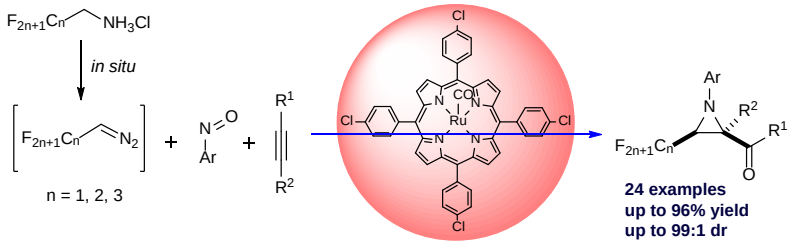
Perfluoroalkyl Aziridines with Ruthenium Porphyrin Carbene Intermediates

Kai Wu, Cong-Ying Zhou,* and Chi-Ming Che*

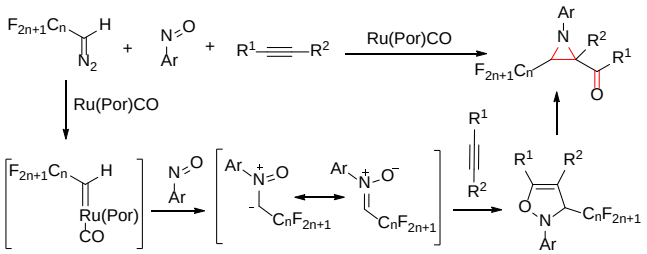
State Key Laboratory of Synthetic Chemistry and Department of Chemistry, The University of Hong Kong, Hong Kong and HKU Shenzhen Institute of Research & Innovation, Shenzhen, China.



ABSTRACT: A new and efficient synthesis of multifunctionalized perfluoroalkyl aziridines via a ruthenium-perfluoroalkylcarbene intermediate was described. With Ru(*p*-Cl-TPP)CO as the catalyst, *in situ* generated $C_nF_{2n+1}CHN_2$ from $C_nF_{2n+1}CH_2NH_3Cl$ underwent a cascade of nitrone formation/1,3-diploar cycloaddition/rearrangement reactions with nitrosoarenes and alkynes to give a variety of multifunctionalized perfluoroalkyl aziridines in good to high yields and with moderate to high diastereoselectivity. The ruthenium perfluoroalkylcarbene intermediates obtained through the stoichiometric reaction of ruthenium porphyrin and $C_nF_{2n+1}CHN_2$ were spectroscopically characterized.

Organofluorine compounds are important for drug discovery because the incorporation of fluorinated groups into bioactive molecules can significantly influence their physicochemical properties.[1] Therefore, there has been considerable interest in developing new and efficient methods for the synthesis of fluorinated building blocks.[2] Aziridines can be readily converted into a variety of nitrogen-containing compounds due to the inherent reactivity of the constrained three-membered ring system and themselves are present in many biologically active molecules.[3] Thus, the synthesis of perfluoroalkyl aziridines[4] is an appealing strategy to access a variety of perfluoroalkyl substituted amines for drug discovery purpose. In the literature, the intramolecular cyclization of fluorinated amines,[5] aza-Darzens reaction [6] and Aza-Corey−Chaykovsky reaction [7] of trifluoroaldimines and [1+2] cycloaddition of fluorinated alkenes [8,9] are frequently employed to synthesize trifluoromethyl aziridines. Although these methods are effective for the preparation of a range of trifluoromethyl aziridines, access to multi-substituted trifluoromethyl aziridines via these methods generally requires advanced starting materials or a multistep synthesis. Several years ago, we described a ruthenium(II)-catalyzed three component reaction of diazoesters or diazophophonates, nitrosoarenes and alkynes for the construction of multifunctionalized aziridines.[10] In this reaction, ruthenium-carbene intermediates generated from diazoesters react with nitrosoarenes to form nitrones. The latter undergo 1,3-dipolar cycloaddition/rearrangement with alkynes to give the desired aziridines. This result prompted us to examine whether trifluoromethyl diazomethane (CF_3CHN_2) and higher perfluorinated homologues are effective carbene precursors for multi-component cascade reactions.

