

α -Fluoroallenoate Synthesis via N-Heterocyclic Carbene-Catalyzed Fluorination Reaction of Alkynals

Xu Wang, Zijun Wu, and Jian Wang*

Department of Pharmacology and Pharmaceutical Science, School of Medicine, Tsinghua University, Beijing 117543, China

S Supporting Information

ABSTRACT: The first catalytic α -fluoroallenoate synthesis is described. With a suitable combination of N-heterocyclic carbene precatalyst, base, and fluorine reagent, the reaction proceeded smoothly to yield a wide range of α -fluoroallenoates with excellent chemoselectivity. These substituted α -fluorinated allenoates have been synthesized for the first time, and they are versatile synthetic intermediates toward other useful fluorine-containing building blocks.



It has become increasingly evident that fluorine has a significant impact on drug discovery.¹ The incorporation of fluorine in a potential drug can lead to a dramatic change in the molecule's properties. For example, fluorine can increase the efficacy of the drug and can make the administration process convenient.¹ Consequently, the insertion of fluorine into organic molecules has drawn long-standing attention from medicinal chemists. In addition, allenes have also been proven to be highly valuable synthons in preparative organic chemistry due to their ability to undergo a variety of transformations.² We speculated that, if the fluorine atom can be installed into the allene scaffold, a variety of fluorinated functional molecules could be feasibly accessed through a late-stage transformation (Figure 1b).

Although significant progress has been made toward the production of C–F bonds, there remains a great need for further development of novel methodology for the construction of diversified functional molecules.³ For example, the efficient incorporation of fluorine into the allenoate backbone remains unknown. In the process of proving the hypothesis, several challenges may be encountered: (1) both α and γ positions of the N-heterocyclic carbene (NHC)–trienolate are nucleophilic; (2) instead of C–F bond formation, the NHC–trienolate can undergo protonation at the α position to afford a nonfluorinated product.

NHCs are well-known for their unique capability to reverse the polarity of aldehydes.^{4,5} On this basis, the Rovis group developed an elegant example of NHC-catalyzed directed hydration of α,β -unsaturated aldehydes, leading to a variety of α -fluoro carboxylic acids.⁶ In 2012, Sun and co-workers reported a catalytic efficient synthesis of β,γ -unsaturated α -fluoroesters catalyzed by NHCs.⁷ More recently, the Wang^{8a} and the Sun groups^{8b} independently disclosed a progress regarding the NHC-catalyzed α -fluorination of aliphatic aldehydes for the synthesis of α -fluoroesters, amides and thioesters (Figure 1). In brief, the above reactions afforded α -fluoro carbonyls through an NHC-catalyzed C_{sp^3} –F bond forming process. To the best of our knowledge, the example of NHC-catalyzed C_{sp^2} –F bond forming process has not yet been reported by far. With this goal, we set out to efficiently construct α -fluoroallenoates⁹ by using a catalytic umpolung strategy.⁹

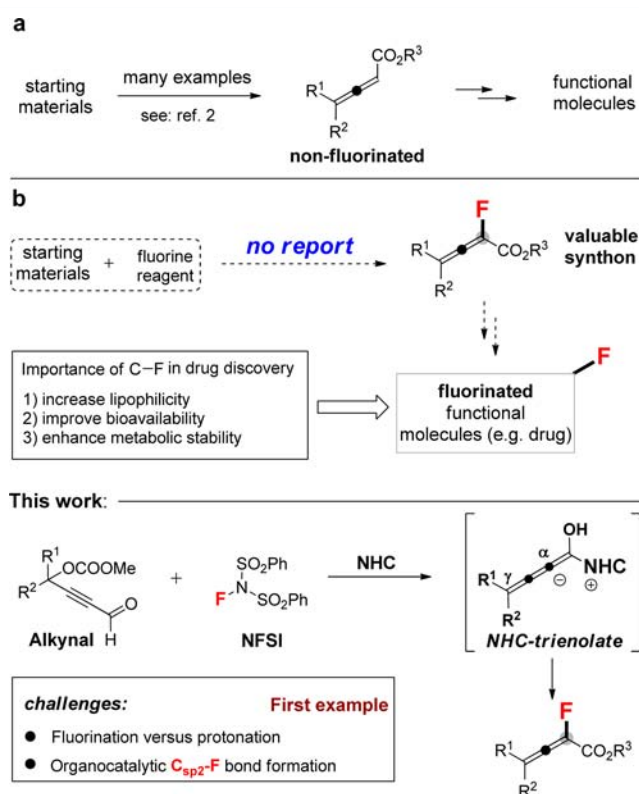
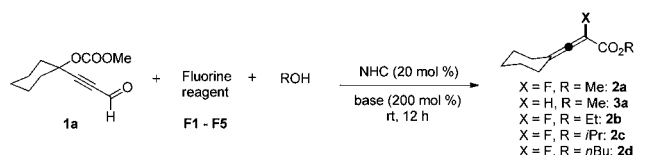


