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# Synthesis of 1,4,5,6-tetrahydropyridazines and pyridazines *via* transition-metal-free (4 + 2) cycloaddition of alkoxyallenes with 1,2-diaza-1,3-dienes†

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We developed an economical and practical protocol for the synthesis of 1,4,5,6-tetrahydropyridazines. A diverse range of alkoxyallenes and 1,2-diaza-1,3-dienes undergo (4 + 2) cycloaddition to generate the desired products in excellent yields. The high efficiency, wide substrate scope and good functional group tolerance of this process, coupled with operational simplicity, render the method synthetically attractive. The utility of the cycloaddition is also demonstrated by the preparation of various pyridazines from 1,4,5,6-tetrahydropyridazines.

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For several years, we have been developing the methodologies of cumulative dienes<sup>1</sup> for the synthesis of heterocyclic compounds.<sup>2</sup> In the past few decades, allenes have attracted significant attention in organic synthesis.<sup>3</sup> By virtue of their reactive and cumulative double bonds, allenes are widely used as valuable C3-feedstocks.<sup>4</sup> Functional groups at the double bonds of allene moieties strongly influence the reactivities, and thus allow site- and regioselective transformations. For example allenates, bearing electron-withdrawing substituents (carboxylic ester groups) at the allene moieties, lead to preferred reactions with nucleophiles attacked on the central carbon, and have been thoroughly studied.<sup>5</sup> Nevertheless, investigations of alkoxyallenes are still limited.<sup>6</sup> As special enol ethers, alkoxyallenes were frequently employed as strong nucleophiles *via* deprotonations and metalations.<sup>7</sup> Moreover, the electronic bias imposed by the alkoxy groups makes them unique dienophiles; the electron-deficient or electron-rich double bonds could engage in cycloadditions.

Recently, Goeke<sup>8</sup> and Luo<sup>9</sup> *et al.* developed (4 + 2) annulation of alkoxyallenes with cyclopentadienes and  $\beta,\gamma$ -unsaturated  $\alpha$ -keto esters, respectively (Scheme 1). These established methods employed expensive heavy metals (Au, In), which maybe

resulting in the contamination of medicinal products. Accordingly, there is a clear demand for the development of transition-metal-free protocols with high efficiency, operational simplicity, atom economy and general applicability.

In 2015, Favi *et al.* developed (4 + 2) cycloaddition of alkoxyallene with  $\alpha$ -halohydrazone (precursors of 1,2-diaza-1,3-dienes), but in which only methoxyallene could be employed as the dienophile (Scheme 2a).<sup>10</sup> The approach allows access to 1,4,5,6-tetrahydropyridazines, which are versatile building blocks and prevalent in a large number of pharmacologically active molecules.<sup>11</sup> However, the cyclization suffered from moderate conversion and narrow substrates scope, required long reaction time (up to 7 days) and high stoichiometric ratio of reactants (methoxyallene/Na<sub>2</sub>CO<sub>3</sub>/ $\alpha$ -halohydrazone = 7 : 5 : 1).

Currently, there is an increased drive to find new ways to maximize synthetic efficiency and minimize waste in chemical and pharmaceutical industries.<sup>12</sup> As part of our group's

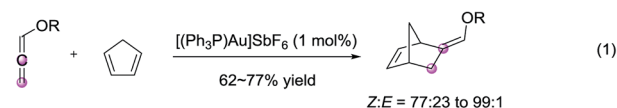
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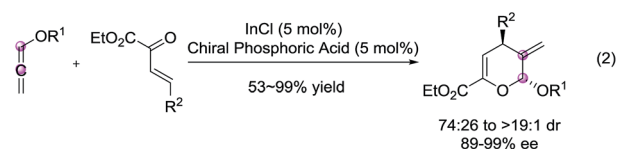
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra. CCDC 1904934 (3aa). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra02712b

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### Electron-deficient double bond engaged in the cycloaddition

