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Electrooxidative dearomatization of biaryls: synthesis of tri- and difluoromethylated spiro[5.5] trienones†

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Radical spirocyclization *via* dearomatization has emerged as an attractive strategy for the rapid synthesis of structurally diverse spiro molecules. We report the use of electrochemistry to perform an oxidative dearomatization of biaryls leading to tri- and difluoromethylated spiro[5.5]trienones in a user friendly undivided cell set-up and a constant current mode. The catalyst- and chemical oxidant-free dearomatization procedure features ample scope, and employs electricity as the green and sole oxidant.

Introduction

The development of new approaches for the construction of CF_3- or CF_2H-containing target molecules is becoming increasingly important owing to the growing applications of organo-fluorinated compounds in *inter alia* pharmaceutical and agrochemical industries.[1–3] Thus, the incorporation of fluoroalkyl groups into organic molecules can significantly improve their physical, chemical, and biological properties, such as permeability, bioavailability, and metabolic stability.[4–6] Although a multitude of methods have been developed for the preparation of trifluoromethylated or difluoromethylated compounds by radical addition to unsaturated bonds,[7] a protocol for directly introducing CF_3 or CF_2H onto spiro[5.5] trienone has thus far proven elusive, despite these motifs being prevalent in a number of natural products and bioactive molecules (Fig. 1).

Electrochemistry has surfaced as an attractive technique for the discovery of new modes of reactivity and transformations that are not readily accessible with chemical reagents.[8] As radical spirocyclization by dearomatization of biaryls is an attractive strategy for the rapid construction of spiro[5.5] molecules,[9,11b] we questioned whether the efficiency and mildness noted in the CF_3-radical formation could be translated into an electrooxidative biaryl dearomatization strategy. However, significant challenges would need to be overcome (Fig. 1). (1) Regioselectivity between 5-*exo*-trig, 6-*exo*-trig and 7-*endo*-trig cyclization needs to be controlled. (2) The low reactivity of alkynes towards fluoroalkyl radicals needs to be addressed. Compared to the radical addition onto alkenes,[10] alkyne functionalization by radical addition is more challenging.[11] Herein, we report an unprecedented dearomatization of biarylynones under green and operationally-simple electrochemical conditions. The salient features of our strategy comprise the following: (a) the first efficient dearomatization of biaryls to CF_3-containing spiro[5.5]trienones, (b) a most user-friendly undivided cell set-up, (c) simple reaction conditions devoid of a redox mediator, (d) the absence of catalysts and chemical oxidants, and (e) high regioselectivity.

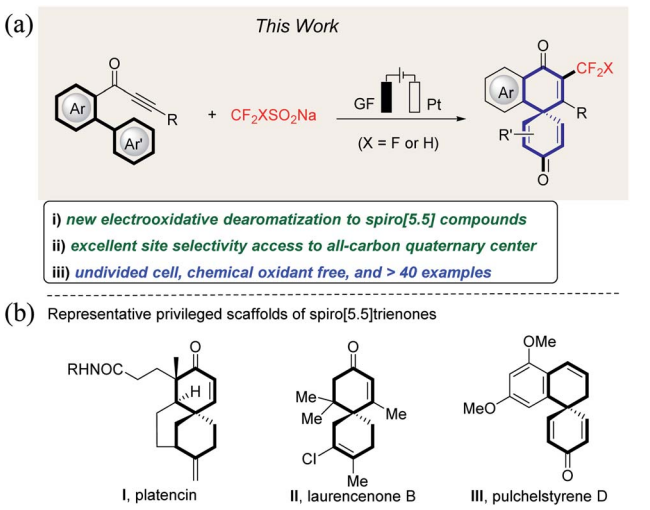

Fig. 1 Electrooxidative biaryl dearomatization: (a) reaction design and (b) selected examples of bioactive spiro compounds.

