Chemical
Science

ROYAL SOCIETY
OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Chem. Sci.*, 2020, **11**, 4482

All publication charges for this article have been paid for by the Royal Society of Chemistry

Intramolecular Csp^3–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 *[ab]
and Ning Jiao *[a]

Received 31st October 2019
Accepted 7th April 2020

DOI: 10.1039/c9sc05522c

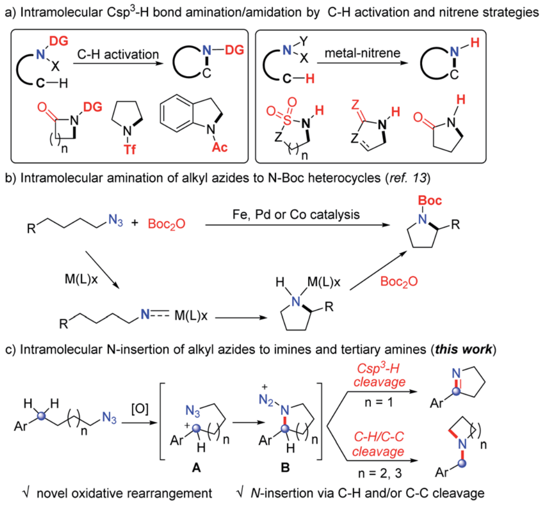
rsc.li/chemical-science

The intramolecular Csp^3–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 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 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 Csp^3–H and/or C–C bonds provides an efficient approach to N-heterocycles.[2–5] The pioneering groups of Aubé[4] and Pearson[5] developed the intramolecular Schmidt reactions[2] and made significant achievements for various N-heterocycle synthesis.[3] The earliest intramolecular aliphatic C–N bond formation named the 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* 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 Csp^3–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 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] 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 Boc$_2$O 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.



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

---

[a] State 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

[b] State Key Laboratory of Drug Research, Shanghai Institute of Materia Medical, Chinese Academy of Sciences, Shanghai 201203, China

† Electronic supplementary information (ESI) available: Characterization data and experimental procedures. See DOI: 10.1039/c9sc05522c

‡ 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 Csp^3–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.

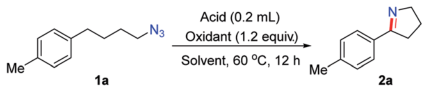
Results and discussion

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 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 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 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 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).

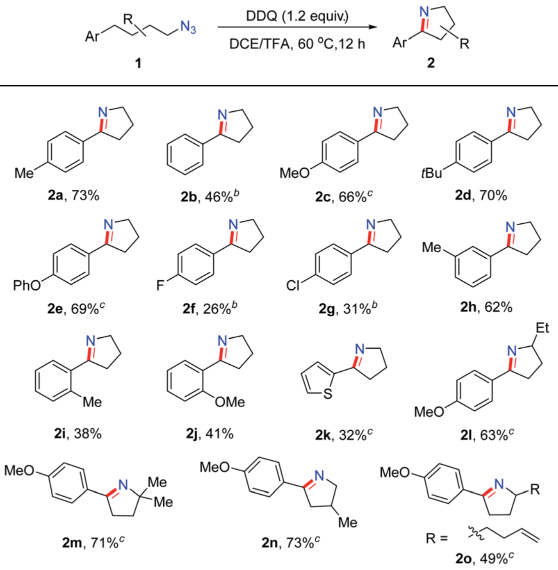
Table 1 Optimization of the reaction conditions[a]



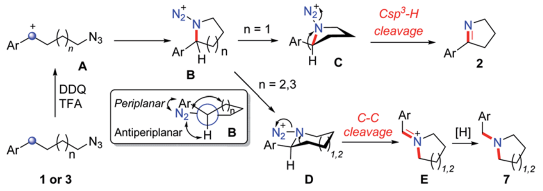
Entry	Oxidant	Acid	Solvent	Yield of **2a**[b]
1	DDQ	TFA	DCE	75%
2	CAN	TFA	DCE	18%
3	TEMPO	TFA	DCE	8%
4	NHPI	TFA	DCE	0
5	PIDA	TFA	DCE	0
6	DDQ	TFA	DMSO	0
7	DDQ	TFA	PhMe	64%
8	DDQ	TFA	MeCN	46%
9	DDQ	TFA	TCE	77%
10	DDQ	AcOH	TCE	10%
11	DDQ	MsOH	TCE	0
12	DDQ	TfOH	TCE	0
13[c]	DDQ	TFA	TCE	84% (73%)[d]
14[e]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

