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Redox-Neutral β-C(sp^3)−H Functionalization of Cyclic Amines via Intermolecular Hydride Transfer

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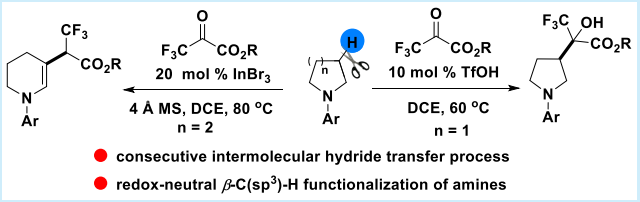
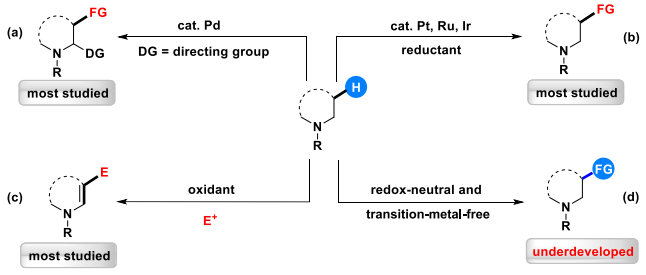
Supporting Information

ABSTRACT: Herein, we report the first redox-neutral and transition-metal-free β-C(sp^3)−H functionalization of cyclic amines via a consecutive intermolecular hydride transfer process. A series of *N*-aryl pyrrolidines and *N*-aryl 1,2,3,4-tetrahydropyridines decorated with CF_3 and carboxylic ester functionalities are directly accessed in good yields from pyrrolidines and piperidines. This work pushes forward the application of the intermolecular hydride transfer strategy in one-step assembly of molecular complexity.



Functionalized cyclic amines are prevalent in numerous natural products and pharmaceutical molecules, which are increasingly momentous targets in drug discovery.[1] Thus, various synthetic methodologies are developed for elaborate diversification of cyclic amines. Among the various methods that enable the direct C(sp^3)−H functionalization of amines, the vast majority of them are devoted to studies regarding the α-position of amines.[2] However, the reports on direct functionalization of challenging and poorly reactive β-C(sp^3)−H bonds of amines are relatively rare. In this context, the transition-metal- and/or oxidant-based reagents have been employed to achieve direct β-C(sp^3)−H functionalization of amines, such as the directing groups assisted and palladium-catalyzed functionalization (Scheme 1a),[3] transition-metal-catalyzed hydrogen-borrowing reactions (Scheme 1b)[4] and stoichiometric amounts of oxidants promoted β-C(sp^3)−H functionalization (Scheme 1c).[5] Despite these advances, the redox-neutral and transition-metal-free β-C(sp^3)−H functionalization of cyclic amines is underdeveloped (Scheme 1d).

Scheme 1. β-C(sp^3)−H Functionalization of Amines



Redox-neutral C−H functionalizations initiated by hydride transfer (HT) enabled the rapid buildup of molecular complexity with high atom and step economy.[6] Recent decades have witnessed the domination of intramolecular hydride transfer triggered C−H functionalizations,[7] and taking advantage of the intermolecular hydride transfer to achieve the diversity-oriented C−H functionalizations has been a long-standing challenge.[8−10] Very recently, the direct β-C(sp^3)−H functionalization of amines has been realized via intermolecular hydride transfer by the Chang group[9] and Ma group[10] with $B(C_6F_5)_3$ as a transient hydride acceptor. Nevertheless, these sporadic examples only involve a single intermolecular hydride transfer process and, to the best of our knowledge, the transformation containing consecutive intermolecular hydride transfer to tackle synthetic obstacles, such as β-C(sp^3)−H functionalization of amines, has never been reported.