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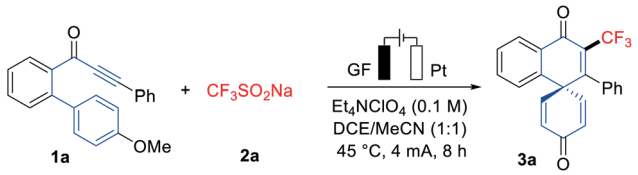
Table 1 Optimization of the electrooxidative dearomatization[a]



Entry	Variation from standard conditions	Yield[b]/%
1	No change	60
2	MeCN	40
3	MeCN/H_2O (2 : 1)	15
4	In the absence of Et_4NClO_4	46
5	*n*-Bu_4NBF_4 instead of Et_4NClO_4	20
6	Et_4NPF_6 instead of Et_4NClO_4	18
7	Na_2CO_3 and H_2O instead of Et_4NClO_4	55[c]
8	At room temperature (25 °C)	40
9	Addition of [Mes-Acr]ClO_4 (10 mol%)	50[d]
10	Addition of Cp_2Fe (10 mol%)	45
11	1 mmol scale (4 mL solvent)	50
12	No electricity	0

[a] Standard conditions: undivided cell, GF anode, Pt cathode, constant current (CCE) = 4 mA, **1a** (0.3 mmol), **2a** (0.6 mmol), Et_4NClO_4 (0.1 M, 0.4 mmol), DCE/MeCN (4 mL), under air, 8 h. [b] Yield of isolated products. [c] H_2O (1 mL) was added. [d] 30 W, blue LED. GF = graphite felt.

