Organic LETTERS

Letter

pubs.acs.org/OrgLett

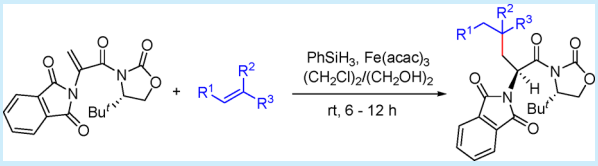
Iron-Catalyzed Diastereoselective Synthesis of Unnatural Chiral Amino Acid Derivatives

Hao Zhang, Haifang Li, Haijun Yang, and Hua Fu*

Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China

Supporting Information

ABSTRACT: An iron-catalyzed diastereoselective synthesis of unnatural chiral (*S*)-α-amino acids with γ-quaternary carbon centers has been developed. The protocol uses inexpensive iron salt as the catalyst, readily available 2-phthaloyl acrylamide and alkenes as the starting materials, and phenylsilane as the reductant, and the reactions were performed well in mixed solvent of 1,2-dichloroethane and ethylene glycol at room temperature. The method shows some advantages including simple and wide substrates, mild conditions, high diastereoselectivity, and easy workup procedures.



Amino acids, especially chiral α-amino acids (α-AAs), are one of the most powerful and versatile building blocks in nature.[1] Compared with the common proteinogenic amino acids, unnatural chiral α-AAs exhibit unique functions. For example, the peptides incorporating unnatural α-AAs can resist hydrolysis of proteinases and show interesting pharmacological activity.[2] The α-AAs are widely used in synthesis of natural products, biomolecules,[3] and the chiral catalysts and ligands.[4] Therefore, the chemical synthesis of these valuable compounds has received tremendous interest.[5] The previous methods for synthesis of α-AAs mainly include the asymmetric Strecker reaction,[6] the asymmetric alkylation of glycine derivatives employing chiral auxiliaries[7] or chiral phase-transfer catalysts,[8] and the enantioselective hydrogenation of dehydroamino acid precursors.[9] Recently, palladium-catalyzed direct C−H functionalization on the side chains of natural α-amino acids to access their unnatural counterparts has gained great progress.[10] The unnatural chiral

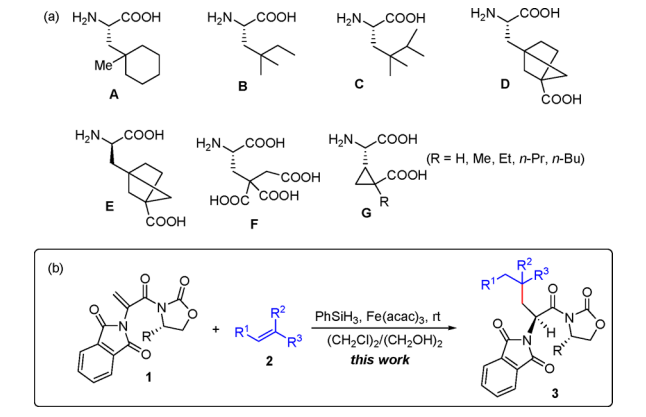
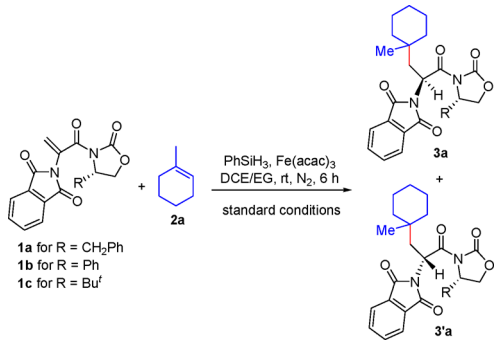


Figure 1. Unnatural α-amino acids with γ-quaternary carbon centers. (a) The biologically active unnatural α-amino acids with γ-quaternary carbon centers. (b) Our strategy for synthesis of unnatural α-amino acids with γ-quaternary carbon centers.

