Organic LETTERS

Letter

pubs.acs.org/OrgLett

Unactivated C(sp^3)−H Bond Functionalization of Alkyl Nitriles with Vinylarenes and Mechanistic Studies

Xing-Wang Lan,[†] Nai-Xing Wang,*[,†] Cui-Bing Bai,[†] Cui-Lan Lan,[‡] Tong Zhang,[†] Shi-Lu Chen,*[,‡] and Yalan Xing*[,§]

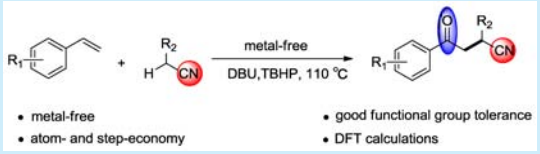
[†]Technical Institute of Physics and Chemistry & University of Chinese Academy of Sciences, Chinese Academy of Sciences, Beijing, 100190, China

[‡]School of Chemistry, Beijing Institute of Technology, Beijing 100081, China

[§]Department of Chemistry, William Paterson University of New Jersey, 300 Pompton Road, Wayne, New Jersey 07470, United States

Supporting Information

ABSTRACT: The first example of a metal-free unactivated C(sp^3)−H bond functionalization of alkyl nitriles with terminal vinylarenes to provide γ-ketonitrile derivatives is described. This protocol features simple operations, a broad substrate scope, and atom and step economy. In addition, Cu-catalyzed C(sp^3)−H bond functionalization of azodiisobutyronitrile (AIBN) and analogues with terminal vinylarenes to generate γ-ketonitriles was also studied. A preliminary free-radical pathway was confirmed by capturing an alkyl radical, and a conjugate system was found that can stabilize radical intermediates and be in favor of this transformation. Density functional theory (DFT) calculations also provide important evidence of the free-radical pathway.

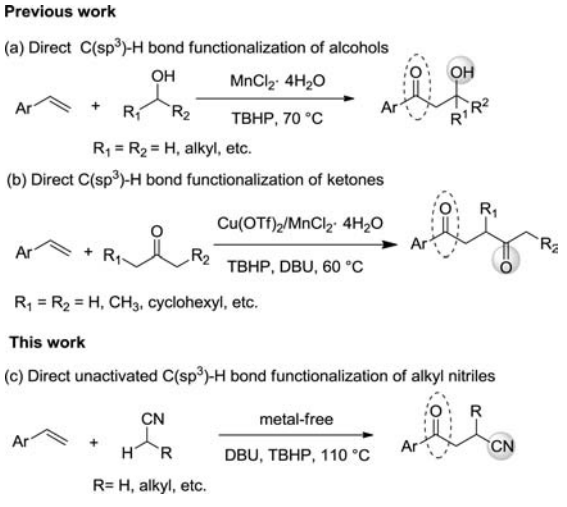


The direct oxidative coupling methodology involving the C−H bond functionalization has attracted much attention due to its step economy and energy efficiency.[1] In this context, using simple alkenes containing ubiquitous functional groups to introduce both a carbonyl group and another functional group has been extensively studied recently.[2] Despite the impressive achievements in this field, direct functionalization of molecules containing C(sp^3)−H bonds is much more challenging because of its high bond-dissociation energy (BDE).[3] Great efforts have been made on terminal alkenes efficiently transferring into complex organic molecules through C(sp^3)−H bond functionalization. For example, Zhang and co-workers[2a] reported the C(sp^3)−H bond functionalization of cyclic ethers with terminal alkenes by copper catalysis. Li and co-workers[2d] reported an example of C(sp^3)−H bond functionalization of amides with terminal alkenes for selective synthesis of β-amino ketones and α,β-unsaturated amides. Certainly, there are still tremendous research opportunities to develop new methods using unactivated alkenes with simple reagents.

