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Silanol: a bifunctional group for peptide synthesis and late-stage functionalization†

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Chemical modification of a specific amino acid residue on peptides represents an efficient strategy to improve their pharmacokinetics and facilitates the potential to achieve post-synthetic diversification of peptides. Herein, we reported the first Pd-catalyzed late-stage *ortho*-olefination of Tyr residues on peptides with high chemo- and site-selectivity, by employing the easily attached and removable silanol as a bifunctional protecting group and directing group. Up to hexapeptides with variation on amino acid sequences or locations of the Tyr residue and different olefins were compatible with this protocol, which enriched the chemical toolbox for late-stage modification *via* C(sp²)-H functionalization. Furthermore, the orthogonal protection strategies of Tyr were also developed and could be applied to SPPS.

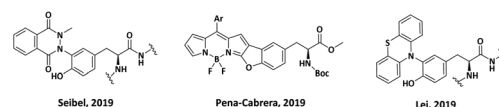
Introduction

Emerged as a class of new therapeutic targets, the study of protein-protein interaction (PPI) is driving the rapid growth of synthetic peptides or peptidomimetics.¹ However, the instability of peptides and analogues *in vivo* greatly depresses their bioactivity and pharmacokinetics.² The incorporation of unnatural amino acids into peptides represents one of the most efficient strategies to improve their *in vivo* stability, which makes the development of new methods that could site-specifically modify the amino acid residues in peptides valuable.³ Successful efforts⁴ have been made to decorate alanine (Ala)⁵ and its homologues,⁶ tryptophan (Trp),⁷ phenylalanine (Phe)⁸ and histidine (His).⁹ We notice that the directed functionalization of the phenol motif has been achieved on small molecules,¹⁰ whereas very few examples related to tyrosine (Tyr)¹¹ (Fig. 1a) have been reported. Particularly, site-selective modification of Tyr residues in polypeptide *via* C-C bond formation is hitherto undisclosed.

The most commonly applied approach to address the site-selectivity in C-H functionalization relies on the installation of a directing group (DG) at a specific position,¹² which is an extra step and might be problematic. Late-stage functionalization directed by the peptide backbone^{8b,c} is an excellent strategy to avoid the installation of additional directing groups, but it is limited to few peptide sequences. We focus on step-economical chemistry and envisioned whether the protecting group (PG) for solid phase peptide synthesis (SPPS) on the phenol motif of Tyr

could also act as the directing group (Fig. 1b), which could be directly employed for late-stage modification after peptide synthesis. A silicon tether seems ideal, as it can easily be attached or removed. Gevorgyan's group developed several silicon-tethered strategies¹³ for C-H functionalization at the *ortho*-position of the phenol motif¹⁴ for small molecules. However, site-selective functionalization⁴ of Tyr residues on peptides is predicted to be more challenging due to the multiple functional groups within the peptide sequence, and the existence of peptide backbones is expected to interfere with the interaction between the catalyst and DG. Herein, we reported the first Pd-catalyzed late-stage *ortho*-olefination of Tyr residues with high chemo- and site-selectivity on peptides, by employing bifunctional silanol on the phenol motif which served as a PG and DG. Silanol could also be applied in orthogonal protection strategies and solid phase peptide synthesis (SPPS).

a). Chemical modification on phenol motif of Tyr:



b). General procedure of site-selective C-H activation and our strategy:

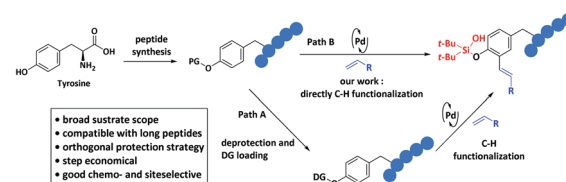


Fig. 1 (a). Previous work about modification of tyrosine residues. (b). Traditional strategy for late-stage modification and our strategy.