Inspired by our research efforts on hydride transfer reactions,[11] we intend to design a new reaction cascade initiated by intermolecular hydride transfer for β-C(sp^3)−H functionalization of amines. As shown in Scheme 2, we envisage that an electrophile could trigger the first intermolecular hydride transfer from amine **1** to generate iminium **I**. The subsequent isomerization of **I** would afford enamine **II**, which could trap another molecule of electrophile to form the β-functionalized iminium ion **III**. Eventually, the

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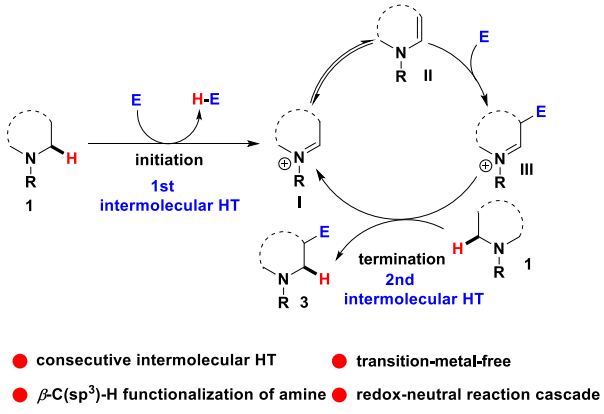
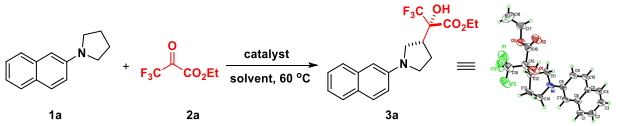
Scheme 2. Design of a New Reaction Cascade Involving Consecutive Intermolecular Hydride Transfer



second intermolecular hydride transfer from **1** to **III** would furnish the β-functionalized amine **3** and regenerate iminium ion **I**, thereby propagating the reaction. This transformation is triggered by the first intermolecular hydride transfer and terminated by the second intermolecular hydride transfer. The key to the success of this transformation is to find a suitable electrophile, which could not only start up the first hydride transfer process but also react with enamine intermediate **II** and undergo the whole catalytic cycle, thus accomplishing the β-C(sp^3)−H functionalization of cyclic amines. Eventually, we found that ethyl trifluoropyruvate could serve as a good partner to accomplish this formidable task (see Supporting Information). Herein, we report the first consecutive intermolecular hydride transfer reaction with amine as the hydride donor and ethyl trifluoropyruvate as the hydride acceptor, which enables the achievement of direct β-C(sp^3)−H functionalization of cyclic amines with ethyl trifluoropyruvate. To our knowledge, this work also represents the first example of transition-metal-free and redox-neutral β-C(sp^3)−H functionalization of amines *via* direct hydride transfer.

At the outset, the feasibility of direct β-C(sp^3)−H functionalization of amines was investigated between 1-(naphthalen-2-yl)pyrrolidine **1a** and ethyl trifluoropyruvate **2a** (Table 1). Initially, 20 mol % of Brønsted acids were employed in 1,2-dichloroethane (DCE) at 60 °C to examine this reaction. Encouragingly, the expected reaction occurred smoothly in the presence of these catalysts, furnishing the β-functionalized amine **3a** embedded with CF_3-substituted tertiary alcohol in good yields, albeit with low diastereoselectivities (entries 1−5). The best result was obtained with trifluoromethanesulfonic acid (TfOH), providing **3a** in 90% yield (entry 1). The structure of **3a** has been unambiguously confirmed by X-ray crystallographic analysis (see Supporting Information). However, the employment of Lewis acid catalysts failed to improve the reaction efficiency and diastereoselectivity (entries 6−9). Afterward, the examination of the ratio of starting materials and catalyst loadings showed that the ratio of **1a** and **2a** being 1.2:1 with 10 mol % of TfOH afforded the best efficiency with slightly higher diastereoselectivity (entries 10−15). The subsequent solvent screening implied that other solvents were all ineffective in this reaction (entries 16−21). Satisfyingly, the preparation of product **3a** (1.5 g) on a large scale proceeded smoothly, which demonstrated the scalability of this protocol (entry 22, see Supporting Information). When 1 equiv of TfOH was used,

