Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue



Cite this: *Chem. Sci.*, 2020, **11**, 6521

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 1st March 2020
Accepted 23rd March 2020

DOI: 10.1039/d0sc01260b

rsc.li/chemical-science

# Late-stage C(sp$^2$)–H and C(sp$^3$)–H glycosylation of *C*-aryl/alkyl glycopeptides: mechanistic insights and fluorescence labeling†‡

Jun Wu,§[a] Nikolaos Kaplaneris,§[a] Shaofei Ni,[a] Felix Kaltenhäuser[a] and Lutz Ackermann *[ab]

C(sp$^3$)–H and C(sp$^2$)–H glycosylations of structurally complex amino acids and peptides were accomplished through the assistance of triazole peptide-isosteres. The palladium-catalyzed peptide–saccharide conjugation provided modular access to structurally complex *C*-alkyl glycoamino acids, glycopeptides and *C*-aryl glycosides, while enabling the assembly of fluorescent-labeled glycoamino acids. The C–H activation approach represents an expedient and efficient strategy for peptide late-stage diversification in a programmable as well as chemo-, regio-, and diastereo-selective fashion.

## Introduction

Glycosylation is a biological function that regulates the structure and activity of a given peptide or protein, introducing considerable structural diversity.[1] The attachment of carbohydrates onto peptides can improve their metabolic stability, water solubility, and protect the peptide backbone from proteolytic attack, while playing key structural roles in numerous biological recognition processes.[2] As a consequence, glycopeptides have emerged as valuable vaccine candidates and therapeutics.[3] However, their chemical and enzymatic instability under physiological conditions limited the utility of *O*/*N*-glycopeptides as drugs.[4] In contrast, *C*-glycoside – stabilized isosteres of *O*/*N*-glycosides[5] – possess improved metabolic stability towards acids, bases and enzymatic hydrolysis,[6] thus being promising inhibitors of cell-surface recognition events and regulators of glycoside metabolism (Fig. 1a).[7] The targeted modification of biologically active peptides is an important strategy for the elucidation of structure–activity relationships (SAR). During the past decade, the direct C–H manipulation[8] of a peptide side-chain mediated by transition metal catalysis has emerged as a powerful paradigm,[9] with key contributions from Lavilla/Albericio,[10] Chen,[11] Daugulis,[12] Wang,[13] Shi,[14] Yu,[15] and Ackermann[16] among others.[17] However, efficient methods for the synthesis of *C*-alkyl/aryl glycopeptides continue to be rare,[18] which contrasts with numerous examples of metal-catalyzed cross-couplings for the construction of *C*-aryl glycoside with two prefunctionalized substrates.[19] Within our program on sustainable C–H activation,[20] we herein disclose unprecedented C(sp$^3$)/(sp$^2$)–H glycosylations of amino acids, peptides and (hetero)arenes (Fig. 1b). Notable features of our findings include (1) internal peptide-isosteric click-triazole[21] as powerful amide surrogates in various bioactive peptidomimetics, (2) modification of terminal and internal peptides by secondary C(sp$^3$)–H alkenylation with remarkable chemo- and diastereoselectivities, and (3) detailed mechanistic insights by

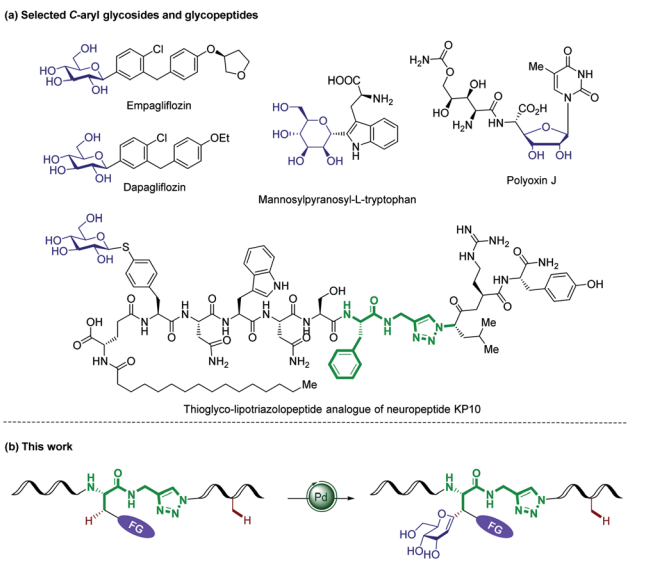



Fig. 1 (a) Selected *C*-aryl glycosides and glycopeptides. (b) C(sp$^3$)–H glycosylation of labeled amino acids and peptides.

[a]*Institut fuer Organische und Biomolekulare Chemie, Georg-August-Universitaet Gottingen, Tammannstrasse 2, 37077 Goettingen, Germany. E-mail: Lutz.Ackermann@chemie.uni-goettingen.de*

[b]*German Center for Cardiovascular Research (DZHK), Potsdamer Strasse 58, 10785 Berlin, Germany*

† Dedicated to the memory of Prof. Kilian Muñiz.

‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/d0sc01260b

§ These authors contributed equally.

experiment and computation as well as (4) versatile fluorescence labeling with structurally complex glycopeptides.

