ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2019, **55**, 14458

Received 2nd October 2019,
Accepted 4th November 2019

DOI: 10.1039/c9cc07726j

rsc.li/chemcomm

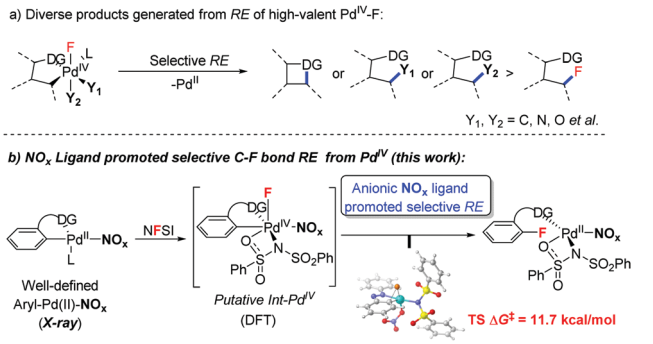
Anion ligand promoted selective C–F bond reductive elimination enables C(sp^2)–H fluorination†

Yang-Jie Mao, [a] Gen Luo, *[b] Hong-Yan Hao,[a] Zhen-Yuan Xu,[a] Shao-Jie Lou *[a] and Dan-Qian Xu *[a]

A detailed mechanism study on the anion ligand promoted selective C–H bond fluorination is reported. The role of the anion ligand has been clarified by experimental evidence and DFT calculations. Moreover, the nitrate promoted C–F bond reductive elimination enabled a selective C–H bond fluorination of various symmetric and asymmetric azobenzenes to access diverse *o*-fluoroanilines.

The strategies to incorporate fluorine into organic molecules have long been explored due to the unique properties of fluorinated motifs.[1] Pd catalysis plays an important role in this field. However, given the low nucleophilicity of the fluorine anion, C–F bond reductive elimination from aryl-Pd(II)–F species is usually challenging.[2] Metals in higher oxidation states are more favorable to undergo reductive eliminations and facilitate the construction of new chemical bonds,[3] thus a high-valent aryl-Pd(IV)–F species has emerged as a useful alternative for the synthesis of aryl fluorides *via* C–H bond activation.[4] Despite the advances, the selective reductive elimination from octahedral Pd(IV) intermediates remains the central goal of this chemistry. Owing to the sluggish C–F reductive elimination, a number of different anion ligands such as acetoxyl, halo or N-anions adopted at high-valent Pd(IV)–F species will participate in the competing reductive elimination (RE) to afford diverse products other than fluorides, which renders F^+ reagents as so-called bystanding oxidants (Scheme 1, a).[3e,5] Therefore, general strategies to control the selectivity of RE from high-valent Pd(IV) fluorides are highly desirable in developing reliable procedures for C–F bond formation.

Several strategies have been developed to control the selective C–F bond RE from Pd(IV)–F intermediates. In 2014, Sanford's group studied the selective C(sp^3)–F reductive elimination of Pd(IV) with diverse oxygen nucleophiles. Interestingly, a special cation effect was observed to enable the disfavored C(sp^3)–F coupling.[5b] Very recently, Yu's group exhibited a selective benzylic C–H fluorination controlled by adjusting the ligand environment of Pd(IV) fluoride species.[6] Another practical and efficient pathway to achieve selective C–F bond reductive eliminations is to replace the competing nucleophilic anions with less nucleophilic anion ligands especially in a catalytic fashion. For instance, Yu previously used palladium triflates to avoid the side C–H acetoxylation in their C–H bond fluorination.[4e,7] Our group developed a Pd–nitrate catalytic system for the selective C(sp^2)–H bond fluorination of diverse fundamental substrates, albeit with a deficient understanding of the mechanism.[8] Herein, we report detailed mechanism studies on the role of anionic NO_x additives in C–H bond fluorination. Two well-defined aryl-Pd(II)–NO_x complexes were obtained and studied for the first time (Scheme 1, b). NO_x anions such as nitrate or nitrite have received increasing attention due to their unique reactivity in several palladium-catalyzed reactions.[9] However, the catalytic behavior of putative Pd(II)–NO_x complexes in catalytic processes is somehow elusive.



