Organic LETTERS

Letter

pubs.acs.org/OrgLett

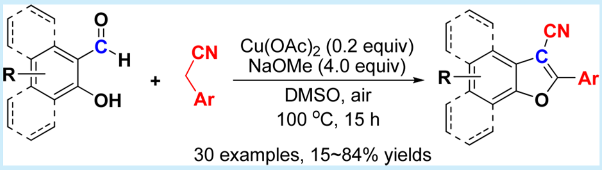
Copper-Catalyzed Preparation of 2-Aryl-3-cyanobenzofurans with Bright Blue Photoluminescence

Lianpeng Zhang,[†] Zhixing Peng,[†] Qiaodong Wen, Xihui Li, Ping Lu,* and Yanguang Wang*

Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. China

Supporting Information

ABSTRACT: Copper-catalyzed cascade synthesis of 2-aryl-3-cyanobenzofurans from *o*-hydroxybenzaldehydes and arylacetonitriles in the presence of copper acetate and sodium methoxide is reported. The synthesized 2-aryl-3-cyanobenzofurans emit bright blue under UV light with a quantum yield up to 88.9%.



Compounds containing a benzofuran ring are abundant and important in nature. They have been widely used in life[1] and material[2] science. For instance, the benzofuran skeleton constitutes a part of the bioactive molecules that could effectively inhibit hepatitis C virus (HCV) (Figure 1). Published approaches to this class of bioactive molecules include the synthesis of 2-aryl-3-cyanobenzofurans as intermediates.[3] Two strategies have been developed for the construction of 2-aryl-3-cyanobenzofurans. One is the direct cyanation of 2-arylbenzofuran with the benzofuran ring formation preceding the C−CN bond formation, and the other involves formation of the benzofuran ring as the last step. Direct cyanation has been approached by S_EAr of 2-arylbenzofuran with BrCN in the presence of Lewis acid (Scheme 1, route a).[4] Transition metal (TM) catalyzed cyanation of benzofurans or 3-halobenzofurans with various cyanide sources such as DMF,[5] $K_4Fe(CN)_6$,[6] and CuCN[7] provides an alternative method. By using functional group inversion (FGI), 3-cyanobenzofurans could be derived from the corresponding amides (Scheme 1, route b).[8] Considering the option with C−CN bond formation prior to benzofuran ring formation, a series of works have hitherto focused on TM-catalyzed C−C and C−O coupling (Scheme 1, routes c and d).[9−12] For more specific examples, electrochemical oxidation of catechols in the presence of $PhCOCH_2CN$ could provide 3-cyanobenzofurans by using the strategy of "aromatic ring umpolung" (Scheme 1, route e).[13] As an interesting example, cycloaddition of benzyne with iodonium ylide produces 2-aryl-3-cyanobenzofurans (Scheme 1, route f).[14] Here, we report a green reaction between 2-hydroxybenzaldehyde and $PhCH_2CN$ in the presence of copper salt, which produces 2-aryl-3-cyanobenzofuran with only a loss of water.

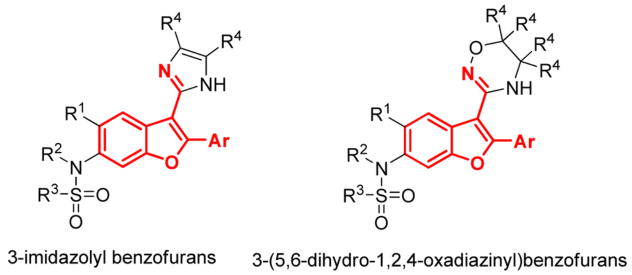
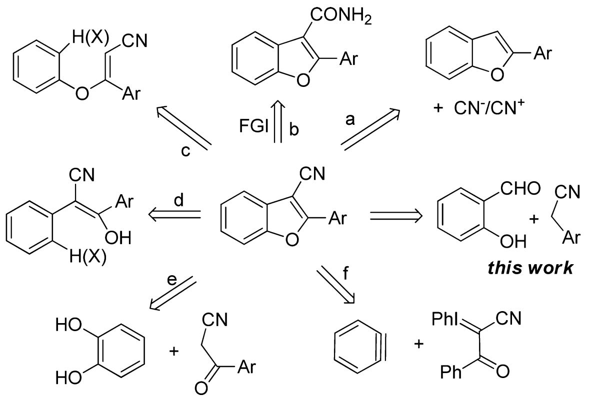


Figure 1. Molecules effectively inhibiting hepatitis C virus.