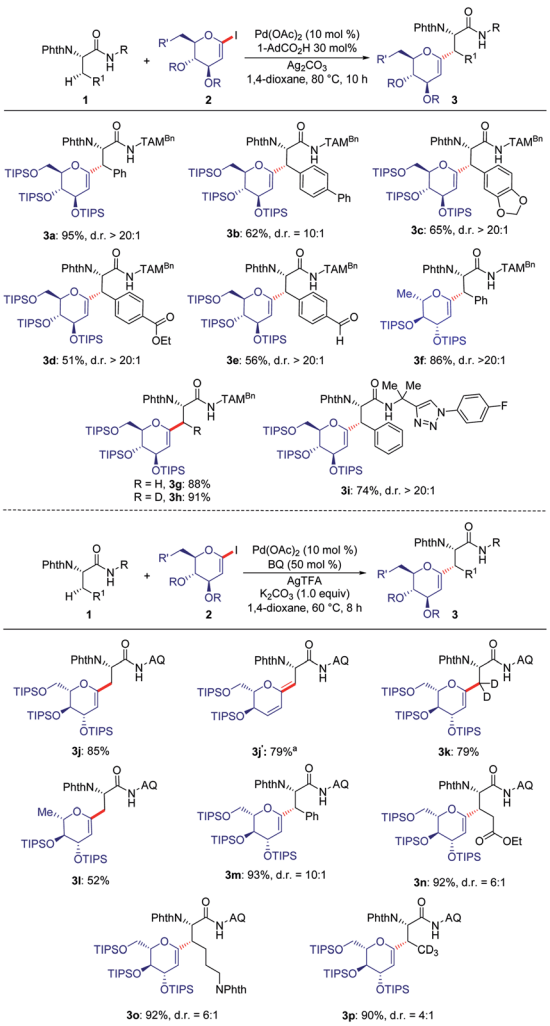
## Results and discussion

### Optimization of reaction conditions

We initiated our studies by exploring reaction conditions for the challenging secondary C($sp^3$)–H glycosylation of triazolyldimethylmethyl (TAM) amide **1a** (Table 1). Preliminary optimization indicated that 60 °C was a less suitable temperature, whilst a slight increase led to the formation of product **3a** in 85% yield with $Pd(TFA)_2$ as the catalyst, 1,4-dioxane as the solvent and AgOAc as the additive. When replacing AgOAc by other silver salts (AgTFA, $Ag_2CO_3$, and $AgBF_4$), $Ag_2CO_3$ stood out, providing glycopeptide **3a** in 95% yield (entries 3–5). Notably, further optimization indicated that 1,4-dioxane was the solvent of choice, and DCE, PhMe, or THF provided diminished or trace amounts of the desired product **3a** (entries 6–8). When 8-aminoquinoline (AQ) was employed, which was independently utilized by Liu for the synthesis of *C*-alkyl glycoamino acids,[22] the reaction also proceeded efficiently, albeit under slightly modified reaction conditions. Under otherwise identical reaction conditions the use of 2-iodo-glycals provided as of yet unsatisfactory results.

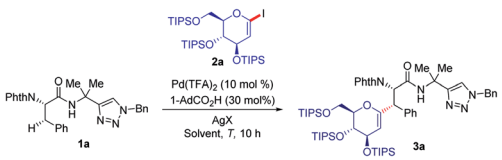
### Substrate scope

With the optimized reaction conditions for the challenging C($sp^3$)–H glycosylation in hand, we subsequently examined its versatility. Phenylalanine derivatives **1** bearing a variety of functional groups, such as esters or aldehydes, were well tolerated, leading to the formation of products **3a–e** with high diasteroselectivities (Scheme 1a). Besides the substrate **2a**, the reaction of rhamnose-derived glycal **2b** also occurred efficiently. In addition, primary C($sp^3$)–H bonds of deuterated or non-deuterated Ala-TAM **[$D_3$]-1f** and **1f** were likewise converted,




Scheme 1 Scope of glycosylation with TAM and AQ as auxiliaries. (a) 100 °C.

Table 1 Optimization of C($sp^3$)–H glycosylation[a]




| Entry | [Ag] | Solvents | *T*/°C | Yield[b]/% |
|---|---|---|---|---|
| 1 | AgOAc | 1,4-Dioxane | 60 | 49 |
| 2 | AgOAc | 1,4-Dioxane | 80 | 85 |
| 3 | AgTFA | 1,4-Dioxane | 80 | Trace |
| ***4*** | ***$Ag_2CO_3$*** | ***1,4-Dioxane*** | ***80*** | ***95*** |
| 5 | $AgBF_4$ | 1,4-Dioxane | 80 | Trace |
| 6 | $Ag_2CO_3$ | DCE | 80 | 45 |
| 7 | $Ag_2CO_3$ | PhMe | 80 | 28 |
| 8 | $Ag_2CO_3$ | THF | 80 | <5% |

