Cobalt-Catalyzed Domino Transformations via Enantioselective C–H Activation/Nucleophilic [3+2] Annulation Towards Chiral Bridged Bicycles

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ABSTRACT: Selective synthesis of chiral bridged (hetero)bicyclic scaffolds via asymmetric C–H activation constitutes substantial challenges, due to the multiple reactivities of strained bicyclic structures. Herein, we develop the domino transformations through an unprecedent cobalt-catalyzed enantioselective C–H activation/nucleophilic [3+2] annulation with symmetrical bicyclic alkenes. The methods offer straightforward accesses to a wide range of chiral molecules bearing [2.2.1]-bridged bicyclic cores with four and five consecutive stereocenters in a single step. Two elaborated salicyloxazoline (Salox) ligands were synthesized based on the rational design and mechanistic understanding. The well-defined chiral pockets generated from asymmetric coordination around trivalent cobalt catalyst direct the orientation of bicyclic alkenes, leading to the excellent enantioselectivity.

INTRODUCTION

Chiral bridged bicycles are valuable structural motifs present in biologically important molecules. Especially, the chiral [2.2.1]-bridged bicyclic cores are not only widely applied in asymmetric catalysis[1a-d] and material synthesis,[1e, f] but also commonly found in natural products and drugs (Figure 1A).[1g,h] The establishment of new methodologies for the elaboration of [2.2.1]-bridged bicyclic templates thus has value in the development of pharmaceutical discovery and material science.

Bridged bicyclic alkenes (BBAs), particularly bridged heterobicyclic alkenes (BHAs), have been recognized as essential synthetic intermediates to create highly substituted chiral ring systems.[2,3] Among various approaches, the recently emerged transition metal-catalyzed asymmetric C–H functionalization reactions using BBAs as the coupling partners provide direct routes to various chiral molecules.[3-5] Thus far, three distinct synthetic routes merging desymmetrization of *meso*-BBAs with C–H activation have been introduced (Figure 1B). The first synthetic route involves β-heteroatom elimination of **Int-A** that generated by C–H metalation/migratory insertion to give the asymmetric ring opening products (Figure 1B, **Route I**), which has been well explored by Li,[5a,b] Cramer,[5c] and You.[5d] The resulting ring opening products (X = O) might undergo subsequent aromatization to give C–H naphthylation products (**Route II**).[5e] The third synthetic route represents an attractive and straightforward tool for building-up chiral bridged bicycles, and is an area of recent interest. The groups of Perekalin,[5f] Cramer,[5g,h] and Ellmann[5i] respectively reported the asymmetric aminoarylation of BBAs via reductive elimination of **Int-A** to deliver without chiral bridged bicycles without ring opening (**Route III**). Although **Route III** has found application in the synthesis of various chiral bridged bicycles, it relies on the use of chiral cyclopentadienyl (Cp) ligands prepared in lengthy steps. As a consequence, the discovery of new catalytic system using more sustainable metal catalysts and easily available and modular chiral ligands that can not only enable high levels of enantiocontrol, but also offer new opportunity to discover new mode of synthetic route, will be highly desirable.

Cobalt is one of the most promising earth-abundant 3d metals for enantioselective C–H activation reactions owing to its sustainable nature and unique reactivities.[6-8] In particular, cobalt catalysts exhibit unique reactivities and might provide complementary reactivity.[9] For instance, in the seminal study by Matsunaga and Kanai, they disclosed the unique nucleophilic activity of cobalt(III)-carbon intermediates.[10] The Cheng group elegantly demonstrated the cobalt-catalyzed C-H activation/intramolecular nucleophilic addition reaction assisted by bidentate 8-aminoquinoline directing group.[11,12] Inspried by these precedents and our continuous interest in cobalt-catalyzed enantioselective C-H activation,[7c,e,f,8a-c,f-h] we rationalized that a unique synthetic route involving an intramolecular nucleophilic addition of **Int-B** might be feasible, leading to the formation of a new type of chiral bridged bicyclic

