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Chemo- and regioselective reductive deoxygenation of 1-en-4-yn-ols into 1,4-enynes through FeF_3 and TfOH co-catalysis†

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We report chemo- and regioselective direct reductive deoxygenation of 1-en-4-yn-3-ols into 1,4-enynes through FeF_3 and TfOH cooperative catalysis under NBSH-mediated conditions. Further, we show the efficient synthesis of a pharmaceutically significant 1,4-enyne. The present methodology can also be used for chemo- and regioselective direct deoxygenation of other alcohols.

Deoxygenation of alcohol into hydrocarbons plays a significant role in organic synthesis, especially in total synthesis and modification of natural products.[1] Thus far, alcohol deoxygenation has been approached through various routes,[2] which can be categorised into a direct procedure with reductive deoxygenation of alcohols in a single step[2,3] or an indirect procedure with alcohols converted into other functional groups prior to reduction.[2,4] Direct reductive dehydroxylation of a hydroxyl group under mild reaction conditions is challenging due to the high dissociation energy of the C–O bond and strong alkaline nature of the hydroxide ion (OH^-) generated during the reaction. The most widely applied strategy for alcohol dehydroxylation is ionic hydrogenation.[5]

In natural products, 1,4-enynes are important structural motifs;[6] further, 1,4-enynes can be applied in organic synthesis.[7] Moreover, 1,4-enynes such as hypoxoside (isolated from the corms of Hypoxis plants),[6] rooperol[8a] and (*E*)-1-methoxy-4-(5-phenylpent-4-en-1-yn-1-yl)benzene[8b] exhibit remarkable anticancer activities against oesophageal carcinoma cells. Thus, researchers have actively investigated versatile methods for the synthesis of 1,4-enynes over the past few decades.[9–12] These methods are numerous and include the direct synthesis of 1,4-enynes *via* palladium-catalysed decarboxylation of allylic alkynoates (Fig. 1a);[9a] nickel-catalysed addition of terminal alkynes to 1,3-dienes (Fig. 1b);[9b,c] Wittig reaction with propargylic aldehydes (Fig. 1c);[9d] alkynylation of allylic halides,[7a–c,9e] allylic alcohols,[9f,g] allylic acetates[9h,i] or allylic carbonates[9j] with the appropriate alkynyl compounds (Fig. 1d); coupling propargylic alcohols with alkenes,[9k,l] vinyl silanes[9m] or vinyl iodides[7d] (Fig. 1e); enantioselective synthesis of 1,4-enynes[8b,10] *via* double bond migration; alkynylation of allylic alcohols,[8b] allylic phosphates[10a–c] or allylic picolinates[10d] (Fig. 1f); miscellaneous methods;[11] and indirect methods.[7e,12] Nonetheless, the direct alcohol deoxygenation approach to this kind of compounds has not yet been established so far.