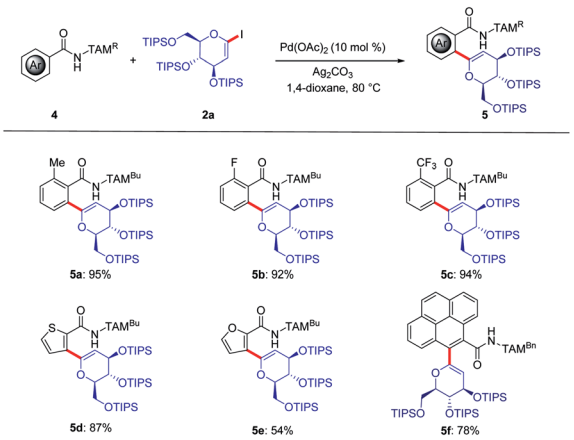
[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), $Pd(TFA)_2$ (10 mol%), $Ag_2CO_3$ (0.20 mmol), 1,4-dioxane (0.5 mL) at 80 °C for 10 h. [b] Yield of isolated products.

giving product **3g** and **3h** in 88% and 93% yields respectively, without racemization of the stereogenic centers (see Pages S46–S47 of the ESI‡). The optimized glycosylation proved amenable to substrate **1h** with an *N*-aryl substituent. Similarly, we also proved the reactivity of substrates **1h–j** with 8-amino quinoline as a terminal auxiliary. We were pleased to find that glycosylation of primary and secondary C($sp^3$)–H bonds of alanine, phenylalanine, glutamic acid and even lysine proved to viable. Interestingly, when the reaction temperature was raised to 100 °C, 1,3-diene **3j′** was isolated because of the elimination of the OTIPS group.

When deuterated L-α-aminobutyramide **[$D_3$]-1l** was employed as the substrate, deuterium-labeled glycopeptide **3p** was obtained.

Due to the unique role of *C*-aryl glycosides as privileged glycomimetics,[19a] we next probed the TAM-assisted C($sp^2$)–H glycosylation by palladium catalysis (Scheme 2). Hence, arenes **4a–c** with electron-donating or electron-withdrawing substituents were compatible, furnishing the desired products **5a–5c** in 92% to 97% yields. It was found that the heteroarenes furan and thiophene



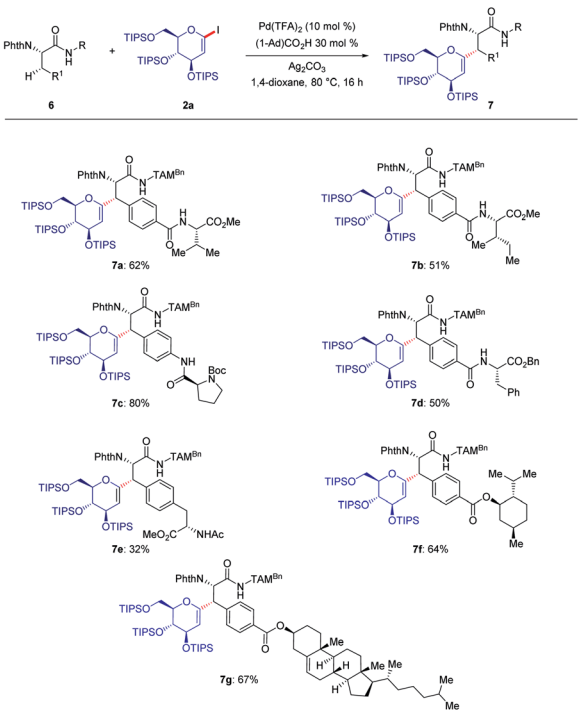

Scheme 2 Scope of C(sp$^2$)–H glycosylation to *C*-aryl glycosides.

were likewise tolerated by the versatile palladium catalyst to deliver conjugate saccharides. Moreover, the fluorescent label pyrene could be successively attached to the glycoside **5f**.

Next, we studied the bio-conjugation to form versatile glycopeptides and the hybrids derived thereof (Scheme 3). Various terminal peptides and peptide-natural product hybrids were employed, and late-stage modified peptides **7a–g** were obtained by C–H glycosylation. Thereby, the possibilities for accessing structurally complex peptides for drug discovery were showcased.

## Mechanistic studies

As shown in Fig. 2, a minor deuterium kinetic isotope effect (KIE) with deuterated and non-deuterated Ala-TAM **[D$_3$]-1f** and




Scheme 3 Scope of glycosylation of terminal peptides and hybrids.

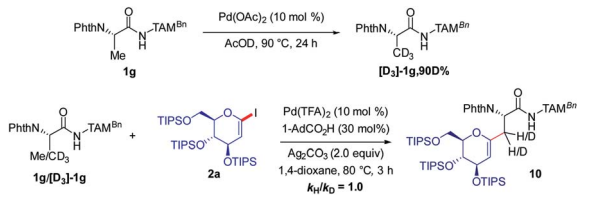



Fig. 2 H/D exchange and KIE experiments.