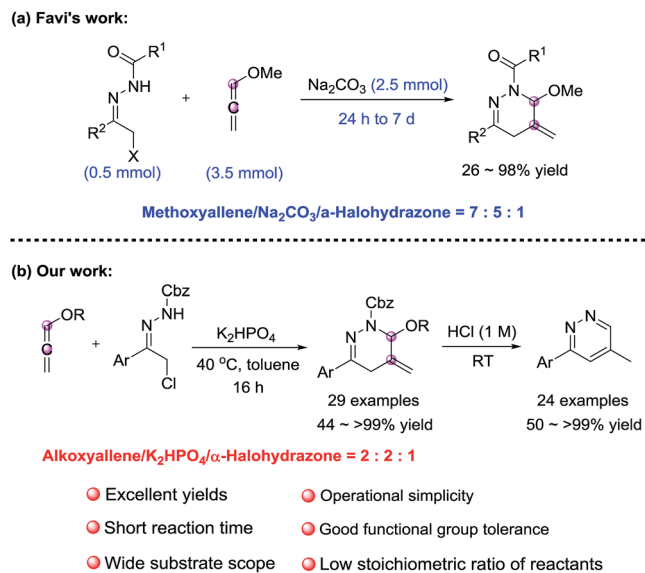


### Electron-rich double bond engaged in the cycloaddition



Scheme 1 Transition-metal-catalyzed (4 + 2) cycloadditions of alkoxyallenes.





Scheme 2 (4 + 2) cycloadditions of alkoxyallenes with 1,2-diaza-1,3-dienes.

continuous interest in cumulene chemistry and transition-metal-free synthesis,<sup>13</sup> the (4 + 2) annulation of alkoxyallene with 1,2-diaza-1,3-dienes was thus systematically reinvestigated, and in this context, we demonstrate that the cyclization can proceed with a broad range of substrates, producing a wide variety of 1,4,5,6-tetrahydropyridazines in high efficiency. Besides, it was found that these adducts could further convert into pyridazines (Scheme 2b).

The investigations began with assaying the (4 + 2) cycloaddition between benzyloxyallene **1a** and  $\alpha$ -halohydrazone **2a**, as shown in Table 1. A survey of solvents identified toluene as the most suitable media (entries 1–4). Protic solvent (MeOH) did not promote the reaction. Several bases were screened to evaluate their ability to promote the cyclization at ambient temperature (entries 4–9). Trace cycloadduct was generated by using organic base [TEA, DIPEA] (entries 5 and 6), whereas inorganic base [ $\text{K}_2\text{CO}_3$ , KOAc] afforded the desired product in good yields (entries 7–8).  $\text{K}_2\text{HPO}_4$  was found to be most efficient and afforded predominantly the desired 1,4,5,6-tetrahydropyridazine **3a** in 94% yield at room temperature for 72 h (entry 9). Then, in order to speed up the cycloaddition, changes of temperature was made (entries 10 and 11). To our delight, a breakthrough was achieved. Raising the reaction temperature to 40 °C benefited the reaction rate dramatically and the full conversion was reached in only 16 h (entry 10). To our surprise, when the temperature was increased to 50 °C, the yield of **3a** decreased to 45% (entry 11). The negative impact on the yield may blame the low stability of **1a** at higher temperature. Besides,  $\alpha$ -halohydrazone **2** bearing different protecting groups [Cbz, Ac, Boc] were all suitable substrates, producing the corresponding products in uniformly high yields, and the yield is slightly higher when **2b** was employed (entries 12–14). Meanwhile, we also investigated the effect of the stoichiometric ratio of **1a/2b** (entries 15 and 16).

After extensive experimentation to reduce the amount of  $\alpha$ -halohydrazone **2b**, we identified the following optimal protocol: reaction of **1a** and **2b** with a stoichiometric ratio of 2.0 : 1.0 in the presence of  $\text{K}_2\text{HPO}_4$  (2.0 equiv.) in toluene at 40 °C for 16 h