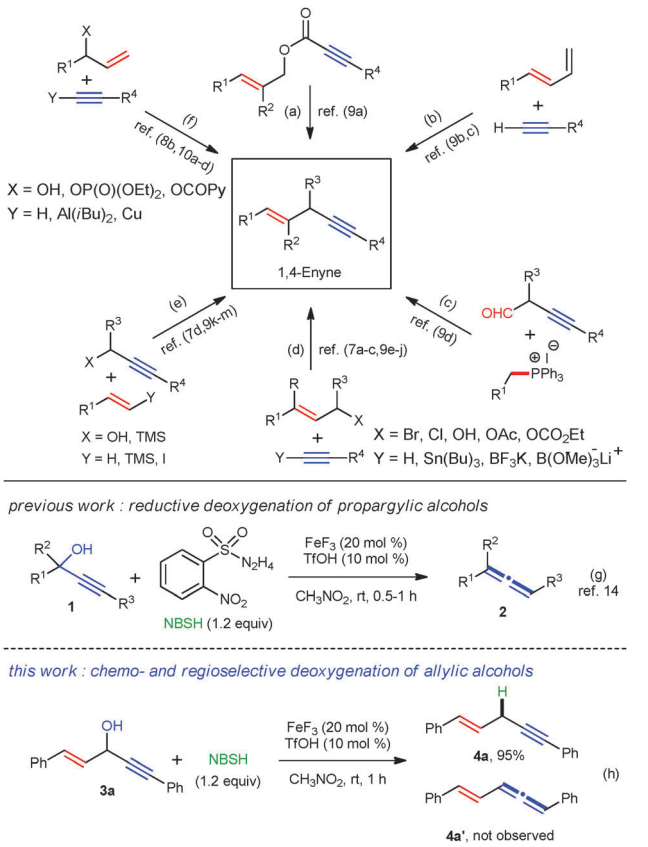

Fig. 1 Methods for synthesizing 1,4-enynes.

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From our persistent efforts in the development of new reactions based on alkyne functionalisation,[13] we recently reported Lewis and Brønsted acid-catalysed and 2-nitrobenzenesulfonylhydrazide (NBSH)-mediated reductive deoxyallenylation of 3°-propargylic alcohols (**1**) into a variety of mono-, di- and trisubstituted allenes (**2**) (Fig. 1g).[14] During this investigation, we observed reductive dehydroxylation of 1,5-diphenylpent-1-en-4-yn-3-ol (**3a**) into an 1,4-enyne, pent-1-en-4-yne-1,5-diyldibenzene (**4a**), with a 95% isolated yield (Fig. 1h). The 1,5-diphenylpent-1-en-4-yn-3-ol (**3a**) may have converted into an 1,4-enyne (**4a**) rather than an allene (**4a′**) due to propargylic carbocation resonance rearrangement into a benzylic carbocation for extra stability (see the plausible mechanism; Fig. 2). To the best of our knowledge, using 1-en-4-yn-ols as substrates to synthesise 1,4-enynes has not previously been demonstrated.[9–12] Because this method of reductive deoxygenation of alcohols into hydrocarbons is novel in organic chemistry (*vide supra*),[1–5] and 1,4-enynes are important chemicals, we believe that investigation into reductive dehydroxylation of 1-en-4-yn-ols (**3**) into 1,4-enynes (**4**) is significant in modern organic synthesis.

Later, we performed the control experiments to check the possible alterations to the standard reaction conditions (Table 1). Performing the reaction without FeF_3 sharply decreased the yield of **3a** to 70% (Table 1, entry 1) whereas, the reaction in the absence of TfOH, completely ceased the reaction (entry 2).

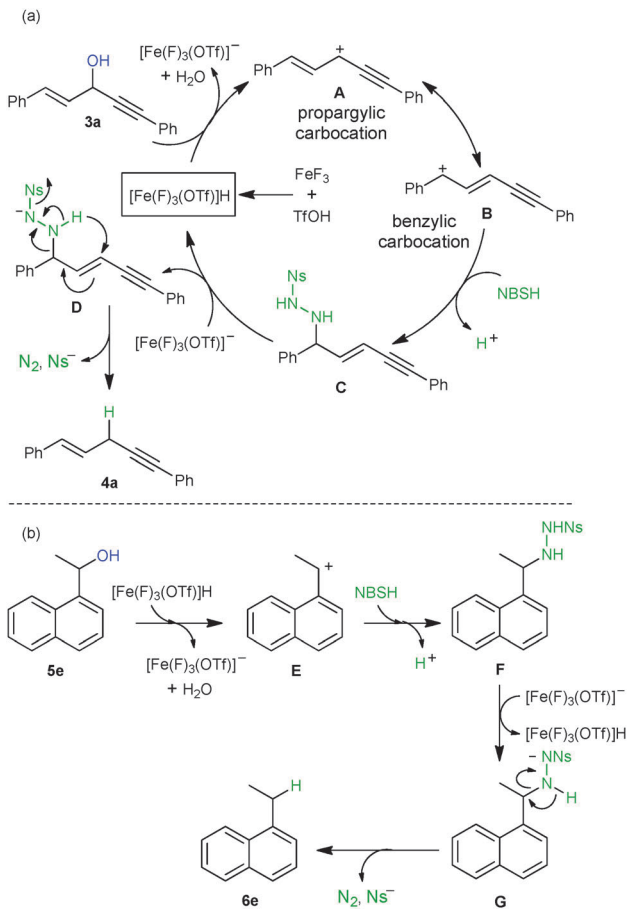
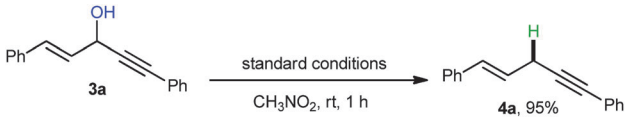