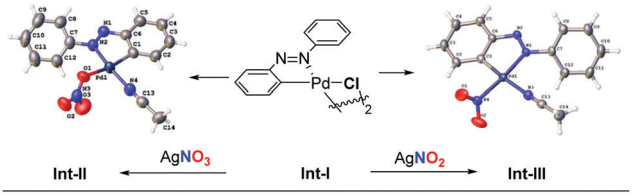
Scheme 1 Selective reductive elimination from Pd(IV).

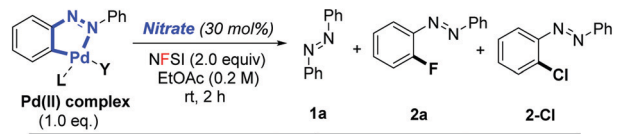
At the outset of the project, the preliminary reaction conditions were screened for the C–H bond fluorination of azobenzene **1a**. As anticipated, the Pd catalyst and nitrate are indispensable in

[a] College of Chemical Engineering, Catalytic Hydrogenation Research Center, State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Zhejiang University of Technology, Hangzhou 310014, P. R. China. E-mail: loushaojie@zjut.edu.cn, chrc@zjut.edu.cn

[b] State Key Laboratory of Fine Chemicals, School of Chemical Engineering, Dalian University of Technology, Dalian 116024, P. R. China. E-mail: luogen@dlut.edu.cn

† Electronic supplementary information (ESI) available. CCDC 1853333, 1949005–1949006. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc07726j





Pd(II) complex	Nitrate ligand	1a (%)	2a (%)	2-Cl (%)
Int-I (Y = Cl)	none	53	trace	43
	KNO_3	2	41	49
	$CsNO_3$	4	37	39
	$AgNO_3$	2	66	26
	w/o nitrate & NFSI	62	/	0
Int-II (Y = ONO_2)	none	N.D.	78	/
Int-III (Y = NO_2)	none	8	73	/

Scheme 2 Preparation and transformation of Pd(II) complexes.

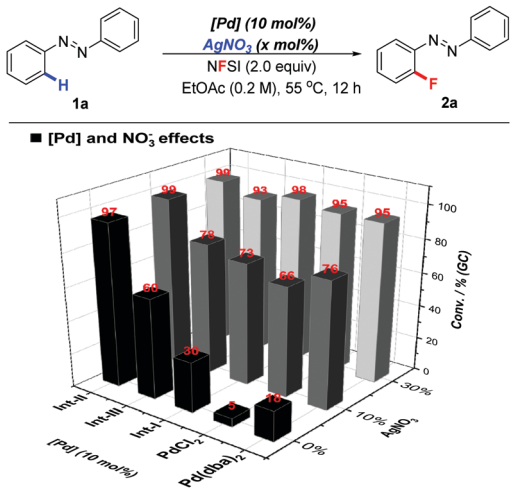


Fig. 1 Catalytic activity of [Pd] complexes with varying equivalents of $AgNO_3$.

this reaction. **1a** was largely converted into the desired product 1-(2-fluorophenyl)-2-phenyldiazene **2a** when a catalytic amount of $AgNO_3$ or $AgNO_2$ was used as an additive in EtOAc. The reaction efficiency decreased sharply when the nitrate additive was replaced by other anion ligands (see the ESI,† S4).[10]

