How to cite: *Angew. Chem. Int. Ed.* **2022,** *61,* e202210106
International Edition: doi.org/10.1002/anie.202210106
German Edition: doi.org/10.1002/ange.202210106

Cobalt Catalysis

Cobalt/Salox-Catalyzed Enantioselective Dehydrogenative C–H Alkoxylation and Amination

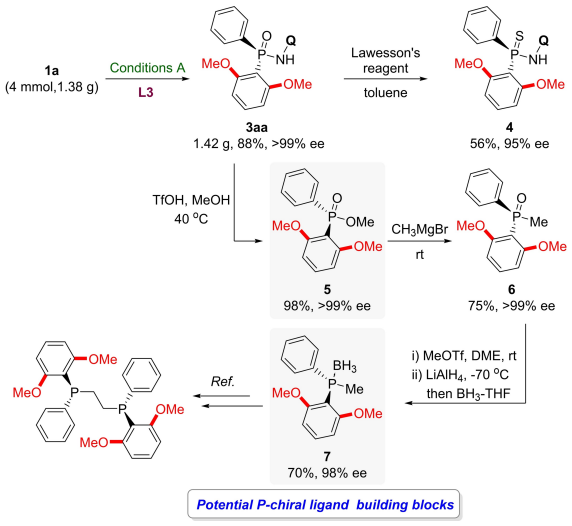
Jia-Hao Chen, Ming-Ya Teng, Fan-Rui Huang, Hong Song, Zhen-Kai Wang, He-Lin Zhuang, Yong-Jie Wu, Xu Wu, Qi-Jun Yao, and Bing-Feng Shi**

Abstract: The past decade has witnessed a rapid progress in asymmetric C–H activation. However, the enantioselective C–H alkoxylation and amination with alcohols and free amines remains elusive. Herein, we disclose the first enantioselective dehydrogenative C–H alkoxylation and amination enabled by a simple cobalt/salicyloxazoline (Salox) catalysis. The use of cheap and readily available cobalt(II) salts as catalysts and Saloxs as chiral ligands provides an efficient method to access P-stereogenic compounds in excellent enantioselectivities (up to >99% ee). The practicality of this protocol is demonstrated by gram-scale preparation and further derivatizations of the resulting P-stereogenic phosphinamides, which offering a flexible asymmetric alternative to access P-stereogenic mono- and diphosphine chiral ligands. Preliminary mechanistic studies on the enantioselective C–H alkoxylation reaction suggest that a cobalt(III/IV/II) catalytic cycle might be involved.

Introduction

The development of carbon–heteroatom (C–X) bond-forming reactions involving asymmetric C–H activation is of vital importance, as heteroatom-containing chiral compounds are prevalent in natural products, pharmaceuticals, and agrochemicals.[1] However, only a few examples of enantioselective C–O/C–N bond-forming reactions have been reported thus far.[2] Previous reports in this field are largely restricted to Pd^{II}-catalyzed intramolecular C–H lactonization[3a] and lactamization,[3b–d] and group 9 chiral cyclopentadienyl (Cp^x)–M^{III}-catalyzed enantioselective C–H amidation using nitrene precursors (e.g. organic azides, dioxazolones, or iodonium imides) as amidating agents,[4] to avoid the competitive coordination caused by the large amount of oxygenation or amination agents. The enantioselective dehydrogenative C–H alkoxylation and amination with alcohols and free amines would be a more appealing and atom-economical alternative. Despite the apparent efficacy, this strategy remains elusive, largely due to the following inherent hurdles: 1) superstoichiometric amounts of strongly coordinating amine reactants might outcompete the catalytic amount of chiral ligand, leading to the erosion of enantiocontrol or even inhibiting the C–H activation reaction. 2) alcohols and free amines can undergo oxidation/decomposition reactions under the oxidative conditions in the presence of various transition metal catalysts.[5] Given the importance of C–O/C–N bond formation and the potential efficacy of enantioselective dehydrogenative C–H alkoxylation and amination, the development of novel chiral catalytic systems is highly desired.

P-stereogenic molecules are an important class of compounds that have been widely used as chiral ligands and organocatalysts in asymmetric synthesis.[6] Since the pioneering work by Knowles on the introduction of DIPAMP as an efficient chiral ligand for asymmetric hydrogenation,[7a] a number of P-stereogenic ligands, such as BRAF,[7b] MiniPhos,[7c] QuinoxP*,[7d] and BIBOP,[7e] have been developed for various asymmetric reactions (Figure 1a). The promising applications of P-stereogenic phosphine ligands have inspired significant efforts to develop efficient methods to access these chiral compounds.[6e–g] Recently, group 9 transition metal-catalyzed asymmetric C–H activation has provided a novel avenue to access P-stereogenic compounds, as demonstrated by the groups of Cramer, Li, Duan, Phipps,



Scheme 1. Gram-scale preparation and synthetic transformations.

[*] J.-H. Chen, M.-Y. Teng, F.-R. Huang, Dr. H. Song, Z.-K. Wang, H.-L. Zhuang, Dr. Y.-J. Wu, X. Wu, Dr. Q.-J. Yao, Prof. Dr. B.-F. Shi
Center of Chemistry for Frontier Technologies, Department of Chemistry, Zhejiang University
Hangzhou 310027 (China)
E-mail: 3110000156@zju.edu.cn
bfshi@zju.edu.cn
Homepage: http://mypage.zju.edu.cn/en/bfshi/