Scheme 1. Literature Approaches to 2-Aryl-3-cyanobenzofurans and Our Design



Initially, we tested the reaction of 2-hydroxy-5-methylbenzaldehyde (**1a**, 0.5 mmol) and $PhCH_2CN$ (**2a**, 0.75 mmol) in the presence of hydrated copper acetate (0.1 mmol) and NaOMe (2 mmol) in 2 mL of DMSO in air at 100 °C for 15 h. After the reaction, **3a** was isolated in 54% yield. The structure of **3a** was established by its single-crystal analysis.[15] Attracted by this result, we optimized the reaction conditions. Among the solvents tested, DMSO was the optimal choice (Table S1, entries 1−4). When toluene was used, reaction did not occur with 31% recovery of **1a**. When NMP was used, 6-methyl-3-phenyl-2*H*-chromen-2-one (**4**) was obtained in 52% yield except for the formation of **3a** in 28% yield. By altering the atmosphere from air to O_2, the yield of **3a** slightly decreased. If anhydrous copper acetate was used, the yield of **3a** increased to 69% (Table S1, entry 5). After the reaction mixture was further dried by addition of 0.1 g of 4 Å MS, the yield of **3a** decreased to 38%. The yield of

Received: December 30, 2015

DOI: 10.1021/acs.orglett.5b03704
Org. Lett. XXXX, XXX, XXX−XXX

3a decreased to 45% if the reaction was conducted in N_2. By screening other Cu(II) and Cu(I) sources (Table S1, entries 6–16), $Cu(OAc)_2$ was found to be the optimal choice. Metal copper could also catalyze the reaction and provide **3a** in 54% yield (Table S1, entry 17). Moreover, the reaction could be catalyzed by $Pd(OAc)_2$, and **3a** was isolated in 52% yield either with NaOMe or with Na_2CO_3 (Table S1, entries 18 and 19). To our surprise, **3a** could be obtained in 35% yield without any metal catalysts (Table S1, entry 20). However, any further explorations aiming to increase the yield without metal catalyst failed (Table S1, entries 21–27). In comparison with other bases, NaOMe was found to be optimal (Table S1, entries 28–37). Reaction did not occur when no base was used (Table S1, entry 38). The optimal amount of NaOMe was found to be 4 equiv of **1a** (Table S1, entries 39 and 40). Dried DMSO, distilled from CaH_2, provided **3a** in 74% yield (Table S1, entry 41). Decreasing the catalyst loading to 0.1 equiv of **1a** slightly decreased the yield of **3a** (Table S1, entry 42). Finally, the standard reaction conditions were established. A mixture of **1a** (0.5 mmol), **2a** (0.75 mmol), $Cu(OAc)_2$ (0.1 mmol), NaOMe (2.0 mmol), and dry DMSO (2 mL) was reacted at 100 °C in air for 15 h.

