Organic LETTERS

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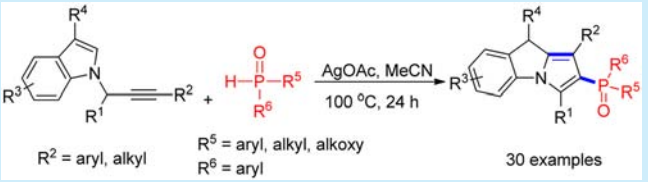
# Cascade Phosphinoylation/Cyclization/Isomerization Process for the Synthesis of 2-Phosphinoyl-9*H*-pyrrolo[1,2-*a*]indoles

Su Chen,[†] Pengbo Zhang,[†] Wanyun Shu, Yuzhen Gao, Guo Tang,* and Yufen Zhao

Department of Chemistry, College of Chemistry and Chemical Engineering, and the Key Laboratory for Chemical Biology of Fujian Province, Xiamen University, Xiamen, Fujian 361005, China

Supporting Information

**ABSTRACT:** Pyrrolo[1,2-*a*]indole is a common structural motif found in many natural products and pharmaceuticals. A silver-mediated oxidative phosphinoylation of *N*-propargyl-substituted indoles was used to construct a variety of 2-phosphinoyl-9*H*-pyrrolo[1,2-*a*]indoles under mild conditions. This transformation offers a straightforward route to the formation of the C−P bond, cyclization, and isomerization in one step.

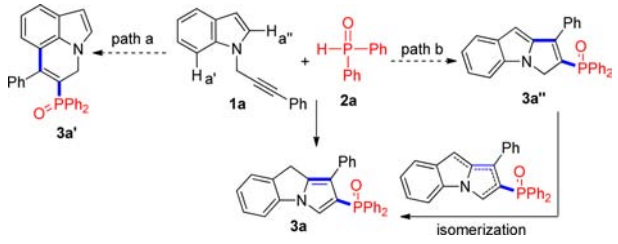



Pyrrolo[1,2-*a*]indole is a distinctive structural motif found in many natural products and pharmaceuticals.[1] For example, the natural product mitomycin-C, exhibiting powerful antibacterial and anticancer activities, has been studied extensively.[2] Another important class of heterocyclic compounds, flinderoles, shows potent antimalarial activities.[3] Because of the current interest in these pharmacologically important pyrrolo[1,2-*a*]indoles, many new synthetic methods have been reported for their rapid generation.[4]

However, heterocycle-containing organophosphorus compounds have drawn great interest in their wide application in organic synthesis, medicinal chemistry, and material science.[5] These compounds are commonly accessed through the transition-metal catalyzed cross-coupling reaction[6] and the reaction of an electrophilic phosphorus reagent with a carbon nucleophile.[7] Since the addition of P-centered radicals to unsaturated systems exhibits high reactivity, it provides a direct and atom economic method to construct the C−P bond.[8] Oxidative radical phosphinoylation−cyclization−aromatization reaction represents an important method for rapidly constructing aromatic heterocyclic organophosphorus compounds.[9] It is known that molecular modifications involving the introduction of organophosphorus functionalities could increase their biological activity.[10] If both the phosphinoyl group and the pyrrolo[1,2-*a*]indole skeleton motif can be simultaneously introduced into organic compounds, a series of new pyrrolo-[1,2-*a*]indole-containing organophosphorus compounds might be expected and might provide an opportunity to introduce phosphinoyl group into the original lead compounds or drugs to adjust their bioactivity. Yet, methods for the synthesis of phosphinoyl-pyrrolo[1,2- a]indoles are lacking.[11]

Herein, we considered that *N*-propargyl-substituted indoles could react with P(O)−H compounds via a radical way for the construction of phosphinoyl-pyrrolo[1,2-*a*]indoles (Scheme 1). To test the idea, the reaction of 1-(3-phenylprop-2-yn-1-yl)-1*H*-indole (**1a**) and diphenylphosphine oxide (**2a**) were performed in the presence of AgOAc in MeCN under argon. However, no

**Scheme 1. Reaction of *N*-Propargyl-substituted Indole with Diphenylphosphine Oxide**




direct phosphinoylation−cyclization product **3a′** or **3a″** was detected, and the unexpected isomerized product **3a** was obtained, albeit with a very low yield. The structure of **3a** was unambiguously confirmed by X-ray crystal structure analysis (see Figure 1 and the Supporting Information).

