Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthesis of 4-Ynamides and Cyclization by the Vilsmeier Reagent to Dihydrofuran-2(3*H*)-ones

Zhaocheng Zhang,[‡] Rapolu Kiran Kumar,[†] Guangzhi Li,[‡] Dongmei Wu,*[,‡] and Xihe Bi*[,†,‡,§]

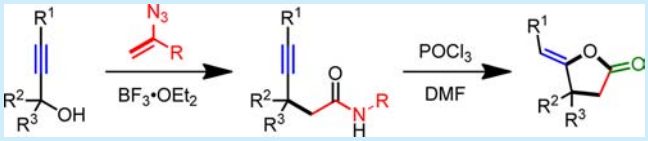
[†]Department of Chemistry, Northeast Normal University, Changchun 130024, China

[‡]College of Pharmacy, Jiamusi University, Jiamusi 154007, China

[§]State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

Supporting Information

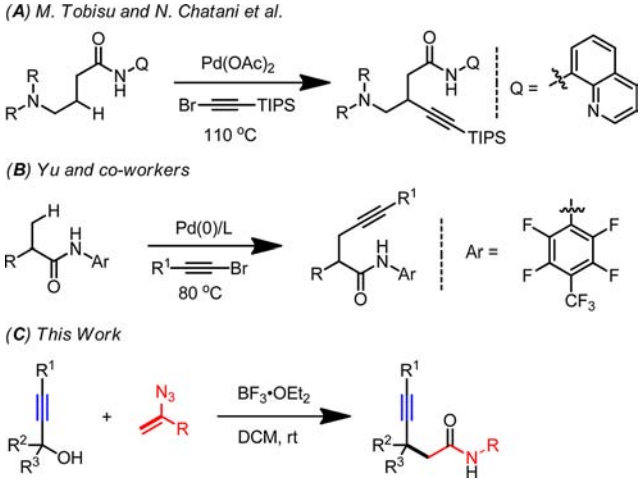
ABSTRACT: The room-temperature nucleophilic addition of vinyl azides to propargylic alcohols under $BF_3{\cdot}Et_2O$ catalysis provides an efficient synthesis of 4-ynamides. The procedure is operationally convenient, shows broad substrate scope, and is viable for the synthesis of multifunctional 4-ynamides. Further, a Vilsmeier intramolecular cyclization of 4-ynamides into dihydrofuran-2(3*H*)-ones has also been discovered, which represents the first report of alkynes being used as the nucleophiles in Vilsmeier-type reactions.



Ynamides are multifunctionable synthetic building blocks that can provide access to important structural motifs found in natural products and molecules of medicinal interest. One can modulate the electronic properties and reactivity of ynamides through structural modification and the selection of specific reaction conditions.[1] 4-Ynamides are one such type of structurally altered derivative. Worthy features of 4-ynamides are the increased flexible nature of their C≡C bond and amide group toward cycloaddition, inter/intramolecular cyclization, addition, and metathesis reactions.[2] More importantly, the 4-ynamide moiety can be found in biologically active molecules.[3]

Although classical multistep and recently reported synthetic methods are available,[4] methods which are convenient to access multifunctional 4-ynamides remain elusive. So far, two methods of $C(sp^3)-H$ activation have proven useful for providing convenient access to 4-ynamides. For example, Chatani et al. in 2011 reported a synthesis of 4-ynamides via quinoline-directed Pd(II)-catalyzed $C(sp^3)-H$ β-activation of aliphatic amides, effecting a subsequent coupling with alkynyl halides (Scheme 1, eq A).[5] Later in 2013, Yu and co-workers also reported $C(sp^3)-H$ β-activation of specially designed aliphatic amides, performing alkynylations using a Pd(0)/NHC carbene and $Pd(0)/PR_3$ catalyst system (Scheme 1, eq B).[6] Nevertheless, these two methods have some noteworthy limitations such as not being applicable to the synthesis of 4-ynamides with multiple substituent groups at the propargylic position and the need for special structural alignment for alkynylation. Other drawbacks include the use of expensive palladium catalysts, high reaction temperatures, multistep synthesized starting materials, and the inability to synthesize 4-ynamides with substituent groups at the amide and the alkyne terminal positions. Therefore, the development of an operationally convenient protocol for the synthesis of substituted 4-ynamides would indeed be significant.