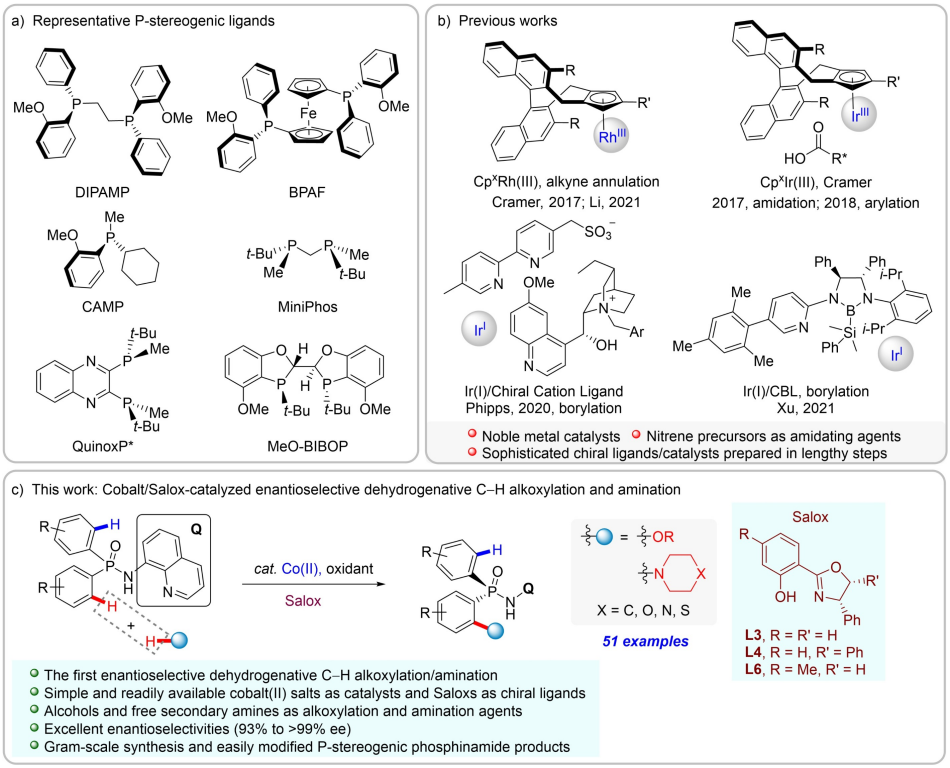


Figure 1. The synthesis of P-stereogenic compounds via group 9 transition metal-catalyzed enantioselective C–H activation. DIPAMP = 1,2-ethanediylbis[(*o*-methoxyphenyl)phenylphosphine]. BPAF = 1,1′-bis[phenyl-(2-methoxyphenyl)phosphino]-ferrocene. CAMP = methylcyclohexyl-*o*-anisylphosphane. BIBOP = bisdihydrobenzooxaphosphole. CBL = chiral bidentate boryl ligand.

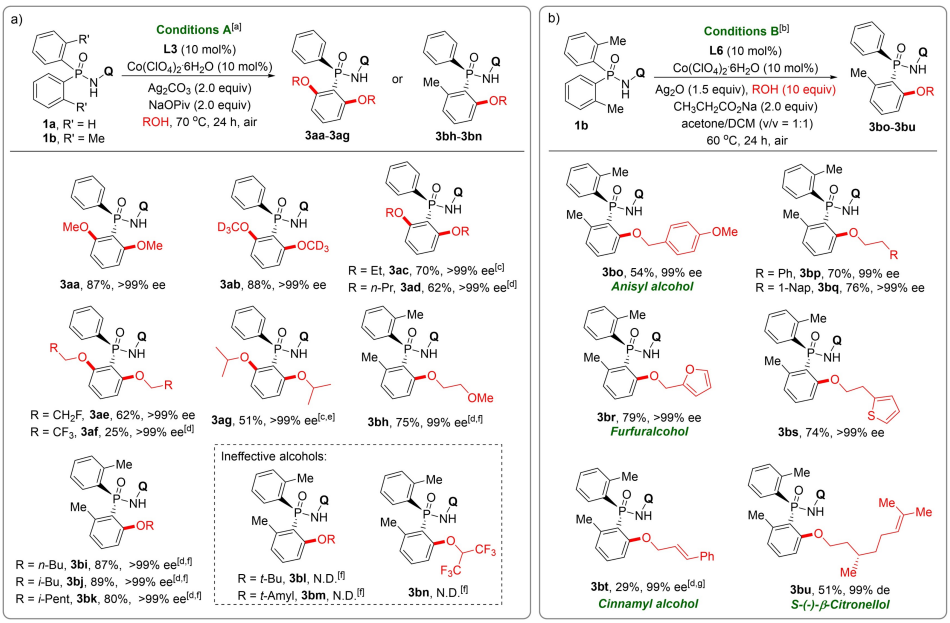
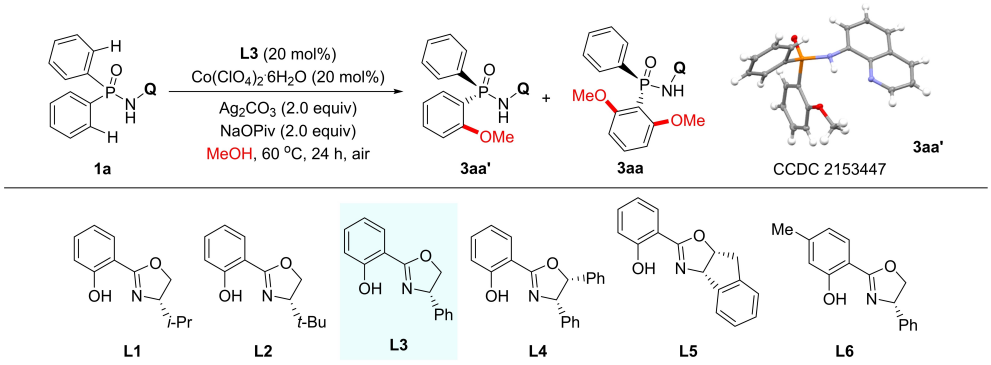


Figure 2. Scope of alcohols. [a] **Conditions A**: **1** (0.10 mmol), ROH (1.5 mL), $Co(ClO_4)_2{\cdot}6H_2O$ (10 mol%), **L3** (10 mol%), Ag_2CO_3 (2.0 equiv), NaOPiv (2.0 equiv), 70 °C, 24 h. [b] **Conditions B**: **1 b** (0.10 mmol), ROH (10 equiv), $Co(ClO_4)_2{\cdot}6H_2O$ (10 mol%), **L6** (10 mol%), Ag_2O (1.5 equiv), $CH_3CH_2CO_2Na$ (2.0 equiv), acetone: DCM = 0.5 mL: 0.5 mL, 60 °C, 24 h. [c] 96 h. [d] 48 h. [e] 60 °C. [f] 1.0 equiv Ag_2CO_3. [g] $Co(ClO_4)_2{\cdot}6H_2O$ (20 mol%), **L6** (20 mol%), Ag_2O (2.0 equiv). N.D. = no detected. DCM = dichloromethane.