Fig. 2 Plausible mechanism.

Table 1 The control experiments[a]



standard conditions: NBSH (1.2 equiv), FeF_3 (20 mol %), TfOH (10 mol %)

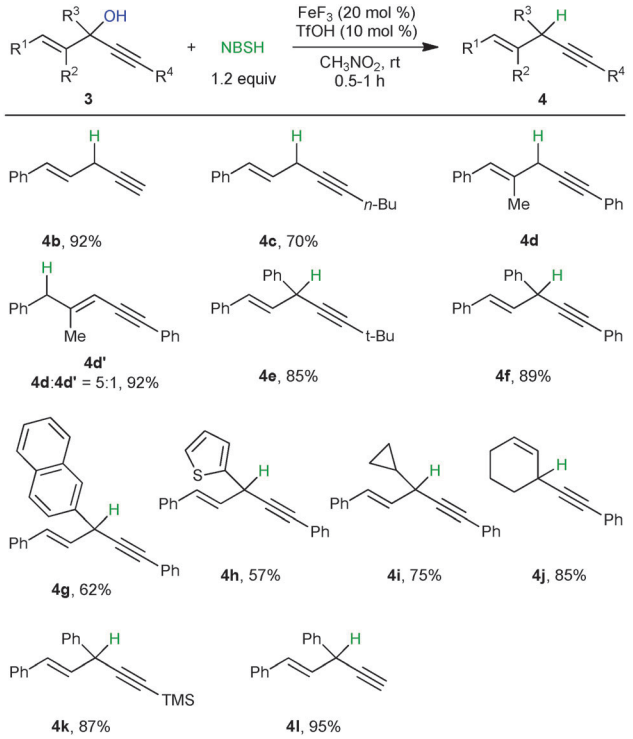
Entry	Difference from standard conditions	**4a** yield[b] (%)
1	Without FeF_3	70
2	No TfOH	0
3	Acetic acid (10 mol%) instead of TfOH	0
4	No NBSH	0
5	$FeCl_2$ (20 mol%) instead of FeF_3	70
6	$FeCl_3$ (20 mol%) intead of FeF_3	72

[a] Reactions were performed on a 0.5 mmol scale of **3a** in 3.0 mL nitromethane as solvent at rt for 1 h. [b] Isolated yields.

These two reactions indicate the significance of combining both FeF_3 and TfOH. Replacing the TfOH with acetic acid, did not allow any reaction to occur (entry 3). Likewise, the reaction without added NBSH did not afford the product (entry 4). Later, performing the reactions in the presence of other iron salts like $FeCl_2$ or $FeCl_3$ in the place of FeF_3, decreased the yield of **4a** to 70–72% isolated yields (entries 5–6). With this, the optimal reaction conditions for 0.5 mmol of **3a** are NBSH (1.2 equiv.), FeF_3 (20 mol%), TfOH (10 mol%) in nitro-methane (3.0 mL) as solvent at RT.