Nitriles are among the most versatile scaffolds and can serve as precursors for aldehydes, amides, nitrogen-containing heterocycles and carboxylic acids, etc.[4] In particular, ketonitriles have served as a key unit in the synthesis of various pharmaceuticals and bioactive compounds.[5] Directly C−H activation to incorporate nitriles groups represents one of the most efficient and economic strategies for the synthesis of substituted nitrile compounds. In fact, the addition of nitriles, especially simple alkyl nitriles, to alkenes via a radical process has been rarely investigated due to its enolate formation. Only a few examples have been reported by Liu,[6] You,[7] Liu,[8] Ji,[9,10] Tang,[11] Zhu,[12] etc. involving direct oxidative cyanomethylation reactions by incorporating the alkyl nitriles with alkenes.

In order to realize the high-value transformation of styrenes, our group developed C(sp^3)−H bond functionalization of alcohols with terminal vinylarenes to provide complex products in one step (Scheme 1a).[2i] The reaction features use of simple reagents, mild conditions, and good functional group tolerance. In the same year, we also developed a copper/manganese dual catalyst which cocatalyzed the direct unactivated C(sp^3)−H bond functionalization of ketones with terminal vinylarenes to

Scheme 1. Direct C(sp^3)−H Bond Functionalization of Simple Reagents with Vinylarenes



Received: September 7, 2016
Published: November 11, 2016

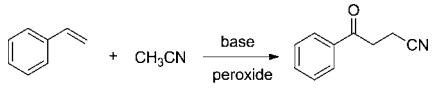
DOI: 10.1021/acs.orglett.6b02692
Org. Lett. 2016, 18, 5986−5989

construct dicarbonyl compounds with good regioselectivity and functional group tolerance (Scheme 1b).[2j] This protocol afforded an excellent strategy for the synthesis of complex dicarbonyl compounds only using simple reagents and mild conditions. As part of our efforts on the development of direct unactivated C(sp^3)−H bond functionalization, we envisage whether unactivated C(sp^3)−H bond functionalization of alkyl nitriles with terminal vinylarenes to synthesize high-value γ-ketonitriles can be realized. Herein, we describe a metal-free catalyzed unactivated C(sp^3)−H bond functionalization of alkyl nitriles with terminal vinylarenes to construct γ-ketonitriles (Scheme 1c), which is convenient and economical, shows a broad substrate scope, and exhibits good functional group tolerance. To the best of our knowledge, this is the first report of γ-ketonitrile preparation through direct unactivated C(sp^3)−H bond functionalization of alkyl nitriles in one pot. Both of the two previous reactions involve the free-radical pathway, but a preliminary mechanism was just proposed. In this paper, by means of radical trapping experiments, nonconjugate substrates, and a competing kinetic isotope effect, a free radical mechanism of this transformation is confirmed. Finally, density functional theory (DFT) calculations were performed to further verify the mechanism.

We commenced our investigations with styrene (**1a**) and acetonitrile (**2a**) (both as reactant and solvent) as model substrates in the presence of base and peroxide, with the results shown in Table 1. Initially, we explored the cage effect[8] of solvent (Table 1, entries 1−4). It was found that 6 mL of acetonitrile were optimal and a 70% yield of the γ-ketonitrile **3a** was achieved in the presence of 1 equiv of DBU and 4 equiv of TBHP. Encouraged by the result, a series of bases were examined, but DBU was found to be the most efficient base (entry 3 vs entries 5−9). Subsequently, we screened the peroxides, finding that TBHP exhibited the best effect, while other peroxides had poor or no activity at all (entries 3 and 10 vs entries 11−13). After varying the amount of base and peroxide, the yield was not further improved (entries 14−16). Prolonging the reaction time to 48 h improved the yield to only 72%. Notably, when the reaction was performed without DBU or TBHP, no desired product was obtained, revealing that using a base and peroxide is critical for this transformation.

