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Iron–Phosphine Complex-Catalyzed Intramolecular C(sp^3)–H Amination of Azides

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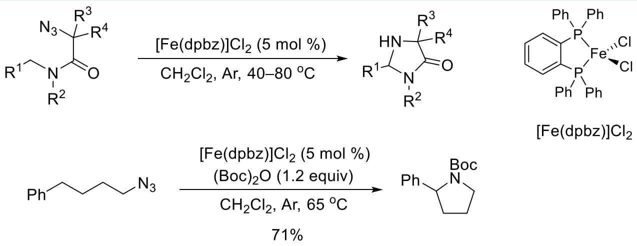
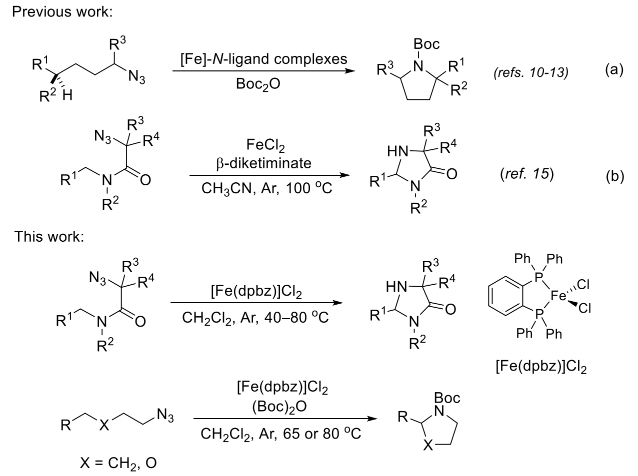
ABSTRACT: Fe(II)–phosphine complex [Fe(dpbz)]Cl_2 was demonstrated to be effective for the intramolecular C(sp^3)–H amination of organic azides. This catalyst exhibited a high catalytic capacity for the transformations from *α*-azido amides to imidazolinones. Cyclization of simple aliphatic azides can be realized as well by using [Fe(dpbz)]Cl_2 as the catalyst.



Catalytic C–H amination mediated by metal–nitrene intermediates is of great interest to chemists because of its potential usefulness in the synthesis of nitrogen-containing compounds.[1] These transformations provide a powerful means for the preparation of N-heterocycles in an atom-economical and step-economical way.[2] Although noble transition metals such as rhodium and ruthenium can readily react with iminoiodinanes or azides to form nitrenoids of high C–H insertion capacity,[3,4] increasing attention has recently been paid to the reactions promoted by late first-row transition metals such as iron[5] and cobalt.[6] These first-row metals are cheap, earth-abundant, and less toxic and therefore are highly preferable as catalysts in practical synthesis.

Organic azides are very useful compounds in organic synthesis.[7] They are viewed as attractive nitrogen sources for C–H amination because of their ready availability as well as their high reactivity.[8] Moreover, using azides as the precursors of nitrenoids is highly desirable in terms of atom economy because only nitrogen gas is released as the byproduct. Recent studies by Betley show that high-spin iron complexes can form iron–imido or iron–iminyl species with organic azides, and these reactive species are capable of aliphatic C–H insertion.[9] By using high-spin iron–dipyrrinato complexes as a catalyst, Betley developed a new atom-economical strategy for the synthesis of pyrrolidines from aliphatic azides via intramolecular C(sp^3)–H amination.[10] The same transformations were also achieved by using other nitrogen-bound iron complexes, as reported by Lin,[11] van der Vlugt and de Bruin,[12] and Che[13] (Scheme 1a). During our investigation of the iron-catalyzed amination reactions of organic azides,[14] we found that the intramolecular C(sp^3)–H amination can be enabled by using a simple catalytic system composed of $FeCl_2$ and a *β*-diketiminate ligand,[15] and thus we developed a new efficient method for the synthesis of structurally useful imidazolinone compounds from *α*-azido amides (Scheme 1b).[16] Although this catalytic system has the merit of simplicity, a high reaction temperature is required to guarantee complete conversion and a high yield. This problem drove us to search for more effective iron catalysts. So far, the reported iron catalysts used for the C(sp^3)–H amination of aliphatic azides are mostly limited to the nitrogen-ligand-bound complexes,[5,17] and to our knowledge, there has not been a