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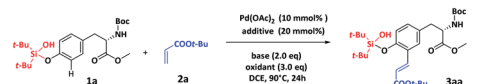
† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0sc02439b



Results and discussion

To test the feasibility of our hypothesis, we initiated our study by utilizing Tyr derived Boc-Y(Sil)-OME (**1a**) as the model substrate and acrylate *tert*-butyl ester (**2a**) as the olefination reagent. Several C–H functionalization conditions (Table 1, entries 1–4)^{14a,15} that have been successfully applied to modify small molecules were tested. Perhaps unsurprisingly, we could not detect the formation of **3aa**, probably due to the inefficient oxidation of Pd(0). Luckily, the desired product **3aa** was obtained in 12% yield by using Ag₂CO₃ (Table 1, entry 5). Several other oxidants were screened (ESI, Table S1†); we were excited to find that PhI(OAc)₂ could improve the reaction yield to 47% (Table 1, entry 6). Further investigation of the base showed that Li₃PO₄ was optimal and gave **3aa** in 58% yield (Table 1, entry 10). Continuous efforts on screening of additives (ESI, Table S4†) showed that addition of benzoquinone (BQ) exhibited the best reactivity and delivered **3aa** in 76% yield after 24 h, which might have resulted from the addition of BQ that could suppress the formation of palladium black.¹⁶ Remarkably, a mono-olefination product was solely isolated from the reaction, no di-olefination product was detected. We envisioned that this might be because the two bulky *tert*-butyl groups on silicon blocked the rotation of silanol,^{14a} thus preventing the second olefination. NMR analysis of **3aa** confirmed that the olefination occurred at the *ortho*-position of the phenol motif, and the double bond was determined to be in *E*-configuration (ESI, Fig. S5 and S6†). The optimal reaction conditions for site-selective olefination are as follows: amino acid or peptide (1.0 eq.) and olefination reagent (4.0 eq.), with 10% mol of Pd(OAc)₂, 3.0 eq. of PhI(OAc)₂, 2.0 eq. of Li₃PO₄, and 0.2 eq. of BQ in DCE and agitation for 24 h at 90 °C.

Table 1 Optimization of the reaction conditions^a

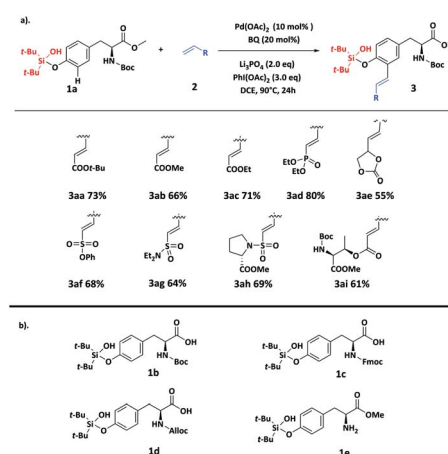


Entry	Base	Oxidant	Solvent	Additive	Yield ^b [%]
1	Li ₂ CO ₃	AgOAc	DCE	L1 ^c	n.d
2	KHCO ₃	O ₂	<i>t</i> -AmOH ^d	—	n.d
3	Li ₂ CO ₃	AgOAc	DCE	—	n.d
4	—	Ag ₂ CO ₃	HFIP	L2 ^e	n.d
5	Li ₂ CO ₃	Ag ₂ CO ₃	DCE	—	12
6	Li ₂ CO ₃	PhI(OAc) ₂	DCE	—	47
7	NaHCO ₃	PhI(OAc) ₂	DCE	—	22
8	LiOAc	PhI(OAc) ₂	DCE	—	<10
9	LiH ₂ PO ₄	PhI(OAc) ₂	DCE	—	38
10	Li ₃ PO ₄	PhI(OAc) ₂	DCE	—	58
11	Li ₃ PO ₄	PhI(OAc) ₂	DCE	L1	51
12	Li ₃ PO ₄	PhI(OAc) ₂	DCE	BQ ^f	76(73 ^g)

