

## EDGE ARTICLE

Cite this: *Chem. Sci.*, 2021, 12, 10467

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

Received 21st April 2021  
Accepted 30th June 2021

DOI: 10.1039/d1sc02212a

rsc.li/chemical-science

A general strategy for the synthesis of  $\alpha$ -trifluoromethyl- and  $\alpha$ -perfluoroalkyl- $\beta$ -lactams via palladium-catalyzed carbonylation†Yang Li,<sup>ab</sup> Cai-Lin Zhang,<sup>a</sup> Wei-Heng Huang,<sup>b</sup> Ning Sun,<sup>a</sup> Meng Hao,<sup>a</sup> Helfried Neumann<sup>b</sup> and Matthias Beller<sup>ab</sup>

$\beta$ -Lactam compounds play a key role in medicinal chemistry, specifically as the most important class of antibiotics. Here, we report a novel one-step approach for the synthesis of  $\alpha$ -(trifluoromethyl)- $\beta$ -lactams and related products from fluorinated olefins, anilines and CO. Utilization of an advanced palladium catalyst system with the Ruphos ligand allows for selective cycloaminocarbonylations to give diverse fluorinated  $\beta$ -lactams in high yields.

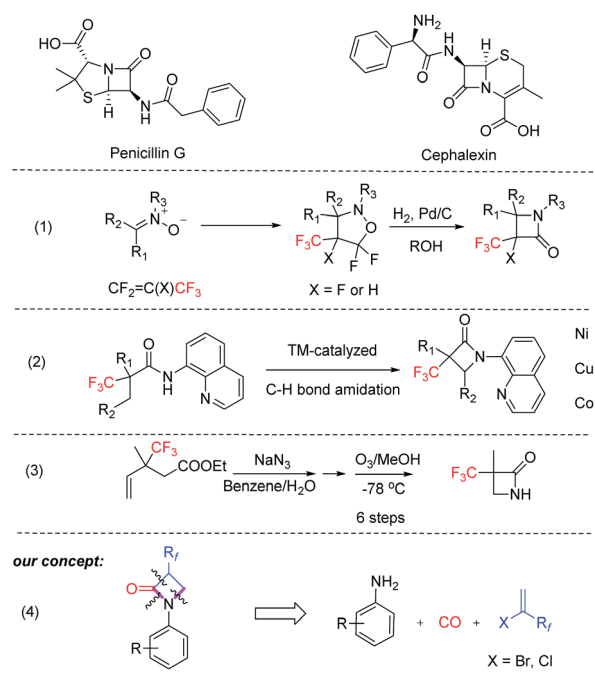
## Introduction

The synthesis of fluorinated organic molecules has become one of the most active and dynamic areas in chemistry.<sup>1,2</sup> In fact, the launch of modern pharmaceuticals and plant protection agents as well as precise materials, *e.g.* for energy technologies (batteries, *etc.*), would be impossible without appropriate organofluorine compounds. In this respect, the development of new synthetic methodologies for the preparation of such molecules is crucial, too. Although in the past decades, many elegant protocols to directly introduce fluorine atoms or fluoroalkyl groups into a given organic substrate have been disclosed,<sup>3–6</sup> there is a continuing interest in complementary and improved procedures, specifically the development of new methods potentially applicable on a practical scale.

Among the established synthetic toolbox for incorporation of fluorine-containing units, in particular processes for introducing CF<sub>3</sub>-groups are important. Notable examples include trifluoromethylated arenes,<sup>7</sup> olefins,<sup>8,9</sup> ethers,<sup>10</sup> and allylic compounds.<sup>11</sup> In addition, especially trifluoromethylated heterocycles<sup>11,12</sup> are emerging as promising building blocks for many life science and material applications.

$\beta$ -Lactam molecules (azetidin-2-ones) belong to a family of heterocycles, which are most known for their antibiotic properties (Scheme 1); however, it has been shown that several members of this group present many other pharmaceutical effects, *e.g.* neuroprotective, antioxidant, analgesic or

immunomodulatory capabilities as well as interesting material properties.<sup>13–15</sup> Despite the synthesis of many structural variants, relatively few examples of  $\alpha$ -fluoroalkyl-substituted derivatives are known. So far, such products and especially  $\alpha$ -(trifluoromethyl)- $\beta$ -lactams are based on multistep syntheses,<sup>21,22</sup> or special methods such as hydrogenolysis of N–O bonds,<sup>16</sup> 1,3-dipolar cycloadditions of nitrones to fluoroalkenes,<sup>17</sup> and metal-catalyzed intramolecular C–H amidations (Scheme 1).<sup>18–20</sup> Unfortunately, all these methods have

Scheme 1 Selected examples of bio-relevant  $\beta$ -lactams and known synthesis routes for  $\alpha$ -(trifluoromethyl)- $\beta$ -lactams.

<sup>a</sup>Xi'an Key Laboratory of Textile Chemical Engineering Auxiliaries, School of Environmental and Chemical Engineering, Xi'an Polytechnic University, No. 19 Jinhua South Road, 710048, Xi'an, China. E-mail: liyang@xpu.edu.cn

<sup>b</sup>Leibniz-Institut für Katalyse e.V., Rostock/Albert-Einstein-Straße 29a, 18059, Rostock, Germany. E-mail: Matthias.Beller@catalysis.de

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1sc02212a



certain shortcomings, which limit their applications to small scale.<sup>21</sup>

Based on our long-standing interest in carbonylation reactions<sup>22</sup> and inspired by palladium-catalyzed three component coupling reactions,<sup>23</sup> we got the idea to build up the central 4-membered ring of  $\alpha$ -fluoroalkyl- $\beta$ -lactams by a novel palladium-catalyzed aminocarbonylation of  $\alpha$ -halo- $\alpha$ -fluoroalkylolefins, anilines and CO (Scheme 1). At this point, it is worthwhile mentioning that transition metal-catalyzed carbonylation reactions are not only of value for a variety of organic syntheses, but can be easily upscaled as shown by the industrial production of many fine and even bulk chemicals.<sup>24</sup> Following our concept, apart from the inexpensive and readily available C1 source and ubiquitous anilines, also selected  $\alpha$ -halo-fluoroalkenes are commercially available and are used to prepare various fluorinated products at present.

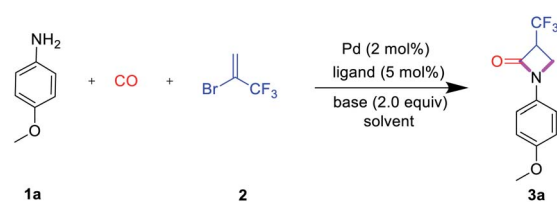
Herein, we report useful methodology for a direct synthesis of  $\alpha$ -(trifluoromethyl)- $\beta$ -lactams and related fluoroalkyl derivatives by selective three component carbonylation reaction in the presence of a specific palladium catalyst.

