Organic LETTERS

Letter

pubs.acs.org/OrgLett

A Synthesis of "Dual Warhead" β-Aryl Ethenesulfonyl Fluorides and One-Pot Reaction to β-Sultams

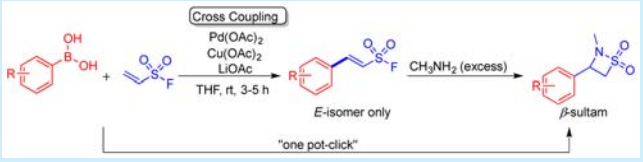
Praveen K. Chinthakindi,[§] Kimberleigh B. Govender,[§,⊥] A. Sanjeeva Kumar,[§,⊥] Hendrik G. Kruger,[§] Thavendran Govender,[§] Tricia Naicker,[§] and Per I. Arvidsson*[,§,†]

[§]Catalysis and Peptide Research Unit, University of KwaZulu-Natal, Durban, South Africa

[†]Science for Life Laboratory, Drug Discovery & Development Platform & Division of Translational Medicine and Chemical Biology, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden

Supporting Information

ABSTRACT: Herein, we report an operationally simple, ligand- and additive-free oxidative boron-Heck coupling that is compatible with the ethenesulfonyl fluoride functional group. The protocol proceeds at room temperature with chemoselectivity and *E*-isomer selectivity and offers facile access to a wide range of β-aryl/heteroaryl ethenesulfonyl fluorides from commercial boronic acids. Furthermore, we demonstrate a "one-pot click" reaction to directly transform the products to aryl-substituted β-sultams.



Palladium catalyzed oxidative carbon−carbon bond formation reactions are vital in the synthesis of complex organic molecules. A variety of Pd catalyzed reactions have been developed for the arylation of olefins such as Mizoroki−Heck, Meerwein arylation, Heck−Matsuda, oxidative boron-Heck, etc. Approaches using an oxidative boron-Heck coupling are becoming increasingly attractive for modern organic syntheses[1] as they offer a wide range of advantages such as efficiency, mild reaction conditions, good functional group tolerance, and widespread applications.[2] In particular, organoboronic acids used as nucleophiles offer many advantages, as they are moisture and air stable, and have low toxicity, and a large variety are commercially available.[3] Recently our group developed a Pd catalyzed cross-coupling method between organoboronic acids and halo aryl sulfonyl fluorides.[4] The interest in the sulfonyl fluoride (SF) group was sparked by its recent inclusion as a "click reagent" by the Sharpless laboratory[5] as well as privileged "warheads" for covalent enzyme inhibition by Lyn and co-workers.[6] Moreover, Andrey et al. explored sulfonyl fluorides as an alternative to sulfonyl chlorides[7] and Matthew et al. investigated SFs (PyFluor) as a selective deoxy fluorination reagent.[8] Also, one report has revealed the usefulness of the SF functional group as a PET agent in radio pharmaceuticals.[9] Yet, despite these SFs having many applications in material science,[10] the full potential of SFs as building blocks/intermediates in organic syntheses is yet to be fully realized.

Most recently, Liskamp et al. proposed peptide-derived vinylic sulfonylfluorides as a new class of bielectrophilic warheads for covalent drug discovery which selectively inhibited the threonine residue in the proteasome active site, Figure 1.[11] Based on this report, we became interested in the use of ethenesulfonyl fluoride (ESF)[12] as a starting material for such probes, as it is known to be a good connector,[5,13] Michael acceptor,[14] and Diels−Alder dienophile.[15]

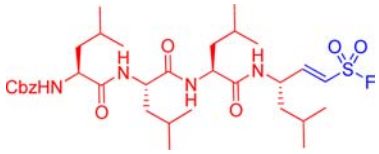


Figure 1. Peptide vinyl sulfonyl fluoride proteasome inhibitor as reported by Liskamp et al.[11]