With the optimal conditions in hand, the substrate scope of the oxidative coupling reaction was investigated (Scheme 2). As shown in Scheme 2, not only electron-donating groups, such as tertiary butyl (**3b**), methyl (**3c**), and methoxyl (**3d**), but also electron-withdrawing groups, such as halogen (F, Cl, Br) (**3e−g**) and cyano (**3h**) on the phenyl ring of the styrene at the *para*-position, could smoothly undergo the reaction, achieving moderate to good yields, which indicated the electronic effect was not an important factor. Exceptionally, only a trace amount of product (**3i**) was generated using *p*-nitryl styrene as th esubstrate; we speculated the strong electron-withdrawing group on the phenyl ring inhibited this transformation. In addition, substituted groups on the phenyl ring of styrene at the *meta*- and *ortho*-position gave less or no yield of the corresponding products (**3j−3o**). The reactivity of *para*-, *meta*-, and *ortho*-cholor-substituted styrenes was as follows: *para* > *meta* > *ortho*, suggesting the position of the substituents impacted the reaction. Thus, the steric effect was thought to be a more crucial factor to this reaction. In addition, the *p*-chloromethyl substituted styrene and 2-vinyl naphthalene were tolerated in this transformation, forming the corresponding products in 24% (**3p**) and 60% (**3q**) yield, respectively. Afterward, valeronitrile and ethyl 2-cyanoacetate as substrates (also as solvent) with styrene were also tested, but poor

Table 1. Modification of the Reaction Conditions[a]

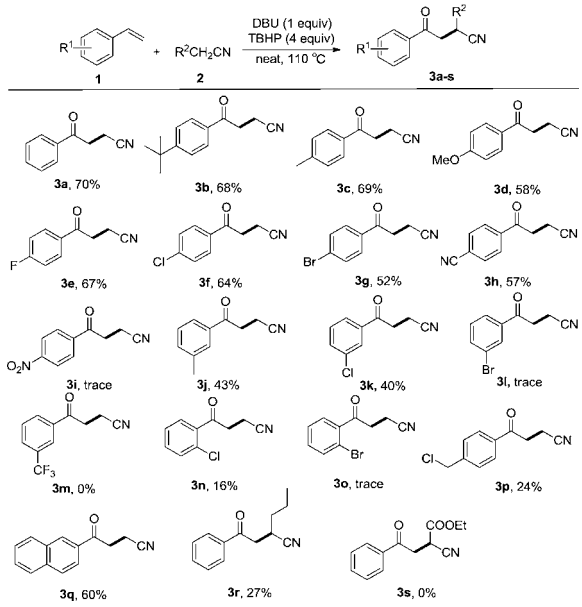


1a 2a 3a

entry	base (equiv)	peroxide (equiv)	solvent (mL)	yield (%)[b]
1	DBU(1)	TBHP (4)	2	23
2	DBU (1)	TBHP (4)	4	57
3	DBU (1)	TBHP (4)	6	70
4	DBU (1)	TBHP (4)	8	61
5	DABCO (1)	TBHP (4)	6	32
6	Et_3N (1)	TBHP (4)	6	29
7	*t*-BuOK (1)	TBHP (4)	6	53
8	K_2CO_3 (1)	TBHP (4)	6	24
9	NaOH(1)	TBHP (4)	6	trace
10[c]	DBU (1)	TBHP (4)	6	63
11	DBU (1)	$K_2S_2O_8$ (4)	6	13
12	DBU (1)	DTBP (4)	6	0
13	DBU (1)	BPO (4)	6	20
14	DBU (0.5)	TBHP (4)	6	42
15	DBU (2)	TBHP (4)	6	65
16	DBU (1)	TBHP (2)	6	45
17[d]	DBU (1)	TBHP (4)	6	70
18[e]	DBU (1)	TBHP (4)	6	18
19[f]	DBU (1)	TBHP (4)	6	72
20	–	TBHP (4)	6	0
21	DBU (1)	–	6	0

[a]Reaction condition: styrene **1a** (1 equiv, 0.2 mmol), acetonitrile **2a** as solvent, base, TBHP (5.5 M in decane) in sealed tube at 110 °C for 24 h, unless otherwise noted. [b]Isolated yields. [c]TBHP (70% in water). [d]3 Å MS, 300 mg. [e]80 °C. [f]48 h.