and Xu (Figure 1b).[4a,8–10] However, these reports are limited to the use of costly noble metal catalysts (e.g. Rh and Ir) and sophisticated chiral ligands/catalysts prepared in lengthy steps. Therefore, the synthesis of acyclic P-stereogenic

Table 1: Optimization of reaction conditions.[a]



Entry	Deviation from standard conditions	**3aa′** Yield [%][b]	ee [%][c]	**3aa** Yield [%][b]	ee [%][c]
1	none	trace	–	95	>99
2	**L1** instead of **L3**	10	76	77	99
3	**L2** instead of **L3**	8	70	n.d.	–
4	**L4** instead of **L3**	trace	–	90	>99
5	**L5** instead of **L3**	47	40	16	84
6	**L6** instead of **L3**	trace	–	90	>99
7	$Co(acac)_2$ instead of $Co(ClO_4)_2{\cdot}6H_2O$	36	95	10	>99
8	$Co(OAc)_2{\cdot}4H_2O$ instead of $Co(ClO_4)_2{\cdot}6H_2O$	trace	–	92	>99
9	$CoCl_2$ instead of $Co(ClO_4)_2{\cdot}6H_2O$	18	97	80	>99
10	Na_2CO_3 instead of PivONa	20	98	8	99
11	Na_2HPO_4 instead of PivONa	14	99	trace	–
12	AgOAc instead of Ag_2CO_3	48	96	22	99
13	Ag_2O instead of Ag_2CO_3	20	99	21	>99
14	$Mn(OAc)_2{\cdot}4H_2O$ instead of Ag_2CO_3	trace	–	n.d.	–
15	$Mn(OAc)_3{\cdot}2H_2O$ instead of Ag_2CO_3	43	95	5	>99
16	1.0 equiv Ag_2CO_3	40	96	27	>99
17	10 mol% $Co(ClO_4)_2{\cdot}6H_2O$	40	98	30	>99
18[d]	10 mol% $Co(ClO_4)_2{\cdot}6H_2O$	trace	–	87[e]	>99

[a] Reaction Conditions: **1a** (0.1 mmol), $Co(ClO_4)_2{\cdot}6H_2O$ (20 mol%), **L3** (20 mol%), Ag_2CO_3 (2.0 equiv), NaOPiv (2.0 equiv) in MeOH at 60 °C for 24 h. [b] Determined by ^1H NMR using CH_2Br_2 as internal standard. [c] Determined by HPLC. [d] 70 °C, **L3** (10 mol%). [e] Isolated yield.

compounds by earth-abundant cobalt catalysis with readily available and tunable chiral ligands is challenging but of great value.[11,12]

Very recently, we achieved an enantioselective C–H annulation of arylphosphinamides with alkynes enabled by a simple cobalt/salicyloxazoline (Salox) catalysis. A precisely assembled chiral octahedral cobaltacycle complex was isolated and characterized as the key intermediate and the annulation reaction was proceeded through a Co^{III}/Co^{I} catalytic cycle.[13] Inspired by this result, we were prompted to advance our study to the more challenging enantioselective dehydrogenative C–H alkoxylation and amination.[14] We are aware that the extension of enantioselective C–H annulation to alkoxylation and amination is not straightforward, as several challenges need to be tackled: 1) in contrast to the Co^{III}/Co^{I} catalytic cycle in the annulation reaction, the dehydrogenative alkoxylation was believed to proceed via a mechanistically different oxidation-induced reductive elimination within a $Co^{III/IV/II}$ pathway, which was experimentally and computationally supported by Ackermann and Hong.[15] 2) the competitive coordination of free amines might inhibit the reactivity and enantioselectivity. Described herein is the first cobalt/Salox-catalyzed enantioselective dehydrogenative C–H alkoxylation and amination with alcohols and secondary amines (Figure 1c). A broad range of enantioenriched acyclic P-stereogenic phosphinamides were obtained in excellent enantioselectivities (up to >99% ee), which provided an efficient method to the synthesis of methylphenyl-*o*-anisylphosphane (PAMP)- and DIPAMP-type P-stereogenic ligands.

Results and Discussion

Optimizing Reaction Conditions

We began our study by investigating the reaction of 8-aminoquinoline-derived diphenylphosphinamide **1a** in MeOH.[16] The desired dimethoxylated product **3aa** was obtained in 95% ^1H NMR yield with >99% ee under the following optimized conditions: 20 mol% $Co(ClO_4)_2{\cdot}6H_2O$, 20 mol% **L3**, 2.0 equiv of Ag_2CO_3, 2.0 equiv of NaOPiv in MeOH at 60 °C for 24 h (Table 1, entry 1), and only trace amount of monomethoxylated product **3aa′** was observed. The absolute configuration of **3aa′** was unambiguously assigned to be *S* by X-ray crystallography analysis and

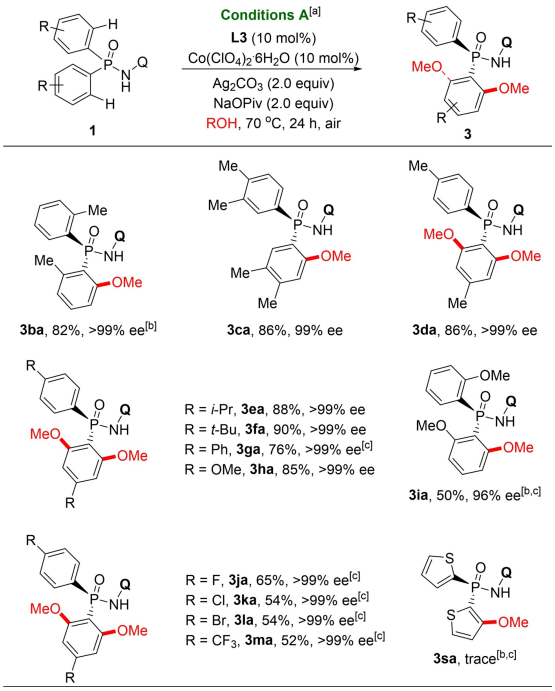


Figure 3. Scope of diarylphosphinamides. [a] **Conditions A**: **1** (0.10 mmol), MeOH (1.5 mL), $Co(ClO_4)_2{\cdot}6H_2O$ (10 mol%), **L3** (10 mol%), Ag_2CO_3 (2.0 equiv), NaOPiv (2.0 equiv), 70 °C, 24 h. [b] 1.0 equiv Ag_2CO_3. [c] 48 h.