Scheme 1. Iron-Catalyzed Intramolecular C(sp^3)–H Amination of Aliphatic Azides



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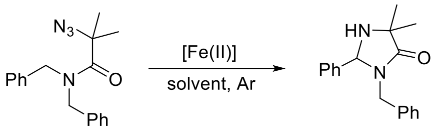
report on using iron−phosphine complexes for this purpose. Our recent investigation shows that the high-spin 1,2-bis(diphenylphosphino)benzene (dpbz) Fe(II) complex [Fe(dpbz)]Br$_2$ ((dpbz = 1,2-bis(diphenylphosphino)benzene)) can catalyze the 1,2-acyl migration of tertiary α-azido ketones.[18] We hoped that the same type of catalyst could also be applicable to the conversion of α-azido amides to imidazolinones. Indeed, it was found that the complex [Fe(dpbz)]Cl$_2$ exhibited high catalytic capacity for the intramolecular C(sp^3)−H amination of α-azido amides. It is superior to the previous catalytic system of FeCl$_2$/β-diketiminate ligand in that the reaction can be realized at a lower temperature with a lower amount of catalyst. Moreover, simple aliphatic azides can also undergo C(sp^3)−H amination by catalysis of [Fe(dpbz)]Cl$_2$ in the presence of di-*tert*-butyl dicarbonate ((Boc)$_2$O). Herein we report our result.

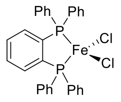
In the initial stage of this investigation, three known high-spin 1,2-bis(diphenylphosphino)benzene Fe(II) complexes (**Cat-1**, **Cat-2**, and **Cat-3**),[19] which were applied in our previous study of the 1,2-acyl migration of tertiary α-azido ketones,[18] were chosen as the catalyst to effect the reaction of 2-azido-*N*,*N*-dibenzyl-2-methylpropanamide (**1a**). The result is summarized in Table 1. It can be seen that all of these catalysts can prompt the anticipated transformation in dichloromethane (DCM) at a moderate temperature of 40 °C, among which [Fe(dpbz)]Cl$_2$ (**Cat-1**) exhibited the highest efficiency. As such, by using 5 mol % of **Cat-1** as the catalyst, compound **2a** was generated in a yield of 99% after 24 h. The reaction also proceeded in chloroform, 1,2-dichloroethane (DCE), 1,2-dibromoethane (DBE), toluene, and acetonitrile, but the yields of **2a** were considerably lower in these solvents. By contrast, the reaction did not take place in chlorobenzene or dimethylformamide (DMF).

Table 1. Screening of the Reaction Conditions[a]

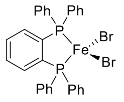


1a **2a**

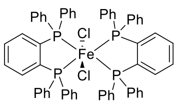
entry	[Fe(II)] (mol %)	solvent	temp (°C)	time (h)	yield (%)[b]
1	**Cat-1** (5)	DCM	40	12	89
2	**Cat-1** (5)	DCM	40	24	99
3	**Cat-1** (5)	DCM	50	12	98
4	**Cat-1** (5)	DCM	25	12	45
5	**Cat-1** (1)	DCM	40	12	52
6	**Cat-1** (10)	DCM	40	12	93
7	**Cat-1** (20)	DCM	40	12	93
8	**Cat-2** (5)	DCM	40	12	30
9	**Cat-3** (5)	DCM	40	12	71
10	**Cat-1** (5)	CHCl$_3$	40	24	61
11	**Cat-1** (5)	DCE	40	24	75
12	**Cat-1** (5)	DBE	40	24	75
13	**Cat-1** (5)	PhCl	40	24	trace[c]
14	**Cat-1** (5)	toluene	40	24	18[d]
15	**Cat-1** (5)	MeCN	40	24	50
16	**Cat-1** (5)	DMF	40	24	trace[c]



Cat-1



Cat-2



Cat-3

[a] Reactions were performed on a 0.2 mmol scale in 2 mL of solvent. [b] Isolated yield. [c] Most of **1a** was recovered. [d] 80% of **1a** was recovered. DCE: 1,2-dichloroethane; DBE: 1,2-dibromoethane.

