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ARTICLE

Intramolecular Csp³-H/C-C Bond Amination of Alkyl Azides for the Selective Synthesis of Cyclic Imines and Tertiary Amines

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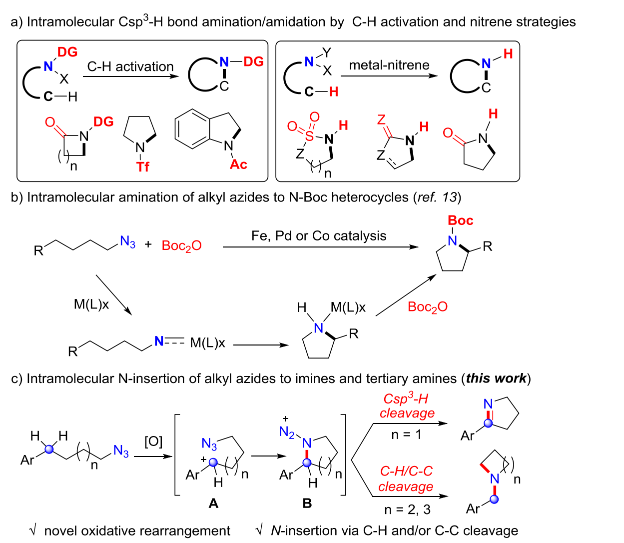
The intramolecular Csp^3-H and/or C-C bond amination is very important in modern organic synthesis due to its efficiency in construction of diversified *N*-heterocycles. Herein, we report a novel intramolecular cyclization of alkyl azides for the synthesis of cyclic imines and tertiary amines through selective Csp^3-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 differentiates from the reported metal nitrene intermediates and therefore enables the 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 Csp^3-H and/or C-C bond provides efficient approach to *N*-heterocycles.[2-5] The groups of Aubé[4] and Pearson[5] pioneeringly developed the intramolecular Schmidt reactions[2] and made significant achievements for various *N*-heterocycles synthesis.[3] The earliest intramolecular aliphatic C-N bond formation named Hofmann-Loffler-Freytag reaction[5] 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 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] metal-nitrene strategy was successfully applied in intramolecular Csp^3-H bond *N*-insertion, providing elegant approaches to amides bearing N-H bond (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 material science.[9] Although the intramolecular Csp^3-H bond amination/amidation of aryl azides[10] and sulfonyl azides[11] has achieved great progress, the corresponding transformation of alkyl azides[12] were rarely developed until recent results.[13] In 2013, Betley and coworkers pioneeringly demonstrated intramolecular aliphatic C-H amination of alkyl azides catalyzed by iron catalyst (Scheme 1b).[13a] The groups of van der Vlugt,[13c] Lin,[13d,e] de Bruin,[13c,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 equivalent Boc_2O reagent to liberate the active catalyst to complete the catalytic circle (Scheme 1b). Despite the advances of above strategies (Scheme 1a-b), these intramolecular aliphatic amination/amidation always delivered *N*-carbonyl or sulfonyl heterocycles with the formation of one C-N single bond.

Inspired by these results, we speculated that the oxidative generation of carbocation **A** may trigger the formation of cyclic intermediate **B** (Scheme 1c), which may undergo other transformations in the absence of transition-metal catalysts and provides opportunity for new products. Herein, we described a novel intramolecular nitrogen-insertion into Csp^3-H and/or C-C



Scheme 1 Intramolecular N-insertion of Csp^3-H bond.

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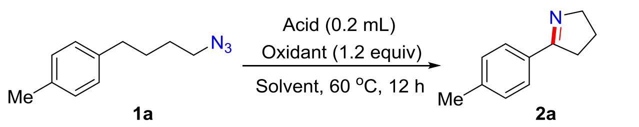
bond of alkyl azides to deliver cyclic imines and tertiary amines (Scheme 1c). The aliphatic C-H or C-C bond was selectively cleaved with the efficient formation of two C-N single bonds or a C=N double bond.

Results and discussion

Table 1 Optimization of the reaction conditions.[a]