molecules (**Route IV**). However, formidable challenges need to be addressed to establish this unprecedent asymmetric synthetic route: 1) Due to the intrinsic ring strain and leaving group ability of bridgehead heteroatoms, **Int-A** is more prone to undergo the undesirable β-heteroatom elimination as demonstrated by You and coworkers in chiral $Cp^xCo(III)$-catalyzed asymmetric ring-opening of 7-oxabenzonorbornadienes (**Route I**).[5d] 2) Even if β-heteroatom elimination is inhibited, the competitive C-N reductive elimination to form [4+2] annulation products is a formidable hurdle. This reaction pattern has been reported by the Cramer group in chiral $Cp^XCo(III)$-catalyzed enantioselective C-H functionalization with BBAs.[5g,h] To address these challenges, we hypothesized that the judicious elaboration of Salox ligands recently developed by Niu and us, might be competent for cobalt-catalyzed enantioselective C-H activation/nucleophilic [3+2] annulaitons (**Route IV**). Herein, we reported the unprecedented cobalt-catalyzed enantioselective C–H insertion/nucleophilic [3+2] annulation for the efficient synthesis of a range of chiral [2.2.1]-bridged bicyclic cores with four and five contiguous stereogenic centers in a single step (Figure 1C, **Route IV**). The rational design of Salox ligands based on mechanistic understanding is crucial for the high levels of chemo- and enantiocontrol.