The unique anionic effect encouraged us to prepare aryl-Pd–NO_x complexes to get further insight into the mechanism. Firstly, a well-established Cl-bridged dinuclear Pd(II) complex **Int-I** was prepared (Scheme 2).[11] Treating **Int-I** with $AgNO_x$ could quantitatively give Pd(II)–NO_x complexes **Int-II** and **Int-III** smoothly (see the ESI†).[12] X-ray analysis of **Int-II** revealed that the NO_3 ligand is *trans* to the sp^2-carbon center and possesses O-bound to the Pd center. In contrast, complex **Int-III** has *cis*-configuration and an N-bound nitrite ligand. Our initial study commenced on evaluating the fluorination of the Pd(II) complexes with NFSI and diverse anion additives. As shown in Scheme 2, treating **Int-I** with NFSI and different additives afforded a mixture of **1a**, **2a** and **2-Cl**. Notably, anion additives had a profound influence on the transformation of **Int-I**. Chlorinated azobenzene **2-Cl** was detected as the sole product in the absence of any additives. Nitrate additives such as KNO_3, $CsNO_3$, and $AgNO_3$ significantly promoted the fluorination. Moreover, **2-Cl** was not observed in the absence of nitrate and NFSI, which suggested that an oxidative induced C(sp^2)–Cl bond reductive elimination from a high-valent Pd(IV) chloride intermediate might be involved in this chlorination. In addition, both the Pd(II)–NO_x complexes transformed smoothly into fluorination product **2a** even at room temperature within 2 hours in the absence of extra anion ligands, which further implied the pivotal role of NO_x in the selective C–F bond formation. Next, an assessment of diverse Pd(II) complexes for the catalytic fluorination of **1a** was done as shown in Fig. 1. In all cases, the addition of a catalytic amount of nitrate could dramatically promote the fluorination of **1a**. $Pd(dba)_2$, $PdCl_2$, and **Int-I** showed negative catalytic reactivity in the absence of $AgNO_3$. In sharp contrast, NO_x^- containing complexes, especially the aryl-Pd(II)–NO_3 complex **Int-II**, gave much better results, which suggested that the aryl-Pd(II)–NO_x complexes should be the key reactive species. In addition, the kinetic experiment displayed a lack of induction period, indicating that the cyclopalladatation complexes might be involved in the catalytic cycle (see the ESI,† S6).[10]

These stoichiometric and catalytic reactions showed a great ligand effect of NO_x additives in the fluorination. We proposed that the NO_x ligands might promote the fluorination by the following two pathways: (1) control the selective C–F bond reductive elimination from high-valent Pd(IV) due to their poor nucleophilicity; (2) make the Pd metal center more electrophilic and attenuate the polarization of the Pd(IV)–F bond due to the coordination of the highly electron-withdrawing NO_x ligand. HRMS analysis and ^{19}F NMR experiments were then conducted in order to capture the putative Pd(IV) species.[13] A *m*/*z* value of 601.9837 was detected when the reaction mixture of **Int-II** with NFSI was subjected to HRMS (ESI-TOF), which was consistent with the *m*/*z* value of the Pd(IV) fluoride intermediate [azobenzene–Pd^{IV}(F)–$N(SO_2Ph)_2$]$^+$. And a fluorine resonance at −180 ppm was monitored by ^{19}F NMR from the reaction mixture of **Int-II** with NFSI in CD_3CN, the pivotal signal of which might be the fluorine resonance of the key [azobenzene–Pd^{IV}–F] intermediate according to the previous reports.[8d,13] After 30 min and heating at 55 °C for another 25 min, the fluorine resonance of the *o*-fluoroazobenzene emerged, indicating that the reductive elimination of the [azobenzene–Pd^{IV}–F] intermediate might take place to give the fluorinated azobenzene. However, probably due to their high reactivity, an attempt to obtain the high-valent aryl-Pd(IV)–NO_x complexes failed. Thus, as an alternative, the reductive elimination processes of Cl^-, NO_3^-, and NO_2^- substituted Pd(IV) species were investigated by DFT calculations.[13] As shown in Fig. 2, the Pd(IV) species (**A**, **B**, and **C**) adopt an octahedron form, in which the azobenzene and $N(SO_2Ph)_2$ anionic ligands occupied the equatorial positions and the F and Cl (or NO_3/NO_2) anionic ligands were located at the axial positions. It was obvious that the equatorial $N(SO_2Ph)_2$ ligand in Pd(IV) species was bound to the Pd center in η^2-form and thus less available to undergo the reductive elimination process