The optimal conditions (Table 1, entry 2) were then applied to variously substituted α-azido amides, and the result is depicted in Scheme 2. The protocol worked well for *N*,*N*-dibenzyl tertiary α-azido amides, with the corresponding imidazolinone products being generated in good to excellent yield. Notably, the reaction can be performed on gram scale without much loss in efficacy (Scheme 2, foonote *a*). Halogen atoms at the phenyl ring have no effect on the reaction, but the yield is influenced to some extent by the position of the methoxy group.[15] When compound **1h** was used as the substrate, the reaction afforded **2h-1** and **2h-2** in a ratio of 1:1. Compounds **1i**−**l**, which bear a heteroaromatic group adjoining the C−H bond, can be converted as well. The electronic nature of the aryl ring affects the yield to some extent but has little influence on the regioselectivity (**2j** and **2l**). The insertion into the methine C−H bond is much more favored than the methylene C−H bond (**2q**), whereas a modest selectivity was observed between the benzyl group and the methyl group (**2p**).[15] An inferior result was obtained for *N*-phenyl substrates **1m**, **1n**, and **1o**, which need to be treated at a higher temperature to guarantee an acceptable yield. A higher temperature are also required for the amination of the unactivated C(sp^3)−H bond (**2r**−**u**). Besides 3,3-disubstituted imidazolinones, α-monoalkyl-substituted **1aa** and **1ab** also reacted in the same way to give the corresponding imidazolinone products **2aa** and **2ab** in good yield. However, this protocol failed when employed to prepare compounds **2x**, **2y**, **2z**, and **2ac**. Overall, these results are comparable to our previous findings, but the milder conditions render the current protocol more attractive in practical synthesis.

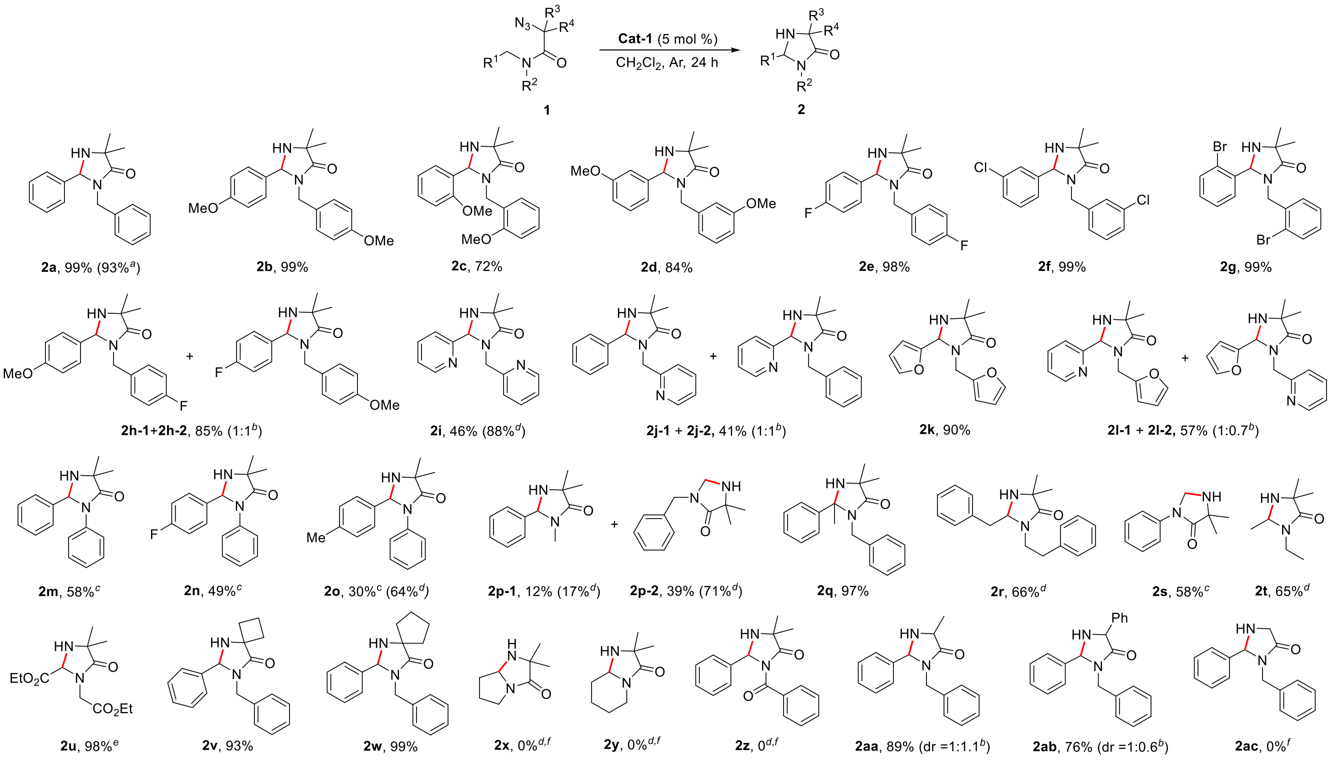
Our previous study showed that the unreactiveness of **1x** and **1y** could be solved by adding Boc$_2$O into the reaction system.[15] Thus a modified protocol with the addition of 1.2 equiv of Boc$_2$O was employed to engender the desired cyclization. As expected, Boc-protected imidazolinones **3x**, **3y**, and **3ac** were generated in good yield under the indicated conditions (Scheme 3).