extrapolated to the other alkoxylaiton products.[17] Control experiments were conducted to reveal the effect of ligands first. The use of **L1**, **L4**, and **L6** as the ligand instead of **L3** led to the formation of **3aa** in equally excellent enantioselectivity but lower yield (entry 2, 77%, 99% ee; entry 4, 90%, >99% ee; entry 6, 90%, >99% ee). Unsatisfactory results were obtained when **L2** and **L5** were used as chiral ligand (entries 3 and 5). These results were consistent with our previous studies, which could be well explained by the π-π stacking interactions between phenyl group of **L3** and the quinoline group of **1a**, as well as one of the phenyl rings of **1a** and the phenolate group of **L3**.[13] Other cobalt catalysts, such as $Co(acac)_2$, $Co(OAc)_2{\cdot}4H_2O$ and $CoCl_2$, maintained the excellent enantioselectivities (>99% ee), but deteriorated the yield of **3aa** (entries 7–9). Replacing NaOPiv with Na_2CO_3 or Na_2HPO_4 led to significantly reduced yield (entries 10 and 11). The use of other oxidants, such as Ag_2O, AgOAc, $Mn(OAc)_2{\cdot}4H_2O$ or $Mn(OAc)_3{\cdot}2H_2O$, instead of Ag_2CO_3 presented inefficient results (entries 12–15). Reducing the loading of Ag_2CO_3 resulted in the decreased yield of **3aa** along with significant amount of monomethoxylated product **3aa′** (entry 16). After increasing the reaction temperature to 70 °C, the loading of $Co(ClO_4)_2{\cdot}6H_2O$ could be reduced to 10 mol%, giving a comparable result (entry 18, 87% yield, >99% ee, **Conditions A**).

Scope of the Enantioselective C–H Alkoxylation

With the established reaction conditions in hand, we commenced to explore the substrate scope of alcohols. An array of linear alcohols such as methanol, methanol-d_3, ethanol, *n*-propanol, 2-fluoroethanol gave the corresponding dialkoxylated products in good yields with excellent enantioselectivities (Figure 2a, **3aa**–**3ae**, >99% ee). Satisfyingly, secondary alcohol **2g** was identified as viable substrate, affording the diisopropoxylated product **3ag** in 51% yield with >99% ee. However, diphenylphosphinamides **1** were decomposed dramatically under acidic trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP). Only 25% yield di-trifluoroethoxylated product **3af** has been isolated when TFE was used as solvent. To avoid the difficulty of separation between starting materials and products, we adopted di(*o*-tolyl)phosphinamide **1b** to investigate the scope of other alcohols and lowered the loading of Ag_2CO_3 from 2.0 equivalents to 1.0 equivalent. Both branched and ether-containing alcohols were well tolerated, giving the desired alkoxylation products in excellent enantioselectivities (**3bh**–**3bk**, 99% to >99% ee). Unfortunately, this protocol is not suitable for tertiary alcohols, such as *t*-BuOH and *t*-AmOH, due to the steric bulkiness.

Although our current protocol gave the alkoxylated products in good yields with excellent enantioselectivities, the use of alcohols as solvents still limited the application in alcohols with high boiling point or expensive ones. Therefore, to overcome those drawbacks and broaden the scope of alcohols, we conducted further investigations to use superstoichiometric alcohols in other commonly used solvents, which is extremely challenging as demonstrated by previous reports.[14a,c] To our delight, the alkoxylation reaction could be conducted in a mixture of acetone and DCM solvent with 10 equiv of MeOH using **L6** as the chiral ligand (**Conditions B**, see Supporting Information for details). *p*-Anisyl alcohol (**2o**) and 2-phenylethanol (**2p**) were compatible with the optimized conditions, affording **3bo** and **3bp** in moderate yields with high enantioselectivities (Figure 2b). Nonetheless, solid alcohols **2q** and **2t** also reacted smoothly to give **3bq** and **3bt** in high ee values. Heterocyclic aromatic alcohols **2r** and **2s** were also tolerated. Notably, *S*-(−)-β-citronellol (**2u**), a naturally occurring alcohol bearing extra chiral center and an alkene moiety, was also compatible with the optimized conditions, giving **3bu** in 51% yield with 99% de.

We next illustrated the versatility of the enantioselective C–H alkoxylation by examining a wide variety of functionalized diarylphosphinamides under **Conditions A** in methanol (Figure 3). The alkoxylation worked well for a variety of diarylphosphinamides bearing o*rtho*- or *para*-substituents (**3ba** and **3da**–**3ia**). *meta*-Substituted diarylphosphinamides **1c** gave the monoalkoxylated product **3ca** in 86% yield with 99% ee. Diarylphosphinamides bearing electron-withdrawing groups in *para*-position, such as fluoro-, chloro-, bromo- or $-CF_3$ were also compatible (**3ja**–**3ma**, 52–65%, >99% ee). However, dithienylphosphinamide **1r** showed a very low activity in the reaction, probably due to the coordinating moiety of thiophene ring.

