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# Asymmetric copper-catalyzed alkynylallylic monofluoroalkylations with fluorinated malonates†

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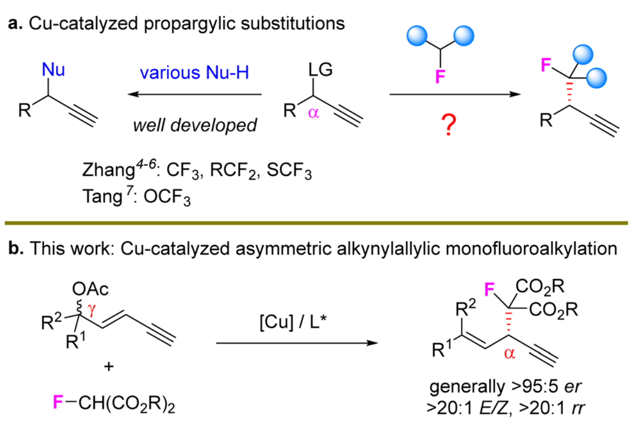
**The unprecedented copper-catalyzed asymmetric alkynylallylic monofluoroalkylation reaction is described *via* the use of 1,3-enynes and fluorinated malonates. A series of 1,4-enynes bearing a monofluoroalkyl unit are achieved in high yields, excellent regio- and enantioselectivity and high *E/Z* selectivity. The asymmetric propargylic monofluoroalkylation is also developed. The reliability and synthetic value of the work are highlighted by a gram-scale test and a couple of downstream transformations. Preliminary mechanistic studies unveil a negative nonlinear effect for the catalytic process.**

Copper-catalyzed asymmetric propargylic substitution reactions have emerged as a reliable and valuable route to construct stereogenic centers.[1] A series of nucleophiles have been efficiently introduced to the propargylic position to construct C–C, C–N, C–S, and C–O bonds with high stereocontrol (Scheme 1(a), left).[2] As the F-containing motif has been widely used in the design of biologically active molecules,[3] the construction of stereocenters bearing fluorine atoms *via* Cu-catalyzed propargylation represents a novel route to achieve such optically active skeletons but related studies are very limited. Zhang *et al.* sequentially developed efficient catalytic systems for the preparation of propargylic $CF_3$, $RCF_2$ and $SCF_3$ units.[4–6] In addition, Tang recently described an elegant protocol to introduce $OCF_3$-based stereocenters *via* propargylic substitution.[7] However, the propargylic monofluoroalkylation and related processes remain unexplored (Scheme 1(a), right).

Different from the typical propargylic substitution requiring an α-leaving group to guarantee the formation of a critical Cu-allenylidene intermediate, an alkyne bearing a remote leaving group is usually not considered as a suitable substrate for propargylation. In 2022, Fang's group first reported a regiodivergent but non-asymmetric Cu-catalyzed alkynylallylic substitution model by using 1,3-enyne with a γ-leaving group as the substrate.[8] Then, we described a highly enantioselective process.[9] In our work, various enantioenriched 1,4-enyne[10] skeletons were achieved in high yields and enantiocontrol. Later, Xu and Qi developed an elegant *in situ* substitution route to prepare various spirocycles in high enantioselectivity.[11] After these initial works, we further established another type of remote stereocontrol model *via* Cu-catalyzed dearomatic substitution.[12] Most recently, several other related works on remote propargylic substitution have been reported to show the synthetic power of this newly emerging strategy.[13] Thus, the development of new catalytic systems for the seldoml studied remote propargylic substitution is highly desired.

We envisioned that with F-containing malonate as the nucleophile, the unprecedented asymmetric remote propargylic




Scheme 1 Cu-catalyzed propargylic substitutions.