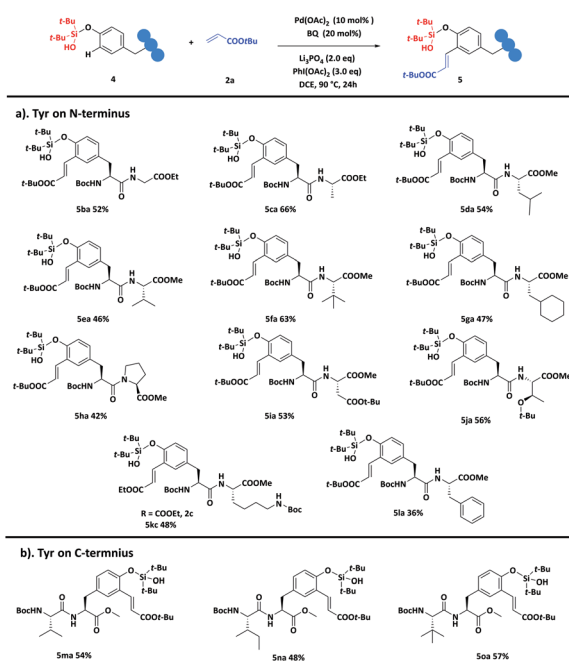
^a Reaction conditions: **1a** (0.1 mmol, 1.0 eq.), **2a** (0.4 mmol, 4.0 eq.), Pd(OAc)₂ (0.01 mmol, 0.1 eq.), additive (0.02 mmol, 0.2 eq.), oxidant (0.3 mmol, 3.0 eq.), and base (0.2 mmol, 2.0 eq.) in solvent (1.0 mL) at 90 °C for 24 h. ^b ¹H NMR yield using 1,3,5-trimethoxybenzene as the internal standard. ^c L1 = (+)-menthyl(O₂C)-Leu-OH. ^d *t*-AmOH = tertiary amyl alcohol. ^e L2 = Ac-Gly-OH. ^f Benzoquinone. ^g Isolated yield.

With the optimized reaction conditions in hand, we started to investigate the scope of olefin coupling partners **2** (ESI, Table S5†). To our delight, a wide range of alkenes could be successfully incorporated at the *ortho*-position of the phenol motif in Tyr residues with moderate to good yield (Scheme 1a), affording the acrylic ester products **3aa**, **3ab** and **3ac** in 66–76% yields. Interestingly, vinyl phosphonate product **3ad**, vinylolefin carbonate product **3ae**, vinyl sulfonated product **3af** and vinyl sulfonamide product **3ag** could also be prepared by this strategy with 55–80% yields, indicating the broad substrate scope of this strategy. To our delight, alkenes **2h** and **2i**, derived from proline (Pro) and Thr, were also efficient coupling partners to give **3ah** and **3ai** in 69% and 61% yields, respectively, suggesting the potential of using this strategy to perform macrocyclization of peptides. The silanol group could be efficiently removed from **3aa** by simply treating with TBAF to get **3b** in 91% yield (ESI, Fig. S1†), suggesting the compatibility of the silanol group with other protecting groups. To further explore the utility of the bifunctional silanol group, we synthesized amino acid building blocks **1b–1e** with the purpose of developing orthogonal protection strategies (ESI, Fig. S2†) for peptide synthesis and the subsequent functionalization. The attachment and removal of traditional protecting groups including *N*-Boc, *N*-Fmoc, *N*-Alloc and methyl esters were all compatible with the silanol group (Scheme 1b).

Next, we turned our attention to explore the compatibility of this method. Pleasingly, most of the dipeptides **4b–4o** (ESI, Fig. S3†) gave the desired mono-*ortho*-olefination products with good results. As shown, dipeptides with alkyl side chain amino acids at the C-terminus could be well tolerated to give the products **5ba–5ha** in 42–66% yields (Scheme 2a). In general, peptides with side chain functional groups were difficult to modify. Gratefully, our catalytic system seemed to be quite compatible; dipeptides **4i–4k** bearing aspartic acid (Asp), threonine (Thr) and lysine (Lys) residues at the C-terminus could also be decorated efficiently, affording the corresponding



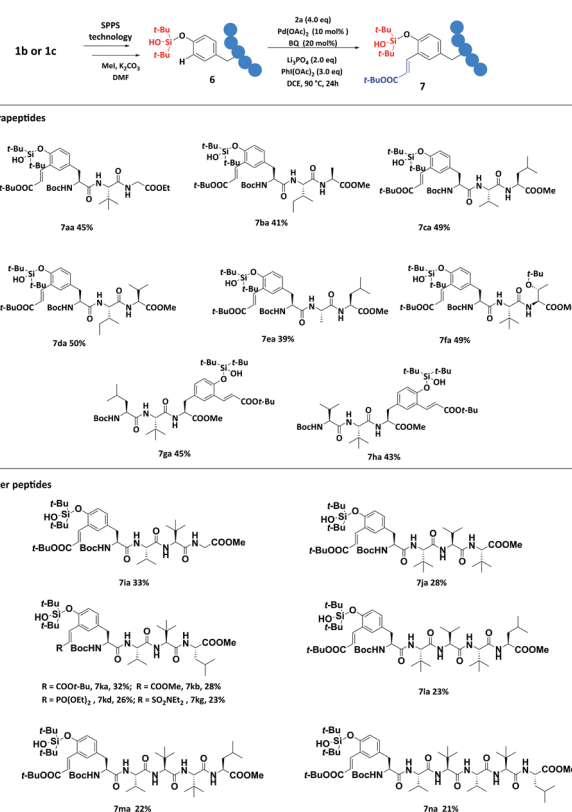
Scheme 1 Scope of coupling partners^a and orthogonal protection strategies.^a Reaction conditions: **1a** (0.2 mmol, 1.0 eq.), **2** (0.8 mmol, 4.0 eq.), Pd(OAc)₂ (0.02 mmol, 0.1 eq.), BQ (0.04 mmol, 0.2 eq.), PhI(OAc)₂ (0.6 mmol, 3.0 eq.), and Li₃PO₄ (0.4 mmol, 2.0 eq.) in DCE (2.0 mL) at 90 °C for 24 h.