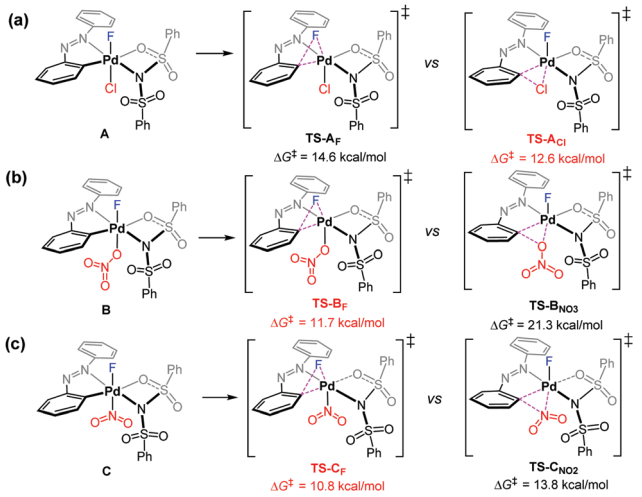


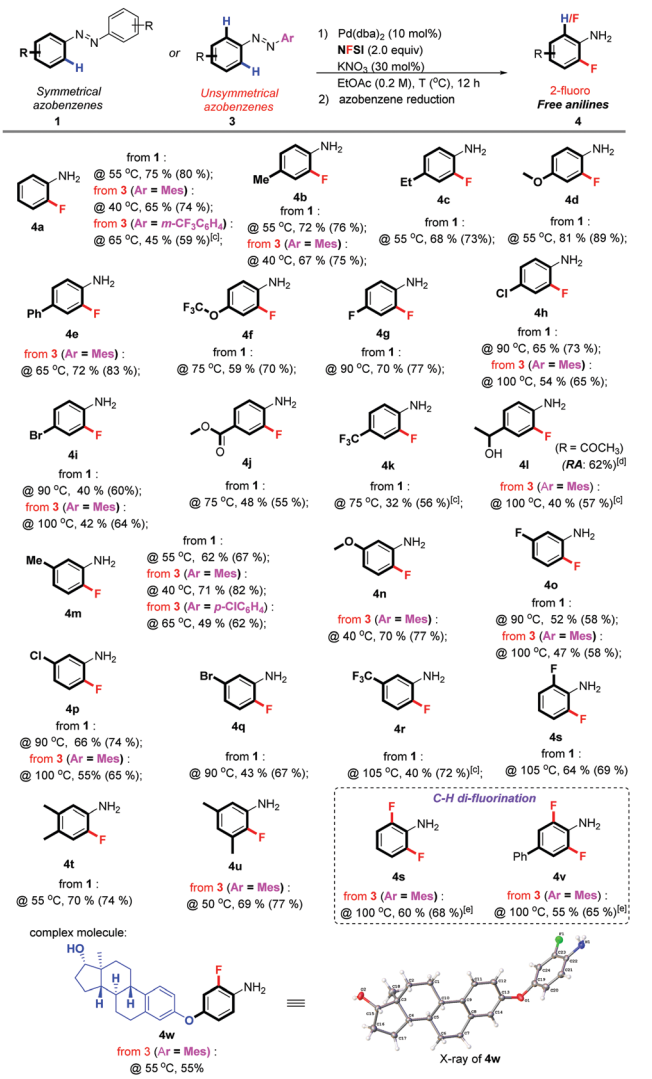
Fig. 2 Computed reductive elimination processes of the species **A**, **B**, and **C**. The relative free energy barriers ($\Delta G^{\ddagger}$) are given in kcal mol^{-1}.

compared with the axial η^1-coordinated F or Cl (NO_3/NO_2) anionic ligands. In Cl-containing species **A** (Fig. 2a), the reductive elimination of C–Cl *via* **TS-A$_{Cl}$** ($\Delta G^{\ddagger}$ = 12.6 kcal mol^{-1}) was more favorable than that of C–F *via* **TS-A$_F$** ($\Delta G^{\ddagger}$ = 14.6 kcal mol^{-1}). This is in good agreement with the experimental observation that a chlorinated product was obtained rather than a fluorinated product. In contrast to **A**, in the cases of **B** and **C**, the reductive elimination processes of C–F were favored compared to those of C–ONO$_2$ or C–NO$_2$, thus leading to fluorinated product (Fig. 2b and c). The computational results clearly suggested that the introduction of NO_3 or NO_2 anions could reduce the energy barrier of C–F reductive elimination and increase the energy barrier of reductive elimination of the other anion (NO_3^- or NO_2^-) in comparison with the Cl-containing case. Therefore, the synthesis of the fluorinated product could be achieved by regulating the anions.