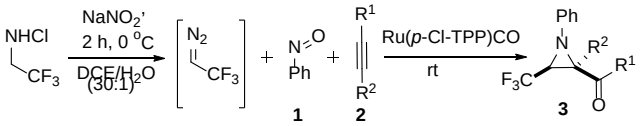
Scheme 1. Synthesis of perfluoroalkyl aziridines via a ruthenium-catalyzed cascade reaction

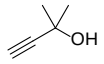
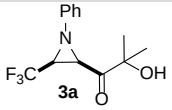
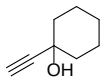
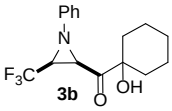
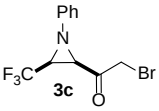
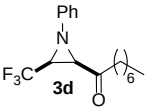
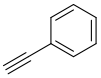
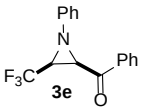
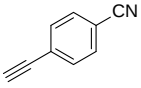
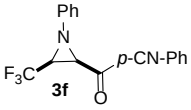
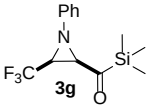
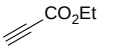
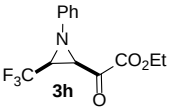
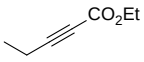
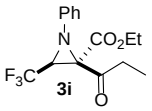
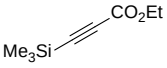
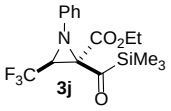
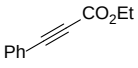
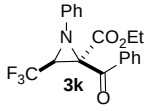
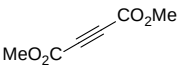
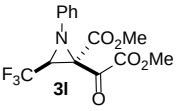


Compared to the extensive studies on α-diazo carbonyl compounds, the use of CF_3CHN_2 as a carbene source for transition metal catalyzed transformations remains underexplored. In 2006, Simonneaux and co-workers described a metal catalyzed carbene transfer reaction of CF_3CHN_2, in which a chiral iron porphyrin catalyzed the cyclopropanation of alkenes with CF_3CHN_2 in moderate to good yield and enantioselectivity.[11] A seminal work in this area was made by Carreira and co-workers in 2010; this group developed a convenient and practical protocol for the generation of CF_3CHN_2 *in situ* from $CF_3CH_2NH_3Cl$ in solution.[12] This protocol avoids the handling of highly toxic and potentially explosive CF_3CHN_2. A survey of the literature reveals that CF_3CHN_2 can undergo various carbene transfer reactions in the presence of transition metal catalysts.[13] Herein we describe our findings on the reaction of perfluoroalkyl diazomethane, nitrosoarenes and alkynes catalyzed by a ruthenium porphyrin. This Ru(II)-catalyzed cascade reaction features a highly efficient formation of four new bonds in a one-pot reaction (one C-C bond, two C-N bonds and one C=O bond) and allows the expeditious construction of multi-functionalized perfluoroalkyl aziridines from simple starting materials (Scheme 1). The ruthenium perfluoroalkylcarbene intermediates have

also been synthesized and spectroscopically characterized through the reaction of ruthenium porphyrin and $C_nF_{2n+1}CHN_2$.

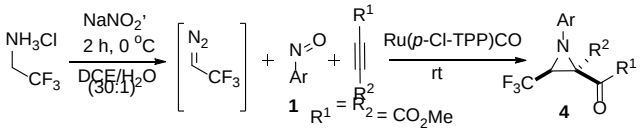
Table 1. Scope of Alkynes [a-c]