Table 1. Optimization of Conditions on Iron-Catalyzed Reaction of 2-Phthaloyl Acrylamide (1a−c) with 1-Methyl-1-cyclohexene (2a) in the Presence of Phenylsilane ($PhSiH_3$)[a]



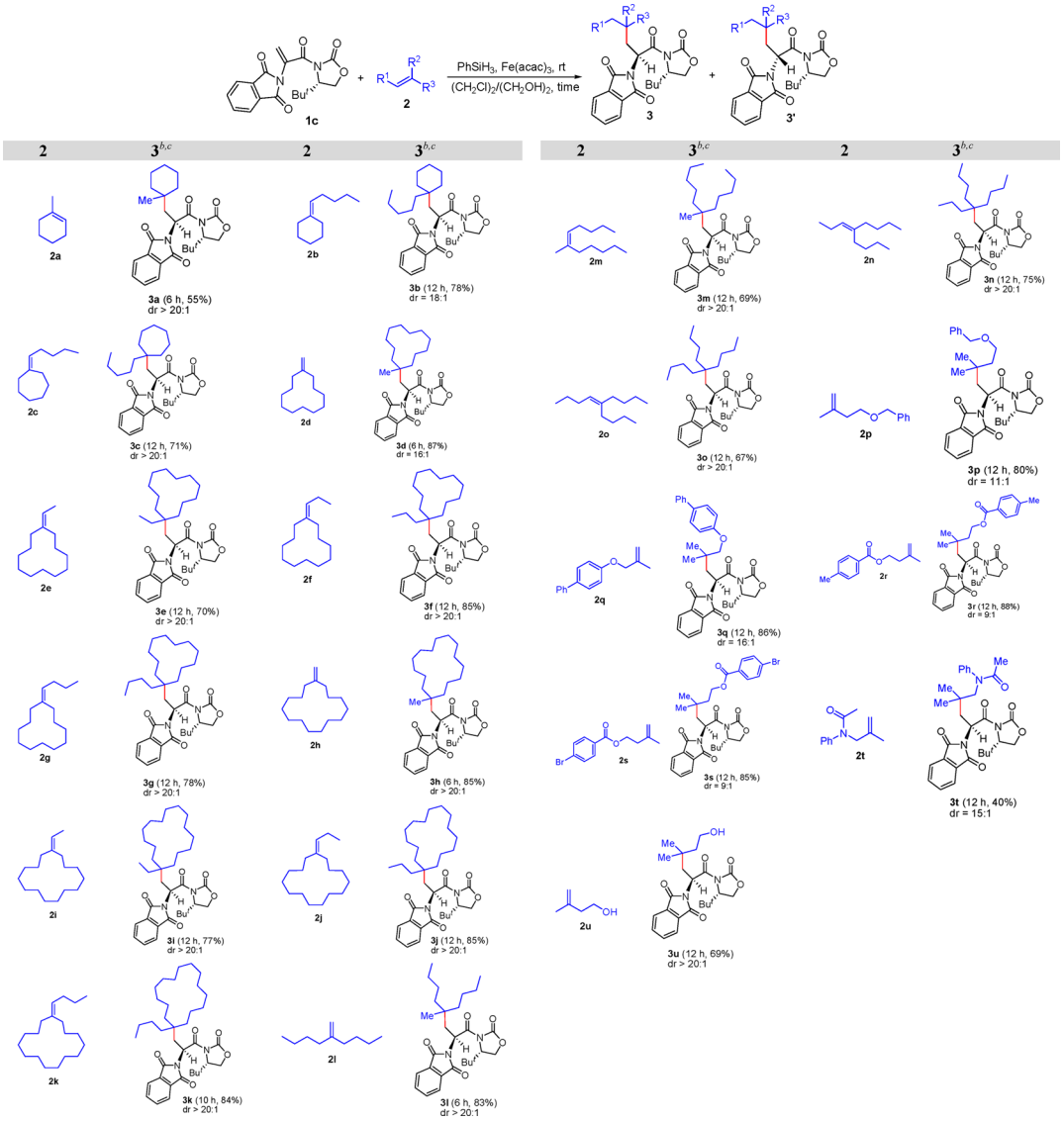
entry	1	ratio (1:2a)	change from the standard conditions	dr (3a/3′a)[b]	yield of 3a (%)[c]
1	1a	1:3	none	4:1	51
2	1b	1:3	none	2.4:1	56
3	1c	1:3	none	>20:1	31
4	1c	1:5	none	>20:1	55
5	1c	1:5	$FeSO_4·7H_2O$ as the catalyst		trace
6	1c	1:5	$FeCl_3$ as the catalyst		trace
7	1c	1:5	$Fe_2(SO_4)_3·H_2O$ as the catalyst		NR
8	1c	1:5	no catalyst		NR
9	1c	1:5	EtOH as the solvent, 2 h	11:1	62
10	1c	1:5	80 °C, 1 h	13:1	50