Guided by this mechanistic blueprint, we commenced to carry out the catalytic C–H bond fluorination of azobenzenes. Though azobenzenes are widely found as substrates in various C–H bond transformations as aniline surrogates, no C–H fluorination has been reported to date.[14] Further detailed screening of the catalytic conditions was conducted (see the ESI†).[10] The substrate scope of symmetrical azobenzenes was then explored under the optimal conditions. Considering the inseparable mixture of mono- and difluorinated arenes, we proposed to eliminate the N=N framework by restoring the azo double bond to the corresponding anilines, which is present widely in various pharmaceuticals and medical intermediates (*i.e.* Cobimetinib, Regorafenib and Finafloxacin, see the ESI†).[15,16] Pleasingly, under the efficient NaBH$_4$–CuCl reductive system,[17] the desired fluorinated anilines could be obtained in moderate to good yields (Table 1).

Various symmetrical *para*- (**4a–d** and **4f–k**), *meta* (**4m** and **4o–r**) or *ortho* (**4s**)-substituted azobenzenes were tested in this fluorination. In general, both electron-donating (**4b–d**, **4m**, and **4t**) and electron-withdrawing (**4f–k** and **4o–s**) groups were well tolerated under the fluorination conditions at indicated temperatures. Electron-rich azobenzenes were more prone to undergo fluorination in good yields under mild conditions at 55 °C. In contrast, substrates

Table 1 C–H Fluorination of symmetrical and unsymmetrical azobenzenes[ab]



[a] Conditions: **1** or **3** (0.30 mmol), Pd(dba)$_2$ (10 mol%), NFSI (0.60 mmol), KNO_3 (30 mol%) in 1.5 mL of EtOAc under air at the indicated oil bath temperature for 12 h. Yield of the mono-fluorination was determined by GC-MS using biphenyl as an internal standard as shown in parentheses. [b] Azobenzene reduction procedure: $NaBH_4$ (7.0 equiv.), CuCl (6.0 equiv.), anhydrous ethanol (0.1 M), RT, air, 5–30 min, unless otherwise noted. Isolated yields of *o*-fluoroanilines over two steps were given, see the ESI for the detailed reaction information of each entry from different starting materials. [c] Reduction process was under reflux. [d] RA = recovered 2,4,6-trimethylaniline. [e] Using 4.0 equiv. NFSI.

with more electron-withdrawing groups required more harsh conditions at temperatures ranging from 75 °C to 105 °C. Halo groups such as chloro (**4h** and **4p**) and bromo (**4i** and **4q**) remained intact under the fluorination conditions. Fluorination of *meta*-substituted substrates took place at the less sterically hindered *para*-sites of the functional groups (**4m** and **4o–r**).

Next, we turned our attention to the scope of diverse unsymmetrical azobenzenes. We envisaged that the inactive aniline moiety in unsymmetrical azobenzene could serve as a removable directing group, which would be utmost practical for the C–H

bond fluorination of more complex anilines. We first chose unsymmetrical azobenzenes with the 2,6-diblocked mesityl group (Table 1). Thankfully, the C–H bond fluorination of unsymmetrical azobenzenes afforded similar results in comparison with symmetrical azobenzenes (**4a–b**, **4e**, **4h–i**, **4l–p**, and **4u**). Notably, the recovery of the trimethyl aniline was also feasible in good yield (**4l**). Azobenzenes bearing electron-deficient anilines were also explored and the fluorination exclusively took place at the more electron-rich aromatic side (**4a** and **4m**). Moreover, C–H bond difluorination of azobenzenes also took place smoothly with additional loading of NFSI at elevated temperatures (**4s–v**). In addition, late-stage C–H fluorination of estrone-containing complex azobenzene took place smoothly, affording the *o*-fluoroaniline derivative **4w** in moderate yield.[10,18]

In conclusion, a nitrate-promoted selective C–H fluorination of diverse azobenzenes was established, which provided the corresponding fluorinated anilines by further reduction. More importantly, the ligand effect of NO_x additives was studied in detail by employing well-defined aryl-Pd(II)–NO_x intermediates. In addition, DFT calculations showcased that utilizing simple nitrate/nitrite as an anion ligand significantly decreased the energy barrier of the C–F bond reductive elimination pathway from the Pd(IV) intermediate. Utilizing this distinct strategy for the selective reductive elimination of other challenging chemical bonds could also be expected in the near future.