The standard conditions were also applied to compounds **4** and **5**, which are analogous in structure to compound **1a**. As shown in Scheme 4, different results were obtained for these two substrates: Whereas **5** can be transformed into the cyclization product **7** in high yield, the reaction did not occur for **4**.

Intramolecular C−H amination of aliphatic azides constitutes an effective approach toward structurally important pyrrolidines. Several different iron complexes[10−13] have been used to engender this transformation. To see if [Fe(dpbz)]Cl$_2$ could also catalyze the cyclization of simple aliphatic azides, we subjected compounds **8**−**14** to the present conditions. As shown in Table 2, these compounds reacted smoothly under the indicated conditions when Boc$_2$O was used, affording the corresponding pyrrolidines in good yield.

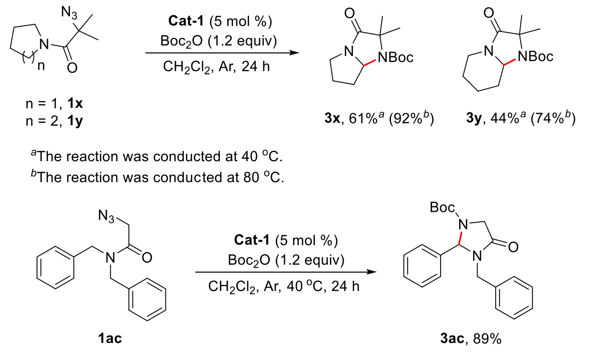
Iron-catalyzed C(sp^3)−H amination of azides is believed to proceed via a radical process that involves a high-spin ferric iminyl or imido radical complex as the intermediate.[9,10] This mechanism might also operate for the present [Fe(dpbz)]Cl$_2$-catalyzed reactions (Scheme 5). This hypothesis is supported by our kinetic isotopic experiment with **1m-d** and **8-d**, which

Scheme 2. Scope of the Reaction[g]



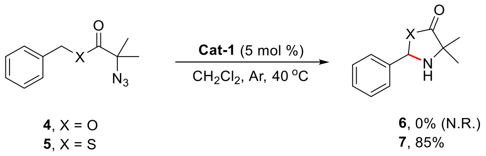
[a] Reaction was conducted on a 5.0 mmol scale in 25 mL of CH_2Cl_2. [b] Ratio was determined by ^{1}H NMR. [c] Reaction was conducted at 60 °C. [d] Reaction was conducted at 80 °C. [e] Reaction was conducted at 65 °C. [f] With most of the reactant recovered. [g] Reactions were conducted on a 0.2 mmol scale at 40 °C unless otherwise specified. The yields are isolated yields.