[a]Reaction conditions: under nitrogen atmosphere, 2-phthaloyl acrylamide (**1**) (0.2 mmol), 1-methyl-1-cyclohexene (**2a**) (0.6−1.0 mmol), iron catalyst (0.06 mmol), 1,2-dichloroethane (DCE) (1.5 mL), ethylene glycol (EG) (0.3 mL), temperature (25 or 80 °C), time (6 h) in a sealed Schlenk. [b]Diastereoselective ratio (dr value) was determined according to the ^{1}H NMR peak areas of α-H in **3a** and **3′a** from the reaction mixture of **1** with **2a**. [c]Isolated yield. acac = acetylacetonate. NR = no reaction.

Received: May 24, 2016

DOI: 10.1021/acs.orglett.6b01493
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Iron-Catalyzed Synthesis of Unnatural Chiral α-Amino Acid Derivatives (3)[a]



[a]Reaction conditions: under nitrogen atmosphere, **1c** (0.2 mmol), alkene (**2**) (1.0 mmol), $Fe(acac)_3$ (0.06 mmol), $PhSiH_3$ (0.3 mmol), 1,2-dichloroethane (1.5 mL), ethylene glycol (0.3 mL), temperature (room temperature, ~25 °C), time (6–12 h) in a sealed Schlenk tube. [b]Diastereoselective ratio (dr value) was determined according to the ^1H NMR peak areas of α-H in **3** and **3′** from the reaction mixture of **1c** with **2**. [c]Isolated yield.

α-AAs with γ-quaternary carbon centers display various interesting biological activity. For example, compounds containing **A** residue are azepanone inhibitors of human cathepsin S,[11a] and molecules containing **B**–**E** residues are used as the ligands of glutamate and NMDA receptors.[11b,c] Compound with **F** residue is a potent inhibitor of tyrosine kinase,[11d] and compounds with **G** residue are applied as the potent *N*-methyl-D-aspartic acid receptor agonists (Figure 1a).[11e] Unfortunately, the methods for their synthesis are very limited thus far, and the synthetic pathways usually are fussy.[11,12] Therefore, it is highly desirable to develop an efficient and practical diastereoselective approach to unnatural chiral α-AAs with γ-quaternary carbon centers.

Iron is an abundant and inexpensive metal on earth, and the iron catalysts are widely used in organic synthesis.[13] Very recently, Baran and co-workers have developed an interesting reductive coupling of olefins through carbon–carbon bond formation, and various novel compounds were prepared.[14] 2-Aminoacrylic acid derivatives are important precursors, and their Michael addition reaction with nucleophiles provides amino acid derivatives.[15] However, the methods using radicals as the partners are very rare for the synthesis of chiral unnatural α-AAs.[16] To the best of our knowledge, synthesis of unnatural chiral α-AAs using 2-aminoacrylic acid derivatives as the radical acceptors and alkenes as the donators has not been reported. Herein, we report an efficient and practical iron-catalyzed diastereoselective synthesis of unnatural chiral α-AAs (**3**) with γ-quaternary carbon centers via reaction of 2-phthaloyl acrylamide (**1**) with chiral auxiliaries with alkenes (**2**) at room temperature (Figure 1b).

