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Pd(II)-Catalyzed enantioselective C–H olefination toward the synthesis of *P*-stereogenic phosphinamides†

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***P*-Stereogenic phosphorus compounds are important structural elements in chiral ligands or organocatalysts. Herein, we report a Pd(II)-catalyzed enantioselective C–H olefination toward the synthesis of *P*-stereogenic phosphinamides using cheap commercially available *L*-pGlu-OH as a chiral ligand. A broad range of *P*-stereogenic phosphinamides were gained in good yields with high enantioselectivities (33 examples, up to 77% yield, 99% ee) via desymmetrization and kinetic resolution.**

Chiral phosphorus compounds play an important role in both laboratory and industrial synthesis due to their extensive applications in asymmetric synthesis as chiral ligands or organocatalysts.¹ However, most of them have chirality located in their backbones, such as a chiral axis, planar-chirality, or a stereogenic carbon center (Scheme 1a). Although better chiral induction may be gained during the transformation because the stereogenic phosphorus atom is coordinated in closer proximity to the catalytic center,² the application of *P*-stereogenic phosphorus compounds is less described due to the lack of general and efficient methods for their enantioselective preparation.³ Classical synthetic methods usually rely on resolution processes or the use of chiral auxiliaries.⁴ In recent years, more and more approaches including desymmetrization reactions⁵ and catalytic asymmetric methods have been developed.⁶

In the past decade, transition metal-catalyzed asymmetric C–H functionalization has been developed rapidly and proved to be a powerful strategy to access chiral building blocks from simple starting materials.⁷ In particular, Pd(II)/mono-*N*-protected amino acid (MPAA)-catalyzed enantioselective C–H activation developed by Yu and coworkers has received extensive attention for the diverse reactivities of palladacycles and the use of cheap and commercially available ligands.⁸ In 2015, Han and coworkers successfully applied this catalytic system for the synthesis of *P*-stereogenic phosphinamides using Boc-Tyr(^tBu)-OH as a chiral ligand (Scheme 1b).⁹ Phosphinamide bearing a 2,3,5,6-tetrafluoro-4-cyanophenylamino (Ar^F) directing group was important for this transformation. And it also should be noted that the arylation products could be used as chiral organocatalysts in the desymmetric enantioselective reduction of cyclic 1,3-diketones.¹⁰ Since then, efficient synthesis of *P*-stereogenic phosphorus compounds *via* asymmetric C–H functionalization has been developed enabled by different catalytic systems.¹¹ However, until

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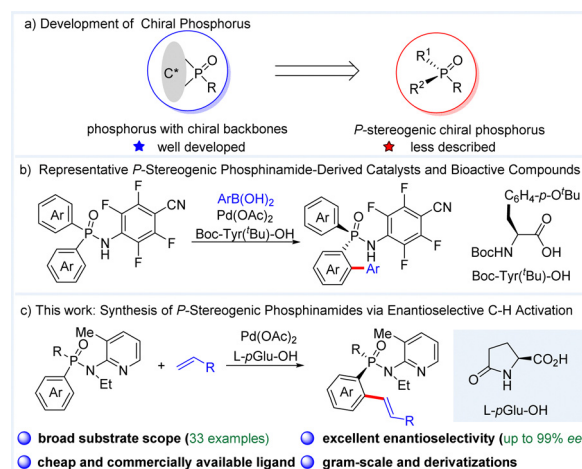
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Scheme 1 Asymmetric synthesis of *P*-stereogenic phosphinamides via enantioselective C–H activation.



recently, another Pd(II)/MPAA-catalyzed enantioselective C–H activation towards the synthesis of chiral phosphorus compounds was reported by our group using cheap and commercially available L-pyrogutamic acid (L-pGlu-OH) as a chiral ligand.¹² A newly developed N-ethyl-N-(3-methylpyridin-2-yl)amino directing group was crucial for the reactivity. Herein, we report the synthesis of P-stereogenic phosphinamides via Pd(II)-catalyzed enantioselective C–H olefination (Scheme 1c). A broad range of P-stereogenic phosphinamides were gained in good yields with high enantioselectivities (33 examples, up to 77% yield and 99% ee) via desymmetrization and kinetic resolution. The P-stereogenic phosphinamide products could be easily transformed to P-chiral phosphine oxides.