Figure 1. (a) Methods for allenoate synthesis. (b) Our strategy for α -fluorinated allenoate synthesis.

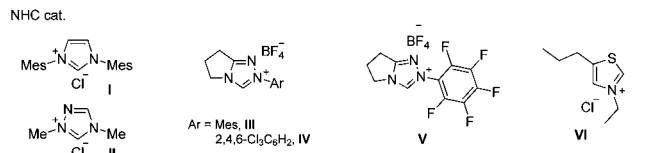
We first undertook the screening of achiral carbene precursors, including thiazoliums, imidazoliums, and triazoliums. Results from our catalyst evaluation are shown in Table 1. Although cat. III and IV¹⁰ indicated moderate to good reactivity, low levels of chemoselectivity were obtained (entries 3 and 4). However, cat.

Received: December 21, 2015

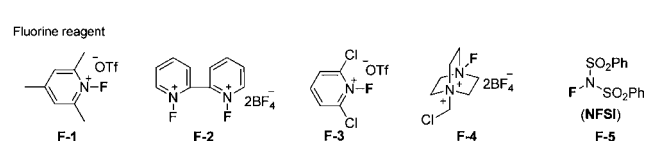
Published: January 15, 2016

Table 1. Optimization of the Reaction Conditions^{a,c}


NHC cat.



Fluorine reagent

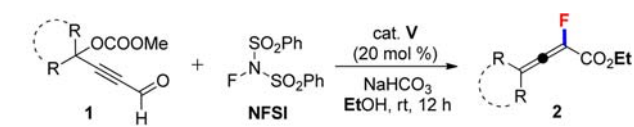


entry	NHC	ROH	base	"F"	F/H	2 (%) ^b
1	I	MeOH	K ₂ CO ₃	F-5	N.D.	<5 (2a)
2	II	MeOH	K ₂ CO ₃	F-5	N.D.	<5 (2a)
3	III	MeOH	K ₂ CO ₃	F-5	1:1	40 (2a)
4	IV	MeOH	K ₂ CO ₃	F-5	3:1	74 (2a)
5	V	MeOH	K ₂ CO ₃	F-5	8:1	71 (2a)
6	VI	MeOH	K ₂ CO ₃	F-5	N.D.	<5 (2a)
7	V	MeOH	Cs ₂ CO ₃	F-5	2:5	23 (2a)
8	V	MeOH	NaHCO ₃	F-5	>19:1	60 (2a)
9	V	MeOH	NaOMe	F-5	1:1	43 (2a)
10	V	MeOH	PhCO ₂ Na	F-5	1:1	32 (2a)
11	V	EtOH	NaHCO ₃	F-5	>19:1	91 (2b)
12 ^d	V	EtOH	NaHCO ₃	F-5	>19:1	98 (2b)
13	V	iPrOH	NaHCO ₃	F-5	>19:1	61 (2c)
14	V	nBuOH	NaHCO ₃	F-5	N.D.	<5 (2d)