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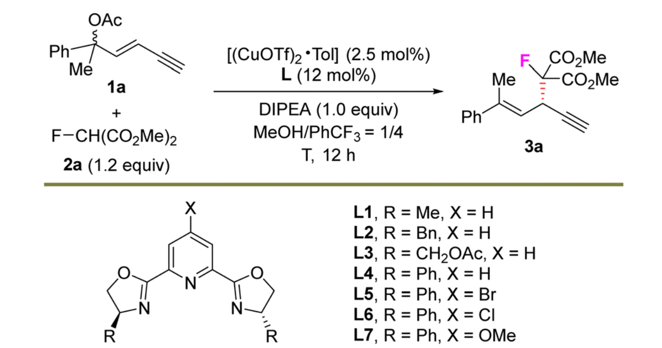
Table 1 Reaction development



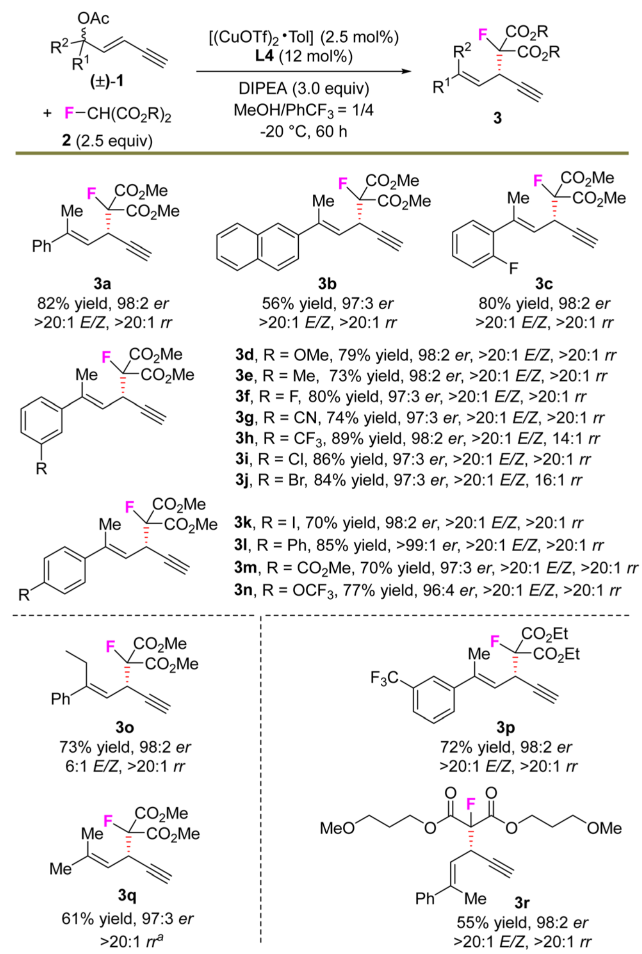

| Entry | L | $T$/°C | Yield[a] (%) | er[b] |
|---|---|---|---|---|
| 1 | **L1** | RT | 30 | 95 : 5 |
| 2 | **L2** | RT | 24 | 68 : 32 |
| 3 | **L3** | RT | 23 | 82 : 18 |
| 4 | **L4** | RT | 24 | 97 : 3 |
| 5 | **L5** | RT | 28 | 95 : 5 |
| 6 | **L6** | RT | 30 | 94 : 6 |
| 7 | **L7** | RT | 29 | 75 : 25 |
| 8[c] | **L4** | RT | 63 | 96 : 4 |
| 9[c,d] | **L4** | RT | 44 | 95 : 5 |
| 10[c,e] | **L4** | RT | 49 | 96 : 4 |
| 11[c,f] | **L4** | RT | 58 | 96 : 4 |
| 12[c,g] | **L4** | RT | 55 | 96 : 4 |
| 13[c,h] | **L4** | 0 | 70 | 97 : 3 |
| 14[c,i] | **L4** | −20 | 82 | 98 : 2 |

[a] The yield was determined by $^1$H NMR with $CH_2Br_2$ as an internal standard. [b] Determined by HPLC analysis. [c] **2a** (2.5 equiv.) was used. [d] CuI (5 mol%) was used instead. [e] CuCN (5 mol%) was used instead. [f] $[Cu(MeCN)_4]BF_4$ (5 mol%) was used instead. [g] $Cu(OTf)_2$ (5 mol%) was used instead. [h] The reaction time was 24 h. [i] Isolated yield and the reaction time was 60 h.

monofluoroalkylation might be feasible. However, this proposal is not straightforward. First, a tertiary carbon nucleophile might be less reactive than the widely adopted secondary and primary carbon centers, due to the increased steric hindrance of the former. Meanwhile, α-fluoro carbonyl compounds are known to be less stable than the non-fluorinated ones.[14,15] In addition, the elevated acidity of the carbon center in the fluoro malonate nucleophile would also lower the corresponding nucleophilicity and might inhibit the expected substitution process.