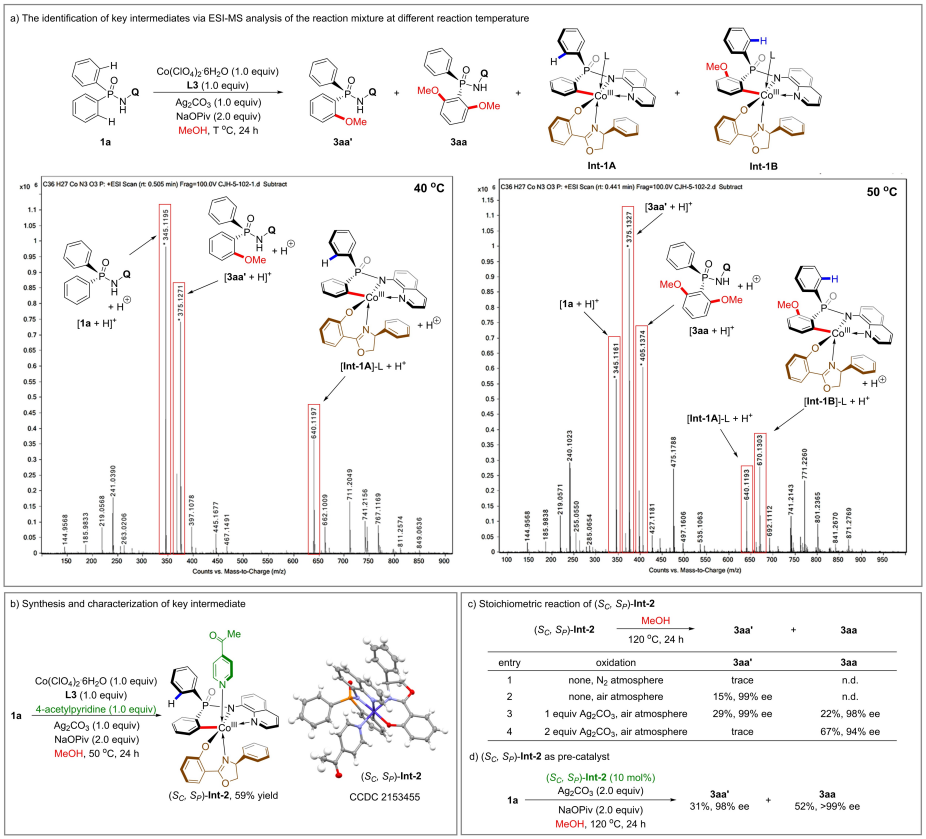


Figure 4. Mechanism studies. L = neutral ligand.

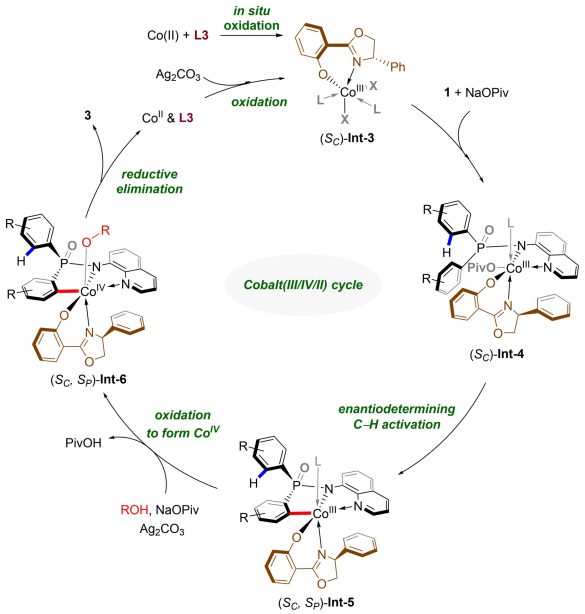


Figure 5. Proposed catalytic cycle. L = neutral ligand. X = anionic ligand.

Gram-Scale Synthesis and Synthetic Transformations

To demonstrate the application of our protocol, several transformations were conducted (Scheme 1). The gram-scale synthesis was easily accomplished in 4.0 mmol scale, giving **3aa** in 88 % yield and > 99 % ee (1.42 g). By treating with Lawesson's reagent, **3aa** was successfully thiolated, delivering **4** in 56 % yield with 95 % ee. The aminoquinoline amide was easily transferred to the corresponding methyl phosphinate **5** in excellent yield with the complete retention of enantiopurity (98 % yield, > 99 % ee). Stereospecific nucleophilic substitution of **5** with CH_3MgBr gave phosphine oxide **6** in 75 % yield without any loss of enantioselectivity (> 99 % ee). Subsequently, **6** was readily reduced to the corresponding phosphine as the BH_3 complex **7**, which could be transformed to DIPAMP analogue according to the previous report.[18] Thus, this protocol provided a flexible asymmetric alternative to access PAMP- and DIPAMP-type P-stereogenic chiral ligands analogues.[6e]

Mechanism Investigations

The results presented above encouraged us to gain insight into the reaction mechanism of the C–H alkoxylation reaction. First, two key intermediates **Int-1A** and **Int-1B** were detected upon mass-spectrometric analysis of the stoichiometric reaction of **1a** at different reaction temperature (Figure 4a). The dissociation of the monodentate neutral ligand occurred under the electrospray ionization (ESI) conditions. Unfortunately, all the attempts to isolate these possible cobaltacycle intermediates failed. However,