To optimize the reaction conditions, some oxidants, such as $Mg(NO_3)_2·6H_2O$, $CuSO_4$, TBHP, and $Mn(OAc)_3·2H_2O$ were tested,[12] but the reaction did not work well under these conditions (Table 1, entries 1−4). It has been found that silver

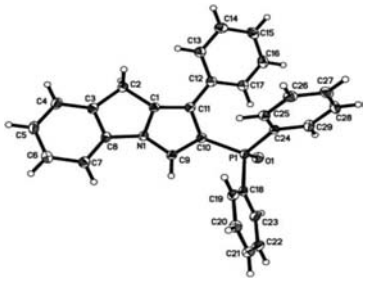


**Figure 1.** X-ray structure of **3a**.

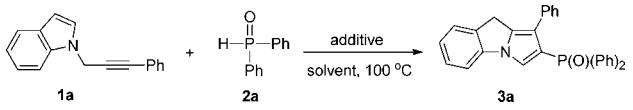
**Received:** September 29, 2016
**Published:** October 25, 2016





DOI: 10.1021/acs.orglett.6b02941
*Org. Lett.* 2016, 18, 5712−5715

**Table 1. Optimization of the Reaction Conditions**[a]



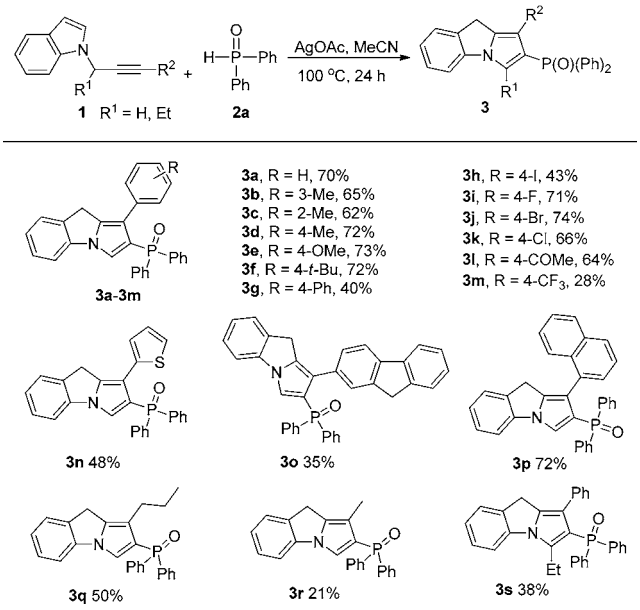

| entry | additive (equiv) | solvent | yield [%] |
|---|---|---|---|
| 1 | AgOAc (0.1) + $Mg(NO_3)_2·6H_2O$ (0.3) | MeCN | 15 |
| 2 | $CuSO_4·5H_2O$ (0.1) + TBHP (3.0) | MeCN | 20 |
| 3 | TBAI (0.1) + TBHP (3.0) | MeCN | trace |
| 4 | $Mn(OAc)_3·2H_2O$ (3.0) | MeCN | trace |
| 5 | $Ag_2CO_3$ (3.0) | MeCN | 17 |
| 6 | $AgNO_3$ (3.0) | MeCN | 13 |
| 7 | AgOAc (3.0) | MeCN | 60 |
| 8 | AgOAc (3.0) | HOAc | 58 |
| 9 | AgOAc (3.0) | 1,4-dioxane | 43 |
| 10 | AgOAc (3.0) | toluene | 50 |
| 11 | AgOAc (3.0) | DMF | 45 |
| 12 | AgOAc (3.0) | MeCN | 22[b] |
| 13 | AgOAc (3.0) | MeCN | 55[c] |
| **14** | **AgOAc (3.0) + $Ph_2P(O)OH$ (1.0)** | **MeCN** | **70** |
| 15 | AgOAc (3.0) + HOAc (1.0) | MeCN | 43 |
| 16 | AgOAc (3.0) + Pival (1.0) | MeCN | 48 |

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), additive in solvent (2 mL) stirring under argon at 100 °C for 24 h. Oil bath temperature. [b]At 80 °C. [c]At 120 °C.