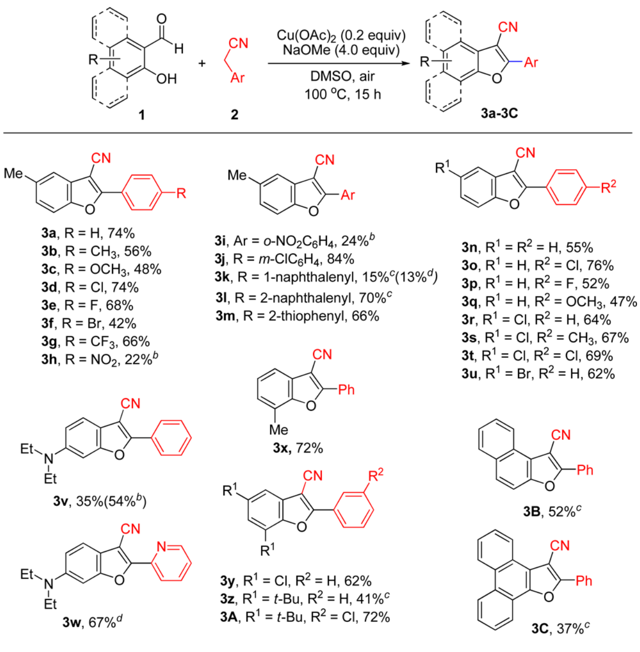
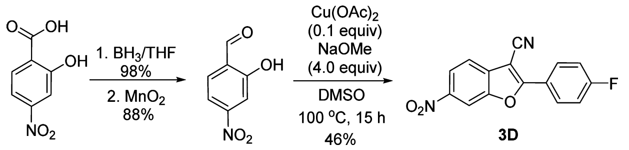


Figure 2. Scope of benzyl cyanides. Reaction conditions: (a) **1a** (0.5 mmol), **2** (0.75 mmol), dry DMSO (2 mL), with a drying tube; iolated yield based on **1a**; (b) 110 °C; (c) 18 h; (d) conducted with 10 mol % $Pd(OAc)_2$ and K_2CO_3 (4.0 equiv).

With the optimized reaction conditions in hand, we tested for substrate diversity (Figure 2). A broad range of benzyl cyanides were applied. Substituents on the *para* position of benzyl cyanides could be altered to Me, MeO, Cl, F, Br, and CF_3, which provided the corresponding 2-aryl-3-cyanobenzofurans **3b–g** in yields varying from 42% to 74%. 2-(4-Nitrophenyl)acetonitrile afforded **3h** in 22% yield at a raised reaction temperature. A relatively lower yield (**3i**, 24%) was also observed when 2-(2-nitrophenyl)acetonitrile was used. Comparing the pair of **3k** and **3l**, the steric effect is obvious. Moreover, 2-(thiophene-2-yl)acetonitrile could also be applied for this reaction and provided **3m** in 66% yield. We further tested the substrate scope of 2-hydroxybenzaldehydes. Reaction of salicyclic aldehyde with $PhCH_2CN$ provided **3n** in 55% yield. With other *para*-substituted benzyl cyanides, such as Cl, F, and CH_3O, **3o**, **3p**, and **3q** were obtained in 76%, 52%, and 47% yields, respectively. With Cl or Br substituted on 5-position of salicyclic aldehyde, **3r–u** were obtained in yields varying from 62% to 69%. 2-Hydroxy-4-(diethylamino)benzaldehyde provided **3v** in 35% yield. By using $Pd(OAc)_2$ as the catalyst, the yield of **3v** increased to 54%. 2-(Pyridin-2-yl)acetonitrile could also be applied and provided **3w** in 67% yield. The methyl on salicyclic aldehyde could be altered from the 5-position to the 3-position. Thus, **3x** was isolated in 72% yield, similar to the yield of **3a**. When the 3-position of salicyclic aldehyde was occupied by *tert*-butyl, **3z** and **3A** were obtained in yields of 41% and 72%, respectively. It implies that the steric hindrance from salicyclic aldehyde side is not significant. A higher reaction temperature was necessary for the preparation of **3B** and **3C**.