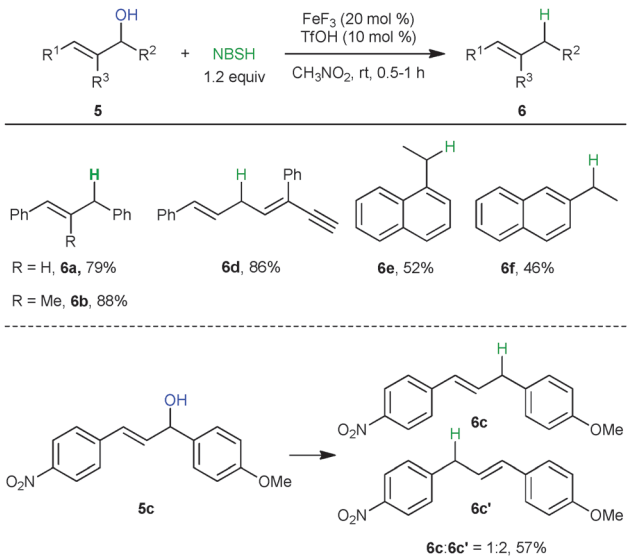
Next, the substrate scope of the protocol was investigated through the reaction of various 1-en-4-yn-ols (**3b–m**) (0.5 mmol) with NBSH (0.6 mmol) in the presence of FeF_3 (20 mol%) and TfOH (10 mol%) in a CH_3NO_2 solvent under an N_2 atmosphere at room temperature (Scheme 1).

The 1-en-4-yn-ols, such as (*E*)-1-phenylpent-1-en-4-yn-3-ol (**3b**) and the internal 1-en-4-yn-ol (**3c**), underwent reductive dihydroxylation, as expected, to generate the corresponding 1,4-enynes (**4b–c**) in 70–92% isolated yields. However, (*E*)-2-methyl-1,5-diphenylpent-1-en-4-yn-3-ol (**3d**) produced a mixture containing a direct deoxygenative 1,4-enyne (**4d**) and rearranged product (**4d′**) at a 5 : 1 ratio and in 92% yield. The greater levels of **4d** are due to the greater stability of the benzylic carbocation. Specifically, the tertiary 1-en-4-yn-ols (**3e–h**) with different structural motifs at propargylic positions, such as phenyl (**3e–f**), 2-naphthyl (**3g**) and 2-thiophenyl (**3h**), participated in reductive dehydroxylation under standard conditions without difficulty, thereby producing the target 1,4-enynes (**4e–h**) in 57–89% isolated yields. Notably, 1-en-4-yn-ols (**3i–j**) with strained alicyclic moieties, such as cyclopropyl (**3i**) and cyclohexenyl (**3j**), also underwent a smooth reductive dehydroxylation reaction, which formed 1,4-enynes (**4i–j**) at 75–85% isolated yields. Finally, 1-en-4-yn-ols with a labile TMS-moiety (**3k**) and terminal 1-en-4-yn-ol (**3l**) were reductively dehydroxylated into 1,4-enynes (**4k–l**) in 87–95% isolated yields. From these data, the substrate scope of the present protocol is quite broad, and both terminal and internal 1-en-4-yn-ols can be applied to FeF_3 and TfOH cooperatively catalysed and NBSH-mediated direct reductive dehydroxylation of 1-en-4-yn-ols into the corresponding 1,4-enynes with moderate to excellent yields.

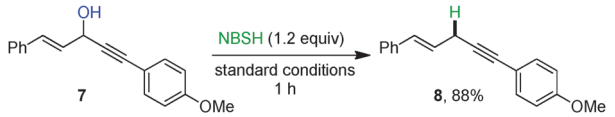


Scheme 1 Synthesis of divergent 1,4-enynes from 1-en-4-yn-ols.

To examine the generality of this FeF_3 and TfOH cooperatively catalysed and the NBSH-mediated reductive dehydroxylation strategy, we further investigated the reaction using allylic alcohols and naphthyl alcohols (Scheme 2). The allylic alcohols **5a** and **5b** bearing phenyl rings at the R^1 and R^2 positions afforded **6a** and **6b** at 79% and 88% isolated yields, respectively. However, allylic alcohol **5c** with different phenyl rings at the R^1 and R^2 positions formed a small quantity of direct deoxygenated product **6c** and a larger quantity of the rearranged



Scheme 2 Reductive deoxygenation of other alcoholic compounds.