## Results and discussion

Initially, the carbonylation of 4-methoxyaniline (**1a**) with commercially available 2-bromo-3,3,3-trifluoro-1-propene (**2**) as the trifluoromethylation reagent was used as the model system to study the general reaction sequence and optimize the conditions (Table 1). In first experiments various palladium precursors (2 mol%) were tested in the presence of PCy<sub>3</sub> (5 mol%) as the ligand in 1,4-dioxane at 100 °C and comparably low CO pressure (8 bar). To our delight, the desired product **3a** was afforded in up to 45% yield demonstrating the feasibility of our approach (Table 1, entries 1–6). Next, several phosphine ligands including monodentate and bidentate ones were tested. Amongst these, the sterically hindered Ru-Phos, introduced by Buchwald and co-workers for Negishi cross-coupling reactions,<sup>25</sup> showed the best result, and the reaction yield of **3a** increased to 72% (Table 1, entries 7–12). In general, the improved catalytic activity of Ruphos compared to other ligands in this palladium-catalyzed coupling process is attributed to its electron-richness and steric bulk. The specific structural features stabilize highly reactive LPd(0) intermediates during the catalytic cycle and allow for the most efficient activation of 2-bromo-3,3,3-trifluoro-1-propene **2**. Changing the base from sodium bicarbonate to triethylamine, the yield of the target compound slightly increased to 78% (Table 1, entries 13–15). Finally, the effect of solvents on this aminocarbonylation process was investigated. Here, dipolar aprotic solvents gave much worse results than non-polar ones indicating that the solvent also plays an important role in the selectivity (Table 1, entries 16–20). With toluene as the optimal solvent, **3a** was detected in 89% yield and isolated after separation in 83%.

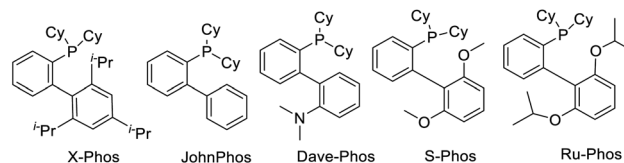
Further to the envisioned cycloaminocarbonylation process, several unwanted side-reactions may take place here (Scheme 2, below). Nevertheless, the combination of Pd(OAc)<sub>2</sub>/Ru-Phos under the optimized conditions gave excellent selectivity for **3a** and no amines or  $\beta$ -amino-acrylates were observed.

**Table 1** Palladium-catalyzed carbonylation of 4-methoxyaniline with 2-bromo-3,3,3-trifluoro-1-propene: screening of the reaction conditions<sup>a</sup>



Entry	Catalyst	Ligand	Base	Solvent	Yield <sup>b</sup> (%)
1	PdCl <sub>2</sub>	PCy <sub>3</sub>	NaHCO <sub>3</sub>	Dioxane	6
2	Pd(OAc) <sub>2</sub>	PCy <sub>3</sub>	NaHCO <sub>3</sub>	Dioxane	45
3	Pd(MeCN) <sub>2</sub> Cl <sub>2</sub>	PCy <sub>3</sub>	NaHCO <sub>3</sub>	Dioxane	19
4	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	PCy <sub>3</sub>	NaHCO <sub>3</sub>	Dioxane	36
5	Pd(PPh <sub>3</sub> ) <sub>4</sub>	PCy <sub>3</sub>	NaHCO <sub>3</sub>	Dioxane	31
6	Pd(TFA)	PCy <sub>3</sub>	NaHCO <sub>3</sub>	Dioxane	26
7	Pd(OAc) <sub>2</sub>	DPPP	NaHCO <sub>3</sub>	Dioxane	19
8	Pd(OAc) <sub>2</sub>	X-Phos	NaHCO <sub>3</sub>	Dioxane	38
9	Pd(OAc) <sub>2</sub>	JohnPhos	NaHCO <sub>3</sub>	Dioxane	41
10	Pd(OAc) <sub>2</sub>	Dave-Phos	NaHCO <sub>3</sub>	Dioxane	51
11	Pd(OAc) <sub>2</sub>	S-Phos	NaHCO <sub>3</sub>	Dioxane	58
12	Pd(OAc) <sub>2</sub>	Ru-Phos	NaHCO <sub>3</sub>	Dioxane	72
13	Pd(OAc) <sub>2</sub>	Ru-Phos	Na <sub>2</sub> HPO <sub>4</sub>	Dioxane	16
14	Pd(OAc) <sub>2</sub>	Ru-Phos	NEt <sub>3</sub>	Dioxane	78
15	Pd(OAc) <sub>2</sub>	Ru-Phos	K <sub>2</sub> CO <sub>3</sub>	Dioxane	49
16	Pd(OAc) <sub>2</sub>	Ru-Phos	NEt <sub>3</sub>	MeCN	23
17	Pd(OAc) <sub>2</sub>	Ru-Phos	NEt <sub>3</sub>	THF	35
18	Pd(OAc) <sub>2</sub>	Ru-Phos	NEt <sub>3</sub>	DMF	14
19	Pd(OAc) <sub>2</sub>	Ru-Phos	NEt <sub>3</sub>	MePh	89, 83 <sup>c</sup>
20	Pd–Ru-Phos <sup>d</sup>	Ru-Phos	NEt <sub>3</sub>	MePh	72 <sup>c</sup>