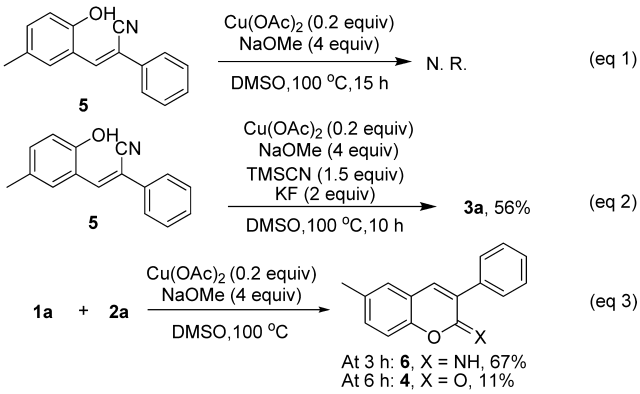
This green methodology provided a shortcut to the preparation of the molecules shown in Scheme 1. Thus, as an intermediate in the preparation of those bioactive molecules, **3D** could be prepared in a sequence of reduction, oxidation,[16] and annulations from commercially available 2-hydroxy-4-nitrobenzoic acid (Scheme 2).

Scheme 2. Preparation of 3D



In order to understand the mechanism, we carried out the controlled experiments. First, cyanation of benzofuran or 2-phenylbenzofuran with $PhCH_2CN/Cu(OAc)_2$ or CuCN was orthogonally tested. No cyanation product was detected. It implied that C–CN bond formation took place prior to the benzofuran ring formation. Second, we assumed PhCH(OH)-CN[17] to be the intermediate. However, no reaction occurred when PhCH(OH)CN was applied as starting material, rejecting our assumption. Thereafter, we assumed that the Knoevenagel condensation product (**5**) was the intermediate (Scheme 3). No reaction occurred when **5** was used as a single starting material (eq 1), rejecting our assumption again. A turning point occurred when this test was carried out by supplementarily adding TMSCN (1.5 equiv) and KF (2 equiv). In this case, **3a** was isolated in 56% yield (eq 2). We tried to isolate **5** by stopping the reaction after 3 h. Instead of obtaining **5**, we isolated

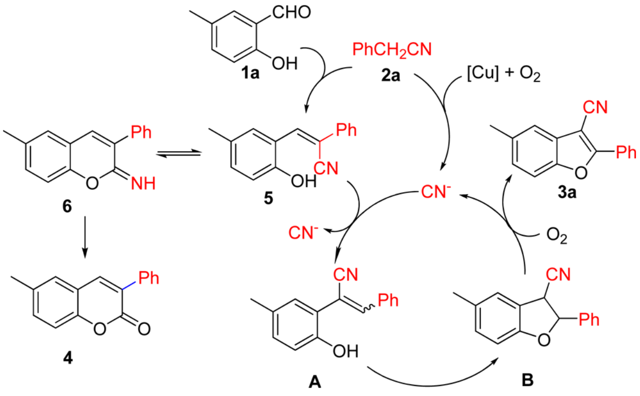
Scheme 3. Controlled Experiments



iminocoumarin **6**. By extending the reaction time to 6 h, coumarin **4** was isolated (eq 3). Compound **6** could not be converted into **3a** unless $PhCH_2CN$ was supplementally added. Thus, it is obvious that free cyanide anion plays a key factor in achieving a successful transformation. A stripe test indicated that free cyanide anion existed during the reaction process.[18]

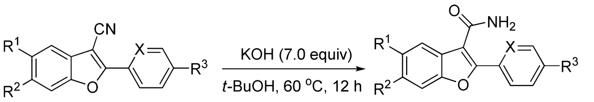
Based on the above observations, we postulated a working mechanism (Scheme 4). Knoevenagel condensation in situ generated **5** that equilibrated with **6**. Compound **6** could be partially, but irreversibly, converted into **4**. In the presence of Cu(II) and O_2, $PhCH_2CN$ was oxidized, and cyanide anion was in situ formed. Subsequent anion transfer[19] led to the formation of **A**. Oxa-Michael addition and aromatization provided **3a**.