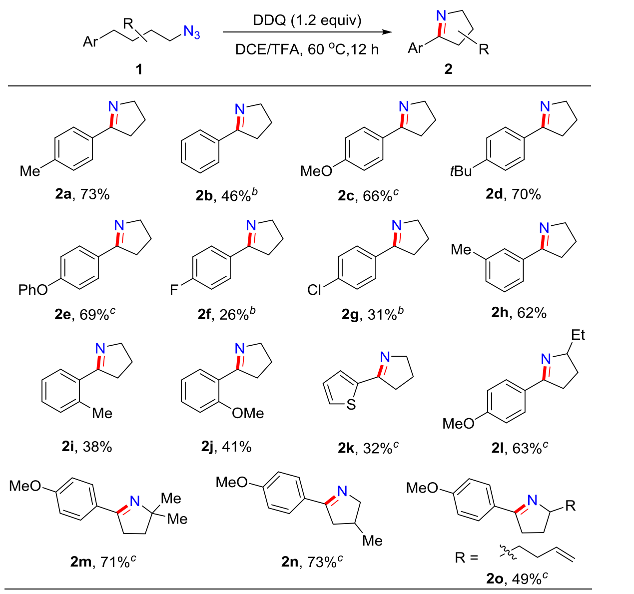
Entry	Oxidant	Acid	Solvent	Yield of **2a**[b]
1	DDQ	TFA	DCE	75%
2	CAN	TFA	DCE	18%
3	TEMPO	TFA	DCE	8%
4	NHPI	TFA	DCE	0
5	PIDA	TFA	DCE	0
6	DDQ	TFA	DMSO	0
7	DDQ	TFA	PhMe	64%
8	DDQ	TFA	MeCN	46%
9	DDQ	TFA	TCE	77%
10	DDQ	AcOH	TCE	10%
11	DDQ	MsOH	TCE	0
12	DDQ	TfOH	TCE	0
13[c]	DDQ	TFA	TCE	84% (73%)[d]
14[e]	DDQ	TFA	TCE	76%

[a] Reaction conditions: **1a** (0.3 mmol), oxidant (0.36 mmol) and acid (0.2 mL) in solvent (0.5 mL) at 60 °C for 12 h. [b] Yield determined by ^1H NMR spectroscopy with dibromomethane as an internal standard. [c] Performed with TFA (0.4 mL). [d] Isolated yields. [e] Performed at room temperature. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, CAN = cerium ammonium nitrate, TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl, NHPI = *N*-hydroxyphthalimide, PIDA = phenyliodine diacetate, TFA = trifluoroacetic acid, MsOH = methanesulfonic acid, TfOH = trifluoromethanesulfonic acid, TCE = 1,1,2,2-tetrachloroethane.

According to our previous elements incorporation reactions through the carbocation intermediates generated in situ with DDQ oxidant,[14] we chose azide **1a** as the model substrate to investigate our speculation. As expected, dihydropyrrole **2a** was obtained in 75% yield in the presence of DDQ and TFA at 60 °C (Table 1, entry 1). Two C-H bonds were cleaved and a C=N double bond was constructed along with the release of N_2 in this case. TEMPO or CAN as the oxidant gave inferior yields (entries 2-3), while PIDA or NHPI could not execute the conversion of **1a** to **2a** (entries 4-5). The chlorinated solvent afforded better yields than that of other solvents such as DMSO, toluene, or MeCN (entries 6-9), and the reaction delivered the highest yield in TCE (entry 9). The pKa of acids influenced the reaction strongly (entries 10-12). **2a** was obtained in only 10% yield in the presence of acetic acid (entry 10), while MsOH or TfOH failed to facilitate this transformation (entries 11-12). Treatment of **1a** with 0.4 mL of TFA afforded **2a** in satisfactory 73% isolated yield (entry 13). Lowering temperature was hampered to the reactivity (entry 14).

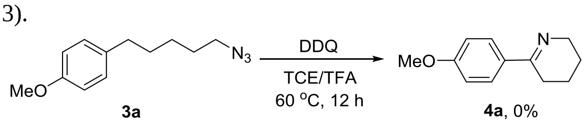
We explored the generality of this intramolecular Csp^3-H nitrogen-insertion for δ-aryl alkyl azides under standard reaction conditions (Table 2). Substrates bearing electron-donating substituents (MeO, *t*Bu, PhO) at the aryl ring worked smoothly to afford the corresponding cyclic imines **2c-e** in good yields. The electron-withdrawing substituents (F, Cl) caused low reactivity, resulting pyrrolines **2f-g** in diminished yields (26-31%). Substituents at the *meta* or *ortho* position of the arene rings **1h-j** slightly affected the efficiency. Besides arenes, the heteroaryl azide 2-(4-azidobutyl)thiophene **1k** was transformed to **2k** in 32% yield. The substituents on the alkyl chain influenced this reaction slightly (**2l-o**). The cyclic imines **2** were easily converted to diversified heterocycles.[15] Compared to the well-established approaches to cyclic imines, the present intramolecular *N*-insertion protocol features mild conditions and high atom economy.

Table 2 Nitrogenation of alkyl azides to imines. [a]

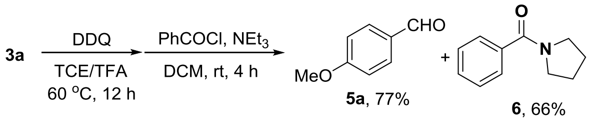


[a] Reaction conditions: **1** (0.3 mmol), DDQ (0.36 mmol) and TFA (0.4 mL) in TCE (0.5 mL) at 60 °C for 12 h. Isolated yields. [b] Performed at 80 °C. [c] Performed with TFA (0.2 mL) at room temperature.