We initiated the study by using 1,3-enyne **1a** bearing a tertiary OAc unit as the electrophile, fluorinated malonate **2a** as the nucleophile and DIPEA as the base under copper catalysis (Table 1). A series of chiral PyBOx ligands were first evaluated (entries 1–7), and **L4** exhibited the highest enantiocontrol, providing $S_N2'$ substitution product **3a** in 97 : 3 er but with only a 24% yield (entry 4). However, the elevation of the amount of nucleophile **2a** greatly increased the yield of **3a** to 63% (entry 8). Next, various copper sources were checked but all failed to furnish **3a** in a higher yield and stereoselectivity (entries 9–12). When the reaction temperature was lowered to 0 °C with an elongated reaction time, both the yield and enantioselectivity were increased slightly (entry 13). Finally, the optimal reaction conditions were determined as the combination of 1,3-enyne **1a** (1.0 equiv.) and fluoro malonate **2a** (2.5 equiv.) as the substrates, $[(CuOTf)_2{\cdot}Tol]$/**L4** as the catalyst, and DIPEA as the base in $MeOH/PhCF_3$ as the mixed solvent at −20 °C for 60 h. In this case, **3a** was prepared in 82% yield, >20 : 1 rr, >20 : 1 $E$ : $Z$ and 98 : 2 er (entry 14).

With the established protocol in hand, the scope for the asymmetric alkynylallylic monofluoroalkylation reaction was evaluated and the results are summarized in Scheme 2. The enynes bearing various substituted arenes exhibited high compatibility with the transformation. For example, the electrophiles containing F, ether, cyano, $CF_3$, Cl, Br, ester, $OCF_3$ units *etc.* in the aryl group proceeded smoothly with the stereoselective substitution, affording fluorinated 1,4-enynes (**3a–3j**, **3l–3n**) in 56–89% yields, 96 : 4–>99 : 1 er, and generally >20 : 1 rr and >20 : 1 $E$ : $Z$. It should be noted that the aryl iodide motif, which is known to be sensitive to transition metals, was also well tolerated in this process, and the corresponding **3k** was formed in 70% yield and 98 : 2 er, highlighting the broad application scope of the protocol. In addition, other modifications of the substituent in the olefin groups or the nucleophiles did not show obvious erosion of the efficiency and stereocontrol (**3o**, **3p**, and **3r**). Alkyl-substituted 1,4-enyne product **3q** was also obtained in a similarly good yield and stereoselectivity.

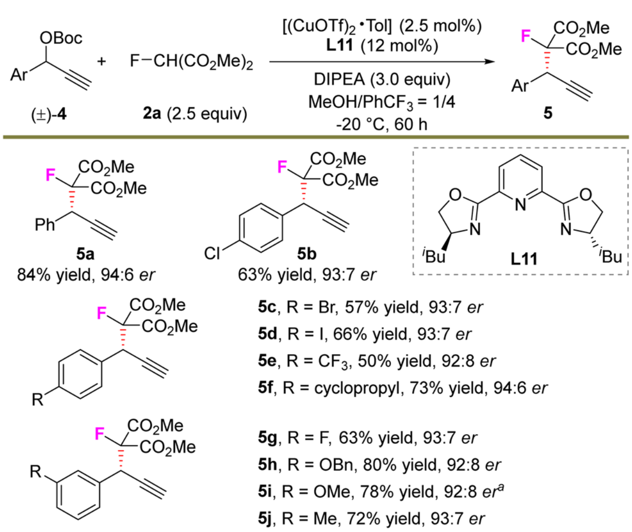



Scheme 2 Scope for the asymmetric alkynylallylic monofluoroalkylation. Isolated yields. [a]120 h.