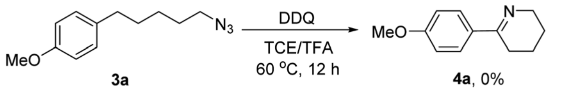
Table 2 Nitrogenation of alkyl azides to imines[a]



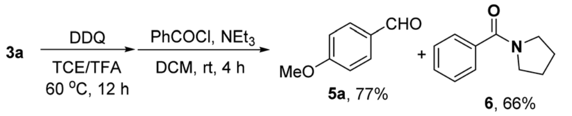
[a] Reaction conditions: **1** (0.3 mmol), DDQ (0.36 mmol) and TFA (0.4 mL) in TCE (0.5 mL) at 60 °C for 12 h. Isolated yields. [b] Performed at 80 °C. [c] Performed with TFA (0.2 mL) at room temperature.



Scheme 2 Proposed mechanism.

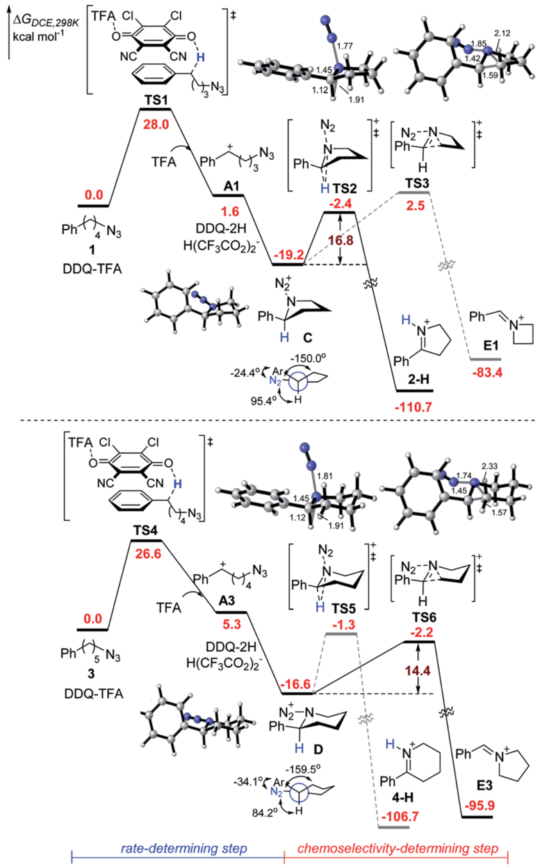


(1)



(2)

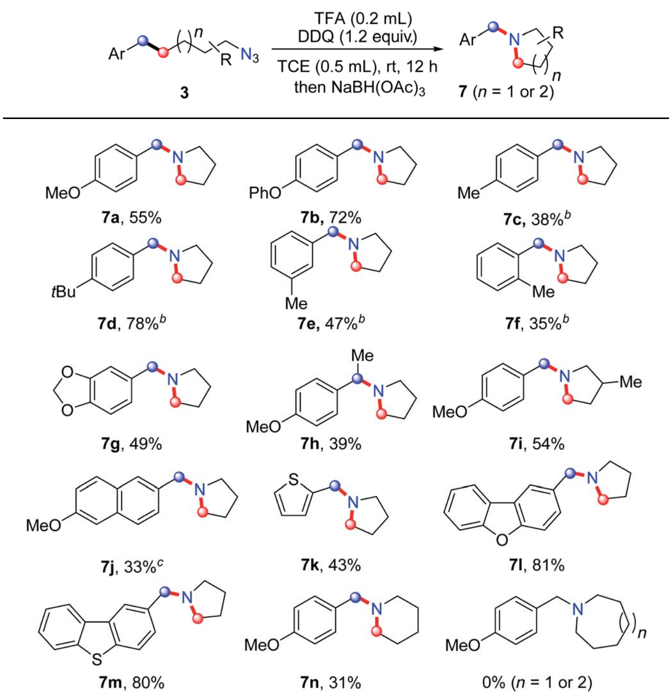
On the basis of this result, we investigated the one-pot reaction of alkyl azide **3** with DDQ and TFA followed by *in situ* reduction. We were delighted to find that the corresponding cyclic tertiary amine **7a** was obtained in 55% yield (Table 3). The substituent on the arene slightly influenced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



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

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 N_2 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 N_2 to afford cyclic imine **2**,