**1f** ($k_H/k_D = 1.0$) indicated that the C(sp$^3$)–H bond cleavage is not likely a kinetically relevant step of the palladium catalysis. In order to gain further insights into the mechanism of the palladium-catalyzed C–H glycosylation DFT calculations were hence performed at the ωB97X-D/6-311++G(d,p), SDD(Pd, I, Ag) + SMD(1,4-dioxane)//ωB97X-D/6-31G(d), LANL2DZ(Pd, I, Ag) level of theory.[23] The calculated barrier for the initial C–H activation is 19.4 kcal mol$^{-1}$ (see Fig. S1 of the ESI‡), which is in good agreement with our previous studies.[16f] Subsequent to the C–H activation, the dissociation of acetic acid and association of substrate **2a** lead to the intermediate I1′, which could be further stabilized by $Ag_2CO_3$ to afford the stable intermediate I1.[24] This process is highly exergonic by 36.8 kcal mol$^{-1}$, thus making the step irreversible. In I1 as shown in Fig. 3, C–I bond cleavage occurs with the assistance of silver *via* the transition state TS1–2 to afford the oxidized palladium(IV) intermediate I2, with a barrier of 19.3 kcal mol$^{-1}$ with respect to I1. In this transition state, it is possible to observe attractive dispersive interactions between the imide of the substrate and $Ag_2CO_3$, which subsequently becomes evident by the bond distances between both moieties as shown in Fig. 4. This could be further confirmed by visualizing the NCI (non-covalent interactions) plot. The reaction continues with the reductive elimination *via* the transition state TS2–3 with a barrier of 18.8 kcal mol$^{-1}$ to

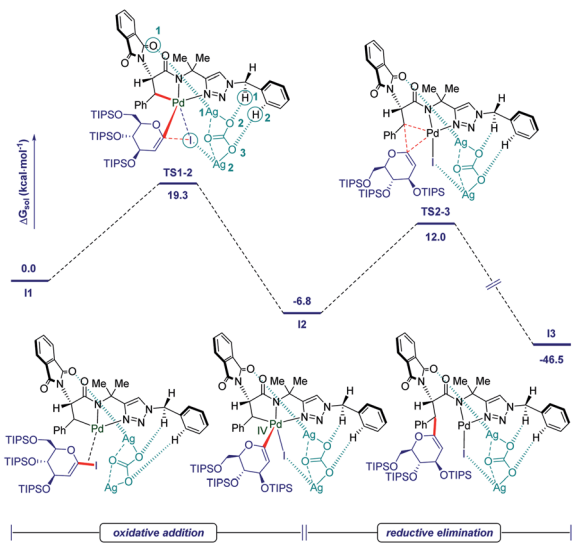



Fig. 3 Calculated Gibbs free energy profiles for the oxidative addition and reductive elimination steps in kcal mol$^{-1}$ at the ωB97X-D/6-311++G(d,p), SDD(Pd, I, Ag) + SMD(1,4-dioxane)//ωB97X-D/6-31G(d), LANL2DZ(Pd, I, Ag) level of theory.

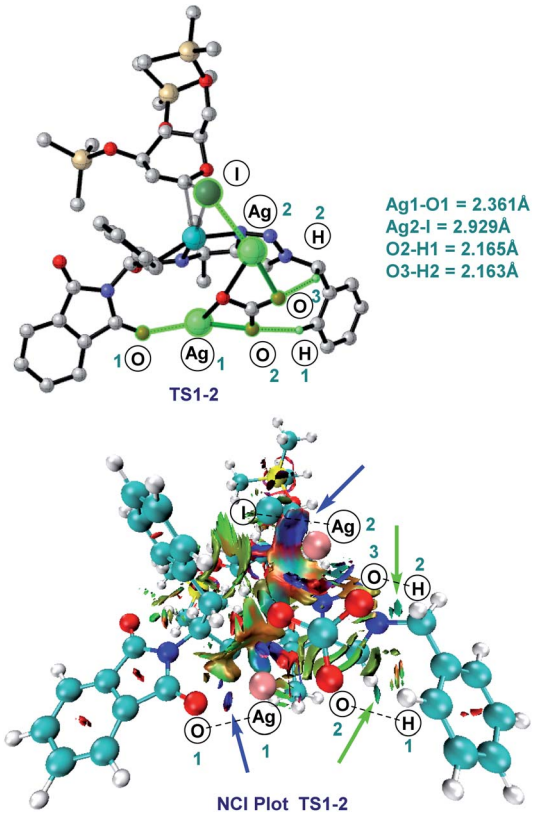
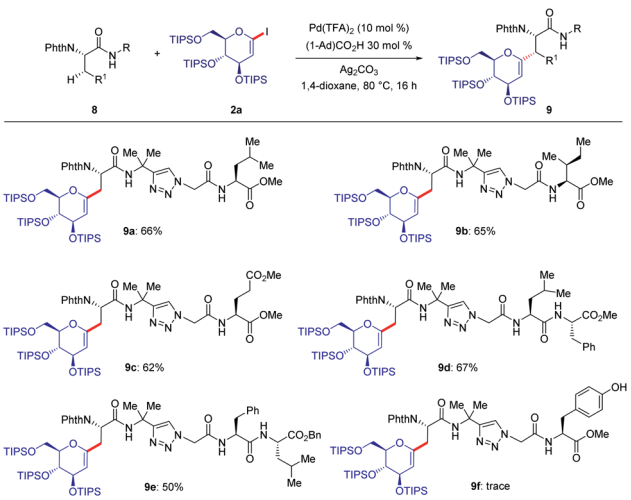