At first, we investigated three Evans-oxazolidinones as the chiral auxiliaries,[17] (*S*)-4-benzyloxazolidin-2-one (**a**), (*S*)-4-phenyloxazolidin-2-one (**b**), and (*S*)-4-*tert*-butyloxazolidin-2-one (**c**), and they were installed on *N*-phthaloyl dehydroalanine to give the corresponding 2-phthaloyl acrylamides (**1a**–**c**). As shown in Table 1, reaction of **1c** with 1-methyl-1-cyclohexene (**2a**) gave the highest diastereoselective ratio of **3a**/**3′a** (dr > 20:1) using $Fe(acac)_3$ as the catalyst in the presence of $PhSiH_3$ in mixed solvent of 1,2-dichloroethane (DCE) and ethylene glycol (EG)[14b] at room temperature (entry 3), and **3a** with *S*-configuration could

DOI: 10.1021/acs.orglett.6b01493
Org. Lett. XXXX, XXX, XXX–XXX

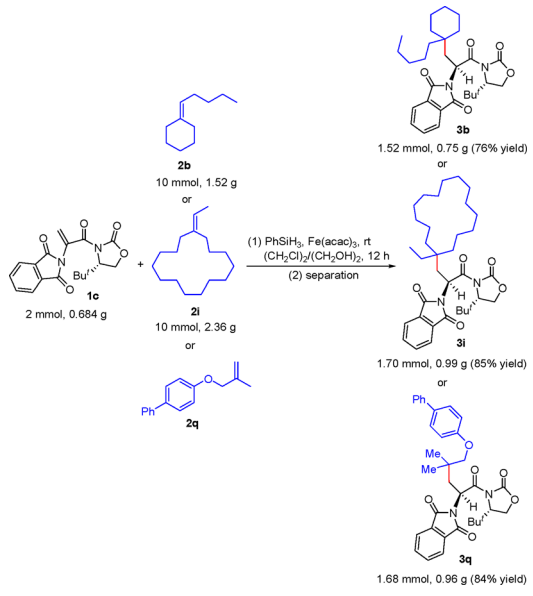
easily be isolated by column chromatography on silica gel using petroleum ether/ethyl acetate as the eluent. Unfortunately, the yield was only 31%. When amount of 1-methyl-1-cyclohexene (**2a**) was increased, the yield greatly improved with homocoupling of alkene occurring (entry 4). Other iron catalysts were attempted (entries 5−7), and they gave poor results. No target products (**3a** and **3′a**) were found in the absence of catalyst (entry 8). Effect of solvents was investigated, and the mixed solvent of DCE and EG was suitable (compare entries 4 and 9). The diastereoselectivity decreased when temperature was raised to 80 °C (entry 10). In order to confirm whether other transition metals are involved in the reaction, the solvent in the resulting solution of entry 4 was removed by a rotary evaporator, and the residue was determined by ICP mass spectrometry. Cu, Co, Mn, Pd, Rh, and Ru almost were not observed (data determined by ICP mass spectrometry: Cu = 0.3 ppm, Co = 3.0 ppb, Mn = 9.0 ppb, Pd = 2.0 ppb, Rh = 0.3 ppb, and Ru = 0.2 ppb). The result displays that the present reaction is an iron-catalyzed process.

Having identified the optimal conditions, we next examined the scope of alkenes for the iron-catalyzed synthesis of unnatural chiral α-amino acid derivatives (**3**). As shown in Table 2, 11 alkenes with different-sized rings (**2a−k**) were attempted, and they provided good to excellent yields with high diastereoselectivity in which the larger cyclic substrates gave higher diastereoselectivity because of bigger steric effect (see **3a−k** in Table 2). For noncyclic alkenes **2l−u**, the substrates with smaller steric substituents such as methyl in **2p−t** afforded slightly lower diastereoselectivity. Interestingly, **2u** also gave a high diastereoselective ratio (dr >20:1). The iron-catalyzed synthesis of unnatural chiral α-amino acid derivatives (**3**) showed tolerance of some functional groups including amides, ethers, esters, and hydroxyl. Therefore, the present methods can easily afford diverse unnatural chiral α-amino acid derivatives.