We initiated our investigation by optimizing the Pd(II)-catalyzed C–H olefination of phosphoramidate **1a** with butyl acrylate **2a**. To our delight, the product **3a** was obtained in 54% yield with 93% ee in the presence of Pd(OAc)₂ (10 mol%), L-pGlu-OH (20 mol%), Ag₂CO₃ (0.05 mmol), and benzoquinone (0.1 mmol) in *t*BuOH for 12 h under air (Table 1). Next, we screened the solvents such as PhCl, dioxane and *t*-AmylOH, and *t*-AmylOH gave the desired product in a higher yield and enantioselectivity. Other silver salts were also investigated, and no better result was observed (entries 5–7). Increasing the temperature to 70 °C or decreasing the temperature to 50 °C resulted in a lower yield (entries 8 and 9). Control experiments showed that L-pGlu-OH and silver salt were crucial to this reaction (entries 10 and 11). In fact, the phosphinamide bearing a 2,3,5,6-tetrafluoro-4-cyanophenylamino directing group (Ar^F), which was used in Han's work, could not afford the olefination product (entry 12).

With the optimal reaction conditions in hand, we then investigated the scope of this enantioselective transformation (Table 2). Diaryl-phosphinamides with electron-donating groups

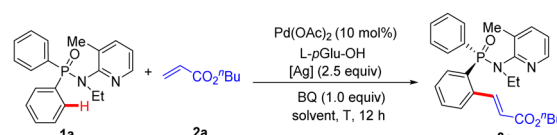
(Me, *t*Bu, Ph and OMe) or electron-withdrawing groups (OCF₃, F, and Cl) on the *para*-position gave the corresponding olefination products in moderate to good yields with high enantioselectivities (**3b–3h**, 50–77% yield, 88–96% ee). *meta*-Me diarylphosphinamide **1i** gave the corresponding product **3i** in 62% yield with 96% ee. Diaryl-phosphinamides with steric properties were also tolerated well, and *ortho*-Me, 1-naphthyl phosphinamide and 2-naphthyl substituted phosphinamide afforded the respective olefination products in good yields with good to high enantioselectivities (**3j–3l**, 88–92% ee). The scope of the coupling partner, olefins, was also evaluated (Table 2b). A broad range of acrylates bearing Me, *t*Bu, Ph, Bn and hydroxyethyl worked well, giving the desired olefination products in good yields with high ee values (**3m–3q**, 93–95% ee). In addition, acrylates with useful functional groups, trifluoromethyl and hydroxyl, were still compatible and gave **3r** in 60% yield with 95% ee and **3s** in 59% yield with 94% ee. Other electronically biased olefins, such as acrylaldehyde, α,β-unsaturated ketone, and acrylamide proceeded well to give the corresponding products in good results (**3t–3v**, 54–58% yield, 94–95% ee). Various styrenes also reacted smoothly using Ag₂SO₄ as an oxidant, affording the desired products in moderate yields with high enantioselectivities (**3w–3aa**, 48–57% yield, 91–94% ee). What's more, chiral phosphinamide bearing core structures of natural products, including L-menthol, tyrosine and estrone, were also obtained in good yields with high enantioselectivities (**3ab–3ad**, 54–69% yield, 95% ee). The absolute configuration of **3a** was ascribed by X-ray diffraction analysis and extrapolated to the other products.¹³

To our delight, kinetic resolution was also compatible under the same conditions (Table 3). Racemic phosphinamides *rac*-4 with Me, Et and *i*Pr substituted afforded the olefination products (*R*)-5 and unreacted (*S*)-4 in good to excellent enantioselectivities.

We then conducted gram-scale preparation and derivatizations to demonstrate the synthetic utility of this protocol. The olefination of **1a** on a 3.0 mmol scale with **2a** afforded **3a** in 66% yield (920.8 mg) with 90% ee (see the ESI† for details). The directing group of olefination product **3w** could be removed in TFOH, giving product **6w** in 72% yield with 92% ee (Scheme 2). The reaction of **6w** with Grignard reagents afforded the desired chiral phosphine oxides **7a** to **7d** in good yields with minimum enantiomeric loss.