salts can work with $R_2P(O)H$ to form the corresponding phosphinoyl radical.[13] After the check of various silver salts, it is found that when AgOAc was chosen as the oxidant, using MeCN as the solvent, the product **3a** was obtained in 60% yield at 100 °C under an argon atmosphere (entries 5−7). Screening a few other solvents, such as HOAc, 1,4-dioxane, toluene, and DMF revealed that MeCN was the best choice (entries 7−11). However, the yield of product **3a** decreased when the temperature was decreased to 80 °C or increased to 120 °C (entries 12−13) indicating that the choice of temperature was also crucial for the reaction. Further, the effect of acid was studied (entries 14−16). When 1 equiv of diphenylphosphinic acid $Ph_2P(O)OH$ was added, the desired product **3a** was obtained in 70% yield, and other additions displayed decreased activity. After optimization of the reaction conditions, we established an efficient route to formation of 2-phosphinoyl-9*H*-pyrrolo[1,2-*a*]indoles. The optimal reaction conditions are **1a** (0.2 mmol), **2a** (0.4 mmol), AgOAc (0.6 mmol), $Ph_2P(O)OH$ (0.2 mmol), and MeCN (2 mL) at 100 °C for 24 h under an argon atmosphere.

With the optimized reaction conditions in hand, the generality of the method was explored, and the results are summarized in Scheme 2. First, various functional groups on the benzene ring were examined, and most of the functional groups were tolerated under the optimized conditions. With methyl substituted on benzene, these compounds reacted efficiently to give the desired products (**3b−3d**) in 72−62% yields, indicating the position of the substituent on the benzene ring exhibited slightly negative effect. Some electron-donating (methoxy and *tert*-butyl) groups were investigated and gave the corresponding products **3e** and **3f** in 73 and 62% yields. More bulk biphenyl group at the triple bond could be transferred and gave **3g** in moderate yield. Halogen atoms such as iodo, fluoro, bromo, and chloro on the aromatic ring were unaffected under the present reaction conditions to afford the corresponding products **3h−3k** in moderate to good yields, which could allow for further synthetic transformations. Substrate bearing acetyl group on the benzene

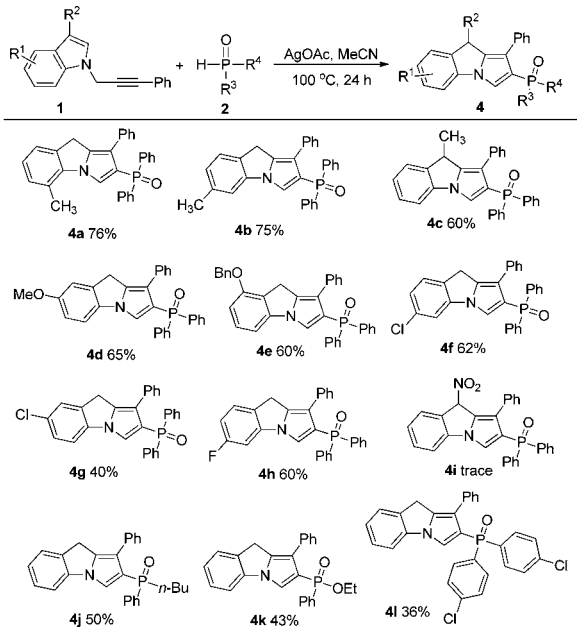
**Scheme 2. Scope of *N*-Propargyl-substituted Indoles**




ring was converted into product **3l** in 64% yield. Due to the strong electron-withdrawing property of $CF_3$-group, **3m** was obtained in 28% yield. In addition, compounds with thienyl, fluorenyl, and naphthyl could also react smoothly with **2a** to afford the expected products **3n−3p** in 72−35% yield. When $R^2$ was an aliphatic chain, **3q** and **3r** could be obtained in moderate to low yields. Moreover, *N*-propargyl-substituted indoles with two groups ($R^1$, Et; $R^2$, Ph) also reacted smoothly with diphenylphosphine oxide to afford product **3r** in 38% yield, along with unidentified byproducts, and no starting materials were recovered. Contrary to expectation, $Ph_2P(S)H$ or $Ph_2PH$ was not competent to this reaction, only trace amount of desired product was detected.