Scheme 2. Substrate Scope for Reaction of Vinylarenes with Nitriles[a]



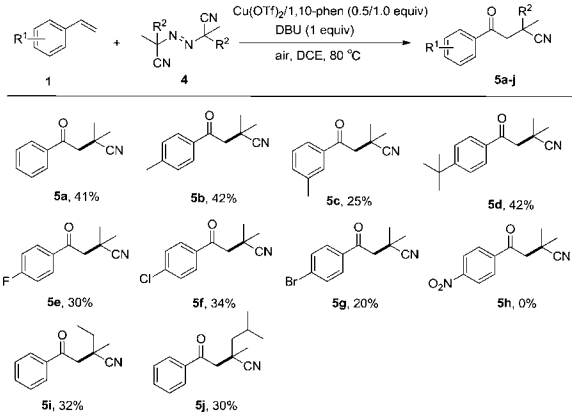
[a]Reaction conditions: vinylarenes (1 equiv, 0.2 mmol), alkyl nitriles (6 mL) as solvent, DBU (1 equiv), TBHP (5.5 M in decane, 4 equiv) in sealed tube at 110 °C for 24 h, unless otherwise noted; yields of the isolated products.

DOI: 10.1021/acs.orglett.6b02692
Org. Lett. 2016, 18, 5986−5989

or no yield was afforded; we speculated that the solvent and cage effects inhibited this transformation.

Considering that azodiisobutyronitrile (AIBN) and its analogues, which are commercially available, can easily form a tertiary radical containing a cyano group, we turned our attention to the coupling of terminal vinylarenes with AIBN and its analogues to construct γ-ketonitriles via a radical process. Initial studies on reaction conditions revealed that this transformation differed from the reaction of vinylarenes with acetonitrile. Thus, we further explored the reaction conditions by employing a transition metal to promote this transformation. After screening a series of catalytic systems, we found that $Cu(OTf)_2$/1,10-phen/DBU in DCE under air was the optimal condition for this reaction (see Supporting Information (SI), Table S1). Under the optimal reaction conditions, the substrate scope of this reaction was investigated (Scheme 3). Styrene with an electron-donating (*p*-

Scheme 3. Substrate Scope for Reaction of Vinylarenes with AIBN and Analogues[a]

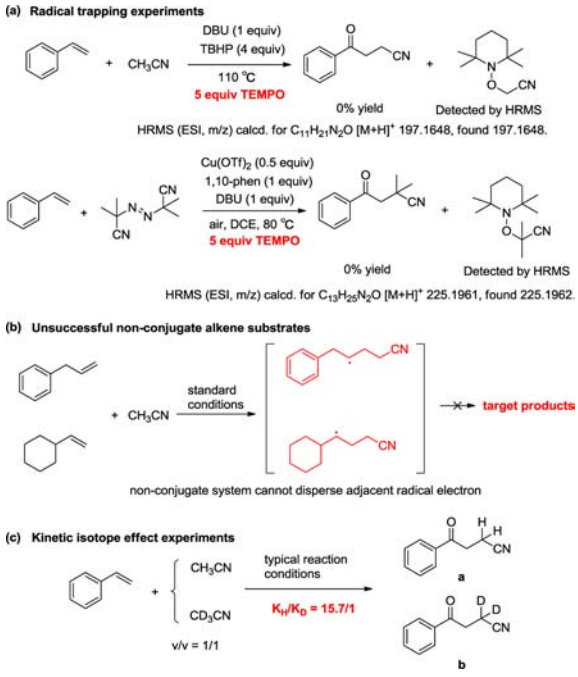


[a]Reaction conditions: vinylarenes (0.3 mmol, 1 equiv), AIBN or analogues (0.6 mmol, 2 equiv), $Cu(OTf)_2$ (0.5 equiv), 1,10-phen (1 equiv), DBU (1 equiv) and DCE (3 mL) at 80 °C under air for 24 h; yields of the isolated products.

methyl, *m*-methyl, *p*-tertiary butyl) and electron-withdrawing (*p*-halide) substituents provided the corresponding products in moderate yields, but *p*-nitryl styrene still afforded no corresponding product. Similarly, the diazo analogues with styrene also smoothly formed the corresponding product **5i** and **5j**, respectively.