Scheme 2 ^aScope of dipeptide substrates. ^aReaction conditions: **4** (0.2 mmol, 1.0 eq.), **2a** (0.8 mmol, 4.0 eq.), Pd(OAc)₂ (0.02 mmol, 0.1 eq.), BQ (0.04 mmol, 0.2 eq.), PhI(OAc)₂ (0.6 mmol, 3.0 eq.), and Li₃PO₄ (0.4 mmol, 2.0 eq.) in DCE (2.0 mL) at 90 °C for 24 h.

products **5ia**, **5ja** and **5kc** in 48–56% yields. Interestingly, dipeptide **4l** with Phe residues at the C-terminus gave the desired product **5la** in 36% yield, with no functionalization of Phe residues detected. The promising results indicated that this strategy could achieve unique chemo-selective Tyr modification and discriminate the subtle differences between Phe and Tyr residues, suggesting that the directing ability of silanol is superior to that of the peptide backbone in this catalytic system. In addition, olefination of dipeptides **4m–4o** bearing Tyr residues on the C-terminus could also be achieved, and delivered the modified products **5ma**, **5na** and **5oa** in 48–57% yields (Scheme 2b). Compared to the Tyr monomer, the incomplete conversion of dipeptides made the yields slightly decreased. We considered that this might be caused by the chelation between the amides on the peptide backbone^{ab} and the catalyst.

To further expand the application of this strategy, polypeptides **6a–6n** were synthesized by using **1b** or **1c** as building blocks according to the standard SPPS. The bifunctional silanol group seemed quite compatible and delivered polypeptide precursors (ESI, Fig. S4†) in good yields compared with the commercially available amino acid building blocks. As shown in scheme 3a, tripeptides (**6a–6h**) bearing Tyr residues on the N-terminus could be well decorated with **2a**, afforded the corresponding products **7aa–7fa** in 41–50% yields. Moreover, tripeptides **6g** and **6h** bearing Tyr residues on the C-terminus could also be well functionalized to give the products **7ga** and **7ha** in 45% and 43% yields respectively. We were excited to find that the olefination of longer peptides **6i–6n** was also successful by employing this protocol (Scheme 3b), affording the modified tetrapeptides **7ia–7ka** in 28–33% yields and the modified pentapeptides **7la** and **7ma** in 23% and 22% yields respectively.



Scheme 3 Application^a and late-stage peptide modification.^b ^aFor peptide synthesis, see the ESI.† ^bReaction conditions: **6** (0.2 mmol, 1.0 eq.), **2a** (0.8 mmol, 4.0 eq.), Pd(OAc)₂ (0.02 mmol, 0.1 eq.), BQ (0.04 mmol, 0.2 eq.), PhI(OAc)₂ (0.6 mmol, 3.0 eq.), and Li₃PO₄ (0.4 mmol, 2.0 eq.) in DCE (2.0 mL) at 90 °C for 24 h.

In addition, the modification of long peptides might be difficult and thus was rarely reported.⁴ We noticed that the solution of polypeptide substrates became dark quickly while adding Pd(OAc)₂, which indicated the strong chelation of the peptide backbone and resulted in reduced conversion. Surprisingly, the olefinated hexapeptide **7na** was eventually obtained in 21% yield by employing the strategy. We further explored the utilities of our newly developed methods by decorating tetrapeptide **6k** with different alkenes, and delivered the corresponding acrylic ester product **7kb** in 31% yield, vinyl phosphonate product **7kd** in 26% yield, and vinyl sulfonamide product **7kg** in 23% yield.