Several experiments were conducted to gain mechanistic insights. The H/D exchange experiment was carried out firstly. The recovered **1a** was incorporated with no deuterium when **1a** reacted in the absence of **2a**. The kinetic isotope effect (KIE) experiments were then conducted and a KIE value of $k_H/k_D = 2.38$ was obtained. These results indicate that the C–H cleavage step is irreversible and likely the rate-determining step (see the ESI† for details). We then revealed the chiral induction model through DFT calculations. The C–H bond activation transition states of the two phenyl groups (colored by blue and black) of phosphoramidate are located (Fig. S2a, ESI†). In TS2-*R*, there is a significant steric repulsion between the methyl group on the directing group and the phenyl group of phosphoramidate, so the favorable conformer for generating the *R* enantiomer is TS1-*R*. In the transition states that generate the *S* enantiomer, due to

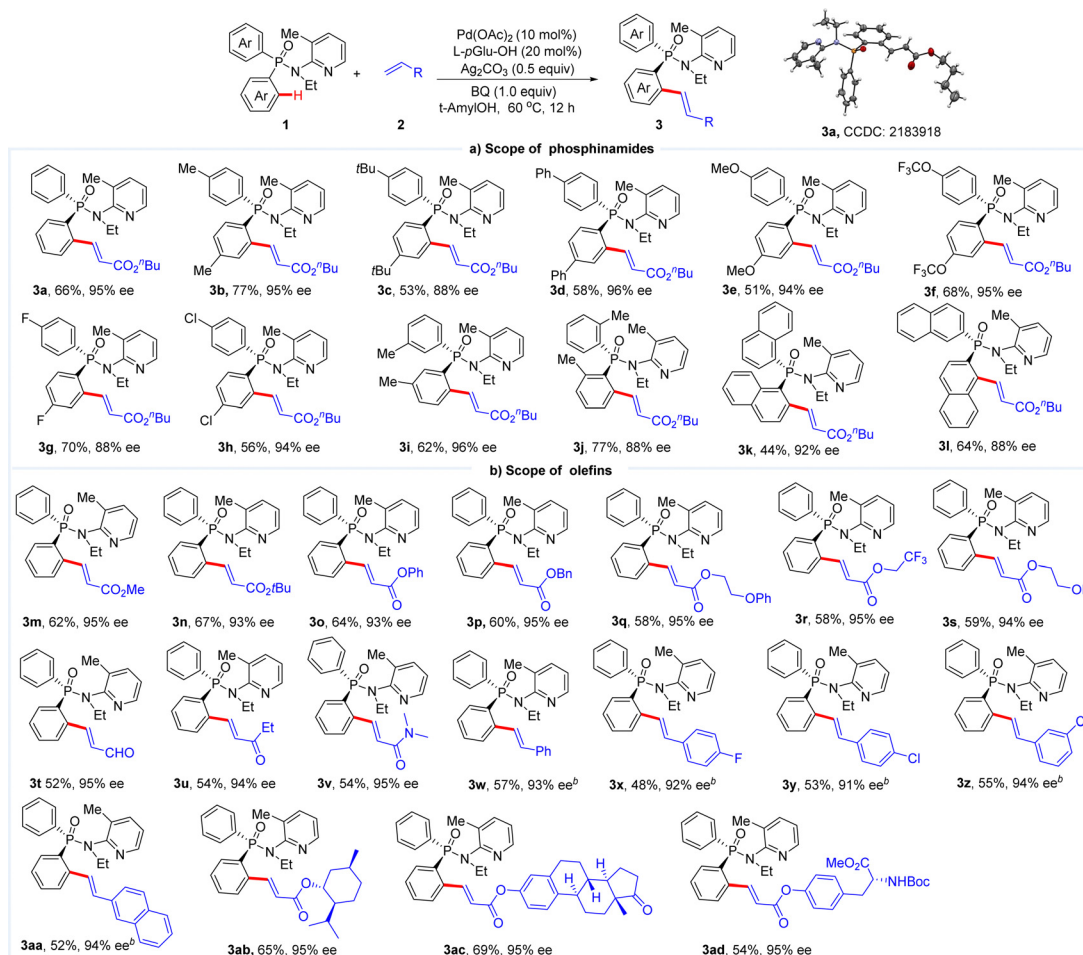
Table 1 Optimization of the reaction conditions^a