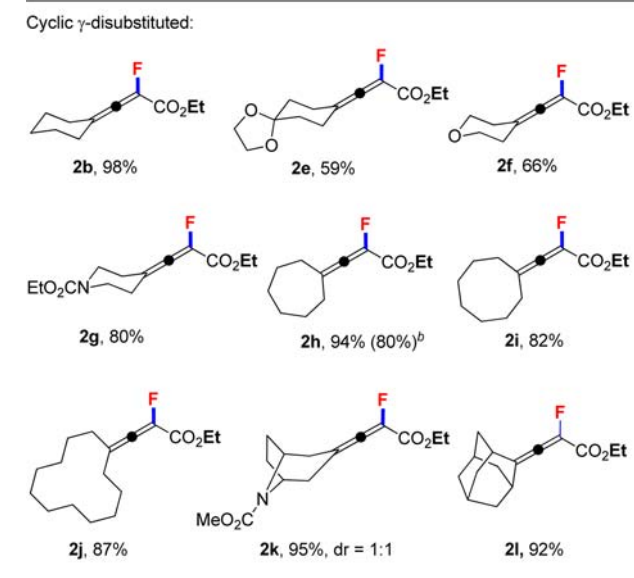
^aReaction conditions: A mixture of **1a** (0.10 mmol), catalyst (20 mmol %), fluorine reagent (0.15 mmol), base (0.2 mmol) in MeOH (1.0 mL) was stirred at room temperature for 12 h. ^bIsolated yield after flash chromatography. ^cUnder standard conditions, other F-reagents (F-1 to F-4) gave no desired product **2a** or **2b**. ^dF-5 (0.2 mmol %).

V¹¹ provided **2a** in a 71% yield and also with a ratio of **2a/3a** = 8:1 (entry 5). Based on these findings, we further investigated other reaction parameters, such as base and fluorination reagent, in order to achieve a better chemoselectivity and a higher chemical yield. Pleasingly, NaHCO₃ was found to be an ideal base for this α -fluorination study (entry 8, ratio of **2a/3a** > 19:1). Examination of a range of fluorination reagents revealed that *N*-fluorobenzenesulfonimide (NFSI) was superior with respect to reaction efficiency. The use of other fluorine reagents, such as *N*-fluoropyridine salts (F-1, F-2, and F-3) and Selectfluor (F-4), resulted in poor yield or no reaction. Further improvement was achieved via the use of EtOH (a replacement of MeOH) and 2 equiv of NFSI (product **2b**, 98% yield, >19:1 chemoselectivity). The critical effect of the size of alcohols was demonstrated by comparison to various dimensional alcohols (**2c** and **2d**, 61% and <5%, respectively). Moreover, a brief survey of different leaving groups at the alkynyl γ -position, e.g., OMe, OAc, and OTs, reveals that the methyl carbonate group (OCO₂Me) is the most suitable one.

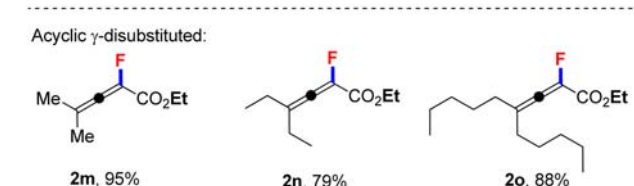
We then investigated the scope of this method. In general, symmetric cyclic γ -disubstituted alkynals were efficiently converted to desired products (Tables 2 and 3). Notably, a wide array of carbocyclic and heterocyclic γ -disubstituted alkynals (six-, seven-, eight-, and 12-membered) is amenable to this

Table 2. Scope of Symmetric Germinal Disubstituted Alkynals^a


Cyclic γ -disubstituted:



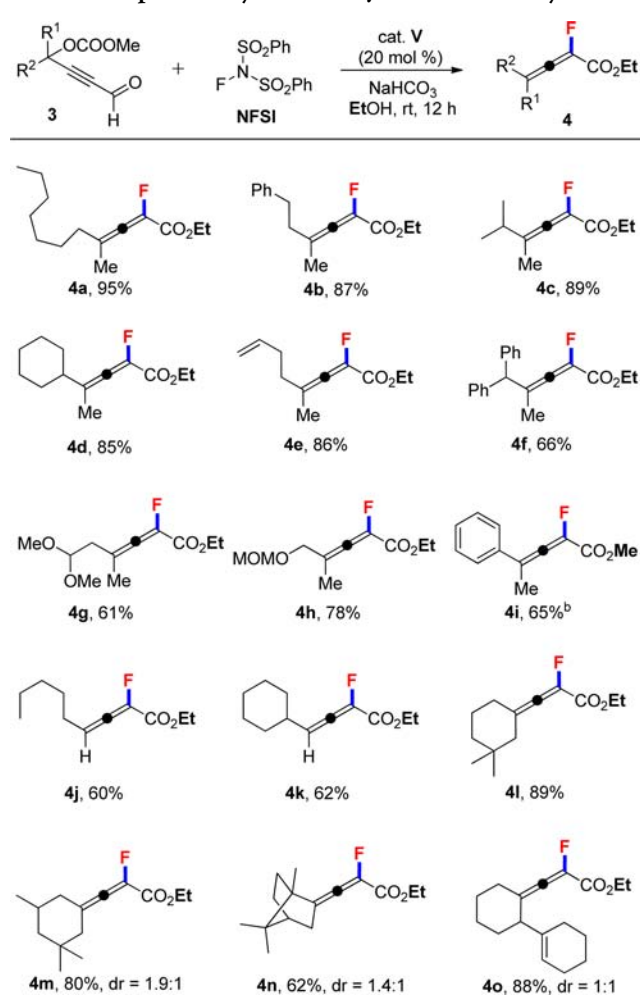
Acyclic γ -disubstituted:



^aReaction conditions: alkynyl **1** (0.5 mmol), cat. **V** (0.1 mmol), NFSI (1.0 mmol), NaHCO₃ (1.0 mmol), EtOH (5.0 mL), rt, 12 h. ^bYield in parentheses was obtained at a scale of 5.0 mmol.

approach (**2b**, **2e–2j**). In addition, two specific α -fluoroalleloates, built on scaffolds of azabicyclooctane and adamantane, had been successfully constructed (Table 2, **2k** and **2l**, 95% and 92%, respectively). Moreover, introduction of symmetric acyclic γ -disubstituted alkynals could be tolerated without loss in yield or chemoselectivity (**2m–2o**). A large scale synthesis of **2h** was also examined and provided a good chemical yield (Table 2, 80%, data in parentheses).

Lastly, we turned our attention to unsymmetric γ -disubstituted alkynal. It should be noted that this new protocol has yet to be successfully implemented with this type of alkynals, bearing unsymmetric disubstitution at the alkynyl γ -position. Using alkyl–alkyl γ -disubstituted alkynals, high conversions were observed (**4a–4f**, 85–95%). With respect to functional group tolerance, protected alcohols and aldehydes are readily tolerated using these mild reaction conditions (**4g** and **4h**, 61% and 78%, respectively). Importantly, we have found that this new protocol can be readily applied to alkyl–aryl γ -disubstituted alkynals (**4i**, 65%). Moreover, γ -monosubstituted alkynals were also found to be suitable partners and afforded the corresponding products in good chemical yields (**4j** and **4k**, 60% and 62%, respectively). Having successfully examined a series of commonly used alkynals, we next directed our standard fluorination conditions to more complex substrates. Remarkably, an array of cyclic γ -disubstituted alkynals was successfully fluorinated, affording the

Table 3. Scope of Unsymmetrical γ -Substituted Alkynals^a

^aReaction conditions: alkynal **3** (0.5 mmol), cat. **V** (0.1 mmol), NFSI (1.0 mmol), NaHCO_3 (1.0 mmol), EtOH (5.0 mL), rt, 12 h. ^bMeOH (5.0 mL) as solvent.

corresponding α -fluoroallenoates **4l–4o** in good to high yields and moderate dr. Additionally, the α -fluoroallenoates can be smoothly transformed into other useful fluorinated molecules (Figure 2).

