CJC Chinese Journal of Chemistry
中国化学 - An International Journal

Check for updates

Accepted Article

Title: Iron-Catalyzed Primary C–H Amination of Sulfamate Esters and Its Application in the Synthesis of Azetidines

Authors: Yan Zhang, Dayou Zhong, Muhammad Usman, Peng Xue, and Wen-Bo Liu*

This manuscript has been accepted and appears as an Accepted Article online.

This work may now be cited as: *Chin. J. Chem.* **2020**, *38,* 10.1002/cjoc.202000299.

The final Version of Record (VoR) of it with formal page numbers will soon be published online in Early View: http://dx.doi.org/10.1002/cjoc.202000299.

WILEY-VCH SIOC CCS

ISSN 1001-604X • CN 31-1547/O6
mc.manuscriptcentral.com/cjoc
www.cjc.wiley-vch.de

Concise Report

Iron catalysis, Primary C–H activation, Amination, Heterocycle, Azetidine

CJC Chinese Journal of Chemistry 中国化学 - An International Journal

Iron-Catalyzed Primary C–H Amination of Sulfamate Esters and Its Application in the Synthesis of Azetidines

Yan Zhang, Dayou Zhong, Muhammad Usman, Peng Xue, and Wen-Bo Liu*

Sauvage Center for Molecular Sciences, Engineering Research Center of Organosilicon Compounds & Materials (Ministry of Education), College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, Hubei 430072, China

Cite this paper: *Chin. J. Chem.* **2019**, *37*, XXX—XXX. **DOI: 10.1002/cjoc.201900XXX**

Summary of main observation and conclusion The direct amination of unactivated primary C–H bonds is extremely challenging due to their inert nature. Here we report an intramolecular primary C–H amination of sulfamate esters using an iron catalyst derived from iron(II) triflate and bipyridine. An array of oxathiazinanes were synthesized in moderate to good yields, which were further converted into biologically important azetidines by a one-pot procedure. This research demonstrates the potential of applying simple nitrogen ligands in iron-catalyzed C–H functionalization and offers an accessible alternative to state-of-the-art iron-nitrene chemistry.

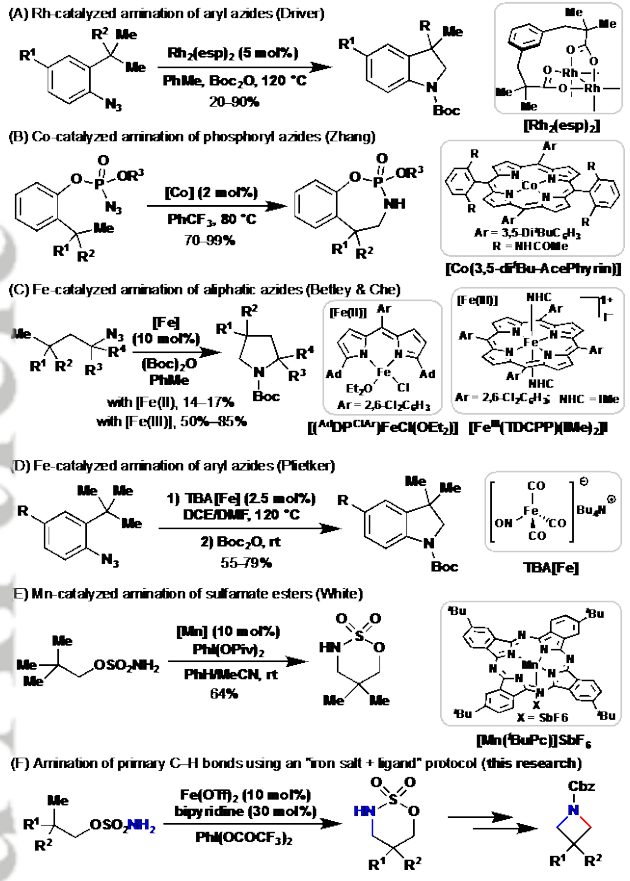
Background and Originality Content

Nitrogen-containing heterocycles are omnipresent in many synthetic intermediates, natural products, and pharmaceuticals.[1] In last several decades, considerable endeavors have been committed to develop efficient methods toward their synthesis.[2] As one of the most straightforward and economical methods, direct C–H amination of ubiquitous hydrocarbons by means of transition metal mediated nitrene insertion has drawn numerous attentions of the community.[3,4] Significant advances have been achieved albeit primarily employing source-limited metals (i.e., rhodium, iridium, and ruthenium).[3g–3n] Recently, remarkable examples of non-precious metal-catalyzed nitrene insertion reactions[4] have been emerged as a powerful C–N bond formation method by the contributions of Che,[5] White,[6] Zhang,[7] Betley,[8] and other.[4,9]