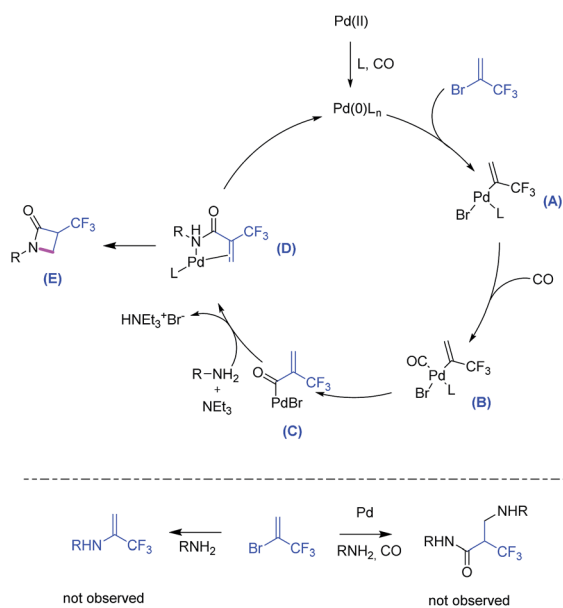
Structure of ligands



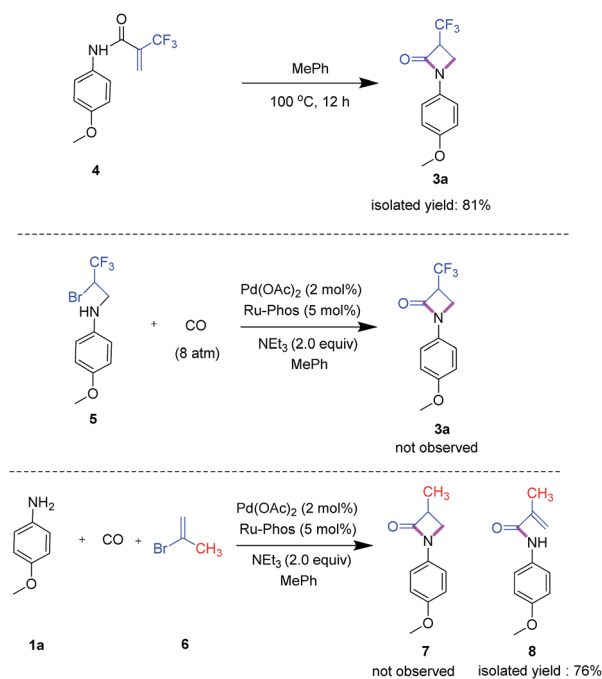
<sup>a</sup> Reaction conditions: **1a** (1.0 mmol), **2** (2.0 mmol), catalyst (5 mol%), base (2.0 mmol), solvent (2.0 mL), CO (8 atm), 100 °C, 12 h. <sup>b</sup> Determined by <sup>19</sup>F NMR analysis using (trifluoromethoxy)benzene as internal standard. <sup>c</sup> Isolated yield. <sup>d</sup> A commercially available 3rd generation Buchwald palladacycle (CAS: 1445085-77-7) was used.

We assume that this reaction proceeds *via* the following steps: first, the active Pd(0) catalyst is generated from the more stable Pd(II) precursor by reduction with phosphine, base or CO. Then, oxidative addition of Pd(0) into 2-bromo-3,3,3-trifluoro-1-propene forms intermediate **A**. Subsequent CO coordination (intermediate **B**) and carbonyl insertion through ligand migration forms acyl palladium compound **C**. Nucleophilic attack of the amine occurs to provide amide **D**, which finally undergoes an intramolecular Michael addition to obtain  $\beta$ -lactam **E**.

To explore the mechanism of this novel carbonylation reaction, several control experiments were performed (Scheme 3). First, we synthesized amide **4** by reaction of 2-bromo-1,1,1-trifluoro-1-propene and phenyl isocyanate under microwave conditions. Indeed, **4** easily convert by an intramolecular Michael addition to product **3a** in the presence or absence of the



Scheme 2 Proposed mechanism and potential side reactions.

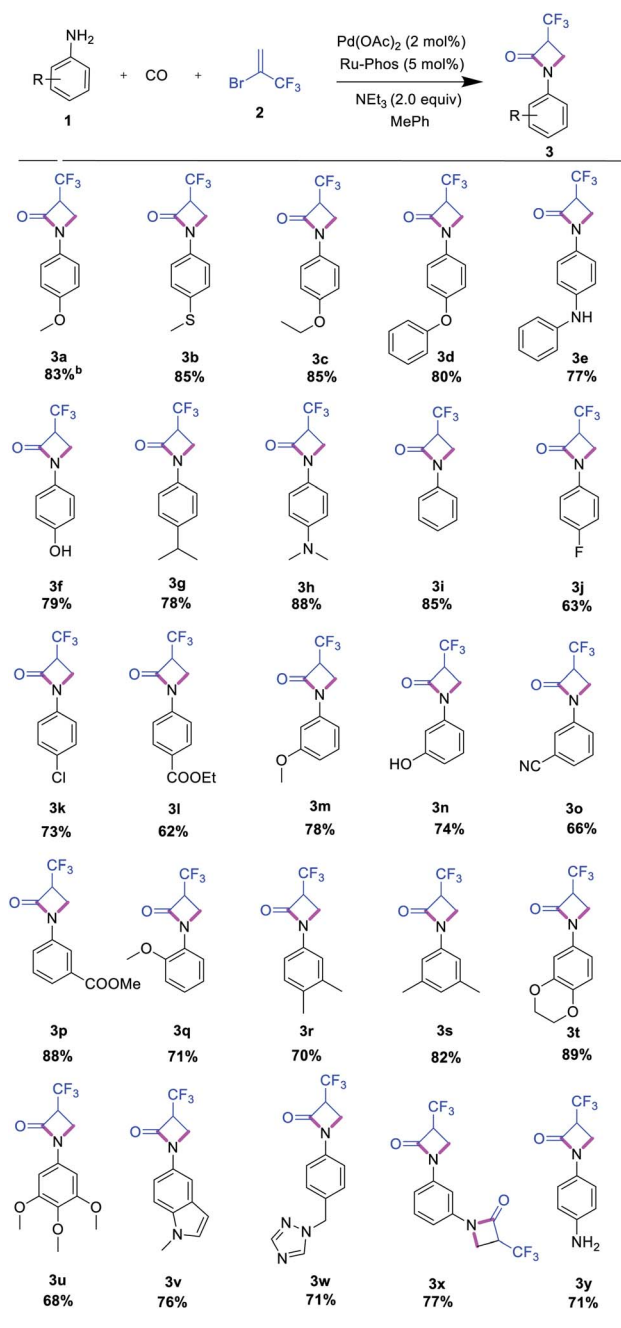


Scheme 3 Control experiments.

palladium catalyst with excellent yield. Next, the potential intermediate 5 was prepared by addition of 4-methoxy-1-iodobenzene to 2-bromo-1,1,1-trifluoropropylamine and subsequently reacted with carbon monoxide in the presence of the palladium catalyst under standard conditions. However, in this case, we did not observe target compound 3a. To investigate the importance of the trifluoromethyl group for this transformation, 2-bromopropene 6 was applied as reagent under standard reaction conditions. Notably, the related  $\beta$ -lactam 7 was not obtained, but instead amide 8 was formed, which shows

that fluoroalkyl groups play a pivotal role in this overall transformation.

After having optimal reaction conditions in hand, the selective cyclocarbonylation of several anilines was investigated (Table 2). After completion, the reaction mixtures were purified by column chromatography, and isolated product yields were determined. The results show that the electronic property of

Table 2 Palladium-catalyzed synthesis of  $\alpha$ -trifluoromethyl- $\beta$ -lactams: variation of anilines<sup>a</sup>

<sup>a</sup> Reaction conditions: aniline (1.0 mmol), 2 (2.0 mmol), Pd(OAc)<sub>2</sub> (2 mol%), Ru-Phos (5 mol%), NEt<sub>3</sub> (2.0 eq.) and MePh (2.0 mL), CO (8 atm), 100 °C, 12 h. <sup>b</sup> Isolated yield.

substituents on the aniline have no pronounced effect on the conversion and selectivity. In general, anilines with electron-rich substituents in *ortho*-, *para*- or *meta*-position such as alkoxy, alkyl, and amino provided the corresponding lactam products in high yield.