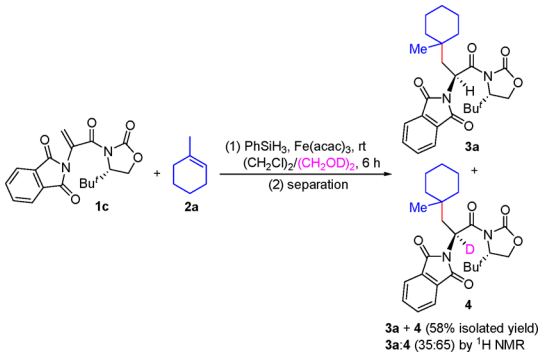
As shown in Scheme 1, we attempted synthesis of **3b**, **3i**, and **3q** on gram-scale under the standard conditions, and the results showed the present method was also effective.

In order to explore the reaction mechanism on the iron-catalyzed synthesis of unnatural chiral α-amino acid derivatives (**3**), two control experiments were performed. A deuterium-labeled study

Scheme 1. Iron-Catalyzed Synthesis of 3b, 3i, and 3q on Gram-Scale under the Standard Conditions



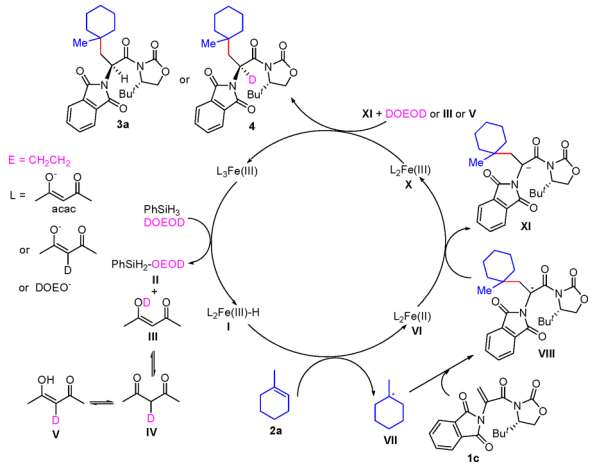
Scheme 2. Reaction of 1c with 2a in the Presence of Ethylene Glycol-d_2 under the Standard Conditions



was first investigated as shown in Scheme 2. Reaction of **1c** with **2a** was carried out under the standard conditions using ethylene glycol-d_2 instead of ethylene glycol in Table 2, and ^{1}H NMR showed that mixtures of **3a** and **4** were obtained after purification, and **4** was a major product. Subsequently, a radical trapping experiment was performed. 1,1-Diphenylethylene as a radical-trapping reagent[18] was added to the system of 1-methyl-1-cyclohexene (**2a**), $PhSiH_3$, and $Fe(acac)_3$ in DCE/ethylene glycol, and adduct of 1,1-diphenylethylene and **2a** was observed by GC−MS (see Supporting Information for the details). The result exhibited that iron-catalyzed reaction of **2a** with $PhSiH_3$ first formed a radical intermediate **VII** in Scheme 3.

Therefore, a plausible mechanism is proposed in Scheme 3 using reaction of **1c** with **2a** in mixed solvent of DCE and

Scheme 3. Plausible Mechanism for the Iron-Catalyzed Coupling of 1c and 2a in Mixed Solvent of DCE and Ethylene Glycol-d_2