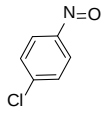
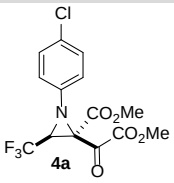
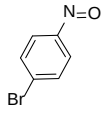
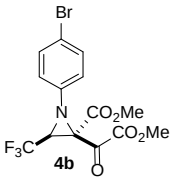
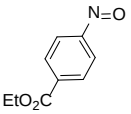
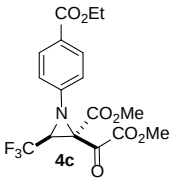
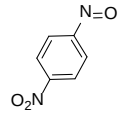
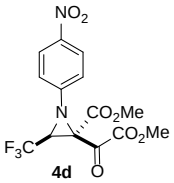
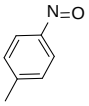
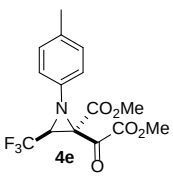
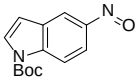
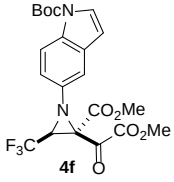
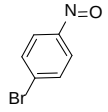
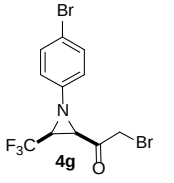


entry	alkyne	product	%yield cis/trans
1		 **3a**	95 69:31
2		 **3b**	96 69:31
3		 **3c**	90 67:33
4[d]		 **3d**	48 71:29
5		 **3e**	71 71:29
6		 **3f**	74 71:29
7		 **3g**	75 84:16
8		 **3h**	78 71:29
9		 **3i**	47 >99:1
10		 **3j**	68 >99:1
11[d]		 **3k**	70 >99:1
12		 **3l**	84 90:10

[a] CF_3CHN_2:nitrosoarene:alkyne:Ru(*p*-Cl-TPP)CO = 2:1:2:0.01. [b] Isolated yield. [c] Determined by ^{1}H NMR of reaction mixture. [d] Reaction temperature = 40 °C

Table 2. Scope of Nitrosoarenes [a-c]



entry	nitrosoarene	product	%yield cis/trans
1		 **4a**	67 92:8
2		 **4b**	74 >99:1
3		 **4c**	85 >99:1
4		 **4d**	78 >99:1
5		 **4e**	30 >99:1
6		 **4f**	47 >99:1
7		 **4g**	96 67:33
8		**4h**	95 64:36

[a] CF_3CHN_2:nitrosoarene:alkyne:Ru(*p*-Cl-TPP)CO = 2:1:2:0.01. [b] Isolated yield. [c] Determined by ^{1}H NMR of reaction mixture.

At the outset, we examined the cascade reaction with Ru(*p*-Cl-TPP)CO (H_2*p*-Cl-TPP = *meso*-tetrakis(4-chlorophenyl)porphyrin) as a catalyst.[10] CF_3CHN_2 was prepared *in situ* by the reaction of $CF_3CH_2NH_3Cl$ and $NaNO_2$ in a mixture of dichloroethane and water,[11] followed by addition of nitrosobenzene, 3-methyl butynol and Ru(*p*-Cl-TPP)CO. The resulting mixture was stirred at room temperature for 10 h. The corresponding trifluoromethyl aziridine **3a** was obtained in 95% yield with *cis:trans* ratio of 69:31 (Table 1, entry 1). We did not observe any carbene insertion into the OH bond of H_2O or alcohol or dimerization of CF_3CHN_2. As depicted in Table 1, a broad range of alkynes, including electron-rich, electron-deficient and electron-neutral alkynes, underwent the nitrone formation/1,3-dipolar cycloaddition/rearrangement cascade to give corresponding functionalized trifluoromethyl aziridines in good to high yields and with moderate to high diastereo-selectivties. While electron-rich and electron-neutral internal alkynes failed to give aziridination products, electron-deficient internal alkynes were found to be reactive for the cascade reaction to give multi-functionalized aziridines **3i-3l** in good yields (47-84%) and with excellent diastereoselectivities (*dr* = 90:10-99:1, entries 9-12). It is noteworthy that these multifunctionalized trifluoromethyl aziridines are difficult to synthesize using traditional methods. The structure of trifluoromethyl aziridines **3** has been inferred by the X-ray crystal structure of their analogue **4d** (Figure 1) and NOE experiments (see Supporting Information).