Next, we further turned our attention to exploring various indole derivatives under standard conditions (Scheme 3). With

**Scheme 3. Scope of Substituted Indols**



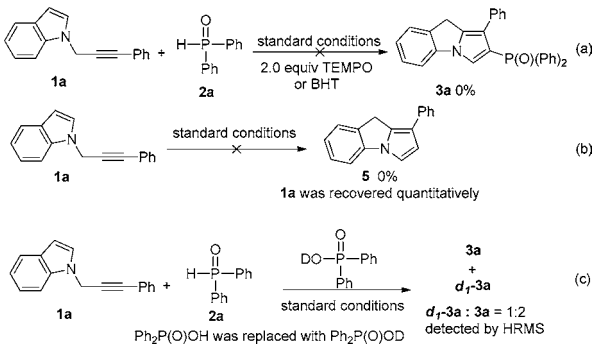



DOI: 10.1021/acs.orglett.6b02941
*Org. Lett.* 2016, 18, 5712−5715

methyl substituted on the indole ring, such as 7-Me, 6-Me, and 3-Me, these compounds reacted efficiently to give the desired products (**4a**−**4c**) in satisfactory yields 76−60%. Some electron-donating groups, such as methoxy and benzyloxy, were investigated and gave the corresponding products **4d** and **4e** in 65% and 60% yields. A series of halogen-containing indoles were tested, and the results showed that halogens could be well tolerated in this reaction (**4f**−**4h**). Additionally, indole bearing strong electron-withdrawing group $NO_2$ failed to give the desired product (**4i**). Moreover, the reactions between variously P(O)−H compounds and **1a** were also examined, giving the corresponding products **4j**−**4l** in 50−36% yields.

In an effort to improve our understanding of the reaction profile, preliminary studies were carried out (Scheme 4). When

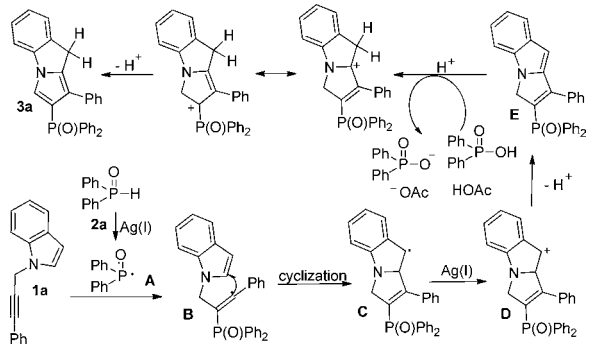
**Scheme 4. Experiments for the Mechanistic Study**




2.0 equiv of the radical inhibitor 2,2,6,6-tetramethylpiperidine oxide (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) were added to this system under standard conditions, as we expected, no product **3a** was detected (Scheme 4a), which suggested that this transformation might undergo a radical process. Without **2a**, **1a** was treated under the standard conditions, no intermediate was detected, and **1a** was recovered quantitatively (Scheme 4b). When $Ph_2P(O)OD$ was added to the reaction mixture under the optimal conditions, isotope-labeled product was detected in HRMS spectra, which suggested that diphenylphosphinic acid might play an important role in the process of isomerization of intermediate **E** (Scheme 4c).

A plausible mechanism can be proposed based on the above experiments (Scheme 5). First, diphenylphosphine oxide **2a** reacts with AgOAc to form the phosphinoyl radical **A**, which then adds to **1a** to give the alkenyl radical **B**. The resulting alkenyl radical **B** participates in an intramolecular radical reaction to generate the intermediate **C**, which goes through a single

**Scheme 5. Tentative Mechanistic Pathway**




electron transfer process to generate intermediate **D**. Finally, intermediate **D** undergoes deprotonation to produce **E**, and the isomerization of **E** in the presence of $Ph_2P(O)OH$ and acetic acid affords the targeted product **3a**.

In summary, we have developed a highly efficient protocol for the preparation of various 2-phosphinoyl-9*H*-pyrrolo[1,2-*a*]-indoles by silver-mediated cascade phosphinoylation−cyclization−isomerization involving C−P and C−C bond formation under mild conditions. Given that both the phosphinoyl group and the pyrrolo[1,2-*a*]indole motif were simultaneously introduced into organic compounds, this simple protocol may provide a general approach to 2-phosphinoyl-9*H*-pyrrolo[1,2-*a*]indole frameworks of importance in medicinal and synthetic chemistry.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02941.

Copies of $^1$H NMR and $^{13}$C NMR spectra of compounds **3a**−**3s**, **4a**−**4h**, and **4j**−**4l**; single-crystal X-ray spectrum of compound **3a** (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: t12g21@xmu.edu.cn.

### Author Contributions

†These authors contributed equally to this work.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank NSFC (21232005, 21375113) and the National Basic Research Program of China (2013CB910700), and the Fundamental Research Funds for the Central Universities (20720160030).