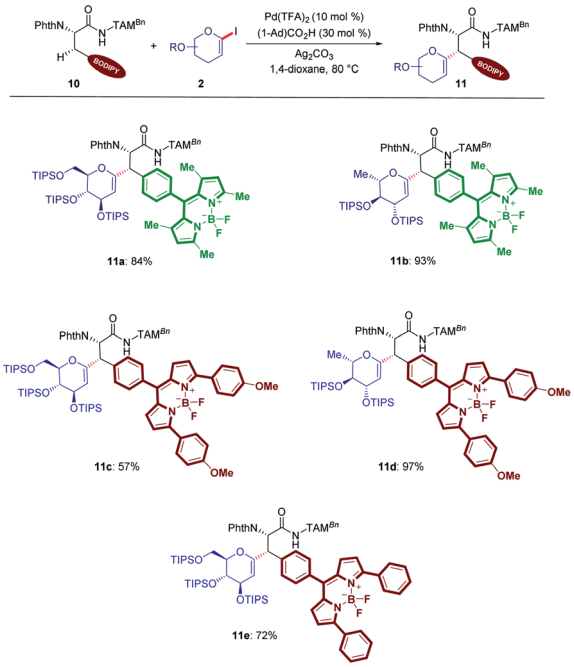

Fig. 4 The 3D structures and the non-covalent interactions visualized through NCI-plots of the transition state TS1–2 (strong and weak attractive interactions are given in blue and green, respectively, while red corresponds to strong repulsive interactions).

finalize the C–C formation process, followed by subsequent protonation to release the desired product.

In order to illustrate the robustness of our C($sp^3$)–H activation, we explored the unprecedented late-stage glycosylation of internal peptides (Scheme 4). With the sterically congested *gem*-disubstituted substrates **8a–8e** various peptides **9a–9e** were




Scheme 4 Scope of glycosylation of terminal peptides.




Scheme 5 Scope of BODIPY labeled glycoamino acids.

converted into value-added glycopeptides under exceedingly mild reaction conditions. When unprotected peptide Phth-Ala-Tzl-Tyr-OMe was employed, only trace amounts of product **9f** were observed. Here, the peptidomimetic Tzl scaffold set the stage for expedient site-selective peptide late-stage glycosylations.

Intrigued by the unique potential of BODIPYs as biocompatible fluorescent probes,[16e,25] glycosylation of different BODIPY labeled amino acids was explored for our C($sp^3$)–H activation process (Scheme 5). Hence, the C–H activation enabled the unprecedented preparation of BODIPY labeled glycoamino acids (**11a–11e**).

## Conclusion

In summary, we have reported a versatile C($sp^3$)–H/C($sp^2$)–H glycosylation strategy enabled by peptide isosteric click-triazoles. Thus, the *de novo* synthesis of structurally complex *C*-alkyl glycoamino acids, glycopeptides and *C*-aryl glycosides was achieved by palladium-catalyzed C($sp^3$)–H/C($sp^2$)–H activation with excellent levels of regio-, chemo- and diastereoselectivities. The synthetic utility of our strategy was reflected *inter alia* by the assembly of BODIPY fluorescent labeled glycoamino acids and the racemization-free late-stage diversification of structurally complex molecules. Our approach holds major potential for the preparation of *C*-alkyl and *C*-aryl glycosyl amino acid building blocks for their subsequent use in glycopeptide assembly and molecular labeling.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

Generous support by the DFG (Gottfried-Wilhelm-Leibniz award to L. A. and SPP1807), the CSC (fellowship to J. W.) and the Onassis Foundation (fellowship to N. K.) is gratefully acknowledged.

## Notes and references

1 (*a*) J. N. deGruyter, L. R. Malins and P. S. Baran, *Biochemistry*, 2017, **56**, 3863–3873; (*b*) L. Krasnova and C.-H. Wong, *Annu. Rev. Biochem.*, 2016, **85**, 599–630; (*c*) S. J. Danishefsky and J. R. Allen, *Angew. Chem., Int. Ed.*, 2000, **39**, 836–863.

2 (*a*) B. Lepenies and P. H. Seeberger, *Nat. Biotechnol.*, 2014, **32**, 443–445; (*b*) O. Werdelin, M. Meldal and T. Jensen, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 9611–9613; (*c*) A. Varki, *Glycobiology*, 1993, **3**, 97–130; (*d*) P. Sears and C. H. Wong, *Cell. Mol. Life Sci.*, 1998, **54**, 223–252; (*e*) C.-H. Wong, *J. Org. Chem.*, 2005, **70**, 4219–4225.

3 M.-L. Hecht, P. Stallforth, D. V. Silva, A. Adibekian and P. H. Seeberger, *Curr. Opin. Chem. Biol.*, 2009, **13**, 354–359.

4 (*a*) P. H. Seeberger and D. B. Werz, *Nature*, 2007, **446**, 1046–1051; (*b*) D. C. Koester, A. Holkenbrink and D. B. Werz, *Synthesis*, 2010, **2010**, 3217–3242.