Table 1 Screening of reaction conditions<sup>a</sup>

Entry	R	2	X	Base	Solvent	Temp. (°C)	Time (h)	Yield <sup>b</sup> (%)
1	Bz	2a	4.0	$\text{Na}_2\text{CO}_3$	MeOH	RT	72	NR
2	Bz	2a	4.0	$\text{Na}_2\text{CO}_3$	DCM	RT	72	87
3	Bz	2a	4.0	$\text{Na}_2\text{CO}_3$	$\text{CHCl}_3$	RT	72	89
4	Bz	2a	4.0	$\text{Na}_2\text{CO}_3$	Toluene	RT	72	90
5	Bz	2a	4.0	TEA	Toluene	RT	72	<5
6	Bz	2a	4.0	DIPEA	Toluene	RT	72	<5
7	Bz	2a	4.0	$\text{K}_2\text{CO}_3$	Toluene	RT	72	72
8	Bz	2a	4.0	KOAc	Toluene	RT	72	80
9	Bz	2a	4.0	$\text{K}_2\text{HPO}_4$	Toluene	RT	72	94
10	Bz	2a	4.0	$\text{K}_2\text{HPO}_4$	Toluene	40	16	92
11	Bz	2a	4.0	$\text{K}_2\text{HPO}_4$	Toluene	50	16	45
12	Cbz	2b	4.0	$\text{K}_2\text{HPO}_4$	Toluene	40	16	94
13	Ac	2c	4.0	$\text{K}_2\text{HPO}_4$	Toluene	40	16	68
14	Boc	2d	4.0	$\text{K}_2\text{HPO}_4$	Toluene	40	16	90
15	Cbz	2b	2.0	$\text{K}_2\text{HPO}_4$	Toluene	40	16	94
16	Cbz	2b	1.0	$\text{K}_2\text{HPO}_4$	Toluene	40	16	89

<sup>a</sup> Reaction conditions: **1a** (X equiv.), **2** (0.2 mmol), base (2.0 equiv., 0.4 mmol), solvent (2 mL). <sup>b</sup> Yield was that of the isolated product. NR: no reaction.



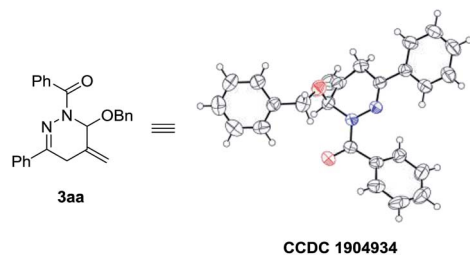


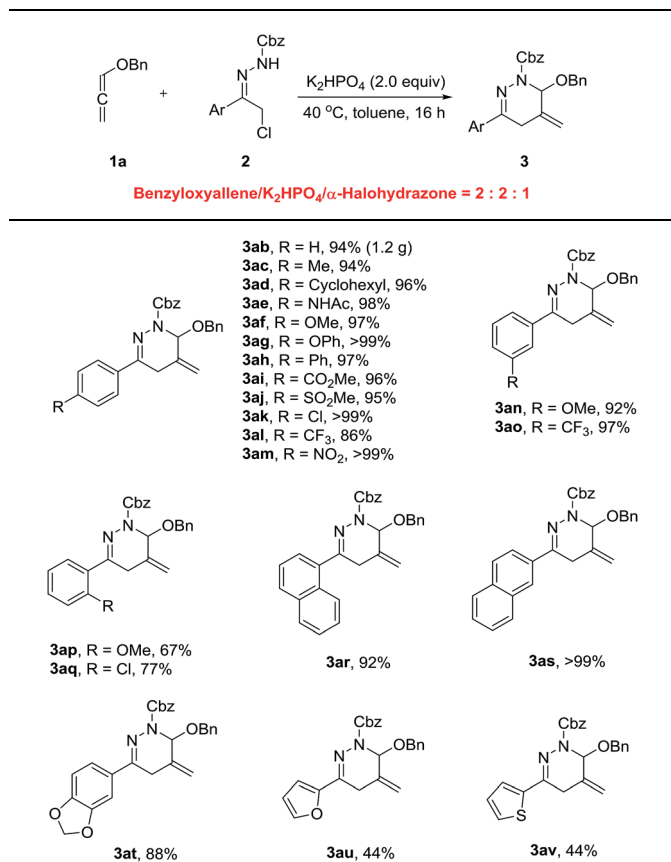
Fig. 1 Determining the structure of **3aa**.

(benzyloxyallene/ $K_2HPO_4$ / $\alpha$ -halohydrazone = 2 : 2 : 1). It is also worth mentioning that all the reactions were conducted open to air with no need for exclusion of air or moisture.