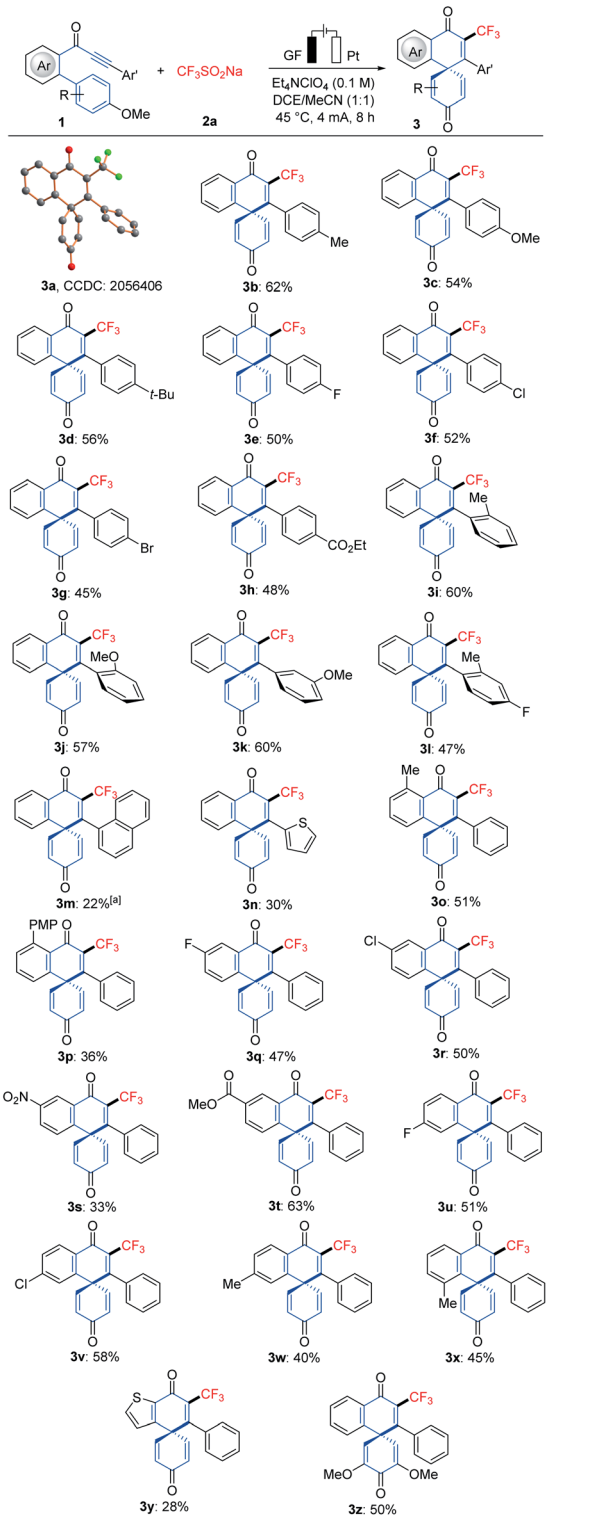
Results and discussion

Optimization of reaction conditions

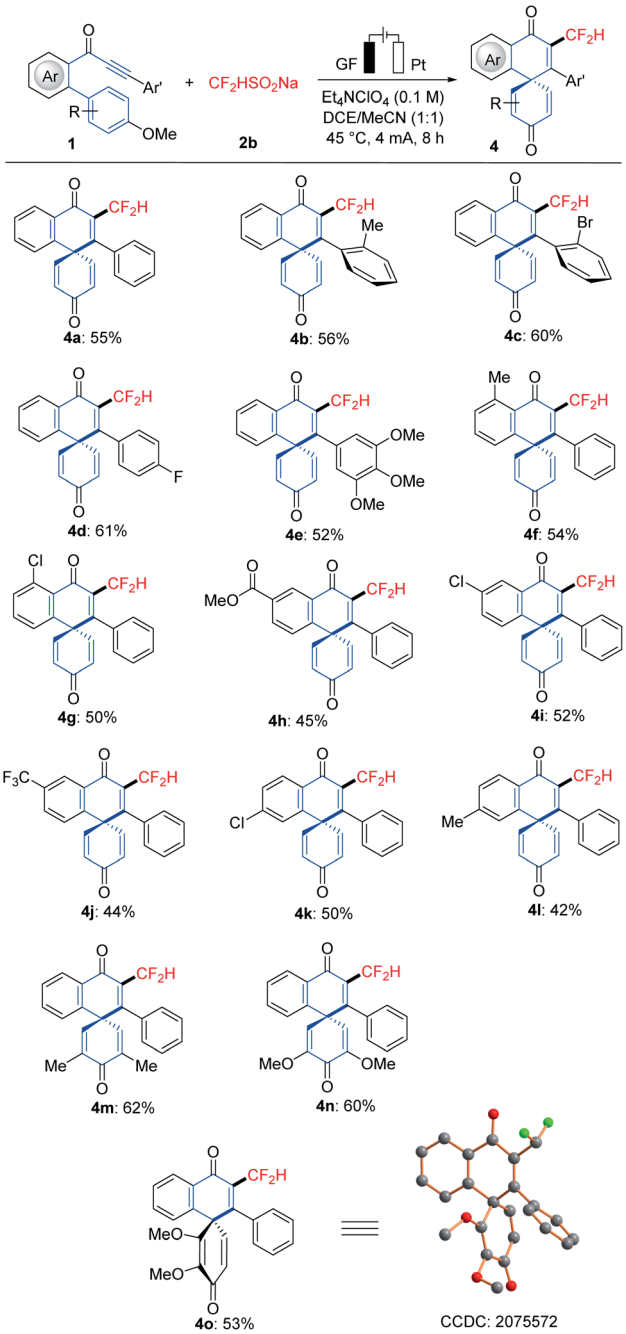
We initiated our studies by probing various reaction conditions for the envisioned electrochemical dearomatization reaction of biarylynone **1a** in a most user-friendly undivided cell set-up (Tables 1 and S2 in the ESI†), using the bench-stable and inexpensive Langlois' reagent (CF_3SO_2Na, **2a**) as the CF_3 source. After considerable preliminary experimentation, we observed that the desired trifluoromethylation/dearomatization was accomplished with a mixed solvent system consisting of DCE/MeCN (1 : 1) and Et_4NClO_4 as the electrolyte (entry 1). Different solvents and a series of supporting electrolytes were tested but found not to be beneficial (entries 2–7). Neither decreasing nor increasing the reaction temperature improved the yield of product **3a** (entry 8). In contrast to previous literature reports,[12–14] a catalytic redox mediator was not required for this transformation (entries 9 and 10). When the dearomative reaction was performed on a 1 mmol scale, the product **3a** was isolated in 50% yield (entry 11). Control experiments confirmed the essential role of electricity for the electrooxidative dearomatization (entry 12). The structure of **3a** was unambiguously confirmed by single-crystal X-ray analysis (Scheme 1).[15a]