5 (*a*) R. J. Payne and C.-H. Wong, *Chem. Commun.*, 2010, **46**, 21–43; (*b*) M. J. McKay and H. M. Nguyen, *ACS Catal.*, 2012, **2**, 1563–1595; (*c*) M. A. Bonache, F. Nuti, A. Le Chevalier Isaad, F. Real-Fernández, M. Chelli, P. Rovero and A. M. Papini, *Tetrahedron Lett.*, 2009, **50**, 4151–4153; (*d*) M. R. Pratt and C. R. Bertozzi, *Chem. Soc. Rev.*, 2005, **34**, 58–68; (*e*) Z. Guo and N. Shao, *Med. Res. Rev.*, 2005, **25**, 655–678; (*f*) B. Wang, Y. Liu, R. Jiao, Y. Feng, Q. Li, C. Chen, L. Liu, G. He and G. Chen, *J. Am. Chem. Soc.*, 2016, **138**, 3926–3932; (*g*) H. Herzner, T. Reipen, M. Schultz and H. Kunz, *Chem. Rev.*, 2000, **100**, 4495–4538; (*h*) J. Rodriguez, S. O'Neill and M. A. Walczak, *Nat. Prod. Rep.*, 2018, **35**, 220–229; (*i*) D. P. Gamblin, E. M. Scanlan and B. G. Davis, *Chem. Rev.*, 2009, **109**, 131–163; (*j*) Y. Dai, B. Tian, H. Chen and Q. Zhang, *ACS Catal.*, 2019, **9**, 2909–2915.

6 A. Dondoni and A. Marra, *Chem. Rev.*, 2000, **100**, 4395–4422.

7 (*a*) J. W. Dennis, I. R. Nabi and M. Demetriou, *Cell*, 2009, **139**, 1229–1241; (*b*) C. R. Bertozzi and L. L. Kiessling, *Science*, 2001, **291**, 2357–2364; (*c*) B. Imperiali, *Acc. Chem. Res.*, 1997, **30**, 452–459; (*d*) D. Montoir, M. Amoura, Z. E. A. Ababsa, T. M. Vishwanatha, E. Yen-Pon, V. Robert, M. Beltramo, V. Piller, M. Alami, V. Aucagne and S. Messaoudi, *Chem. Sci.*, 2018, **9**, 8753–8759.

8 (*a*) S. Rej, Y. Ano and N. Chatani, *Chem. Rev.*, 2020, **120**, 1788–1887; (*b*) L. Ackermann, *Acc. Chem. Res.*, 2020, **53**, 84–104; (*c*) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754–8786; (*d*) Z. Dong, Z. Ren, S. J. Thompson, Y. Xu and G. Dong, *Chem. Rev.*, 2017, **117**, 9333–9403; (*e*) B. Ye and N. Cramer, *Acc. Chem. Res.*, 2015, **48**, 1308–1318; (*f*) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726–11743; (*g*) L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885–1898; (*h*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215–1292; (*i*) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074–1086; (*j*) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826.

9 (*a*) W. Wang, M. M. Lorion, J. Shah, A. R. Kapdi and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 14700–14717; (*b*) M. Jbara, S. K. Maity and A. Brik, *Angew. Chem., Int. Ed.*, 2017, **56**, 10644–10655; (*c*) A. F. M. Noisier and M. A. Brimble, *Chem. Rev.*, 2014, **114**, 8775–8806.

10 (*a*) A. F. M. Noisier, J. García, I. A. Ionuț and F. Albericio, *Angew. Chem., Int. Ed.*, 2017, **56**, 314–318; (*b*) R. Subiros-Funosas, L. Mendive-Tapia, J. Sot, J. D. Pound, N. Barth, Y. Varela, F. M. Goñi, M. Paterson, C. D. Gregory, F. Albericio, I. Dransfield, R. Lavilla and M. Vendrell, *Chem. Commun.*, 2017, **53**, 945–948; (*c*) L. Mendive-Tapia, S. Preciado, J. García, R. Ramón, N. Kielland, F. Albericio and R. Lavilla, *Nat. Commun.*, 2015, **6**, 7160; (*d*) S. Preciado, L. Mendive-Tapia, F. Albericio and R. Lavilla, *J. Org. Chem.*, 2013, **78**, 8129–8135; (*e*) J. Ruiz-Rodríguez, F. Albericio and R. Lavilla, *Chem.–Eur. J.*, 2010, **16**, 1124–1127.

11 (*a*) B. Li, X. Li, B. Han, Z. Chen, X. Zhang, G. He and G. Chen, *J. Am. Chem. Soc.*, 2019, **141**, 9401–9407; (*b*) 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**, 18230–18237; (*c*) 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**, 540–548; (*d*) B. Wang, X. Wu, R. Jiao, S. Y. Zhang, W. A. Nack, G. He and G. Chen, *Org. Chem. Front.*, 2015, **2**, 1318–1321; (*e*) B. Wang, W. A. Nack, G. He, S.-Y. Zhang and G. Chen, *Chem. Sci.*, 2014, **5**, 3952–3957; (*f*) B. Wang, C. Lu, S.-Y. Zhang, G. He, W. A. Nack and G. Chen, *Org. Lett.*, 2014, **16**, 6260–6263; (*g*) G. He, S.-Y. Zhang, W. A. Nack, R. Pearson, J. Rabb-Lynch and G. Chen, *Org. Lett.*, 2014, **16**, 6488–6491; (*h*) S.-Y. Zhang, Q. Li, G. He, W. A. Nack and G. Chen, *J. Am. Chem. Soc.*, 2013, **135**, 12135–12141; (*i*) G. He and G. Chen, *Angew. Chem., Int. Ed.*, 2011, **50**, 5192–5196.