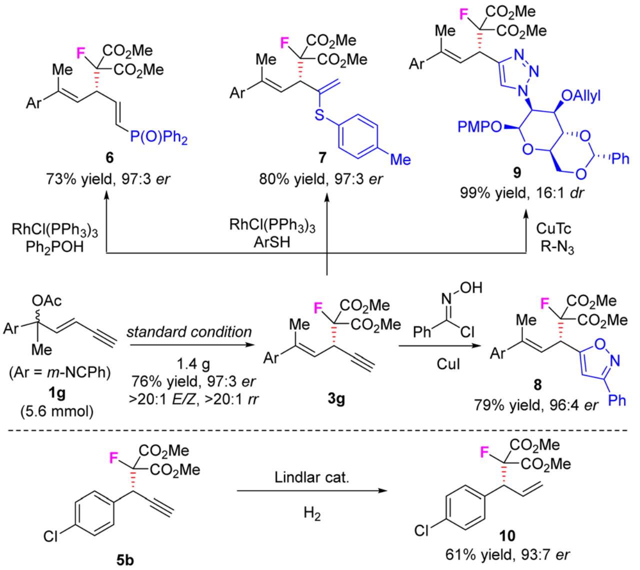
Next, we continued to explore the feasibility of the undeveloped asymmetric propargylic monofluoroalkylation reaction (Scheme 3). With the use of **L11** instead of **L4** as the chiral ligand, the transformation proceeded smoothly, providing **5a** in an 84% yield and 94 : 6 er (see ESI† for the detailed optimization process). A series of substituted aryl-derived alkynes were further evaluated and all showed high compatibility with the reaction. For example, substituents including Cl, Br, I, $CF_3$, cyclopropyl, F, an ether unit *etc.* in the electrophile reacted with **2a** well and generated the corresponding products **5b–5j** in 50–80% yields and with 92 : 8–94 : 6 er. In addition, the trial to prepare a quaternary stereocenter failed, presumably due to the high steric hindrance for the construction of vicinal quaternary carbon centers.

To highlight the robustness and practical use of the present protocol, a gram-scale test was carried out (Scheme 4(a)). When 5.6 mmol of racemic **1g** was used, **3g** was prepared in 1.4 g in a 76% yield, 97 : 3 er, > 20 : 1 rr and > 20 : 1 *E* : *Z*, comparable to that in 0.1 mmol scale. A set of downstream transformations of **3g** were easily conducted and various chiral skeletons were obtained efficiently with high enantioselectivity (**6–9**). For example, enantioenriched fluoroalkyl-tethered isoxazole **8** was conveniently prepared from **3g** *via* [3+2] cyclization in 79% yield and 96 : 4 er. The absolute configuration of **5b** was determined to be *R* by the conversion of **5b** to a known compound **10** *via* controlled hydrogenation.[16]

To probe the possible reaction mechanism, nonlinear relationship experiments were conducted (Scheme 5(a)) and a negative nonlinear effect was observed, indicating that multiple ligands might be involved in the enantio-determining step and the heterochiral metal–ligand complex might be more reactive than the homochiral combination.[17] Kinetic studies showed that the reaction was first order on the copper catalyst (Scheme 5(b)), suggesting that a monocopper catalyst might be involved in the rate-limiting step.

