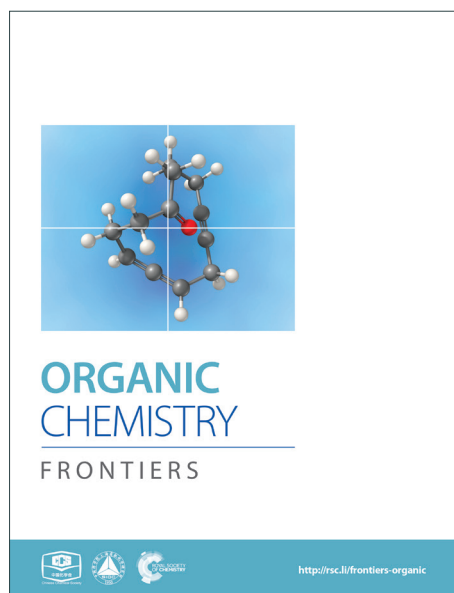
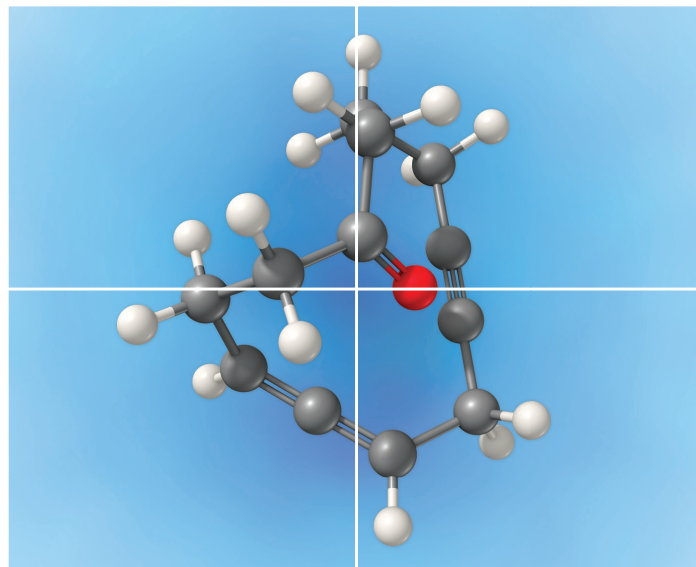


ORGANIC CHEMISTRY

FRONTIERS

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

One Pot Cascade Synthesis of Fused Heterocycles from Furan-tethered Terminal Alkynes and Aldehydes in the Presence of Amines and CuBr

Yan-Yan Zhang,^a Jian Hao^{a,*} and Min Shi^{b,*}⁵ Received (in XXX, XXX) Xth XXXXXXXXXX 20XX, Accepted Xth XXXXXXXXXX 20XX

DOI: 10.1039/b000000x

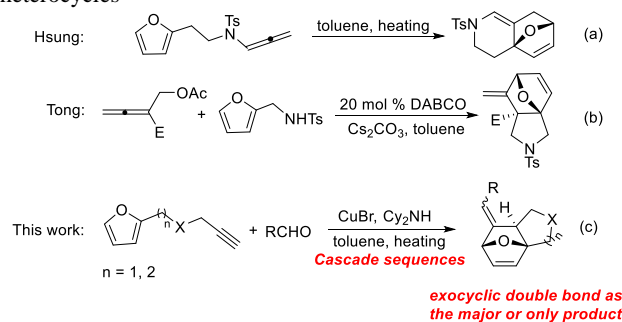
A novel one-pot protocol for the construction of complex heterocycles through furan tethered terminal alkynes, aldehydes, amines and CuBr upon heating has been developed, giving the cycloadducts in moderate to high yields along with moderate to good regioselectivities. The reactions proceed through a two-component domino reaction including allenation and subsequent intramolecular Diels–Alder reaction. A wide range of aliphatic or aromatic aldehydes and furan tethered terminal alkynes are well-tolerated, enriching the chemistry of intramolecular Diels–Alder reaction related with furan.