Scheme 4. Possible Reaction Mechanism



Aryl nitriles could be smoothly extended to aryl amides. Thus, amides (**7a**−**e**) were prepared by using KOH in *t*-BuOH at 60 °C for 12 h (Scheme 5).

Scheme 5. Preparation of Aryl Amides



7a, $R^1 = CH_3$, $R^2 = R^3 = H$, X = CH, 92%
7b, $R^1 = CH_3$, $R^2 = H$, $R^3 = Cl$, X = CH, 93%
7c, $R^1 = CH_3$, $R^2 = H$, $R^3 = OMe$, X = CH, 91%
7d, $R^1 = H$, $R^2 = Et_2N$, $R^3 = H$, X = CH, 88%
7e, $R^1 = H$, $R^2 = Et_2N$, $R^3 = H$, X = N, 90%

During the preparation of **3**, we found that these compounds (**3a**−**D**) were strongly emissive under UV light and the structure of 2-aryl-3-cyanobenzofuran was indeed a new fluorophore. Because of the versatile uses of fluorescence in life and material sciences, we measured their photophysical properties. Results are summarized in Table S2.

The maximum absorption wavelength (λ_{max}) for **3a**−**g** in CH_2Cl_2 is about 320 nm with a molar absorption coefficient (ε) around 2.60×10^4. The substituent effect of the *para*-position of 2-phenyl is not apparent. It is observed that **3h** absorbs light at 357 nm ($\varepsilon = 2.64 \times 10^4$), while **3i** absorbs light at 301 nm ($\varepsilon = 0.56 \times 10^4$). The absorption behavior is largely dependent on the dihedral angle arising from benzofuran and the arene on 2-position of benzofuran. The smaller the dihedral angle is, the larger the maximum absorption wavelength and the higher molar absorption coefficient presents. Thus, the red-shifted absorption of **3h** could be ascribed to the planarization of the phenyl and benzofuran. Compound **3i**, possessing a larger dihedral angle (41.3°) due to the existence of the *o*-nitro group, absorbs light at 301 nm. A similar situation is observed for the pair of **3k** and **3l**. Compound **3l** absorbs light at a lower energy band with a higher molar absorption coefficient than **3k** does.

The substituent effect of the 5-position of benzofuran on the absorption spectra is not apparent. Compounds **3a**, **3n**, **3r**, and **3u** present similar absorption spectra. However, with Et_2N occupied on the 6-position of benzofuran, **3v** absorbs light at 386 nm ($\varepsilon = 1.93 \times 10^4$). In comparison with **3v**, **3w** absorbs light at a lower energy band (402 nm) because of pyridinyl group. A good electron push−pull system exists in the molecule of **3w**. For comparison, we synthesized **8** (Figure 3). With cyano substituted on the 3-position of benzofuran, absorption of **3v** is red-shifted in comparison with naked **8**. However, when the cyano group is replaced by amide, the conjugation is interupted. The dihedral angle for benzofuran and benzene in **7d** is calculated to be 21.7°. As a result, absorption of **7d** is blue-shifted in comparison with the absorption of **3v**.

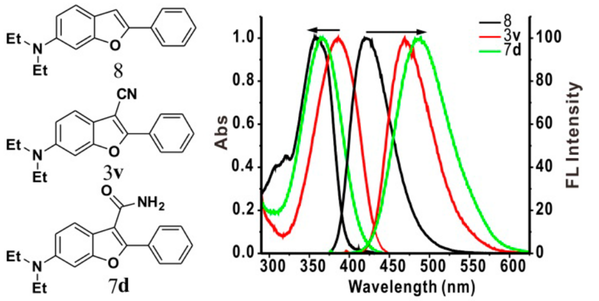


Figure 3. Absorption and emission spectra of **8**, **3v**, and **7d**.

