EDGE ARTICLE

Synthesis of chiral α-amino acids *via* Pd(II)-catalyzed enantioselective C−H arylation of α-aminoisobutyric acid†

Zi-Yu Zhang,‡[a] Tao Zhang, ‡[a] Yuxin Ouyang,[a] Peng Lu,[a] Jennifer X. Qiao[b] and Jin-Quan Yu *[a]

Non-natural chiral α,α-disubstituted α-amino acids (α,α-AAs) constitute an attractive α-aminoisobutyric acid (Aib) replacement for improving bioavailability of linear peptides as therapeutics due to the ability of these amino acids to induce the peptides to form helical structures. Enantioselective β-C(sp³)−H arylation of Aib could potentially provide a versatile one-step strategy for accessing diverse α,α-AAs, but the installation and removal of external directing groups was found in our previously reported work to reduce the efficiency of this approach. Herein we report a Pd(II)-catalyzed enantioselective C−H arylation of *N*-phthalyl-protected Aib enabled by a *N*-2,6-difluorobenzoyl aminoethyl phenyl thioether (MPAThio) ligand, affording α,α-AAs with up to 72% yield and 98% ee. Use of this newly developed chiral catalyst has also significantly improved enantioselective C(sp³)−H arylation of cyclopropanecarboxylic acids by expanding the substrate scope to heterocyclic coupling partners and increasing enantioselectivity to 99% ee.

Introduction

Non-natural chiral α,α-disubstituted α-amino acids (α,α-AAs) are crucial building blocks in biochemistry and medicinal chemistry[1] (Scheme 1A) for the assembly of peptides and proteins with restrictive conformational flexibility and high metabolic resistance.[2] This unique property of α,α-AAs has been applied to the development of enzyme inhibitors and bioactive molecules that have received the extensive attention of industry and academia.[3] In the area of asymmetric catalysis, various methods have been developed for the construction of chiral α,α-AAs, among which the classical Strecker reaction,[4] Mannich reaction,[5] alkylation of amino acids,[6] and α-amination of carboxylic acids are the most significant developments.[7,8] From the viewpoint of expanding chemical space in drug discovery through high-throughput synthesis, we envision that a wide range of chiral α,α-AAs can be obtained by carrying out various examples of a one-step enantioselective β-C−H functionalization of a single readily available α-aminoisobutyric acid (Aib), followed by functionalization of the remaining methyl group (Scheme 1B).

Carboxylic acids constitute one of the most abundant classes of substrates in organic synthesis.[9] The recently developed ligand-enabled β- and γ-C−H activation reactions of free acids have provided new avenues for harnessing the synthetic utility of aliphatic acids.[10] We have envisioned that the enantioselective β-C(sp³)−H functionalization of Aib could serve as a versatile platform for the diversity-oriented synthesis of chiral α,α-AAs.[11] In 2017, we reported on enantioselective arylation of *N*-phthalyl-protected Aib to access a series of chiral α,α-AAs with *N*-methoxy amide as the directing group in up to 96% ee (Scheme 2A).[12] However, the reaction necessitates the installation and removal of a directing group that enhances the coordination with Pd to facilitate C(sp³)−H cleavage. These additional two steps make the application of this method in high-throughput synthesis of chiral amino acids less attractive.

[a]*Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA. E-mail: yu200@scripps.edu*

[b]*Small Molecule Drug Discovery, Bristol Myers Squibb Research and Early Development, Cambridge, Massachusetts 02140, USA*

‡ These authors contributed equally to this work.
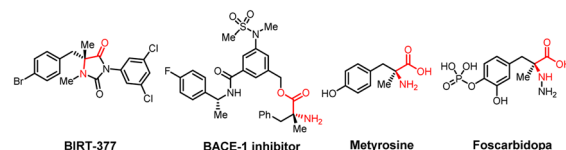
Scheme 1 Construction of a sequential C−H activation platform for α,α-AAs.

A) Previous work: Enantioselective Arylation of Methoxy Carboxamide

DG = NHOMe

Up to 96% ee

MPAO
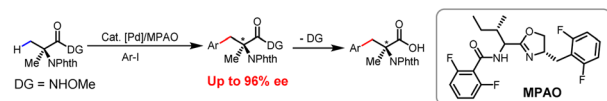
B) This work: Enantioselective Arylation of Free Carboxylic Acid

Up to 98% ee

MPAThio
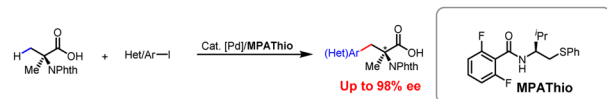
Scheme 2   Pd(II)-catalyzed enantioselective arylation of Aib.