To date, the nitrene insertion reactions of aliphatic C(sp^3)–H bonds are mainly limited to activated substrates such as allylic and benzylic C–H bonds.[3,4] Amination of unactivated aliphatic C–H bonds is of substantial challenge owing to their thermodynamic stability, in particular for primary C–H bonds with a bond-dissociation energy (BDE) of 100.5 kcal/mol.[10] Only a handful of examples capable of primary C–H amination have been known. Driver and co-workers realized an intramolecular reaction of aryl azides catalyzed by a thermally robust Rh(II) complex for the synthesis of indolines (Scheme 1A).[3i] In 2010, the Zhang group reported an excellent cobalt-catalyzed amination of the primary C–H bond of phosphoryl azides (Scheme 1B).[7a] In 2013, the Betley group employed an iron(II)-dipyrrinato catalyst [($^{Ad}DP^{ClAr}$)FeCl(OEt_2)] to achieve the amination of a variety of C–H bonds, but exhibited poor reactivity toward primary C–H bonds (Scheme 1C).[8b] Remarkably, a bis-NHC-stabilized iron(III) porphyrin catalyst, [Fe(TDCPP)($IMe)_2$]I, was developed by Che et al. enabling the amination of inert aliphatic C–H bonds in good yields.[5c] In 2017, amination of aryl azides was disclosed by the Plietker group using a nucleophilic iron catalyst $Bu_4N[Fe(CO)_3(NO)]$ (Scheme 1D).[11]

Scheme 1 Transition-metal-catalyzed nitrene insertion of primary C–H

bonds



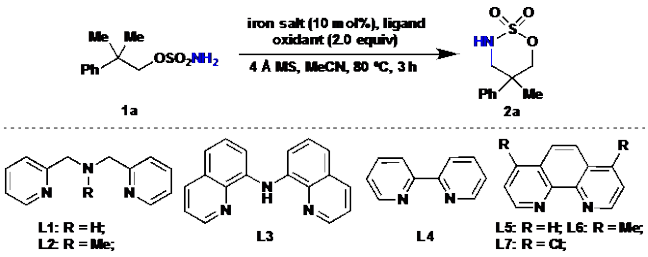
Additionally, a notable manganese-catalyzed amination of sulfamate esters under mild conditions was accomplished by the White group in 2015, and a wide range of substrates were tolerated in excellent reactivity and selectivity (Scheme 1E).[6b]

Utilizing abundant iron salts and readily available nitrogen ligands to generate the active iron catalysts in situ has advantages in practical synthesis due to their easy accessibility.[12] Seminal reports using the "iron salt + ligand" protocol were independently disclosed by the Che[12a] and Chan[12b] groups. In 2019, our group developed an iron/aminopyridine-catalyzed amination of aliphatic secondary and tertiary C–H bonds.[13] Encouraged by these results, we sought to further expand this simple iron system to realize more challenging primary C–H amination (Scheme 1F). Herein, we report the successful development of an intramolecular primary C–H bond amination of sulfamate esters using an iron catalyst derived from $Fe(OTf)_2$ and bipyridine. Furthermore, a variety of azetidines, conformationally rigid scaffold widely existed in potential drug candidates and other bio-important compounds,[14] are accessed from the amination products.

Results and Discussion

We commenced our studies with 2-methyl-2-phenylpropyl sulfamate ester **1a** as a model substrate to optimize reaction conditions (see Tables S1–S6 in the SI for details). The representative results were outlined in Table 1. Among the examined ligands (entries 1–7, and Table S1), tridentate ligands (**L1–L3**) generally showed inferior reactivity to bidentate ligands (**L4–L7**). Aminopyridine-type ligands, previously used in iron-catalyzed amination of sulfamate esters and sulfonamides,[12] resulted in poor reactivity. We were delighted to find that the use of bipyridine **L4** offered 60% NMR yield of the desired oxathiazinane **2a** (entry 4). Examination of 1,10-phenanthroline-type ligands (**L5–L7**) revealed that dichloro-substituted **L7** is more efficient (entry 7). Although slightly lower yield was obtained with **L4** in comparison with **L7** (60% vs 63%, entries 4 vs 7), we decided to use **L4** as the ligand for further optimization due to its readily availability and low cost. A number of oxidants were tested, and $PhI(OCOCF_3)_2$ was found superior. Further examination of iron sources, solvents, and temperature (entries 11–15) revealed that the use of $Fe(OTf)_2$ at 100 °C in acetonitrile improved the isolation yield to 81%, which was identified as the optimal reaction conditions (entry 15). Control experiment without the use of ligand resulted in no product formation (entry 16).