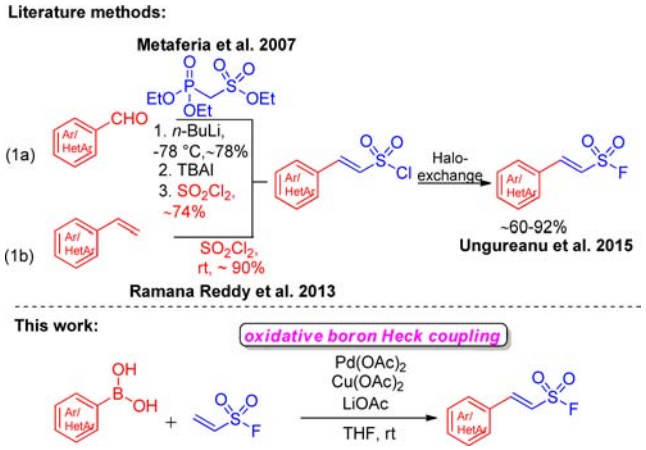
Albeit useful in a wide range of pharmaceutical and material intermediates synthesis,[12,16] the synthetic procedures to access substituted ethenesulfonyl fluoride derivatives require multistep syntheses (Scheme 1a, b) and suffer from disadvantages such as the use of highly pyrophoric (*n*-BuLi),[17] toxic and corrosive reagents ($SOCl_2$).[18,16b] Therefore, approaches that use simple and commercial starting materials, such as ethenesulfonyl fluoride and aryl boronic acids (cross-coupling), in a single step would be highly advantageous. This method could be a valuable addition to transition metal catalyzed late-stage functionalization[19] and bioorthogonal chemistry.[20]

Our earlier findings on palladium catalyzed cross-coupling development[4,21,4,6b] inspired us to carry out Pd catalyzed arylation of ESF. Herein we report the first and efficient ligand-free oxidative boron-Heck coupling reaction to access diverse aryl substituted ethenesulfonyl fluorides. The obtained substituted ethenesulfonyl fluorides are handy building blocks for consequent synthetic transformations.[16a] Until the finalization of this work, this was the first method where ESF was used directly as a coupling partner in Pd catalyzed reactions.

Received: December 6, 2016
Published: January 11, 2017

DOI: 10.1021/acs.orglett.6b03634
Org. Lett. 2017, 19, 480−483

Scheme 1. Synthesis of β-Aryl Ethenesulfonyl Fluorides

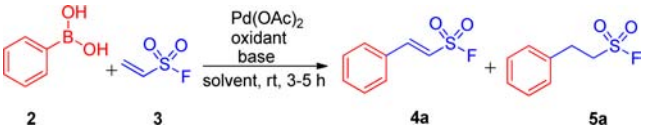


However, it is to be noted that while we awaited HRMS data of our products, a report from the Sharpless group appeared that describes the synthesis of β-aryl ethenesulfonyl fluoride derivatives from arenediazonium tetrafluoroborates and ethenesulfonyl fluoride using a palladium catalyzed Heck−Matsuda cross-coupling reaction.[16a] Our work presents the synthesis of β-aryl ethenesulfonyl fluoride derivatives from stable and commercially available aryl boronic acids and demonstrates the utility of the resulting β-aryl ethenesulfonyl fluoride as starting materials for a mild one-pot synthesis of β-sultams that are otherwise difficult to access.

To find a suitable catalytic system for the arylation of ethenesulfonyl fluoride, a model reaction with phenyl boronic acid and ethenesulfonyl fluoride was investigated using the oxidative boron Heck conditions reported by Jung and co-workers, i.e. $Pd(OAc)_2$, O_2, and Na_2CO_3 in DMF at 50 °C.[22] However, under these conditions we observed the formation of undesired homocoupling as the major product with only a trace amount of the desired product (8%). Therefore, we attempted to optimize the reaction conditions by evaluating various Pd catalysts {i.e., $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd(PPh_3)_2Cl_2$, and Pd−C}; however, this did not improve the reaction yield. We then shifted our focus to explore various oxidants {i.e., $Cu(OAc)_2$, DDQ, O_2, and Air} and bases {NaOAc, Cs_2CO_3, DIPEA, TEA} (Table 1). In the presence of DDQ as the oxidant no product formation was observed (data not shown). Similarly, air oxidation (data not shown) and O_2 offered only low yields (Table 1, entry 1). However, in the presence of a stoichiometric amount of $Cu(OAc)_2$, good improvement in yield was observed (Table 1, entry 2); this is due to good synergy between Pd and Cu in the catalytic cycle,[23] which is known to enhance the rate of the oxidation of Pd(0) to Pd (II).

