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Intramolecular Csp³–H/C–C bond amination of alkyl azides for the selective synthesis of cyclic imines and tertiary amines†Xiaojin Wen,^{‡a} Xinyao Li,^{‡a} Xiao Luo,^a Weijin Wang,^a Song Song^{ID} *^{ab} and Ning Jiao^{ID} *^a

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.

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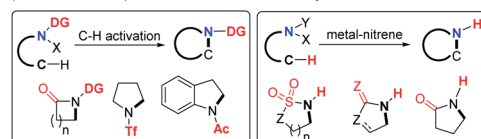
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Introduction

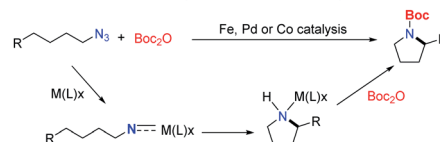
N-Heterocycles are undoubtedly important chemicals in organic synthesis, and have been considered as key functionality regulators in pharmaceuticals.¹ The intramolecular nitrogen insertion into Csp³–H and/or C–C bonds provides an efficient approach to N-heterocycles.^{2–5} The pioneering groups of Aubé⁴ 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

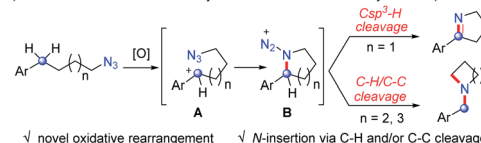
and sulfonyl azides¹¹ has achieved great progress, the corresponding transformation of alkyl azides¹² was rarely developed until recent results.¹³ In 2013, Betley and coworkers demonstrated the pioneering intramolecular aliphatic C–H amination of alkyl azides catalyzed by an iron catalyst (Scheme 1b).^{13a} 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.

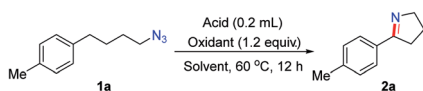
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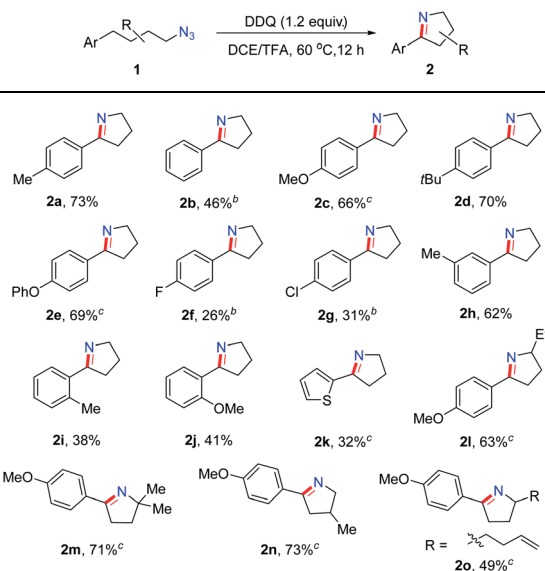
‡ These authors contributed equally to this work.

Results and discussion

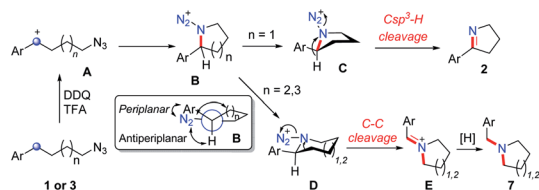
Table 1 Optimization of the reaction conditions^a

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%

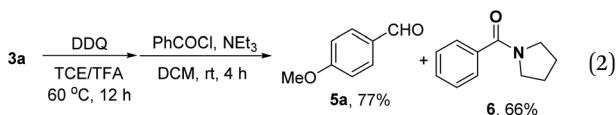
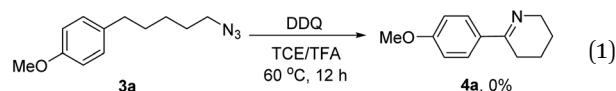
In order to synthesize a six-membered cyclic imine, we conducted the reaction of alkyl azide **3a** under standard conditions. However, the target imine product **4a** was not detected (eqn (1)). We conducted the capture experiment by the addition of benzoyl chloride to the reaction of **3a** (eqn (2)).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

Table 2 Nitrogenation of alkyl azides to imines^a

Chem. Sci., 2020, 11, 4482-4487 | 4483



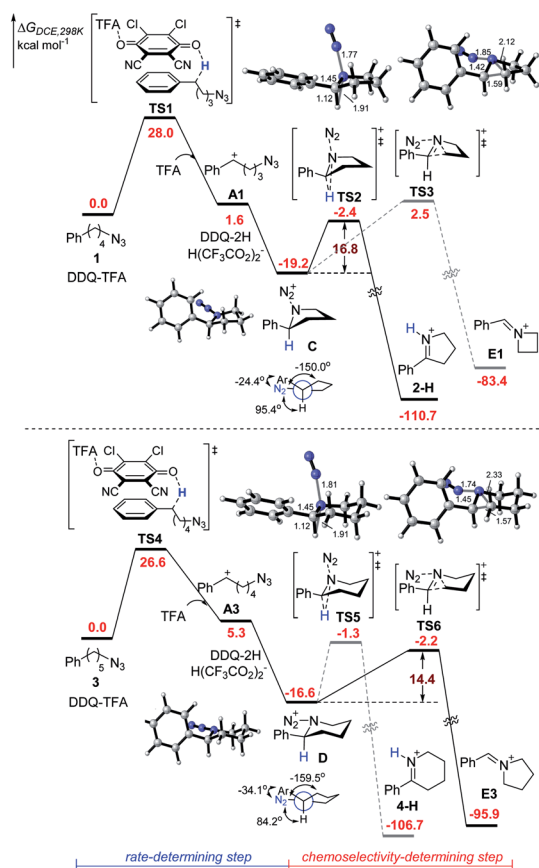
Scheme 2 Proposed mechanism.



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

$\text{Ar}-\text{CH}_2-\text{CH}_2-\text{N}_3 \xrightarrow[\text{TCE (0.5 mL), rt, 12 h}]{\text{TFA (0.2 mL), DDQ (1.2 equiv)}} \text{Ar}-\text{CH}_2-\text{CH}_2-\text{N} \xrightarrow{\text{then NaBH(OAc)}_3} \text{Ar}-\text{CH}_2-\text{CH}_2-\text{N} \text{ (7 (n = 1 or 2))}$		
7a, 55%	7b, 72%	7c, 38% ^b
7d, 78% ^b	7e, 47% ^b	7f, 35% ^b
7g, 49%	7h, 39%	7i, 54%
7j, 33% ^c	7k, 43%	7l, 81%
7m, 80%	7n, 31%	0% (n = 1 or 2)

^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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