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Diastereoselective C(sp³)-H acetoxylation of phosphoramidites†

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Chiral phosphines are important ligands in asymmetric catalysis, yet their potential as directing groups for asymmetric C–H activation remains unexplored due to the oxidative nature of these reactions. We present a Pd-catalysed, P(III)-directed diastereoselective acetoxylation of phosphoramidites, with DFT calculations elucidating their unique reactivity and supporting the proposed reaction mechanism.

In the past decades, transition-metal-catalysed C–H functionalisation has established itself as one of the cornerstones of synthetic organic chemistry.^{1,2} Compared to the traditional approaches to install functional groups such as cross-coupling reactions, the activation and subsequent functionalisation of C–H bonds offers atom- and step-economic methodology as no installation of intermediate functional groups (*e.g.* halides, triflates, boron or metal-compounds) is required.² Moreover, the recent advances in C–H functionalisation protocols have revolutionised synthetic organic chemistry in the context of natural product synthesis and development of biologically active molecules by enabling late stage functionalisation and rapid diversification of complex molecules.³ The direct C–H functionalisation faces two major challenges, namely the inert character of C–H bonds and the selectivity during replacement of one hydrogen atom among several similar ones.⁴ In particular, the chemo-, regio- and especially stereoselectivity of C–H functionalisation remains challenging even 40 years after its discovery, due to the difficulty associated with differentiating between multiple similar hydrogen atoms.⁵ Among the different C–H bonds to be modified,⁶ direct methods for an enantioselective C(sp³)-H functionalisation still remain underdeveloped.^{5b,7} Over the past decade, a number of elegant studies on the asymmetric C(sp³)-H activation have emerged.^{5b,8}

The two main approaches involve the enantioselective methylene C–H activation of 2° C–H bonds⁹ and the C–H

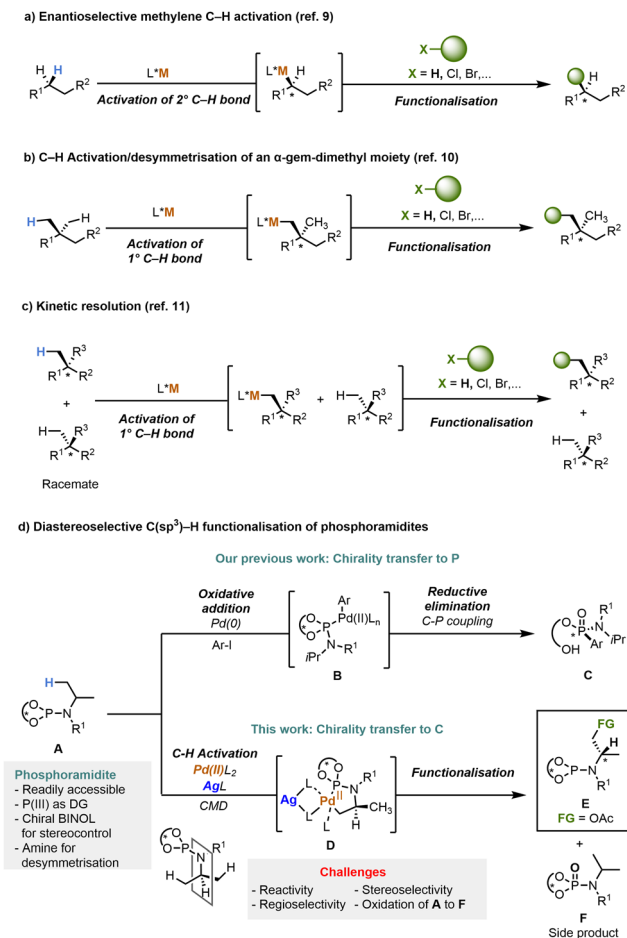
activation/desymmetrisation of 1° C–H bonds,¹⁰ pioneered by Yu and co-workers (Schemes 1a and b, respectively). In the latter case, the selective differentiation between six equivalent C–H bonds of an α -gem-dimethyl moiety is particularly challenging¹⁰ and its C–H functionalisation will be discussed in this work. A kinetic resolution, the preferential recognition of one enantiomer of a racemate by a chiral catalyst, is being reported in the context of the asymmetric C(sp³)-H functionalisation (Scheme 1c).¹¹ Fascinated by the potential of the asymmetric C(sp³)-H functionalisation combined with our longstanding efforts exploring new classes of chiral phosphoramidite ligands in asymmetric transformations,^{12,13} we devised a strategy for the Pd-catalysed P(III)-directed diastereoselective β -C–H functionalisation of amines *via* an iPr desymmetrisation reaction (Scheme 1d). As depicted in Scheme 1d, we propose that this diastereoselective C–H functionalisation involves the generation of a five-membered cyclometalated species **D**¹⁴ bearing a newly formed carbon stereocenter distal to the reacting side *via* a concerted metalation deprotonation (CMD) mechanism.¹⁵ A desymmetrisation reaction of the identical Me-substituents at the iPr-moiety is expected to take place due to the stereodirecting effect of the chiral binaphthol moiety in close vicinity of the reacting center. Subsequently, the reductive elimination from the transient Pd(IV)-intermediate enables the carbon–heteroatom bond formation. Thereby, the phosphoramidites show three distinct key functions: (i) P(III) as directing group for selective C–H activation; (ii) chiral BINOL for stereocontrol; (iii) amine moiety for desymmetrisation. Nevertheless, there are few other synthetic challenges that we need to address: first, unreactive C(sp³)-H bonds are substantially less prone to C–H cleavage/C–H insertion due to their high bond dissociation energy.¹⁶ Second, both the regio- and stereoselectivity might be difficult to control. However, tuning the starting material including the chiral BINOL auxiliary might be a good solution to tackle this problem. Finally, the oxidation of P(III) to P(V) poses a major challenge under the oxidising conditions of the reaction. In contrast to numerous reports on elegant Pd-catalysed C(sp³)-H functionalisations controlled by synthetically versatile and oxidant-compatible