Robustness

With the optimized reaction conditions in hand, we explored the viable scope of the electrochemical transformation. Various biarylynones **1** were investigated and the results are shown in Scheme 1. Generally, the electronic effect of substituents on the arene Ar′ did not influence the reaction efficiency and synthetically useful yields of spiro[5.5]trienones were obtained (**3a–3h**). We were pleased to find that *ortho*- and *meta*-substituted arene Ar′ underwent this transformation efficiently despite a possible steric repulsion (**3i–3l**), even for

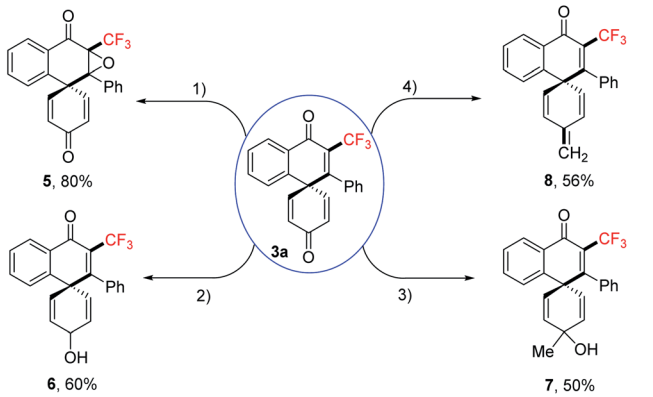


Scheme 1 Scope of trifluoromethylated spiro[5.5]trienones **3**. [a] NMR yield.



Scheme 2 Scope of difluoromethylated spiro[5.5]trienones **4**.

polysubstituted substrates. A naphthyl substituent was also compatible (**3m**). Substitutions on the phenome scaffold were next examined. Substrates bearing either electron-withdrawing or electron-donating groups did not significantly alter the reaction outcome and the spiro compounds **3** were efficiently obtained (**3o–3x**). As depicted, the dearomatization approach was compatible with several functional groups, such as chloro, bromo, ether, nitro and ester. A heterocyclic substrate was also applicable in this electrooxidative transformation to afford the corresponding product **3y** in a moderate yield. It is noteworthy that a substrate with a substituent at the *ortho*-position of OMe (**1z**) also formed the desired compound **3z**.[16]



Scheme 3 Reaction conditions: (1) H_2O_2 (1.5 equiv.), Na_2CO_3 (1.5 equiv.), EtOH, 45 °C, 2 h. (2) DIBAL (1.0 equiv.), THF, −78 °C, 3 h. (3) CH_3MgCl (2.0 equiv.), THF, room temperature, 3 h. (4) Methyltriphenylphosphonium bromide (2.0 equiv.), *t*-BuOK (2.0 equiv.), THF, room temperature, 6 h.

As the difluoromethyl group (CF_2H) can serve as a hydrogen bond donor, it has been employed as a lipophilic isostere in drug design for functionalities such as amides, alcohols, thiols and hydroxamic acids.[17] Thus, we turned our attention to electrochemical difluoromethylation/dearomatization with differently substituted biarylynones **1** and CF_2HSO_2Na (**2b**). Similarly, the electronic properties of arenes Ar and Ar′ in substrate **1** did not have distinct influence on the efficiency of the dearomatization, and moderate to good yields of the spiro[5.5]trienones **4** were obtained (Scheme 2). The structure of product **4o** was unambiguously verified by X-ray crystallographic analysis.[15b]

We further demonstrated the synthetic utility and showed that the trifluoromethylated spiro[5.5]trienones are a versatile framework that can be readily transformed into more value-added scaffolds in single step reactions (Scheme 3). The biologically relevant epoxyquinone **5** could be obtained in excellent yield *via* oxidation, while reduction of the ketone selectively furnished alcohol **6**. Alcohol **7** was synthesized by selective addition of Grignard reagent, while alkene **8** could be prepared by a Wittig reaction.