In our previous efforts, enantioselective arylation of the C(sp^3)–H of N-phthalyl-protected Aib with various chiral ligands only yielded chiral α,α-AAs with moderate enantioselectivity (72–86% ee). Furthermore, the success of the reaction was found to be heavily contingent on the structure of the aryl iodide, resulting in limited functional group compatibility.[13] Herein, we report a significantly improved Pd(II)-catalyzed enantioselective β-C–H arylation of N-phthalyl-protected Aib, affording a wide range of chiral α,α-AAs. Also, the method could provide an effective way to prepare α,α-disubstituted cyclopropyl α-amino acids with two chiral centers (Scheme 2B). The development of a chiral N-2,6-difluorobenzoyl aminoethyl phenyl thioether (MPAThio) ligand was crucial for this enantioselective transformation.

Results and discussion

We commenced our investigations with the commercially available N-phthalyl-protected Aib (**1a**) as the main substrate and methyl 4-iodobenzoate (**2a**) as the coupling partner for

Table 1   Investigation of ligands for enantioselective arylation of Aib[a]

[a] Conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Pd(OAc)$_2$ (10 mol%), ligand (12 mol%), Ag$_2$CO$_3$ (2.0 equiv.), NaHCO$_3$ (0.5 equiv.) in HFIP (0.5 mL) 70 °C, 24 h. Yields were determined from the results of ^{1}H NMR spectroscopy using CH$_2$Br$_2$ as the internal standard. [b] Isolated yield.

optimization studies (Table 1). No desirable products were observed in the absence of ligand, demonstrating ligand development to be essential for this reaction. The chiral bidentate N-acetyl aminoethyl amine (MPAAM) ligand (**L1**) and amino acid (MPAA) ligand (**L2**) developed for the enantioselective arylation of cyclopropanecarboxylic acid were found to be active for this transformation, with 20–47% yields and moderate enantioselectivities (52–72% ee). Other chiral ligands such as the N-acetyl amino quinoline (MPAQ) (**L3**), amino O-methylhydroxamic acid (MPAA) (**L4**) and amino oxazoline (MPAO) (**L5**) did not provide any products. To our delight, when we employed another chiral bidentate ligand, namely N-acetyl aminoethyl phenyl thioether (MPAThio) (**L6**), initially developed for the enantioselective γ-C(sp^3)–H functionalization of cyclopropylmethylamines,[14] the desired arylation product **3a** was obtained in 56% yield with 80% ee. The ligand with a benzyl substituent on the side chain (**L7**) provided good stereoselectivity but a lower yield (32%). Surprisingly, replacing the acetyl group with an N-Boc protected group (**L8**) resulted in a complete loss of reactivity, showing the critical function of the acetyl group. **L9** and **L10** showed inefficient performances, which could be attributed to ortho-C–H activation of the benzoyl group of the ligands as previously observed with MPAA ligands.[15] The N-2,6-difluorobenzoyl aminoethyl phenyl thioether (**L11**) with two ortho-positions blocked by fluorine atoms was found to be the optimal ligand, affording the desired product in 71% yield and 91% ee. The replacement of the isopropyl group on the side chain with other groups decreased the reactivity and enantioselectivity (**L12** and **L13**), illustrating the influence of the steric environment.