Scheme 1. Coupling Reactions for the Synthesis of 4-Ynamides



While continuing research investigations in to the use of propargylic alcohols for a variety of novel reactions,[7] we recently reported a practical Ag(I)-catalyzed hydroazidation of terminal alkynes to establish a quite convenient method for the synthesis of diverse vinyl azides.[7a,8] A report by the Chiba group,[9] in which vinyl azides are used as enamine-type nucleophiles for $BF_3{\cdot}Et_2O$-promoted addition reactions to carbon electrophiles, led us to envision using propargylic alcohols as electrophile partners for the synthesis of 4-ynamides (Scheme 1, eq C). The convenient features of our protocol over the aforementioned $BF_3{\cdot}Et_2O$-mediated nucleophilic addition of vinyl azides to carbon electrophiles[9] are the use

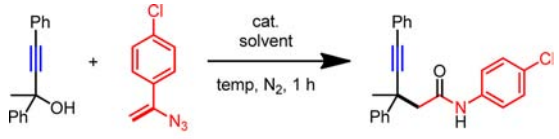
Received: November 4, 2015
Published: December 9, 2015

DOI: 10.1021/acs.orglett.5b03189
Org. Lett. 2015, 17, 6190−6193

of a catalytic quantity of $BF_3{\cdot}Et_2O$, thereby obviating the need for the slow addition of $BF_3{\cdot}Et_2O$ to the reaction mixture and avoiding the decomposition of the vinyl azides. While preparing this manuscript, another report appeared from the Chiba research group announcing the coupling of 3-hydroxy-3-indolyloxindoles with vinyl azides. It described one example of the coupling of propargylic alcohol and vinyl azide to synthesize a 4-ynamide, but it worked under triflimide (Tf_2NH) catalysis.[10]

To check our assumption, 1-(1-azidovinyl)-4-chlorobenzene (**2a**) was synthesized from *p*-chlorophenylacetylene according to our previous report of Ag(I)-catalyzed hydroazidation of terminal alkynes.[11] When a trial reaction was performed with 2,4-diphenylbut-3-yn-2-ol (**1a**) (1.0 mmol) and vinyl azide **2a** (0.5 mmol) in CH_2Cl_2 (3.0 mL) as solvent at −40 °C under N_2 atmosphere, in the presence of $BF_3{\cdot}Et_2O$ (2.0 equiv), the target 4-ynamide **3aa** was obtained in 60% isolated yield (Table 1, entry 1). Later, careful optimization of reaction conditions (entries 2−7) not only increased the yield of **3aa** to 83% yield but also allowed the successful use of a catalytic quantity of $BF_3{\cdot}Et_2O$ (30 mol %) at ambient temperature (entry 3).

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3aa**

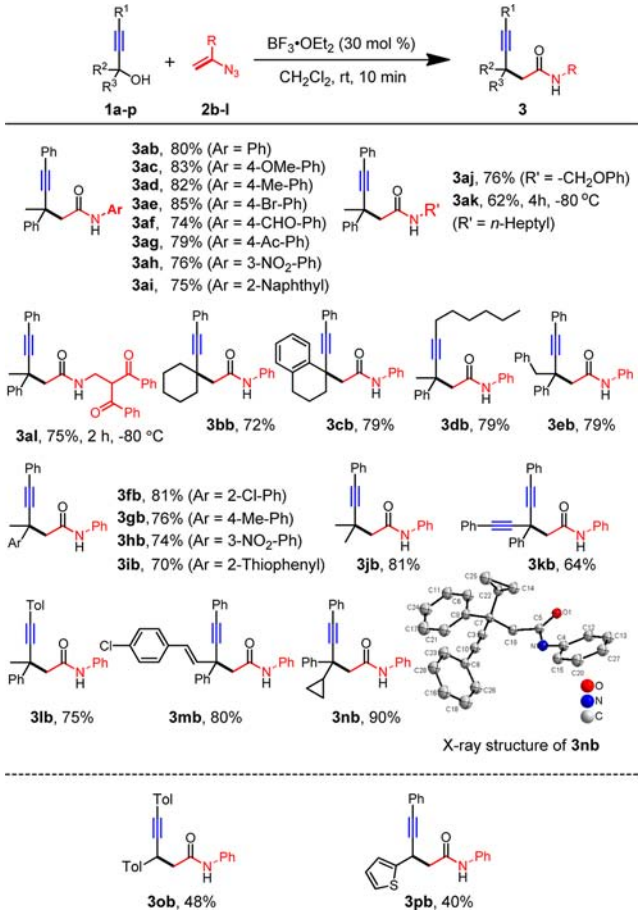
entry	catalyst	mol %	temp (°C)	solvent	**3aa** (%)[b]
1	$BF_3{\cdot}OEt_2$	200	−40	CH_2Cl_2	60
2	$BF_3{\cdot}OEt_2$	200	25	CH_2Cl_2	74
3	**$BF_3{\cdot}OEt_2$**	**30** (10)[c]	**25**	**CH_2Cl_2**	**83** (40)[c]
4	$BF_3{\cdot}OEt_2$	30	25	1,4-dioxane	65
5	$BF_3{\cdot}OEt_2$	30	25	DCE	75
6	$FeCl_3$	30	25	CH_2Cl_2	58
7	TFA	30	25	CH_2Cl_2	43