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Scheme 1 Approaches to asymmetric C(sp³)–H functionalisation via (a) enantioselective methylene C–H activation, (b) C–H activation/desymmetrisation and (c) kinetic resolution (d) proposed asymmetric C(sp³)–H functionalisation of phosphoramidites.

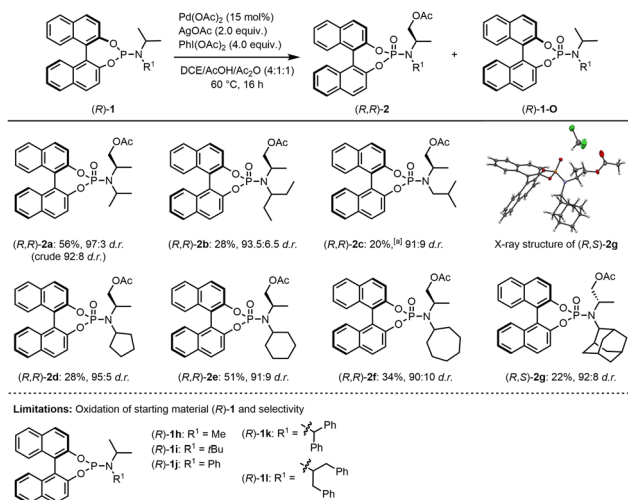
directing groups containing O-, N- or S-atoms,^{2f,4,17} to the best of our knowledge, the use of the P(III) as the directing group for asymmetric C(sp³)–H activation has not been reported before. Very recently, two examples of the oxidant-compatible P(III)-directed Pd-catalysed transformations have been reported *i.e.* C(sp²)–H carbonylation¹⁸ and silylation of indoles.¹⁹ However, they have not been used in the functionalisation of C(sp³)–H bonds. Herein, we report a versatile Pd-promoted diastereoselective C(sp³)–H acetoxylation of phosphoramidites involving alkyl amine desymmetrisation providing valuable chiral amino alcohol precursors.

To evaluate the proposed transformation shown in Scheme 1d the preliminary studies began with standard reaction conditions for C–H acetoxylation²⁰ using phosphoramidite (*R*)-**1a** as substrate, namely PhI(OAc)₂ (5.0 equiv.) and Pd(OAc)₂ (10 mol%) in a deoxygenated AcOH/Ac₂O-mixture (1:1) as solvent at 100 °C. A comprehensive summary of the optimisation results is provided in Tables S1–S7 (see ESI†). It was found that the phosphoramidite (*R*)-**1a** mainly oxidised to (*R*)-**1a-O** and only a small amount of the product (*R,R*)-**2a** (<10% conversion, 88:12 d.r.) was formed (Table S1, entry 1, ESI†). This preliminary observation showed

