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Intramolecular Csp³–H/C–C bond amination of alkyl azides for the selective synthesis of cyclic imines and tertiary amines†

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The intramolecular Csp³–H and/or C–C bond amination is very important in modern organic synthesis due to its efficiency in the construction of diversified N-heterocycles. Herein, we report a novel intramolecular cyclization of alkyl azides for the synthesis of cyclic imines and tertiary amines through selective Csp³–H and/or C–C bond cleavage. Two C–N single bonds or a C=N double bond are efficiently constructed in these transformations. The carbocation mechanism differs from the reported metal nitrene intermediates and therefore enables metal-free and new transformation.

Introduction

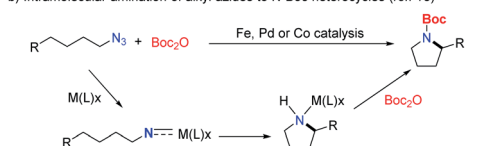
N-Heterocycles are undoubtedly important chemicals in organic synthesis, and have been considered as key functionality regulators in pharmaceuticals.¹ The intramolecular nitrogen insertion into Csp³–H and/or C–C bonds provides an efficient approach to N-heterocycles.^{2–5} The pioneering groups of Aubé⁴ and Pearson⁵ developed the intramolecular Schmidt reactions² and made significant achievements for various N-heterocycle synthesis.³ The earliest intramolecular aliphatic C–N bond formation named the Hofmann–Löffler–Freitag reaction⁵ always started from unstable halogenated amines to construct N-heterocycles. Over the past two decades, the aliphatic C–H amination has achieved great progress *via* the C–H activation strategy.⁶ However, most of these reactions required electron withdrawing directing groups and delivered amide products (Scheme 1a). Beginning with Breslow's pioneering work,⁷ a metal-nitrene strategy was successfully applied in intramolecular Csp³–H bond N insertion, providing elegant approaches to amides bearing N–H bonds (Scheme 1a).⁸ Thus, the development of direct aliphatic C–H/C–C amination is still highly desirable.

Organic azides are synthetically useful in drug discovery, bioconjugation and materials science.⁹ Although the intramolecular Csp³–H bond amination/amidation of aryl azides¹⁰

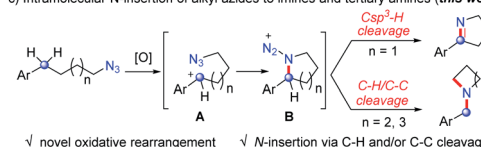
and sulfonyl azides¹¹ has achieved great progress, the corresponding transformation of alkyl azides¹² was rarely developed until recent results.¹³ In 2013, Betley and coworkers demonstrated the pioneering intramolecular aliphatic C–H amination of alkyl azides catalyzed by an iron catalyst (Scheme 1b).^{13a} The groups of van der Vlugt,^{13c} Lin,^{13d,e} de Bruin,^{13e,f} and Chi^{13g} independently developed the same elegant intramolecular cyclization of alkyl azides by iron, palladium or cobalt catalysis to deliver N-Boc heterocycles (Scheme 1b), in which the involved nitrene type intermediates required an equivalent of Boc₂O reagent to liberate the active catalyst to complete the catalytic cycle (Scheme 1b). Despite the advances of the above strategies (Scheme 1a and b), these intramolecular aliphatic amination/amidation processes always delivered N-carbonyl or sulfonyl heterocycles with the formation of one C–N single bond.

a) Intramolecular Csp³–H bond amination/amidation by C–H activation and nitrene strategies

b) Intramolecular amination of alkyl azides to N-Boc heterocycles (ref. 13)



c) Intramolecular N-insertion of alkyl azides to imines and tertiary amines (this work)

Scheme 1 Intramolecular N-insertion of the Csp³–H bond.

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Scheme 2 Proposed mechanism.



On the basis of this result, we investigated the one-pot reaction of alkyl azide **3** with DDQ and TFA followed by *in situ* reduction. We were delighted to find that the corresponding cyclic tertiary amine **7a** was obtained in 55% yield (Table 3). The substituent on the arene slightly influenced the yield and

a series of N-Bn pyrrolidines were synthesized in moderate yields. The azide substrates bearing alkyl substituents also smoothly delivered benzyl-substituted **7h** or pyrrolidine **7i** in moderate yield. In addition, naphthalene, thiophene, dibenzofuran and dibenzothiophene were all well tolerated to afford cyclic tertiary amines **7j–m** in 33–81% yields. It is noteworthy that the transformation of **3** to **7** with the release of nitrogen as the only by-product, is thus highly atom-economic. Moreover, the present strategy cleaves the Csp³–Csp³ bond¹⁶ without strained rings or assisted functional groups. Besides pyrrolidine, piperidine derivative **7n** also could be synthesized by the intramolecular N-insertion of alkyl azide **3n**. Unfortunately, the present strategy could not be applied in the construction of seven- or eight-membered N-heterocycles.