The range of nitrosoarenes investigated for the cascade reaction is provided in Table 2. Nitrosobenzenes with electron-withdrawing groups (Cl, Br, CO_2Et, NO_2) gave corresponding trifluoromethyl aziridines in good yields (67-85%) and high diastereoselectivities (diastereomeric ratio [dr] > 92:8, Table 2, entries 1-4). *p*-Methyl nitrosobenzene was less reactive, giving a moderate product yield and high dr (entry 5). A heteroaromatic nitroso compound, 6-nitrosoindole, was also reactive, giving the corresponding aziridine **4f** in 47% yield and dr of 99:1 (entry 6).

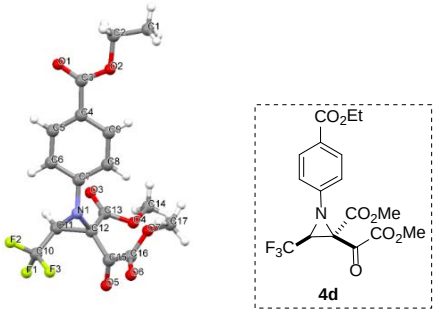
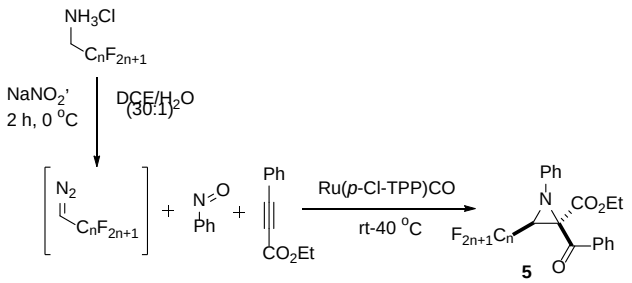


Figure 1. X-ray crystal structure of **4d**

Scheme 2. Synthesis of C_2F_5- and C_3F_7-aziridines



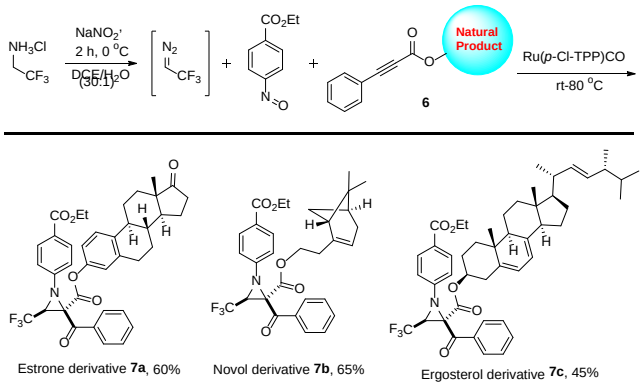
5a, n = 2, 68%, *cis/trans*>99:1
5b, n = 3, 79%, *cis/trans*>99:1

In recent years, C_2F_5 and C_3F_7, as more lipophilic CF_3 surrogates, have drawn increasing attention since compounds with a higher degree of perfluorination often display interesting activities.[14] In the present study, we generated $C_2F_5CHN_2$ and $C_3F_7CHN_2$ in a similar fashion from $C_2F_5CH_2NH_3Cl$ and $C_3F_7CH_2NH_3Cl$, respectively, and reacted them with nitrosobenzene and methyl 3-phenylpropiolate under the Ru(II) catalysis to give the corresponding C_2F_5- and C_3F_7-aziridines in good yields and high diastereoselectivity (Scheme 2).

It is noteworthy that the Ru(II)-catalyzed cascade reaction is compatible with a variety of functionalities, including halo, hydroxyl, ester, nitro, cyano and silane, as depicted in Table 1 and Table 2. These functionalities are synthetically useful, allowing for many further manipulations.[15]