In order to synthesize six-membered cyclic imine, we conducted the reaction of alkyl azide **3a** under standard condition. However, the target imine product **4a** was not detected (eq 1). We conducted the capture experiment by the addition of benzoyl chloride to the reaction of **3a** (eq 2). Aldehyde **5a** and amide **6** were obtained in 77% and 66% yields, respectively (eq 2), which indicated that the azide **3a** was converted to amine via an imine cation intermediate and a hydrolysis process (for detailed mechanism, see Scheme 2 and 3).



(eq 1)



(eq 2)

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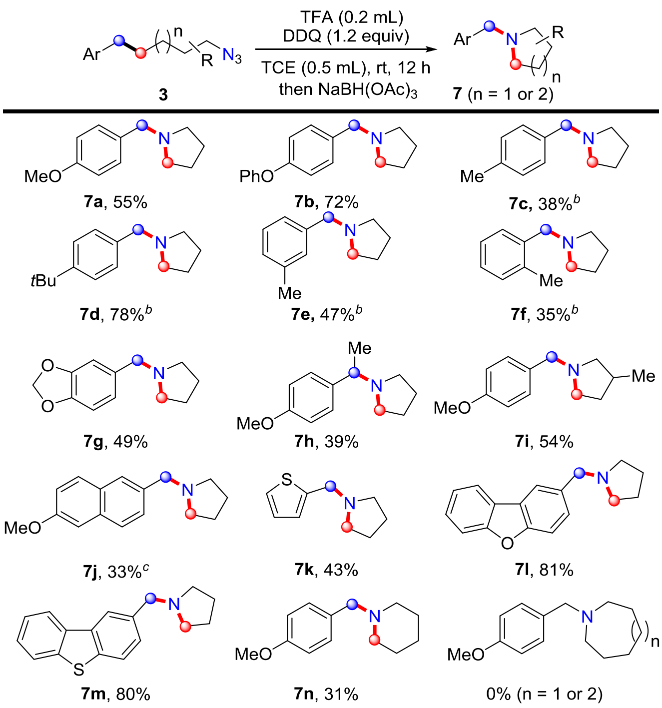
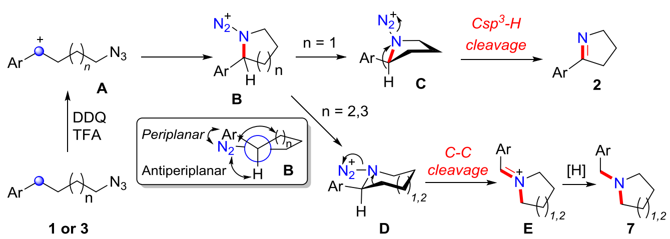
On the basis of this result, we investigated the one-pot reaction of alkyl azide **3** with DDQ and TFA followed by *in situ* reduction. We were delighted to find that the corresponding cyclic tertiary amine **7a** was obtained in 55% yield (Table 3). The substituent on the arene slightly influenced 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 releasing nitrogen as the only by-product, is thus high atom-economic. Moreover, the present strategy cleaves the C(sp^3)-C(sp^3) bond[16] 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.

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 ºC. [c] Performed at 60 ºC.

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 performs a small torsion angle with azide moiety. As a result, the following Schmidt rearrangement of **B** with the concerted release of N_2 and aryl shift is unfavorable through periplanar migration, while hydrogen or alkyl shift is potentially feasible through antiperiplanar migration. The five-membered ring species **C** undergoes the deprotonation with the release of N_2 to afford cyclic imine **2**, 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**.



Scheme 2 Proposed mechanism.

To further understand the mechanism, we performed preliminary DFT calculation into 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 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 $H(CF_3CO_2)_2^-$ 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 performs a small torsion angle (-24.4º) with azide moiety, while the benzylic hydrogen and alkyl group has big dihedral angles (95.4º and -150.0º, respectively) with azide moiety. Therefore, the following Schmidt rearrangement[2] of **C** with the concerted release of N_2 and hydrogen or alkyl shift is potentially feasible through antiperiplanar migration. The Schmidt rearrangement with 1,2-H shift through the antiperiplanar transition state **TS2** with free energy barrier of 16.8 kcal mol^{-1} gives **2-H**. The barrier of 1,2-alkyl shift to imine cation **E1** through **TS3** ($\Delta G^{\ddagger}$ = 21.7 kcal mol^{-1}) is much higher than 1,2-H shift pathway.