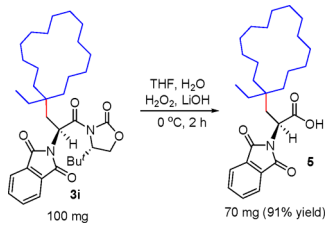


ethylene glycol-d_2 as an example of this novel iron-catalyzed process according to the results above and the previous references.[14] First, treatment of iron catalyst $L_3Fe(III)$ with $PhSiH_3$ and ethylene glycol-d_2 ($DOCH_2CH_2OD$) provides $L_2Fe(III)$-H (**I**), $PhSiH_2OCH_2CH_2OD$ (**II**), and **III**, and isomerization of **III** leads to **IV** and **V**. Reaction of **I** with **2a** gives $L_2Fe(II)$ (**VI**) and radical **VII**, and Michael addition of **VII** to **1c** yields **VIII**. Redox between **VI** and **VIII** produces $L_2Fe(III)$ (**X**) and anion **XI**.[14b] Treatment of **X**, **XI** with $DOCH_2CH_2OD$ or **III**, **V** affords products **3a** (minor) and **4** (major) regenerating iron-catalyst ($L_3Fe(III)$).

Hydrolysis of **3i** was performed in mixed solvent of THF and water in the presence of H_2O_2 and LiOH at 0 °C for 2 h, and **5** was obtained in 91% yield (Scheme 4). In order to confirm

DOI: 10.1021/acs.orglett.6b01493
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Hydrolysis of 3i Leading to 5



whether the procedure led to racemization of **5**, a pair of racemates, *Rac*-**5**, was first prepared (see Supporting Information for details). Next, HPLC analysis of *Rac*-**5** and **5** was performed with CHIRALPAK QN-AX (QN07163) chiral column using methanol/acetic acid/triethylamine (100:2:0.2) as the mobile phase (flow rate = 0.5 mL/min). The results displayed that 99.5% ee value for **5** was observed (see Supporting Information for the details). In addition, single crystal of **5** was prepared, and its structure was unambiguously confirmed by X-ray diffraction analysis (see Supporting Information for details). It is known that deprotection of the phthalimido amino acids with hydrazine can get free amino acid without erosion of chirality.[19]

In summary, we have developed a convenient, efficient, and practical iron-catalyzed method for diastereoselective synthesis of unnatural chiral α-(*S*)-amino acids with γ-quaternary carbon centers. The protocol uses inexpensive iron salt as the catalyst, readily available 2-phthaloyl acrylamide with (*S*)-4-*tert*-butyloxazolidin-2-one chiral auxiliary and alkenes as the starting materials, and phenylsilane as the reductant, and the reactions were performed well in mixed solvent of 1,2-dichloroethane and ethylene glycol at room temperature under nitrogen atmosphere. The method shows some advantages including simple and wide substrates, mild conditions, high diastereoselectivity, and easy workup procedures. Therefore, the present method provides a novel and valuable strategy for synthesis of diverse unnatural chiral α-amino acids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01493.

General procedures, characterization data, and NMR spectra of obtained compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: fuhua@mail.tsinghua.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors wish to thank the National Natural Science Foundation of China (Grant Nos. 21372139 and 21221062), and Shenzhen Sci & Tech Bureau (CXB201104210014A) for financial support.

■ REFERENCES

(1) Hughes, A. B. *Amino Acids, Peptides and Proteins in Organic Chemistry, Analysis and Function of Amino Acids and Peptides*; Wiley, Hoboken, 2013.

(2) Hughes, A. B. *Amino Acids, Peptides and Proteins in Organic Chemistry*; Wiley-VCH, Weinheim, 2009.

(3) Ambrogelly, A.; Palioura, S.; Söll, D. *Nat. Chem. Biol.* **2007**, *3*, 29.

(4) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*; Wiley: New York, 1987.

(5) (a) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584. (b) Constantinou-Kokotou, V.; Kokotos, G. *Amino Acids* **1999**, *16*, 273.

(6) (a) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795. (b) Wang, J.; Liu, X.; Feng, X. *Chem. Rev.* **2011**, *111*, 6947 and references therein.

(7) (a) Abellán, T.; Chinchilla, R.; Galindo, N.; Guillena, G.; Nájera, C.; Sansano, J. M. *Eur. J. Org. Chem.* **2000**, *2000*, 2689. (b) Noisier, A. F. M.; Harris, C. S.; Brimble, M. A. *Chem. Commun.* **2013**, *49*, 7744.