To gain insight into the mechanism, some mechanistic studies were designed and performed (Scheme 4). First, 5 equiv of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) were respectively added into the two systems under standard conditions, and it was found that the two transformations were completely inhibited. Adducts of TEMPO and alkyl radical could be detected by HRMS. Thus, these results suggested that the present reactions should involve a free radical process (Scheme 4a). Then, we chose two typical nonconjugate alkenes as substrates to verify the free-radical mechanism. No desired γ-ketonitriles were formed when using allylbenzene or vinylcyclohexane as the substrate, suggesting that nonconjugate alkenes were not suitable for this transformation (Scheme 4b). Thus, we believed that the phenyl group could disperse the electron of the free radical to stabilize the nascent radical intermediate due to the p-π conjugate effect. Finally, we studied the intermolecular competing kinetic isotope effect (KIE) and the value of K_H/K_D = 15.7 was delivered (Scheme 4c), indicating that

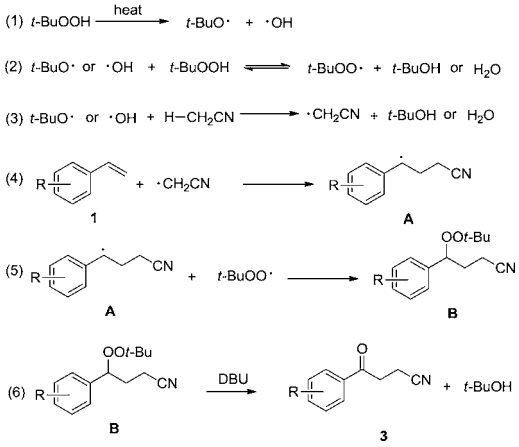
Scheme 4. Mechanistic Studies



the C(sp^3)−H bond cleavage of acetonitrile is involved in the rate-determining step.

On the basis of our experimental results and previous literature,[2i,j] a plausible mechanism was proposed for the reaction (Scheme 5). First, highly activated *t*-BuO· and HO· could be

Scheme 5. Plausible Reaction Mechanism

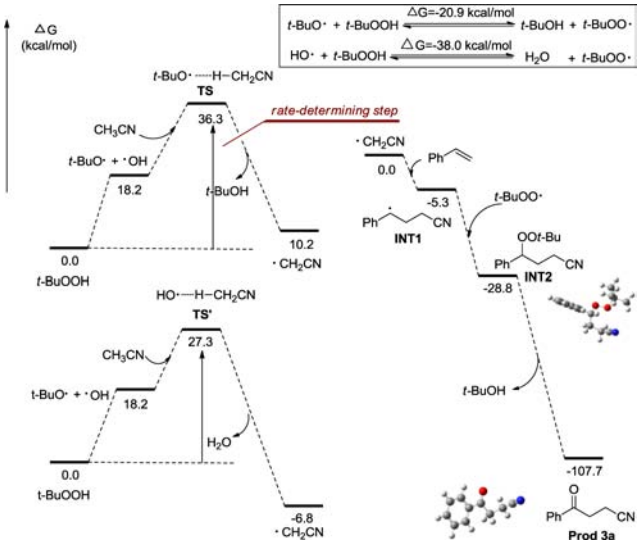


generated from TBHP under heating with the aid of bases through several procedures, which could activate the C(sp^3)−H bond of acetonitrile and abstract the α-H atom of acetonitrile to generate a primary alkyl radical. Addition of the alkyl radical to the double bond of vinylarenes **1** afforded a transient intermediate radical **A**, and then **A** and *t*-BuOO· form intermediate **B**. Finally, intermediate **B** could be converted to the target product **3** in the presence of DBU. Further studies regarding the detailed mechanism are currently underway.