The intramolecular Diels–Alder reaction related with furan (IMDAF) is one of the most widely utilized reactions for the construction of heterocyclic ring systems because furan is an excellent diene in Diels–Alder reactions.^{[1][2]} On the other hand, allenes have been widely used as dienophiles in Diels–Alder reaction upon heating or in the presence of metal catalysts.^[3] Among the intramolecular cycloaddition reactions between furan and allene moiety, two modes are mainly involved as shown in Scheme 1. The first one is the cycloaddition of furan with the distal double bond of allene, giving rise to a bridged bicyclic skeleton containing an endocyclic double bond. The second one is the cycloaddition of furan with the proximal double bond of allene, affording a bridged bicyclic skeleton bearing an exocyclic double bond.^[11]

Due to the importance of complex aza-heterocycles, recently, an array of transition-metal-catalyzed cycloaddition reactions of dienes with allenes have been reported.^[4] Paralleling with metal-catalyzed ones, thermal and DABCO (1,4-diazabicyclo[2.2.2]octane) catalyzed cycloaddition have been also developed to construct these scaffolds. For example, Hsung and coworkers have reported a thermal intramolecular [4+2] cycloadditions of furan tethered allenamides without assistance of any metal catalyst for rapid assembly of highly functionalized nitrogen heterocycles (reaction a, Scheme 1).^[5] In addition, Tong et al. revealed DABCO-triggered cascade S_N2/cycloaddition seq-

uence between 2-(acetoxymethyl)buta-2,3-dienoate and various π -system functionalized tosylamides to construct structurally diverse aza-heterocycles (reaction b, Scheme 1).^[6]

Scheme 1. Previous cycloaddition modes for the synthesis of heterocycles



Inspired by these findings, herein, we wish to report a one-pot protocol for the synthesis of fused heterocycles through furan tethered allenes via a two-component reaction by use of aldehydes, furan tethered terminal alkynes, and dicyclohexamine as the reactants (reaction c, Scheme 1). This one-pot manner featured a powerful synthetic approach to the construction of fused heterocycles with increased molecular diversity and complexity.^[7]

Initially, we attempted to *in situ* synthesize furan tethered allene using alkyne **1a**, paraformaldehyde and amine in 1,4-dioxane according to Ma's procedures and subsequently to explore the next sequential IMDAF.^[8] Therefore, we first examined the reaction outcome using *N*-(furan-2-ylmethyl)-4-methyl-*N*-(prop-2-yn-1-yl) benzenesulfonamide **1a** as substrate, and the results are shown in Table 1. Under the reported standard conditions, the reaction of **1a** with paraformaldehyde (2.5 equiv), *i*-Pr₂NH (1.8 equiv) and CuBr (0.3 equiv) in 1,4-dioxane afforded the desired cycloadducts **2a** and **3a** in 36% total yield as a 1:3 regioisomers (Table 1, entry 1). Their structures have been confirmed by X-ray diffraction (Figure 1) and the related CIF data are shown in the Supporting Information.^{[9][10]} The structures of **2a** and **3a** clearly indicated that the subsequent IMDAF indeed took place with the distal and proximal double bond of allene moiety to give the fused heterocycles bearing endocyclic and exocyclic double bond, respectively (Figure 1).

Next, by screening of different amines, we found that the total yield of **2a** and **3a** was improved to 78% when dicyclohexylamine was employed as the base (Table 1, entries 2–3). Further investigations led to the observation that when toluene was used as solvent, the corresponding products **2a** and **3a** could

^aDepartment of Chemistry, Shanghai University, 99 Shangda Road, Shanghai 200444, China

^bState Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032 China. mshi@mail.sioc.ac.cn. Fax: 86-21-64166128

[†] Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data of new compounds. See DOI: 10.1039/b000000x/

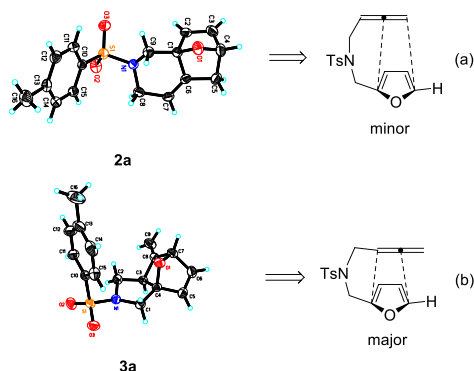



Figure 1. X-ray crystal structures of **2a** (a) and **3a** (b) and the regioselectivity for [4+2] cycloaddition.

be isolated in 86% total yield (Table 1, entry 5). The examinations on the amounts of dicyclohexylamine, paraformaldehyde and CuBr as well as the reaction temperature revealed that the use of 1.8 equiv of amine, 2.5 equiv of aldehyde and 0.3 equiv of CuBr under reflux in toluene gave the best performance (Table 1, entries 6-9).