Based on the above experiments, we proposed the possible mechanism of the reaction (Scheme 2). The oxidation of alkyl azides **1** and **3** at the benzylic position by DDQ with TFA provides benzylic cation intermediate **A**, which is attacked by the azide group to generate cyclic intermediate **B**. In the most stable conformation of **B**, the aryl group should stand on the equatorial bond, which makes a small torsion angle with the azide moiety. As a result, the following Schmidt rearrangement of **B** with the concerted release of N₂ and the aryl shift is unfavorable through periplanar migration, while the hydrogen or alkyl shift is potentially feasible through antiperiplanar migration. The five-membered ring species **C** undergoes deprotonation with the release of N₂ to afford cyclic imine **2**,

Scheme 3 Energy profile for the DDQ-mediated amination of alkyl azides **1** and **3**.Table 3 Nitrogenation of alkyl azides to tertiary amines^a

^a Reaction conditions: **3** (0.3 mmol), DDQ (0.36 mmol) and TFA (0.2 mL) in TCE (0.5 mL) at room temperature for 12 h. Isolated yields. ^b Performed with TFA (0.4 mL) at 60 °C. ^c Performed at 60 °C.



while the six-membered ring intermediate **D** undergoes 1,2-alkyl migration to generate the imine cation **E**, which is sequentially reduced to deliver tertiary amine **7**.

To further understand the mechanism, we performed preliminary DFT calculations on the model reaction of alkyl azides **1** and **3** with DDQ and TFA (Scheme 3).¹⁷ We first studied the oxidation of **1** at the benzylic position by DDQ with TFA through O-attack hydride transfer pathway, which is the most thermodynamically favorable pathway in some similar cases.¹⁸ The hydride transfer from **1** to the complex of DDQ and TFA through **TS1** requires a Gibbs free energy barrier of 28.0 kcal mol⁻¹ to form the benzylic carbocation intermediate **A1** and DDQH-TFA⁻ anion, which could be stabilized by another TFA molecule to afford DDQ-2H and H(CF₃CO₂)₂⁻ species. Subsequently, the azide moiety would attack the formed carbocation in **A1** to generate five-membered ring **C**, which is exothermic by 19.2 kcal mol⁻¹. In the most stable conformation of **C**, the phenyl group on the equatorial bond has a small torsion angle (-24.4°) with the azide moiety, while the benzylic hydrogen and alkyl group have big dihedral angles (95.4° and -150.0°, respectively) with the azide moiety. Therefore, the following Schmidt rearrangement² of **C** with the concerted release of N₂ and the hydrogen or alkyl shift is potentially feasible through antiperiplanar migration. The Schmidt rearrangement with the 1,2-H shift through the antiperiplanar transition state **TS2** with a free energy barrier of 16.8 kcal mol⁻¹ gives **2-H**. The barrier of the 1,2-alkyl shift to imine cation **E1** through **TS3** ($\Delta G^\ddagger = 21.7$ kcal mol⁻¹) is much higher than that of the 1,2-H shift pathway.

Alternatively, the hydride transfer from **3** to the complex of DDQ and TFA through **TS4** requires a Gibbs free energy barrier of 26.6 kcal mol⁻¹ to form the benzylic carbocation **A3**. The azide moiety is favorable to attack the intramolecular carbocation to generate six-membered ring **D**, which is exothermic by 16.6 kcal mol⁻¹. In the most stable conformation of **D**, the dihedral angle of the azide moiety with the alkyl group increases to -159.5°, while the one with hydrogen decreases to 84.2°. This is likely to provide an advantage for the 1,2-alkyl shift. The following Schmidt rearrangement of **D** including the 1,2-H shift through **TS5** requires a free energy barrier of 15.3 kcal mol⁻¹ to give **4-H**. In contrast with **C**, **D** undergoes a 1,2-alkyl shift through **TS6** with a free energy barrier of 14.4 kcal mol⁻¹, which is favorable compared to the 1,2-H shift pathway, indicating that the 1,2-alkyl shift pathway becomes predominant. Reviewing the whole energy profile, it is revealed that the oxidation with hydride transfer is the rate-determining step, while the chemoselectivity in the nitrogenation of alkyl azides is essentially controlled by the conformation of the cyclic intermediate and the ring-side in the Schmidt rearrangement process. The experimentally observed electronic effects on the Ar group are consistent with the first oxidation step with hydride transfer as the rate-determining step (see the ESI† for details).

Conclusions

In summary, we have demonstrated a novel metal-free intramolecular Csp³-H/C-C amination of alkyl azides for the

synthesis of cyclic imines and tertiary amines. Two C-N single bonds or a C=N double bond are efficiently constructed in these transformations through the highly selective benzyl Csp³-H or C-C bond cleavage. The mechanistic studies and DFT calculation indicate a carbocation pathway for this novel protocol. The present chemistry not only provides a new approach to N-heterocycles, but also expands the transformation and application of C-H/C-C amination in organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

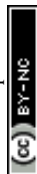
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