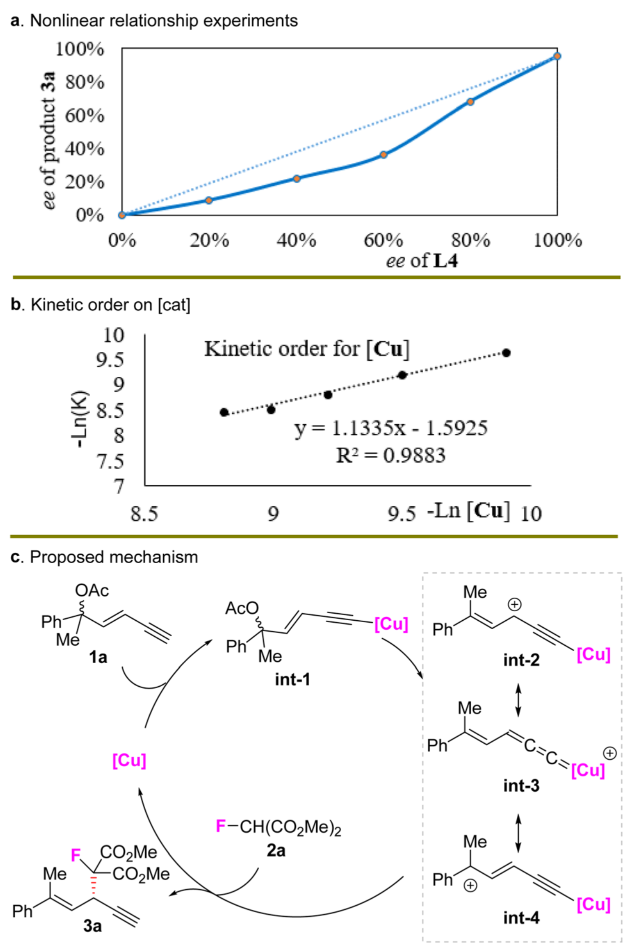



Scheme 3 Asymmetric propargylic monofluoroalkylations. Isolated yields. The er values were determined by HPLC analysis. [a]When 1.0 gram of electrophile was used, 1.0 gram of **5i** was obtained (88% yield, 92 : 8 er).




Scheme 4 Gram-scale test and transformations.

These facts indicated that the observed nonlinear effect might arise from the existence of both an inactive homo dimer




Scheme 5 Proposed mechanism.

of ligands and active mono-Cu(**L4**) species in the enantiodetermining step. Based on this fact and prior work,[9] a potential mechanism is described in Scheme 5(c). The copper catalyst reacted with the terminal alkyne first to provide alkynyl copper complex **int-1**, which was converted to the critical electrophilic olefin-conjugated Cu-allenylidene intermediate **int-3** and other tautomers **int-2** and **int-4**. A subsequent nucleophilic attack then occurred on **int-3** by **2a** to provide fluorinated 1,4-enyne **3a** and regenerate the catalyst.

In conclusion, the first copper-catalyzed asymmetric monofluoroalkylation protocol was developed *via* alkynylallylic substitutions. The related propargylic monofluoroalkylation process is also established. A series of optically active 1,4-enynes bearing a fluoroalkyl unit were prepared in high yields, good regio- and enantioselectivity and excellent *E*/*Z* selectivity. The products were conveniently transformed into various privileged chiral skeletons. The preliminary mechanistic studies uncovered a rare negative nonlinear effect.

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## Conflicts of interest

There are no conflicts to declare.

## Notes and references

1 For reviews on Cu-catalyzed asymmetric propargylic substitutions, see: (*a*) Y. Miyake, S. Uemura and Y. Nishibayashi, *ChemCatChem*, 2009, **1**, 342–356; (*b*) R. J. Detz, H. Hiemstra and J. H. van Maarseveen, *Eur. J. Org. Chem.*, 2009, 6263–6276; (*c*) D.-Y. Zhang and X.-P. Hu, *Tetrahedron Lett.*, 2015, **56**, 283–295; (*d*) A. F. Adeleke, A. P. N. Brown, L.-J. Cheng, K. A. M. Mosleh and C. J. Cordier, *Synthesis*, 2017, 790–801; (*e*) S. W. Roh, K. Choi and C. Lee, *Chem. Rev.*, 2019, **119**, 4293–4356; (*f*) Y. Nishibayashi, *Chem. Lett.*, 2021, **50**, 1282–1288; (*g*) Y.-P. Zhang, Y. You, J.-Q. Yin, Z.-H. Wang, J.-Q. Zhao, Q. Li and W.-C. Yuan, *Eur. J. Org. Chem.*, 2023, e202300728; (*h*) Y. You, Y.-P. Zhang, Z.-H. Wang, J.-Q. Zhao, J.-Q. Yin and W.-C. Yuan, *Chem. Commun.*, 2023, **59**, 7483–7505.