Next, we investigated the influence of various bases on the reaction yield. Using Cs_2CO_3 as a base there was no product formation observed, which could be due to hydrolysis of the sulfonyl fluoride, similar to our earlier findings on the cross-coupling of halo aryl sulfonyl fluorides.[4] The organic bases (DIPEA, TEA) did not provide any further improvement in yield (Table 1, entries 3 and 4). However, in the case of LiOAc as a base there was an improved reaction yield. Interestingly, reaction conditions using 10 mol % $Pd(OAc)_2$, 2.0 equiv of $Cu(OAc)_2$, and 1.0 equiv of LiOAc in DMF at room temperature exclusively gave the alkenyl product in 58% yield (Table 1, entry 5) along with a minor amount of the conjugate addition product. Conjugate addition has been reported by

Table 1. Optimization of Reaction Conditions[a]



2 3 4a 5a

entry	oxidant	base	solvent	yield[b] (%)	ratio[c] (4a:5a)
1	O_2	LiOAc	DMF	9.9	100:0
2	$Cu(OAc)_2$	DIPEA	DMF	26.5	100:0
3	$Cu(OAc)_2$	TEA	DMF	12	100:0
4	$Cu(OAc)_2$	Cs_2CO_3	DMF	NR	–
5	$Cu(OAc)_2$	LiOAc	DMF	58	95:5
6	$Cu(OAc)_2$	LiOAc	CH_3CN	28	92:8
7	$Cu(OAc)_2$	LiOAc	THF	77	100:0
8	$Cu(OAc)_2$	LiOAc	DCE	16.8	59:41
9	$Cu(OAc)_2$	LiOAc	toluene	9.5	31:69
10	$Cu(OAc)_2$	LiOAc	H_2O	trace	27:73

[a]Reaction conditions: Boronic acid (1.0 equiv), ethenesulfonyl fluoride (3.0 equiv), $Pd(OAc)_2$ (10 mol %), base (1.2 equiv), oxidant (2.0 equiv for $Cu(OAc)_2$) under dry conditions in 4.0 mL of solvent. [b]Isolated yield of **4a**. [c]Percentages based on GC/MS analysis of the crude reaction mixture (**4a** and **5a**).

several other research groups for various other α,β-unsaturated cyclic/acyclic carbonyl systems.[2,24]

To avoid the undesired homocoupling and conjugate addition, we slowly added the aryl boronic acid to the reaction mixture over a period of ∼30 min; thereby, we were able to avoid the homocoupling and observed a small improvement in the yield. Still, a small amount of conjugate addition product was observed under these conditions.

Finally, to achieve the optimized reaction conditions we explored various solvents {CH_3CN, toluene, THF, DCE, and H_2O}. Polar aprotic solvents (CH_3CN, THF) gave moderate to good yields with minimum, or no, conjugate product formation (Table 1, entries 6 and 7). This suggested that nitrogen- and oxygen-containing solvents could act as ligands that stabilize the palladium coordination complex[25] and promote/switch the oxidative addition over conjugate addition. The use of chlorinated non-polar aprotic solvents such as DCE resulted in an almost equal amount of the oxidative addition and conjugate addition products (Table 1, entry 8). Again, this could be due to the absence of coordinating heteroatoms (O and N) in this solvent. This hypothesis was further supported by observations of a nonpolar aprotic solvent, i.e. toluene, where the conjugate addition product was observed as a major product; lower yields were also seen in toluene due to poor solubility of the starting materials (aryl boronic acid, LiOAc) in this solvent (Table 1, entry 9). In contrast to our previous report on cross-coupling reactions,[4] water as a reaction solvent drastically decreased the reaction yield (Table 1, entry 10). Only a trace amount of product formation was observed with some other byproducts, as well as small amounts of unreacted starting material; most likely, the super Michael acceptor ethenesulfonyl fluorides reacts with water under these conditions.[14]