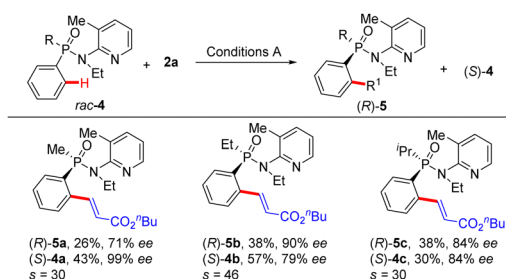
Entry	Solvent	[Ag]	T (°C)	Yield of 3a ^b (%)	ee of 3a ^c (%)
1	<i>t</i> -BuOH	Ag ₂ CO ₃	60	54	93
2	PhCl	Ag ₂ CO ₃	60	20	81
3	Dioxane	Ag ₂ CO ₃	60	63	89
4	<i>t</i> -AmylOH	Ag ₂ CO ₃	60	66	95
5	<i>t</i> -AmylOH	Ag ₂ SO ₄	60	32	92
6	<i>t</i> -AmylOH	AgOAc	60	41	92
7	<i>t</i> -AmylOH	Ag ₃ PO ₄	60	47	95
8	<i>t</i> -AmylOH	Ag ₂ CO ₃	50	43	94
9	<i>t</i> -AmylOH	Ag ₂ CO ₃	60	57	94
10	<i>t</i> -AmylOH	No [Ag]	60	10	53
11 ^d	<i>t</i> -AmylOH	Ag ₂ CO ₃	10	4	0
12 ^e	<i>t</i> -AmylOH	Ag ₂ CO ₃	70	nr	—

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Pd(OAc)₂ (0.01 mmol), [Ag] (0.05 mmol), L-pGlu-OH (0.02 mmol), BQ (0.1 mmol), solvent (1.0 mL), air for 12 h. ^b Isolated yield. ^c The ee was determined by chiral HPLC. ^d Without L-pGlu-OH. ^e 2,3,5,6-Tetrafluoro-4-cyanophenylamino (Ar^F) directing group was used.

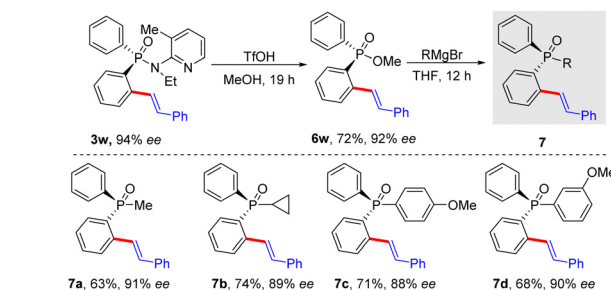


Table 2 Scope of Pd(II)-catalyzed C–H olefination^a

^a Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), Pd(OAc)₂ (0.01 mmol), L-pGlu-OH (0.02 mmol), Ag₂CO₃ (0.05 mmol), BQ (0.1 mmol), *t*-AmylOH (1.0 mL) for 12 h at 60 °C in a sealed reaction tube, isolated yield. ^b Ag₂SO₄ (0.05 mmol) was used.

Table 3 Kinetic resolution^a

^a Reaction conditions: *rac*-**4** (0.2 mmol), **2a** (0.4 mmol), Pd(OAc)₂ (0.02 mmol), L-pGlu-OH (0.04 mmol), Ag₂CO₃ (0.1 mmol), BQ (0.2 mmol), *t*-AmylOH (1.0 mL) at 60 °C for 12 h under air in a sealed reaction tube, isolated yield. Selectivity factors: $s = \ln[(1 - C)(1 - ee_4)] / \ln[(1 - C)(1 + ee_4)]$, $C = (ee_4)/(ee_4 + ee_5)$.