Alternatively, the hydride transfer from **3** to the complex of DDQ and TFA through **TS4** requires Gibbs free energy barrier of 26.6 kcal mol^{-1} to form the benzylic carbocation **A3**. The azide moiety is facile to attacks 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 azide moiety with the alkyl group increases to -159.5º, while the one with hydrogen decreases to 84.2º. This is likely to provide the advantage for 1,2-alkyl shift. The following Schmidt rearrangement of **D** including 1,2-H shift through **TS5** requires free energy barrier of 15.3 kcal mol^{-1} to give **4-H**. In contrast with **C**, **D** undergoes 1,2-alkyl shift through **TS6** with free energy barrier of 14.4 kcal mol^{-1}, which is favorable than 1,2-H shift pathway, indicating that 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 cyclic intermediate and the ring-side in the Schmidt rearrangement process. The experimental observed electronic effects

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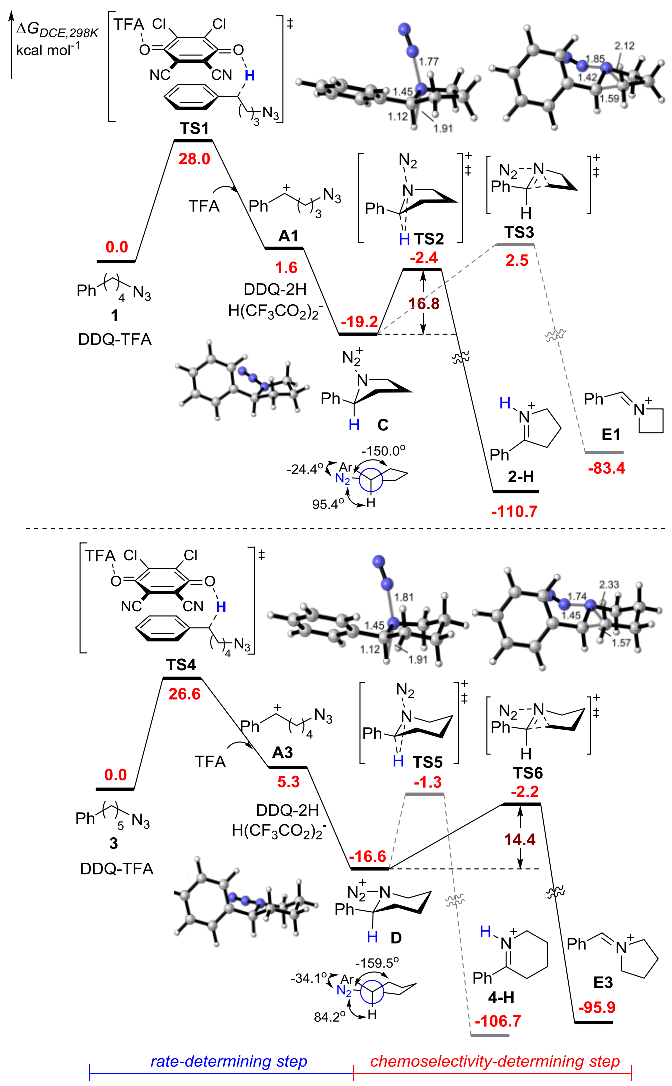
on the Ar group is consistent with first oxidation step with hydride transfer as the rate-determining step (see ESI for details).



Scheme 3 Energy profile for the DDQ-mediated amination of alkyl azides **1** and **3**.

Conclusions

In summary, we have demonstrated a novel metal-free intramolecular Csp^3-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 Csp^3-H or C-C bond cleavage. The mechanistic studies and DFT calculation indicate a carbon cation 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.

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Gaussian 09. All of the energies discussed in the paper are Gibbs free energies at the def2-TZVP basis set based on the structures with the PCM solvation correction in DCE at the 6-31+G(d,p)basis set. Computational details and references are given in the ESI.

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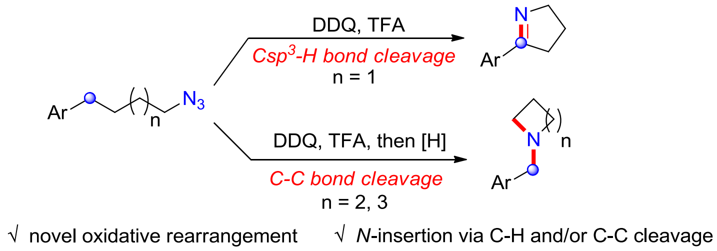

A novel intramolecular cyclization of alkyl azides for the synthesis of cyclic imines and tertiary amines has been developed. The aliphatic C-H or C-C bond was selectively cleaved with the efficient formation of two C-N single bonds or a C=N double bond.