With the optimized conditions in hand (10 mol % $Pd(OAc)_2$, 2.0 equiv of $Cu(OAc)_2$, and 1.0 equiv of LiOAc in THF at room temperature) we next investigated the substrate scope of the reaction using various substituted arylboronic acids and ethenesulfonyl fluoride as coupling partners (Figure 2). Reaction with simple phenyl boronic acids proceeded smoothly in an oxidative boron-Heck cross-coupling, without any

DOI: 10.1021/acs.orglett.6b03634
Org. Lett. 2017, 19, 480−483

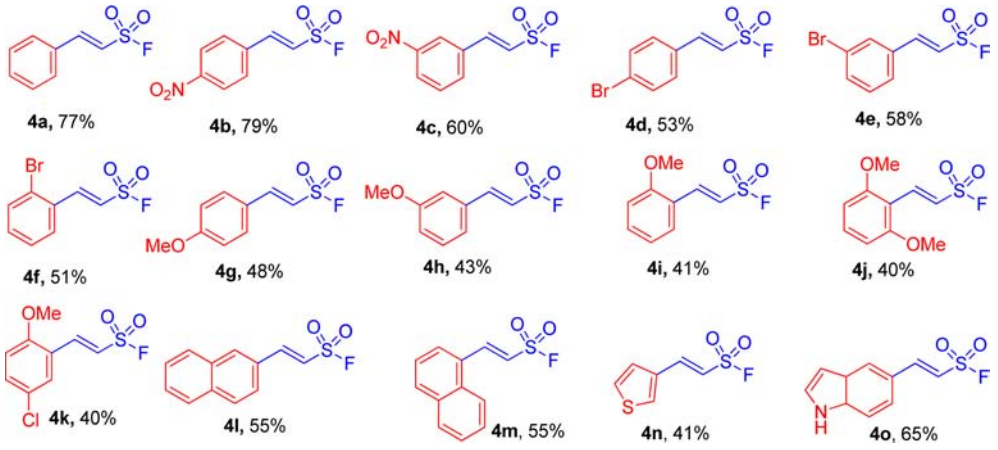


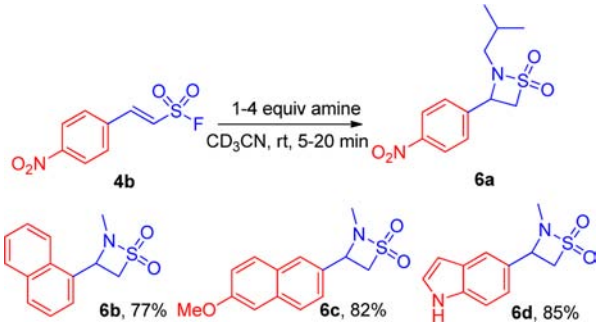
Figure 2. Substrate scope for the synthesis of aryl substituted ethenesulfonyl fluorides using oxidative Heck coupling of boronic acids and ethenesulfonyl fluoride (ESF).

conjugated addition, offering product **4a** in 77% yield. The electron-withdrawing groups (EWGs) (NO_2 and Br) offered products **4b**, **4c**, **4d**, **4e**, and **4f** in moderate to good yields without any conjugate addition product. However, substrates with electron-donating groups (EDGs), i.e. yielding products **4g** and **4h** in 48% and 43% yield respectively, gave a small amount of conjugate addition (<1%) byproduct. Steric effects did not seem to significantly influence the reaction, as substrates with 2-OMe, 2,6-di-OMe, and 2-OMe-5-chloro groups offered the corresponding products in moderate yields. Bicyclic (naphthalene; **4l** and **4m** in 55% and 55% yield) and heterocyclic (thiophene **4n**, 41% yield; indole **4o**, 65%) boronic acids gave only small amounts of conjugate addition product along with an oxidative boron-Heck product. We also attempted the same reaction conditions for heterocyclic boronic acids (i.e., quinazoline and pyridine), but these substrates did not offer any product, presumably due to complexation of the palladium with the nitrogen atoms in these substrates. Similarly, 2-NO_2 phenyl boronic failed to give the respective product. In summary, the reported methodology offers acceptable yields of aryl ethenesulfonyl fluorides through an operationally simple oxidative Heck reaction using widely accessible boronic acids and ethenesulfonyl fluoride as reagents. The limitation in yields was due to unwanted deboronation of the aryl boronic acids, which was confirmed by GC-MS and previously reported in the literature.[26]