Table 1. Optimization of the reaction conditions

entry ^a	amines (equiv)	solvents	yield (%) ^b	
			2a + 3a (ratio) ^c	
1	<i>i</i> -Pr ₂ NH (1.8)	dioxane	36 (1/3)	
2	 (1.8)	dioxane	22 (1/4)	
3	Cy ₂ NH (1.8)	dioxane	78 (1/4)	
4	<i>i</i> -Pr ₂ NH (1.8)	toluene	51 (1/4)	
5	Cy ₂ NH (1.8)	toluene	86 (1/4) ^d	
6 ^e	Cy ₂ NH (1.8)	toluene	21 (1/4)	
7 ^f	Cy ₂ NH (1.8)	toluene	67 (1/4)	
8 ^g	Cy ₂ NH (1.8)	toluene	67 (1/4)	
9	Cy ₂ NH (1.5)	toluene	77 (1/4)	

^a The reactions were carried out in 0.2 mmol scale in 1 mL of solvents.

^b Determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard.

^c The value in the parentheses is the ratio of isomers **2a** and **3a** that was determined by ¹H NMR spectroscopy. ^d Isolated yields. ^e The reaction was carried out at 80 °C. ^f 2.0 equiv (CH₂O)_n was added. ^g 0.20 equiv CuBr was added.

With the optimized conditions in hand, we next sought to determine the scope of alkyne that can be employed in this new tandem cycloaddition protocol. As shown in Table 2, changing the substituent on the nitrogen atom from Ts to Bs or Ns (Bs = *p*-bromobenzenesulfonyl, Ns = 4-nitrobenzenesulfonyl) did not significantly affect the reaction outcome, giving both regioisomers **2** and **3** (1:4 and 1:5 ratio) in 63-80% total yields (Table 2, entries 2-3). Moreover, none **3a** could be detected upon heating **2a** in toluene at 110 °C for 48 h on the basis of ¹H NMR spectroscopy. This result indicated that **2a** can not be transformed into **3a** via retro-cycloaddition and cycloaddition process. Substrates **1d-1e** with different furan substitutions produced the corresponding cycloadducts **2** and **3** (1:1 and 1:4 ratio) in 60% total yields (Table 2, entries 4 and 5). Notably, as for substrate **1f** having a methyl substituent at the carbon tether, the reaction also proceeded smoothly to give the desired products **2f** and **3f** in 81% total yield as a 1:2 regioisomers (Table 2, entry 6). Furthermore, substrate **1g** with a C(CO₂Et)₂ carbon linkage was also found to

be suitable in this reaction, furnishing the desired product **3g** in 46% yield as a single regioisomer (Table 2, entry 7). Substrate **1h** connected by an oxygen atom was also tolerated in this protocol, albeit affording **3h** in 14% yield (Table 2, entry 8).^[11]

Table 2. Substrate scope of **1**

entry ^a	substrate	yield (%) ^b	
		2+3 (ratio) ^c	
1		86 (1/4)	
2		63 (1/4)	
3		80 (1/5)	
4		60 (1/1)	
5		60 (1/4)	
6		81 (1/2) ^d	
7 ^e		46	
8 ^f		14	

^a The reactions were carried out on 0.2 mmol scale in 1.0 mL of toluene. ^b Isolated yields.

^c The value in the parentheses is the ratio of isomers **2** and **3** that was determined by ¹H NMR spectroscopy. ^d **2f** was found as ~ 3/1 inseparable isomeric mixture and **3f** was found as ~ 2/1 inseparable isomeric mixture. ^e Only **3g** was isolated. ^f Only **3h** was isolated.