The structure of **3aa** (CCDC 1904934) was unambiguously assigned by single crystal X-ray diffraction analysis (Fig. 1). The structure of **3** were assigned by analog.<sup>14</sup>

Having identified the optimized reaction conditions, the substrate scope of the cyclization was studied, and a variety of 1,4,5,6-tetrahydropyridazines **3** were synthesized in decent yields (Table 2). From a practical perspective, gram scale reaction was performed, **3ab** was obtained without erosion of the

Table 2 Substrate scope with respect to  $\alpha$ -halohydrazone **2**<sup>a,b</sup>



<sup>a</sup> Reactions were performed with **1a** (0.4 mmol), **2** (0.2 mmol),  $K_2HPO_4$  (0.4 mmol) in toluene (2.0 mL) at 40 °C for 16 h. <sup>b</sup> Yield was that of the isolated product. See ESI for details.

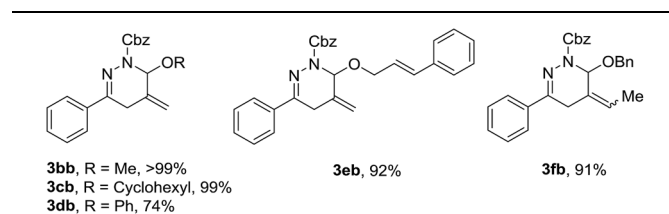
yield, as shown in the parenthesis. We investigated the electronic effects of different aryl groups at the *para* positions of 1,2-diaza-1,3-dienes. All the  $\alpha$ -halohydrazone **2** could well tolerate the existence of electron-neutral, electron-rich or electron-poor phenyl rings, and furnished the products **3ac–3am** in uniformly excellent yields. In addition, we also demonstrated that the position of substituents at the *meta* positions of phenyl groups did not affect the reaction. However, when the substituents (MeO, Cl) were introduced at the *ortho* positions of the aromatic rings, the yields were decreased dramatically, maybe due to the steric hindrance on the aromatic rings (**3ap–3aq**). Besides, on replacement of the phenyl groups with  $\alpha$ -naphthyl,  $\beta$ -naphthyl and 5-benzo[*d*][1,3]dioxolyl group, respectively, the reactions could still undergo smoothly, affording the desired 1,4,5,6-tetrahydropyridazines (**3ar–3at**) in high yields. In contrast,  $\alpha$ -halohydrazone bearing 2-furanyl or 2-thiophenyl group showed lower reactivity for the cycloaddition, tended to give the cyclization product in diminished yields (**3au–3av**).

We next explored the possibility that the alkoxyallenes can bear other substituents, such as methyl (**1b**), cyclohexyl (**1c**), phenyl (**1d**) and cinnamyl (**1e**) groups. In fact, these alkoxyallenes proved to be compatible with the reaction conditions and led to smooth cyclization with  $\alpha$ -halohydrazone **2b** in good to excellent yields (Table 3). More interestingly, we also noticed that a similarly excellent yield was obtained when the reaction was conducted with racemic 3-methyl-substituted benzyloxyallene (**1f**).<sup>15</sup> Unfortunately, despite vigorous efforts, a qualified single crystal of **3fb** for X-ray crystallographic analysis could not be obtained to determine the relative configuration. Systematic experimentation of the annulation of 3-substituted alkoxyallenes is ongoing.

To further underscore the synthetic utility of the current method, we next sought to examine its application to nitrogen-substituted allenes,<sup>16</sup> with the goal to provide a versatile approach for drug leads. As expected, the same reaction conditions could be utilized for the cycloaddition of allenamine (**1g**) and allenamide (**1h**) with  $\alpha$ -halohydrazone **2b**, respectively, providing the corresponding cycloadducts in excellent yields, albeit allenamide (**1i**) afforded a lower yield, maybe due to the strong electron-withdrawing effect of the phthalimido substituent (Table 4).

A possible mechanism for this cyclization was presented in Scheme 3. The 1,2-diaza-1,3-dienes is supposed to be produced

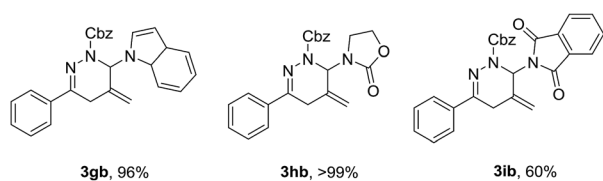
Table 3 Substrate scope with respect to allene **1**<sup>a,b</sup>



<sup>a</sup> Reactions were performed with **1** (0.4 mmol), **2b** (0.2 mmol),  $K_2HPO_4$  (0.4 mmol) in toluene (2.0 mL) at 40 °C for 16 h. <sup>b</sup> Yield was that of the isolated product. See ESI for details.