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), and the catalyst in solvent (3.0 mL) for 1 h under N_2 atmosphere. [b]Yield of **3aa** isolated. [c]Reaction with 10 mol % $BF_3{\cdot}Et_2O$.

Later, the optimized conditions (Table 1, entry 3) were applied for the coupling of 2,4-diphenylbut-3-yn-2-ol (**1a**) with divergent vinyl azides (**2b−l**) (Scheme 2). It was found that **1a** smoothly reacted with 1-azidovinylbenzene (**2b**) and vinyl azides bearing a phenyl ring with electron-donating (**2c,d**) or electron-withdrawing groups (**2e−h**), and with 2-(1-azidovinyl)naphthalene (**2i**) to afford the corresponding 4-ynamides (**3ab−ai**) in 74−85% isolated yields. Aliphatic vinyl azides such as ((2-azidoallyl)oxy)benzene (**2j**), 2-azidonon-1-ene (**2k**), and 2-(2-azidoallyl)-1,3-diphenylpropane-1,3-dione (**2l**) also successfully participated in the reaction to afford corresponding 4-ynamides (**3aj−al**) in 62−76% isolated yields. These results clearly indicated that the propargylic alcohol (**1a**) underwent reaction with all the vinyl azides regardless of their electronic nature, thereby affording a broad scope of multi-substituted 4-ynamides.

Next, we assessed the potential of the protocol in the case of other propargylic alcohols **1b−n** and 1-azidovinylbenzene (**2b**). The 4-ynamides with a quaternary propargylic carbon atom, which were not accessible by previous methods (Scheme 1, eqs A and B), were synthesized using the present protocol. For

Scheme 2. Scope of the Protocol for Various Propargylic Alcohols and Vinyl Azides[a,b]



[a]Reaction conditions: **1a−p** (1.0 mmol), **2b−l** (0.5 mmol), and $BF_3{\cdot}Et_2O$ (30 mol %) in DCM (3.0 mL) as solvent at rt for 10 min under N_2 atmosphere. [b]Yields of isolated products.

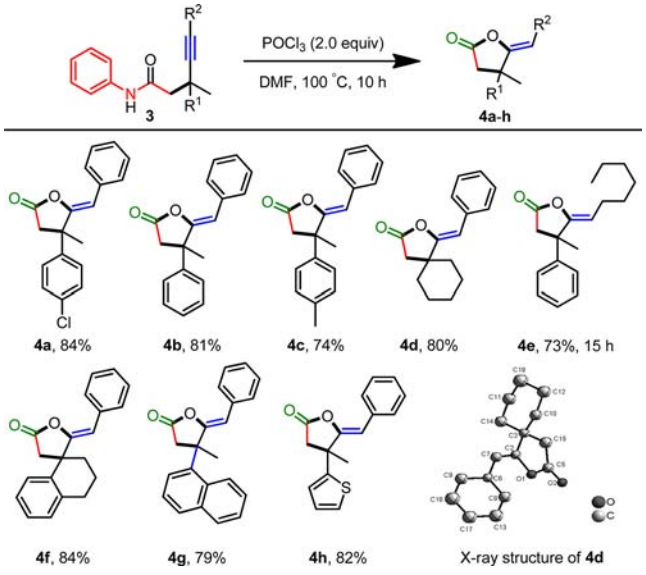
example, propargylic alcohols **1b** and **1c** with a cyclohexyl and a tetrahydronaphthalene moiety at the propargylic position underwent the target reaction without any difficulty, leading to formation of 4-ynamides **3bb** in 72% and **3cb** in 79% yields. The propargylic alcohol **1d** with an *n*-hexyl chain at the other end of the C≡C triple bond gave **3db** in 79% yield. Likewise, the reaction with propargylic alcohol **1e** was also completed quickly within 10 min and led to the formation of **3eb** in 79% yield. Further, it was found that the propargylic alcohols **1f−i**, in which the propargylic position was substituted with a variety of aryl moieties with varying electronic densities, and propargylic alcohol **1j**, with two methyl moieties, all smoothly reacted with 1-azidovinylbenzene (**2b**) to afford the corresponding 4-ynamides **3fb−ib** and **3jb** in 70−81% and 81% yields, respectively. Likewise, 1,3-diphenylprop-2-yn-1-ols with alkynyl (**1k**), methyl (**1l**), alkenyl (**1m**), and cyclopropyl (**1n**) moieties at the propargylic position afforded the substituted 4-ynamides **3kb−nb** in 64−90% yields. The structure of **3nb** is confirmed by X-ray diffraction of its single crystal (see the Supporting Information for details). These results highlight the potential utility of the protocol without affecting other substituent groups in the propargylic alcohols. We also checked the scope of the protocol toward secondary propargylic alcohols. Both the symmetrical propargylic alcohol **1o** and unsymmetrical propargylic alcohol **1p** smoothly reacted with 1-