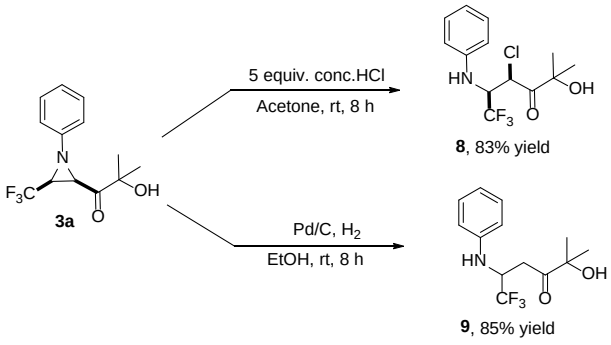
Incorporation of heterocyclic privileged scaffolds into natural products is an efficient method for diversity-oriented synthesis of natural product-based libraries for drug discovery.[16] The Ru(II)-catalyzed cascade reaction can be used to synthesize a hybrid of trifluoromethyl aziridines and natural products. For example, when the Estrone derivative **6a** was subjected to the Ru(II)-catalyzed cascade reaction at 80 °C, the trifluoromethyl aziridine-containing estrone **7a** was obtained in 60% yield (Scheme 3). Likewise, trifluoromethyl aziridination of Novol and Ergosterol derivatives were achieved in 65% (**7b**) and 45% yields (**7c**), respectively.

Scheme 3. Trifluoromethyl aziridination of natural product derivatives

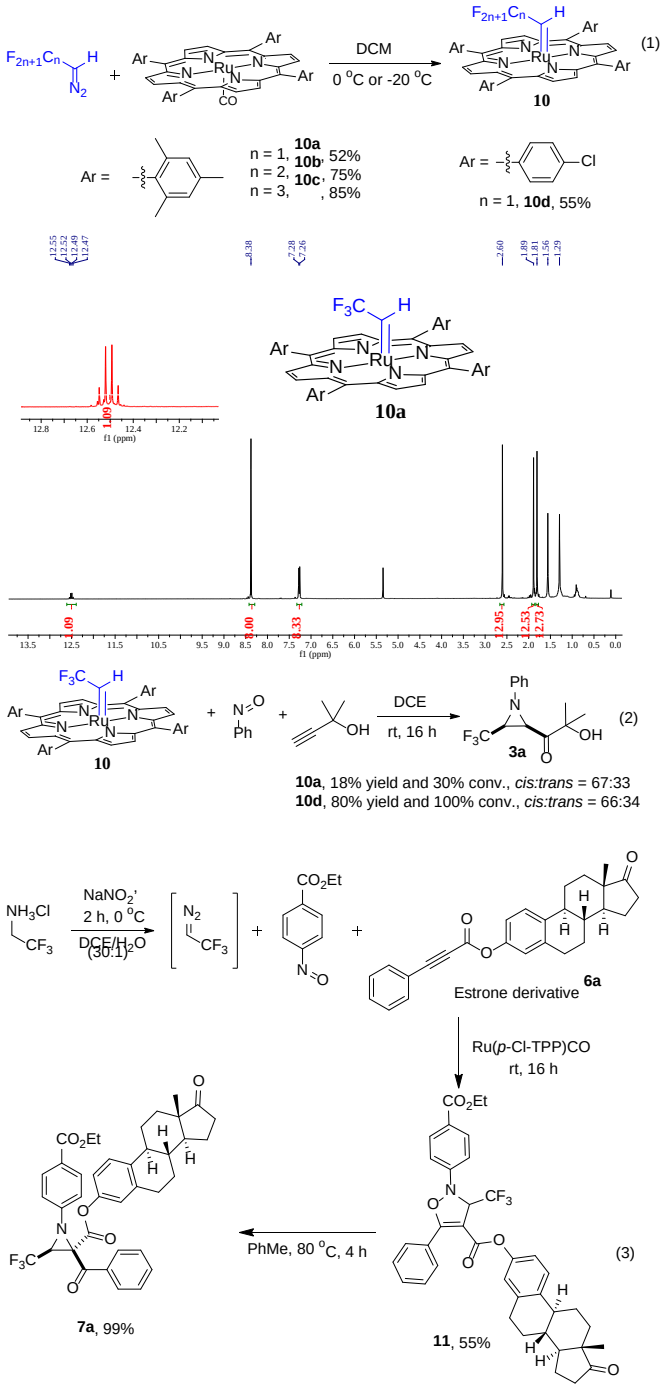


The obtained functionalized trifluoromethyl aziridines are useful building blocks for the synthesis of CF_3-containing amines. For example, trifluoromethyl aziridine **3a** underwent a ring opening reaction upon treatment with hydrogen chloride or "H_2 + Pd/C", giving the corresponding CF_3-containing amines in high yields and with high regio- and diastereo-selectivity (Scheme 4).