Table 4 Substrate scope with respect to nitrogen-substituted allenes<sup>a,b</sup>

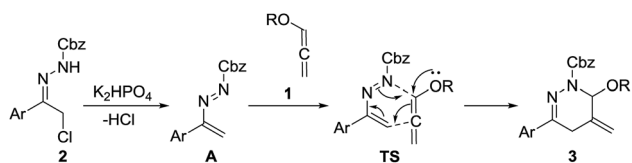


<sup>a</sup> Reactions were performed with **1** (0.4 mmol), **2b** (0.2 mmol), K<sub>2</sub>HPO<sub>4</sub> (0.4 mmol) in toluene (2.0 mL) at 40 °C for 16 h. <sup>b</sup> Yield was that of the isolated product. See ESI for details.

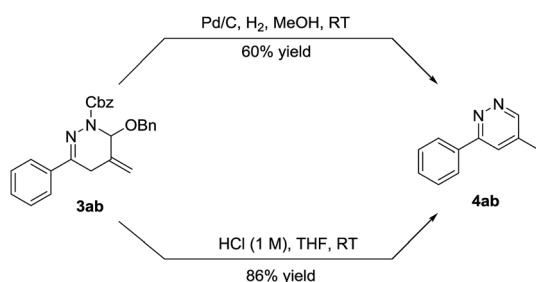
*in situ* from 1,4-elimination of  $\alpha$ -halohydrazone **2** under basic condition, and then intercepted by benzyloxyallene **1** to undergo inverse electron-demand aza-Diels–Alder reaction *via* transition state **TS** which finally results in the formation of **3**.

The high efficiency, wide substrate scope, good functional group tolerance of the above-mentioned processes, coupled with operational simplicity, make the cycloaddition an attractive method for the synthesis of 1,4,5,6-tetrahydropyridazines. Moreover, we found that the cycloadduct **3ab** could be readily transformed into pyridazine **4ab** by reduction in 60% yield or by hydrolysis in 86% yield. Furthermore, the hydrolysis in acidic condition (1 M HCl) proved to be an outstanding synthetic approach to pyridazines, since it was easily performed and provided the desired product in a transition-metal-free, efficient and economical manner, as shown in Scheme 4.

It should be stressed in particular that the pyridazine skeletons are privileged structure moieties in many biologically active natural products, organocatalysts, ligands and synthetic materials.<sup>17</sup> In order to explore the small heterocycles of pharmaceutical interest, we became interested in developing the hydrolysis method. When the cycloadducts 1,4,5,6-tetrahydropyridazines **3** were treated with hydrochloric acid at room temperature, a series of pyridazines were successfully delivered

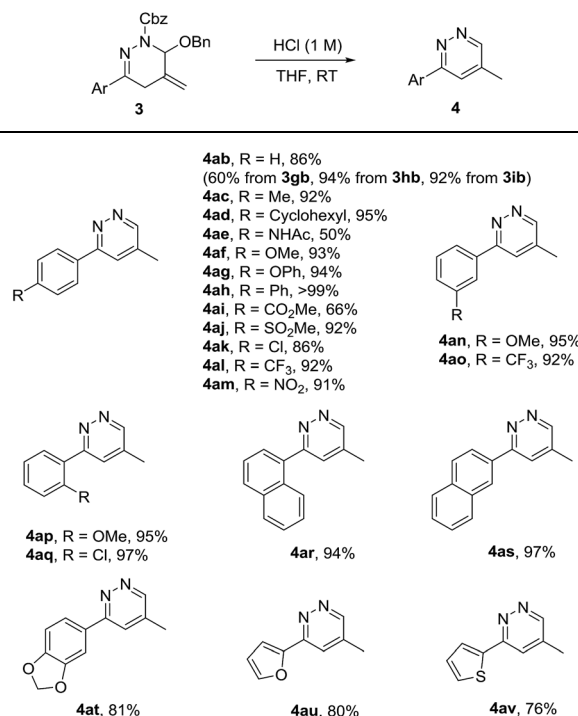


Scheme 3 Proposed mechanism for the transition-metal-free (4 + 2) cycloaddition of alkoxyallenes with 1,2-diaza-1,3-dienes.



Scheme 4 Synthesis of pyridazine. See the ESI† for details.