Table 3 Nitrogenation of alkyl azides to tertiary amines[a]



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 $H(CF_3CO_2)_2^-$ 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 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 rearrangement[2] of **C** with the concerted release of N_2 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 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 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

Financial support from the National Key Research and Development Project (No. 2019YFC1708902), the National Natural Science Foundation of China (No. 21632001, 21602005, and 81821004), and the Drug Innovation Major Project (2018ZX09711-001), Peking University (No. PKU2020PKYZX004) is appreciated. Major changes in the central level support projects (2060302), and the Open Research Fund of Shanghai Key Laboratory of Green Chemistry and Chemical Processes are greatly appreciated. We thank Xiaoxue Yang in this group for reproducing the results of **2m** and **7l**.

Notes and references

1 (*a*) A. Deiters and S. F. Martin, *Chem. Rev.*, 2004, **104**, 2199–2238; (*b*) R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845–5859.

2 (*a*) R. F. Schmidt, *Ber.*, 1924, **57**, 704–706; (*b*) P. A. S. Smith, *J. Am. Chem. Soc.*, 1948, **70**, 320–323; (*c*) L. H. Briggs, G. C. De Ath and S. R. Ellis, *J. Chem. Soc.*, 1942, 61–63; (*d*) H. Wolfe, *Org. React.*, 1946, **3**, 307–336; (*e*) P. A. S. Smith, *Molecular Rearrangements*, John Wiley & Sons, New York, 1963; (*f*) R. A. Abramovich and E. P. Kyba, *The Chemistry of the Azido Group*, John Wiley & Sons, London, 1971; (*g*) A. Wrobleski, T. C. Coombs, C. W. Huh, S.-W. Li and J. Aubé, *Org. React.*, 2012, **78**, 1–320; (*h*) M. Szostak and J. Aubé, *Chem. Rev.*, 2013, **113**, 5701–5765.

3 (*a*) J. Aubé and G. L. Milligan, *J. Am. Chem. Soc.*, 1991, **113**, 8965–8966; (*b*) J. Aubé, G. L. Milligan and C. J. Mossman, *J. Org. Chem.*, 1992, **57**, 1635–1637; (*c*) V. Gracias, G. L. Milligan and J. Aubé, *J. Am. Chem. Soc.*, 1995, **117**, 8047–8048; (*d*) G. L. Milligan, C. J. Mossman and J. Aubé, *J. Am. Chem. Soc.*, 1995, **117**, 10449–10459; (*e*) A. Wrobleski, K. Sahasrabudhe and J. Aubé, *J. Am. Chem. Soc.*, 2004, **126**, 5475–5481.

4 (*a*) W. H. Pearson and J. M. Schkeryantz, *Tetrahedron Lett.*, 1992, **33**, 5291–5294; (*b*) W. H. Pearson, R. Walavalkar, J. M. Schkeryantz, W. Fang and J. D. Blickensdorf, *J. Am. Chem. Soc.*, 1993, **115**, 10183–10194.

5 For selected reviews of C-H amination, see: (*a*) H. M. L. Davies and M. S. Long, *Angew. Chem., Int. Ed.*, 2005, **44**, 3518–3520; (*b*) T. W. Lyons and M. S. Sanford,

Chem. Rev., 2010, **110**, 1147–1169; (*c*) J. L. Jeffrey and R. Sarpong, *Chem. Sci.*, 2013, **4**, 4092–4106; (*d*) X.-X. Guo, D.-W. Gu, Z. Wu and W. Zhang, *Chem. Rev.*, 2015, **115**, 1622–1651; (*e*) J. J. Topczewski and M. S. Sanford, *Chem. Sci.*, 2015, **6**, 70–76; (*f*) Y. Park, Y. Kim and S. Chang, *Chem. Rev.*, 2017, **117**, 9247–9301; (*g*) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754–8786; (*h*) F. Collet, R. H. Dodd and P. Dauban, *Chem. Commun.*, 2009, 5061–5074.