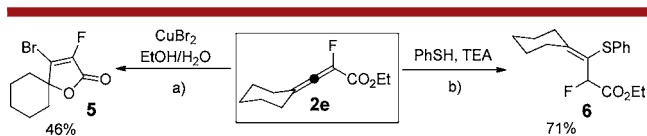


Figure 2. Synthetic transformations.

A postulated mechanism is depicted in Figure 3. The catalytic cycle begins with the addition of NHC catalyst **V** to alkynal **2a** in the presence of NaHCO_3 . The resulting Breslow intermediate **A** then undergoes elimination to afford a cumulative allenol **B**.^{12,13} Nucleophilic addition of intermediate **B** to NFSI generates a NHC-bound α -fluorinated intermediate **C**.¹⁴ Further acyl substitution by ethanol proceeds via intermediate **C** to form the desired product **2b** and regenerate the NHC catalyst. In addition, a plausible competition reaction could take place in the conversion of intermediate **B** to **C**. As highlighted in Figure 3, the nucleophilic addition of intermediate **B** to proton, generated from the NHC catalyst in the presence of base, could lead to the

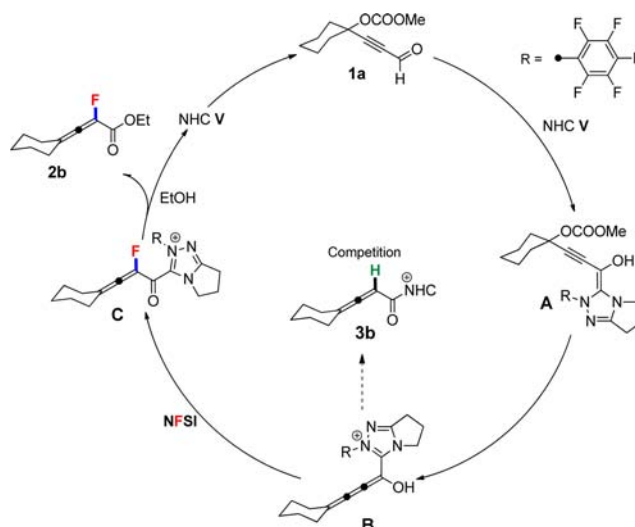


Figure 3. Postulated mechanism.

formation of by product **3b**. The observed excellent chemoselectivity (>19:1) was attributed to below two plausible reasons. First, NFSI exhibits a high electrophilicity,¹⁵ thus facilitating the nucleophilic substitution reaction and resulting in the desired C–F bond; Second, the potential π – π stacking between NFSI (phenyl ring) and intermediate **B** (perfluorophenyl group) allows the C–F bond generation to be an intramolecular-like reaction.

In summary, we have developed an efficient α -fluorination of azolium allenols that were generated from various γ -substituted alkynals. With a suitable combination of NHC precatalyst, base, and fluorine reagent, the reaction proceeded smoothly to yield a wide range of α -fluoroallenoates with excellent chemoselectivity. NFSI serves as the fluorine source in the reactions. These substituted α -fluorinated allenoates have been synthesized for the first time, and they are useful synthetic intermediates toward other fluorine-containing building blocks

■ ASSOCIATED CONTENT

§ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03615.

Experimental procedures and spectral data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wangjian2012@tsinghua.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the “Thousand Plan” Youth program, the Bayer Investigator Fellowship, the Tsinghua-Peking centre for life sciences (CLS), and the Tsinghua University for generous financial support.

■ REFERENCES

- (1) (a) *Fluorine in Pharmaceutical and Medicinal Chemistry*; Gouverneur, V., Müller, K., Eds.; Imperial College Press: London, 2012. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.;

Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.