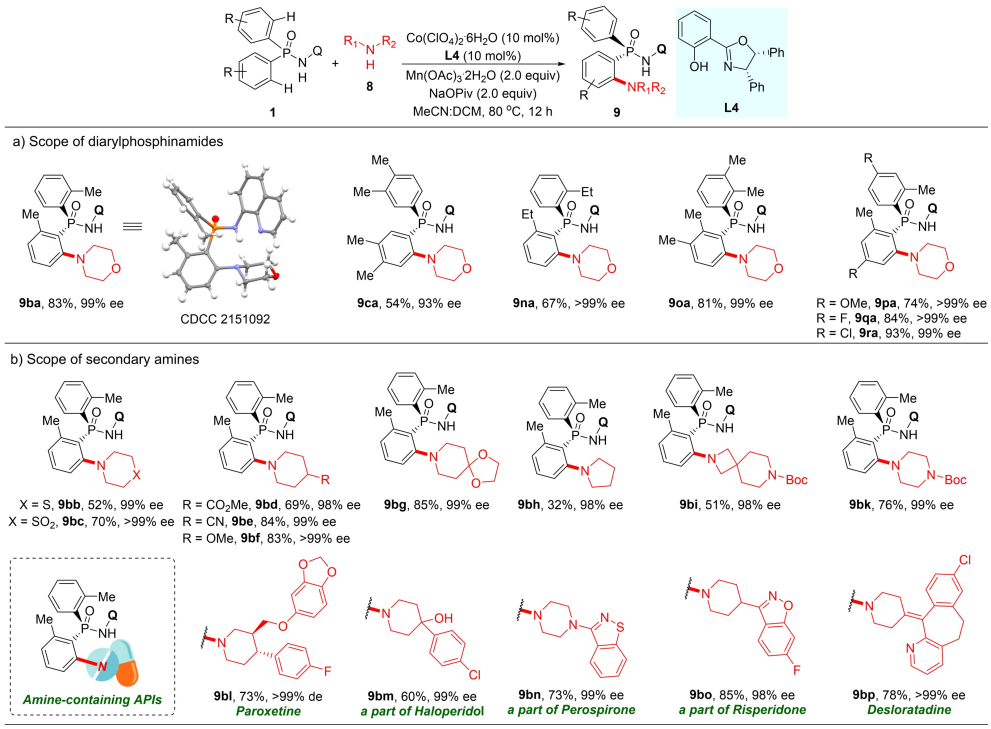


Figure 6. Scope of enantioselective C–H amination. Reaction conditions: **1** (0.10 mmol), **8** (1.2 equiv), $Co(ClO_4)_2{\cdot}6H_2O$ (10 mol%), **L4** (10 mol%), $Mn(OAc)_3{\cdot}2H_2O$ (2.0 equiv), NaOPiv (2.0 equiv), MeCN: DCM = 0.5 mL: 0.5 mL, 80 °C, 12 h.

we succeeded in obtaining a chiral octahedral Co^{III}-complex (S_C, S_P)-**Int-2** stabilized by a 4-acetylpyridine ligand (Figure 4b). (S_C, S_P)-**Int-2** was characterized by NMR, electrospray ionization mass spectrometry (ESI-MS), and X-ray crystallography analysis.[17] Next, we conducted the control experiments of oxidant. Only trace of monomethoxylated product **3aa′** was observed after the (S_C, S_P)-**Int-2** was heated at 120 °C in MeOH for 24 h under N_2 atmosphere (Figure 4c, entry 1), which might be attributed to the disproportionation of the Co^{III} **Int-1** to release a small amount of Co^{IV} species. The yield of **3aa′** was slightly improved to 15 % when the reaction was carried out in air atmosphere (entry 2). When 1.0 equivalent of Ag_2CO_3 was added, the yield of both mono- and dimethoxylated products was significantly improved (entry 3, **3aa′**, 29 %, 99 % ee; **3aa**, 22 %, 98 % ee). Dimethoxylated product **3aa** was isolated in 67 % yield with 94 % ee, when the loading of Ag_2CO_3 was increased to 2.0 equivalents (entry 4). These results indicated that oxidants played an important role in the subsequent reductive elimination step. Based on the insightfully experimental and computational studies by Ackermann and Hong, an oxidation-induced reductive elimination through high-valent Co^{IV} might be involved.[15] Finally, we utilized 10 mol % (S_C, S_P)-**Int-2** as the precatalyst to participate in our reaction. Moderate yield of **3aa′** and **3aa** were obtained with excellent ee values (Figure 4d).

Based on the above mechanistic studies and previous insightful reports,[13,15] a plausible catalytic cycle for the enantioselective C–H alkoxylation was proposed in Figure 5. The reaction was initiated by the in situ oxidation of Co^{II} precatalyst to chiral octahedral Co^{III} complex (S_C)-**Int-3**, which coordinated with diarylphosphinamide **1** to give (S_C)-**Int-4**. An enantiodetermining C–H activation occurred to form Co^{III} intermediate (S_C, S_P)-**Int-5**. Subsequent oxidation with Ag_2CO_3 in the presence of NaOPiv led to the formation of a Co^{IV} species (S_C, S_P)-**Int-6** ligated with an anionic alkoxy. Reductive elimination of Co^{IV} intermediate (S_C, S_P)-**Int-6** and protodemetallation delivered the alkoxylated product **3** and Co^{II} species, which was oxidized to Co^{III} catalyst to close the catalytic cycle. Thus, this enantioselective C–H alkoxylation via $Co^{III/IV/II}$ cycle mechanistically differed from our previous work on enantioselective C–H annulation.[13]

Enantioselective C–H Amination with Secondary Amines

Encouragingly, our catalytic system was also applicable to the enantioselective dehydrogenative C–H amination with cyclic secondary amines, when **Conditions B** were adjusted slightly (see Supporting Information for details). As summarized in Figure 6a, several diarylphosphinamides were well tolerated, delivering the enantioenriched aminated products in moderate to good yields with excellent enantioselectivities (**9ba**–**9ca** and **9na**–**9ra**, 54–93 % yield, 93 % to >99 % ee). The absolute configuration of **9ba** was assigned to be *S* by X-ray crystallography and the others were assigned accordingly.[17] Next, various cyclic secondary amines were tested (Figure 6b). Morpholine (**8a**), thiomorpholine (**8b**), thiomorpholine-1,1-dioxide (**8c**), and *N*-Boc-protected piperazine (**8k**), were well tolerated, giving the

desired products **9ba–9bc** and **9bk** in 52–83 % yield and 99 % to >99 % ee. In terms of the functional-group tolerance, piperidine derivatives bearing ester, cyano, methoxy, or ketal at the C4 position all served as suitable partners to furnish **9bd–9bg** (69–85 %, 98 % to >99 % ee). Notably, cyclic secondary amines containing 4- or 5-membered rings also participated in the amination reaction to give the amination products **9bh–9bi** in moderate yields with excellent ee values. Unfortunately, acyclic secondary amines were not compatible for this reaction, which is consistent with previous observations.[14b,d,e] Finally, a series of amine-containing active pharmaceutical ingredients (APIs), such as Paroxetine (**8l**), a part of Haloperidol (**8m**), a part of Perospirone (**8n**), a part of Risperidone (**8o**) and Desloratidine (**8p**) were also compatible, affording the aminated products **9bl–9bp** in gratifying yields with excellent enantioselectivities.

Conclusion

In conclusion, we developed the first enantioselective dehydrogenative C–H alkoxylation and amination with alcohols and free secondary amines. Commercially available cobalt(II) salts were used as precatalysts and the readily available Saloxs were used as efficient chiral ligands, providing a broad range of acyclic P-stereogenic phosphinamides in excellent enantioselectivities (93 % to >99 % ee). Preliminarily mechanistic studies provided support for a $Co^{III/IV/II}$ catalytic mode for the alkoxylation reaction. Further interests concerning the potential utility of these P-stereogenic compounds in asymmetric synthesis are ongoing in our laboratory.