To our delight, the peptide backbone directed *meta*-olefination product was not detected even in these long chain peptides, which further confirmed that the directing ability of silanol was better than that of the peptide backbone. The possible mechanism might be related to the formation of a kinetically less-favored six-membered palladacycle with silanol rather than the peptide backbone, and BQ could work as a special ligand.^{16a} Further mechanistic studies and modification of longer polypeptides are currently underway.

Conclusions

In summary, we have developed the first efficient Pd-catalyzed *ortho*-olefination of Tyr residues by employing the traditional

protecting group silanol as the directing group to achieve high chemo- and site-selectivity, which avoided the conventional directing group loading step. A broad range of substrates could be well applied in this protocol, which is tolerant to various amino acids and peptide lengths up to hexamers. Furthermore, the novel orthogonal protection strategies involving silanol on the phenol motif of Tyr are also successfully applied to prepare polypeptides *via* SPPS. Moreover, both N-terminal and C-terminal elongated peptides are compatible with this protocol, suggesting the potential applications of this strategy in medicinal chemistry and drug discovery.

Conflicts of interest

The authors declare no conflict of interest.

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Notes and references

- (a) J. L. Lau and M. K. Dunn, *Bioorg. Med. Chem.*, 2018, **26**, 2700; (b) K. Fosgerau and T. Hoffmann, *Drug Discov. Today*, 2015, **20**, 122; (c) P. G. Dougherty, A. Sahni and D. Pei, *Chem. Rev.*, 2019, **119**, 10241.
- (a) D. J. Drucker, *Nat. Rev. Drug Discov.*, 2020, **19**, 277; (b) H. Malhaire, J. C. Gimel, E. Roger, J. P. Benoit and F. Lagarce, *Adv. Drug Deliv. Rev.*, 2016, **106**, 320; (c) M. Goldberg and I. Gomez-Orellana, *Nat. Rev. Drug Discov.*, 2003, **2**, 289; (d) A. F. B. Rader, M. Weinmuller, F. Reichart, A. Schumacher-Klinger, S. Merzbach, C. Gilon, A. Hoffman and H. Kessler, *Angew. Chem., Int. Ed.*, 2018, **57**, 14414.
- (a) J. N. deGruyter, L. R. Malins and P. S. Baran, *Biochemistry*, 2017, **56**, 3863; (b) Y. Yu, C. Hu, L. Xia and J.-Y. Wang, *ACS Catal.*, 2018, **8**, 1851; (c) E. Remond, C. Martin, J. Martinez and F. Cavelier, *Chem. Rev.*, 2016, **116**, 11654.
- W. Wang, M. M. Lorion, J. Shah, A. R. Kapdi and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 14700.
- (a) B. V. S. Reddy, L. R. Reddy and E. J. Corey, *Org. Lett.*, 2006, **8**, 3391; (b) L. D. Tran and O. Daugulis, *Angew. Chem., Int. Ed.*, 2012, **51**, 5188; (c) B. Wang, C. Lu, S.-Y. Zhang, G. He, W. A. Nack and G. Chen, *Org. Lett.*, 2014, **16**, 6260; (d) Y.-J. Liu, Y.-H. Liu, Z.-Z. Zhang, S.-Y. Yan, K. Chen and B.-F. Shi, *Angew. Chem., Int. Ed.*, 2016, **55**, 13859; (e) T. Liu, J. X. Qiao, M. A. Poss and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2017, **56**, 10924; (f) M. Bauer, W. Wang, M. M. Lorion, C. Dong and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 203.