6 (*a*) A. W. Hofmann, *Ber. Dtsch. Chem. Ges.*, 1883, **16**, 558–560; (*b*) K. Lçffler and C. Freytag, *Chem. Ber.*, 1909, **42**, 3427–3431; (*c*) S. Lang and J. A. Murphy, *Chem. Soc. Rev.*, 2006, **35**, 146–156; (*d*) P. S. Baran, K. Chen and J. M. Richter, *J. Am. Chem. Soc.*, 2008, **130**, 7247–7249; (*e*) C. Martínez and K. Muñiz, *Angew. Chem., Int. Ed.*, 2015, **54**, 8287–8291; (*f*) E. A. Wappes, S. C. Fosu, T. C. Chopko and D. A. Nagib, *Angew. Chem., Int. Ed.*, 2016, **55**, 9974–9978; (*g*) P. Becker, T. Duhamel, C. J. Stein, M. Reiher and K. Muñiz, *Angew. Chem., Int. Ed.*, 2017, **56**, 8004–8008; (*h*) S. Liu, J. Li, D. Wang, F. Liu, X. Liu, Y. Gao, J. Dai and X. Cheng, *Chin. J. Chem.*, 2019, **37**, 570–574.

7 (*a*) R. Breslow and S. H. Gellman, *J. Chem. Soc., Chem. Commun.*, 1982, 1400–1401; (*b*) R. Breslow and S. H. Gellman, *J. Am. Chem. Soc.*, 1983, **105**, 6728–6729.

8 (*a*) J. L. Roizen, M. E. Harvey and J. Du Bois, *Acc. Chem. Res.*, 2012, **45**, 911–922; (*b*) S.-M. Au, J.-S. Huang, W.-Y. Yu, W.-H. Fung and C.-M. Che, *J. Am. Chem. Soc.*, 1999, **121**, 9120–9132; (*c*) E. Milczek, N. Boudet and S. Blakey, *Angew. Chem., Int. Ed.*, 2008, **47**, 6825–6828; (*d*) M. E. Harvey, D. G. Musaev and J. Du Bois, *J. Am. Chem. Soc.*, 2011, **133**, 17207–17216; (*e*) S. M. Paradine and M. C. White, *J. Am. Chem. Soc.*, 2012, **134**, 2036–2039; (*f*) J. W. Rigoli, C. D. Weatherly, J. M. Alderson, B. T. Vo and J. M. Schomaker, *J. Am. Chem. Soc.*, 2013, **135**, 17238–17241; (*g*) J. M. Alderson, A. M. Phelps, R. J. Scamp, N. S. Dolan and J. M. Schomaker, *J. Am. Chem. Soc.*, 2014, **136**, 16720–16723; (*h*) S. M. Paradine, J. R. Griffin, J. Zhao, A. L. Petronico, S. M. Miller and M. C. White, *Nat. Chem.*, 2015, **7**, 987–994; (*i*) S. Y. Hong, Y. Park, Y. Hwang, Y. B. Kim, M.-H. Baik and S. Chang, *Science*, 2018, **359**, 1016–1021; (*j*) H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417–424; (*k*) K. J. Stowers, K. C. Fortner and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 6541–6544; (*l*) C. G. Espino, P. M. Wehn, J. Chow and J. Du Bois, *J. Am. Chem. Soc.*, 2001, **123**, 6935–6936; (*m*) C. G. Espino, K. W. Fiori, M. Kim and J. Du Bois, *J. Am. Chem. Soc.*, 2004, **126**, 15378–15379; (*n*) D. N. Zalatan and J. Du Bois, *J. Am. Chem. Soc.*, 2008, **130**, 9220–9221.

9 For selected reviews, see: (*a*) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596–2599; (*b*) K. Shin, H. Kim and S. Chang, *Acc. Chem. Res.*, 2015, **48**, 1040–1052; (*c*) S. Bräse, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem., Int. Ed.*, 2005, **44**, 5188–5240; (*d*) E. Leemans, M. D'hooghe and N. De Kimpe, *Chem. Rev.*, 2011, **111**, 3268–3333.

10 (*a*) S. Murata, R. Yoshidome, Y. Satoh, N. Kato and H. Tomioka, *J. Org. Chem.*, 1995, **60**, 1428–1434; (*b*) K. Sun, R. Sachwani, K. J. Richert and T. G. Driver, *Org. Lett.*, 2009, **11**, 3598–3601; (*c*) Q. Nguyen, K. Sun and T. G. Driver, *J. Am. Chem. Soc.*, 2012, **134**, 7262–7265; (*d*) Q. Nguyen, T. Nguyen and T. G. Driver, *J. Am. Chem. Soc.*, 2013, **135**, 620–623; (*e*) O. Villanueva, N. M. Weldy, S. B. Blakey and C. E. MacBeth, *Chem. Sci.*, 2015, **6**, 6672–6675; (*f*) I. T. Alt, C. Guttroff and B. Plietker, *Angew. Chem., Int. Ed.*, 2017, **56**, 10582–10586; (*g*) T. G. Driver, *Org. Biomol. Chem.*, 2010, **8**, 3831–3846.