Scheme 2 Synthetic applications.

calculated the stereoselective outcome for the kinetic resolution result when one of the phenyl is replaced with methyl. The energy span that determines the enantioselectivity is reduced to 0.9 kcal mol⁻¹ (TS1-R(Me) vs. TS1-S(Me)), which is consistent with the experimental results (71% ee).

In summary, we have developed the efficient synthesis of *P*-stereogenic phosphinamides *via* Pd(II)-catalyzed enantioselective olefination. A broad range of *P*-stereogenic phosphinamides were



gained in moderate to good yields with high enantioselectivities *via* desymmetrization and kinetic resolution (33 examples, up to 77% yield, 99% ee). Gram-scale preparation was also compatible with good yield and high ee value. And the olefination *P*-stereogenic phosphinamide products could be transformed to potentially useful *P*-chiral phosphine oxides. The practical applications of these new *P*-stereogenic phosphinamides are currently being explored.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029; (b) S. J. Connon, *Angew. Chem., Int. Ed.*, 2006, **45**, 3909; (c) H. Fernández-Pérez, P. Etayo, A. Panossian and A. Vidal-Ferran, *Chem. Rev.*, 2011, **111**, 2119; (d) P. W. N. M. van Leeuwen, P. C. J. Kamer, C. Claver, O. Pàmies and M. Diéguez, *Chem. Rev.*, 2011, **111**, 2077; (e) D. Parmar, E. Sugiono, S. Raja and M. Rueping, *Chem. Rev.*, 2014, **114**, 9047.
- (a) A. Grabulosa, *P-Stereogenic Ligands in Enantioselective Catalysis*, RSC, Cambridge, 2011; (b) W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029.
- For select reviews, see: (a) J. S. Harvey and V. Gouverneur, *Chem. Commun.*, 2010, **46**, 7477; (b) I. Wauters, W. Debruyere and C. V. Stevens, *Beilstein J. Org. Chem.*, 2014, **10**, 1064.
- (a) K. M. Pietrusiewicz and M. Zablocka, *Chem. Rev.*, 1994, **94**, 1375; (b) A. Grabulosa, J. Granell and G. Muller, *Coord. Chem. Rev.*, 2007, **251**, 25; (c) O. I. Kolodiazny, *Tetrahedron: Asymmetry*, 2012, **23**, 1. For select examples, see: (d) Z. S. Han, N. Goyal, M. A. Herbage, J. D. Sieber, B. Qu, Y. Xu, Z. Li, J. T. Reeves, J.-N. Desrosiers, S. Ma, N. Grinberg, H. Lee, H. P. R. Mangunuru, Y. Zhang, D. Krishnamurthy, B. Z. Lu, J. J. Song, G. Wang and C. H. Senanayake, *J. Am. Chem. Soc.*, 2013, **135**, 2474; (e) S. Rast, B. Mohar and M. Stephan, *Org. Lett.*, 2014, **16**, 2688; (f) E. Bergin, C. T. O'Connor, S. B. Robinson, E. M. McGarrigle, C. P. O'Mahony and D. G. Gilheany, *J. Am. Chem. Soc.*, 2007, **129**, 9566; (g) Z. S. Han, H. Wu, Y. Xu, Y. Zhang, B. Qu, Z. Li, D. R. Caldwell, K. R. Fandrick, L. Zhang, F. Roschangar, J. J. Song and C. H. Senanayake, *Org. Lett.*, 2017, **19**, 1796.