the potential of the chiral P(III) as a directing group for the C–H acetoxylation. However, the main challenge is the competing oxidation of the starting material to (*R*)-**1a-O** which does not undergo the desired transformation (as revealed by a control experiment using (*R*)-**1a-O** as the starting material, see ESI†, Table S7). To expedite C–H activation, we tested various silver salts, which are commonly used additives to enhance Pd-catalysed C–H activation in terms of selectivity and conversion.^{21,22} Gratifyingly, the C–H acetoxylation reaction of (*R*)-**1a** in the presence of AgOAc (2.0 equiv.) afforded (*R,R*)-**2a** with same level of d.r. (88:12), although with higher conversion (Table S2, entry 1, ESI†) which indicates that AgOAc accelerates the C–H activation step and, most importantly, hinders the early oxidation of the starting material. It's worth noting that no other Ag-salts were found to be as effective as AgOAc (see Table S2, ESI†). Next, various Pd-catalysts were evaluated in the acetoxylation of (*R*)-**1a**. No improved conversion was observed for the other Pd-complexes/salts tested and mainly oxidation of the directing group was detected (see Table S1, ESI†). However, an improved reactivity was found when an increased catalyst loading (15 mol%) was used, affording (*R,R*)-**2a** in 38% yield and 89:11 d.r. (Table S1, entry 7, ESI†). As solvent tuning for specific C–H functionalisations is an emerging topic of current research,²³ the solvent influence was investigated next. The best result was achieved using a DCE/AcOH/Ac₂O-mixture in 4:1:1 ratio yielding the product (*R,R*)-**2a** with much improved conversion and diastereoselectivity (44%, 92:8 d.r., Table S3, entry 9, ESI†). Finally, we shifted our attention towards the optimisation of both the stoichiometry between the PhI(OAc)₂/AgOAc and temperature. It was found that optimal results were obtained using 15 mol% of Pd catalyst, 4.0 equiv. of hypervalent iodine reagent, 2.0 equiv. of AgOAc in deoxygenated DCE/AcOH/Ac₂O (4:1:1) at 60 °C and a reaction time of 16 h (Table S5, entry 4, ESI†).

Next, the scope in terms of phosphoramidites containing 1°, 2° and 3° C–H bonds at the β-position were investigated (Scheme 2). Under the optimised reaction conditions, the standard acetoxylation substrate (*R,R*)-**2a** was obtained with a moderate isolated yield of 56% and excellent selectivity (97:3 d.r.). We were pleased to find that the C–H functionalisation was only taking place on the primary C–H bond, affording the desired products both with branched ((*R,R*)-**2b-c**) as well as cyclic aliphatic moieties ((*R,R*)-**2d-f** and (*R,S*)-**2g**) on the amine in low to moderate yields (22–51%), however, with excellent chemo-, regio- and diastereoselectivities (90:10–95:5 d.r.). The high level of diastereocontrol is attributed to: (i) the well-established preference for C–H functionalisation at the least hindered positions; and (ii) pre-arrangement of the C–H activation transition state by complexation of Ag.²⁴ The absolute configuration of all products was predicted based on the known configuration of the BINOL moiety in the phosphoramidite and DFT analysis²⁵ (Scheme 2). Additionally, the phenyl substituted substrate exhibited lower reactivity under the optimal reaction conditions ((*R*)-**1j**, Ph substituent), resulting in exclusive oxidation of the P(III)-directing group. Unexpectedly, the introduction of a bulkier ^tBu-group ((*R*)-**1i**) instead of Me or *i*Pr had an adverse impact on the regioselectivity, leading to the formation





Scheme 2 Investigations on scope and limitations of the developed $\text{C}(\text{sp}^3)\text{-H}$ acetoxylation. ^a NMR yield. The stereochemistry of the acetoxylation products is assumed to be (*R,R*) based on DFT predictions, except for (*R,S*)-**2g**, which was confirmed by X-ray analysis.