11 (*a*) J. V. Ruppel, R. M. Kamble and X. P. Zhang, *Org. Lett.*, 2007, **9**, 4889–4892; (*b*) M. Ichinose, H. Suematsu, Y. Yasutomi, Y. Nishioka, T. Uchida and T. Katsuki, *Angew. Chem., Int. Ed.*, 2011, **50**, 9884–9887; (*c*) H. Lu, K. Lang, H. Jiang, L. Wojtas and X. P. Zhang, *Chem. Sci.*, 2016, **7**, 6934–6939; (*d*) H. Lu, H. Jiang, L. Wojtas and X. P. Zhang, *Angew. Chem., Int. Ed.*, 2010, **49**, 10192–10196; (*e*) J. A. McIntosh, P. S. Coelho, C. C. Farwell, Z. J. Wang, J. C. Lewis, T. R. Brown and F. H. Arnold, *Angew. Chem., Int. Ed.*, 2013, **52**, 9309–9312; (*f*) H. Lu, C. Li, H. Jiang, C. L. Lizardi and X. P. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 7028–7032; (*g*) T. K. Hyster, C. C. Farwell, A. R. Buller, J. A. McIntosh and F. H. Arnold, *J. Am. Chem. Soc.*, 2014, **136**, 15505–15508; (*h*) P. Dydio, H. M. Key, H. Hayashi, D. S. Clark and J. F. Hartwig, *J. Am. Chem. Soc.*, 2017, **139**, 1750–1753.

12 (*a*) J. E. Forsee and J. Aubé, *J. Org. Chem.*, 1999, **64**, 4381–4385; (*b*) B. T. Smith, V. Gracias and J. Aubé, *J. Org. Chem.*, 2000, **65**, 3771–3774; (*c*) D. J. Gorin, N. R. Davis and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 11260–11261; (*d*) A. Kapat, E. Nyfeler, G. T. Giuffredi and P. Renaud, *J. Am. Chem. Soc.*, 2009, **131**, 17746–17747; (*e*) M. Szostak and J. Aubé, *J. Am. Chem. Soc.*, 2010, **132**, 2530–2531; (*f*) R. Liu, O. Gutierrez, D. J. Tantillo and J. Aubé, *J. Am. Chem. Soc.*, 2012, **134**, 6528–6531; (*g*) H. F. Motiwala, C. Fehl, S.-W. Li, E. Hirt, P. Porubsky and J. Aubé, *J. Am. Chem. Soc.*, 2013, **135**, 9000–9009; (*h*) X. Sun, C. Gao, F. Zhang, Z. Song, L. Kong, X. Wen and H. Sun, *Tetrahedron*, 2014, **70**, 643–649; (*i*) X.-J. Wang, Y. Su, R. Li and P. Gu, *J. Org. Chem.*, 2018, **83**, 5816–5824; (*j*) M. Charaschanya and J. Aubé, *Nat. Commun.*, 2018, **9**, 934–942.

13 (*a*) E. T. Hennessy and T. A. Betley, *Science*, 2013, **340**, 591–595; (*b*) D. A. Iovan, M. J. T. Wilding, Y. Baek, E. T. Hennessy and T. A. Betley, *Angew. Chem., Int. Ed.*, 2017, **56**, 15599–15602; (*c*) B. Bagh, D. L. J. Broere, V. Sinha, P. F. Kuijpers, N. P. van Leest, B. de Bruin, S. Demeshko, M. A. Siegler and J. I. van der Vlugt, *J. Am. Chem. Soc.*, 2017, **139**, 5117–5124; (*d*) N. C. Thacker, Z. Lin, T. Zhang, J. C. Gilhula, C. W. Abney and W. Lin, *J. Am. Chem. Soc.*, 2016, **138**, 3501–3509; (*e*) Z. Lin, N. C. Thacker, T. Sawano, T. Drake, P. Ji, G. Lan, L. Cao, S. Liu, C. Wang and W. Lin, *Chem. Sci.*, 2018, **9**, 143–151; (*f*) P. F. Kuijpers, M. J. Tiekink, W. B. Breukelaar, D. L. J. Broere, N. P. van Leest, J. I. van der Vlugt, J. N. H. Reek and B. de Bruin, *Chem. –Eur. J.*, 2017, **23**, 7945–7952; (*g*) K.-P. Shing, Y. Liu, B. Cao, X.-Y. Chang, T. You and C.-M. Che, *Angew. Chem., Int. Ed.*, 2018, **57**, 11947–11951; (*h*) D. L. J. Broere, B. de Bruin, J. N. H. Reek, M. Lutz, S. Dechert and J. I. van der