Table 1 Condition optimizations

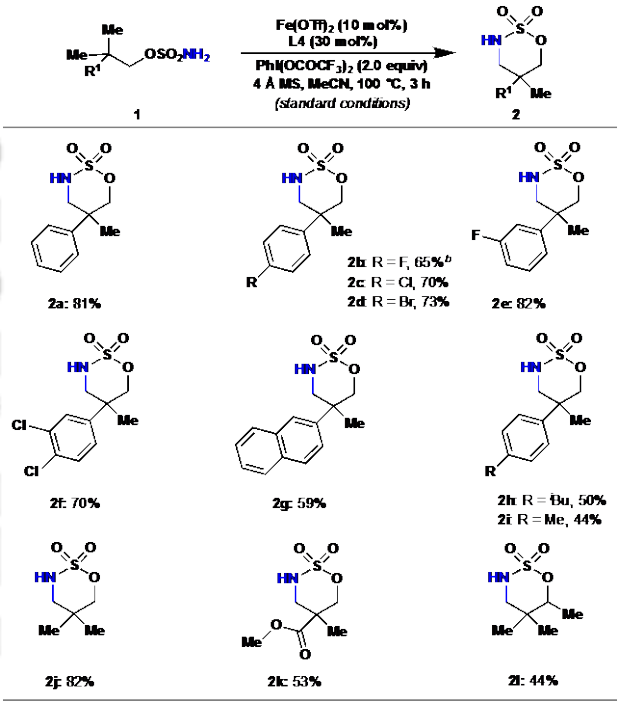


entry[a]	iron salt	ligand (x mol%)	oxidant	**2a** (%)[b]
1	$Fe(ClO_4)_2$	**L1** (20)	$PhI(OCOCF_3)_2$	20
2	$Fe(ClO_4)_2$	**L2** (20)	$PhI(OCOCF_3)_2$	11
3	$Fe(ClO_4)_2$	**L3** (20)	$PhI(OCOCF_3)_2$	28
4	$Fe(ClO_4)_2$	**L4** (30)	$PhI(OCOCF_3)_2$	60 (55)[c]
5	$Fe(ClO_4)_2$	**L5** (30)	$PhI(OCOCF_3)_2$	52
6	$Fe(ClO_4)_2$	**L6** (30)	$PhI(OCOCF_3)_2$	44
7	$Fe(ClO_4)_2$	**L7** (30)	$PhI(OCOCF_3)_2$	63
8	$Fe(ClO_4)_2$	**L4** (30)	$PhI(OAc)_2$	22
9	$Fe(ClO4)_2$	**L4** (30)	PhI(DMM)	33
10	$Fe(ClO_4)_2$	**L4** (30)	$PhI(OPiv)_2$	21
11	$FeCl_2$	**L4** (30)	$PhI(OCOCF_3)_2$	33[c]
12	$Fe(acac)_2$	**L4** (30)	$PhI(OCOCF_3)_2$	48[c]
13	$Fe(OAc)_2$	**L4** (30)	$PhI(OCOCF_3)_2$	70[c]
14	$Fe(OTf)_2$	**L4 (30)**	$PhI(OCOCF_3)_2$	73[c]
15[d]	**$Fe(OTf)_2$**	**L4 (30)**	**$PhI(OCOCF_3)_2$**	**81**[c]
16[e]	$Fe(OTf)_2$	–	$PhI(OCOCF_3)_2$	N.D.

[a]Reaction conditions: **1a** (0.2 mmol), iron salt (0.02mmol, 10 mol%), oxidant (0.4 mmol), and 4 Å MS (50 mg) in MeCN (2 mL) at 80 °C for 3 h. [b]NMR yield

using 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield. [d]100 °C. PhI(DMM), phenyliodonium dimethylmalonate.[15] [e]Without ligand. N.D., not detected.

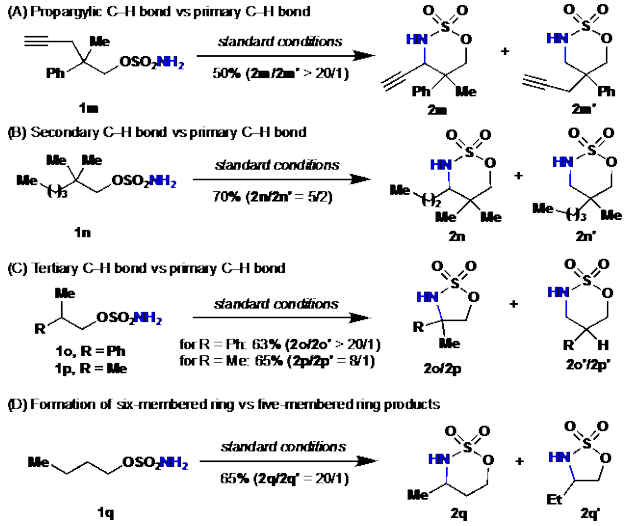
Table 2 Substrate scope[a]



[a]Reaction conditions: **1** (0.4 mmol), $Fe(OTf)_2$ (0.04 mmol, 10 mol%), **L4** (0.12 mmol, 30 mol%), $PhI(OCOCF_3)_2$ (0.8 mmol), and 4 Å MS (100 mg) in MeCN (4 mL) at 100 °C for 3 h. [b]0.2 mmol scale.

Next, the substrate scope was explored (Table 2). Substrates (**1b–1f**) bearing electron-deficient groups, such as F, Cl, and Br, on the aryl ring generated the corresponding oxathiazinanes **2b–2f** in 65–82% yields. Substrate **1g** containing an *α*-naphthyl group, provided the corresponding product **2g** in 59% yield. *para*-Isobutyl- and *para*-methyl-substituted 2-aryl-2-methylpropyl sulfamates (**2h**, **2i**) were also investigated and resulted in moderate yields (44–50%). Previously, synthesis of oxathiazinane **2j** from the corresponding starting material **1j** catalyzed by an iron phthalocyanine catalyst ([FePc]·SbF_6) resulted in only 3% yield.[6b] An significant improvement (64% yield) was achieved by the use of a manganese *tert*-butylphthalocyanine catalyst ([Mn(*t*BuPc)]·SbF_6).[6b] By contrast, our chemistry afforded **2j** in 82% yield under the standard reaction conditions. Additionally, an ester-containing substrate **1k** was also tolerated delivering the oxathiazinane **2k** in 53% yield. Secondary alcohol-derived sulfamate substrate **1l** was compatible to form the corresponding product **2l** in 44% yield. A sulfonamide substrate was also subjected to the standard reaction conditions, but failed to afford any desired product (Scheme S1 in the SI).

