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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.

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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-Freytag 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

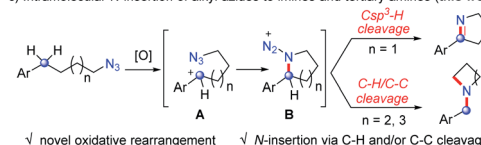
and sulfonyl azides¹¹ has achieved great progress, the corresponding transformation of alkyl azides¹² was rarely developed until recent results.¹³ In 2013, Betley and coworkers demonstrated the pioneering intramolecular aliphatic C-H amination of alkyl azides catalyzed by an iron catalyst (Scheme 1b).^{13a}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

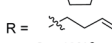


Entry	Oxidant	Acid	Solvent	Yield of 2a ^b
1	DDQ	TFA	DCE	75%
2	CAN	TFA	DCE	18%
3	TEMPO	TFA	DCE	8%
4	NHPI	TFA	DCE	0
5	PIDA	TFA	DCE	0
6	DDQ	TFA	DMSO	0
7	DDQ	TFA	PhMe	64%
8	DDQ	TFA	MeCN	46%
9	DDQ	TFA	TCE	77%
10	DDQ	AcOH	TCE	10%
11	DDQ	MsOH	TCE	0
12	DDQ	TfOH	TCE	0
13 ^c	DDQ	TFA	TCE	84% (73%) ^d
14 ^e	DDQ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



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	R = 	

^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

^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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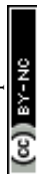
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Notes and references

- (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.
- (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. Wroblewski, 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.
- (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. Wroblewski, K. Sahasrabudhe and J. Aubé, *J. Am. Chem. Soc.*, 2004, **126**, 5475–5481.
- (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.
- 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. Löffler 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.