Table 5 Synthesis of pyridazines<sup>a,b</sup>



<sup>a</sup> **3** (0.24 mmol), THF (10 mL), 1 M HCl (0.15 mL), at room temperature for 12 h. <sup>b</sup> Yield was that of the isolated product. See ESI for details.

in good to excellent yield, regardless of the nature and the positions of the aryl substituent. In contrast, the desired compounds **4ae** and **4ai** were afforded in moderate yields, due to the susceptibility of amide (–NHAc) and ester (–CO<sub>2</sub>Me) groups to hydrolysis in the acidic condition (Table 5). What's more, pyridazine **4ab** could be prepared likewise using **3gb**, **3hb** and **3ib** as starting materials despite that **3gb** underwent slower hydrolysis even employing higher concentration of HCl (3 M).

## Conclusions

In summary, we have introduced a straightforward transition-metal-free method to synthesize 1,4,5,6-tetrahydropyridazines from alkoxyallenes and  $\alpha$ -halohydrazone. This transformation proceeds with lower stoichiometric ratio of reactants in shorter reaction time, and produces a dramatic increase in yield and substrate scope, compared with the existing methods. The utility of the cycloaddition is demonstrated by the preparation of various pyridazines from the cycloadducts. As such, it is more applicable to the pharmaceutically promising 1,4,5,6-tetrahydropyridazines and pyridazines, specifically with respect to substitution pattern and functional group compatibility. Further studies to expand the application in drug synthesis are in progress.

## Conflicts of interest

There are no conflicts to declare.