In order to verify the accuracy of these mechanisms, the investigation used DFT calculations along with hybrid functional B3LYP, as it is implemented in the Gaussian 09 package (Scheme 6; for details see SI).[13] Initially, *t*-BuOOH was decomposed into two activated radicals, requiring a free energy of 18.2 kcal/mol.

DOI: 10.1021/acs.orglett.6b02692
Org. Lett. 2016, 18, 5986−5989

Scheme 6. DFT-Computed Energy Profiles for C(sp^3)−H Bond Functionalization of Acetonitrile with Styrene



These two radicals could easily activate CH_3CN to deliver the alkyl radical through transition state **TS** and **TS′**, respectively. Additionally, the dissociation of CH_3CN to the alkyl radical required an activation free energy of 75.3 kcal/mol in the absence of a radical initiator, which is hardly realized. When the alkyl radical was formed, its addition to styrene was facile to give the intermediate **INT1** that was further trapped by *t*-BuOO· to furnish **INT2** barrierlessly. Finally, the **INT2** could spontaneously transform to **Prod 3a**. These results indicated the radical reaction mechanism is feasible.

In summary, we have discovered a novel and efficient metal-free unactivated C(sp^3)−H bond functionalization of alkyl nitriles with terminal vinylarenes for the synthesis of γ-ketonitriles. The reactions afforded a variety of nitrile-bearing carbonyl compounds in moderate to good yields with good functional group tolerance. In this process, AIBN and analogues as partners with terminal vinylarenes to generate γ-ketonitriles were also studied. A free-radical pathway was involved in this method. In this process, the alkyl radical could be captured, and the conjugate system that can stabilize radical intermediates was in favor of this transformation. DFT calculations also provided important evidence of the mechanistic pathways.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02692.

Segmental experimental results and procedures, characterization data, and copies of spectra for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: nxwang@mail.ipc.ac.cn.
*E-mail: shlchen@bit.edu.cn.
*E-mail: xingy@wpunj.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this research was provided by the Natural Science Foundation of China (21572240).

■ REFERENCES

(1) For selected reviews on oxidative coupling, see: (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (b) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (c) Shi, W.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2011**, *40*, 2761. (d) Shang, X.; Liu, Z.-Q. *Chem. Soc. Rev.* **2013**, *42*, 3253. (e) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (f) Liu, C.; Liu, D.; Lei, A. *Acc. Chem. Res.* **2014**, *47*, 3459. (g) Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**, *114*, 9219. (h) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138.

(2) For selected examples on oxidative coupling for a carbonyl group and another functional group, see: (a) Cheng, K.; Huang, L.; Zhang, Y. *Org. Lett.* **2009**, *11*, 2908. (b) Wei, W.; Ji, J.-X. *Angew. Chem., Int. Ed.* **2011**, *50*, 9097. (c) Deb, A.; Manna, S.; Modak, A.; Patra, T.; Maity, S.; Maiti, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 9747. (d) Yang, X.-H.; Wei, W.-T.; Li, H.-B.; Song, R. -J; Li, J.-H. *Chem. Commun.* **2014**, *50*, 12867. (e) Jiang, Y.; Loh, T.-P. *Chem. Sci.* **2014**, *5*, 4939. (f) Du, P.; Li, H.; Wang, Y.; Cheng, J.; Wan, X. *Org. Lett.* **2014**, *16*, 6350. (g) Zhang, F.; Du, P.; Chen, J.; Wang, H.; Luo, Q.; Wan, X. *Org. Lett.* **2014**, *16*, 1932. (h) Singh, A. K.; Chawla, R.; Yadav, L. D. S. *Tetrahedron Lett.* **2014**, *55*, 4742. (i) Zhang, W.; Wang, N.-X.; Bai, C.-B.; Wang, Y.-J.; Lan, X.-W.; Xing, Y.; Li, Y.-H.; Wen, J.-L. *Sci. Rep.* **2015**, *5*, 15250. (j) Lan, X.-W.; Wang, N.-X.; Zhang, W.; Wen, J.-L.; Bai, C.-B.; Xing, Y.; Li, Y.-H. *Org. Lett.* **2015**, *17*, 4460.