- For selected examples, see: (a) Z. Huang, X. Huang, B. Li, C. Mou, S. Yang, B.-A. Song and Y. R. Chi, *J. Am. Chem. Soc.*, 2016, **138**, 7524; (b) B. Pérez-Saavedra, N. Vázquez-Galiñanes, C. Saá and M. Fañanás-Maestrá, *ACS Catal.*, 2017, **7**, 6104; (c) Y. Zhang, F. Zhang, L. Chen, J. Xu, X. Liu and X. Feng, *ACS Catal.*, 2019, **9**, 4834; (d) B. M. Trost, S. M. Spohr, A. B. Rolka and C. A. Kalnins, *J. Am. Chem. Soc.*, 2019, **141**, 14098; (e) Y. Huang, Y. Li, P.-H. Leung and T. Hayashi, *J. Am. Chem. Soc.*, 2014, **136**, 14734.
- For selected examples, see: (a) V. S. Chan, I. C. Stewart, R. G. Bergman and F. D. Toste, *J. Am. Chem. Soc.*, 2006, **128**, 2786; (b) C. Scriban and D. S. Glueck, *J. Am. Chem. Soc.*, 2006, **128**, 2788; (c) C. Scriban, D. S. Glueck, J. A. Golen and A. L. Rheingold, *Organometallics*, 2007, **26**, 1788; (d) B. J. Anderson, M. A. Guino-o, D. S. Glueck, J. A. Golen, A. G. DiPasquale, L. M. Liable-Sands and A. L. Rheingold, *Org. Lett.*, 2008, **10**, 4425; (e) V. S. Chan, M. Chiu, R. G. Bergman and F. D. Toste, *J. Am. Chem. Soc.*, 2009, **131**, 6021; (f) X.-T. Liu, Y.-Q. Zhang, X.-Y. Han, S.-P. Sun and Q.-W. Zhang, *J. Am. Chem. Soc.*, 2019, **141**, 16584; (g) J. R. Moncarz, N. F. Laritcheva and D. S. Glueck, *J. Am. Chem. Soc.*, 2002, **124**, 13356; (h) C. Korff and G. Helmchen, *Chem. Commun.*, 2004, 530; (i) S. Pican and A.-C. Gaumont, *Chem. Commun.*, 2005, 2393; (j) T. J. Brunker, B. J. Anderson, N. F. Blank, D. S. Glueck and A. L. Rheingold, *Org. Lett.*, 2007, **9**, 1109; S. Zhang, J.-Z. Xiao, Y.-B. Li, C.-Y. Shi and L. Yin, *J. Am. Chem. Soc.*, 2021, **143**, 9912; (k) N. F. Blank, J. R. Moncarz, T. J. Brunker, C. Scriban, B. J. Anderson, O. Amir, D. S. Glueck, L. N. Zakharov, J. A. Golen, C. D. Incavito and A. L. Rheingold, *J. Am. Chem. Soc.*, 2007, **129**, 6847; (l) V. S. Chan, R. G. Bergman and F. D. Toste, *J. Am. Chem. Soc.*, 2007, **129**, 15122; Q. Dai, W. Li, Z. Li and J. Zhang, *J. Am. Chem. Soc.*, 2019, **141**, 20556; (m) R. Beaud, R. J. Phipps and M. J. Gaunt, *J. Am. Chem. Soc.*, 2016, **138**, 13183; (n) Q. Dai, L. Li and J. Zhang, *Angew. Chem., Int. Ed.*, 2021, **60**, 27247; (o) X.-T. Liu, X.-Y. Han, Y. Wu, Y.-Y. Sun, L. Gao, Z. Huang and Q.-W. Zhang, *J. Am. Chem. Soc.*, 2021, **143**(30), 11309; (p) W.-H. Wang, Y. Wu, H.-T. Wang, P.-J. Qi, W.-N. Lan and Q.-W. Zhang, *Nat. Synth.*, 2022, **1**, 738.