Interestingly, more demanding methylthio, hydroxyl, and amino groups as well as heterocycles (indole, triazole) are well tolerated, too (Table 2, entries 3a–3i, 3q, 3v–3w). Similarly, anilines with electron-deficient substituents in *meta*- and *para*-position, e.g. fluorine, chlorine, nitrile, and ester groups, led to the corresponding trifluoromethylated lactams in 63–88% yield (Table 2, entries 3j–3l). Further investigations utilizing di- and tri-substituted anilines proceeded well, too (Table 2, entries 3r–3t). Finally, we investigated the cyclocarbonylations of *p*-phenylenediamine and *m*-phenylenediamine. Here, depending on the substitution pattern, selectively mono- or double- $\beta$ -lactam formation can be observed using an excess amount (4 equiv.) of trifluoromethyl reagent (Table 2, entries 3x, 3y). We explain this behaviour by the decreased nucleophilicity of the second amino group after the first aminocarbonylation reaction in case of 1,4-phenylenediamine.

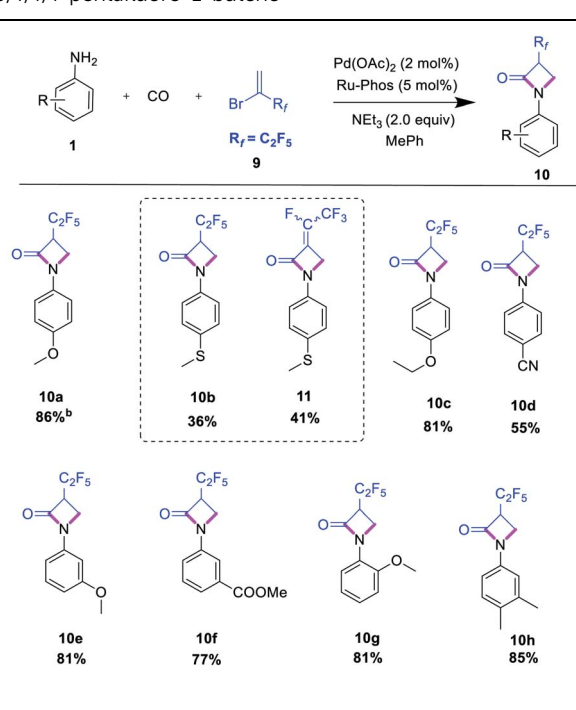
In addition, we explored the reactivity of alkyl amines, including linear and branched ones as well as N-heterocycles. Unfortunately, none of these amines furnished the desired products. Apparently, the increased nucleophilicity/basicity of these substrates significantly decrease the activity of the catalyst by blocking coordination sides.

After studying the reactions of 2-bromo-3,3,3-trifluoro-1-propene as available fluorinated building block, we investigated reactions of the related 2-bromo-3,3,4,4,4-pentafluoro-1-butene **9** with various aromatic amines. Except for 4-thio-methylaniline **1b**, all anilines delivered the corresponding products **10** in good yield (Table 3). Interestingly, in case of **1b** partial dehydrofluorination reaction occurred to give the  $\alpha,\beta$ -unsaturated amide **11** as a *cis/trans* mixture (4 : 1). Furthermore, the domino aminocarbonylation sequence was tested with methyl 2-chloro-acrylate as another olefin. However, no desired product was observed, probably due to polymerization of the highly reactive olefin.

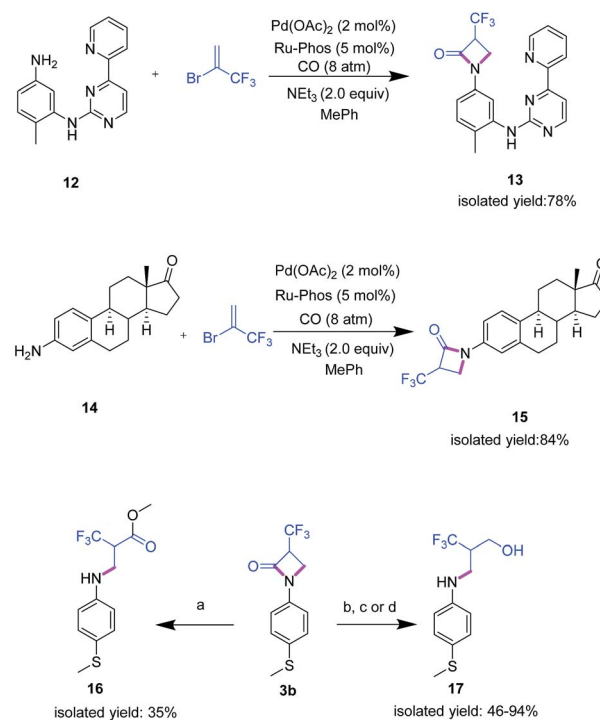
Apart from the preparation of novel fluorinated  $\beta$ -lactam building blocks, we envisioned that this methodology would be amenable to more biologically relevant substrates. To demonstrate this potential, two case studies were performed: imatinib mesylate, a synthetic tyrosine kinase inhibitor widely used in the clinical treatment of chronic myeloid leukemia<sup>26,27</sup> and prostatic hyperplasia,<sup>28</sup> was subjected to the cycloaminocarbonylation reaction with **2** to give the target compound **13** in 78% isolated yield (Scheme 4). In addition, 3-aminoestrone **14**, a versatile precursor of various biologically active compounds to treat hormone-sensitive diseases such as prostate and breast cancers,<sup>29</sup> led to  $\beta$ -lactam **15** in high isolated yield (84%). Notably, in both cases no further optimization of the reaction conditions was necessary showing the robustness of the procedure.

Having a general protocol *vide supra* for the functionalization of aromatic amines to the corresponding  $\alpha$ -

Table 3 Palladium-catalyzed cycloaminocarbonylation of 2-bromo-3,3,4,4,4-pentafluoro-1-butene<sup>a</sup>



<sup>a</sup> Reaction conditions: aniline (1.0 mmol), **9** (2.0 mmol), Pd(OAc)<sub>2</sub> (2 mol%), Ru-Phos (5 mol%), NEt<sub>3</sub> (2.0 eq.) and MePh (4.0 mL), CO (8 atm), 100 °C, 12 h. <sup>b</sup> Isolated yield.



Reaction conditions: a) HCl (MeOH solution), reflux, 5 h; b) NaBH<sub>4</sub> (2.0 eq), MeOH, rt, 2 h; c) LiAlH<sub>4</sub> (2.0 eq), THF, rt, 1 h; d) Ru-Macho complex (5 mol%), H<sub>2</sub> (50 atm), 80 °C, 12 h.

Scheme 4 Synthesis of biologically relevant  $\alpha$ -trifluoromethyl- $\beta$ -lactams and derivatizations.



trifluoromethylated  $\beta$ -lactams and related compounds in hand, this straightforward and practical methodology offers also access to a variety of other interesting fluoroalkyl building blocks following standard procedures. For example,  $\alpha$ -trifluoromethyl- $\beta$ -arylamino acid derivatives should be easily available by classic amide hydrolysis, while (catalytic) reductions offer an entrée to 2-trifluoromethyl-3-aminopropanols (Scheme 4). Indeed, simply refluxing **3b** in an anhydrous hydrogen chloride methanol solution gave **16**. Furthermore, using **3b** the respective amino alcohol **17** is obtained by reduction with  $\text{NaBH}_4$  or  $\text{LiAlH}_4$ . Alternatively, **17** can be formed by Ru-catalyzed hydrogenation (for details see ESI†).