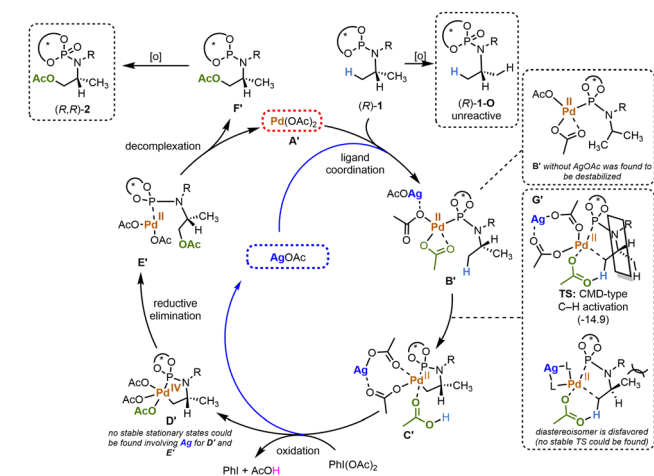
of a mixture of multiple acetoxylation products. A preliminary mechanism of the $\text{C}(\text{sp}^3)\text{-H}$ acetoxylation is proposed based on previous C-H acetoxylation studies²⁶ and density functional theory (DFT) calculations (obtained at the B3LYP/def2-SVP/PCM(DCM) level of theory) as shown in Scheme 3. The phosphoramidite (*R*)-**1** first coordinates to $\text{Pd}(\text{OAc})_2$ and $\text{Ag}(\text{OAc})$ *via* the P(III) atom to afford the catalytic intermediate **B'**. The complexation of both $\text{Pd}(\text{OAc})_2$ and $\text{Ag}(\text{OAc})$ is strongly exothermic ($-33.7 \text{ kcal mol}^{-1}$), and is highly stabilized by the $\text{Ag}(\text{OAc})$ (by $12.9 \text{ kcal mol}^{-1}$ *versus* a **B'** catalytic complex without the $\text{Ag}(\text{OAc})$, only coordinating the $\text{Pd}(\text{OAc})_2$). This species **B'** then undergoes an intramolecular C-H activation through a concerted metalation deprotonation (CMD-type) mechanism¹⁵ to the five membered complex **C**. We envisioned that the cyclopalladated species **C'** is formed with high diastereoselectivity by

desymmetrisation resulting from transfer of axial (BINOL) to point chirality. Indeed, the diastereoselective C-H activation step was calculated to proceed *via* a stereochemically pre-arranged transition state involving both Pd and Ag, with a ΔG^\ddagger of $37.5 \text{ kcal mol}^{-1}$, and with an exothermic driving force of $7.8 \text{ kcal mol}^{-1}$. Accordingly, the C-H activation transition state leading to the opposite diastereoisomer is proposed to be destabilized due to steric hindrance (see Scheme 3), and no viable transition state for the opposite diastereoisomer was found at the B3LYP/def-2SVP/PCM(DCM) level of theory. Intermediate **C'** is then proposed to undergo an oxidative step by $\text{PhI}(\text{OAc})_2$ to form $\text{Pd}(\text{IV})$ species **D'**. A C-O reductive elimination step *via* an intermediate **E'** follows, furnishing the desired chiral acetoxyated phosphoramidite product **F'**. Furthermore, both the acetoxyated product and the unreacted starting material undergo oxidation to form the final products (*R,R*)-**2**²⁷ and (*R*)-**1-O**, respectively. It's not clear from our current DFT studies whether the $\text{Ag}(\text{OAc})$ is involved in the proposed steps beyond **C'**. The preliminary DFT investigations strongly support the cooperative effect of the Ag-salt (Scheme 3, intermediates **B'** and **C'**, and the accompanying C-H activation transition state) under the tested reaction conditions. Similar to our DFT results, it has been previously reported that formation of bimetallic Pd-Ag complexes facilitates C-H cleavage by lowering the energy barrier of the transition states leading to the desired functionalized products.²⁴

It is important to note that the stereochemical organisation predicted by our DFT studies to lead to the (*R,R*)-**2** stereochemistry could be overridden by bulkier phosphoramidite reactants, suggesting a degree of substrate-control is also at play here. Indeed, the obtained X-ray diffraction structure of product **2g** bearing a bulky adamantane substituent shows that the (*R,S*)-**2g** stereochemistry was formed. We propose that in the formation of (*R,R*)-**2**, the steric bulk of BINOL causes C-H activation to proceed on the least sterically encumbered isopropyl functionality. However, in the formation of (*R,S*)-**2g** we anticipate that the adamantyl moiety, which cannot undergo this C-H functionalisation reaction, takes up the least sterically hindered space. Thereby in this specific case, the C-H activation may proceed *via* the more sterically encumbered *N*-substituent, forming the product with the opposite point chirality to that determined from the calculations. Further mechanistic studies are currently underway in our labs.

In summary, we have shown the first example of P(III) directed Pd-catalysed diastereoselective acetoxylation using readily available phosphoramidites. Remarkably, this study demonstrates the potential utility of P(III) as a directing group under highly oxidising conditions in the development of new asymmetric C-H functionalisation reactions. In particular, the critical role of the Ag-additive in preventing initial oxidation of directing group and preliminary DFT studies proposing a bimetallic intermediate lowering the C-H activation energy are noteworthy. The excellent stereocontrol provides a basis to access highly valuable chiral amino alcohol derivatives *via* asymmetric C-H activation.