12 L. D. Tran and O. Daugulis, *Angew. Chem., Int. Ed.*, 2012, **51**, 5188–5191.

13 (*a*) J. Tan, J. Wu, S. Liu, H. Yao and H. Wang, *Sci. Adv.*, 2019, **5**, eaaw0323; (*b*) Q. Luo, Y. Tao, W. Sheng, J. Lu and H. Wang, *Nat. Commun.*, 2019, **10**, 142; (*c*) J. Lu, J. Li, Y. Wu, X. Fang, J. Zhu and H. Wang, *Org. Lett.*, 2019, **21**, 4676–4679; (*d*) S. Chen, B. Xu, E. Chen, J. Wang, J. Lu, S. Donadio, H. Ge and H. Wang, *Proc. Natl. Acad. Sci. U. S. A.*, 2019, **116**, 2533–2538; (*e*) J. Tang, H. Chen, Y. He, W. Sheng, Q. Bai and H. Wang, *Nat. Commun.*, 2018, **9**, 3383; (*f*) Z. Bai, C. Cai, Z. Yu and H. Wang, *Angew. Chem., Int. Ed.*, 2018, **57**, 13912–13916; (*g*) J. Tang, Y. He, H. Chen, W. Sheng and H. Wang, *Chem. Sci.*, 2017, **8**, 4565–4570.

14 (*a*) L. Liu, Y.-H. Liu and B.-F. Shi, *Chem. Sci.*, 2020, **11**, 290–294; (*b*) B.-B. Zhan, J. Fan, L. Jin and B.-F. Shi, *ACS Catal.*, 2019, **9**, 3298–3303; (*c*) 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**, 5858–5862; (*d*) S. Q. Zhang, H. Z. Jiang, J. W. Xu and B. F. Shi, *Chemistry*, 2015, **21**, 3264–3270; (*e*) Q. Zhang, X. S. Yin, K. Chen, S. Q. Zhang and B. F. Shi, *J. Am. Chem.*

*Soc.*, 2015, **137**, 8219–8226; (*f*) K. Chen, S. Q. Zhang, J. W. Xu, F. Hu and B. F. Shi, *Chem. Commun.*, 2014, **50**, 13924–13927; (*g*) K. Chen and B. F. Shi, *Angew. Chem., Int. Ed.*, 2014, **53**, 11950–11954; (*h*) Q. Zhang, K. Chen, W. Rao, Y. Zhang, F. J. Chen and B. F. Shi, *Angew. Chem., Int. Ed.*, 2013, **52**, 13588–13592; (*i*) K. Chen, F. Hu, S.-Q. Zhang and B.-F. Shi, *Chem. Sci.*, 2013, **4**, 3906.

15 (*a*) T. Liu, J. X. Qiao, M. A. Poss and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2017, **56**, 10924–10927; (*b*) G. Chen, T. Shigenari, P. Jain, Z. Zhang, Z. Jin, J. He, S. Li, C. Mapelli, M. M. Miller, M. A. Poss, P. M. Scola, K.-S. Yeung and J.-Q. Yu, *J. Am. Chem. Soc.*, 2015, **137**, 3338–3351; (*c*) J. He, S. Li, Y. Deng, H. Fu, B. N. Laforteza, J. E. Spangler, A. Homs and J.-Q. Yu, *Science*, 2014, **343**, 1216–1220; (*d*) W. Gong, G. Zhang, T. Liu, R. Giri and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 16940–16946; (*e*) L. Chu, K.-J. Xiao and J.-Q. Yu, *Science*, 2014, **346**, 451–455.

16 (*a*) A. Schischko, N. Kaplaneris, T. Rogge, G. Sirvinskaite, J. Son and L. Ackermann, *Nat. Commun.*, 2019, **10**, 3553; (*b*) M. M. Lorion, N. Kaplaneris, J. Son, R. Kuniyil and L. Ackermann, *Angew. Chem., Int. Ed.*, 2019, **58**, 1684–1688; (*c*) N. Kaplaneris, T. Rogge, R. Yin, H. Wang, G. Sirvinskaite and L. Ackermann, *Angew. Chem., Int. Ed.*, 2019, **58**, 3476–3480; (*d*) W. Wang, M. M. Lorion, O. Martinazzoli and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 10554–10558; (*e*) A. Schischko, H. Ren, N. Kaplaneris and L. Ackermann, *Angew. Chem., Int. Ed.*, 2017, **56**, 1576–1580; (*f*) Y. Zhu, M. Bauer and L. Ackermann, *Chem.–Eur. J.*, 2015, **21**, 9980–9983; (*g*) Y. Zhu, M. Bauer, J. Ploog and L. Ackermann, *Chem.–Eur. J.*, 2014, **20**, 13099–13102.

17 (*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.

18 (*a*) Q. Wang, S. An, Z. Deng, W. Zhu, Z. Huang, G. He and G. Chen, *Nat. Catal.*, 2019, **2**, 793–800; (*b*) N. Probst, G. Grelier, S. Dahaoui, M. Alami, V. Gandon and S. Messaoudi, *ACS Catal.*, 2018, **8**, 7781–7786; (*c*) M. Liu, Y. Niu, Y.-F. Wu and X.-S. Ye, *Org. Lett.*, 2016, **18**, 1836–1839.