## Conclusion

In summary, we developed a general and convenient palladium-catalyzed cycloaminocarbonylation of 2-fluoroalkyl-2-haloolefins. Through this novel reaction,  $\alpha$ - $\text{CF}_3$ - and related fluoroalkyl-substituted lactams can be synthesized in one step from commercially available **3** and anilines. The palladium catalyst system containing the Ru-Phos ligand allows the selective preparation of a variety of interesting functionalized synthetic building blocks in good to high yields.

## Author contributions

Yang Li discovered the reaction. Cai-Lin Zhang, Wei-Heng Huang, Ning Sun, Meng Hao were preparing the scope and the experimental data. Helfried Neumann has corrected the article and checked the NMR data and Matthias Beller wrote the article.

## Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

## Acknowledgements

We are grateful for the financial support by the National Natural Science Foundation of China (GZ1645), the Key Research & Development Project in Shaanxi Province (2017ZDXM-GY-040), and the Doctoral Scientific Research Foundation of Xi'an Polytechnic University (107020336). In addition, we acknowledge funding by the Federal Ministry BMBF, Germany and the state of Mecklenburg-Western Pomerania.

## Notes and references

- (a) R. D. Chambers, *Fluorine in Organic Chemistry*; Blackwell Publishing: Oxford, UK, 2004; (b) P. Kirsch, *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, Germany, 2004; (c) T. Hiyama, K. Kanie, T. Kusumoto, Y. Morizawa and M. Shimizu, *Organofluorine Compounds: Chemistry and Applications*, Springer-Verlag, Berlin, Germany, 2000.
- (a) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330; (b) P. K. Mykhailiuk, *Chem. Rev.*, 2021, **121**, 1670–1715; (c) J. Moschner, V. Stulberg, R. Fernandes, S. Huhmann, J. Leppkes and B. Koksich, *Chem. Rev.*, 2019, **119**, 10718–10801; (d) B. Linclau, A. Ardá, N.-C. Reichardt, M. Sollogoub, L. Unione, S. P. Vincent and J. Jiménez-Barbero, *Chem. Soc. Rev.*, 2020, **49**, 3863–3888.
- (a) J. Wiedemann, T. Heiner, G. Mloston, G. K. Surya, S. Prakash and G. A. Olah, *Angew. Chem.*, 1998, **110**, 880–881; *Angew. Chem., Int. Ed.*, 1998, **37**, 820–821; (b) N. Aiguabella, C. Pozo, X. Verdager, S. Fustero and A. Riera, *Angew. Chem.*, 2013, **125**, 5463–5467; *Angew. Chem. Int. Ed.*, 2013, **52**, 5355–5359; (c) M. Brambilla and M. Tredwell, *Angew. Chem.*, 2017, **129**, 12143–12147; *Angew. Chem. Int. Ed.*, 2017, **56**, 11981–11985; (d) A. M. Cook and C. Wolf, *Angew. Chem.*, 2016, **128**, 2982–2986; *Angew. Chem. Int. Ed.*, 2016, **55**, 2929–2933.
- (a) A. Tinoco, V. Steck, V. Tyagi and R. Fasan, *J. Am. Chem. Soc.*, 2017, **139**, 5293–5296; (b) C.-P. Zhang and D. Vicić, *J. Am. Chem. Soc.*, 2012, **134**, 183–185; (c) Q.-W. Zhang, A. Brusoe, V. Mascitti, K. D. Hesp, D. C. Blakemore, J. Kohrt and J. Hartwig, *Angew. Chem.*, 2016, **128**, 9910–9914; *Angew. Chem., Int. Ed.*, 2016, **55**, 9758–9762; (d) Q. Wang, C. Ni, M. Hu, Q. Xie, Q. Liu, S. Pan and J. Hu, *Angew. Chem.*, 2020, **132**, 8585–8589; *Angew. Chem., Int. Ed.*, 2020, **59**, 8507–8511.
- (a) J. Nie, H.-C. Guo, D. Cahard and J.-A. Ma, *Chem. Rev.*, 2011, **111**, 455–529; (b) X. Liu, C. Xu and Q. Liu, *Chem. Rev.*, 2015, **115**, 683–730; (c) Z. Xiong, F. Zhang, Y. Yu, Z. Tan and G. Zhu, *Org. Lett.*, 2020, **22**, 4088–4092; (d) M. B. Johansen, O. R. Gedde, T. S. Mayer and T. Skrydstrup, *Org. Lett.*, 2020, **22**, 4068–4072; (e) K. Zhou, J. Geng, D. Wang, J. Zhang and Y. Zhao, *Org. Lett.*, 2020, **22**, 5109–5114; (f) N. J. Young, V. W. Pike and C. Taddei, *ACS Omega*, 2020, **5**, 19557–19564, DOI: 10.1021/acsomega.0c02027; (g) X. Gao, Y.-L. Xiao, X. Wan and X. Zhang, *Angew. Chem.*, 2018, **130**, 3241–3245; *Angew. Chem., Int. Ed.*, 2018, **57**, 3187–3191; (h) R. Cheng, H.-Y. Zhao, S. Zhang and X. Zhang, *ACS Catal.*, 2020, **10**, 36–42.
- (a) J. Ge, Q. Ding, X. Wang and Y. Peng, *J. Org. Chem.*, 2020, **85**, 7658–7665; (b) B. M. Trost, Y. Wang and C.-I. Hung, *Nat. Chem.*, 2020, **12**, 294–301; (c) J. Dong, L. Shi, L. Pan, X. Xu and Q. Liu, *Nat. Catal.*, 2020, DOI: 10.1038/srep26957; (d) P. Sarver, V. Bacauanu, D. M. Schultz, D. A. DiRocco, Y.-H. Lam, E. C. Sherer and D. W. C. MacMillan, *Nat. Chem.*, 2020, **12**, 459–467; (e) R. C. Simon, E. Busto, N. Richter, V. Resch, K. N. Houk and W. Kroutil, *Nat. Commun.*, 2016, **7**, 13323–13328; (f) S. Choi, S. M. Kim, J. W. Yang, S. W. Kim and J. Cho, *Nat. Commun.*, 2014, **5**, 4881–4887.
- (a) E. Mejía and A. Togni, *ACS Catal.*, 2012, **2**, 521–552; (b) T. Liu and Q. Shen, *Org. Lett.*, 2011, **13**, 2342–2345; (c) L. Chu and F.-L. Qing, *Org. Lett.*, 2010, **12**, 5060–5063; (d) R. J. Lundgren and M. Stradiotto, *Angew. Chem.*, 2010, **122**, 9510–9512; *Angew. Chem., Int. Ed.*, 2010, **49**, 9322–9324; (e) E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson and S. L. Buchwald, *Science*, 2010, **328**, 1679–1681; (f)