Scheme 3 Synthesis of the pharmaceutically significant 1,4-enyne.

product **6c′** at a 1 : 2 ratio and in 57% yield. These products were generated due to the greater stability of the *p*-methoxybenzylic carbocation. Likewise allylic alcohol **5d** underwent dehydroxylation to afford the corresponding **6d** as the product in 86% yield. However, naphthyl alcohol (**5e–f**) deoxygenation produced relatively low 1-ethyl-naphthalene (**6e–f**) yields.

Finally, a pharmaceutical application for this methodology is demonstrated through the synthesis of (*E*)-1-methoxy-4-(5-phenylpent-4-en-1-yn-1-yl)benzene, which is a 1,4-enyne with anticancer properties against oesophageal carcinoma cells.[8b] When (*E*)-5-(4-methoxyphenyl)-1-phenylpent-1-en-4-yn-3-ol (**7**) (0.5 mmol) reacted with NBSH (1.2 equiv.) in the presence of FeF_3 (20 mol%) and TfOH (10 mol%) in a nitromethane solvent, it successfully underwent reductive deoxygenation and efficiently formed (*E*)-1-methoxy-4-(5-phenylpent-4-en-1-yn-1-yl)benzene (**8**) at an 88% isolated yield (Scheme 3).

Based on the above results and our previous report,[14] we propose a plausible reaction mechanism for FeF_3 and TfOH cooperatively catalysed and NBSH-mediated reductive dehydroxylation of 1-en-4-yn-3-ols (**3**) into 1,4-enynes (**4**) (Fig. 2a). The reaction may have been initiated by forming the superacid species $[Fe(F)_3(OTf)]H$ from FeF_3 and TfOH; $[Fe(F)_3(OTf)]H$ reacts with the –OH moiety of 1,5-diphenylpent-1-en-4-yn-3-ol (**3a**) to generate a propargylic carbocation intermediate **A**. This propargylic carbocation rearranges into a benzylic carbocation intermediate **B** through resonance; supporting this step, the formation of an allene product **4a′** (Fig. 1h) is not observed. Furthermore, supporting carbocation resonance, a small quantity of **6c** is formed from **5c** due to rearrangement of the stable *p*-methoxybenzylic carbocation into an unstable *p*-nitrobenzylic carbocation through resonance (Scheme 2). This intermediate **B** reacts with NBSH to form the hydrazide intermediate **C**; supporting this step, we isolated the hydrazide intermediate in our previous investigation.[14] Proton abstraction from the hydrazide **C** by $[Fe(F)_3(OTf)]^-$ instigates the decomposition of **D** into **4a** as the final product and completes the catalytic cycle through regeneration of $[Fe(F)_3(OTf)]H$ whereas, in the case of naphthyl alcohols such as **5e–5f** reductive deoxygenation takes place without the involvement of the carbocation rearrangement step (Fig. 2b).

In conclusion, we have developed a method for chemo- and regio-selective direct reductive deoxygenation of alcohols. This investigation afforded a series of divergent 1,4-enynes. Further, we show the reductive deoxygenation of other alcohols into corresponding hydrocarbons and the efficient synthesis of a pharmaceutically significant 1,4-enyne. The cost-effective catalytic system and general practicality at an ambient temperature are additional appealing features illuminated through this investigation.

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Notes and references

1 (*a*) L. L. Adduci, M. P. McLaughlin, T. A. Bender, J. J. Becker and M. R. Gagné, *Angew. Chem., Int. Ed.*, 2014, **53**, 1646; (*b*) D. S. Palacios, T. M. Anderson and M. D. Burke, *J. Am. Chem. Soc.*, 2007, **129**, 13804; (*c*) G. E. Veitch, E. Beckmann, B. J. Burke, A. Boyer, S. L. Maslen and S. V. Ley, *Angew. Chem., Int. Ed.*, 2007, **46**, 7629; (*d*) K. C. Nicolaou, T. V. Koftis, S. Vyskocil, G. Petrovic, W. Tang, M. O. Frederick, D. Y. K. Chen, Y. Li, T. Ling and Y. M. A. Yamada, *J. Am. Chem. Soc.*, 2006, **128**, 2859.