(8) (a) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (b) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656.

(9) (a) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103. (b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(10) (a) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391. (b) Tran, L. D.; Daugulis, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 5188. (c) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (d) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. (e) He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, *343*, 1216.

(11) (a) Kerns, J. K.; Nie, H.; Bondinell, W.; Widdowson, K. L.; Yamashita, D. S.; Rahman, A.; Podolin, P. L.; Carpenter, D. C.; Jin, Q.; Riflade, B.; Dong, X.; Nevins, N.; Keller, P. M.; Mitchell, L.; Tomaszek, T. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4409. (b) Deboves, H. J. C.; Grabowska, U.; Rizzo, A.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4284. (c) Filosa, R.; Fulco, M. C.; Marinozzi, M.; Giacchè, N.; Macchiarulo, A.; Peduto, A.; Massa, A.; de Caprariis, P.; Thomsen, C.; Christoffersen, C. T.; Pellicciari, R. *Bioorg. Med. Chem.* **2009**, *17*, 242. (d) Jiang, S.; Li, P.; Lai, C. C.; Kelley, J. A.; Roller, P. P. *J. Org. Chem.* **2006**, *71*, 7307. (e) Risgaard, R.; Nielsen, S. D.; Hansen, K. B.; Jensen, C. M.; Nielsen, B.; Traynelis, S. F.; Clausen, R. P. *J. Med. Chem.* **2013**, *56*, 4071.

(12) Carrillo-Marquez, T.; Caggiano, L.; Jackson, R. F. W.; Grabowska, U.; Rae, A.; Tozer, M. J. *Org. Biomol. Chem.* **2005**, *3*, 4117.

(13) (a) Bauer, I.; Knölker, H.-J. *Chem. Rev.* **2015**, *115*, 3170. (b) Plietker, B. *Topics in Organometallic Chemistry-Iron Catalysis: Fundamentals and Applications*; Springer Verlag: Berlin, 2011. (c) Plietker, B. *Iron Catalysis in Organic Chemistry*; Wiley-VCH: Weinheim, Germany, 2008.

(14) (a) Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S. *Nature* **2014**, *516*, 343. (b) Lo, J. C.; Yabe, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 1304.

(15) For a reviewers, see: (a) Aceña, J. L.; Sorochinsky, A. E.; Soloshonok, V. *Amino Acids* **2014**, *46*, 2047. and references therein. For the selected papers, see: (b) Huang, T.; Keh, C. C. K.; Li, C.-J. *Chem. Commun.* **2002**, 2440. (c) Navarre, L.; Martinez, R.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2008**, *130*, 6159. (d) Tong, B. M. K.; Chiba, S. *Org. Lett.* **2011**, *13*, 2948. (e) Miyabe, H.; Asada, R.; Takemoto, Y. *Tetrahedron* **2005**, *61*, 385.

(16) (a) Yim, A.-M.; Vidal, Y.; Viallefont, P.; Martinez, J. *Tetrahedron: Asymmetry* **2002**, *13*, 503. (b) Gasanov, R. G.; Ilinskaya, L. V.; Misharin, M. A.; Maleev, V. I.; Raevski, N. I.; Ikonnikov, N. S.; Orlova, S. A.; Kuzmina, N. A.; Belokon, Y. N. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3343.

(17) (a) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1996**, *61*, 6090. (b) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163.

(18) Liu, D.; Liu, C.; Li, H.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 4453.

(19) (a) Yajima, T.; Yamaguchi, K.; Hirokane, R.; Nogami, E. *J. Fluorine Chem.* **2013**, *150*, 1. (b) Mulzer, J.; Angermann, A.; Schubert, B.; Seilz, C. *J. Org. Chem.* **1986**, *51*, 5294. (c) Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2004**, *6*, 3541.

DOI: 10.1021/acs.orglett.6b01493
Org. Lett. XXXX, XXX, XXX−XXX