Vlugt, *J. Am. Chem. Soc.*, 2014, **136**, 11574–11577; (*i*) D. L. J. Broere, N. P. van Leest, B. de Bruin, M. A. Siegler and J. I. van der Vlugt, *Inorg. Chem.*, 2016, **55**, 8603–8611; (*j*) N. P. van Leest, L. Grooten, J. I. van der Vlugt and B. de Bruin, *Chem. –Eur. J.*, 2019, **25**, 5987–5993.

14 (*a*) C. Qin and N. Jiao, *J. Am. Chem. Soc.*, 2010, **132**, 15893–15895; (*b*) F. Chen, C. Qin, Y. Cui and N. Jiao, *Angew. Chem., Int. Ed.*, 2011, **50**, 11487–11491; (*c*) C. Qin, T. Shen, C. Tang and N. Jiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 6971–6975; (*d*) J. Liu, X. Wen, C. Qin, X. Li, X. Luo, A. Sun, B. Zhu, S. Song and N. Jiao, *Angew. Chem., Int. Ed.*, 2017, **56**, 11940–11944; (*e*) J. Liu, X. Qiu, X. Huang, X. Luo, C. Zhang, J. Wei, J. Pan, Y. Liang, Y. Zhu, Q. Qin, S. Song and N. Jiao, *Nat. Chem.*, 2019, **11**, 71–77; (*f*) Y. Liang, Y.-F. Liang and N. Jiao, *Org. Chem. Front.*, 2015, **2**, 403–415.

15 (*a*) M. Ringwald, R. Sturmer and H. H. Brintzinger, *J. Am. Chem. Soc.*, 1999, **121**, 1524–1527; (*b*) C. A. Figueira and P. T. Gomes, *Catal. Lett.*, 2015, **145**, 762–768; (*c*) H. Karoui, C. Nsanzumuhire, F. L. Le Moigne and P. Tordo, *J. Org. Chem.*, 1999, **64**, 1471–1477.

16 For selected reviews of C–C cleavage, see: (*a*) C.-H. Jun, *Chem. Soc. Rev.*, 2004, **33**, 610–618; (*b*) A. Dermenci, J. W. Coe and G. Dong, *Org. Chem. Front.*, 2014, **1**, 567–581; (*c*) L. Souillart and N. Cramer, *Chem. Rev.*, 2015, **115**, 9410–9464; (*d*) M. Murakami and N. Ishida, *J. Am. Chem. Soc.*, 2016, **138**, 13759–13769; (*e*) M. Tobisu and N. Chatani, *Chem. Soc. Rev.*, 2008, **37**, 300–307; (*f*) F. Chen, T. Wang and N. Jiao, *Chem. Rev.*, 2014, **114**, 8613–8661; (*g*) X. Wu and C. Zhu, *Chin. J. Chem.*, 2019, **37**, 171–182.

17 All of the geometry optimizations and frequency calculations were performed with the M06-2X functional implemented in 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.†

18 (*a*) B. Chan and L. Radom, *J. Phys. Chem. A*, 2007, **111**, 6456–6467; (*b*) X. Guo, H. Zipse and H. Mayr, *J. Am. Chem. Soc.*, 2014, **136**, 13863–13873; (*c*) S. Yamabe, S. Yamazaki and S. Sakaki, *Int. J. Quantum Chem.*, 2015, **115**, 1533–1542; (*d*) A. S. K. Tsang, A. S. K. Hashmi, P. Comba, M. Kerscher, B. Chan and M. H. Todd, *Chem. –Eur. J.*, 2017, **23**, 9313–9318; (*e*) C. A. Morales-Rivera, P. E. Floreancig and P. Liu, *J. Am. Chem. Soc.*, 2017, **139**, 17935–17944; (*f*) A. Gouranourimi, A. Chipman, R. Babaahmadi, A. Olding, B. F. Yates and A. Ariafard, *Org. Biomol. Chem.*, 2018, **16**, 9021–9029.