Scheme 4. Transformations of **3a**



Scheme 5. Reaction mechanism



To gain insight into the reaction mechanism, we synthesized ruthenium porphyrin carbene complex **10a** by the reaction of Ru(TMP)CO with CF_3CHN_2 at 0 °C in 52% yield (Scheme 5, eq. 1). The complex was characterized by NMR, UV/Vis and IR spectroscopy as well as mass spectrometry (see Supporting Information). The ^{1}H NMR spectrum of **10a** shows a quartet of Ru=C*H*CF_3 at 12.5 ppm, upfield relative to the peak of (Por)Ru=C*H*CO_2Et (13.0-13.8 ppm). The ^{13}C NMR spectrum shows a characteristic low-field signal for the carbene carbon at 263.1 ppm. Likewise, the higher perfluorinated homologues (TMP)Ru=C*H*C_2F_5 **10b** and (TMP)Ru=C*H*C_2F_5 **10c** were obtained in 75% and 85% yields, respectively. The stoichiometric reaction of **10a** with nitrosobenzene and 3-methyl butynol at room temperature gave aziridine **3a** in 18% yield with 30% substrate conversion (eq. 2). Similarly, the more reactive ruthenium porphyrin carbene complex (*p*-Cl-TPP)Ru=C*H*CF_3 **10d**, generated *in situ* at -20 °C, reacted with nitrosobenzene and 3-methyl butynol to give **3a** in 80% yield and with *cis:trans* ratio of 66:34, which is comparable to the findings obtained under catalytic conditions. When the reaction of CF_3CHN_2, ethyl 4-nitrosobenzoate and the Estrone derivative **6a** in the presence of Ru(*p*-Cl-TPP)CO was carried out at room temperature, the isoxazoline **11** was obtained in 55% yield. This compound was further converted to aziridine **7a** at 80 °C (eq. 3). These results support the involvement of metal carbene and isoxazoline intermediates in the cascade reaction as depicted in Scheme 1.

In conclusion, we have developed a new and efficient synthesis of perfluoroalkyl aziridines via a Ru(II)-catalyzed cascade reaction of *in situ*-generated perfluoroalkyl diazomethane, nitrosoarenes, and alkynes. The one pot protocol provides rapid access to multifunctionalized perfluoroalkyl aziridines from simple starting materials. The obtained trifluoromethyl aziridines can be readily converted to CF_3-containing amines in highly regio- and diastereo-selective manner. The synthesis and isolation of ruthenium perfluoroalkylcarbene intermediates were achieved through the reaction of ruthenium porphyrin and $C_nF_{2n+1}CHN_2$. To the best of our knowledge, this work provides a new means to access multifunctionalized perfluoroalkyl aziridines that are not easily accessible with conventional methods.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Detailed experimental procedures, characterization of new compounds, copies of NMR spectra.

AUTHOR INFORMATION

Corresponding Author

*Email: cmche@hku.hk
*Email: cyzhou@hku.hk

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by Hong Kong Research Grants Council General Research Fund (17306714, 17303815, 17301817), National Natural Science Foundation of China (NSFC 21472159), and Basic Research Program-Shenzhen Fund (JCYJ20150629151046879, JCYJ20160229123546997, JCYJ20170412140251576, and JCYJ20170818141858021). We acknowledge UGC funding administered by The University of Hong Kong for supporting the Matrix Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry Facilities under the Support for Interdisciplinary Research in Chemical Science.

REFERENCES

(1) Reviews: (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529. (d) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, 114, 2432. (e) Meanwell, N. A. *J. Med. Chem.*, **2018**, *61*, 5822.