(3) For selected examples and reviews on C(sp^3)−H bond functionalization, see: (a) Cui, Z.; Shang, X.; Shao, X.-F.; Liu, Z.-Q. *Chem. Sci.* **2012**, *3*, 2853. (b) Wei, W.-T.; Zhou, M.-B.; Fan, J.-H.; Liu, W.; Song, R.-J.; Liu, Y.; Hu, M.; Xie, P.; Li, J.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 3638. (c) Xie, J.; Pan, C.; Abdukader, A.; Zhu, C. *Chem. Soc. Rev.* **2014**, *43*, 5245. (d) Liu, D.; Liu, C.; Li, H.; Lei, A. *Chem. Commun.* **2014**, *50*, 3623. (e) Schweitzer-Chaput, B.; Demaerel, J.; Engler, H.; Klussmann, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 8737. (f) Zhu, Y.; Wei, Y. *Chem. Sci.* **2014**, *5*, 2379. (g) Ji, J.; Liu, P.; Sun, P. *Chem. Commun.* **2015**, *51*, 7546. (h) Cheng, J.-K.; Loh, T.-P. *J. Am. Chem. Soc.* **2015**, *137*, 42. (i) Correa, A.; Fiser, B.; Gómez-Bengoa, E. *Chem. Commun.* **2015**, *51*, 13365. (j) Tang, S.; Liu, K.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2015**, *44*, 1070. (k) Bunescu, A.; Wang, Q.; Zhu, J. *Org. Lett.* **2015**, *17*, 1890. (l) Zhang, H.; Gu, Z.; Xu, P.; Hu, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2016**, *52*, 477.

(4) (a) Liskey, C. W.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 11389. (b) Jinzaki, T.; Arakawa, M.; Kinoshita, H.; Ichikawa, J. J.; Miura, K. *Org. Lett.* **2013**, *15*, 3750. (c) Zheng, Y.; He, Y.; Rong, G.; Zhang, X.; Weng, Y.; Dong, K.; Xu, X.; Mao, J. *Org. Lett.* **2015**, *17*, 5444.

(5) (a) Girgis, A. S.; Mishriky, N.; Farag, A. M.; El-Eraky, W. I.; Farag, H. *Eur. J. Med. Chem.* **2008**, *43*, 1818. (b) Frey, G.; Luu, H.-T.; Bichovski, P.; Feurer, M.; Streuff, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 7131. (c) Krishnaraj, K. U.; Devaky, K. S. *Tetrahedron* **2014**, *70*, 6450.

(6) Wu, T.; Mu, X.; Liu, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 12578.

(7) Li, J.; Wang, Z.; Wu, N.; Gao, G.; You, J. *Chem. Commun.* **2014**, *50*, 15049.

(8) Li, Z.; Xiao, Y.; Liu, Z.-Q. *Chem. Commun.* **2015**, *51*, 9969.

(9) Chu, X.-Q.; Meng, H.; Zi, Y.; Xu, X.-P.; Ji, S.-J. *Org. Chem. Front.* **2015**, *2*, 216.

(10) Chu, X.-Q.; Xing, Z.-H.; Meng, H.; Xu, X.-P.; Ji, S.-J. *Org. Chem. Front.* **2016**, *3*, 165.

(11) Zhou, D.; Li, Z.-H.; Li, J.; Li, S.-H.; Wang, M.-W.; Luo, X.-L.; Ding, G.-L.; Sheng, R.-L.; Fu, M.-J.; Tang, S. *Eur. J. Org. Chem.* **2015**, *2015*, 1606.

(12) Bunescu, A.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 3132.

(13) All of the energies discussed in the paper are Gibbs free energies in the liquid phase. Computational details and references are given in the SI.

DOI: 10.1021/acs.orglett.6b02692
Org. Lett. 2016, 18, 5986−5989