Table 1. Optimization of Direct β-C(sp^3)−H Functionalization of Cyclic Amines[a]



entry	ratio (**1a**:**2a**)	catalyst	solvent	yield (%)[b]	dr
1	2:1	TfOH	DCE	90	1.5:1
2[c]	2:1	(−)-CSA	DCE	84	2:1
3	2:1	TsOH	DCE	82	1.9:1
4[d]	2:1	PA	DCE	53	1.5:1
5	2:1	TFA	DCE	87	2.3:1
6	2:1	$Sc(OTf)_3$	DCE	77	1.9:1
7	2:1	$Cu(OTf)_2$	DCE	83	1.8:1
8	2:1	$Zn(OTf)_2$	DCE	80	1.9:1
9	2:1	$In(OTf)_3$	DCE	80	2.0:1
10	1.5:1	TfOH	DCE	90	2.0:1
11	1.2:1	TfOH	DCE	93	2.1:1
12	1:1.5	TfOH	DCE	75	1.9:1
13[e]	1.2:1	TfOH	DCE	94	2.3:1
14[f]	1.2:1	TfOH	DCE	89	2.5:1
15[g]	1.2:1	TfOH	DCE	84	2.3:1
16[e]	1.2:1	TfOH	DCM	92	2.3:1
17[e]	1.2:1	TfOH	$CHCl_3$	76	1.6:1
18[e]	1.2:1	TfOH	toluene	80	2:1
19[e]	1.2:1	TfOH	dioxane	trace	–
20[e]	1.2:1	TfOH	THF	trace	–
21[e]	1.2:1	TfOH	DMSO	trace	–
22[h]	1.2:1	TfOH	DCE	82	2.3:1
23[i]	1.2:1	TfOH	DCE	89	2.1:1
24[j]	1.2:1	–	DCE	58	2.1:1

[a]The reactions were performed with **1a** (0.2 mmol), **2a** (0.1 mmol), and 20 mol % of catalyst in 1.0 mL of solvent at 60 °C under air for 48 h. [b]Isolated yield after column chromatography; dr was determined by ^{1}H NMR. [c](−)-CSA = (−)-10-camphorsulfonic acid. [d]PA = 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate. [e]10 mol % of TfOH was used. [f]5 mol % of TfOH was used. [g]3 mol % of TfOH was used. [h]**1a** (6.0 mmol), **2a** (5.0 mmol) in 50 mL of DCE. [i]0.1 mmol of TfOH. [j]25 °C for 48 h.

this reaction still worked very well, affording **3a** in 89% yield (entry 23). However, the yield decreased dramatically in the absence of TfOH and only a 58% yield was obtained (entry 24).

With the optimized reaction conditions in hand, the generality of this protocol was investigated with a variety of electronically and sterically diverse *N*-aryl pyrrolidines **1** and keto esters **2** (Scheme 3). Remarkably, either electron-donating or -withdrawing substituents on the naphthalene ring had trivial impacts on this transformation, delivering the corresponding β-functionalized 1-(naphthalen-2-yl)pyrrolidine **3a**−**l** in moderate to good yields, albeit with unsatisfactory diastereoselectivities. Intriguingly, the Friedel−Crafts-type product was not observed, even when strong electron-donating groups were employed, which illustrated the high chemoselectivity of this reaction. It was worth mentioning that a broad range of functional groups, including halogens (**3e**, **3f**, **3j**), ester (**3g**), boronate (**3h**), and an acetyl group (**3l**), were all well tolerated, demonstrating its robust compatibility for preparing diversely functionalized target molecules. In addition to ethyl trifluoropyruvate, methyl trifluoropyruvate and diethyl 2-oxomalonate were also good reaction partners for this