In order to prove the synthetic potential of the disclosed methodology and explore the dual warhead concept of the β-aryl ethenesulfonyl fluorides, the addition of primary amines was investigated. The concurrent manuscript by Sharpless et al., describes the selective conjugate addition of secondary amines to the β-aryl ethenesulfonyl fluoride products without affecting the S−F bond, while Liskamp and co-workers described an unexpected β-sultam formation in the presence of excess of primary amines for their β-aliphatic ethenesulfonyl fluoride reagents. We initiated our investigation using NMR spectroscopy experiments by the addition of only 1.0 eq. of isobutylamine to **4b**; under these conditions, no reaction occurred after 5 min. Keeping the reaction mixture overnight led to 50% conversion to the corresponding β-sultam **6a**; notably, no trace of the corresponding Michael addition product could be detected in the sample. In the next experiment, we added aliquots (0.1 equiv) of the amine sequentially to the NMR tube already containing 1.0 eq. of isobutylamine and **4b**. We observed an increased formation of β-sultam **6a** until a total of 2.5 equiv of amine had been added to reach 100% conversion to the β-sultam over 20 min. A separate experiment in which 4.0 equiv of the amine was directly added to **4b** led to 100% conversion to the β-sultam in 2 min.

We also probed the influence of DBU to see if this changed the reactivity toward the S−F bond or catalyzed the Michael reaction; addition of 1.0 equiv of isobutylamine to **4b** in the presence of 0.1−0.5 equiv of DBU led to slow formation of the β-sultam. With these results in hand, we investigated the scope of the β-sultam formation using excess methylamine in THF (see Supporting Information for details). The transformation worked well for a range of aryl ethenesulfonyl fluorides containing both electron-donating and -withdrawing groups, i.e. producing β-sultams **6b**−**6d** (Scheme 2). It is anticipated that

Scheme 2. Synthesis of β-Sultams

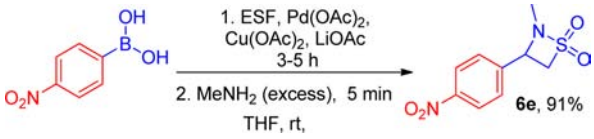


the β-sultam forms via a Michael addition that in a concerted reaction expels F^- and forms a sulfene intermediate, to which the amine adds intramolecularly; substrates with an EWG appears to react faster than those with EDG substituents. Finally, we developed this method as a one-pot procedure. After completion of the oxidative boron-Heck reaction between the boronic acid and ethenesulfonyl fluoride, we directly added excess methylamine to the reaction mixture followed by stirring for another 5 min. This gave the corresponding β-sultam in high yield after column chromatography (Scheme 3).

In summary, we have developed a facile synthetic method to access substituted β-aryl ethenesulfonyl fluorides using an oxidative boron-Heck cross-coupling reaction that proceeds

DOI: 10.1021/acs.orglett.6b03634
Org. Lett. 2017, 19, 480−483

Scheme 3. One Pot-Click Synthesis of β-Sultams



under mild reaction conditions with moderate to good yields. The reported method is complementary to previously reported procedures and utilizes boronic acids, a class of starting material that has widespread commercial availability. The obtained aryl substituted ethenesulfonyl fluorides represent a "dual warhead" with two electrophilic sites that has found use as covalent enzyme inhibitors and as synthetic reagents. We also demonstrate that β-sultams, another class of covalent enzyme inhibitors, may be obtained through a one-pot procedure in which an excess of primary amine is added to the reaction mixture before workup.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03634.

Experimental procedures and full characterization data (^{1}H, ^{19}F, ^{13}C, and GC-MS) with copies of spectra for all the compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: per.arvidsson@scilifelab.se.