Scheme 3. Boc_2O-Facilitated Reactions of 1x, 1y, and 1ac

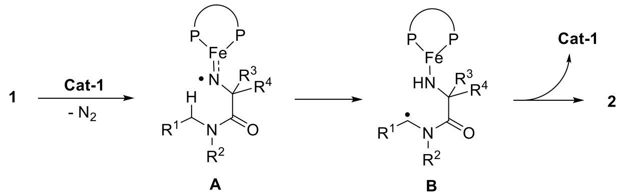


[a] The reaction was conducted at 40 °C.
[b] The reaction was conducted at 80 °C.

Scheme 4. Scope of the Reaction 2

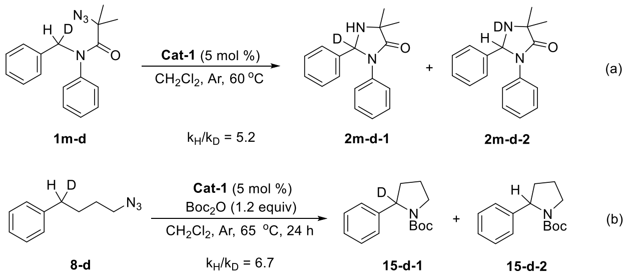


Scheme 5. Plausible Mechanism



gave k_H/k_D values of 5.2 and 6.7 for these two compounds, respectively (Scheme 6). These values are close to the reported ones.[10a,15] Moreover, the result of the radical clock experiment (Scheme 7) also accords with the previous reports. The fact that no ring-opening products were formed in the case of **1ad** reflects a fast radical rebound step. Apart from this scenario, it should be noted that these results are also consistent with a mechanism of direct nitrene insertion into the C−H bond.

Scheme 6. Kinetic Isotopic Experiment



Scheme 7. Radical Clock Experiment

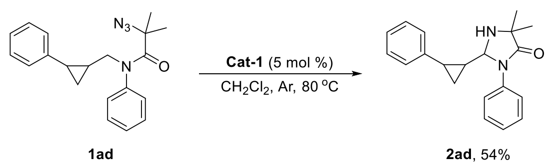
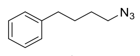
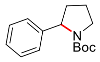
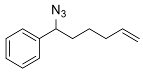
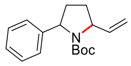
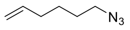
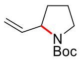
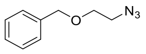
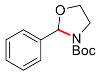
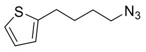
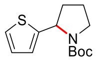
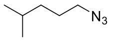
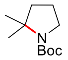
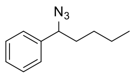
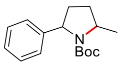


Table 2. $[Fe(dpbz)]Cl_2$-Catalyzed Reactions of Aliphatic Azides[a]

entry	substrate	product	yield (%)[b]
1	 **8**	 **15**	71
2	 **9**	 **16**	75
3	 **10**	 **17**	44 (74[c])
4	 **11**	 **18**	90
5	 **12**	 **19**	87[c]
6	 **13**	 **20**	45 (55[c])
7	 **14**	 **21**	40[c]

[a]Reaction was performed on a 0.2 mmol scale in 2 mL of CH_2Cl_2 with 5 mol % of **Cat-1** and 1.2 equiv of Boc_2O under an argon atmosphere. Reaction time: 24 h. The reaction temperature was 65 °C unless otherwise indicated. [b]Isolated yield. [c]Reaction temperature was 80 °C.

In summary, we have demonstrated that the Fe(II)−phosphine complex $[Fe(dpbz)]Cl_2$ is an competent catalyst for the intramolecular $C(sp^3)$−H amination of organic azides. A variety of differently substituted α-azido amides can be converted to the corresponding imidazolinones by the catalysis of $[Fe(dpbz)]Cl_2$. Compared with the previously used catalytic system of $FeCl_2$ and β-diketiminate, $[Fe(dpbz)]Cl_2$ performed better in that the reaction can be realized under milder conditions at a lower catalyst loading level. Moreover, it is also capable of promoting the cyclization of aliphatic azides in the presence of Boc_2O. Considering the wide applications of chiral phosphine ligands in asymmetric synthesis, we hope that a suitable chiral iron−phosphine complex can be found to enable the enantioselective $C(sp^3)$−H amination of azides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00308.