40

Interestingly, we found that substrate **4a** having a CH₂CH₂ carbon tether at the furan moiety gave the corresponding cycloadduct **5a** as a single regioisomer in 85% yield (Table 3, entry 1), suggesting that extending one carbon atom at the tether provides a sterically demanding in favour of cycloaddition for the furan with the proximal double bond of allene moiety (Figure 2). Its structure has been confirmed by X-ray diffraction (Figure 2) and the related CIF data are shown in the Supporting Information.^[12]

50

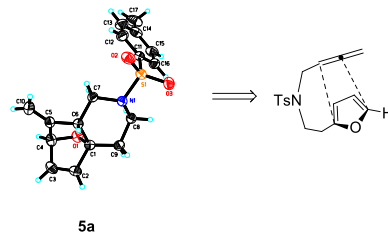


Figure 2. X-ray crystal structure of **5a** and the regioselectivity for [4+2] cycloaddition.

We next attempted to determine the scope of substrates **4** that can be employed in this one-pot protocol. As shown in Table 3, the substrate scope similarly consists of (1) different *N*-substituents (Table 3, entries 1-3); (2) various furan substitutions (Table 3, entries 4-5); (3) the substrates **4f** and **4g** having a methyl group or phenyl group at the carbon tether. All these reactions proceeded efficiently, affording the corresponding products **5b-5g** in 56-87% yields as a single regioisomer or 6:1~7:1 diastereoisomers, respectively (Table 3, entries 2-7). Substrate **4h** tethered by an oxygen atom afforded the corresponding product **5h** in 9% yield (Table 3, entry 8).

To further illustrate the substrate scope, a variety of other aldehydes **6** has been examined in this cascade reaction under the

standard conditions and the results are summarized in Table 4.

Table 3. Substrate scope of **4**

entry ^a	product	yield (%) ^b
1		85
2		80
3		56
4		83
5		87
6		61 (dr 6/1) ^{c, d}
7		71 (dr 7/1) ^{c, d}
8		9

^a All Reactions were carried out in 0.2 mmol scale in 1.0 mL of toluene.

^b Isolated yield. ^c The value in the parentheses of dr was determined by ¹H NMR spectroscopy. ^d Inseparable isomeric mixture.

Substrate **4b** reacted with benzaldehyde **6a** or *p*-chlorobenzaldehyde **6b** smoothly using tetrahydroisoquinoline or dicyclohexylamine as the base respectively,^{[13][14]} affording the corresponding cycloadducts **7a** and **7b** in moderate yields as a single isomer with E-configuration on the basis of NOESY spectra (Table 4, entries 1-2, also see Supporting Information). Heteroaromatic aldehyde such as thiophene-2-carbaldehyde **6c** was also suitable in this transformation (Table 4, entry 3). Moreover, aliphatic aldehydes **6d-6f** have been also tested. It was realized that high reaction temperature and longer reaction time are required, giving the desired products **7d-7f** in 33-43% yields mainly as E-configuration, suggesting a wide substrate range of this domino sequence (Table 4, entries 4-6).

Table 4. Substrate scope of aldehydes

entry	R	temp (°C)	time (h)	yield ^a (%)	ratio (E/Z)
1 ^b	Ph	110	7	55	E
2	<i>p</i> -ClPh	110	14	47	E
3		110	19	32	E
4 ^{c, d}	CH ₃ (CH ₂) ₃	130	24	37	10/1
5 ^{c, d}	CH ₃ (CH ₂) ₄	150	12	43	9/1
6 ^{c, d}	(CH ₃) ₂ CH	150	11	33	25/1

^a Isolated yield. ^b The reaction was carried out using 1,2,3,4-tetrahydroisoquinoline replacing dicyclohexylamine. ^c The reactions were carried out in a sealed tube. ^d Inseparable isomeric mixture.

In conclusion, we have disclosed a novel synthetic protocol for the construction of complex heterocycles through an efficient one-pot reaction of furan tethered alkynes and aldehydes with amines catalyzed by CuBr via a cascade two-component condensation and the subsequent intramolecular Diels–Alder reaction (IMDAF), providing the desired products in moderate to high yields along with moderate to good regioselectivities. A wide range of aliphatic or aromatic aldehydes and furan tethered terminal alkynes are tolerated. Further investigations on expanding the scope of this reaction towards a wide range of other alkynes as well as the applications of this protocol to natural product synthesis are in progress.

Acknowledgement. We are grateful for the financial support from the National Basic Research Program of China (973)-2015CB856603, Shanghai Municipal Committee of Science and Technology (11JC1402600), the National Natural Science Foundation of China (20472096, 21372241, 21361140350, 20672127, 21421091, 21372250, 21121062, 21302203 20732008, and 21172141).