Compounds **3a**−**g** emit bright light at about 370 nm with a Stokes shift about 50 nm. Their quantum yields are in a range from 41.0% to 88.2% except for **3f** ($\Phi = 23.9\%$). Compound **3c** shows a quantum yield of 88.2% because of the methoxy group. A relatively lower quantum yield is found for **3f** because of the bromine effect. Compounds **3h** and **3i** emit light at 392 and 374 nm with quantum yields of 0.2% and 8.0%, respectively. The low quantum yields could be ascribed to the nitro group. The largest Stokes shift (97 nm) is observed for **3k** in the family of 2-aryl-3-cyanobenzofurans. Compounds **3a**, **3n**, **3r**, and **3u** emit light about 365 nm with a Stokes shift about 50 nm. Quantum yields of **3a**, **3n**, **3r**, and **3u** are found to be 41.0%, 39.3%, 23.2%, and 2.3%, respectively. By installing Et_2N- on the 6-position of benzofuran, **3v** ($\Phi = 88.9\%$) shows the highest quantum yield in the family of 2-aryl-3-cyanobenzofurans. Emission spectra of **8**, **3v**, and **7d** are shown in Figure 3. Hydrolysis of cyano to amide led to blue-shifted absorption and red-shifted emission. As a result, **7d** presents the largest Stokes shift (125 nm).

Emission spectra depend on the solvent polarity. As a typical example, emission spectra of **3w** in different solvents are shown in Figure 4a. The maximum emission wavelength is gradually red-shifted when the solvent changes from cyclohexane (CH) to toluene (Tol), dioxane (DIO), THF, DCM, EtOH, MeCN, MeOH, and finally to DMSO. The color change under UV light (365 nm) is significant. As we can see from Figure 4c, the color changes from bright blue to light blue to green when solvent changes from CH to THF to DMSO. We also tested for the fluorescent variation when **3w** aggregates. In this case, aggregation caused by quenching (ACQ) is observed (Figure 4b). As the water fraction in THF solution increased, a gradually decreased fluorescent intensity was measured accompanied by a gradually red-shifted emission. When the ratio of water to THF

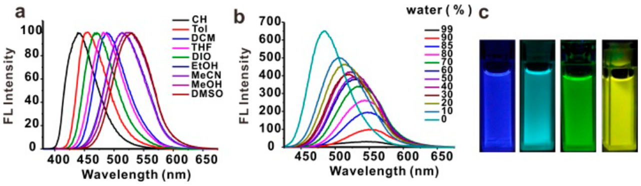


Figure 4. (a) Normalized emission spectra of **3w** in different solvents; (b) emission spectra of **3w** in different ratios of water in THF; (c) solution color of **3w** under UV light, from left to right: CH, THF, DMSO, H_2O/THF(85/15).

increased to 85 to 15, bright yellow emission of **3w** was seen under UV light (Figure 4c). A similar phenomenon is observed for compound **7e** (see the SI).

In conclusion, we have developed a green methodology for the preparation of 2-aryl-3-cyanobenzofurans by using *o*-hydroxybenzaldehydes and arylacetonitriles in the presence of copper acetate and sodium methoxide. Many substituents tolerate the reaction conditions and produce 2-aryl-3-cyanobenzofurans in moderate to good yields. The cascade process includes Knoevenagel condensation, cyanide anion transfer, intramolecular nucleophilic addition, and aromatization. Furthermore, 2-aryl-3-cyanobenzofurans are bright blue under UV irradiation. The highest quantum yield in dilute methylene chloride is determined to be 88.9%. Moreover, emission depends on the solvent polarity. When the solvent is changed from cyclohexane to THF and finally to DMSO, an emission color of **3w** is accordingly altered from bright blue to light blue and finally to green. It implies that compound **3w** might be used as a fluorescent probe for the detection of environmental variation, such as solvent polarity.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03704.

Detailed synthetic procedures and characterization data for all products (PDF)
UV−vis absorption and fluorescence spectra (PDF)
Crystallographic information for compound **3a** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: pinglu@zju.edu.cn.
*E-mail: orgwyg@zju.edu.cn.