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Scheme 3 A proposed catalytic cycle of the investigated $\text{C}(\text{sp}^3)\text{-H}$ acetoxylation of (*R*)-**1** to (*R,R*)-**2**, which is supported by density functional theory calculations (see ESI†).



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Data availability

The data supporting this article have been included as part of the ESI.† Crystallographic data for (R,S)-**2g** has been deposited at the CCDC under 2291901 and can be obtained from https://www.ccdc.cam.ac.uk/data_request/cif.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) R. H. Crabtree, *J. Chem. Soc., Dalton Trans.*, 2001, 2437–2450; (b) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242–3272; (c) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624–655; (d) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754–8786; (e) J. Li, S. De Sarkar and L. Ackermann, *Top. Organomet. Chem.*, 2015, **55**, 217–257; (f) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev.*, 2016, **45**, 2900–2936; (g) R. H. Crabtree and A. Lei, *Chem. Rev.*, 2017, **117**, 8481–8482; (h) J. A. Labinger, *Chem. Rev.*, 2017, **117**, 8483–8496; (i) X.-S. Xue, P. Ji, B. Zhou and J.-P. Cheng, *Chem. Rev.*, 2017, **117**, 8622–8648; (j) D.-S. Kim, W.-J. Park and C.-H. Yun, *Chem. Rev.*, 2017, **117**, 8977–9015; (k) P. Gandeepan and L. Ackermann, *Chem.*, 2018, **4**, 199–222; (l) S. K. Sinha, S. Guin, S. Maiti, J. P. Biswas, S. Porey and D. Maiti, *Chem. Rev.*, 2022, **122**, 5682–5841; (m) T. Rogge, N. Kaplaneris, N. Chatani, J. Kim, S. Chang, B. Punji, L. L. Schafer, D. G. Musaev, J. Wencel-Delord, C. A. Roberts, R. Sarpong, Z. E. Wilson, M. A. Brimble, M. J. Johansson and L. Ackermann, *Nat. Rev. Methods Primers*, 2021, **1**, 43; (n) Q. Shao, K. Wu, Z. Zhuang, S. Qian and J.-Q. Yu, *Acc. Chem. Res.*, 2020, **53**, 833–851.
- (a) B. Trost, *Science*, 1991, **254**, 1471–1477; (b) J. A. Labinger and J. E. Bercaw, *Nature*, 2002, **417**, 507–514; (c) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy and J. F. Hartwig, *Chem. Rev.*, 2010, **110**, 890–931; (d) H. M. L. Davies, J. Du Bois and J.-Q. Yu, *Chem. Soc. Rev.*, 2011, **40**, 1855–1856; (e) R. R. Karimov and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2018, **57**, 4234–4241; (f) T. Dalton, T. Faber and F. Glorius, *ACS Cent. Sci.*, 2021, **7**, 245–261.
- (a) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J. Q. Yu, *Chem. Rev.*, 2017, **117**(13), 8754–8786; (b) L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885–1898; (c) W. R. Gutekunst and P. S. Baran, *Chem. Soc. Rev.*, 2011, **40**, 1976–1991; (d) D. Y.-K. Chen and S. W. Youn, *Chem. – Eur. J.*, 2012, **18**, 9452–9474; (e) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960–9009; (f) D. J. Abrams, P. A. Provencher and E. J. Sorensen, *Chem. Soc. Rev.*, 2018, **47**, 8925–8967.
- T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169.
- (a) J. F. Hartwig and M. A. Larsen, *ACS Cent. Sci.*, 2016, **2**, 281–292; (b) T. G. Saint-Denis, R.-Y. Zhu, G. Chen, Q.-F. Wu and J.-Q. Yu, *Science*, 2018, **359**, eaao4798.
- C. G. Newton, S.-G. Wang, C. C. Oliveira and N. Cramer, *Chem. Rev.*, 2017, **117**, 8908–8976.
- F. Colobert and J. Wencel-Delord, *C–H Activation for Asymmetric Synthesis*, Wiley-VCH, Weinheim, Germany, 2019.
- A. P. Smalley, J. D. Cuthbertson and M. J. Gaunt, *J. Am. Chem. Soc.*, 2017, **139**, 1412–1415.