To gain mechanistic insight into this electrochemical dearomatization reaction, the radical clock reaction using (1-cyclopropylvinyl)benzene (**1′**) as the radical-trapping reagent provided the known product **9** in 25% yield (Fig. 2a). Based on these results, a radical mechanism is proposed in Fig. 2c for this electrooxidative dearomatization reaction. First, radical $CF_3^{\bullet}$ is generated from **2a** through anodic oxidation. Radical addition of $CF_3^{\bullet}$ to C–C triple bonds of **1a** affords a vinyl radical **A**, which undergoes 6-*exo*-trig cyclization to the radical species **B**. Intermediate **B** is reoxidized to oxocarbenium ion **C** at the anode. Finally, the corresponding product **3a** is formed after demethylation. The incorporation of the diflouro moiety proceeds *via* the same mechanism, but the oxidation peak of CF_2HSO_2Na was found much lower than that of CF_3SO_2Na by a cyclic voltammetry (CV) experiment.[18] In addition, inspired by the pioneering work of Jiao for 1,2-dichloroethane (DCE) dehydrochlorination,[19] we also found that when the model

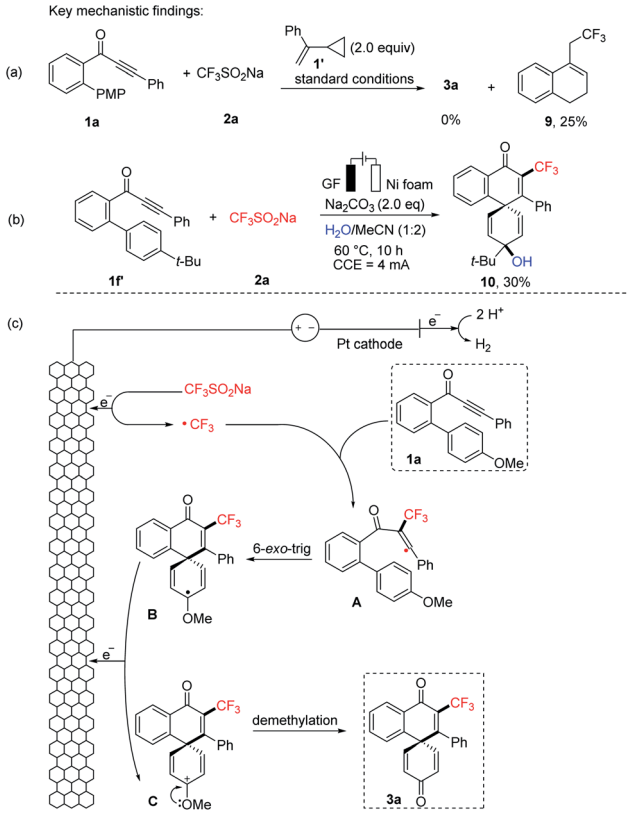


Fig. 2 Mechanistic investigation of the electrooxidative biaryl dearomatization: (a) radical clock experiment, (b) trapping experiment for the key intermediate, and (c) proposed mechanism.

reaction between **1a** and **2a** was performed under the standard conditions, the reaction mixture clearly became acidic as shown by pH measurement (in ESI†). Hence, we propose that HCl was generated from the dehydrochlorination of DCE. Notably, the analogue of ion **C** could be trapped by water while changing the reaction solvent system with 1-(4′-(*tert*-butyl)-[1,1′-biphenyl]-2-yl)-3-phenylprop-2-yn-1-one **1f′**. The trapping product **10** was here isolated in 30% yield (Fig. 2b).

Conclusions

In summary, we have developed an efficient approach for the electrochemical dearomatization of biaryls under metal catalyst- and chemical oxidant-free conditions. This green and environmentally friendly strategy showed a broad scope and great compatibility with sensitive functional groups, affording a series of CF_3- and CF_2H-substituted spiro[5.5]trienones in moderate to good yields. It represents the first electrooxidative 6-*exo*-trig radical dearomative spirocyclization process, and a plausible mechanism was proposed.

Data availability

All experimental data, procedures for data analysis and pertinent data sets are provided in the ESI.