DOI: 10.1021/acs.orglett.5b03189
Org. Lett. 2015, 17, 6190−6193

azidovinylbenzene (**2b**) under the optimal conditions (BF_3·Et_2O (30 mol %)) in DCM in a manner similar to tertiary propargylic alcohols to afford the corresponding 4-ynamides **3ob** and **3pb** but with a slight decrease in yield to 48% and 40%, respectively.

To prove the resulting 4-ynamide products can serve as versatile reagents, we thought of converting the 4-ynamides into other chemical assets. A literature survey[12,13] disclosed the use of Vilsmeier reagent for the functionalization of the −CONH− moiety[12,13a] and/or intramolecular cyclization reactions,[13] and our research experience on ynamides[14] motivated us to investigate the possibility of using a Vilsmeier ($POCl_3$/DMF) mediated intramolecular cyclization. When the 4-ynamides (**3**) (0.30 mmol) were allowed to react with $POCl_3$ (0.6 mmol) in DMF at 100 °C for 10 h under air atmosphere, an unexpected intramolecular cyclization was discovered, leading to the formation of (*Z*)-5-alkylidene-dihydrofuran-2(3*H*)-ones (**4a**−**h**) in 73−84% yields (Scheme 3).[15] The

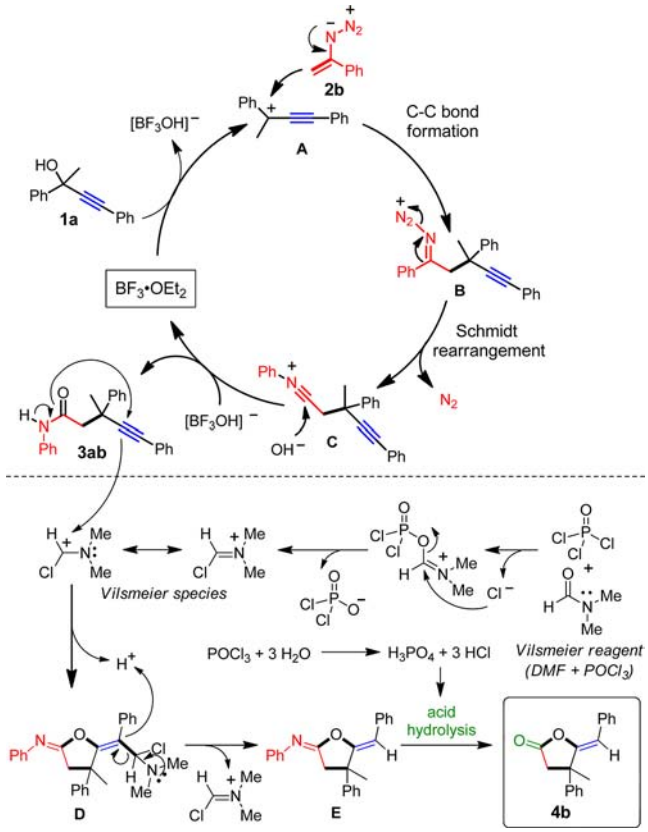
Scheme 3. Vilsmeier Reagent Promoted Intramolecular Cyclization of 4-Ynamides



stereospecific formation of (*Z*)-dihydrofuran-2(3*H*)-ones rather than (*E*)-dihydrofuran-2(3*H*)-ones might be the steric hindrance at the 4-position of dihydrofuran-2(3*H*)-ones (**4**). To the best of our knowledge, this is the first example of alkynes acting as the nucleophiles in a Vilsmeier-type reaction. Note that the dihydrofuran-2(3*H*)-ones are much sought after heterocyclic compounds with significant biological activities,[16] and we have provided a new and practical route to this kind of important heterocyclic framework.