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## Notes and references

- 1 A. D. Allen and T. T. Tidwell, *Chem. Rev.*, 2013, **113**, 7287.
- 2 (a) X.-L. Huang, L. He, P.-L. Shao and S. Ye, *Angew. Chem., Int. Ed.*, 2009, **48**, 192; (b) P.-L. Shao, X.-Y. Chen and S. Ye, *Angew. Chem., Int. Ed.*, 2010, **49**, 8412; (c) P.-L. Shao, X.-Y. Chen, L.-H. Sun and S. Ye, *Tetrahedron Lett.*, 2010, **51**, 2316; (d) P.-L. Shao, L.-T. Shen and S. Ye, *Chin. J. Chem.*, 2012, **30**, 2688; (e) J.-Y. Liao, P.-L. Shao and Y. Zhao, *J. Am. Chem. Soc.*, 2015, **137**, 628; (f) Z. Wang, H. Xu, Q. Su, P. Hu, P.-L. Shao, Y. He and Y. Lu, *Org. Lett.*, 2017, **19**, 3111; (g) G. P. Y. Kok, P.-L. Shao, J.-Y. Liao, S. N. F. B. S. Ismail, W. Yao, Y. Lu and Y. Zhao, *Chem.–Eur. J.*, 2018, **24**, 10513.
- 3 (a) *Modern Allene Chemistry*, ed. N. Krause and A. S. K. Hashmi, Wiley-VCH, Weinheim, 2004; for selected reviews on allene, see: (b) S. Ma, *Acc. Chem. Res.*, 2003, **36**, 701; (c) S. Ma, *Chem. Rev.*, 2005, **105**, 2829; (d) Z. Wang, X. Xu and O. Kwon, *Chem. Soc. Rev.*, 2014, **43**, 2927; (e) F. López and J. L. Mascareñas, *Chem. Soc. Rev.*, 2014, **43**, 2904; (f) H. Ni, W.-L. Chan and Y. Lu, *Chem. Rev.*, 2018, **118**, 9344; (g) T. Cañeque, F. M. Truscott, R. Rodriguez, G. Maestri and M. Malacria, *Chem. Soc. Rev.*, 2014, **43**, 2916.
- 4 For recent studies on allene, see: (a) H. Zhou, Y. Wang, L. Zhang, M. Cai and S. Luo, *J. Am. Chem. Soc.*, 2017, **139**, 3631; (b) T. M. Beck and B. Breit, *Angew. Chem., Int. Ed.*, 2017, **56**, 1903; (c) N. Casanova, K. P. D. Rio, R. García-Fandiño, J. L. Mascareñas and M. Gulías, *ACS Catal.*, 2016, **6**, 3349; (d) L. A. Schwartz, M. Holmes, G. A. Brito, T. P. Gonçalves, J. Richardson, J. C. Ruble, K.-W. Huang and M. J. Krische, *J. Am. Chem. Soc.*, 2019, **141**, 2087; (e) M. Holmes, K. D. Nguyen, L. A. Schwartz, T. Luong and M. J. Krische, *J. Am. Chem. Soc.*, 2017, **139**, 8114; (f) J. Liu, Q. Liu, R. Franke, R. Jackstell and M. Beller, *J. Am. Chem. Soc.*, 2015, **137**, 8556; (g) L.-Y. Mei, Y. Wei, X.-Y. Tang and M. Shi, *J. Am. Chem. Soc.*, 2015, **137**, 8131; (h) Y. Jiang, A. B. Diagne, R. J. Thomson and S. E. Schaus, *J. Am. Chem. Soc.*, 2017, **139**, 1998; (i) W. Zhao and J. Montgomery, *J. Am. Chem. Soc.*, 2016, **138**, 9763; (j) W. Yao, X. Dou and Y. Lu, *J. Am. Chem. Soc.*, 2015, **137**, 54; (k) H. Wu, F. Haeffner and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2014, **136**, 3780.
- 5 (a) B. J. Cowen and S. J. Miller, *Chem. Soc. Rev.*, 2009, **38**, 3102; (b) N. Krause and C. Winter, *Chem. Rev.*, 2011, **111**, 1994.
- 6 For selected reviews on alkoxyallene, see: (a) R. Zimmer and H.-U. Reissig, *Chem. Soc. Rev.*, 2014, **43**, 2888; (b) M. Brasholz, H.-U. Reissig and R. Zimmer, *Acc. Chem. Res.*, 2009, **42**, 45; (c) M. A. Tius, *Chem. Soc. Rev.*, 2014, **43**, 2979; (d) H.-U. Reissig and R. Zimmer, *Synthesis*, 2017, **49**, 3291.
- 7 For recent studies on alkoxyallene, see: (a) H. Zhou, Z. Wei, J. Zhang, H. Yang, C. Xia and G. Jiang, *Angew. Chem., Int. Ed.*, 2017, **56**, 1077; (b) B. M. Trost, J. Xie and J. D. Sieber, *J. Am. Chem. Soc.*, 2011, **133**, 20611; (c) H. Kim, W. Lim, D. Im, D. G. Kim and Y. H. Rhee, *Angew. Chem., Int. Ed.*, 2012, **51**, 12055; (d) W. Lim, J. Kim and Y. H. Rhee, *J. Am. Chem. Soc.*, 2014, **136**, 13618; (e) Z. Wang, C. Nicolini, C. Hervieu, Y.-F. Wong, G. Zanoni and L. Zhang, *J. Am. Chem. Soc.*, 2017, **139**, 16064; (f) J. Zhang, L. Zhu, K. Shen, H. Yang, X.-C. Hang and G. Jiang, *Chem. Sci.*, 2019, **10**, 1070; (g) N. W. Mszar, F. Haeffner and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2014, **136**, 3362; (h) Y. Tani, T. Fujihara, J. Terao and Y. Tsuji, *J. Am. Chem. Soc.*, 2014, **136**, 17706; (i) T. H. Meyer, J. C. A. Oliveira, S. C. Sau, N. W. J. Angand and L. Ackermann, *ACS Catal.*, 2018, **8**, 9140; (j) R. Kuppasamy, R. Santhoshkumar, R. Boobalan, H.-R. Wu and C.-H. Cheng, *ACS Catal.*, 2018, **8**, 1880.
- 8 G. Wang, Y. Zou, Z. Li, Q. Wang and A. Goeke, *Adv. Synth. Catal.*, 2011, **353**, 550.
- 9 S. Li, J. Lv and S. Luo, *Org. Chem. Front.*, 2018, **5**, 1787.
- 10 O. A. Attanasi, G. Favi, F. Mantellini, S. Mantenuto, G. Moscatelli and S. Nicolini, *Synlett*, 2015, **26**, 193.
- 11 (a) S. M. M. Lopes, A. L. Cardoso, A. Lemos and T. M. V. D. Pinho e Melo, *Chem. Rev.*, 2018, **118**, 11324; (b) A. M. Shelke and G. Suryavanshi, *Org. Lett.*, 2016, **18**, 3968; (c) P. J. Rybczynski, D. W. Combs, K. Jacobs, R. P. Shank and B. Dubinsky, *J. Med. Chem.*, 1999, **42**, 2403; (d) H. Huo, R. A and Y. Gong, *J. Org. Chem.*, 2019, **84**, 2093; (e) X. Zhong, J. Lv and S. Luo, *Org. Lett.*, 2015, **17**, 1561; (f) S. M. M. Lopes, A. F. Brigas, F. Palacios, A. Lemos and T. M. V. D. P. e Melo, *Eur. J. Org. Chem.*, 2012, 2152.
- 12 Y. Hayashi, *Chem. Sci.*, 2016, **7**, 866.
- 13 (a) P.-L. Shao, Z.-R. Li, Z.-P. Wang, M.-H. Zhou, Q. Wu, P. Hu and Y. He, *J. Org. Chem.*, 2017, **82**, 10680; (b) Z.-P. Wang, Y. He and P.-L. Shao, *Org. Biomol. Chem.*, 2018, **16**, 5422.
- 14 CCDC 1904934 (3aa) contain the crystallographic data for this paper. Selected data are also included in the ESI.†
- 15 (a) T. Pecchioli, F. Cardona, H.-U. Reissig, R. Zimmer and A. Goti, *J. Org. Chem.*, 2017, **82**, 5835; (b) A. Hausherr and H.-U. Reissig, *Synthesis*, 2018, **50**, 2546.
- 16 (a) T. Lu, Z. Lu, Z.-X. Ma, Y. Zhang and R. P. Hsung, *Chem. Rev.*, 2013, **113**, 4862; (b) R. Blicke, R. A. A. Abdine, M. Taillefer and F. Monnier, *Org. Lett.*, 2018, **20**, 2232; (c) L. Perego, R. Blicke, A. Groué, F. Monnier, M. Taillefer, I. Ciofini and L. Grimaud, *ACS Catal.*, 2017, **7**, 4253; (d) R. Blicke, J. Bahri, M. Taillefer and F. Monnier, *Org. Lett.*, 2016, **18**, 1482; (e) X.-X. Li, L.-L. Zhu, W. Zhou and Z. Chen, *Org. Lett.*, 2012, **14**, 436; (f) S. Pang, X. Yang, Z.-H. Cao, Y.-L. Zhang, Y. Zhao and Y.-Y. Huang, *ACS Catal.*, 2018, **8**, 5193; (g) Y. Liu, A. De Nisi, A. Cerveri, M. Monari and M. Bandini, *Org. Lett.*, 2017, **19**, 5034.
- 17 (a) M. Borger and J. H. Frederich, *Org. Lett.*, 2019, **21**, 2397; (b) M. Saldías, N. Guzmán, F. Palominos, C. Sandoval-Altamirano, G. Günther, N. Pizarro and A. Vega, *ACS Omega*, 2019, **4**, 4679; (c) C. Liu, J. Lin, R. Moslin, J. S. Tokarski, J. Muckelbauer, C. Chang, J. Tredup, D. Xie, H. Park, P. Li, D.-R. Wu, J. Strnad, A. Zupa-Fernandez,