(2) Reviews: (a) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (b) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950. (c) Barata-Vallejo, S.; Postigo, A. *Coord. Chem. Rev.* **2013**, *257*, 3051. (d) Egami, H.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2014**, 53, 8294. (e) Merino, E.; Nevado, C. *Chem. Soc. Rev.* **2014**, *43*, 6598. (f) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683.

(3) Selected recent reviews: (a) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (b) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194. (c) Singh, G. S.; D'hooge, M.; Kimpe, N. D. *Chem. Rev.* **2007**, *107*, 2080. (d) Stanković, S.; D'hooge, M.; Catak, S.; Eum, H.; Waroquier, M.; Speybroeck, V. V.; Kimpe, N. D.; Ha, H.-J. *Chem. Soc. Rev.* **2012**, *41*, 643. (e) Zhu, Y.; Wang, Q.; Cornwall, R. G.; Shi, Y. *Chem. Rev.* **2014**, *114*, 8199. (f) Callebaut, G.; Meiresonne, T.; Kimpe, N. D.; Mangelinckx, S. *Chem. Rev.* **2014**, *114*, 7954. (g) Rotstein, B. H.; Zaretsky, S.; Rai, V.; Yudin, A. K. *Chem. Rev.* **2014**, *114*, 8323. (h) He, Z.; Zajdlik, A.; Yudin, A. K. *Acc. Chem. Res.* **2014**, *47*, 1029. (i) Degennaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* **2014**, *114*, 7881.

(4) Review：Meyer, F. *Chem. Commun.* **2016**, *52*, 3077.

(5) (a) Min, Q.; He, C.; Zhou, H.; Zhang, X. *Chem. Commun.* **2010**, *46*, 8029. (b) Katagiri, T.; Katayama, Y.; Taeda, M.; Ohshima,T.; Iguchi, N.; Uneyama, K. *J. Org. Chem.*, **2011**, *76*, 9305. (c) Moens, M.; Kimpe, N. D.; D'hooghe, M. *J. Org. Chem.* **2014**, *79*, 5558.

(6) (a) Künzi, S. A.; Morandi, B.; Carreira, E. M. *Org. Lett.* **2012**, *14*, 1900. (b) Chai, Z.; Bouillon, J.-P.; Cahard, D. *Chem. Commun.* **2012**, *48*, 9471. (c) Kenis, S.; D'Hooghe, M.; Verniest, G.; Reybroeck, M.; Thi, T. A. D.; The, C. P.; Pham, T. T.; Törnroos, K. W.; Tuyen, N. V.; Kimpe, N. D. *Chem. – Eur. J.* **2013**, *19*, 5966.

(7) (a) Duan, Y.; Zhou, B.; Lin, J.-H.; Xiao, J.-C. *Chem. Commun.* **2015**, *51*, 13127. (b) Marsini, M. A.; Reeves, J. T.; Desrosiers, J.-N.; Herbage, M. A.; Savoie, J.; Li, Z.; Fandrick, K. R.; Sader, C. A.; McKibben, B.; Gao, D. A.; Cui, J.; Gonnella, N. C.; Lee, H.; Wei, X.; Roschangar, F.; Lu, B. Z.; Senanayake, C. H. *Org. Lett.* **2015**, *17*, 5614. (c) Huang, Q.-X.; Zheng, Q.-T.; Duan, Y.; Lin, J.-H.; Xiao, J.-C.; Zheng, X. *J. Org. Chem.* **2017**, *82*, 8273.

(8) (a) Colantoni, D.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Org. Lett.* **2004**, *6*, 197. (b) Colantoni, D.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *J. Org. Chem.* **2005**, *70*, 9648. (c) Maeda, R.; Ooyama, K.; Anno, R.; Shiosaki, M.; Azema, T.; Hanamoto, T. *Org. Lett.* **2010**, *12*, 2548. (d) Chung, T. S.; Lopez, S. A.; Houk, K. N.; Garcia-Garibay, M. A. *Org. Lett.* **2015**, *17*, 4568. (e) Mészáros, Á.; Székely, A.; Stirling, A.; Novák, Z. *Angew. Chem., Int. Ed.* **2018**, *57*, 6643.