## ■ REFERENCES


(1) (a) Paris, D.; Cottin, M.; Demonchaux, P.; Augert, G.; Dupassieux, P.; Lenoir, P.; Peck, M. J.; Jasserand, D. *J. Med. Chem.* **1995**, *38*, 669. (b) Bass, P. D.; Gubler, D. A.; Judd, T. C.; Williams, R. M. *Chem. Rev.* **2013**, *113*, 6816.

(2) (a) Wolkenberg, S. E.; Boger, D. L. *Chem. Rev.* **2002**, *102*, 2477. (b) Galm, U.; Hager, M.-H.; Van Lanen, S.-G.; Ju, J.; Thorson, J.-S.; Shen, B. *Chem. Rev.* **2005**, *105*, 739.

(3) (a) Fernandez, L. S.; Sykes, M. L.; Andrews, K. T.; Avery, V. M. *Int. J. Antimicrob. Agents* **2010**, *36*, 275. (b) Dethe, D. H.; Erande, R. D.; Ranjan, A. *J. Am. Chem. Soc.* **2011**, *133*, 2864. (c) Zeldin, R. M.; Toste, F. D. *Chem. Sci.* **2011**, *2*, 1706. (d) Vallakati, R.; May, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 6936.

(4) For a general review on the synthesis of pyrrolo[1,2-*a*]indoles, see: Monakhova, N.; Ryabova, S.; Makarov, V. *J. Heterocyclic Chem.* **2016**, *53*, 685.

(5) For selected reviews, see: (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (b) Tomashenko, O.-A.; Grushin, V.-V. *Chem. Rev.* **2011**, *111*, 4475. (c) George, A.; Veis, A. *Chem. Rev.* **2008**, *108*, 4670. (d) Queffélec, C.; Petit, M.; Janvier, P.; Knight, D. A.; Bujoli, B. *Chem. Rev.* **2012**, *112*, 3777.

(6) For selected publications, see: (a) Gao, Y.; Deng, H.; Zhang, S.; Xue, W.; Wu, Y.; Qiao, H.; Xu, P.; Zhao, Y. *J. Org. Chem.* **2015**, *80*, 1192. (b) Hu, G.; Gao, Y.; Zhao, Y. *Org. Lett.* **2014**, *16*, 4464. (c) Mi, X.; Huang, M.; Zhang, J.; Wang, C.; Wu, Y. *Org. Lett.* **2013**, *15*, 6266. (d) Yang, B. T.; Yang, T.; Li, X.-A.; Wang, J.-J.; Yang, S. D. *Org. Lett.*




DOI: 10.1021/acs.orglett.6b02941
*Org. Lett.* 2016, 18, 5712−5715

**2013**, *15*, 5024. (e) Li, C.; Yano, T.; Ishida, N.; Murakami, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 9801. (f) Xu, J.; Zhang, P.; Gao, Y.; Chen, Y.; Tang, G.; Zhao, Y. *J. Org. Chem.* **2013**, *78*, 8176.

(7) For selected publications, see: (a) Zhou, X.-A.; Mao, L.-L.; Wang, G.-W.; Yang, S.-D. *Chem. Commun.* **2014**, *50*, 8529. (b) Gao, Y.; Huang, Z.; Zhuang, R.; Xu, J.; Zhang, P.; Tang, G.; Zhao, Y. *Org. Lett.* **2013**, *15*, 4214.

(8) (a) Pan, X.-Q.; Zou, J.-P.; Yi, W.-B.; Zhang, W. *Tetrahedron* **2015**, *71*, 7481. and references cited therein. (b) Gao, Y.; Li, X.; Chen, W.; Tang, G.; Zhao, Y. *J. Org. Chem.* **2015**, *80*, 11398. (c) Zheng, J.; Zhang, Y.; Wang, D.; Cui, S. *Org. Lett.* **2016**, *18*, 1768. (d) Xiong, B.; Feng, X.; Zhu, L.; Chen, T.; Zhou, Y.; Au, C. T.; Yin, S. F. *ACS Catal.* **2015**, *5*, 537. (e) Zhou, M.; Chen, M.; Zhou, Y.; Yang, K.; Su, J.; Du, J.; Song, Q. *Org. Lett.* **2015**, *17*, 1786. (f) Zhang, H. Y.; Mao, L. L.; Yang, B.; Yang, S. D. *Chem. Commun.* **2015**, *51*, 4101. (g) Chen, X.; Li, X.; Chen, X. L.; Qu, L. B.; Chen, J. Y.; Sun, K.; Liu, Z. D.; Bi, W. Z.; Xia, Y. Y.; Wu, H. T.; Zhao, Y. F. *Chem. Commun.* **2015**, *51*, 3846. (h) Zhou, S.-F.; Li, D.-P.; Liu, K.; Zou, J.-P.; Asekun, O. T. *J. Org. Chem.* **2015**, *80*, 1214. (i) Xue, J.-F.; Zhou, S.-F.; Liu, Y.-Y.; Pan, X.; Zou, J.-P.; Asekun, O. T. *Org. Biomol. Chem.* **2015**, *13*, 4896. (j) Richard, V.; Fisher, H. C.; Montchamp, J. L. *Tetrahedron Lett.* **2015**, *56*, 3197.

