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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}

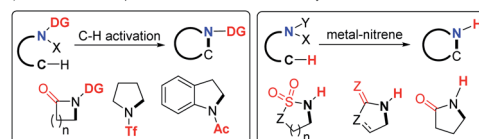
The intramolecular Csp³–H and/or C–C bond amination is very important in modern organic synthesis due to its efficiency in the construction of diversified N-heterocycles. Herein, we report a novel intramolecular cyclization of alkyl azides for the synthesis of cyclic imines and tertiary amines through 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.

Introduction

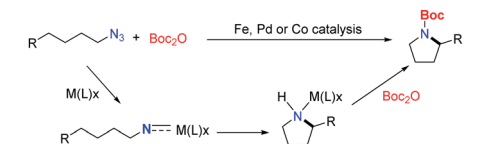
N-Heterocycles are undoubtedly important chemicals in organic synthesis, and have been considered as key functionality regulators in pharmaceuticals.¹ The intramolecular nitrogen insertion into Csp³–H and/or C–C bonds provides an efficient approach to N-heterocycles.^{2–5} The pioneering groups of Aubé⁴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

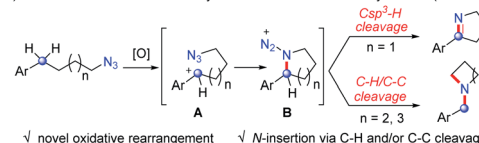
and sulfonyl azides¹¹ has achieved great progress, the corresponding transformation of alkyl azides¹² was rarely developed until recent results.¹³ In 2013, Betley and coworkers demonstrated the pioneering intramolecular aliphatic C–H amination of alkyl azides catalyzed by an iron catalyst (Scheme 1b).^{13a}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

^aState Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Xue Yuan Rd. 38, Beijing 100191, China. E-mail: ssong@bjmu.edu.cn; jiaoning@pku.edu.cn

^bState Key Laboratory of Drug Research, Shanghai Institute of Materia Medical, Chinese Academy of Sciences, Shanghai 201203, China

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‡ These authors contributed equally to this work.



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 provide opportunities for new products. Herein, we described a novel intramolecular nitrogen insertion into a Csp³-H and/or C-C 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

According to our previous element incorporation reactions through the carbocation intermediates generated *in situ* with the 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 N₂ 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 pK_a 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). The treatment of **1a** with 0.4 mL of TFA afforded **2a** in a satisfactory 73% isolated yield (entry 13). Lowering the temperature hampered the reactivity (entry 14).

We explored the generality of this intramolecular Csp³-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 in 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.

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 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 a 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, and TCE = 1,1,2,2-tetrachloroethane.

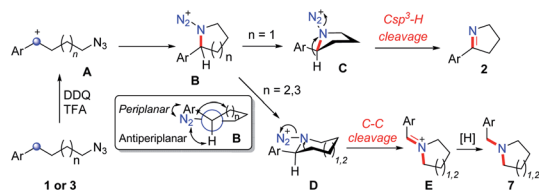
Table 2 Nitrogenation of alkyl azides to imines^a

Product	Yield (%)
2a	73%
2b	46% ^b
2c	66% ^c
2d	70%
2e	69% ^c
2f	26% ^b
2g	31% ^b
2h	62%
2i	38%
2j	41%
2k	32% ^c
2l	63% ^c
2m	71% ^c
2n	73% ^c
2o	49% ^c

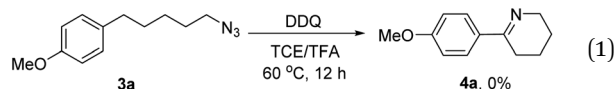
R = $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$

^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.





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

Alkyl azide 3	Reaction conditions	Tertiary amine 7 (n = 1 or 2)	Yield (%)
Ar-CH ₂ -CH ₂ -N ₃	TFA (0.2 mL), DDQ (1.2 equiv), TCE (0.5 mL), rt, 12 h, then NaBH(OAc) ₃	Ar-CH ₂ -CH ₂ -N(CH ₂) _n	7 (n = 1 or 2)
MeO-C ₆ H ₄ -CH ₂ -CH ₂ -N ₃		MeO-C ₆ H ₄ -CH ₂ -CH ₂ -N(CH ₂) _n	7a , 55%
PhO-C ₆ H ₄ -CH ₂ -CH ₂ -N ₃		PhO-C ₆ H ₄ -CH ₂ -CH ₂ -N(CH ₂) _n	7b , 72%
Me-C ₆ H ₄ -CH ₂ -CH ₂ -N ₃		Me-C ₆ H ₄ -CH ₂ -CH ₂ -N(CH ₂) _n	7c , 38% ^b
<i>t</i> Bu-C ₆ H ₄ -CH ₂ -CH ₂ -N ₃		<i>t</i> Bu-C ₆ H ₄ -CH ₂ -CH ₂ -N(CH ₂) _n	7d , 78% ^b
Me-C ₆ H ₄ -CH ₂ -CH ₂ -N ₃		Me-C ₆ H ₄ -CH ₂ -CH ₂ -N(CH ₂) _n	7e , 47% ^b
Me-C ₆ H ₄ -CH ₂ -CH ₂ -N ₃		Me-C ₆ H ₄ -CH ₂ -CH ₂ -N(CH ₂) _n	7f , 35% ^b
MeO-C ₆ H ₃ (O)-CH ₂ -CH ₂ -N ₃		MeO-C ₆ H ₃ (O)-CH ₂ -CH ₂ -N(CH ₂) _n	7g , 49%
MeO-C ₆ H ₄ -CH ₂ -CH ₂ -N ₃		MeO-C ₆ H ₄ -CH ₂ -CH ₂ -N(CH ₂) _n	7h , 39%
MeO-C ₆ H ₄ -CH ₂ -CH ₂ -N ₃		MeO-C ₆ H ₄ -CH ₂ -CH ₂ -N(CH ₂) _n	7i , 54%
MeO-C ₁₀ H ₇ -CH ₂ -CH ₂ -N ₃		MeO-C ₁₀ H ₇ -CH ₂ -CH ₂ -N(CH ₂) _n	7j , 33% ^c
MeO-C ₄ H ₃ S-CH ₂ -CH ₂ -N ₃		MeO-C ₄ H ₃ S-CH ₂ -CH ₂ -N(CH ₂) _n	7k , 43%
MeO-C ₁₂ H ₉ O-CH ₂ -CH ₂ -N ₃		MeO-C ₁₂ H ₉ O-CH ₂ -CH ₂ -N(CH ₂) _n	7l , 81%
MeO-C ₁₂ H ₉ S-CH ₂ -CH ₂ -N ₃		MeO-C ₁₂ H ₉ S-CH ₂ -CH ₂ -N(CH ₂) _n	7m , 80%
MeO-C ₆ H ₄ -CH ₂ -CH ₂ -N ₃		MeO-C ₆ H ₄ -CH ₂ -CH ₂ -N(CH ₂) _n	7n , 31%
MeO-C ₆ H ₄ -CH ₂ -CH ₂ -N ₃		MeO-C ₆ H ₄ -CH ₂ -CH ₂ -N(CH ₂) _n	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.

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