General experimental procedures, characterization data, and copies of ^1H NMR and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417−424. (b) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061−5074. (c) Dequirez, G.; Pons, V.; Dauban, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 7384−7395. (d) Suarez, A. I. O.; Lyaskovskyy, V.; Reek, J. N. H.; van der Vlugt, J. I.; de Bruin, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 12510−12529. (e) Shimbayashi, T.; Sasakura, K.; Eguchi, A.; Okamoto, K.; Ohe, K. *Chem. - Eur. J.* **2018**, *25*, 3156−3180. (f) Park, Y.; Kim, Y.; Chang, S. *Chem. Rev.* **2017**, *117*, 9247−9301.

(2) (a) Stokes, B. J.; Driver, T. G. *Eur. J. Org. Chem.* **2011**, *2011*, 4071−4088. (b) Roizen, J. L.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Res.* **2012**, *45*, 911−922. (c) Jeffrey, J. L.; Sarpong, R. *Chem. Sci.* **2013**, *4*, 4092−4106. (d) Chu, J. C. K.; Rovis, T. *Angew. Chem., Int. Ed.* **2018**, *57*, 62−101.

(3) (a) Jiao, J.; Murakami, K.; Itami, K. *ACS Catal.* **2016**, *6*, 610−633. (b) Park, Y.; Kim, Y.; Chang, S. *Chem. Rev.* **2017**, *117*, 9247−9301.

(4) (a) Yuan, S.-W.; Han, H.; Li, Y.-L.; Wu, X.; Bao, X.; Gu, Z.-Y.; Xia, J.-B. *Angew. Chem., Int. Ed.* **2019**, *58*, 8887−8892. (b) Qin, J.; Zhou, Z.; Cui, T.; Hemming, M.; Meggers, E. *Chem. Sci.* **2019**, *10*, 3202−3207.

(5) (a) Zhang, L.; Deng, L. *Chin. Sci. Bull.* **2012**, *57*, 2352−2360. (b) Wang, P.; Deng, L. *Chin. J. Chem.* **2018**, *36*, 1222−1240. (c) Plietker, B.; Röske, A. *Catal. Sci. Technol.* **2019**, *9*, 4188−4197. (d) Liu, Y.; You, T.; Wang, T.; Che, C.-M. *Tetrahedron* **2019**, *75*, 130607.

(6) (a) Ruppel, J. V.; Kamble, R. M.; Zhang, X. P. *Org. Lett.* **2007**, *9*, 4889−4892. (b) Lu, H.; Subbarayan, V.; Tao, J.; Zhang, X. P. *Organometallics* **2010**, *29*, 389−393. (c) Lyaskovskyy, V.; Suarez, A. I. O.; Lu, H.; Jiang, H.; Zhang, X. P.; de Bruin, B. *J. Am. Chem. Soc.* **2011**, *133*, 12264−12273. (d) Villanueva, O.; Weldy, N. M.; Blakey, S. B.; MacBeth, C. E. *Chem. Sci.* **2015**, *6*, 6672−6675. (e) Tseberlidis, G.; Zardi, P.; Caselli, A.; Cancogni, D.; Fusari, M.; Lay, L.; Gallo, E. *Organometallics* **2015**, *34*, 3774−3781. (f) Kuijpers, P. F.; Tiekink, M. J.; Breukelaar, W. B.; Broere, D. J.; van Leest, N. P.; van der Vlugt, J. I.; Reek, J. N. H.; de Bruin, B. *Chem. - Eur. J.* **2017**, *23*, 7945−7952. (g) Goswami, M.; Geuijen, P.; Reek, J. N. H.; de Bruin, B. *Eur. J. Inorg. Chem.* **2018**, *2018*, 617−626. (h) Baek, Y.; Betley, T. A. *J. Am. Chem. Soc.* **2019**, *141*, 7797−7806. (i) Baek, Y.; Hennessy, E. T.; Betley, T. A. *J. Am. Chem. Soc.* **2019**, *141*, 16944−16953.

(7) (a) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297−368. (b) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188−5240. (c) *Organic Azides: Syntheses and Applications*; Bräse, S., Banert, K., Eds.; John Wiley & Sons: Chichester, U.K., 2010.