- (a) J. Wencel-Delord and F. Colobert, *Chem. – Eur. J.*, 2013, **19**, 14010–14017; (b) C. Zheng and S.-L. You, *RSC Adv.*, 2014, **4**, 6173; (c) C. G. Newton, S.-G. Wang, C. C. Oliveira and N. Cramer, *Chem. Rev.*, 2017, **117**, 8908; (d) T. G. Saint-Denis, R.-Y. Zhu, G. Chen, Q.-F. Wu and J.-Q. Yu, *Science*, 2018, **359**, eaao4798; (e) J. Loup, U. Dhawa, F. Pescioli, J. Wencel-Delord and L. Ackermann, *Angew. Chem., Int. Ed.*, 2019, **58**, 12803; (f) G. Liao, Z.-K. Lin and B.-F. Shi, *Angew. Chem., Int. Ed.*, 2020, **59**, 19773; (g) T. Yoshino, S. Satake and S. Matsunaga, *Chem. – Eur. J.*, 2020, **26**, 7346; (h) T. K. Achar, S. Maiti, S. Jana and D. Maiti, *ACS Catal.*, 2020, **10**, 13748; (i) O. Vykhivskiy, A. Kudashev, T. Miyakoshi and O. Baudoin, *Chem. – Eur. J.*, 2021, **27**, 1231; (j) Q. Zhang and B.-F. Shi, *Acc. Chem. Res.*, 2021, **54**, 2750; (k) Y.-Q. Han and B.-F. Shi, *Acta Chim. Sin.*, 2023, **81**, 1522.
- (a) Q. Shao, K. Wu, Z. Zhuang, S. Qian and J.-Q. Yu, *Acc. Chem. Res.*, 2020, **53**, 833; (b) K. M. Engle and J.-Q. Yu, *J. Org. Chem.*, 2013, **78**, 8927; (c) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242; (d) B.-F. Shi, N. Y.-H. Maugel, Y.-H. Zhang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2008, **47**, 4882.
- Z.-J. Du, J. Guan, G.-J. Wu, P. Xu, L.-X. Gao and F.-S. Han, *J. Am. Chem. Soc.*, 2015, **137**, 632.
- (a) X.-L. Qin, A. Li and F.-S. Han, *J. Am. Chem. Soc.*, 2021, **143**, 2994; (b) G.-J. Wu, D.-X. Tan and F.-S. Han, *Acc. Chem. Res.*, 2021, **54**, 4354.
- (a) J. Diesel and N. Cramer, *ACS Catal.*, 2019, **9**, 9164; (b) P.-F. Qian, J.-Y. Li, T. Zhou and B.-F. Shi, *Synthesis*, 2022, 4784. For selected examples see: (c) Z.-Q. Lin, W.-Z. Wang, S.-B. Yan and W.-L. Duan, *Angew. Chem., Int. Ed.*, 2015, **54**, 6265; (d) L. Liu, A. A. Zhang, Y. Wang, F. Zhang, Z. Zuo, W. X. Zhao, C. L. Feng and W. Ma, *Org. Lett.*, 2015, **17**, 2046; (e) G. Xu, M. Li, S. Wang and W. Tang, *Org. Chem. Front.*, 2015, **2**, 1342; (f) Y. Sun and N. Cramer, *Angew. Chem., Int. Ed.*, 2017, **56**, 364; (g) Y. Sun and N. Cramer, *Chem. Sci.*, 2018, **9**, 2981; (h) P. Hu, L. Kong, F. Wang, X. Zhu and X. Li, *Angew. Chem., Int. Ed.*, 2021, **60**, 20424; (i) C.-W. Zhang, X.-Q. Hu, Y.-H. Dai, P. Yin, C.-Y. Wang and W.-L. Duan, *ACS Catal.*, 2022, **12**, 193; (j) S.-Y. Song, Y. Li, Z. Ke and S. Xu, *ACS Catal.*, 2021, **11**, 13445; (k) G. R. Genov, J. L. Douthwaite, A. S. K. Lahdenperä, D. C. Gibson and R. J. Phipps, *Science*, 2020, **367**, 1246; (l) Q.-J. Yao, J.-H. Chen, H. Song, F.-R. Huang and B.-F. Shi, *Angew. Chem., Int. Ed.*, 2022, e202202892; (m) J.-H. Chen, M.-Y. Teng, F.-R. Huang, H. Song, Z.-K. Wang, H.-L. Zhuang, Y.-J. Wu, X. Wu, Q.-J. Yao and B.-F. Shi, *Angew. Chem., Int. Ed.*, 2022, e202210106.
- T. Zhou, L.-J. Fan, Z.-J. Chen, M.-X. Jiang, P.-F. Qian, X. Hu, K. Zhang and B.-F. Shi, *Org. Lett.*, 2023, **25**, 5724.
- CCDC 2183918 (3a) contain the supplementary crystallographic data for this paper†.