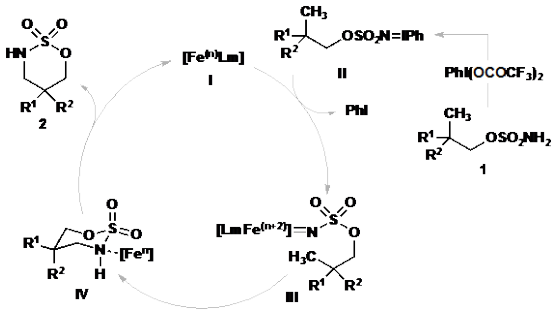
Scheme 2 Investigation of site selectivity



Systematic studies by White and Che disclosed that the reactivity trends of amination using both heme-like[6a] and nonheme[5b] iron catalysts are in accordance to the C—H bond dissociation energies. The selectivity of this method toward sulfamate esters with multiple C–H bond types were also studied (Scheme 2). The amination of substrate **1m**, bearing both propargylic and primary C–H bonds, occurred at the propargylic site exclusively to provide **2m** in moderate yield (Scheme 2A). Treatment of substrate **1n** under the standard conditions delivered a 5:2 mixture of secondary C–H versus primary C–H amination products (Scheme 2B). Although sterically hindered, tertiary C–H amination is much more preferred over primary C–H amination, as showcasing by the reactions of substrates **1o** and **1p** (Scheme 2C). Moreover, with substrate **1q**, six-membered ring oxathiazinae **2q** is formed preferentially over the five-membered ring product **2q'** (Scheme 2D). Those trends of selectivity, intrinsically driven by the substrates themselves, are in line with previous observations.[5b,6a]

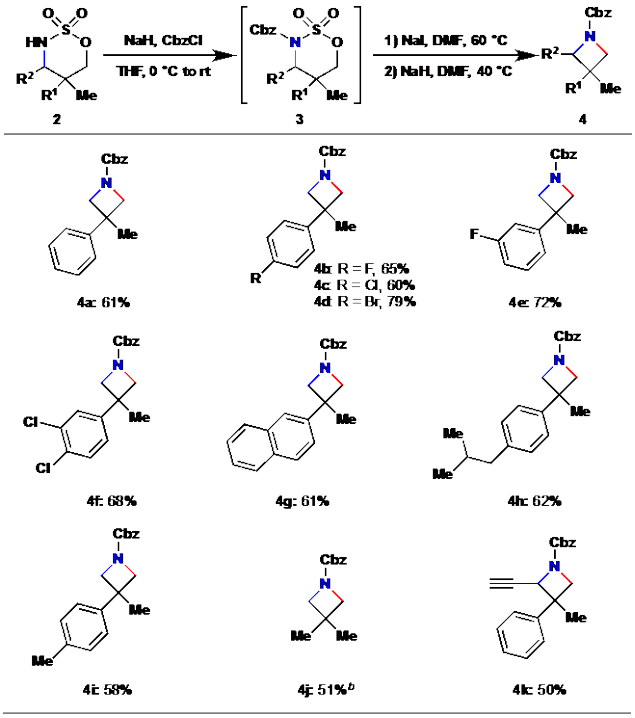
According to the literature precedent[5b,c,8b], a possible reaction pathway was proposed (Scheme 3). Treatment of substrate **1** with $PhI(OCOCF3)_2$ generates compound **II**, which upon reacts with the iron catalyst **I** leading to the formation of an imido-iron species **III** together with iodobenzene. Then direct C–H insertion or H-atom abstraction/radical recombination[5c,8b] of **III** yields the desired product **2** and regenerates the catalyst.

Scheme 3 Proposed reaction pathway



As showcased in literature, oxathiazinanes are valuable intermediates for heterocycles,[16a] 1,3-amino ethers,[16b] and other bioactive targets.[16] To further demonstrate the utility of this iron-catalyzed amination reaction, a one-pot procedure was used to convert oxathiazinanes synthesized above to azetidines, a structurally and biologically important class of *N*-heterocyclic compounds.[14] Protection of the amination products **2** with CbzCl afforded *N*-Cbz oxathiazinanes **3**. Without chromatographic purification of the intermediates **3**, NaI was added followed by NaH to generate azetidines **4** through sequential ring-opening/ring-closing steps.[17] As shown in Table 3, the azetidines **4a–4m** were synthesized in 50–79% yields by this one-pot procedure. Delightedly, 3,3-dimethylazetidine **4j** was also generated in 51% yield. Notably, 3,3-dimethyl-azetidine is an important pattern in a number of biologically active molecules, such as an dopamine receptor antagonist zetidoline,[14c] a PDE4 inhibitor,[14d] and an acetylcholine receptor agonist[14e] as shown in Figure 1.