L. Cheng, C. Chaudhry, J. Chen, C. Chen, H. Sun, P. Elzinga, C. D'arienzo, K. Gillooly, T. L. Taylor, K. W. McIntyre, L. Salter-Cid, L. J. Lombardo, P. H. Carter, N. Aranibar, J. R. Burke and D. S. Weinstein, *ACS Med. Chem. Lett.*, 2019, **10**, 383; (d) H. R. Kalhor and A. N. Khodadadi, *Chem. Res. Toxicol.*, 2018, **31**, 1092; (e) M. Li, Y. Yuan and Y. Chen, *ACS Appl. Mater. Interfaces*, 2018, **10**, 1237; (f)

A. T. Londregan, D. W. Piotrowski and L. Wei, *ACS Comb. Sci.*, 2016, **18**, 651; (g) A. Tamaki, S. Kojima and Y. Yamamoto, *J. Org. Chem.*, 2016, **81**, 8710; (h) H. B. Abed, O. Mammoliti, O. Bande, G. Van Lommen and P. Herdewijn, *J. Org. Chem.*, 2013, **78**, 7845; (i) T. J. Ritchie, S. J. F. Macdonald, S. Peace, S. D. Pickett and C. N. Luscombe, *Med. Chem. Commun.*, 2012, **3**, 1062.