Notes and references

- For selected examples, see: (a) W. Oppolzer, *Angew. Chem. Int. Ed.* **1977**, *16*, 10. (b) G. Brieger, J. N. Bennett, *Chem. Rev.* **1980**, *80*, 63. (c) A. G. Fallis, *Can. J. Chem.* **1984**, *62*, 183. (d) D. Craig, *Chem. Soc. Rev.* **1987**, *16*, 187. (e) A. G. Fallis, *Acc. Chem. Res.* **1999**, *32*, 464. (f) B. R. Bear, S. M. Sparks, K. J. Shea, *Angew. Chem. Int. Ed.* **2001**, *40*, 820. (g) E. Marsault, A. Toro, P. Nowak, P. Deslongchamps, *Tetrahedron* **2001**, *57*, 4243.
- For selected reviews, see: (a) C. S. Schindler, E. M. Carreira, *Chem. Soc. Rev.* **2009**, *38*, 3222. (b) K. -i. Takao, R. Munakata, K. -i. Tadano, *Chem. Rev.* **2005**, *105*, 4779. (c) G. Brieger, J. N. Bennett, *Chem. Rev.* **1980**, *80*, 63.
- (a) N. Krause, A. S. K. Hashmi, *Modern Allene Chemistry*; Wiley-VCH: Weinheim, 2004. (b) T. Yoshino, F. Ng, S. J. Danishefsky, *J. Am. Chem. Soc.* **2006**, *128*, 14185. (c) S. P. Cook, A. Polara, S. J. Danishefsky, *J. Am. Chem. Soc.* **2006**, *128*, 16440. (d) M. Nendel, L. M. Tolbert, L. E. Herring, M. N. Islam, K. N. Houk, *J. Org. Chem.* **1999**, *64*, 976. (e) H. V. Pham, K. N. Houk, *J. Org. Chem.* **2014**, *79*, 8968. (f) M. E. Jung, N. Nishimura, *Org. Lett.* **2001**, *3*, 2113. (g) J. K. Lam, Y. Schmidt, C. D. Vanderwal, *Org. Lett.* **2012**, *14*, 5566.
- For selected examples, see: (a) B. Trillo, F. López, M. Gulás, L. Castedo, J. L. Mascareñas, *Angew. Chem., Int. Ed.* **2008**, *47*, 951. (b) B. Trillo, F. López, S. Montserrat, G. Ujaque, L. Castedo, A. Lledós, J. L. Mascareñas, *Chem.-Eur. J.* **2009**, *15*, 3336. (c) P. Mauleón, R. M. Zeldin, A. Z. González, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 6348. (d) C. Nevado, A. M. Echavarren, *Synthesis* **2005**, 167. (e) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410. (f) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266. (g) H. C. Shen, *Tetrahedron* **2008**, *64*, 3885. (h) H. C. Shen, *Tetrahedron* **2008**, *64*, 7847. (i) I. Fernández, J. L. Mascareñas, *Org. Biomol. Chem.* **2012**, *10*, 699.
- (a) A. G. Lohse, R. P. Hsung, *Org. Lett.* **2009**, *11*, 3430. (b) J. E. Antoline, R. P. Hsung, *Synlett* **2008**, 739. (c) L. F. You, R. P. Hsung, A. A. Bedermann, A. V. Kurdyumov, Y. Tang, G. S. Buchanan, K. P. Cole, *Adv. Synth. Catal.* **2008**, *350*, 2885. (d) J. B. Feltenberger, R. Hayashi, Y. Tang, E. S. C. Babiash, R. P. Hsung, *Org. Lett.* **2009**, *11*, 3666. (e) E. H. Krenske, K. N. Houk, A. G. Lohse, J. E. Antoline, R. P. Hsung, *Chem. Sci.* **2010**, *1*, 387. (f) R. Hayashi, J. B. Feltenberger, R. P. Hsung, *Org. Lett.* **2010**, *12*, 1152. (g) A. G. Lohse, E. H. Krenske, J. E. Antoline, K. N. Houk, R. P. Hsung, *Org. Lett.* **2010**, *12*, 5506. (h) A. G. Lohse, R. P. Hsung, *Chem. Eur. J.* **2011**, *17*, 3812. (i) J. E. Antoline, E. H. Krenske, A. G. Lohse, K. N. Houk, R. P. Hsung, *J. Am. Chem.*