- (a) G. He, Y. Zhao, S. Zhang, C. Lu and G. Chen, *J. Am. Chem. Soc.*, 2012, **134**, 3; (b) G. He, S.-Y. Zhang, W. A. Nack, R. Pearson, J. Rabb-Lynch and G. Chen, *Org. Lett.*, 2014, **16**, 6488; (c) G. He, B. Wang, W. A. Nack and G. Chen, *Acc. Chem. Res.*, 2016, **49**, 635; (d) D. Mu, F. Gao, G. Chen and G. He, *ACS Catal.*, 2017, **7**, 1880; (e) X. Zhang, G. Lu, M. Sun, M. Mahankali, Y. Ma, M. Zhang, W. Hua, Y. Hu, Q. Wang, J. Chen, G. He, X. Qi, W. Shen, P. Liu and G. Chen, *Nat. Chem.*, 2018, **10**, 540; (f) L. Liu, Y.-H. Liu and B.-F. Shi, *Chem. Sci.*, 2020, **11**, 290; (g) B.-B. Zhan, Y. Li, J.-W. Xu, X.-L. Nie, J. Fan, L. Jin and B.-F. Shi, *Angew. Chem., Int. Ed.*, 2018, **57**, 5858; (h) B.-B. Zhan, J. Fan, L. Jin and B.-F. Shi, *ACS Catal.*, 2019, **9**, 3298.
- (a) Y. Yu, L.-K. Zhang, A. V. Buevich, G. Li, H. Tang, P. Vachal, S. L. Colletti and Z.-C. Shi, *J. Am. Chem. Soc.*, 2018, **140**, 6797; (b) M. J. Terrey, A. Holmes, C. C. Perry and W. B. Cross, *Org. Lett.*, 2019, **21**, 7902; (c) A. Schischko, H. Ren, N. Kaplaneris and L. Ackermann, *Angew. Chem., Int. Ed.*, 2017, **56**, 1576; (d) H. Zhang, H.-Y. Wang, Y. Luo, C. Chen, Y. Cao, P. Chen, Y.-L. Guo, Y. Lan and G. Liu, *ACS Catal.*, 2018, **8**, 2173; (e) N. Kaplaneris, T. Rogge, R. Yin, H. Wang, G. Sirvinskaite and L. Ackermann, *Angew. Chem. Int. Ed.*, 2019, **58**, 3476; (f) M. M. Lorion, N. Kaplaneris, J. Son, R. Kuniyil and L. Ackermann, *Angew. Chem., Int. Ed.*, 2019, **58**, 1684; (g) Z. Ruan, N. Sauermann, E. Manoni and L. Ackermann, *Angew. Chem., Int. Ed.*, 2017, **56**, 3172; (h) W. Wang, M. M. Lorion, O. Martinazzoli and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 10554; (i) A. Schischko, N. Kaplaneris, T. Rogge, G. Sirvinskaite, J. Son and L. Ackermann, *Nat. Commun.*, 2019, **10**, 3553.
- (a) J. Tang, Y. He, H. Chen, W. Sheng and H. Wang, *Chem. Sci.*, 2017, **8**, 4565; (b) Z.-B. Bai, C.-X. Cai, Z.-L. Yu and H. Wang, *Angew. Chem., Int. Ed.*, 2018, **57**, 13912; (c) M. J. Terrey, C. C. Perry and W. B. Cross, *Org. Lett.*, 2019, **21**, 104; (d) M. San Segundo and A. Correa, *Chem. Sci.*, 2019, **10**, 8872.
- (a) X. Chen, F. Ye, X. Luo, X. Liu, J. Zhao, S. Wang, Q. Zhou, G. Chen and P. Wang, *J. Am. Chem. Soc.*, 2019, **141**, 18230; (b) A. F. M. Noisier, M. J. Johansson, L. Knerr, M. A. Hayes, W. J. Drury III, E. Valeur, L. R. Malins and R. Gopalakrishnan, *Angew. Chem., Int. Ed.*, 2019, **58**, 19096.
- (a) J. Xu, J. Chen, F. Gao, S. Xie, X. Xu, Z. Jin and J.-Q. Yu, *J. Am. Chem. Soc.*, 2019, **141**, 1903; (b) L. Y. Liu, J. X. Qiao, K. S. Yeung, W. R. Ewing and J.-Q. Yu, *J. Am. Chem. Soc.*, 2019, **141**, 14870; (c) Z. Huang and J.-P. Lumb, *ACS Catal.*, 2018, **9**, 521; (d) J.-L. Dai, N.-Q. Shao, J. Zhang, R.-P. Jia and D.-H. Wang, *J. Am. Chem. Soc.*, 2017, **139**, 12390; (e) Q. Bu, T. Rogge, V. Kotek and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 765; (f) Q.-Q. Wang, S. An, Z.-Q. Deng, W.-J. Zhu, Z.-Y. Huang, G. He and G. Chen, *Nat. Catal.*, 2019, **2**, 793.
- (a) J. Ertl, M. E. Ortiz-Soto, T.-A. Le, J. Bechold, J. Shan, J. Tessmar, B. Engels and J. Seibel, *Chem.-Eur. J.*, 2019, **25**, 6533; (b) J. L. Belmonte-Vazquez, E. Avellanal-Zaballa, E. Enriquez-Palacios, L. Cerdan, I. Esnal, J. Banuelos, C. Villegas-Gomez, I. Lopez Arbeloa and E. Pena-Cabrera, *J. Org. Chem.*, 2019, **84**, 2523; (c) C.-L. Song, K. Liu,