(9) (a) Wu, J.; Gao, Y.; Zhao, X.; Zhang, L.; Chen, W.; Tang, G.; Zhao, Y. *RSC Adv.* **2016**, *6*, 303. (b) Zhang, P.; Gao, Y.; Zhang, L.; Li, Z.; Liu, Y.; Tang, G.; Zhao, Y. *Adv. Synth. Catal.* **2016**, *358*, 138. (c) Gao, Y.; Lu, G.; Zhang, P.; Zhang, L.; Tang, G.; Zhao, Y. *Org. Lett.* **2016**, *18*, 1242. (d) Yoo, W. J.; Kobayashi, S. *Green Chem.* **2013**, *15*, 1844. (e) Xuan, J.; Zeng, T. T.; Chen, J. R.; Lu, L. Q.; Xiao, W. J. *Chem. - Eur. J.* **2015**, *21*, 4962. (f) Luo, K.; Chen, Y.-Z.; Yang, W.-C.; Zhu, J.; Wu, L. *Org. Lett.* **2016**, *18*, 452. (g) Quint, V.; Morlet-Savary, F.; Lohier, J.-F.; Lalevée, J.; Gaumont, A.-C.; Lakhdar, S. *J. Am. Chem. Soc.* **2016**, *138*, 7436.

(10) (a) Bansal, R. K., Ed. Phosphorus Heterocycles II. In *Topics in Heterocyclic Chemistry*; Springer, Berlin, 2010; Vol. *21*. (b) Zhou, X. J.; Garner, R. C.; Nicholson, S.; Kissling, C. J.; Mayers, D. *J. Clin. Pharmacol.* **2009**, *49*, 1408. (c) La Regina, G.; Coluccia, A.; Silvestri, R. *Antiviral Chem. Chemother.* **2010**, *20*, 213. (d) Alexandre, F. R.; Amador, A.; Bot, S.; Caillet, C.; Convard, T.; Jakubik, J.; Musiu, C.; Poddesu, B.; Vargiu, L.; Liuzzi, M.; Roland, A.; Seifer, M.; Standring, D.; Storer, R.; Dousson, C. B. *J. Med. Chem.* **2011**, *54*, 392.

(11) Hua, H.-L.; Zhang, B.-S.; He, Y.-T.; Qiu, Y.-F.; Wu, X.-X.; Xu, P.-F.; Liang, Y.-M. *Org. Lett.* **2016**, *18*, 216.

(12) (a) Ma, D.; Chen, W.; Hu, G.; Zhang, Y.; Gao, Y.; Yin, Y.; Zhao, Y. *Green Chem.* **2016**, *18*, 3522. (b) Zhu, L.; Yu, H.; Guo, Q.; Chen, Q.; Xu, Z.; Wang, R. *Org. Lett.* **2015**, *17*, 1978. (c) Zhang, P.; Zhang, L.; Gao, Y.; Tang, G.; Zhao, Y. *RSC Adv.* **2016**, *6*, 60922. (d) Gao, Y.; Li, X.; Xu, J.; Wu, Y.; Chen, W.; Tang, G.; Zhao, Y. *Chem. Commun.* **2015**, *51*, 1605. (e) Li, Y.-M.; Sun, M.; Wang, H.-L.; Tian, Q.-P.; Yang, S.-D. *Angew. Chem., Int. Ed.* **2013**, *52*, 3972.

(13) (a) Zhang, B.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2014**, *16*, 250. (b) Unoh, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12975. (c) Chen, Y.-R.; Duan, W.-L. *J. Am. Chem. Soc.* **2013**, *135*, 16754.



DOI: 10.1021/acs.orglett.6b02941
*Org. Lett.* 2016, 18, 5712−5715