Table 3 One-pot synthesis of azetidines from oxathiazinanes[a]



[a]Reaction conditions: **2** (0.1 mmol), CbzCl (0.2 mmol), NaH (0.2 mmol in THF (1 mL) at room temperature for 30 min; NaI (0.15 mmol) in DMF (1 mL) at 60 °C for 1 h, then NaH (0.3 mmol) at 40 °C for 3 h. [b]0.2 mmol.

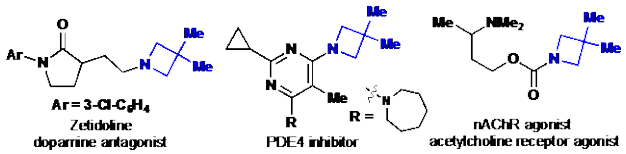


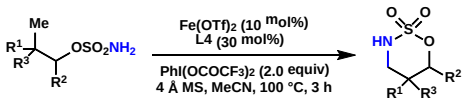
Figure 1 Selected examples of biologically relevant azetidines.

Conclusions

In summary, we have developed an iron-catalyzed intramolecular primary C–H amination of sulfamate esters. A range of oxathiazinanes were produced in moderate to good yields using an iron catalyst derived from $Fe(OTf)_2$ and bipyridine. The synthetic utility of the amination reaction to construct azetidines is demonstrated by a one-pot procedure. Given the readily availability and high reactivity of the catalyst toward aliphatic substrates, this method offers a practical alternative to heterocycle synthesis.

Experimental

General procedure for Fe-catalyzed C–H amination.



1 2

To a 10 mL vial equipped with a magnetic stirring bar were added $Fe(OTf)_2$ (14.2 mg, 0.04 mmol, 10 mol%), **L4** (18.7 mg, 0.12 mmol, 30 mol%), and 2 mL of MeCN. After the mixture was stirred at 30 °C for 30 min, substrate **1** (0.4 mmol), $PhI(OCOCF_3)_2$ (344.0 mg, 0.8 mmol, 2 equiv), 4 Å MS (100 mg), and another 2 mL of MeCN were added. Then the vial was sealed and the mixture was stirred at 100 °C for 3 h. The reaction was cooled to room temperature, filtered through a pad of celite, and washed with CH_2Cl_2 (3 × 5 mL). The filtrate was concentrated under reduce pressure, and the residue was purified by flash chromatography on silica gel (200 ~ 300 mesh) to give the desired products **2**.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

Acknowledgement

We thank the NSFC (Nos. 21971198 and 21772148) and Wuhan University (WHU) for financial support.

References

[1] (a) Das, P.; Delost, M. D.; Qureshi, M. H.; Smith, D. T.; Njardarson, J. T. A Survey of the Structures of US FDA Approved Combination Drugs. *J. Med. Chem.* **2019**, *62*, 4265–4311; (b) O'Hagan, D. Pyrrole, Pyrrolidine, Pyridine, Piperidine and Tropane Alkaloids. *Nat. Prod. Rep.* **2000,** *17*, 435–446.

[2] (a) (a) Wang, R.; Luan, Y.; Ye, M. Transition Metal-Catalyzed Allylic C(sp^3)–H Functionalization via η^3-Allylmetal Intermediate. *Chin. J. Chem.* **2019**, *37*, 720–743; (b) Ye, Z.; Zhang, F. Recent Advances in Constructing Nitrogen-Containing Heterocycles via Electrochemical Dehydrogenation. *Chin. J. Chem.* **2019**, *37*, 513–528; (c) Liu, S.; Li, J.; Wang, D.; Liu, F.; Liu, X.; Gao, Y.; Jie, D.; Cheng, X. An Electrochemical Cinnamyl C–H Amination Reaction Using Carbonyl Sulfamate. *Chin. J. Chem.* **2019**, *37*, 570–574; (d) Zhou, W.; Zhang, L.; Jiao, N. Direct Transformation of Methyl Arenes to Aryl Nitriles at Room Temperature. *Angew. Chem. Int. Ed.* **2009**, *48*, 7094–7097; (e) Liu, J.; Wu, K.; Shen, T.; Liang, Y.; Zou, M.; Zhu, Y.; Li, X.; Li, X.; Jiao, N. Fe-Catalyzed Amination of (Hetero)Arenes with a Redox-Active Aminating Reagent under Mild Conditions. *Chem. Eur. J.* **2017**, *23*, 563–567; (f) Wen, X.; Li, X.; Luo, X.; Wang, W.; Song, S.; Jiao, N. Intramolecular Csp^3–H/C–C Bond Amination of Alkyl Azides for the Selective Synthesis of Cyclic Imines and Tertiary Amines. *Chem. Sci.* **2020**, *11*, 4482–4487; (g) Liu, J.; Qiu, X.; Huang, X.; Luo, X.; Zhang, C.; Wei, J.; Pan, J.; Liang, Y.; Zhu, Y.; Qin, Q.; Song, S.; Jiao, N. From Alkylarenes to Anilines via Site Directed Carbon-Carbon Amination. *Nat. Chem.* **2019**, *11*, 71–77.