ORCID

Per I. Arvidsson: 0000-0002-9453-6812

Author Contributions

⊥K.B.G. and A.S.K. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is based on the research supported in part by the National Research Foundation of South Africa for the Grant 87706. We are also grateful to the Claude Leon Foundation for postdoctoral fellowship to P.K.C., UKZN postdoctoral fellowship to S.K.A., master fellowship to K.B.G., and to Dr. Lisa D. Haigh at Imperial College London for assistance with HRMS.

■ REFERENCES

(1) Karimi, B.; Behzadnia, H.; Elhamifar, D.; Akhavan, P. F.; Esfahani, F. K.; Zamani, A. *Synthesis* **2010**, *2010*, 1399−1427.

(2) Lee, A. L. *Org. Biomol. Chem.* **2016**, *14*, 5357−5366.

(3) Andappan, M. M. S.; Nilsson, P.; Larhed, M. *Mol. Diversity* **2003**, *7*, 97−106.

(4) Chinthakindi, P. K.; Kruger, H. G.; Govender, T.; Naicker, T.; Arvidsson, P. I. *J. Org. Chem.* **2016**, *81*, 2618−2623.

(5) Dong, J.; Krasnova, L.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2014**, *53*, 9430−9448.

(6) (a) Narayanan, A.; Jones, L. H. *Chem. Sci.* **2015**, *6*, 2650−2659. (b) Fadeyi, O.; Parikh, M. D.; Chen, M. Z.; Kyne, R. E.; Taylor, A. P.; O'Doherty, I.; Kaiser, S. E.; Barbas, S.; Niessen, S.; Shi, M.; Weinrich, S. L.; Kath, J. C.; Jones, L. H.; Robinson, R. P. *ChemBioChem* **2016**, *17*, 1925−1930.

(7) Bogolubsky, A. V.; Moroz, Y. S.; Mykhailiuk, P. K.; Pipko, S. E.; Konovets, A. I.; Sadkova, I. V.; Tolmachev, A. *ACS Comb. Sci.* **2014**, *16*, 192−197.

(8) Nielsen, M. K.; Ugaz, C. R.; Li, W.; Doyle, A. G. *J. Am. Chem. Soc.* **2015**, *137*, 9571−9574.

(9) Inkster, J. A. H.; Liu, K.; Ait-Mohand, S.; Schaffer, P.; Guérin, B.; Ruth, T. J.; Storr, T. *Chem. - Eur. J.* **2012**, *18*, 11079−11087.

(10) (a) Yatvin, J.; Brooks, K.; Locklin, J. *Angew. Chem.* **2015**, *127*, 13568−13571. (b) Yatvin, J.; Brooks, K.; Locklin, J. *Chem. - Eur. J.* **2016**, *22*, 16348−16354. (c) Li, S.; Beringer, L. T.; Chen, S.; Averick, S. *Polymer* **2015**, *78*, 37−41.

(11) Brouwer, A. J.; Herrero Álvarez, N.; Ciaffoni, A.; van de Langemheen, H.; Liskamp, R. M. J. *Bioorg. Med. Chem.* **2016**, *24*, 3429−3435.

(12) Krutak, J. J.; Burpitt, R. D.; Moore, W. H.; Hyatt, J. A. *J. Org. Chem.* **1979**, *44*, 3847−3858.

(13) Moore, J. A. *Reactions on Polymers: Proceedings of the NATO Advanced Study Institute held at Rensselaer Polytechnic Institute*; Springer: 2012.

(14) Chen, Q.; Mayer, P.; Mayr, H. *Angew. Chem., Int. Ed.* **2016**, *55*, 12664−12667.

(15) Truce, W. E.; Hoerger, F. D. *J. Am. Chem. Soc.* **1954**, *76*, 3230−3232.

(16) (a) Qin, H.-L.; Zheng, Q.; Bare, G. A. L.; Wu, P.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2016**, *55*, 14155−14158. (b) Ungureanu, A.; Levens, A.; Candish, L.; Lupton, D. W. *Angew. Chem., Int. Ed.* **2015**, *54*, 11780−11784. (c) Reddy, E. P.; Reddy, M. V. R.; Bell, S. C. *N*-(Aryl)-2-arylethenesulfonamides and therapeutic uses thereof. Google Patents, 2011.