2 (*a*) R. J. Detz, M. M. E. H. Delville, H. Hiemstra and J. H. van Maarseveen, *Angew. Chem., Int. Ed.*, 2008, **47**, 3777–3780; (*b*) G. Hattori, H. Matsuzawa, Y. Miyake and Y. Nishibayashi, *Angew. Chem., Int. Ed.*, 2008, **47**, 3781–3783; (*c*) G. Hattori, K. Sakata, H. Matsuzawa, Y. Tanabe, Y. Miyake and Y. Nishibayashi, *J. Am. Chem. Soc.*, 2010, **132**, 10592–10608; (*d*) C. Zhang, X.-H. Hu, Y.-H. Wang, Z. Zheng, J. Xu and X.-P. Hu, *J. Am. Chem. Soc.*, 2012, **134**, 9585–9588; (*e*) F.-L. Zhu, Y. Zou, D.-Y. Zhang, Y.-H. Wang, X.-H. Hu, S. Chen, J. Xu and X.-P. Hu, *Angew. Chem., Int. Ed.*, 2014, **53**, 1410–1414; (*f*) K. Nakajima, M. Shibata and Y. Nishibayashi, *J. Am. Chem. Soc.*, 2015, **137**, 2472–2475; (*g*) W. Shao, H. Li, C. Liu, C.-J. Liu and S.-L. You, *Angew. Chem., Int. Ed.*, 2015, **54**, 7684–7687; (*h*) Q. Wang, T.-R. Li, L.-Q. Lu, M.-M. Li, K. Zhang and W.-J. Xiao, *J. Am. Chem. Soc.*, 2016, **138**, 8360–8363; (*i*) K. Tsuchida, Y. Senda, K. Nakajima and Y. Nishibayashi, *Angew. Chem., Int. Ed.*, 2016, **55**, 9728–9732; (*j*) J. E. Gómez, W. Guo, S. Gaspa and A. W. Kleij, *Angew. Chem., Int. Ed.*, 2017, **56**, 15035–15038; (*k*) H. Xu, L. Laraia, L. Schneider, K. Louven, C. Strohmann, A. P. Antonchick and H. Waldmann, *Angew. Chem., Int. Ed.*, 2017, **56**, 11232–11236; (*l*) K. Zhang, L.-Q. Lu, S. Yao, J.-R. Chen, D.-Q. Shi and W.-J. Xiao, *J. Am. Chem. Soc.*, 2017, **139**, 12847–12854; (*m*) R.-Z. Li, H. Tang, L. Wan, X. Zhang, Z. Fu, J. Liu, S. Yang, D. Jia and D. Nius, *Chem*, 2017, **3**, 834–845; (*n*) J. Song, Z.-J. Zhang and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2017, **56**, 5212–5216; (*o*) R.-Z. Li, H. Tang, K. R. Yang, L.-Q. Wan, X. Zhang, J. Liu, Z. Fu and D. Niu, *Angew. Chem., Int. Ed.*, 2017, **56**, 7213–7217; (*p*) Z.-J. Zhang, L. Zhang, R.-L. Geng, J. Song, X.-H. Chen and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2019, **58**, 12190–12194; (*q*) J. E. Gómez, À. Cristòfol and A. W. Kleij, *Angew. Chem., Int. Ed.*, 2019, **58**, 3903–3907; (*r*) R.-Z. Li, D.-Q. Liu and D. Niu, *Nat. Catal.*, 2020, **3**, 672–680; (*s*) W. Guo, L. Zuo, M. Cui, B. Yan and S. Ni, *J. Am. Chem. Soc.*, 2021, **143**, 7629–7634; (*t*) J.-T. Xia, L. Li and X.-P. Hu, *ACS Catal.*, 2021, **11**, 11843–11848; (*u*) H.-D. Qian, Z.-H. Li, S. Deng, C. Yao, H.-M. Xiang, G. Xu, Z.-Q. Geng, Z. Wang, L. Chen, C. Liu, C. Zhu, X. Qi and H. Xu, *J. Am. Chem. Soc.*, 2022, **144**, 15779–15785; (*v*) F. Gong, X. Meng, S. Lan, J. Liu, S. Yang and X. Fang, *ACS Catal.*, 2022, **12**, 12036–12044; (*w*) B.-C. Wang, T. Fan, F.-Y. Xiong, P. Chen, K.-X. Fang, Y. Tan, L.-Q. Lu and W.-J. Xiao, *J. Am. Chem. Soc.*, 2022, **144**, 19932–19941; (*x*) X. Pu, Q.-D. Dang, L. Yang, X. Zhang and D. Niu, *Nat. Commun.*, 2022, **13**, 2457; (*y*) A. Garcia-Roca, R. Pérez-Soto, G. Stoica, J. Benet-Buchholz, F. Maseras and A. W. Kleij, *J. Am. Chem. Soc.*, 2023, **145**, 6442–6452.