According to literature reports and our investigation results, a plausible mechanism for the reaction of vinyl azides[9] with propargylic alcohols for the formation of 4-ynamides[10] and the subsequent intramolecular cyclization with the Vilsmeier reagent[12,13] is proposed (Scheme 4). First, initiation of the reaction by the electrophilic attack of BF_3·Et_2O on the −OH group of propargylic alcohol (**1a**) facilitates formation of the propargylic carbocation intermediate **A**, which instigates the nucleophilic addition of vinyl azide (**2b**) to afford intermediate **B**. This intermediate **B** subsequently undergoes Schmidt rearrangement[17] to form the nitrilium intermediate **C**. The yields of 4-ynamides (**3**) imply that the electron-rich aryl rings

Scheme 4. Proposed Mechanism



are more favorable for the Schmidt rearrangement than the electron-poor aryl rings and aliphatic moieties. The nitrilium intermediate **C** then immediately extracts −OH[9] from the $[BF_3OH]^-$ anion and rearranges to the final product **3ab**. Meanwhile, the catalyst BF_3·Et_2O is regenerated by the elimination of hydroxyl anion, thereby completing the catalytic cycle. The Vilsmeier reagent mediated intramolecular cyclization involves the generation of a resonance-stabilized Vilsmeier species (immonium chloride/chloromethylium salt) from the Vilsmeier reagent (DMF and $POCl_3$).[13] A tandem nucleophilic attack of 4-ynamide upon the Vilsmeier species then occurs.[13a] An active Vilsmeier intermediate was further supported because no **4b** was obtained when the reaction was performed in toluene instead of DMF. Liberation of the Vilsmeier species by the displacement with proton generates **E**, a latent dihydrofuran-2(3*H*)-one. Acid hydrolytic cleavage of the Schiff's base affords the dihydrofuran-2(3*H*)-one **4b** as the final product.

In summary, we have developed convenient protocol for the synthesis of diverse functionalized 4-ynamides from the easily available propargylic alcohols and vinyl azides using BF_3·Et_2O catalysis. Functional group tolerance, wide substrate scope, and applicability in the synthesis of natural product based 4-ynamides are additional advantages of the protocol. We further discovered a novel cyclization of these readily prepared compounds using the Vilsmeier reagent, thereby converting 4-ynamides into biologically important dihydrofuran-2(3*H*)-ones in good yields. This unprecedented application undoubtedly opens new horizons in the Vilsmeier reaction. In addition, both of the 4-ynamides and dihydrofuran-2(3*H*)-ones can serve as vital synthons in organic synthesis.

DOI: 10.1021/acs.orglett.5b03189
Org. Lett. 2015, 17, 6190−6193

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03189.

Experimental procedures and spectra copies (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

* E-Mail: wudmei67@163.com.
* E-Mail: bixh507@nenu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NSFC (21172029, 21202016, 21372038), the Ministry of Education of the People's Republic of China (NCET-13-0714), the Jilin Provincial Research Foundation for Basic Research (20140519008JH), the Fundamental Research Funds for the Central Universities (2412015BJ005), and Excellent Young Scientist of NSFC (21522202).

■ REFERENCES

(1) For recent reviews on ynamides, see: (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840.

(2) For reactions of 4-ynamides, see: (a) Momiyama, N.; Kanan, M. W.; Liu, D. R. *J. Am. Chem. Soc.* **2007**, *129*, 2230. (b) Espinosa-Jalapa, N. Á.; Ke, D.; Nebra, N.; Le Goanvic, L.; Mallet-Ladeira, S.; Monot, J.; Martin-Vaca, B.; Bourissou, D. *ACS Catal.* **2014**, *4*, 3605. (c) Tellitu, I.; Serna, S.; Herrero, M. T.; Moreno, I.; Domínguez, E.; SanMartin, R. *J. Org. Chem.* **2007**, *72*, 1526. (d) Zhou, Y.; Feng, E.; Liu, G.; Ye, D.; Li, J.; Jiang, H.; Liu, H. *J. Org. Chem.* **2009**, *74*, 7344. (e) Grammatikopoulou, M.; Thysiadis, S.; Sarli, V. *Org. Biomol. Chem.* **2015**, *13*, 1169. (f) Chiou, W.-H.; Lin, Y.-H.; Chen, G.-T.; Gao, Y.-K.; Tseng, Y.-C.; Kao, C.-L.; Tsai, J.-C. *Chem. Commun.* **2011**, *47*, 3562. (g) Fadel, S.; Hajbi, Y.; Khouili, M.; Lazar, S.; Suzenet, F.; Guillaumet, G. *Beilstein J. Org. Chem.* **2014**, *10*, 282.