Author Contributions

†L.Z. and Z.P. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the National Natural Science Foundation of China (Nos 21472173 and 21272203) for financial support.

■ REFERENCES

(1) (a) Halabalaki, M.; Aligiannis, N.; Papoutsi, Z.; Mitakou, S.; Moutsatsou, P.; Sekeris, C.; Skaltsounis, A.-L. *J. Nat. Prod.* **2000**, *63*, 1672. (b) Bakunova, S. M.; Bakunov, S. A.; Wenzler, T.; Barszcz, T.; Werbovetz, K. A.; Brun, R.; Hall, J. E.; Tidwell, R. R. *J. Med. Chem.* **2007**, *50*, 5807.

(2) Komori, N.; Jakkampudi, S.; Motoishi, R.; Abe, M.; Kamada, K.; Furukawa, K.; Katan, C.; Sawada, W.; Takahashi, N.; Kasai, H.; Xue, B.; Kobayashi, T. *Chem. Commun.* **2016**, *52*, 331.

(3) Maring, C. J.; Pratt, J. K.; Carroll, W. A.; Liu, D.; Betebenner, D. A.; Hutchinson, D. K.; Tufano, M. D.; Rockway, T. W.; Schoen, U.; Pahl, A.; Witte, A. WO 2012/087833, 2012.

(4) Okamoto, K.; Watanabe, M.; Murai, M.; Hatano, R.; Ohe, K. *Chem. Commun.* **2012**, *48*, 3127.

(5) Ding, S.; Jiao, N. *J. Am. Chem. Soc.* **2011**, *133*, 12374.

(6) Okitsu, T.; Nakazawa, D.; Taniguchi, R.; Wada, A. *Org. Lett.* **2008**, *10*, 4967.

(7) Swamy, N. K.; Yazici, A.; Pyne, S. G. *J. Org. Chem.* **2010**, *75*, 3412.

(8) Shchekotikhin, A. E.; Shevtsova, E. K.; Traven', V. F. *Russ. J. Org. Chem.* **2007**, *43*, 1686.

(9) Zhou, W.; Zhang, Y.; Li, P.; Wang, L. *Org. Biomol. Chem.* **2012**, *10*, 7184.

(10) Yuan, H.; Bi, K.-J.; Li, B.; Yue, R.-C.; Ye, J.; Shen, Y.-H.; Shan, L.; Sun, Y.; Zhang, W.-D. *Org. Lett.* **2013**, *15*, 4742.

(11) Liang, Z.; Hou, W.; Du, Y.; Zhang, Y.; Pan, Y.; Mao, D.; Zhao, K. *Org. Lett.* **2009**, *11*, 4978.

(12) Chen, C.; Dormer, P. G. *J. Org. Chem.* **2005**, *70*, 6964.

(13) Nematollahi, D.; Atlasi-Pak, A. R.; Esmaili, R. *Helv. Chim. Acta* **2012**, *95*, 1605.

(14) Huang, X.-C.; Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Wang, F.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1525.

(15) X-ray crystal structure of **3a**, which is numbered CCDC 1438893, is available from the Cambridge Crystallographic Data Centre.

(16) MacMillan, K. S.; Nguyen, T.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 1187.

(17) (a) Jin, J.; Wen, Q.; Lu, P.; Wang, Y. *Chem. Commun.* **2012**, *48*, 9933. (b) Wen, Q.; Jin, J.; Mei, Y.; Lu, P.; Wang, Y. *Eur. J. Org. Chem.* **2013**, *2013*, 4032.

(18) (a) Kim, J.; Choi, J.; Shin, K.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 2528. (b) Pawar, A. B.; Chang, S. *Chem. Commun.* **2014**, *50*, 448. (c) Zhang, L.; Lu, P.; Wang, Y. *Chem. Commun.* **2015**, *51*, 2840.

(19) Chapas, R. B.; Nystrom, R. F.; Snyder, H. R. *J. Org. Chem.* **1972**, *37*, 314.