Author contributions

Y. Z. and L. A. conceived the project. Y. Z. and C. M. performed the experiments, Y. Z., J. F. and J. S. analyzed and interpreted the experimental data. Y. Z. and J. S. drafted the paper. G. Z., Y. Z. and L. A. supervised the project. All of the authors discussed the results and contributed to the preparation of the final manuscript.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (*a*) K. Haranahalli, T. Honda and I. Ojima, *J. Fluorine Chem.*, 2019, **217**, 29–40; (*b*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330; (*c*) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (*d*) M. Shimizu and T. Hiyama, *Angew. Chem., Int. Ed.*, 2005, **44**, 214–231.
2 J. Peter, *ChemBioChem*, 2004, **5**, 570.
3 (*a*) M. Reichel and K. Karaghiosoff, *Angew. Chem., Int. Ed.*, 2020, **59**, 12268–12281; (*b*) A. Harsanyi and G. Sandford, *Green Chem.*, 2015, **17**, 2081–2086; (*c*) P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, Germany, 2013; (*d*) J. P. Begue and D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, Hoboken, 2008.
4 J. A. Erickson and I. J. McLoughlin, *J. Org. Chem.*, 1995, **60**, 1626–1631.
5 C. A. Veale, P. R. Bernstein, C. M. Bohnert, F. J. Brown, C. Bryant, J. R. Damewood Jr, R. Earley, S. W. Feeney, P. D. Edwards, B. Gomes, J. M. Hulsizer, B. J. Kosmider, R. D. Krell, G. Moore, T. W. Salcedo, A. Shaw, D. S. Silberstein, G. B. Steelman, M. Stein, A. Strimpler, R. M. Thomas, E. P. Vacek, J. C. Williams, D. J. Wolanin and S. Woolson, *J. Med. Chem.*, 1997, **40**, 3173–3181.
6 N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529–2591.
7 For selected reviews, see: (*a*) C. Alonso, E. M. De Marigorta, G. Rubiales and F. Palacios, *Chem. Rev.*, 2015, **115**, 1847; (*b*) L. Chu and F.-L. Qing, *Acc. Chem. Res.*, 2014, **47**, 1513; (*c*) S. Barata-Vallejo, B. Lantaño and A. Postigo, *Chem.–Eur. J.*, 2014, **20**, 16806; (*d*) H. Egami and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2014, **53**, 8294; (*e*) E. Merino and C. Nevado, *Chem. Soc. Rev.*, 2014, **43**, 6598; (*f*) P. Chen and G. Liu, *Synthesis*, 2013, **45**, 2919; (*g*) A. Studer, *Angew. Chem., Int. Ed.*, 2012, **51**, 8950.
8 For reviews on electrochemical synthesis, see: (*a*) C. Zhu, N. W. J. Ang, T. H. Meyer, Y. Qiu and L. Ackermann, *ACS Cent. Sci.*, 2021, **7**, 415–431; (*b*) J. C. Siu, N. Fu and S. Lin, *Acc. Chem. Res.*, 2020, **53**, 547–560; (*c*) L. Ackermann, *Acc.*

Chem. Res., 2020, **53**, 84–104; (*d*) G. M. Martins, G. C. Zimmer, S. R. Menders and N. Ahmed, *Green Chem.*, 2020, **22**, 4849–4870; (*e*) P. Xiong and H.-C. Xu, *Acc. Chem. Res.*, 2019, **52**, 3339–3350; (*f*) Y. Jiang, K. Xu and C. Zeng, *Chem. Rev.*, 2018, **118**, 4485–4540; (*g*) Q.-L. Yang, P. Fang and T.-S. Mei, *Chin. J. Chem.*, 2018, **36**, 338–352; (*h*) M. D. Kärkäs, *Chem. Soc. Rev.*, 2018, **47**, 5786–5865; (*i*) N. Sauermann, T. H. Meyer, Y. Qiu and L. Ackermann, *ACS Catal.*, 2018, **8**, 7086–7103; (*j*) K. D. Moeller, *Chem. Rev.*, 2018, **118**, 4817–4833; (*k*) M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230–13319; (*l*) A. Jutand, *Chem. Rev.*, 2008, **108**, 2300–2347.

9 Access to spiro[5.5] compounds through radical addition: (*a*) T. Lanza, R. Leardini, M. Minozzi, D. Nanni, P. Spagnolo and G. Zanardi, *Angew. Chem., Int. Ed.*, 2008, **47**, 9439–9442; (*b*) F. G.-L. de Turiso and D. P. Curran, *Org. Lett.*, 2005, **7**, 151–154.