G. L. thanks the Fundamental Research Funds for the Central Universities (DUT18RC(3)002) and the Network and Information Center of Dalian University of Technology for computational resources.

Conflicts of interest

The authors declare no competing financial interests.

References

1 (*a*) Q. Cheng and T. Ritter, *Trends Chem.*, 2019, **1**, 461; (*b*) Y. Zhu, J. Han, J. Wang, N. Shibata, M. Sodeoka, V. A. Soloshonok, J. A. S. Coelho and F. D. Toste, *Chem. Rev.*, 2018, **118**, 3887; (*c*) D. A. Petrone, J. Ye and M. Lautens, *Chem. Rev.*, 2016, **116**, 8003; (*d*) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422; (*e*) C. Ni and J. Hu, *Chem. Soc. Rev.*, 2016, **45**, 5441; (*f*) J. He, S. Lou and D. Xu, *Chin. J. Chem.*, 2016, **36**, 1218; (*g*) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432; (*h*) Y. Li, Y. Wu, G.-S. Li and X.-S. Wang, *Adv. Synth. Catal.*, 2014, **356**, 1412; (*i*) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214; (*j*) T. M. Beale, M. G. Chudzinski, M. G. Sarwar and M. S. Taylor, *Chem. Soc. Rev.*, 2013, **42**, 1667; (*k*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.

2 (*a*) A. C. Sather and S. L. Buchwald, *Acc. Chem. Res.*, 2016, **49**, 2146; (*b*) A. C. Sather, H. G. Lee, V. Y. D. L. Rosa, Y. Yang, P. Müller and S. L. Buchwald, *J. Am. Chem. Soc.*, 2015, **137**, 13433; (*c*) H. G. Lee, P. J. Milner and S. L. Buchwald, *J. Am. Chem. Soc.*, 2014, **136**, 3792; (*d*) D. A. Watson, M. Su, G. Teverovskiy, Y. Zhang, J. Garcia-Fortanet, T. Kinzel and S. L. Buchwald, *Science*, 2009, **325**, 1661.

3 (*a*) S. Vásquez-Céspedes, X. Wang and F. Glorius, *ACS Catal.*, 2018, **8**, 242; (*b*) M. Simonetti, D. M. Cannas, X. Just-Baringo, I. J. Vitorica-Yrezabal and I. Larrosa, *Nat. Chem.*, 2018, **10**, 724; (*c*) K. Shin, Y. Park, M.-H. Baik and S. Chang, *Nat. Chem.*, 2017, **10**, 218; (*d*) E. Chong, J. W. Kampf, A. Ariafard, A. J. Canty and M. S. Sanford, *J. Am. Chem. Soc.*, 2017, **139**, 6058; (*e*) I. M. Pendleton, M. H. Pérez-Temprano, M. S. Sanford and P. M. Zimmerman, *J. Am. Chem. Soc.*, 2016, **138**, 6049; (*f*) J. J. Topczewski and M. S. Sanford, *Chem. Sci.*, 2015, **6**, 70; (*g*) N. M. Camasso and M. S. Sanford, *Science*, 2015, **347**, 1218; (*h*) J. R. Bour, N. M. Camasso and M. S. Sanford, *J. Am. Chem. Soc.*, 2015, **137**, 8034; (*i*) A. J. Hickman and M. S. Sanford, *Nature*, 2012, **484**, 177; (*j*) J. M. Racowski, N. D. Ball and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 18022; (*k*) L.-M. Xu, B.-J. Li, Z. Yang and Z.-J. Shi, *Chem. Soc. Rev.*, 2010, **39**, 712; (*l*) T. Furuya, H. M. Kaiser and T. Ritter, *Angew. Chem., Int. Ed.*, 2008, **47**, 5993.