(8) (a) Intrieri, D.; Zardi, P.; Caselli, A.; Gallo, E. *Chem. Commun.* **2014**, *50*, 11440−11453. (b) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040−1052.

(9) (a) King, E. R.; Hennessy, E. T.; Betley, T. A. *J. Am. Chem. Soc.* **2011**, *133*, 4917−4923. (b) Iovan, D. A.; Betley, T. A. *J. Am. Chem. Soc.* **2016**, *138*, 1983−1993. (c) Wilding, M. J. T.; Iovan, D. A.; Betley, T. A. *J. Am. Chem. Soc.* **2017**, *139*, 12043−12049. (d) Wilding, M. J. T.; Iovan, D. A.; Wrobel, A. T.; Lukens, J. T.; MacMillan, S. N.; Lancaster, K. M.; Betley, T. A. *J. Am. Chem. Soc.* **2017**, *139*, 14757−14766.

(10) (a) Hennessy, E. T.; Betley, T. A. *Science* **2013**, *340*, 591−595. (b) Iovan, D. A.; Wilding, M. J.; Baek, Y.; Hennessy, E. T.; Betley, T. A. *Angew. Chem., Int. Ed.* **2017**, *56*, 15599−15602.

(11) (a) Thacker, N. C.; Lin, Z.; Zhang, T.; Gilhula, J. C.; Abney, C. W.; Lin, W. J. *J. Am. Chem. Soc.* **2016**, *138*, 3501−3509. (b) Thacker, N. C.; Ji, P.; Lin, Z.; Urban, A.; Lin, W. *Faraday Discuss.* **2017**, *201*, 303−315.

(12) Bagh, B.; Broere, D. L. J.; Sinha, V.; Kuijpers, P. F.; van Leest, N. P.; de Bruin, B.; Demeshko, S.; Siegler, M. A.; van der Vlugt, J. I. *J. Am. Chem. Soc.* **2017**, *139*, 5117−5124.

(13) Shing, K.-P.; Liu, Y.; Cao, B.; Chang, X.-Y.; You, T.; Che, C.-M. *Angew. Chem., Int. Ed.* **2018**, *57*, 11947−11951. (b) Du, Y.-D.; Xu, Z.-J.; Zhou, C.-Y.; Che, C.-M. *Org. Lett.* **2019**, *21*, 895−899.

(14) Yang, T.; Fan, X.; Zhao, X.; Yu, W. *Org. Lett.* **2018**, *20*, 1875−1879.

(15) (a) Zhao, X.; Liang, S.; Fan, X.; Yang, T.; Yu, W. *Org. Lett.* **2019**, *21*, 1559−1563. (b) Correction: Zhao, X.; Liang, S.; Fan, X.; Yang, T.; Yu, W. *Org. Lett.* **2020**, DOI: 10.1021/acs.orglett.0c00658.

(16) A similar ruthenium-catalyzed enantioselective intramolecular C(sp^3)−H amination of 2-azidoacetamides was reported by Meggers. See: Zhou, Z.; Chen, S.; Qin, J.; Nie, X.; Zheng, X.; Harms, K.; Riedel, R.; Houk, K. N.; Meggers, E. *Angew. Chem., Int. Ed.* **2019**, *58*, 1088−1093.

(17) The intramolecular C(sp^3)−H amination has also been realized by using $Bu_4N[Fe(CO)_3(NO)]$ as a catalyst. Alt, I. T.; Guttroff, C.; Plietker, B. *Angew. Chem., Int. Ed.* **2017**, *56*, 10582−10586.

(18) Yang, T.; Lin, Y.; Yang, C.; Yu, W. *Green Chem.* **2019**, *21*, 6097−6102.

(19) (a) Barclay, J. E.; Leigh, G. J.; Houlton, A.; Silver, J. *J. Chem. Soc., Dalton Trans.* **1988**, 2865−2870. (b) Bedford, R. B.; Huwe, M.; Wilkinson, M. C. *Chem. Commun.* **2009**, 600−602. (c) Kumar, V. P.; Babu, V. S.; Yahata, K.; Kishi, Y. *Org. Lett.* **2017**, *19*, 2766−2768.