[3] For selected reviews: (a) Jeffrey, J. L.; Sarpong, R. Intramolecular C(sp^3)–H Amination. *Chem. Sci.* **2013**, *4*, 4092–4106; (b) Park, Y.; Kim, Y.; Chang, S. Transition Metal-Catalyzed C–H Amination: Scope, Mechanism, and Applications. *Chem. Rev.* **2017**, *117*, 9247-9301; (c) Singh, R.; Mukherjee, A. Metalloporphyrin Catalyzed C–H Amination. *ACS Catal.* **2019**, *9*, 3604–3617; (d) Hazelard, D.; Nocquet, P.-A.; Compain, P. Catalytic C–H amination at its Limits: Challenges and Solutions. *Org. Chem. Front.* **2017,** *4*, 2500–2521; For seminal reports: (e) Breslow, R.; Gellman, S. H. Tosylamidation of Cyclohexane by a Cytochrome P-450 Model. *J. Chem. Soc., Chem. Commun.* **1982**, *1*, 1400–1401; (f) Breslow, R.; Gellman, S. H. Intramolecular Nitrene C–H Insertions Mediated by Transition-Metal Complexes as Nitrogen Analogues of Cytochrome P-450 Reactions. *J. Am. Chem. Soc.* **1983**, *105*, 6728–6729; Selected examples: (g) Espino, C. G.; Du Bois, J. A Rh-Catalyzed C–H Insertion Reaction for the Oxidative Conversion of Carbamates to Oxazolidinones. *Angew. Chem. Int. Ed.* **2001**, *40*, 598–600; (h) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. Synthesis of 1,3-Difunctionalized Amine Derivatives through Selective C–H Bond Oxidation. *J. Am. Chem. Soc.* **2001**, *123*, 6935–6936; (i) Nguyen, Q.; Sun, K.; Driver, T. G. Rh^2(II)-Catalyzed Intramolecular Aliphatic C–H Bond Amination Reactions Using Aryl Azides as the *N*-Atom Source. *J. Am. Chem. Soc.* 2012, *134*, 7262–7265; (j) Alderson, J. M.; Phelps, A. M.; Scamp, R. J.; Dolan, N. S.; Schomaker, J. M. Ligand-Controlled, Tunable Silver-Catalyzed C–H Amination. *J. Am. Chem. Soc.* **2014**, *136*, 16720–16723; (k) Hong, S. Y.; Park, Y.; Hwang, Y.; Kim, Y. B.; Baik, M.-H.; Chang, S. Selective Formation of γ-Lactams via C–H Amidation Enabled by Tailored Iridium Catalysts. *Science* **2018**, *359*, 1016–1021; (l) Wang, H.; Park, Y.; Bai, Z.; Chang, S.; He, G.; Chen, G. Iridium-Catalyzed Enantioselective C(sp^3)–H Amidation Controlled by Attractive Noncovalent Interactions. *J. Am. Chem. Soc.* **2019**, *141*, 7194–7201; (m) Liang, J.- L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. Highly Diastereo- and Enantioselective Intramolecular Amidation of Saturated C–H Bonds Catalyzed by Ruthenium Porphyrins. *Angew. Chem. Int. Ed.* **2002**, *41*, 3465–3468; (n) Yu, Y.; Luo, G.; Yang, J.; Luo, Y. Theoretical Mechanistic Studies of Rh-catalyzed C(sp^3)–H Amination: A Comparison with Co Analogue and Metal Effects. *Chin. J. Chem.* **2020**, *38*, 10.1002/cjoc.202000153.

[4] (a) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. Direct C–H Transformation via Iron Catalysis. *Chem. Rev.* **2011**, *111*, 1293–1314; (b) Zhang, L.; Deng, L. C–H Bond Amination by Iron-Imido/Nitrene Species. *Chin. Sci. Bull.* **2012**, *57*, 2352–2360; (c) Wang, P.; Deng, L. Recent Advances in Iron-Catalyzed C–H Bond Amination via Iron Imido Intermediate. *Chin. J. Chem.* **2018**, *36*, 1222–1240; (d) Liu, Y.; You, T.; Wang, T.-T.; Che, C.-M. Iron-Catalyzed C–H Amination and its Application in Organic Synthesis. *Tetrahedron* **2019**, *75*, 130607–130624.

[5] (a) Liu, P.; Wong, E. L.-M.; Yuen, A. W.-H.; Che, C.-M. Highly Efficient Alkene Epoxidation and Aziridination Catalyzed by Iron(II) Salt + 4,4′,4′′-Trichloro-2,2′:6′,2′′-terpyridine/4,4′′-Dichloro-4′-*O*-PEG-OCH_3-2,2′:6′,2′′-terpyridine. *Org. Lett.* **2008**, *10*, 3275–3278; (b) Liu, Y.; Guan, X.; Wong, E. L.-M.; Liu, P.; Huang, J.-S.; Che, C.-M. Nonheme Iron-Mediated Amination of C(sp^3)–H Bonds. Quinquepyridine-Supported Iron-Imide/Nitrene Intermediates by Experimental Studies and DFT Calculations. *J. Am. Chem. Soc.* **2013**, *135*, 7194–7204; (c) Shing, K.-P.; Liu, Y.; Cao, B.; Chang, X.-Y.; You, T.; Che, C.-M. *N*-Heterocyclic Carbene Iron(III) Porphyrin-Catalyzed Intramolecular C(sp^3)–H Amination of Alkyl Azides. *Angew. Chem. Int. Ed.* **2018**, *57*, 11947–11951.