(3) Lee, S.; Nam, Y.; Koo, J. Y.; Lim, D.; Park, J.; Ock, J.; Kim, J.; Suk, K.; Park, S. B. *Nat. Chem. Biol.* **2014**, *10*, 1055.

(4) (a) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2006**, *128*, 6499. (b) Feng, C.; Feng, D.; Luo, Y.; Loh, T.-P. *Org. Lett.* **2014**, *16*, 5956. (c) Cheng, D.; Ling, F.; Li, Z.; Yao, W.; Ma, C. *Org. Lett.* **2012**, *14*, 3146. (d) Ito, J.-i.; Fujii, K.; Nishiyama, H. *Chem. - Eur. J.* **2013**, *19*, 601.

(5) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984.

(6) He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387.

(7) (a) Liu, Z.; Liu, J.; Zhang, L.; Liao, P.; Song, J.; Bi, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 5305. (b) Fang, Z.; Liu, J.; Liu, Q.; Bi, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 7209. (c) Liu, J.; Liu, Z.; Liao, P.; Bi, X. *Org. Lett.* **2014**, *16*, 6204. (d) Liu, Z.; Liao, P.; Bi, X. *Chem. - Eur. J.* **2014**, *20*, 17277. (e) Liu, J.; Liu, Z.; Wu, N.; Liao, P.; Bi, X. *Chem. - Eur. J.* **2014**, *20*, 2154. (f) Meng, X.; Liao, P.; Liu, J.; Bi, X. *Chem. Commun.* **2014**, *50*, 11837.

(8) Ning, Y.; Wu, N.; Yu, H.; Liao, P.; Li, X.; Bi, X. *Org. Lett.* **2015**, *17*, 2198.

(9) Zhang, F.-L.; Wang, Y.-F.; Lonca, G. H.; Zhu, X.; Chiba, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 4390.

(10) Zhang, F.-L.; Zhu, X.; Chiba, S. *Org. Lett.* **2015**, *17*, 3138.

(11) Liu, Z.; Liao, P.; Bi, X. *Org. Lett.* **2014**, *16*, 3668.

(12) Rajput, A. P.; Girase, P. D. *IJPCBS* **2013**, *3*, 25.

(13) (a) Wuts, P. G. M.; Northuis, J. M.; Kwan, T. A. *J. Org. Chem.* **2000**, *65*, 9223. (b) Barrett, A. G. M.; Braddock, D. C.; James, R. A.; Koike, N.; Procopiou, P. A. *J. Org. Chem.* **1998**, *63*, 6273. (c) Wang, K.; Xiang, D.; Liu, J.; Pan, W.; Dong, D. *Org. Lett.* **2008**, *10*, 1691.

(14) Xu, S.; Liu, J.; Hu, D.; Bi, X. *Green Chem.* **2015**, *17*, 184.

(15) (a) Ahmar, S.; Fillion, E. *Org. Lett.* **2014**, *16*, 5748. (b) Sun, C.; Fang, Y.; Li, S.; Zhang, Y.; Zhao, Q.; Zhu, S.; Li, C. *Org. Lett.* **2009**, *11*, 4084. (c) Li, S.; Jia, W.; Jiao, N. *Adv. Synth. Catal.* **2009**, *351*, 569. (d) Nagendiran, A.; Verho, O.; Haller, C.; Johnston, E. V.; Backvall, J.-E. *J. Org. Chem.* **2014**, *79*, 1399. (e) Nebra, N.; Monot, J.; Shaw, R.; Martin-Vaca, B.; Bourissou, D. *ACS Catal.* **2013**, *3*, 2930.

(16) Jia, W.; Li, S.; Yu, M.; Chen, W.; Jiao, N. *Tetrahedron Lett.* **2009**, *50*, 5406.

(17) (a) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (b) Schmidt, K. F. Z. *Angew. Chem.* **1923**, *36*, 511. (c) Schmidt, K. F. Z. *Ber. Dtsch. Chem. Ges. B* **1924**, *57*, 704.

DOI: 10.1021/acs.orglett.5b03189
Org. Lett. 2015, 17, 6190−6193