1 Soc. **2011**, *133*, 14443. (j) A. G. Lohse, R. P. Hsung, M. D.
 2 Leider, S. K. Ghosh, *J. Org. Chem.* **2011**, *76*, 3246. (k) J. B.
 3 Feltenberger, R. P. Hsung, *Org. Lett.* **2011**, *13*, 3114. (l) H. Li, Y.
 4 Tang, R. P. Hsung, *Tetrahedron Lett.* **2012**, *53*, 6138. (m) R.
 5 Hayashi, Z. X. Ma, R. P. Hsung, *Org. Lett.* **2012**, *14*, 252. (n) E.
 6 H. Krenske, S. Z. He, J. Huang, Y. F. Du, K. N. Houk, R. P.
 7 Hsung, *J. Am. Chem. Soc.* **2013**, *135*, 5242. (o) Y. F. Du, E. H.
 8 Krenske, J. E. Antoline, A. G. Lohse, K. N. Houk, R. P. Hsung, *J.*
 9 *Org. Chem.* **2013**, *78*, 1753. (p) L. C. Fang, R. P. Hsung, Z. X.
 10 Ma, W. R. Presser, *Org. Lett.* **2013**, *15*, 4842. (q) L. C. Fang, R. P.
 11 Hsung, *Org. Lett.* **2014**, *16*, 1826. (r) S. Z. He, R. P. Hsung, W. R.
 12 Presser, Z. X. Ma, B. J. Haugen, *Org. Lett.* **2014**, *16*, 2180.

6. J. Hu, B. Tian, X.-Y. Wu, X.-F. Tong, *Org. Lett.* **2012**, *14*,
 13 5074.

14 7. (a) E. A. Anderson, *Org. Biomol. Chem.* **2011**, *9*, 3997. (b)
 15 K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int.*
 16 *Ed.* **2006**, *45*, 7134. (c) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115.

8. (a) J.-Q. Kuang, S.-M. Ma, *J. Org. Chem.* **2009**, *74*, 1763.
 17 (b) J.-Q. Kuang, S.-M. Ma, *J. Am. Chem. Soc.* **2010**, *132*, 1786.

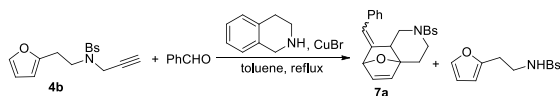
20 9. The crystal data of **2a** have been deposited in CCDC with
 19 number 999306.

10. The crystal data of **3a** have been deposited in CCDC with
 20 number 995122.

11. The low yield of this product may be due to that it is quite
 21 volatile.

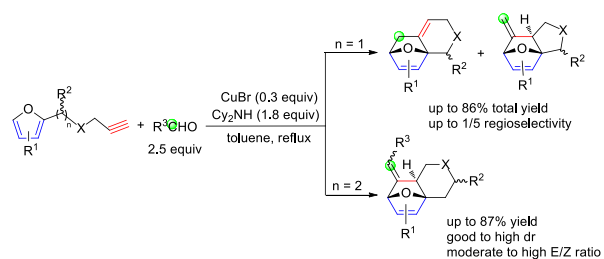
12. The crystal data of **5a** have been deposited in CCDC with
 22 number 1009701.

13. When using **4b** as substrate, we did not observe the targeted
 23 product under the standard conditions. Replacing
 24 dicyclohexylamine with tetrahydroisoquinoline afforded **7a** in
 25 55% isolated yield along with *N*-(2-(furan-2-yl)ethyl)-4-
 26 methylbenzenesulfonamide in 10% yield.



35 14. G. J. Jiang, Q. H. Zheng, M. Dou, L. G. Zhuo, W. Meng, Z.
 36 X. Yu, *J. Org. Chem.* **2013**, *78*, 11783.

One Pot Cascade Synthesis of Fused Heterocycles from Furan-tethered Terminal Alkynes and Aldehydes in the Presence of Amines and CuBr



A novel one-pot protocol for the construction of complex heterocycles through furan tethered terminal alkynes, aldehydes, amines and CuBr upon heating has been developed, giving the cycloadducts in moderate to high yields along with moderate to good regioselectivities.

Yan-Yan Zhang,^a Jian Hao^{a,*} and Min Shi^{b,*}

5