[6] (a) Paradine, S. M.; White, M. C. Iron-Catalyzed Intramolecular Allylic

C–H Amination. *J. Am. Chem. Soc.* **2012**, *134*, 2036–2039; (b) Paradine, S. M.; Griffin, J. R.; Zhao, J.; Petronico, A. L.; Miller, S. M.; White, M. C. A Manganese Catalyst for Highly Reactive yet Chemoselective Intramolecular C(sp^3)–H Amination. *Nat. Chem.* **2015**, *7*, 987–994; (c) Clark, J. R.; Feng, K.; Sookezian, A.; White, M. C. Manganese-Catalysed Benzylic C(sp^3)–H Amination for Late-Stage Functionalization. *Nat. Chem.* **2018**, *10*, 583–591.

[7] (a) Lu, H.; Tao, J.; Jones, J. E.; Wojtas, L.; Zhang, X. P. Cobalt(II)-Catalyzed Intramolecular C–H Amination with Phosphoryl Azides: Formation of 6- and 7-Membered Cyclophosphoramidates. *Org. Lett.* **2010**, *12*, 1248–1251; (b) Lu, H.; Jiang, H.; Wojtas, L.; Zhang, X. P. Selective Intramolecular C–H Amination through the Metalloradical Activation of Azides: Synthesis of 1,3-Diamines under Neutral and Nonoxidative Conditions. *Angew. Chem. Int. Ed.* **2010**, *49*, 10192–10196; (c) Lu, H.; Li, C.; Jiang, H.; Lizardi, C. L.; Zhang, X. P. Chemoselective Amination of Propargylic C(sp^3)–H Bonds by Cobalt(II)-Based Metalloradical Catalysis. *Angew. Chem. Int. Ed.* **2014**, *53*, 7028–7032; (d) Li, C.; Lang, K.; Lu, H.; Hu, Y.; Cui, X.; Wojtas, L.; Zhang, X. P. Catalytic Radical Process for Enantioselective Amination of C(sp^3)–H Bonds. *Angew. Chem. Int. Ed.* **2018**, *57*, 16837–16841.

[8] (a) King, E. R.; Betley, T. A. C–H Bond Amination from a Ferrous Dipyrromethene Complex. *Inorg. Chem.* **2009,** *48*, 2361–2363; (b) Hennessy, E. T.; Betley, T. A. Complex *N*-Heterocycle Synthesis via Iron-Catalyzed, Direct C–H Bond Amination. *Science* **2013,** *340*, 591–595; (c) Iovan, D. A.; Wilding, M. J. T.; Baek, Y.; Hennessy, E. T.; Betley, T. A. Diastereoselective C–H Bond Amination for Disubstituted Pyrrolidines. *Angew. Chem. Int. Ed.* **2017,** *56*, 15599–15602.

[9] (a) Nguyen, Q.; Nguyen, T.; Driver, T. G. Iron(II) Bromide-Catalyzed Intramolecular C–H Bond Amination [1,2]-Shift Tandem Reactions of Aryl Azides. *J. Am. Chem. Soc.* **2013,** *135*, 620–623; (b) 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. Catalytic Synthesis of *N*-Heterocycles via Direct C(sp^3)−H Amination Using an Air-Stable Iron(III) Species with a Redox-Active Ligand. *J. Am. Chem. Soc.* **2017,** *139*, 5117–5124; (c) Shehata, M. F.; Ayer, S. K.; Roizen, J. L. Iron(MCP) Complexes Catalyze Aziridination with Olefins as Limiting Reagents. *J. Org. Chem.* **2018,** *83*, 5072–5081; (d) Zhao, X.; Liang, S.; Fan, X.; Yang, T.; Yu, W. Iron-Catalyzed Intramolecular C–H Amination of α-Azidyl Amides. *Org. Lett*. **2019**, *21*, 1559–1563.

[10] Xue, X.-S.; Ji, P.; Zhou, B.; Cheng, J.-P. The Essential Role of Bond Energetics in C–H Activation/Functionalization. *Chem. Rev.* **2017**, *117*, 8622–8648.

[11] Alt, I. T.; Guttroff, C.; Plietker, B. Iron-Catalyzed Intramolecular Aminations of C(sp^3)–H Bonds in Alkylaryl Azides. *Angew. Chem. Int. Ed.* **2017**, *56*, 10582–10586.

[12] (a) Chen, G.-Q.; Xu, Z.-J.; Liu, Y.; Zhou, C.-Y.; Che, C.-M. Iron-Catalyzed Nitrene Insertion Reaction for Facile Construction of Amide Compounds. *Synlett* **2011**, *2011*, 1174–1178; (b) Ton, T. M. U.; Tejo, C.; Tania, S.; Chang, J. W. W.; Chan, P. W. H. Iron(II)-Catalyzed Amidation of Aldehydes with Iminoiodinanes at Room Temperature and Under Microwave-Assisted Conditions. *J. Org. Chem.* **2011**, *76*, 4894–4904.