- For selected examples see: (a) S. Pan, K. Endo and T. Shibata, *Org. Lett.*, 2011, **13**, 4692–4695; (b) C. He, W. G. Whitehurst and M. Gaunt, *Chem.*, 2019, **5**, 1031–1058; (c) J. Pedroni, M. Boghi, T. Saget and N. Cramer, *Angew. Chem., Int. Ed.*, 2014, **53**, 9064–9067; (d) P. Jain, P. Verma, G. Xia and J.-Q. Yu, *Nat. Chem.*, 2017, **9**, 140–144; (e) F.-L. Zhang, K. Hong, T.-J. Li, H. Park and J.-Q. Yu, *Science*, 2016, **351**, 252–256; (f) M. Wasa, K. S. L. Chan, X.-G. Zhang, J. He, M. Miura and J.-Q. Yu, *J. Am. Chem. Soc.*, 2012, **134**, 18570–18572; (g) G. Chen, W. Gon, Z. Zhuang, M. S. Adra, J.-Q. Chen, X. Hong, Y.-F. Yang, T. Liu, K. N. Houk and J.-Q. Yu, *Science*, 2016, **353**, 1023–1027.
- For selected examples see: (a) B.-F. Shi, N. Maugel, Y.-H. Zhang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2008, **47**, 4882–4886; (b) D. G. Musaev, T. M. Figg and A. L. Kaledin, *Chem. Soc. Rev.*, 2014, **43**, 5009–5031; (c) 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.
- (a) D. Katayev, M. Nakanishi, T. Burgi and E. P. Kündig, *Chem. Sci.*, 2012, **3**, 1422–1425; (b) L. Yang, R. Melot, M. Neuburger and O. Baudoin, *Chem. Sci.*, 2017, **8**, 1344–1349.
- (a) J. F. Teichert and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2010, **49**, 2486–2528; (b) B. L. Feringa, *Acc. Chem. Res.*, 2000, **33**, 346–353.
- (a) A. Mondal, N. O. Thiel, R. Dorel and B. L. Feringa, *Nat. Catal.*, 2022, **5**, 10–19; (b) X.-B. Chen, D. Padin, C. N. Stindt and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2023, **62**, e20230745.
- C. A. Kiener, C. Shu, C. Incarvito and J. F. Hartwig, *J. Am. Chem. Soc.*, 2003, **125**, 14272–14273.
- S. I. Gorelsky, D. Lapointe and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 10848–10849.
- S. J. Blanksby and G. B. Ellison, *Acc. Chem. Res.*, 2003, **36**, 255–263.
- (a) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788–802; (b) F. Zhang and D. R. Spring, *Chem. Soc. Rev.*, 2014, **43**, 6906–6919.
- B. Dong, J. Qian, M. Li, Z.-J. Wang, M. Wang, D. Wang, C. Yuan, Y. Han, Y. Zhao and Z. Shi, *Sci. Adv.*, 2020, **6**, eabd1378.
- D. Wang, X. Chen, J. J. Wong, L. Jin, M. Li, Y. Zhao, K. N. Houk and Z. Shi, *Nat. Commun.*, 2021, **12**, 524.
- L. V. Desai, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 9542–9543.
- (a) O. Daugulis and V. G. Zaitsev, *Angew. Chem., Int. Ed.*, 2005, **44**, 4046–4048; (b) X. Ye, Z. He, T. Ahmed, K. Weise, N. G. Akhmedov, J. L. Petersen and X. Shi, *Chem. Sci.*, 2013, **4**, 3712–3716; (c) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754–8786.
- (a) S. Y. Lee and J. F. Hartwig, *J. Am. Chem. Soc.*, 2016, **138**, 15278–15284; (b) K. L. Bay, Y.-F. Yang and K. N. Houk, *J. Organomet. Chem.*, 2018, **864**, 19–25.
- C. Yu, J. Sanjosé-Orduna, F. W. Patureau and M. H. Pérez-Temprano, *Chem. Soc. Rev.*, 2020, **49**, 1643–1652.
- (a) 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; (b) D. Leow, G. Li, T.-S. Mei and J.-Q. Yu, *Nature*, 2012, **486**, 518–522.
- The absolute configuration of all products was fixed as R,S determined by the crystals of (R,S)-**2g**.
- (a) C. S. Buettner, D. Wilcox, B. G. N. Chappell and M. J. Gaunt, *Chem. Sci.*, 2019, **10**, 83–89; (b) A. K. Cook and M. S. Sanford, *J. Am. Chem. Soc.*, 2015, **137**, 3109–3118.
- The absolute configuration of the products in DFT calculations were fixed as R,R.