10 For selected representative examples of radical addition to alkenes, see: (*a*) T. Patra, P. Bellotti, F. Strieth-Kalthoff and F. Glorius, *Angew. Chem., Int. Ed.*, 2020, **59**, 3172–3177; (*b*) Y. Yang, C.-H. Xu, Z.-Q. Xiong and J.-H. Li, *Chem. Commun.*, 2020, **56**, 9549–9552; (*c*) R. Wei, H. Xiong, C. Ye, Y. Li and H. Bao, *Org. Lett.*, 2020, **22**, 3195–3199; (*d*) L. Wu, F. Wang, P. Chen and G. Liu, *J. Am. Chem. Soc.*, 2019, **141**, 1887–1892; (*e*) N. Fu, L. Song, J. Liu, Y. Shen, J. C. Siu and S. Lin, *J. Am. Chem. Soc.*, 2019, **141**, 14480–14485; (*f*) M. A. Ashley, C. Yamauchi, J. C. K. Chu, S. Otsuka, H. Yorimitsu and T. Rovis, *Angew. Chem., Int. Ed.*, 2019, **58**, 4002–4006; (*g*) Y. Jiao, M.-F. Chiou, Y. Li and H. Bao, *ACS Catal.*, 2019, **9**, 5191–5197; (*h*) K.-Y. Ye, G. Pombar, N. Fu, G. S. Sauer, I. Keresztes and S. Lin, *J. Am. Chem. Soc.*, 2018, **140**, 2438–2441; (*i*) L. Fu, S. Zhou, X. Wan, P. Chen and G. Liu, *J. Am. Chem. Soc.*, 2018, **140**, 10965–10969; (*j*) A. Tlahuext-Aca, R. A. Garza-Sanchez, M. Schäfer and F. Glorius, *Org. Lett.*, 2018, **20**, 1546–1549; (*k*) L. Zhang, G. Zhang, P. Wang, Y. Li and A. Lei, *Org. Lett.*, 2018, **20**, 7396–7399; (*l*) N. Fu, G. S. Sauer, A. Saha, A. Loo and S. Lin, *Science*, 2017, **357**, 575–579; (*m*) A. J. Musacchio, B. C. Lainhart, X. Zhang, S. G. Naguib, T. C. Sherwood and R. R. Knowles, *Science*, 2017, **355**, 729–730; (*n*) Z.-L. Li, X.-H. Li, N. Wang, N.-Y. Yang and X.-Y. Lin, *Angew. Chem., Int. Ed.*, 2016, **55**, 15100–15104; (*o*) L. Huang, L. Ye, X.-H. Li, Z.-L. Li, J.-S. Lin and X.-Y. Liu, *Org. Lett.*, 2016, **18**, 5384–5388; (*p*) Z. Gu, H. Zhang, P. Xu, Y. Cheng and C. Zhu, *Adv. Synth. Catal.*, 2015, **357**, 3057–3063; (*q*) J.-Y. Wang, Y.-M. Su, F. Yin, Y. Bao, X. Zhang, Y.-M. Xu and X.-S. Wang, *Chem. Commun.*, 2014, **50**, 4108–4111; (*r*) C. Feng and T.-P. Loh, *Angew. Chem., Int. Ed.*, 2013, **52**, 12414–12417; (*s*) C.-J. Wallentin, J. D. Nguyen, P. Finkbeiner and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2012, **134**, 8875–8884; (*t*) A. Studer, *Angew. Chem., Int. Ed.*, 2012, **51**, 8950–8958.