[13] (a) Liu, W.; Zhong, D.; Yu, C.-L.; Zhang, Y.; Wu, D.; Feng, Y.-L.; Cong, H.; Lu, X.; Liu, W.-B. Iron-Catalyzed Intramolecular Amination of Aliphatic C–H Bonds of Sulfamate Esters with High Reactivity and Chemoselectivity. *Org. Lett.* **2019**, *21*, 2673–2678; (b) Zhong, D.; Wu, D.; Zhang, Y.; Lu, Z.; Muhammad, U.; Liu, W.; Lu, X.; Liu, W.-B. Synthesis of Sultams and Cyclic *N*-Sulfonyl Ketimines via Iron-Catalyzed Intramolecular Aliphatic C–H Amidation. *Org. Lett.* **2019**, *21*, 5808–5812.

[14] (a) Fu, Z.; Xu, J. Synthesis of Azetidines. *Prog. Chem.* **2018,** *30*, 1047–1066; (b) Antermite, D.; Degennaro, L.; Luisi, R. Recent Advances in the Chemistry of Metallated Azetidines. *Org. Biomol. Chem.* **2017,** *15*, 34–50; (c) Collin, S.; Evrard, G.; Vercauteren, D. P.; Durant, F.; Carrupt, P.-A.; van de Waterbeemd, H.; Testa, B. Stereoelectronic Study of Zetidoline, a Dopamine D2 Receptor Antagonist. *J. Med. Chem.* **1989**, *32*, 38–42; (d) Provins, L.; Christophe, B.; Danhaive, P.; Dulieu, J.; Gillard, M.; Quere, L.; Stebbins, K. Dual M_3 Antagonists-PDE4 Inhibitors. Part 2: Synthesis and SAR of 3-Substituted Azetidinyl Derivatives. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3077–3080; (e) Hansen, C. P.; Jensen, A. A.; Christensen, J. K.; Balle, T.; Liljefors, T.; Frølund, B. Novel Acetylcholine and Carbamoylcholine Analogues: Development of a Functionally Selective $\alpha_4\beta_2$ Nicotinic Acetylcholine Receptor Agonist. *J. Med. Chem.* **2008**, *51*, 7380–7395.

[15] He, G.; Lu, G.; Guo, Z.; Liu, P.; Chen, G. Benzazetidine Synthesis via Palladium-Catalysed Intramolecular C−H Amination. *Nat. Chem.* **2016,** *8*, 1131–1136.

[16] (a) Bower, J. F.; Rujirawanich, J.; Gallagher, T. *N*-Heterocycle Construction via Cyclic Sulfamidates. Applications in Synthesis. *Org. Biomol. Chem.* **2010,** *8*, 1505–1519; (b) Shinde, A. H.; Nagamalla, S.; Sathyamoorthi, S. *N*-Arylated Oxathiazinane Heterocycles are Convenient Synthons for 1,3-Amino Ethers and 1,3-Amino Thioethers. *Med. Chem. Res.* **2020,** *29*, 1223–1229; (c) Eskici, M.; Karanfil, A.; Özer, M. S.; Sarıkürkcü, C. Reactivity of Cyclic Sulfamidates towards Lithium Acetylides: Synthesis of Alkynylated Amines. *Tetrahedron Letters* **2011,** *52*, 6336–6341; (d) Tanino, T.; Ichikawa, S.; Shiro, M.; Matsuda, A. Total Synthesis of (-)-Muraymycin D2 and its Epimer. *J. Org. Chem.* **2010,** *75*, 1366–1377.

[17] Thornton, A. R.; Martin, V. I.; Blakey, S. B. π-Nucleophile Traps for Metallonitrene/Alkyne Cascade Reactions: A Versatile Process for the Synthesis of α-Aminocyclopropanes and β-Aminostyrenes. *J. Am. Chem. Soc.* **2009**, *131*, 2434–2435.

(The following will be filled in by the editorial staff)
Manuscript received: XXXX, 2019
Manuscript revised: XXXX, 2019
Manuscript accepted: XXXX, 2019
Accepted manuscript online: XXXX, 2019
Version of record online: XXXX, 2019

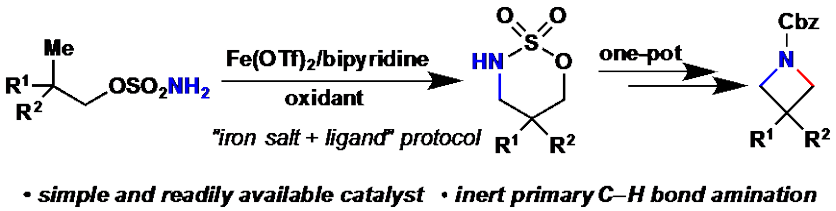
Entry for the Table of Contents

Page No.

Iron-Catalyzed Primary C–H Amination of Sulfamate Esters and Its Application in the Synthesis of Azetidines

Jian Zhang, Dayou Zhong, Muhammad Usman, Peng Xue, and Wen-Bo Liu*

Max. Table height 6 cm



• simple and readily available catalyst • inert primary C–H bond amination

An iron-catalyzed intramolecular primary C–H amination of sulfamate esters using bipyridine ligand has been reported for the construction of oxathiazinanes. A series of azetidines have been synthesized as well from the amination product in a one-pot procedure.