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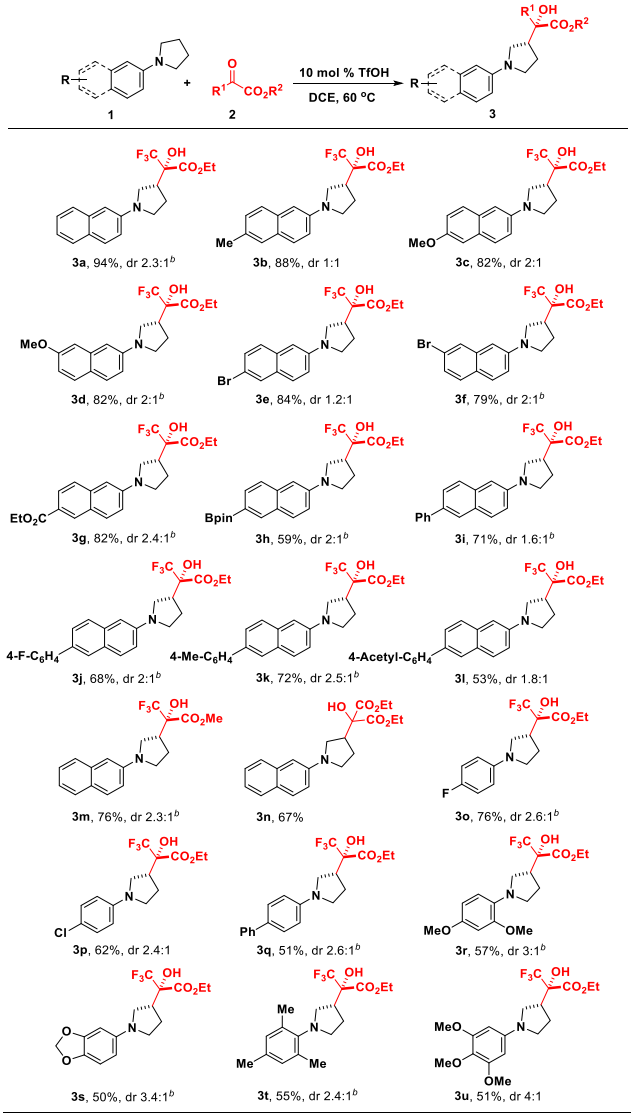
Scheme 3. Substrate Scope for the Synthesis of 3[a]

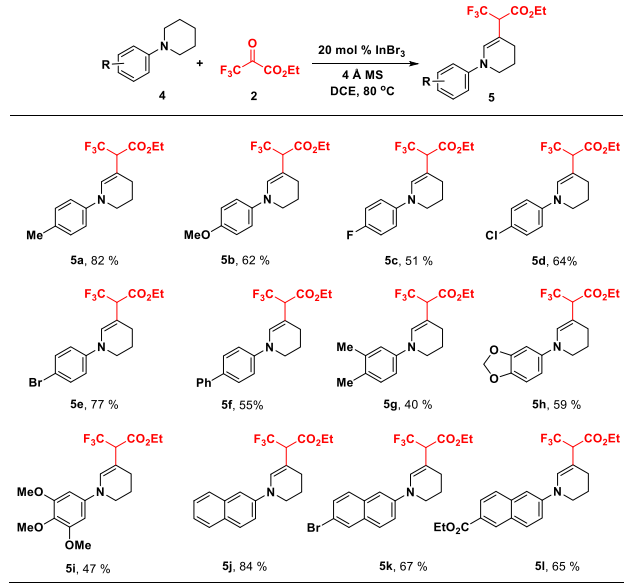


[a]General conditions: The reactions were performed with **1** (0.12 mmol), **2** (0.1 mmol), and TfOH (10 mol %) in 1.0 mL of DCE at 60 °C under air; isolated yield; dr was determined by ^{1}H NMR spectroscopy. [b]Total yield determined by ^{1}H NMR according to the dr and the isolated yield of one isomer.

transformation, furnishing the desired products **3m** and **3n** in 76% and 67% yields, respectively. Moreover, the common benzene rings instead of naphthalenes carrying pyrrolidines were also fully compatible with this system, giving rise to the corresponding *β*-functionalized *N*-Ph pyrrolidines **3o**−**u** in 50−76% yields. As is well-known, generally, the biological activities would be enhanced with the introduction of a trifluoromethyl moiety;[12] the current method provided an efficient route to the *β*-trifluoromethyl substituted amines. Unfortunately, it should be noted that when *N*-*α*-naphthalene pyrrolidine and *para*-position-free *N*-phenylpyrrolidines were used as reaction partners, only Friedel−Crafts-type products were obtained.

