enantioenriched N-heterocycles is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02842.

Experimental procedures and spectra for new compounds (PDF)

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https://dx.doi.org/10.1021/acs.orglett.0c02842
Org. Lett. XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grant Numbers 18K14878 and 20K06957. H.N. thanks The Research Foundation for Pharmaceutical Sciences, and The Uehara Memorial Foundation, for the financial support. We are grateful to Dr. Ryuichi Sawa, Yumiko Kubota, Dr. Kiyoko Iijima, and Yuko Takahashi at the Institute of Microbial Chemistry for technical assistance in NMR and MS analyses.

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