With the optimized conditions in hand, we proceeded to survey the scope of aryl iodides using N-phthalyl-protected Aib (**1a**) as the main substrate (Table 2). Under the standard conditions, use of the simple iodobenzene (**2b**) resulted in a 64% yield with 88% ee. The aryl iodides bearing electron-donating substituents (**2c–g**) or electron-withdrawing CF$_3$ (**2h**) and halide substituents at the para position (**2i–k**) provided the arylated products in 48–74% yields with 86–98% ee. Notably, the arylation product **3k** was previously shown to be a key intermediate for the synthesis of BIRT-377, a potent LFA-1 inhibitor for the treatment of inflammatory and immune disorders.[16] Other para-substituents including NO$_2$ (**2l**), COMe (**2m**) and COPh (**2n**) were also compatible, affording 62–65% yields with 88–93% ee. The reactions with meta-substituted aryl iodides proceeded smoothly to give the arylated products (**3o–u**) with 56–68% yields and 87–92% ee. The 3,5-disubstituted aryl iodide produced the corresponding product (**3v**) in 63% yield with 92% ee. While heteroaryl iodides are often less effective,[17] the thioether ligand as a donor can enhance the Pd(II)/Pd(IV) oxidative addition process, thereby improving the reactivity,[14a] also, 2-substituted iodopyridine gave excellent enantioselectivity (**3w–3y**) (up to 98% ee) under the optimal reaction conditions.
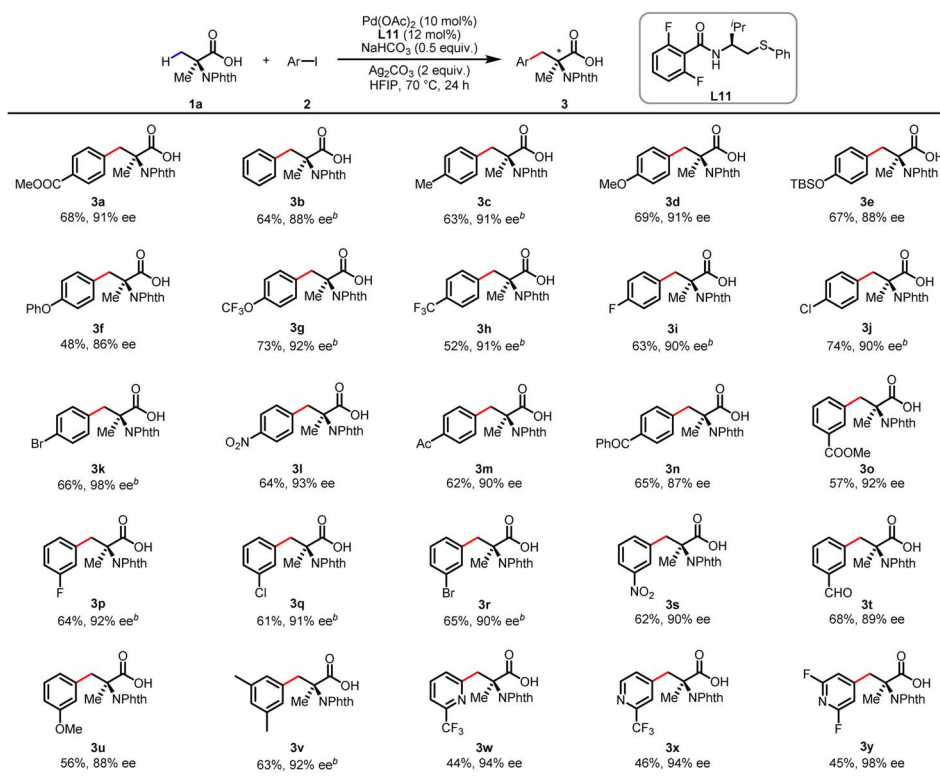
Although our group previously reported stereoselective C(sp^3)–H arylation of cyclopropanecarboxylic acids enabled by chiral MPAAM ligands, heterocyclic coupling partners and α-amino-substituted cyclopropanecarboxylic acid are largely
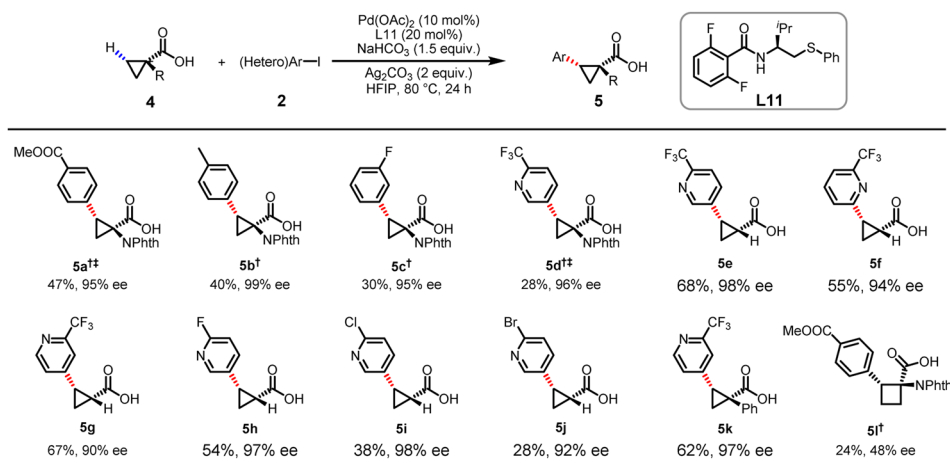
Table 2 Scope of the enantioselective arylation of Aib[a]