In addition to pyrrolidine, we continue to check whether other azacycles could be applied in this system. The piperidine motif constitutes the most prevalent nitrogen ring system; thus, the straightforward late-stage diversification of piperidine is of great importance for drug discovery.[1a,13] When 1-(*p*-tolyl)piperidine **4a** was subjected to the optimal conditions, a new spot was observed in comparatively lower yield. Therefore, the careful screening was carried out and finally the *β*-alkylated 1,2,3,4-tetrahydropyridine **5a** decorated with CF_3 and carboxylic ester groups was obtained in 82% yield in the presence of 20 mol % of $InBr_3$ and 4 Å molecular sieves (see Supporting Information). Because of the potential biological application of *β*-functionalized 1,2,3,4-tetrahydropyridine with CF_3 and carboxylic ester moieties, *N*-aryl piperidines were subjected to the established conditions to investigate the generality (Scheme 4). Remarkably, the

Scheme 4. Substrate Scope for the Synthesis of 5[a]



[a]General conditions: The reactions were performed with **4** (0.1 mmol), **2** (0.2 mmol), $InBr_3$ (20 mol %), and 50 mg of 4 Å MS in 1.0 mL of DCE at 80 °C; isolated yield.

benzene ring carrying electron-donating or -withdrawing substituents almost had no influence on the reaction efficiency, furnishing the corresponding products **5a**−**f** in moderate to good yields. In addition, multisubstituted benzene rings were also tolerated, albeit furnishing the desired products **5g**−**i** in comparatively lower yields. Besides, the naphthalene substituents were also good candidates, obtaining the *β*-functionalized enamines **5j**−**l** in 65−84% yields.

To shed light on the reaction mechanism, the mechanistic studies were conducted (Scheme 5). At first, the unaffected efficiency of the standard reaction under a N_2 atmosphere excluded the possibility of O_2 as an oxidant, which was consistent with our assumption that ethyl trifluoropyruvate would serve as an oxidant to oxidize amine to iminium (eq 1). In order to further confirm the source of hydride donors, the deuterium labeling experiment between deuterated substrate [**D**]-**1a** and ethyl trifluoropyruvate was performed. The observation of >99% deuterium at the *α*-position of [**D**]-**3a** clearly illustrated the redox-neutral chain of this *β*-C(sp^3)−H functionalization (eq 2). Since there was a precedent that the enamine intermediate could be *in situ* generated from *N*-aryl pyrrolidin-2-one **6** with $LiBHEt_3$ in several minutes,[14] subsequently, ethyl trifluoropyruvate was subjected to the solution of the enamine generated *in situ* to meticulously

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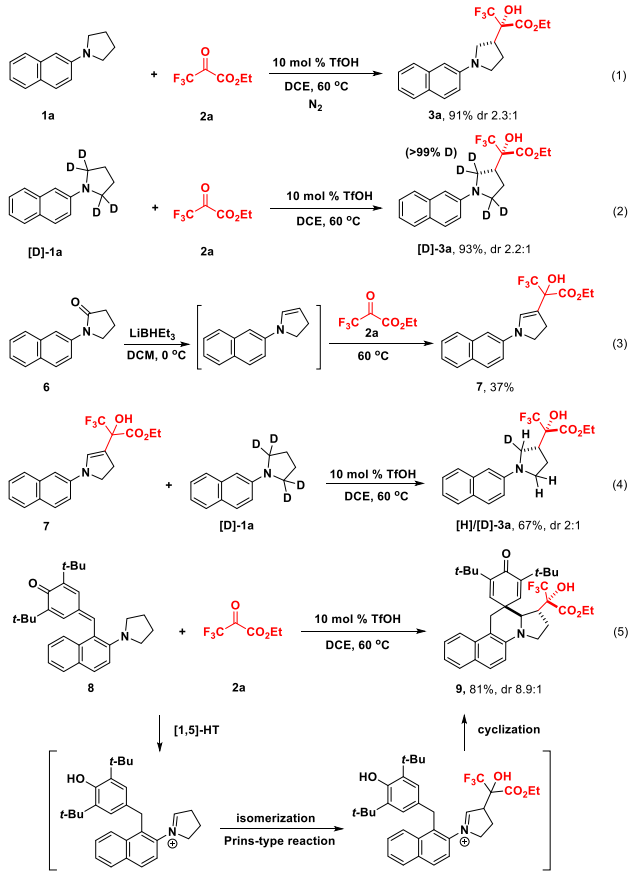
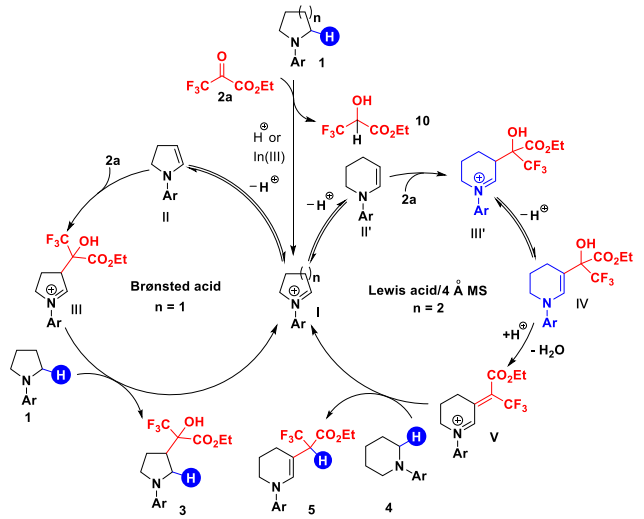
Scheme 5. Mechanistic Studies