2 J. M. Herrmann and B. König, *Eur. J. Org. Chem.*, 2013, 7017.

3 (*a*) A. G. Myers, M. Movassaghi and B. Zheng, *J. Am. Chem. Soc.*, 1997, **119**, 8572; (*b*) H. R. Diéguez, A. López, V. Domingo, J. F. Arteaga, J. A. Dobado, M. M. Herrador, J. F. Quílez der Moral and A. F. Barrero, *J. Am. Chem. Soc.*, 2010, **132**, 254; (*c*) S. Sawadjoon, A. Lundstedt and J. S. M. Samec, *ACS Catal.*, 2013, **3**, 635; (*d*) V. J. Meyer and M. Niggemann, *Chem. – Eur. J.*, 2012, **18**, 4687; (*e*) G. G. K. S. N. Kumar and K. K. Laali, *Org. Biomol. Chem.*, 2012, **10**, 7347; (*f*) J. E. Milne, T. Storz, J. T. Colyer, O. R. Thiel, M. D. Seran, R. D. Larsen and J. A. Murry, *J. Org. Chem.*, 2011, **76**, 9519; (*g*) M. Yasuda, Y. Onishi, M. Ueba, T. Miyai and A. Baba, *J. Org. Chem.*, 2001, **66**, 7741; (*h*) J.-L. Huang, X.-J. Dai and C.-J. Li, *Eur. J. Org. Chem.*, 2013, 6496; (*i*) Y. Nishibayashi, A. Shinoda, Y. Miyake, H. Matsuzawa and M. Sato, *Angew. Chem., Int. Ed.*, 2006, **45**, 4835; (*j*) M. Egi, T. Kawai, M. Umemura and S. Akai, *J. Org. Chem.*, 2012, **77**, 7092.

4 (*a*) H. Dang, N. Cox and G. Lalic, *Angew. Chem., Int. Ed.*, 2014, **53**, 752; (*b*) P. A. Jordan and S. J. Miller, *Angew. Chem., Int. Ed.*, 2012, **51**, 2907; (*c*) D. A. Spiegel, K. B. Wiberg, L. N. Schacherer, M. R. Medeiros and J. L. Wood, *J. Am. Chem. Soc.*, 2005, **127**, 12513; (*d*) L. Zhang and M. Koreeda, *J. Am. Chem. Soc.*, 2004, **126**, 13190; (*e*) R. M. Lopez, D. S. Hays and G. C. Fu, *J. Am. Chem. Soc.*, 1997, **119**, 6949.

5 (*a*) V. Gevorgyan, M. Rubin, S. Benson, J.-X. Liu and Y. Yamamoto, *J. Org. Chem.*, 2000, **65**, 6179; (*b*) V. Gevorgyan, J.-X. Liu, M. Rubin, S. Benson and Y. Yamamoto, *Tetrahedron Lett.*, 1999, **40**, 8919; (*c*) M. Dobmeier, J. M. Herrmann, D. Lenoir and B. Koenig, *Beilstein J. Org. Chem.*, 2012, **8**, 330.

6 V. P. Nair, A. Dairam, A. Agbonon, J. T. Arnason, B. C. Foter and A. I. Kanfer, *J. Agric. Food Chem.*, 2007, **55**, 1707.

7 For some selected applications of 1,4-enynes in organic synthesis, see: (*a*) A. Buzas and F. Gagosz, *J. Am. Chem. Soc.*, 2006, **128**, 12614; (*b*) R. F. Keyes, J. C. Carter, E. E. Englund, M. M. Daly, G. G. Stone, A. M. Nilius and Z. Ma, *J. Med. Chem.*, 2003, **46**, 1795; (*c*) F. Yang, K.-G. Ji, S.-C. Zhao, S. Ali, Y.-Y. Ye, X.-Y. Liu and Y.-M. Liang, *Chem. – Eur. J.*, 2012, **18**, 6470; (*d*) T. P. Heffron and T. F. Jamison, *Org. Lett.*, 2003, **5**, 2339; (*e*) G. Stork and M. Isobe, *J. Am. Chem. Soc.*, 1975, **97**, 4745.