- V. V. Grushin and W. J. Marshall, *J. Am. Chem. Soc.*, 2006, **128**, 12644–12645; (g) T. D. Senecal, A. T. Parsons and S. L. Buchwald, *J. Org. Chem.*, 2011, **76**, 1174–1176; (h) N. D. Ball, J. W. Kampf and M. S. Sanford, *J. Am. Chem. Soc.*, 2010, **132**, 2878–2879; (i) X. Wang, L. Truesdale and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 3648–3649; (j) B. Yang, D. Yu, X.-H. Xu and F.-L. Qing, *ACS Catal.*, 2018, **8**, 2839–2843; (k) M. J. Orstein, H. Hou, C. Cheng and J. F. Hartwig, *Angew. Chem.*, 2016, **128**, 8186–8189; *Angew. Chem. Int. Ed.*, 2016, **55**, 8054–8057; (l) F. Ye, F. Berger, H. Jia, J. Ford, A. Wortman, B. J. el, C. Genicot and T. Ritter, *Angew. Chem.*, 2019, **131**, 14757–14761; *Angew. Chem. Int. Ed.*, 2019, **58**, 14615–14619; (m) L. Chang, N. Klipfel, L. Dechoux and S. Thorimbert, *Green Chem.*, 2018, **20**, 1491–1498.
- 8 (a) A. T. Parsons, T. D. Senecal and S. L. Buchwald, *Angew. Chem.*, 2012, **124**, 3001–3004; *Angew. Chem., Int. Ed.*, 2012, **51**, 2947–2950; (b) C. Feng and T.-P. Loh, *Chem. Sci.*, 2012, **3**, 3458–3462; (c) C. Feng and T.-P. Loh, *Angew. Chem.*, 2013, **125**, 12640–12643; *Angew. Chem., Int. Ed.*, 2013, **52**, 12414–12417; (d) X. Wang, Y. Ye, G. Ji, Y. Xu, S. Zhang, J. Feng, Y. Zhang and J. Wang, *Org. Lett.*, 2013, **15**, 3730–3733; (e) N. O. Ilchenko, P. G. Janson and K. J. Szabó, *Chem. Commun.*, 2013, **49**, 6614–6616; (f) X.-P. Wang, J.-H. Lin, C.-P. Zhang, J.-C. Xiao and X. Zheng, *J. Org. Chem.*, 2013, **9**, 2635–2640; (g) Z. Fang, Y. Ning, P. Mi, P. Liao and X. Bi, *Org. Lett.*, 2014, **16**, 1522–1525; (h) A. Prieto, E. Jeamet, N. Monteiro, D. Bouyssi and O. Baudoin, *Org. Lett.*, 2014, **16**, 4770–4773; (i) N. Iqbal, S. Choi, E. Kim and E. J. Cho, *J. Org. Chem.*, 2012, **77**, 11383–11387; (j) Z.-B. He, T. Luo, M.-Y. Hu, Y.-J. Cao and J.-B. Hu, *Angew. Chem.*, 2012, **124**, 4010–4013; *Angew. Chem., Int. Ed.*, 2012, **51**, 3940–3947.
- 9 (a) S. Qi, S. Gao, X. Xie, J. Yang and J. Zhang, *Org. Lett.*, 2020, **22**, 5229–5234; (b) F. Tian, G. Yan and J. Yu, *Chem. Commun.*, 2019, **55**, 13486–13505; (c) P. V. Ramachandran and B. Otoo, *Chem. Commun.*, 2015, **51**, 12388–12390; (d) L. Debien, B. Quiclet-Sire and S. S. Zard, *Org. Lett.*, 2012, **14**, 5118–5121; (e) M. Kawatsura, J. Namioka, K. Kajita, M. Yamamoto, H. Tsuji and T. Itoh, *Org. Lett.*, 2011, **13**, 3285–3287.
- 10 For allylic trifluoromethylation, see: (a) A. T. Parsons and S. L. Buchwald, *Angew. Chem.*, 2011, **123**, 9286–9289; *Angew. Chem., Int. Ed.*, 2011, **50**, 9120–9123; (b) X. Wang, Y. Ye, S. Zhang, J. Feng, Y. Xu, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2011, **133**, 16410–16413; (c) R. Shimizu, H. Egami, Y. Hamashima and M. Sodeoka, *Angew. Chem.*, 2012, **124**, 4655–4658; *Angew. Chem., Int. Ed.*, 2012, **51**, 4577–4580; (d) S. Mizuta, O. Galicia-Lopez, K. M. Engle, S. Verhoog, K. Wheelhouse, G. Rassias and V. Gouverneur, *Chem.–Eur. J.*, 2012, **18**, 8583–8587; (e) W. Yang, D. Ma, Y. Zhou, X. Dong, Z. Lin and J. Sun, *Angew. Chem.*, 2018, **130**, 12273–12277; *Angew. Chem., Int. Ed.*, 2018, **57**, 12097–12101; (f) Y. Karuo, T. Hayashi, A. Tarui, K. Sato, K. Kawai and M. Omote, *J. Org. Chem.*, 2020, **85**, 5104–5108.