Acknowledgements

This work was supported by National Key R&D Program of China (2021YFF0701603 for B.-F.S.), National Natural Science Foundation of China (21925109 for B.-F.S.), Zhejiang Provincial NSFC (LD22B030003 for B.-F.S.), the Fundamental Research Funds for the Central Universities (226-2022-00224 for B.-F.S.), and China Postdoctoral Science Foundation (2021M690133, BX2021257 for Q.-J.Y).

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: C–H Alkoxylation · C–H Amination · Enantioselectivity · Octahedral Cobalt Catalysis · Salicyloxazoline

[1] a) C. Zheng, S.-L. You, *RSC Adv.* **2014**, *4*, 6173–6214; b) C. G. Newton, S.-G. Wang, C. C. Oliveira, N. Cramer, *Chem. Rev.* **2017**, *117*, 8908–8976; c) T. G. Saint-Denis, R.-Y. Zhu, G. Chen, Q.-F. Wu, J.-Q. Yu, *Science* **2018**, *359*, eaao4798; d) G. Liao, T. Zhou, Q.-J. Yao, B.-F. Shi, *Chem. Commun.* **2019**, *55*, 8514–8523; e) T. Yoshino, S. Satake, S. Matsunaga, *Chem. Eur. J.* **2020**, *26*, 7346–7357; f) T. Kumar, S. Maiti, S. Jana, D. Maiti, *ACS Catal.* **2020**, *10*, 13748–13793; g) O. Vyhivskyi, A. Kudashev, T. Miyakoshi, O. Baudoin, *Chem. Eur. J.* **2021**, *27*, 1231–1257.

[2] Q. Zhang, L.-S. Wu, B.-F. Shi, *Chem* **2022**, *8*, 384–413.

[3] a) X.-F. Cheng, Y. Li, Y.-M. Su, F. Yin, J.-Y. Wang, J. Sheng, H. U. Vora, X.-S. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 1236–1239; b) A. P. Smalley, J. D. Cuthbertson, M. J. Gaunt, *J. Am. Chem. Soc.* **2017**, *139*, 1412–1415; c) T. Zhou, M.-X. Jiang, X. Yang, Q. Yue, Y.-Q. Han, Y. Ding, B.-F. Shi, *Chin. J. Chem.* **2020**, *38*, 242–246; d) H.-R. Tong, W. Zheng, X. Lv, G. He, P. Liu, G. Chen, *ACS Catal.* **2020**, *10*, 114–120.

[4] a) Y.-S. Jang, M. Dieckmann, N. Cramer, *Angew. Chem. Int. Ed.* **2017**, *56*, 15088–15092; *Angew. Chem.* **2017**, *129*, 15284–15288; b) S. Fukagawa, Y. Kato, R. Tanaka, M. Kojima, T. Yoshino, S. Matsunaga, *Angew. Chem. Int. Ed.* **2019**, *58*, 1153–1157; *Angew. Chem.* **2019**, *131*, 1165–1169; c) S. Fukagawa, M. Kojima, T. Yoshino, S. Matsunaga, *Angew. Chem. Int. Ed.* **2019**, *58*, 18154–18158; *Angew. Chem.* **2019**, *131*, 18322–18326; d) Y.-H. Liu, P.-X. Li, Q.-J. Yao, Z.-Z. Zhang, D.-Y. Huang, M. D. Le, B.-F. Shi, *Org. Lett.* **2019**, *21*, 1895–1899; e) L. Liu, H. Song, Y.-H. Liu, L.-S. Wu, B.-F. Shi, *ACS Catal.* **2020**, *10*, 7117–7122; f) B. Liu, P. Xie, J. Zhao, J. Wang, M. Wang, Y. Jiang, J. Chang, X. Li, *Angew. Chem. Int. Ed.* **2021**, *60*, 8396–8400; *Angew. Chem.* **2021**, *133*, 8477–8481; g) Y. Kato, L. Lin, M. Kojima, T. Yoshino, S. Matsunaga, *ACS Catal.* **2021**, *11*, 4271–4277; h) W. Liu, W. Yang, J. Zhu, Y. Guo, N. Wang, J. Ke, P. Yu, C. He, *ACS Catal.* **2020**, *10*, 7207–7215.

[5] a) K. E. Torraca, X. Huang, C. A. Parrish, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 10770–10771; b) K. Ouyang, W. Hao, W.-X. Zhang, Z. Xi, *Chem. Rev.* **2015**, *115*, 12045–12090; c) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247–9301; d) J. Jiao, K. Murakami, K. Itami, *ACS Catal.* **2016**, *6*, 610–633.

[6] a) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029–3070; b) P. W. N. M. van Leeuwen, P. C. J. Kamer, C. Claver, O. Pàmies, M. Diéguez, *Chem. Rev.* **2011**, *111*, 2077–2118; c) S. J. Connon, *Angew. Chem. Int. Ed.* **2006**, *45*, 3909–3912; *Angew. Chem.* **2006**, *118*, 4013–4016; d) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047–9153; e) M. Dutartre, J. Bayardon, S. Jugé, *Chem. Soc. Rev.* **2016**, *45*, 5771–5794; f) G. Xu, C. H. Senanayake, W. Tang, *Acc. Chem. Res.* **2019**, *52*, 1101–1112; g) S. Lemouzy, L. Giordano, D. Hérault, G. Buono, *Eur. J. Org. Chem.* **2020**, 3351–3366.

[7] a) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, *99*, 5946–5952; b) U. Nettekoven, M. Widhalm, P. C. J. Kamer, P. W. N. M. van Leuwen, *Tetrahedron: Asymmetry* **1997**, *8*, 3185–3188; c) Y. Yamanoi, T. Imamoto, *J. Org. Chem.* **1999**, *64*, 2988–2989; d) T. Imamoto, K. Sugita, K. Yoshida, *J. Am. Chem. Soc.* **2005**, *127*, 11934–11935; e) W. Tang, B. Qu, A. G. Capacci, S. Rodriguez, X. Wei, N. Haddad, B. Narayanan, S. Ma, N. Grinberg, N. K. Yee, D. Krishnamurthy, C. H. Senanayake, *Org. Lett.* **2010**, *12*, 176–179.