4 (*a*) R. Szpera, D. F. J. Moseley, L. B. Smith, A. J. Sterling and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2019, **27**, 2; (*b*) X.-Y. Chen and E. J. Sorensen, *J. Am. Chem. Soc.*, 2018, **140**, 2789; (*c*) C. Testa, É. Gigot, S. Genc, R. Decréau, J. Roger and J.-C. Hierso, *Angew. Chem., Int. Ed.*, 2016, **55**, 5555; (*d*) C. Chen, C. Wang, J. Zhang and Y. Zhao, *J. Org. Chem.*, 2015, **80**, 942; (*e*) K. S. L. Chan, M. Wasa, X. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2011, **50**, 9081.

5 (*a*) N. M. Camasso, M. H. Pérez-Temprano and M. S. Sanford, *J. Am. Chem. Soc.*, 2014, **136**, 12771; (*b*) M. H. Pérez-Temprano, J. M. Racowski, J. W. Kampf and M. S. Sanford, *J. Am. Chem. Soc.*, 2014, **136**, 4097; (*c*) K. M. Engle, T.-S. Mei, X. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2011, **50**, 1478; (*d*) N. D. Ball, J. W. Kampf and M. S. Sanford, *J. Am. Chem. Soc.*, 2010, **132**, 2878.

6 H. Park, P. Verma, K. Hong and J.-Q. Yu, *Nat. Chem.*, 2018, **10**, 755.

7 X. Wang, T.-S. Mei and J.-Q. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 7520.

8 (*a*) Y.-J. Mao, S.-J. Lou, H.-Y. Hao and D.-Q. Xu, *Angew. Chem., Int. Ed.*, 2018, **57**, 14085; (*b*) X.-Q. Ning, S.-J. Lou, Y.-J. Mao, Z.-Y. Xu and D.-Q. Xu, *Org. Lett.*, 2018, **20**, 2445; (*c*) S.-J. Lou, Q. Chen, Y.-F. Wang, D.-Q. Xu, X.-H. Du, J.-Q. He, Y.-J. Mao and Z.-Y. Xu, *ACS Catal.*, 2015, **5**, 2846; (*d*) S.-J. Lou, D.-Q. Xu and Z.-Y. Xu, *Angew. Chem., Int. Ed.*, 2014, **53**, 10330.

9 I. J. S. Fairlamb, *Angew. Chem., Int. Ed.*, 2015, **54**, 10415.

10 For detailed information, see the ESI†.

11 T. Janecki, J. A. D. Jeffreys, P. L. Pauson, A. Pietrzykowski and K. J. McCullough, *Organometallics*, 1987, **6**, 1553.

12 M. N. Wenzel, P. K. Owens, J. T. W. Bray, J. M. Lynam, P. M. Aguiar, C. Reed, J. D. Lee, J. F. Hamilton, A. C. Whitwood and I. J. S. Fairlamb, *J. Am. Chem. Soc.*, 2017, **139**, 1177.

13 C. Testa, J. Roger, P. Fleurat-Lessard and J.-C. Hierso, *Eur. J. Org. Chem.*, 2019, 233.

14 (*a*) T. H. L. Nguyen, N. Gigant and D. Joseph, *ACS Catal.*, 2018, **8**, 1546; (*b*) I. Omae, *Chem. Rev.*, 1979, **79**, 287.

15 C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2015, **54**, 3216.

16 (*a*) S. H. Hwang, A. T. Wecksler, G. Zhang, C. Morisseau, L. V. Nguyen, S. H. Fu and B. D. Hammock, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 3732; (*b*) N.-C. Emrich, A. Heisig, W. Stubbings, H. Labischinski and P. Heisig, *J. Antimicrob. Chemother.*, 2010, **65**, 2530.

17 Y. He, H. Zhao, X. Pan and S. Wang, *Synth. Commun.*, 1989, **19**, 3047.

18 D. E. Yerien, S. Bonesi and A. Postigo, *Org. Biomol. Chem.*, 2016, **14**, 8398.