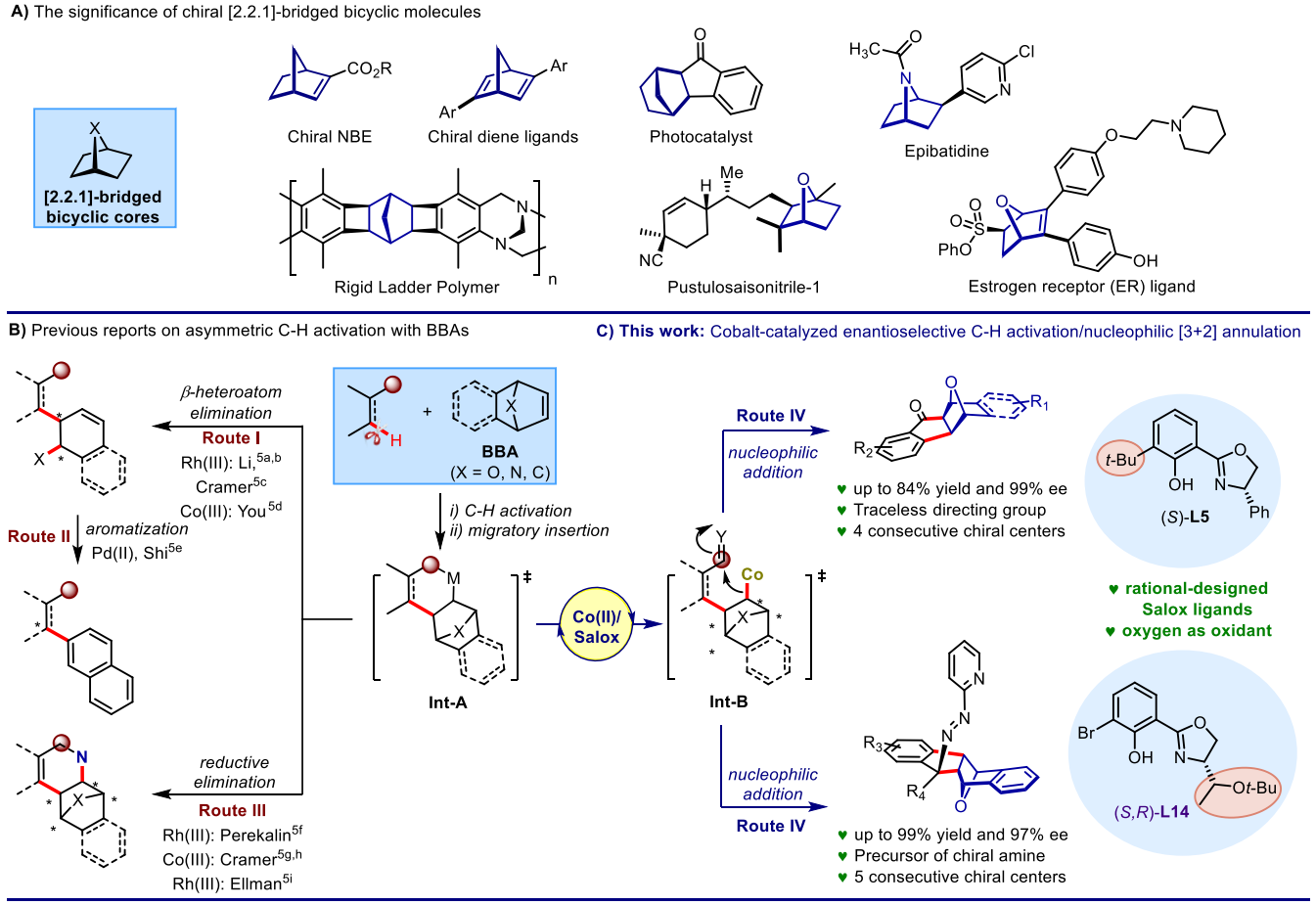

Figure 1. The application and synthetic methods for chiral bridged bicycles. (**A**) The significance of chiral [2.2.1]-bridged bicyclic molecules. (**B**) Previous reports on asymmetric C–H activation with bridged bicyclic alkenes. (**C**) Cobalt/Salox-catalyzed enantioselective C–H activation / nucleophilic [3+2] annulations towards chiral bridged (hetero)bicycles.

RESULTS AND DISCUSION

Reaction discovery and mechanistic studies. The study was initialed by transformation of C–Co complex with 7-oxabenzonorbornadiene (Figure 2). First, octahedral cobaltacyle (R_c)-**Co-1** was synthesized from *N*-(quinolin-8-yl)benzamide **1a** with Salox ligand (*R*)-**L1** (see supporting information for details).[8f] When complex **Co-1** was treated with 1.0 equivalent of 7-oxabenzonorbornadiene **2a** at 80 °C in 2,2,2-trifluoroethanol (TFE), the unprecedented [3+2] annulation product **3aa** was obtained in 60% yield with 76% ee as a single diastereoisomer, which reveals that enantioselective C–H insertion is followed by a nucleophilic addition procedure instead of C–N reductive elimination or β-oxygen elimination. The steric map of the chiral pocket in carbon-cobalt complex (R_c)-**Co-1** was generated with the *SambVca 2* tool[13] and shows an open-wide plane for alkene coordination which is responsible for the low ee value of **3aa**. We rationalized that the introduction of steric hindrance at *ortho*-position of phenolic hydroxy group might direct the orientation of alkene coordination and achieve excellent enantioselectivity.[8f]

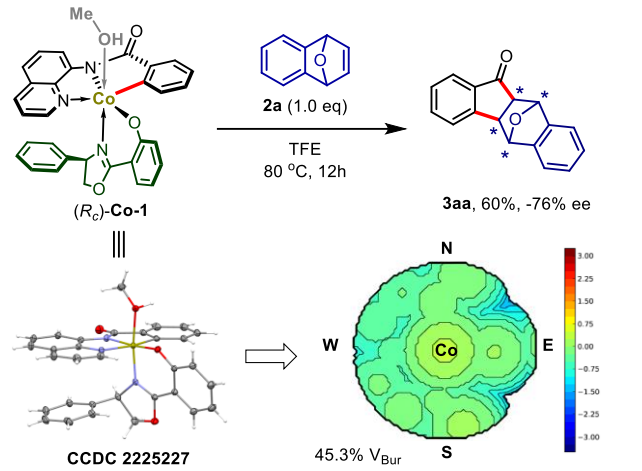

Figure 2. Initial discovery through stoichiometric reaction of (R_c)-**Co-1** (CCDC 2225227) and the steric maps of the chiral pocket of (R_c)-**Co-1**.