[8] a) J. Diesel, N. Cramer, *ACS Catal.* **2019**, *9*, 9164–9177; b) P.-F. Qian, J.-Y. Li, T. Zhou, B.-F. Shi, *Synthesis* **2022**, https://doi.org/10.1055/a-1802-6793.

[9] a) Y. Sun, N. Cramer, *Angew. Chem. Int. Ed.* **2017**, *56*, 364–367; *Angew. Chem.* **2017**, *129*, 370–373; b) Y.-S. Jang, Ł. Woźniak, J. Pedroni, N. Cramer, *Angew. Chem. Int. Ed.* **2018**, *57*, 12901–12905; *Angew. Chem.* **2018**, *130*, 13083–13087; c) P. Hu, L. Kong, F. Wang, X. Zhu, X. Li, *Angew. Chem. Int. Ed.* **2021**, *60*, 20424–20429; *Angew. Chem.* **2021**, *133*, 20587–20592; d) C.-W. Zhang, X.-Q. Hu, Y.-H. Dai, P. Yin, C. Wang, W.-L. Duan, *ACS Catal.* **2022**, *12*, 193–199.

[10] a) G. R. Genov, J. L. Douthwaite, A. S. K. Lahdenperä, D. C. Gibson, R. J. Phipps, *Science* **2020**, *367*, 1246–1251; b) S.-Y. Song, Y. Li, Z. Ke, S. Xu, *ACS Catal.* **2021**, *11*, 13445–13451.

[11] a) J. Loup, U. Dhawa, F. Pesciaioli, J. Wencel-Delord, L. Ackermann, *Angew. Chem. Int. Ed.* **2019**, *58*, 12803–12818; *Angew. Chem.* **2019**, *131*, 12934–12949; b) Ł. Woźniak, N. Cramer, *Trends Chem.* **2019**, *1*, 471–484.

[12] a) F. Pesciaioli, U. Dhawa, J. C. A. Oliveira, R. Yin, M. John, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 15425–15429; *Angew. Chem.* **2018**, *130*, 15651–15655; b) S. Fukagawa, Y. Kato, R. Tanaka, M. Kojima, T. Yoshino, S. Matsunaga, *Angew. Chem. Int. Ed.* **2019**, *58*, 1153–1157; *Angew. Chem.* **2019**, *131*, 1165–1169; c) D. Sekine, K. Ikeda, S. Fukagawa, M. Kojima, T. Yoshino, S. Matsunaga, *Organometallics* **2019**, *38*, 3921–3926; d) Y. H. Liu, P. X. Li, Q. J. Yao, Z. Z. Zhang, D. Y. Huang, M. D. Le, H. Song, L. Liu, B. F. Shi, *Org. Lett.* **2019**, *21*, 1895–1899; e) Y.-H. Liu, P.-P. Xie, L. Liu, J. Fan, Z.-Z. Zhang, X. Hong, B.-F. Shi, *J. Am. Chem. Soc.* **2021**, *143*, 19112–19120; f) W.-K. Yuan, B.-F. Shi, *Angew. Chem. Int. Ed.* **2021**, *60*, 23187–23192; *Angew. Chem.* **2021**, *133*, 23371–23376; g) K. Ozols, Y.-S. Jang, N. Cramer, *J. Am. Chem. Soc.* **2019**, *141*, 5675–5680; h) K. Ozols, S. Onodera, Ł. Woźniak, N. Cramer, *Angew. Chem. Int. Ed.* **2021**, *60*, 655–659; *Angew. Chem.* **2021**, *133*, 665–669; i) A. G. Herraiz, N. Cramer, *ACS Catal.* **2021**, *11*, 11938–11944.

[13] Q.-J. Yao, J.-H. Chen, H. Song, F.-R. Huang, B.-F. Shi, *Angew. Chem. Int. Ed.* **2022**, *61*, e202202892; *Angew. Chem.* **2022**, *134*, e202202892.

[14] a) L.-B. Zhang, X.-Q. Hao, S.-K. Zhang, Z.-J. Liu, X.-X. Zheng, J.-F. Gong, J.-L. Niu, M.-P. Song, *Angew. Chem. Int. Ed.* **2015**, *54*, 272–275; *Angew. Chem.* **2015**, *127*, 274–277; b) L.-B. Zhang, S.-K. Zhang, D. Wei, X. Zhu, X.-Q. Hao, J.-H. Su, J.-L. Niu, M.-P. Song, *Org. Lett.* **2016**, *18*, 1318–1321; c) N. Sauermann, T. H. Meyer, C. Tian, L. Ackermann, *J. Am. Chem. Soc.* **2017**, *139*, 18452–18455; d) N. Sauermann, R. Mei, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 5090–5094; *Angew. Chem.* **2018**, *130*, 5184–5188; e) X. Gao, P. Wang, L. Zeng, S. Tang, A. Lei, *J. Am. Chem. Soc.* **2018**, *140*, 4195–4199.

[15] a) T. H. Meyer, J. C. A. Oliveira, D. Ghorai, L. Ackermann, *Angew. Chem. Int. Ed.* **2020**, *59*, 10955–10960; *Angew. Chem.* **2020**, *132*, 11048–11053; b) X.-R. Chen, S.-Q. Zhang, T. H. Meyer, C.-H. Yang, Q.-H. Zhang, J.-R. Liu, H.-J. Xu, F.-H. Cao, L. Ackermann, X. Hong, *Chem. Sci.* **2020**, *11*, 5790–5796.

[16] a) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155; b) L. Grigorjeva, O. Daugulis, *Angew. Chem. Int. Ed.* **2014**, *53*, 10209–10212; *Angew. Chem.* **2014**, *126*, 10373–10376; c) O. Daugulis, J. Roane, L. D. Tran, *Acc. Chem. Res.* **2015**, *48*, 1053–1064.

[17] Deposition Numbers 2153447, 2153455, and 2151092 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[18] B. Zupančič, B. Mohar, M. Stephan, *Adv. Synth. Catal.* **2008**, *350*, 2024–2032.

Manuscript received: July 10, 2022
Accepted manuscript online: August 2, 2022
Version of record online: August 17, 2022