[a] Conditions: carboxylic acid **1** (0.1 mmol), **2** (0.2 mmol), Pd(OAc)$_2$ (10 mol%), **L11** (12 mol%), Ag$_2$CO$_3$ (2.0 equiv.), NaHCO$_3$ (0.5 equiv.) in HFIP (0.5 mL), 70 °C, 24 h. Isolated yields. The ee values were determined from the results of SFC analysis on a chiral stationary phase. [b] Isolated as the corresponding methyl ester.

incompatible.[18] Since such incompatibility has substantially restricted applications in drug discovery, we decided to re-evaluate the enantioselective heteroarylation of cyclo-propanecarboxylic acids with our newly developed MPAThio ligands (Table 3). The arylation of **4a** with **2a** afforded the

coupling product in 47% yield and 95% ee. The *para-* or *meta-*substituted aryl iodides and even heteroaryl iodide were found to be compatible, providing the arylated products (**5a–d**) with moderate yields and excellent ee. The heteroarylation of α-*H*-substituted cyclopropanecarboxylic acids with 5-iodo-2-

Table 3 Scope of the enantioselective (hetero)arylation of cyclopropanecarboxylic acids[a]

[a] Conditions: carboxylic acid **4** (0.1 mmol), **2** (0.2 mmol), Pd(OAc)$_2$ (10 mol%), **L11** (12 mol%), Ag$_2$CO$_3$ (2.0 equiv.), NaHCO$_3$ (1.5 equiv.) in HFIP (1.0 mL), 80 °C, 24 h. Isolated yields. The ee values were determined from the results of SFC analysis on a chiral stationary phase. [†] Isolated as the corresponding methyl ester. [‡] K$_2$CO$_3$ (1.0 equiv.) was used and the reaction was carried out a temperature of 100 °C.
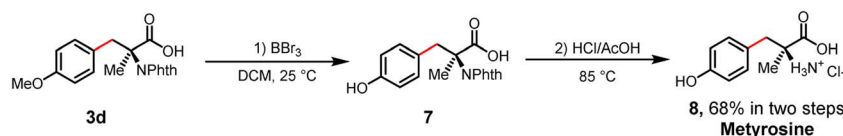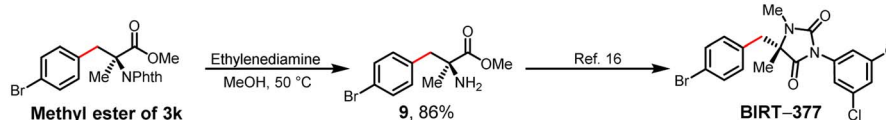
Table 4 Practical applications
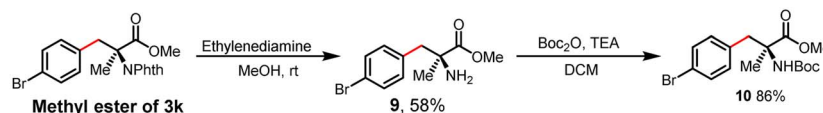

(A) Di-Arylation of Aib
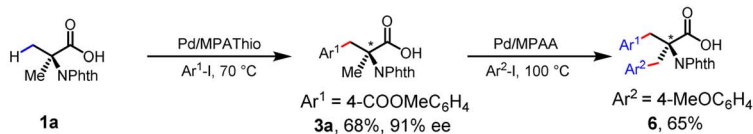
(B) Synthesis of Metyrosine

(C) Synthesis of BIRT–377

(D) Synthesis of the Boc-Protected Amino Acid

(trifluoromethyl)pyridine provided the desired chiral product (**5e**) in 68% yield and 98% ee under the optimized conditions. The position of the iodo substituent on the pyridine was found to impact the reactivity and enantioselectivity. In general, the iodo substituent at the C3 position gave higher ee than it did at the C2 and C4 positions (**5f–g**). Pyridines bearing fluoro, chloro and bromo groups at the C2 position were all found to be compatible, affording excellent enantioselectivity levels (**5h, 5i**) (97 and 98% ee). The α-phenyl-substituted cyclopropanecarboxylic acid also reacted successfully, providing a moderate product yield (**5k**) (62%) with high enantioselectivity (97% ee). Although the desired arylated product was obtained for the α-amino-substituted cyclobutanecarboxylic acid (**4l**), the yield (24%) and ee (48%) were significantly reduced.