examine the reaction process. As expected, the β-functionalized enamine **7** was isolated in 37% yield without any catalyst, which certificated our presumption that an enamine was the key intermediate for this transformation (eq 3). Eventually, the formation of product [**H**/**D**]-**3a** by reaction of enamine **7** with deuterated substrate [**D**]-**1a** under standard conditions fully proved the hypothesis that another molecule of amine would reduce the iminium ion to accomplish the redox-neutral chain process (eq 4). Besides, the designed experiment to capture the iminium ion intermediate was conducted with the employment of substrate **8**. To our delight, the α- and β-position dual functionalized amine **9** was obtained in 81% yield under the standared reaction conditions (eq 5), which underwent a cascade [1,5]-hydride transfer/isomerization/Prins-type reaction/dearomatization process.

On the basis of the experimental observation and literature precedents, a plausible mechanism was proposed as shown in Scheme 6. As our initial hypothesis, the amine **1** was oxidized by ethyl trifluoropyruvate **2a** to form iminium ion **I** and alcohol **10**, initiating the whole catalytic cycle. The existence of compound **10** has been confirmed by the ^{19}F spectrum (see Supporting Information). After isomerization of **I** to **II** or **II′**, the followed nucleophilic addition to ethyl trifluoropyruvate afforded intermediate **III** or **III′**. The intermolecular hydride transfer from the α-position of pyrrolidine to intermediate **III** successively occurred, affording the corresponding β-functionalized *N*-aryl pyrrolidine **3** and regenerating the iminium ion **1**. Different from the fate of **III**, the intermediate **III′** suffered from dehydration preferentially to give **IV** when *N*-aryl piperidine was employed, which might be ascribed to the

Scheme 6. Proposed Mechanism



conformation difference between pyrrolidine and piperidine rings. The formed vinylogous iminium intermediate **V** was reduced immediately by another *N*-aryl piperidine, furnishing the β-functionalized enamine **5** and iminium ion **I**, which proceeded into the next catalytic cycle.

In conclusion, we have developed the first two consecutive intermolecular hydride transfer process to realize the β-C(sp^3)−H functionalization of cyclic amines via a redox-neutral chain process. A series of *N*-aryl pyrrolidines and *N*-aryl 1,2,3,4-tetrahydropyridines decorated with CF_3 and carboxylic ester functionalities were directly accessed in good yields from pyrrolidines and piperidines, which possessed potential biological activities. The compatibility with gram-scale reaction further enhanced the synthetic practicality of this protocol. We are optimistic that these reports will not only offer synthetic chemists a distinctive toolbox for generation of diverse β-functionalized amine libraries but also advance the application of the intermolecular hydride transfer strategy in one-step assembly of molecular complexity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03004.

Experimental procedures and characterization data for all the products (PDF)

Accession Codes

CCDC 1871940 and 1887048 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257−10274. (b) Kittakoop, P.; Mahidol, C.; Ruchirawat, S. *Curr. Top. Med. Chem.* **2013**, *14*, 239−252. (c) Cushnie, T. P. T.; Cushnie, B.; Lamb, A. J. *Int. J. Antimicrob. Agents* **2014**, *44*, 377−386.

(2) For reviews, see: (a) Mahato, S.; Jana, C. K. *Chem. Rec.* **2016**, *16*, 1477−1488. (b) Seidel, D. *Acc. Chem. Res.* **2015**, *48*, 317−328. (c) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem. - Eur. J.* **2012**, *18*, 10092−10142. (d) Shi, L.; Xia, W. *Chem. Soc. Rev.* **2012**, *41*, 7687−7697. (e) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069−1084.