3 (*a*) I. M. Jacobson, S. C. Gordon, K. V. Kowdley, E. M. Yoshida, M. Rodriguez-Torres, M. S. Sulkowski, M. L. Shiffman, E. Lawitz, G. Everson, M. Bennett, E. Schiff, M. T. Al-Assi, G. M. Subramanian, D. An, M. Lin, J. McNally, D. Brainard, W. T. Symonds, J. G. McHutchison, K. Patel, J. Feld, S. Pianko and D. R. Nelson, *N. Engl. J. Med.*, 2013, **368**, 1867–1877; (*b*) H. Su, Y. Xie, W.-B. Liu and S.-L. You, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 3578–3582; (*c*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2007, **37**, 320–330; (*d*) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422–518.

4 X. Gao, Y.-L. Xiao, X.-L. Wan and X. Zhang, *Angew. Chem., Int. Ed.*, 2018, **57**, 3187–3191.

5 X. Gao, R. Cheng, Y.-L. Xiao, X.-L. Wan and X. Zhang, *Chem.*, 2019, **5**, 2987–2999.

6 X. Gao, Y.-L. Xiao, S. Zhang, J. Wu and X. Zhang, *CCS Chem.*, 2021, **3**, 1463–1471.

7 Y. Hou, Z. Zhang, X. Sun, Z. Yang, Y.-X. Luan and P. Tang, *Angew. Chem., Int. Ed.*, 2023, **62**, e202218919.

8 S. Niu, Y. Luo, C. Xu, J. Liu, S. Yang and X. Fang, *ACS Catal.*, 2022, **12**, 6840–6850.

9 (*a*) J.-S. Ma, H.-Y. Lu, Y.-W. Chen, W.-C. Zhao, Y.-Z. Sun, R.-P. Li, H.-X. Wang, G.-Q. Lin and Z.-T. He, *Nat. Synth.*, 2023, **2**, 37–48; (*b*) J. H. van Maarseveen, *Nat. Synth.*, 2023, **2**, 11–12.

10 H.-Y. Lu and Z.-T. He, *Chin. Chem. Lett.*, 2023, **34**, 108105.

11 H.-H. Kong, C. Zhu, S. Deng, G. Xu, R. Zhao, C. Yao, H.-M. Xiang, C. Zhao, X. Qi and H. Xu, *J. Am. Chem. Soc.*, 2022, **144**, 21347–21355.

12 Y.-Z. Sun, Z.-Y. Ren, Y.-X. Yang, Y. Liu, G.-Q. Lin and Z.-T. He, *Angew. Chem., Int. Ed.*, 2023, **62**, e202314517.

13 (*a*) M.-D. Li, Z.-H. Wang, H. Zhu, X.-R. Wang, J.-R. Wang and T.-Y. Lin, *Angew. Chem., Int. Ed.*, 2023, **62**, e202313911; (*b*) S.-Y. Luo, G.-Q. Lin and Z.-T. He, *Org. Chem. Front.*, 2024, **11**, 690–695; (*c*) H.-D. Qian, X. Li, T. Yin, W.-F. Qian, C. Zhao, C. Zhu and H. Xu, *Sci. China: Chem.*, 2024, DOI: **10.1007/s11426-023-1922-5**.

14 Z. Jiao, J. J. Beiger, Y. Jin, S. Ge, J. R. Zhou and J. F. Hartwig, *J. Am. Chem. Soc.*, 2016, **138**, 15980–15986.

15 Z.-T. He, X. Jiang and J. F. Hartwig, *J. Am. Chem. Soc.*, 2019, **141**, 13066–13073.

16 N. Gao, X.-M. Zhao, C.-S. Cai and J.-W. Cai, *Org. Biomol. Chem.*, 2015, **13**, 9551–9558.

17 T. Satyanarayana, S. Abraham and H. B. Kagan, *Angew. Chem., Int. Ed.*, 2009, **48**, 456–494.