19 (*a*) Y. Yang and B. Yu, *Chem. Rev.*, 2017, **117**, 12281–12356; (*b*) X. Li and J. Zhu, *Eur. J. Org. Chem.*, 2016, **2016**, 4724–4767; (*c*) Y. Dai, B. Tian, H. Chen and Q. Zhang, *ACS Catal.*, 2019, **9**, 2909–2915; (*d*) J. Liu and H. Gong, *Org. Lett.*, 2018, **20**, 7991–7995; (*e*) F. Zhu, J. Rodriguez, S. O'Neill and M. A. Walczak, *ACS Cent. Sci.*, 2018, **4**, 1652–1662; (*f*) F. Zhu, J. Rodriguez, T. Yang, I. Kevlishvili, E. Miller, D. Yi, S. O'Neill, M. J. Rourke, P. Liu and M. A. Walczak, *J. Am. Chem. Soc.*, 2017, **139**, 17908–17922; (*g*) L. Adak, S. Kawamura, G. Toma, T. Takenaka, K. Isozaki, H. Takaya, A. Orita, H. C. Li, T. K. M. Shing and M. Nakamura, *J. Am. Chem. Soc.*, 2017, **139**, 10693–10701; (*h*) F. Zhu, M. J. Rourke, T. Yang, J. Rodriguez and M. A. Walczak, *J. Am. Chem. Soc.*, 2016, **138**, 12049–12052; (*i*) J. Zeng, J. Ma, S. Xiang, S. Cai and X.-W. Liu, *Angew. Chem., Int. Ed.*, 2013, **52**, 5134–5137; (*j*) L. Nicolas, P. Angibaud, I. Stansfield, P. Bonnet, L. Meerpoel, S. Reymond and J. Cossy, *Angew. Chem., Int. Ed.*, 2012, **51**, 11101–11104; (*k*) H. Gong and M. R. Gagné, *J. Am. Chem. Soc.*, 2008, **130**, 12177–12183.

20 (*a*) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz and L. Ackermann, *Chem. Rev.*, 2019, **119**, 2192–2452; (*b*) L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281–295; (*c*) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315–1345.

21 (*a*) H. C. Kolb and K. B. Sharpless, *Drug Discovery Today*, 2003, **8**, 1128–1137; (*b*) C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057–3064; (*c*) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2021.

22 During the preparation of our manuscript, Liu independently reported on a modification of simple amino acids with 8-aminoquinoline assistance:(*a*) Y. Liu, Y. Wang, W. Dai, W. Huang, Y. Li and H. Liu, *Angew. Chem., Int. Ed.*, 2020, **59**, 3491–3494; (*b*) Q. Wang, S. An, Z. Deng, W. Zhu, Z. Huang, G. He and G. Chen, *Nat. Catal.*, 2019, **2**, 793–800; (*c*) For previous manganese catalysis, see: W. Wang, P. Subramanian, O. Martinazzoli, J. Wu and L. Ackermann, *Chem.–Eur. J.*, 2019, **25**, 10585–10589.

23 For detailed information, see the ESI.‡

24 For previous reports on the stabilization of intermediates by complexation of silver, see:(*a*) S. Guin, P. Dolui, X. Zhang, S. Paul, V. K. Singh, S. Pradhan, H. B. Chandrashekar, S. S. Anjana, R. S. Paton and D. Maiti, *Angew. Chem., Int. Ed.*, 2019, **58**, 5633–5638; (*b*) I. Funes-Ardoiz and F. Maseras, *Chem.–Eur. J.*, 2018, **24**, 12383–12388; (*c*) Y.-F. Yang, G. Chen, X. Hong, J.-Q. Yu and K. N. Houk, *J. Am. Chem. Soc.*, 2017, **139**, 8514–8521; (*d*) P. Xiao, H. Yuan, J. Liu, Y. Zheng, X. Bi and J. Zhang, *ACS Catal.*, 2015, **5**, 6177–6184; (*e*) Y.-F. Yang, G.-J. Cheng, P. Liu, D. Leow, T.-Y. Sun, P. Chen, X. Zhang, J.-Q. Yu, Y.-D. Wu and K. N. Houk, *J. Am. Chem. Soc.*, 2014, **136**, 344–355.

25 For representative references, see:(*a*) M. Virelli, W. Wang, R. Kuniyil, J. Wu, G. Zanoni, A. Fernandez, J. Scott, M. Vendrell and L. Ackermann, *Chem.–Eur. J.*, 2019, **25**, 12712–12718; (*b*) M. Bauer, W. Wang, M. M. Lorion, C. Dong and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 203–207; (*c*) L. Mendive-Tapia, R. Subiros-Funosas, C. Zhao, F. Albericio, N. D. Read, R. Lavilla and M. Vendrell, *Nat. Protoc.*, 2017, **12**, 1588–1619; (*d*) A. Fernandez, M. Vermeren, D. Humphries, R. Subiros-Funosas, N. Barth, L. Campana, A. MacKinnon, Y. Feng and M. Vendrell, *ACS Cent. Sci.*, 2017, **3**, 995–1005; (*e*) L. Mendive-Tapia, C. Zhao, A. R. Akram, S. Preciado, F. Albericio, M. Lee, A. Serrels, N. Kielland, N. D. Read, R. Lavilla and M. Vendrell, *Nat. Commun.*, 2016, **7**, 10940; (*f*) A. Vázquez-Romero, N. Kielland, M. J. Arévalo, S. Preciado, R. J. Mellanby, Y. Feng, R. Lavilla and M. Vendrell, *J. Am. Chem. Soc.*, 2013, **135**, 16018–16021, and cited references.