The enantioselective β-C–H arylation of Aib followed by sequential C–H arylation of the remaining methyl group could lead to a diverse range of chiral α,α-AAs. The diarylation product of **6** was obtained with 65% yield using the MPAA ligand (Table 4A). We also applied this enantioselective arylation reaction to the syntheses of drug molecules. As a therapeutic agent for hypertension, metyrosine has been employed to alleviate blood pressure elevation in individuals afflicted with adrenal tumors.[19] In the current work, the synthesis of metyrosine was achieved through a two-step process from **3d**, with this process involving demethylation utilizing BBr₃ in anhydrous dichloromethane followed by acidic hydrolysis to remove the *N*-phthalimide group (68% in two steps) (Table 4B). The methyl ester of **3k** was also successfully deprotected to give chiral amino acid **9**, a key intermediate for the synthesis of BIRT-377 (Table 4C).[16] Given the importance and common use of Boc-protected amino acids in peptide chemistry, we set out to synthesize the Boc-

protected α,α-AAs (**10**) using free amine (**9**) under mild conditions, and did so successfully (Table 4D).

Conclusions

In summary, we have developed Pd(ıı)-catalyzed enantioselective β-C–H arylation of *N*-phthalyl-protected Aib using the newly developed *N*-2,6-difluorobenzoyl aminoethyl phenyl thioether (MPAThio) ligand **L11**. Various aryl iodides and C2-substituted pyridyl iodides were tolerated, affording chiral non-natural α,α-AAs in 44–74% yields with 86–98% ee. The *N*-phthalyl group of the product can be removed under mild conditions for synthetic applications as demonstrated in the synthesis of metyrosine. Notably, use of this newly developed chiral MPAThio ligand has also substantially improved the scope and enantioselectivity of β-C(sp³)–H arylation of cyclopropanecarboxylic acids.

Data availability

All the data have been presented in the manuscript and ESI.†

Author contributions

Z.-Y. Z. and T. Z. discovered and developed the reactions. Y. O. and P. L. performed a portion of the synthetic experiments. J. X. Q. participated in substrate scope surveys and discussions. J.-Q. Y. directed the project. Z.-Y. Z. and T. Z. wrote the ESI.†

Conflicts of interest

The authors declare no competing financial interests.

Acknowledgements

References

1 (a) K. H. Hsieh and G. R. Marsall, *J. Med. Chem.*, 1986, **29**, 1968–1971; (b) B. Bellier, I. McCort-Tranchepain, B. Ducos, S. Danascimento, H. Meudal, F. Noble, C. Garbay and B. P. Roques, *J. Med. Chem.*, 1997, **40**, 3947–3956.

2 (a) A. W. Burgess and S. J. Leach, *Biopolymers*, 1973, **12**, 2599–2605; (b) I. L. Karle, R. Kaul, R. B. Rao, S. Raghothama and P. Balaram, *J. Am. Chem. Soc.*, 1997, **119**, 12048–12054; (c) C. Toniolo, M. Crisma, F. Formaggio, G. Valle, G. Cavicchioni, G. Precigoux, A. Aubry and J. Kamphuis, *Biopolymers*, 1993, **33**, 1061–1072; (d) C. E. Schafmeister, J. Po and G. L. Verdine, *J. Am. Chem. Soc.*, 2000, **122**, 5891–5892.

3 (a) H. Vogt and S. Bräse, *Org. Biomol. Chem.*, 2007, **5**, 406–430; (b) C. Nájera and J. M. Sansano, *Chem. Rev.*, 2007, **107**, 4584–4671.

4 (a) H. Gröger, *Chem. Rev.*, 2003, **103**, 2795–2827; (b) J. Wang, X. Liu and X. Feng, *Chem. Rev.*, 2011, **111**, 6947–6983; (c) P. Vachal and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 10012–10014; (d) S. Masumoto, H. Usuda, M. Suzuki, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 5634–5635.

5 (a) S. Saaby, K. Nakama, M. A. Lie, R. G. Hazell and K. A. Jørgensen, *Chem.–Eur. J.*, 2003, **9**, 6145–6454; (b) W. Zhuang, S. Saaby and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2004, **43**, 4476–4478; (c) Y. Suto, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2007, **129**, 500–501; (d) B. Eftekhari-Sis and M. Zirak, *Chem. Rev.*, 2017, **117**, 8326–8419.

6 (a) U. Schöllkopf, *Tetrahedron*, 1983, **39**, 2085–2091; (b) T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2007, **107**, 5656–5682.