(2) (a) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701. (b) Sydnese, L. K. *Chem. Rev.* **2003**, *103*, 1133. (c) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (d) Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074. (e) Tejedor, D.; Méndez-Abt, G.; Cotos, L.; García-Tellado, F. *Chem. Soc. Rev.* **2013**, *42*, 458. (f) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954. (g) Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196. (h) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470.

(3) For selected leading examples, see: (a) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359. (b) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530. (c) Suzuki, T.; Hamashima, Y.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5435. (d) Paull, D. H.; Scerba, M. T.; Alden-Danforth, E.; Widger, L. R.; Lectka, T. *J. Am. Chem. Soc.* **2008**, *130*, 17260. (e) Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2010**, *352*, 2708. (f) Brunet, V. A.; o'Hagan, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1179. (g) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. (h) Prakash, G. K. S.; Beirer, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2172. (i) Pihko, P. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 544. (j) Brunet, V. A.; O'Hagan, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2. (k) Katcher, M. H.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 17402.

(4) Selected reviews on NHC catalysis: (a) Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichimica Acta* **2009**, *42*, 55. (b) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2010**, *291*, 77. (c) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182. (d) Vora, H. U.; Rovis, T. *Aldrichimica Acta* **2011**, *44*, 3. (e) Rong, Z. Q.; Zhang, W.; Yang, G. Q.; You, S.-L. *Curr. Org. Chem.* **2011**, *15*, 3077. (f) Cohen, D. T.; Scheidt, K. A. *Chem. Sci.* **2012**, *3*, 53. (g) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511. (h) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314. (i) Douglas, J.; Churchill, G.; Smith, A. D. *Synthesis* **2012**, *44*, 2295. (j) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11686. (k) Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* **2014**, *47*, 696. (l) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485. (m) Binanzer, M.; Hsieh, S.-Y.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 19698. (n) Flanagan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *15*, 9307.

(5) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239. (b) Romanov-Michailidis, F.; Rovis, T. *Nature* **2015**, *523*, 417. (c) Wu, Y.; Hu, L.; Deng, L. *Nature* **2015**, *523*, 445. (d) Denmark, S. E.; Wilson, T. W. *Nat. Chem.* **2010**, *2*, 937.

(6) (a) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 2860. (b) Wheeler, P.; Vora, H. U.; Rovis, T. *Chem. Sci.* **2013**, *4*, 1674.

(7) Zhao, Y.-M.; Cheung, M. S.; Lin, Z.; Sun, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 10359.

(8) (a) Li, F. Y.; Wu, Z. J.; Wang, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 656. (b) Dong, X.; Yang, W.; Hu, W.; Sun, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 660.

(9) Zhao, Y.-M.; Tam, Y.; Wang, Y.-J.; Lim, Z.; Sun, J. *Org. Lett.* **2012**, *14*, 1398.

(10) (a) Sohn, S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873. (b) Wanner, B.; Mahatthananchai, J.; Bode, J. W. *Org. Lett.* **2011**, *13*, 5378.

(11) (a) Reynolds, N.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406. (b) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725.

(12) Mahatthananchai, J.; Zheng, P.; Bode, J. W. *Angew. Chem., Int. Ed.* **2011**, *50*, 1673.

(13) For examples on NHC-catalyzed reactions of alkynals, see: (a) Zeitler, K. *Org. Lett.* **2006**, *8*, 637. (b) Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810. (c) Zhu, Z.; Xiao, J. *Adv. Synth. Catal.* **2010**, *352*, 2455. (d) Qi, J.; Xie, X.-G.; Han, R.-F.; Ma, D.-H.; Yang, J.; She, X.-G. *Chem. - Eur. J.* **2013**, *19*, 4146. (e) Lee, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 7594.

(14) (a) Zhao, Y.; Cheung, S.; Lin, Z.; Sun, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 10359. (b) Paul, S.; Schweizer, B.; Rugg, G.; Senn, H.; Gilmour, R. *Tetrahedron* **2013**, *69*, 5647.

(15) (a) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1–PR43. (b) Baudoux, J.; Cahard, D. *Org. React.* **2007**, *69*, 347.