This unprecedent result encouraged us to commence investigations on the optimization of catalytic reaction conditions (Figure 3A). After extensive screening of solvents, cobalt salts, and Salox ligands, we were delighted to find that, as the alkyl substituent at the 6-position of Salox ligand became bulkier [6-Me-Salox (**L2**), 74% ee; 6-*n*-Pr-Salox (**L3**), 82% ee; 6-*i*-Pr-Salox (**L4**), 84% ee; 6-*t*-Bu-Salox (**L5**), 93% ee], the enantioselectivity of the desired product **3aa** was significantly improved, which is consistent with our hypothesis. With (*S*)-**L5** as chiral ligand and $Co(acac)_3$ as precatalyst, the reaction of benzamide **1a** with 7-oxabenzonorbornadiene **2a** in the presence of the 2-methylbutyraldehyde and *t*-BuOLi in TFE at 80 °C for 5 hours gave the desired product **3aa** in 73% yield with 93% ee. The configuration of **3aa** (CCDC 2225215) illustrates the predisposition of cobalt catalysts towards coordination from the *exo*-face biases the reaction outcome towards *exo*-selective products.

To gain more understanding on the catalytic system, a series of mechanistic experiments were conducted. First, the hexa-coordinated cabaltacycle (S_c)-**Co-2** was obtained in 87% yield by the stoichiometric reaction of $Co(acac)_3$, **1a**, (*S*)-**L5** and 4-dimethylaminopyridine (DMAP) under standard reaction conditions (Figure 3B, entry 1). Control experiments indicated that: 1) the use of *t*-BuOLi as base was crucial for the reaction (entry 2); 2) the addition of 2-methylbutyraldehyde did not affect the C–H metalation procedure (entry 3). The stoichiometric reaction of (S_c)-**Co-2** with **2a** delivered **3aa** in 81% yield with >99% ee (Figure 3C, entry 1), which suggests the involvement of (S_c)-**Co-2** in the catalytic cycle. Since 8-aminoquinolin (AQ) acted as a traceless directing group during the reaction, Cheng and the co-workers found that the *in situ* removed AQ inhibit the catalytic activity by coordinating with Co catalyst.[11] It is noticeable that the combination of 2-methylbutyraldehyde and *t*-BuOLi is conducive to the liberation of **L5** in 78% recovered yield. Thus, we rationalized that 2-methylbutyraldehyde could be the trapping agent for AQ to generate imine which might be perishable under reaction conditions, and thereby liberated cobalt catalyst and Salox ligand.

The crystallizable complex (S_c)-**Co-3** is an analogue of (S_c)-**Co-2**, which has been synthesized and characterized in our previous work.[8f] As shown in Figure 3D, the structure of (S_c)-**Co-3** demonstrated that the chirality-at-cobalt was secured by the π-π stacking between the phenyl group of oxazoline in Salox and the quinoline moiety of benzamide, leaving a chiral cave for coordination of **2a**.[8f] Then, steric maps of the chiral cave provide information to foster understanding of the coordination framework/selectivity relationship.[13] Comparing the steric heatmap of chiral pocket in (R_c)-**Co-1** in Figure 2 and (S_c)-**Co-3**, the buried volume increases from 45.3% V_{Bur} of **Co-1** to 50.8% V_{Bur} of **Co-3**. The map for **Co-3** reveals quinoline backbone twisted by *tert*-butyl group generates significant bulk in the NW quadrant, and the massive bulk of the *tert*-butyl group diminishes access to the northern hemisphere, thus forcing a specific orientation for **2a** in the SW quadrant. The poor enantioselectivity of **L1** can be attribute to a lack of this guiding interaction by *tert*-butyl group and the open space of **Co-1**.

A simplified catalytic procedure was proposed in Figure 3E to illustrate the reaction pathway and the mode of stereocontrol. 7-Oxabenzonorbornadiene **2a** underwent an *exo*-coordination with cobaltacycle **Int-1-1** to generate **Int-1-2**, guiding by the elaborated chiral cave in **Int-1-1**. Subsequently, an exo-migratory insertion led to the formation of seven-membered Co–alkyl intermediate **Int-1-3**. Due to the nucleophilic character of C–Co bond, the intermolecular nucleophilic attack onto carbonyl group of amide furnishes **Int-1-4**. The desired product **3aa** was obtained after subsequent C–N bond-cleavage proceed. The resulting Co(III) complex **Int-1-5** releases the trivalent cobalt and Salox ligand **L5**, which could be assisted by 2-methylbutyraldehyde and *t*-BuOLi, and the catalytic cycle is finally closed.