(3) (a) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature* **2014**, *510*, 129−133. (b) Affron, D. P.; Davis, O. A.; Bull, J. A. *Org. Lett.* **2014**, *16*, 4956−4959. (c) Calleja, J.; Pla, D.; Gorman, T. W.; Domingo, V.; Haffemayer, B.; Gaunt, M. J. *Nat. Chem.* **2015**, *7*, 1009−1016. (d) Willcox, D.; Chappell, B. G. N.; Hogg, K. F.; Calleja, J.; Smalley, A. P.; Gaunt, M. J. *Science* **2016**, *354*, 851−857. (e) Hogg, K. F.; Trowbridge, A.; Alvarez-Perez, A.; Gaunt, M. J. *Chem. Sci.* **2017**, *8*, 8198−8203. (f) Antermite, D.; Affron, D. P.; Bull, J. A. *Org. Lett.* **2018**, *20*, 3948−3952.

(4) (a) Sundararaju, B.; Achard, M.; Sharma, G. V. M.; Bruneau, C. *J. Am. Chem. Soc.* **2011**, *133*, 10340−10343. (b) Yuan, K.; Jiang, F.; Sahli, Z.; Achard, M.; Roisnel, T.; Bruneau, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 8876−8880. (c) Takasu, N.; Oisaki, K.; Kanai, M. *Org. Lett.* **2013**, *15*, 1918−1921.

(5) (a) Lai, J.; Chang, L.; Yuan, G. *Org. Lett.* **2016**, *18*, 3194−3197. (b) Schultz, D. M.; Levesque, F.; DiRocco, D. A.; Reibarkh, M.; Ji, Y.; Joyce, L. A.; Dropinski, J. F.; Sheng, H.; Sherry, B. D.; Davies, I. W. *Angew. Chem., Int. Ed.* **2017**, *56*, 15274−15278. (c) Griffiths, R. J.; Kong, W. C.; Richards, S. A.; Burley, G. A.; Willis, M. C.; Talbot, E. P. A. *Chem. Sci.* **2018**, *9*, 2295−2300.

(6) For reviews, see: (a) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1683−1684. (b) Peng, B.; Maulide, N. *Chem. - Eur. J.* **2013**, *19*, 13274−13287. (c) Wang, L.; Xiao, J. *Adv. Synth. Catal.* **2014**, *356*, 1137−1171. (d) Wang, L.; Xiao, J. *Top. Curr. Chem.* **2016**, *374*, 17. (e) Wang, L.; Xiao, J. *Org. Chem. Front.* **2016**, *3*, 635−638. (f) Pan, S. C. *Beilstein J. Org. Chem.* **2012**, *8*, 1374−1384. (g) Haibach, M. C.; Seidel, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 5010−5036. (h) Xiao, M.; Zhu, S.; Shen, Y.-B.; Wang, L.; Xiao, J. *Youji Huaxue* **2018**, *38*, 328−340. (i) Kwon, S. J.; Kim, D. Y. *Chem. Rec.* **2016**, *16*, 1191−1203.

(7) For representative examples, see: (a) Pastine, S. J.; McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180−12181. (b) McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 402−403. (c) Zhang, C. C.; De, K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416−417. (d) Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 6166−6169. (e) Mori, K.; Sueoka, S.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 2424−2426. (f) Haibach, M. C.; Deb, I.; De, C. K.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 2100−2103. (g) Gandamana, D. A.; Wang, B.; Tejo, C.; Bolte, B.; Gagosz, F.; Chiba, S. *Angew. Chem., Int. Ed.* **2018**, *57*, 6181−6185. (h) Mori, K.; Isogai, R.; Kamei, Y.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2018**, *140*, 6203−6207. (i) Idiris, F. I. M.; Majesté, C. E.; Craven, G. B.; Jones, C. R. *Chem. Sci.* **2018**, *9*, 2873−2878. (j) Jurberg, I. D.; Peng, B.; Wöstefeld, E.; Wasserloos, M.; Maulide, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 1950−1953.