- 11 For oxytrifluoromethylation, see: (a) R. Zhu and S. L. Buchwald, *J. Am. Chem. Soc.*, 2012, **134**, 12462–12465; (b) Y. Li and A. Studer, *Angew. Chem.*, 2012, **124**, 8345–8348; *Angew. Chem., Int. Ed.*, 2012, **51**, 8221–8224; (c) H. Egami, R. Shimizu and M. Sodeoka, *Tetrahedron Lett.*, 2012, **53**, 5503–5506; (d) P. G. Janson, I. Ghoneim, N. O. Ilchenko and K. J. Szabo, *Org. Lett.*, 2012, **14**, 2882–2885; (e) R. Zhu and S. L. Buchwald, *Angew. Chem.*, 2013, **125**, 12887–12890; *Angew. Chem., Int. Ed.*, 2013, **52**, 12655–12658; (f) D.-F. Lu, C.-L. Zhu and H. Xu, *Chem. Sci.*, 2013, **4**, 2478–2482; (g) Y.-T. He, L.-H. Li, Y.-F. Yang, Y.-Q. Wang, J.-Y. Luo, X.-Y. Liu and Y.-M. Liang, *Chem. Commun.*, 2013, **49**, 5687–5689; (h) L. Li, Q.-Y. Chen and Y. Guo, *J. Org. Chem.*, 2014, **79**, 5145–5152; (i) Y.-P. Xiong, M.-Y. Wu, X.-Y. Zhang, C.-L. Ma, L. Huang, L.-J. Zhao, B. Tan and X.-Y. Liu, *Org. Lett.*, 2014, **16**, 1000–1003; (j) H. Egami, R. Shimizu, Y. Usui and M. Sodeoka, *J. Fluorine Chem.*, 2014, **167**, 172–178; (k) H. Egami, T. Ide, M. Fujita, T. Tojo, Y. Hamashima and M. Sodeoka, *Chem.–Eur. J.*, 2014, **20**, 12061–12065; (l) J.-B. Liu, C. Chen, L. Chu, Z.-H. Chen, X.-H. Xu and F.-L. Qing, *Angew. Chem.*, 2015, **127**, 12005–12008; *Angew. Chem., Int. Ed.*, 2015, **54**, 11839–11842; (m) Q.-W. Zhang and J. F. Hartwig, *Chem. Commun.*, 2018, **54**, 10124–10127; (n) M. Zhou, C. Ni, Y. Zeng and J. Hu, *J. Am. Chem. Soc.*, 2018, **140**, 6801–6805.
- 12 (a) F. Li, J. Wang, M. Xu, X. Zhao, X. Zhou, W.-X. Zhao and Q. Liu, *Org. Biomol. Chem.*, 2016, **14**, 3981–3988; (b) L. Zhao, P. Li, X.-Y. Xie and L. Wang, *Org. Chem. Front.*, 2018, **5**, 1689–1697; (c) X.-M. Ji, W. Liang, C. Fan and R.-Y. Tang, *RSC Adv.*, 2015, **5**, 29766–29773; (d) C. Fan, J. Song, G. L. Qiu, G. Liu and J. Wu, *Org. Chem. Front.*, 2014, **1**, 924–928; (e) T. N. Ngo, S. A. Ejaz, T. Q. Hung, T. Dang, J. Iqbal, J. Lecka, J. Sévigny and P. Langer, *Org. Biomol. Chem.*, 2015, **13**, 8277–8290; (f) X. Zhou, C. Huang, Y. Zeng, J. Xiong, Y. Xiao and J. Zhang, *Chem. Commun.*, 2017, **53**, 1084–1087; (g) B. Garudachari, A. M. Isloor, M. N. Satyanaraya, K. Ananda and H.-K. Fun, *RSC Adv.*, 2014, **4**, 30864–30875; (h) B. Jismy, M. Akssira, D. Knez, G. Guillaumet, S. Gobec and M. Abarbri, *New J. Chem.*, 2019, **43**, 9961–9968.
- 13 (a) W.-Q. Zuo, N.-Y. Wang, Y.-X. Zhu, L. Liu, K.-J. Xiao, L.-D. Zhang, C. Gao, Z.-H. Liu, X.-Y. You, Y.-J. Shi, C.-T. Peng, K. Ran, H. Tang and L.-T. Yu, *RSC Adv.*, 2016, **6**, 40277–40286; (b) C. Masusai, D. Soorukram, C. Kuhakarn, P. Tuchinda, C. Pakawatchai, S. Saithong, V. Reutrakal and M. Pohmakotr, *Org. Biomol. Chem.*, 2013, **11**, 6650–6658; (c) A. Rahman and X. Lin, *Org. Biomol. Chem.*, 2018, **16**, 1367–1374; (d) K. Clapham, A. S. Batsanow, M. R. Bryce and B. Tarbit, *Org. Biomol. Chem.*, 2009, **7**, 2155–2161; (e) F.-Z. Xu, Y.-Y. Wang, D.-X. Luo, G. Yu, S.-X. Guo, H. Fu, Y. H. Zhao and J. Wu, *RSC Adv.*, 2018, **8**, 6306–6314; (f) V. M. Tkachuk, V. A. Sukach, K. V. Kovalchuk, M. V. Vovk and V. G. Nenajdenko, *Org. Biomol. Chem.*, 2015, **13**, 1420–1428; (g) M. B. Johansen and A. T. Lindhardt, *Org. Biomol. Chem.*, 2020, **18**, 1417–1425; (h) A. T. Davies, P. M. Pickett, A. M. Z. Slawin and A. D. Smith, *ACS Catal.*, 2014, **4**, 2696–2700; (i) H.-Y. Li, I. Delucca, S. Drummond and G. A. Boswell, *J. Org. Chem.*, 1997, **62**, 2550–2554; (j)