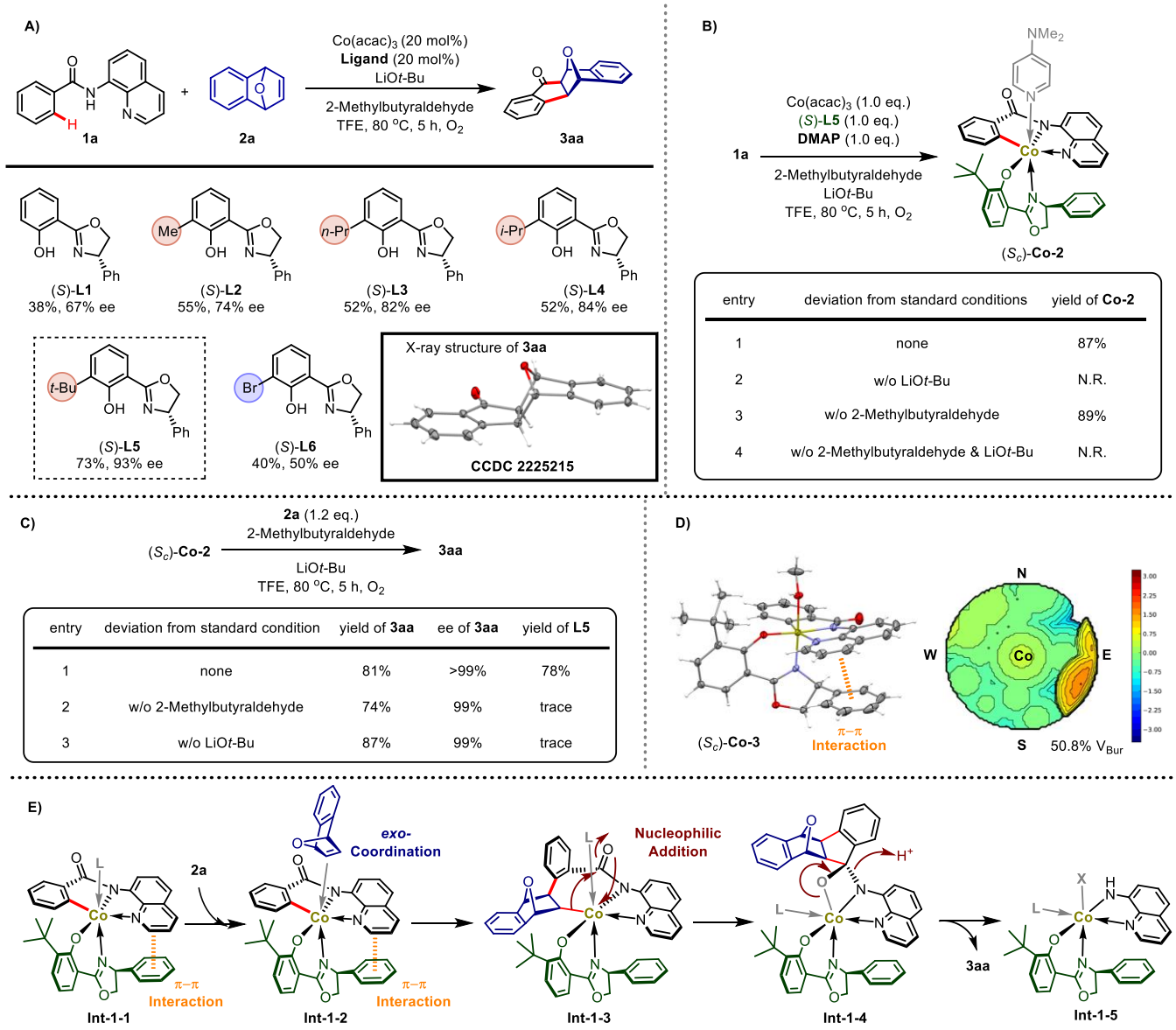

Figure 3. Enantioselective C–H activation/nucleophilic [3+2] annulations of benzamides and mechanistic studies. (**A**) The screening of chiral Salox ligands. (**B**) The synthesis of intermediate (S_c)-**Co-2** and control experiments. (**C**) The stoichiometric reaction of (S_c)-**Co-2** and control experiments. (**D**) The steric map of chiral pocket of (S_c)-**Co-3**. (**E**) Plausible reaction pathway.