- Z.-J. Wang, B. Ding, S.-C. Wang, Y. Weng, C. W. Chiang and A.-W. Lei, *Chem. Sci.*, 2019, **10**, 7982.
- 12 (a) G. Li, L. Wan, G. Zhang, D. Leow, J. Spangler and J.-Q. Yu, *J. Am. Chem. Soc.*, 2015, **137**, 4391; (b) S. Lee, H. Lee and K.-L. Tan, *J. Am. Chem. Soc.*, 2013, **135**, 18778; (c) K. Hong, H. Park and J.-Q. Yu, *ACS Catal.*, 2017, **7**, 6938; (d) B. E. Haines and D. G. Musaev, *ACS Catal.*, 2015, **5**, 830; (e) F.-L. Zhang, K. Hong, T.-J. Li, H. Park and J.-Q. Yu, *Science*, 2016, **351**, 252; (f) 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; (g) R.-Y. Zhu, Z.-Q. Li, H. S. Park, C. H. Senanayake and J.-Q. Yu, *J. Am. Chem. Soc.*, 2018, **140**, 3564; (h) M. Shang, K. S. Feu, J. C. Vantourout, L. M. Barton, H. L. Osswald, N. Kato, K. Gagaring, C. W. McNamara, G. Chen, L. Hu, S. Ni, P. Fernandez-Canelas, M. Chen, R. R. Merchant, T. Qin, S. L. Schreiber, B. Melillo, J. Q. Yu and P. S. Baran, *Proc. Natl. Acad. Sci.*, 2019, **116**, 8721; (i) P. Gandeepan and L. Ackermann, *Chem*, 2018, **4**, 199.
- 13 (a) M. Parasram and V. Gevorgyan, *Acc. Chem. Res.*, 2017, **50**, 2038; (b) Y. Wang and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2017, **56**, 3191; (c) D. Sarkar, A. V. Gulevich, F. S. Melkonyan and V. Gevorgyan, *ACS Catal.*, 2015, **5**, 6792; (d) D. Sarkar, F. S. Melkonyan, A. V. Gulevich and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2013, **52**, 10800; (e) A. V. Gulevich, F. S. Melkonyan, D. Sarkar and V. Gevorgyan, *J. Am. Chem. Soc.*, 2012, **134**, 5528; (f) M. Parasram, P. Chuentragool, D. Sarkar and V. Gevorgyan, *J. Am. Chem. Soc.*, 2016, **138**, 6340.
- 14 (a) C. Huang, B. Chattopadhyay and V. Gevorgyan, *J. Am. Chem. Soc.*, 2011, **133**, 12406; (b) C. Huang, N. Ghavtadze, B. Chattopadhyay and V. Gevorgyan, *J. Am. Chem. Soc.*, 2011, **133**, 17630; (c) Y. Wang and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2015, **54**, 2255.
- 15 (a) P. S. Thuy-Boun, G. Villa, D. Dang, P. Richardson, S. Su and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 17508; (b) L. Liu, H. Yuan, T.-T. Fu, T. Wang, X. Gao, Z.-P. Zeng, J. Zhu and Y.-F. Zhao, *J. Org. Chem.*, 2014, **79**, 80; (c) Y. Lu, D. S. Leow, X.-S. Wang, K. M. Engle and J.-Q. Yu, *Chem. Sci.*, 2011, **2**, 967; (d) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer and O. Baudoin, *Chem. - Eur. J.*, 2010, **16**, 2654.
- 16 (a) C.-G. Jia, W.-J. Lu, T. Kitamura and Y. Fujiwara, *Org. Lett.*, 1999, **1**, 2097; (b) K. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2009, **131**, 9651; (c) B. Milani, A. Anzilutti, L. Vicentini, A. S. Santi, E. Zangrando, S. Geremia and G. Mestroni, *Organometallics*, 1997, **16**, 5064.