(17) Metaferia, B. B.; Fetterolf, B. J.; Shazad-ul-Hussan, S.; Moravec, M.; Smith, J. A.; Ray, S.; Gutierrez-Lugo, M.-T.; Bewley, C. A. *J. Med. Chem.* **2007**, *50*, 6326−6336.

(18) Reddy, M. V. R.; Mallireddigari, M. R.; Pallela, V. R.; Cosenza, S. C.; Billa, V. K.; Akula, B.; Subbaiah, D. R. C. V.; Bharathi, E. V.; Padgaonkar, A.; Lv, H.; Gallo, J. M.; Reddy, E. P. *J. Med. Chem.* **2013**, *56*, 5562−5586.

(19) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev.* **2016**, *45*, 546−576.

(20) (a) Ourailidou, M. E.; van der Meer, J.-Y.; Baas, B.-J.; Jeronimus-Stratingh, M.; Gottumukkala, A. L.; Poelarends, G. J.; Minnaard, A. J.; Dekker, F. J. *ChemBioChem* **2014**, *15*, 209−212. (b) Yang, M.; Li, J.; Chen, P. R. *Chem. Soc. Rev.* **2014**, *43*, 6511−6526.

(21) (a) Wakchaure, P. B.; Borhade, S. R.; Sandström, A.; Arvidsson, P. I. *Eur. J. Org. Chem.* **2015**, *2015*, 213−219. (b) Nandi, G. C.; Kota, S. R.; Wakchaure, P. B.; Chinthakindi, P. K.; Govender, T.; Kruger, H. G.; Naicker, T.; Arvidsson, P. I. *RSC Adv.* **2015**, *5*, 62084−62090. (c) Borhade, S. R.; Sandström, A.; Arvidsson, P. I. *Org. Lett.* **2013**, *15*, 1056−1059.

(22) Jung, Y. C.; Mishra, R. K.; Yoon, C. H.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2231−2234.

(23) Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A.; Nishikata, T.; Hagiwara, N.; Kawata, K.; Okeda, T.; Wang, H. F.; Fugami, K.; Kosugi, M. *Org. Lett.* **2001**, *3*, 3313−3316.

(24) (a) Shockley, S. E.; Holder, J. C.; Stoltz, B. M. *Org. Process Res. Dev.* **2015**, *19*, 974−981. (b) He, Q.; Xie, F.; Fu, G.; Quan, M.; Shen, C.; Yang, G.; Gridnev, I. D.; Zhang, W. *Org. Lett.* **2015**, *17*, 2250−2253. (c) Kim, Y. W.; Georg, G. I. *Org. Lett.* **2014**, *16*, 1574−1577. (d) Walker, S. E.; Boehnke, J.; Glen, P. E.; Levey, S.; Patrick, L.; Jordan-Hore, J. A.; Lee, A.-L. *Org. Lett.* **2013**, *15*, 1886−1889. (e) Lu, X.; Lin, S. *J. Org. Chem.* **2005**, *70*, 9651−9653.

(25) (a) Dickstein, J. S.; Curto, J. M.; Gutierrez, O.; Mulrooney, C. A.; Kozlowski, M. C. *J. Org. Chem.* **2013**, *78*, 4744−4761. (b) Dyson, P. J.; Jessop, P. G. *Catal. Sci. Technol.* **2016**, *6*, 3302−3316.

(26) (a) Liu, C.; Li, X.; Wu, Y.; Qiu, J. *RSC Adv.* **2014**, *4*, 54307−54311. (b) Liu, C.; Li, X.; Wu, Y. *RSC Adv.* **2015**, *5*, 15354−15358. (c) Steinkamp, A.-D.; Wiezorek, S.; Brosge, F.; Bolm, C. *Org. Lett.* **2016**, *18*, 5348−5351.

DOI: 10.1021/acs.orglett.6b03634
Org. Lett. 2017, 19, 480−483