Scope of Substrates. With the optimal conditions in hand, the scope of substrates was next investigated (Figure 4). Benzamides bearing a methyl group at the *para*, *meta*, or *ortho*-position were well tolerated, giving the corresponding products **3ba**-**3da** in 63% to 78% yields with excellent enantioselectivity (93% to 94% ee). Other alkyl substituent, such as ethyl, isopropyl and *tert*-butyl, at the *para*-position were also compatible, affording the corresponding products **3ea**-**3ga** in good yields (78% to 84%) with high ee values (93% to 94% ee). Then, benzamides bearing electron-donating groups, such as methoxy and benzyloxy, at the *para*-position were investigated. The desired chiral bridged bicycles were constructed efficiently (**3ha**: 73%, 95% ee; **3ia**: 75%, 94% ee). The yield and ee values decrease slightly when benzamides with electron-withdrawing groups (fluoride, chloride, bromide, iodide and trifluoromethyl) substituted at the *para*-positions (**3ja**-**3na**, 63% to 68% yields, 86% to 90% ee). Interestingly, the reaction of isonicotinamide (**1o**) gave conjugated product **3oa** (CCDC 2225216) in 73% yield. We supposed that the nitrogen atom on pyridine might coordinated with cobalt, and the Lewis acidity of Co(III) species might promote the aromatization. The scope of various bridged bicyclic alkenes was then investigated. Symmetrically substituted oxabenzonorbornadienes (**2b**, **2c**) reacted smoothly to afford the corresponding products in good yields with excellent enantioselectivities (**3gb**: 80%, 99% ee; **3gc**: 65%, 99% ee). Notably, the reaction also proceeded well with norbornene (**3ad**: 52%, 95% ee; **3ld**: 70%, 97% ee), norbornadiene (**3le**: 45%, 99% ee). The absolute configurations of **3ld** (CCDC 2225218) and **3le** (CCDC 2225219) were confirmed by X-ray analysis and revealed that the catalytic chiral pockets of cobalt intermediates present excellent *exo*-selectivity of two diastereotopic faces. Besides, the product **3ad** is analogues of a class of asymmetric photosensitizers.[1d]