- H. Uno, T. Imai, K. Harada and N. Shibata, *ACS Catal.*, 2020, **10**, 1454–1459; (k) G. Masson, S. Riouton, D. Pardo and G. J. Cossy, *Org. Lett.*, 2018, **20**, 5019–5022; (l) M. A. Honey, R. Pasceri, W. Lewis and C. L. Moody, *J. Org. Chem.*, 2012, **77**, 1396–1405; (m) L. Qin and S. Z. Zard, *Org. Lett.*, 2015, **17**, 1577–1580.
- 14 (a) A. K. Bose, J. C. Kapur, B. Dayal and M. S. Manhas, *J. Org. Chem.*, 1974, **39**, 312–315; (b) A. K. Bose, M. S. Manhas, S. D. Kapur and S. G. Amin, *J. Med. Chem.*, 1974, **17**, 541–544; (c) M. S. Manhas, M. Ghosh and A. K. Bose, *J. Org. Chem.*, 1990, **55**, 575–580; (d) G. M. Torres, M. L. H. Macias and J. S. Quesnel, *J. Org. Chem.*, 2016, **81**, 12106–12115; (e) X.-F. Ren, M. I. Konaklieva, H. Shi, S. Dickey, D. V. Lim, J. Gonzalez and E. Turos, *J. Org. Chem.*, 1998, **63**, 8898–8917; (f) R. M. Williams, B. H. Lee, M. M. Miller and O. P. Anderson, *J. Am. Chem. Soc.*, 1989, **111**, 1073–1081; (g) A. Bonardi, M. Costa, B. Gabriele, G. Salerno and G. P. Chiusoli, *Tetrahedron Lett.*, 1995, **36**, 7495–7498.
- 15 (a) S. Dekeukeleire, M. D. hooghe and N. D. Kimpe, *J. Org. Chem.*, 2009, **74**, 1644–1649; (b) R. F. Pratt, *J. Med. Chem.*, 2016, **59**, 8207–8220; (c) C. González-Bello, D. Rodríguez, M. Pernas, Á. Rodríguez and E. Colchón, *J. Med. Chem.*, 2020, **63**, 1859–1881; (d) G. M. Torres, M. L. H. Macias, J. S. Quesnel, O. P. Williams, V. Yempally, A. A. Bengali and B. A. Arndtsen, *J. Org. Chem.*, 2016, **81**, 12106–12115.
- 16 (a) C. R. Pitts and T. Lectka, *Chem. Rev.*, 2014, **114**, 7930–7953; (b) M. Szostak and J. Aubé, *Chem. Rev.*, 2013, **113**, 5701–5765; (c) R. J. Worthington and C. Melander, *J. Org. Chem.*, 2013, **78**, 4207–4213; (d) M. S. Lall, Y. Tao, J. T. Arcari, D. C. Boyles, M. F. Brown, D. B. Damon, S. C. Lilley, M. J. Mitton-Fry, J. Starr III, A. M. Stewart and J. Sun, *Org. Process Res. Dev.*, 2018, **22**, 212–218; (e) M. E. Piotti and H. Alper, *J. Am. Chem. Soc.*, 1996, **118**, 111–116; (f) J. A. Deyrup and S. C. Clough, *J. Am. Chem. Soc.*, 1969, **91**, 4590–4591; (g) T. Kaneko, *J. Am. Chem. Soc.*, 1985, **107**, 5490–5492; (h) H. Alper, C. P. Perera and F. R. Ahmed, *J. Am. Chem. Soc.*, 1981, **103**, 1289–1291; (i) A. Yada, S. Okajima and M. Murakami, *J. Am. Chem. Soc.*, 2015, **137**, 8708–8711; (j) M. M. C. Lo and G. C. Fu, *J. Am. Chem. Soc.*, 2002, **124**, 4572–4573; (k) D. Dailler, R. Rocaboy and O. Baudoin, *Angew. Chem. Int. Ed.*, 2017, **56**, 7218–7222; (l) T. Shu, L. Zhao, S. Li, X.-Y. Chen, C. Essen, K. Rissanen and D. Enders, *Angew. Chem., Int. Ed.*, 2018, **57**, 10985–10988; (m) W. Li, C. Liu, H. Zhang, K. Ye, G. Zhang, W. Zhang, Z. Duan, S. You and A. Lei, *Angew. Chem.*, 2014, **126**, 2475–2478; *Angew. Chem., Int. Ed.*, 2014, **53**, 2443–2446.
- 17 J. Jakowiecki, R. Loska and M. Makosza, *J. Org. Chem.*, 2008, **73**, 5436–5441.
- 18 X. Wu, Y. Zhao and H. Ge, *Chem.–Eur. J.*, 2014, **20**, 9530–9533.
- 19 Z. Wang, J. Ni, Y. Kuninobu and M. Kanai, *Angew. Chem.*, 2014, **126**, 3564–3567; *Angew. Chem., Int. Ed.*, 2014, **53**, 3496–3499.
- 20 X. Xu, K. Yang, Y. Zhao, H. Sun, G. Li and H. Ge, *Nat. Commun.*, 2015, **6**, 6462–6471.
- 21 (a) V. Jurčík, A. M. Z. Slawin and D. O'Hagan, *Beilstein J. Org. Chem.*, 2011, **7**, 759–766; (b) T. Kiyoshi, M. Takami and M. Keiryō, *Chem. Lett.*, 1989, **18**, 1115–1118.
- 22 (a) J. Yang, J. Liu, H. Neumann, R. Franke, R. Jackstell and M. Beller, *Science*, 2019, **366**, 1514–1517; (b) J. Liu, J. Yang, W. Baumann, R. Jackstell and M. Beller, *Angew. Chem.*, 2019, **131**, 10793–10797; *Angew. Chem. Int. Ed.*, 2019, **58**, 10683–10687; (c) J. Liu, J. Yang, C. Schneider, R. Franke, R. Jackstell and M. Beller, *Angew. Chem.*, 2020, **132**, 9117–9125; *Angew. Chem., Int. Ed.*, 2020, **59**, 9032–9040; (d) J. Yang, J. Liu, Y. Ge, W. Huang, F. Ferretti, H. Neumann, H. Jiao, R. Franke, R. Jackstell and M. Beller, *Angew. Chem., Int. Ed.*, 2021, **60**, 9527–9533.
- 23 (a) R. H. Munday, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 2754–2755; (b) J. E. R. Sadig, R. Foster, F. Wakenhut and M. C. Wills, *J. Org. Chem.*, 2012, **77**, 9473–9486; (c) B. Nguyen, E. J. Emmett and M. C. Wills, *J. Am. Chem. Soc.*, 2010, **132**, 16372–16373; (d) Y.-H. Yao, H.-Y. Yang, M. Chen, F. Wu, X.-X. Xu and Z.-H. Guan, *J. Am. Chem. Soc.*, 2021, **143**, 85–91.
- 24 (a) G. Kiss, *Chem. Rev.*, 2001, **101**, 3435–3456; (b) X.-F. Wu, H. Neumann and M. Beller, *Chem. Rev.*, 2013, **113**, 1–35; (c) J.-B. Peng, F.-P. Wu and X.-F. Wu, *Chem. Rev.*, 2019, **119**, 2090–2127; (d) Y. Li, Y. Hu and X.-F. Wu, *Chem. Soc. Rev.*, 2018, **47**, 172–194; (e) C. Zhu, J. Liu, M. B. Li and J.-E. Bäckvall, *Chem. Soc. Rev.*, 2020, **49**, 341–353; (f) Z. Yin, J. -X. Xu and X. -F. Wu, *ACS Catal.*, 2020, **10**, 6510–6531; (g) S. Perrone, L. Troisi and A. Salomone, *Eur. J. Org. Chem.*, 2019, 4626–4643; (h) R. Mancuso, N. Della Ca, L. Veltri, I. Ziccarelli and B. Gabriele, *Catalysis*, 2019, **9**, 610–611; (i) G. Albano and L. A. Aronica, *Eur. J. Org. Chem.*, 2017, **48**, 7204–7221; (j) K. Ma, B. S. Martin, X. Yin and M. Dai, *Nat. Prod. Rep.*, 2019, **36**, 174–219; (k) C. Shen and X.-F. Wu, *Chem.–Eur. J.*, 2017, **23**, 2973–2987; (l) B. Gabriele, R. Mancuso and G. Salerno, *Eur. J. Org. Chem.*, 2012, **35**, 6825–6839.
- 25 J. E. Milne and S. L. Buchwald, *J. Am. Chem. Soc.*, 2004, **126**, 13028–13032.
- 26 (a) J. M. Goldman, J. V. Melo and N. Engl, *J. Med.*, 2003, **349**(15), 1451–1464; (b) S. G. O'Brien and M. W. Deininger, *Semin. Hematol.*, 2003, **40**, 26–30; (c) F. Cervantes and M. Mauro, *Cancer*, 2011, **117**, 4343–4354.
- 27 (a) G. W. Krystal, *Leuk. Res.*, 2004, **28**, 53–59; (b) I. El Hajj Dib, M. Gallet, R. Mentaverri, N. Sevenet, M. Brazier and S. Kamel, *Eur. J. Pharmacol.*, 2006, **551**, 27–33.
- 28 (a) F. Labrie, A. Bélanger, L. Cusan, C. Labrie, J. Simard, V. Luu-The, P. Diamond, J.-L. Gomez and B. Candas, *Endocr. Relat. Canc.*, 1996, **3**, 243–278; (b) S. M. Singh, S. Gauthier and F. Labrie, *Curr. Med. Chem.*, 2000, **7**, 211–247.
- 29 I.-I. Radu, D. Poirier and L. Provencher, *Tetrahedron Lett.*, 2002, **43**, 7617–7619.