(9) Other methods: (a) Kano, N.; Daicho, Y.; Nakanishi, N.; Kawashima, T. *Org. Lett.* **2001**, *3*, 691. (b) Kano, N.; Daicho, Y.; Kawashima, T. *Org. Lett.* **2006**, *8*, 4625. (c) Wang, F.; Zhu, N.; Chen, P.; Ye, J.; Liu, G. *Angew. Chem., Int. Ed.* **2015**, *54*, 9356. (d) Zhang, W.; Wang, X.; Zhu, B.; Zhu, D.; Han, J.; Wzorek, A.; Sato, A.; Soloshonok, V. A.; Zhou, J.; Pan, Y. *Adv. Synth. Catal.* **2017**, *359*, 4267.

(10) Reddy, A. R.; Zhou, C.-Y.; Che, C.-M. *Org. Lett.* **2014**, *16*, 1048.

(11) Le Maux, P.; Juillard, S.; Simonneaux, G. *Synthesis* **2006**, 1701.

(12) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 938.

(13) (a) Mykhailiuk, P. K.; Afonin, S.; Palamarchuk, G. V.; Shishkin, O. V.; Ulrich, A. S.; Komarov, I. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 5765. (b) Morandi, B., Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4294. (c) Morandi, B.; Mariampillai, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 1101. (d) Morandi, B.; Cheang, J.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 3080. (e) Liu, C.-B.; Meng, W.; Li, F.; Wang, S.; Nie, J.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2012**, *51*, 6227. (f) Luo, H. Q.; Wu, G. J.; Zhang, Y.; Wang, J. B. *Angew. Chem., Int. Ed.* **2015**, *54*, 14503. (g) Cai, A.-J.; Zheng, Y.; Ma, J.-A. *Chem. Commun.* **2015**, *51*, 8946. (h) Hyde, S.; Veliks, J.; Liegault, B.; Grassi, D.; Taillefer, M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2016**, *55*, 3785. (i) Hock, K. J.; Mertens, L.; Hommelsheim, R.; Spitzner, R.; Koenigs, R. M. *Chem. Commun.* **2017**, *53*, 6577. (j) Tinoco, A.; Steck, V.; Tyagi, V.; Fasan, R. *J. Am. Chem. Soc.* **2017**, *139*, 5293. (k) Zhang, X.-W.; Hu, W.-L.; Chen, S.; Hu, X.-G. *Org. Lett.* **2018**, *20*, 860. (l) Kotozaki, M.; Chanthamath, S.; Fujii, T.; Shibatomi, K.; Iwasa, S. *Chem. Commun.* **2018**, *54*, 5110.

(14) (a) Andrzejewska, M.; Yépez-Mulia, L.; Cedillo-Rivera, R.; Tapia, A.; Vilpo, L.; Vilpo, J.; Kazimierczuk, Z. *Eur. J. Med. Chem.* **2002**, *37*, 973. (b) Johansson, A.; Poliakov, A.; Akerblom, E.; Wiklund, K.; Lindeberg, G.; Winiwarter, S.; Danielson, U. H.; Samuelsson, B.; Hallberg, A. *Bioorg. Med. Chem.* **2003**, *11*, 2551. (c) Croxtall, J. D.; McKeage, K. *Drugs* **2011**, *71*, 363. (d) Jonat, W.; Bachelot, T.; Ruhstaller, T.; Kuss, I.; Reimann, U.; Robertson, J. F. R. *Ann. Oncol.* **2013**, *24*, 2543.

(15) Carey, F. A.; Sundberg, R. J. *Advanced organic chemistry*: *Part B.* **2007**, New York, NY: Springer.

(16) (a) Rosini, M.; Simoni, E.; Bartolini,M.; Tarozzi, A.; Matera, R.; Milelli, A.; Hrelia, P.; Andrisano, V.; Bolognesi, M. L.; Melchiorre, C. *Eur. J. Med. Chem.* **2011**, *46*, 5435. (b)Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2017**, *60*, 1638.