8 (*a*) S. Drewes and R. W. Liebenberg, *U.S. Pat.*, 4652636, 1987; (*b*) Y.-X. Li, Q.-Q. Xuan, L. Liu, D. Wang, Y.-J. Chen and C.-J. Li, *J. Am. Chem. Soc.*, 2013, **135**, 12536.

9 For direct synthesis of 1,4-enynes, see: (*a*) D. K. Rayabarapu and J. A. Tunge, *J. Am. Chem. Soc.*, 2005, **127**, 13510; (*b*) M. Shirakura and M. Suginome, *J. Am. Chem. Soc.*, 2008, **130**, 5410; (*c*) M. Shirakura and M. Suginome, *Angew. Chem., Int. Ed.*, 2010, **49**, 3827; (*d*) T. Sato, T. Onuma, I. Nakamura and M. Terada, *Org. Lett.*, 2011, **13**, 4992; (*e*) D.-M. Cui, N. Hashimoto, S.-I. Ikeda and Y. Sato, *J. Org. Chem.*, 1995, **60**, 5752; (*f*) K. Ren, P. Li, L. Wang and X. Zhang, *Tetrahedron*, 2011, **67**, 2753; (*g*) J. Y. Hamilton, D. Sarlah and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2013, **52**, 7532; (*h*) N. E. Leadbeater, *J. Org. Chem.*, 2001, **66**, 7539; (*i*) Q. Yang, Y. Zhou, J. Chen, X. He, J. Xu, F. Y. Kwong and B. Fan, *Eur. J. Org. Chem.*, 2015, 5330; (*j*) H. Chen and M. Z. Deng, *J. Organomet. Chem.*, 2000, **603**, 189; (*k*) G.-B. Huang, X. Wang, Y.-M. Pan, H.-S. Wang, G.-Y. Yao and Y. Zhang, *J. Org. Chem.*, 2013, **78**, 2742; (*l*) S. Peng, L. Wang and J. Wang, *Org. Biomol. Chem.*, 2012, **10**, 225; (*m*) V. J. Meyer and M. Niggemann, *Eur. J. Org. Chem.*, 2011, 3671.

10 For enantioselective synthesis of 1,4-enynes, see: (*a*) A. Harada, Y. Makida, T. Sato, H. Ohmiya and M. Sawamura, *J. Am. Chem. Soc.*, 2014, **136**, 13932; (*b*) Y. Makida, Y. Takayama, H. Ohmiya and M. Sawamura, *Angew. Chem., Int. Ed.*, 2013, **52**, 5350; (*c*) J. A. Dabrowski, F. Gao and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2011, **133**, 4778; (*d*) Y. Kiyotsuka and Y. Kobayashi, *J. Org. Chem.*, 2009, **74**, 7489.

11 (*a*) H. Li and A. Alexakis, *Angew. Chem., Int. Ed.*, 2012, **51**, 1055; (*b*) M. A. Kacprzynski and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2004, **126**, 10676; (*c*) B. M. Trost, S. Hildbrand and K. Dogra, *J. Am. Chem. Soc.*, 1999, **121**, 10416.

12 For indirect methods for the synthesis of 1,4-enynes, see: (*a*) H. Feng, D. S. Ermolate'v, G. Song and E. V. Van der Eycken, *Org. Lett.*, 2012, **14**, 1942; (*b*) S. Biswas, S. Maiti and U. Jana, *Eur. J. Org. Chem.*, 2009, 2354; (*c*) G. W. Kabala, Z. Wu and Y. Ju, *Org. Lett.*, 2004, **6**, 3929.

13 For a personal account, see: R. K. Kumar and X. Bi, *Chem. Commun.*, 2016, **52**, 853.

14 Z. Liu, P. Liao and X. Bi, *Chem. – Eur. J.*, 2014, **20**, 17277.