11 Selected examples of radical additions onto internal alkynes: (*a*) J. Hua, Z. Fang, J. Xu, M. Bian, C. Liu, W. He, N. Zhu, Z. Yang and K. Guo, *Green Chem.*, 2019, **21**, 4706–4711; (*b*) P. Xiong, H.-H. Xu, J. Song and H.-C. Xu, *J. Am. Chem. Soc.*, 2018, **140**, 2460–2464; (*c*) Y. Zhang, J. Zhang, B. Hu, M. Ji, S. Ye and G. Zhu, *Org. Lett.*, 2018, **20**, 2988–2992; (*d*) Y. Zhang, D. Guo, S. Ye, Z. Liu and G. Zhu, *Org. Lett.*, 2017, **19**, 1302–1305; (*e*) H.-L. Hua, B.-S. Zhang, Y.-T. He, Y.-F. Qiu, J.-Y. Hu, Y.-C. Yang and Y.-M. Liang, *Chem. Commun.*, 2016, **52**, 10396–10399; (*f*) W. Fu, M. Zhu, G. Zou, C. Xu, Z. Wang and B. Ji, *J. Org. Chem.*, 2015, **80**, 4766–4770; (*g*) J. Xu, Y.-L. Wang, T.-J. Gong, B. Xiao and Y. Fu, *Chem. Commun.*, 2014, **50**, 12915–12918; (*h*) G.-C. Ge, X.-J. Huang, C.-H. Ding, S.-L. Wan, L.-X. Dai and X.-H. Hou, *Chem. Commun.*, 2014, **50**, 3048–3051; (*i*) P. Gao, Y.-W. Shen, R. Fang, X.-H. Hao, Z.-H. Qiu, F. Yang, X.-B. Yan, Q. Wang, X.-J. Gong, X.-Y. Liu and Y.-M. Liang, *Angew. Chem., Int. Ed.*, 2014, **53**, 7629–7633; (*j*) Y.-P. Xiong, M.-Y. Wu, X.-Y. Zhang, C.-L. Ma, L. Huang, L.-J. Zhao, B. Tan and X.-Y. Liu, *Org. Lett.*, 2014, **16**, 1000–1003; (*k*) Y.-L. Ji, J.-H. Lin, J.-C. Xiao and Y. C. Gu, *Org. Chem. Front.*, 2014, **1**, 1280–1284.

12 L. Zhu, P. Xiong, Z.-Y. Mao, Y.-H. Wang, X. Yan, X. Lu and H.-C. Xu, *Angew. Chem., Int. Ed.*, 2016, **55**, 2226–2229.

13 Z. Zhang, L. Zhang, Y. Cao, F. Li, G. Bai, G. Liu, Y. Yang and F. Mo, *Org. Lett.*, 2019, **21**, 762–766.

14 Z. Ruan, Z. Huang, Z. Xu, G. Mo, X. Tian, X.-Y. Yu and L. Ackermann, *Org. Lett.*, 2019, **21**, 1237–1240.

15 (*a*) CCDC 2056406.†; (*b*) CCDC 2075572.†

16 Under otherwise identical reaction conditions, 1-(4′-methoxy-[1,1′-biphenyl]-2-yl)-4,4-dimethylpent-2-yn-1-one and 1-(4′-methoxy-[1,1′-biphenyl]-2-yl)hept-2-yn-1-one gave thus far less satisfactory results.

17 Z. Zou, W. Zhang, Y. Wang, L. Kong, G. Karotsis, Y. Wang and Y. Pan, *Org. Lett.*, 2019, **21**, 1857–1862.

18 (*a*) X. Wang, S. Niu, L. Xu, C. Zhang, L. Meng, X. Zhang and D. Ma, *Org. Lett.*, 2017, **19**, 246–249; (*b*) A. J. Reay, L. A. Hammarback, J. T. W. Bray, T. Sheridan, D. Turnbull, A. C. Whitwood and I. J. S. Fairlamb, *ACS Catal.*, 2017, **7**, 5174–5179; (*c*) T. J. Osberger, D. C. Rogness, J. T. Kohrt, A. F. Stepan and M. C. White, *Nature*, 2016, **537**, 214–219; (*d*) B. Mondal, B. Roy and U. Kazmaier, *J. Org. Chem.*, 2016, **81**, 11646–11655; (*e*) B. V. S. Reddy, L. R. Reddy and E. J. Corey, *Org. Lett.*, 2006, **8**, 3391–3394.

19 Y. Liang, F. Lin, Y. Adeli, R. Jin and N. Jiao, *Angew. Chem., Int. Ed.*, 2019, **58**, 4566–4570.