7 (a) J. M. Janey, *Angew. Chem., Int. Ed.*, 2005, **44**, 4292–4300; (b) A. M. R. Smith and K. K. Hii, *Chem. Rev.*, 2011, **111**, 1637–1656; (c) F. Zhou, F.-M. Liao, J.-S. Yu and J. Zhou, *Synthesis*, 2014, **46**, 2983–3003; (d) K. Ohmatsu, Y. Ando, T. Nakashima and T. Ooi, *Chem*, 2016, **1**, 802–810.

8 (a) L. Wei, Q. Zhu, S.-M. Xu, X. Chang and C.-J. Wang, *J. Am. Chem. Soc.*, 2018, **140**, 1508–1513; (b) X. Huo, J. Zhang, J. Fu, R. He and W. Zhang, *J. Am. Chem. Soc.*, 2018, **140**, 2080–2084; (c) J. H. Blackwell, R. Kumar and M. J. Gaunt, *J. Am. Chem. Soc.*, 2021, **143**, 1598–1609; (d) Y. Peng, C. Han, Y. Luo, G. Li, X. Huo and W. Zhang, *Angew. Chem., Int. Ed.*, 2022, **61**, e202203448.

9 (a) L. J. Gooßen, N. Rodriguez and K. Gooßen, *Angew. Chem., Int. Ed.*, 2008, **47**, 3100–3120; (b) K. P. C. Vollhardt and N. E. Schore, *Organische Chemie*, Wiley-VCH, Weinheim, 3rd edn, 2000, pp. 893–952.

10 For selected reviews on enantioselective C–H activation, see: (a) E. L. Lucas, N. Y. S. Lam, Z. Zhuang, H. S. S. Chan, D. A. Strassfeld and J.-Q. Yu, *Acc. Chem. Res.*, 2022, **55**, 537–550; (b) T. G. Saint-Denis, R.-Y. Zhu, G. Chen, Q.-F. Wu and J.-Q. Yu, *Science*, 2018, **359**, eaao4798; (c) C. G. Newton, S.-G. Wang, C. C. Oliveira and N. Cramer, *Chem. Rev.*, 2017, **117**, 8908–8976.

11 (a) G. Chen, Z. Zhuang, G.-C. Li, T. G. Saint-Denis, Y. Hsiao, C. L. Joe and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2017, **56**, 1506–1509; (b) Y. Zhu, X. Chen, C. Yuan, G. Li, J. Zhang and Y. Zhao, *Nat. Commun.*, 2017, **8**, 14904–14911; (c) T. Zhang, Z.-Y. Zhang, G. Kang, T. Sheng, J.-L. Yan, Y.-B. Yang and J.-Q. Yu, *Science*, 2024, **384**, 793–798; (d) C.-H. Yuan, X.-X. Wang, K. Huang and L. Jiao, *Angew. Chem., Int. Ed.*, 2024, **63**, e202405062.

12 Q.-F. Wu, P.-X. Shen, J. He, X.-B. Wang, F. Zhang, Q. Shao, R.-Y. Zhu, C. Mapelli, J. X. Qiao, M. A. Poss and J.-Q. Yu, *Science*, 2017, **355**, 499–503.

13 P.-X. Shen, L. Hu, Q. Shao, K. Hong and J.-Q. Yu, *J. Am. Chem. Soc.*, 2018, **140**, 6545–6549.

14 (a) Z. Zhuang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2020, **142**, 12015–12019; (b) Z. Zhuang, C.-B. Yu, G. Chen, Q.-F. Wu, Y. Hsiao, C. L. Joe, J. X. Qiao, M. A. Poss and J.-Q. Yu, *J. Am. Chem. Soc.*, 2018, **140**, 10363–10367.

15 R. E. Plata, D. E. Hill, B. E. Haines, D. G. Musaev, L. Chu, D. P. Hickey, M. S. Sigman, J.-Q. Yu and D. G. Blackmond, *J. Am. Chem. Soc.*, 2017, **139**, 9238–9245.

16 N. S. Chowdari and C. F. Barbas, *Org. Lett.*, 2005, **7**, 867–870.

17 G. Meng, L. Hu, M. Tomanik and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2022, e202214459.

18 L. Hu, P.-X. Shen, Q. Shao, K. Hong, T.-X. Qiao and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2019, **58**, 2134–2138.

19 D. Kopf, P. E. Goretzki and H. Lehnert, *J. Cancer Res. Clin. Oncol.*, 2001, **127**, 143–155.