(8) For α-C(sp^3)−H functionalization of amines, see: (a) Chen, W.; Ma, L.; Paul, A.; Seidel, D. *Nat. Chem.* **2018**, *10*, 165−169. (b) Shang, M.; Chan, J. Z.; Cao, M.; Chang, Y.; Wang, Q.; Cook, B.; Torker, S.; Wasa, M. *J. Am. Chem. Soc.* **2018**, *140*, 10593−10601. (c) Tian, J. J.; Zeng, N. N.; Liu, N.; Tu, X. S.; Wang, X. C. *ACS Catal.* **2019**, *9*, 295−300. (d) Maier, A. F. G.; Tussing, S.; Zhu, H.; Wicker, G.; Tzvetkova, P.; Flörke, U.; Daniliuc, C. G.; Grimme, S.; Paradies, J. *Chem. - Eur. J.* **2018**, *24*, 16287−16291.

(9) Zhang, J.; Park, S.; Chang, S. *J. Am. Chem. Soc.* **2018**, *140*, 13209−13213.

(10) (c) Li, R.; Chen, Y.; Jiang, K.; Wang, F.; Lu, C.; Nie, J.; Chen, Z.; Yang, G.; Chen, Y.-C.; Zhao, Y.; Ma, C. *Chem. Commun.* **2019**, *55*, 1217−1220.

(11) (a) Li, S.-S.; Lv, X.; Ren, D.; Shao, C.-L.; Liu, Q.; Xiao, J. *Chem. Sci.* **2018**, *9*, 8253−8259. (b) Li, S.-S.; Zhou, L.; Wang, L.; Zhao, H.; Yu, L.; Xiao, J. *Org. Lett.* **2018**, *20*, 138−141. (c) Wang, S.; An, X.-D.; Li, S.-S.; Liu, X.; Liu, Q.; Xiao, J. *Chem. Commun.* **2018**, *54*, 13833−13836. (d) Zhu, S.; Chen, C.; Xiao, M.; Yu, L.; Wang, L.; Xiao, J. *Green Chem.* **2017**, *19*, 5653−5658. (e) Li, S.-S.; Zhu, S.; Chen, C.; Duan, K.; Liu, Q.; Xiao, J. *Org. Lett.* **2019**, *21*, 1058−1062. (f) Lv, X.; Hu, F.; Duan, K.; Li, S.-S.; Liu, Q.; Xiao, J. *J. Org. Chem.* **2019**, *84*, 1833−1844. (g) An, X.-D.; Duan, K.; Li, X.-J.; Yang, J.-M.; Lu, Y.-N.; Liu, Q. *J. Org. Chem.* **2019**, *84*, 11839−11847. (h) Zhu, S.; Chen, C.; Duan, K.; Sun, Y.-M.; Li, S.-S.; Liu, Q.; Xiao, J. *J. Org. Chem.* **2019**, *84*, 8440−8448. (i) Shen, Y.-B.; Li, L.-F.; Xiao, M.-Y.; Yang, J.-M.; Liu, Q.; Xiao, J. *J. Org. Chem.* **2019**, DOI: 10.1021/acs.joc.9b02110.

(12) (a) Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, P. S.; Olsen, D. B.; Carroll, S. S.; Pettibone, D. J.; O'Brien, J. A.; Ball, R. G.; Balani, S. K.; Lin, J. H.; Chen, I.-W.; Schleif, W. A.; Sardana, V. V.; Long, W. J.; Byres, V. W.; Emini, E. A. *Antimicrob. Agents Chemother.* **1995**, *39*, 2602−2605. (b) Putman, D.; Hongenkamp, D.; Dasse, O.; Whittemore, E. R.; Jensan, M. S. US Patent 20080039453A1, 2008.

(13) Petukhov, P. A.; Zhang, J.; Wang, C. Z.; Ye, Y. P.; Johnson, K. M.; Kozikowski, A. P. *J. Med. Chem.* **2004**, *47*, 3009−3018.

(14) Xu, G.-Q.; Xu, J.-T.; Feng, Z.-T.; Liang, H.; Wang, Z.-Y.; Qin, Y.; Xu, P. *Angew. Chem., Int. Ed.* **2018**, *57*, 5110−5114.

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