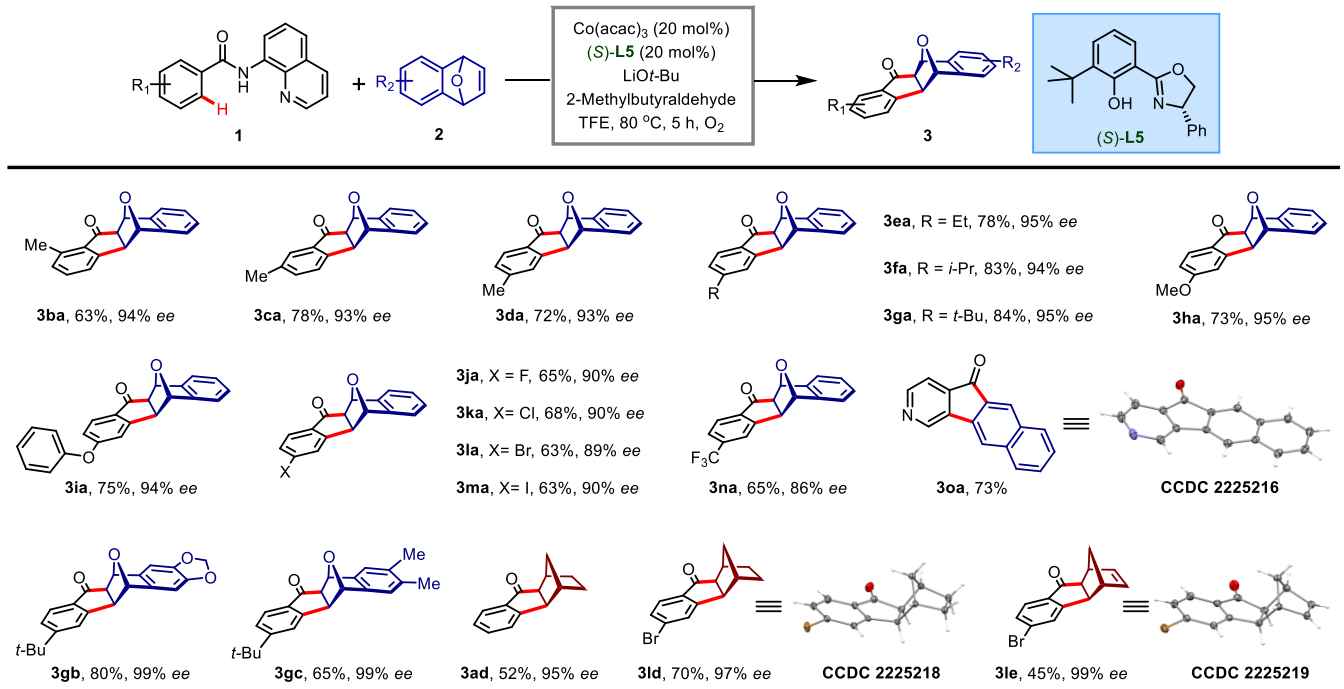

Figure 4. The investigation of substrate scope. Reaction condition: Benzamides **1** (0.2 mmol), **2** (1.2 eq, 0.24 mmol), $Co(acac)_3$ (20 mol%), (*S*)-**L5** (20 mol%), LiO*t*-Bu (4.0 eq), 2-Methylbutyraldehyde (4.0 eq), TFE (4.0 M, 0.5 mL), 80 °C, under O_2 atmosphere for 5 hours. Isolated yield. The ee value was determined by chiral HPLC.

Further Reaction Design. In light of the success of this enantioselective C-H activation/[3+2] annulation of benzamides derived from AQ, we are eager to expand this protocol to other type of substrates, such as aryl hydrazones **4**,[14] especially considering that the resulting products would be precursors of chiral amines. In our aforementioned strategy, benzamides derived from AQ coordinated with cobalt catalyst to generate a X,X,L-Co(III) pincer complex as the key intermediate (X = anionic atom, L = neutral atom).[15] In complex (S_c)-**Co-3**, Co(III) atom is surrounded by one anionic C atom from a C–H activated aryl ring, one anionic N atom and one neutral N atom of *N,N*-bidentate directing group, exhibiting a meridional geometry (Figure 5A). The introduction of steric hindrance at *ortho*-position of phenolic hydroxy group is crucial to direct the orientation of alkene coordination. Based on these mechanistic understanding, we rationalized that in the possible intermediate **Int-2** of aryl hydrazone might adopt a κ^3(X,L,X) coordination mode.[14] Regarding to the electronic aspect, the soft N-donor of oxazoline in Salox may adopt a *trans*-coordination to unsaturated N-donor of hydrazone due to a "push-pull effect" (Figure 5A). Thus, based on the coordination pattern in the possible **Int-2**, we rationalized that the judicious modification of the substituent (R in **Int-2**) next to nitrogen atom of oxazoline moiety would be the key to excellent stereocontrol.

To test the feasibility of our hypothesis, we commenced our studies by investigating various chiral Salox ligands for the envisioned enantioselective transformation of (*E*)-2-(2-(1-phenylethylidene)hydrazinyl) pyridine (**4a**) and 7-oxabenzonorbornadiene (**2a**), a racemic version of which was reported by Volla and co-workers (Figure 5B).[14c] We were delighted to observe the chiral [3+2] annulation product **5aa** was obtained as a single diastereomer in 95% yield with 72% ee using (*S*)-**L1** as chiral ligand. A series of Salox ligands derived from different chiral amino alcohols with the modification at the oxazoline skeleton were tested. Consistent with our hypothesis, the enantioselectivity was significant improved when (*S,R*)-**L11** was used as chiral ligand (90% ee). We then conducted further tuning of the substituents *ortho* to the phenolic hydroxy group. We were delighted to find that (*S,R*)-**L14** was the optimal ligand, giving **5aa** in 99% yield with 96% ee. In the contrast, relatively lower ee value was obtained when (*S*)-**L5** was used as chiral ligand (79% yield, 75% ee, see Table S9 in supporting information). The absolute configuration of chiral bridged bicycle **5aa** (CCDC 2225221) was confirmed by X-ray crystallographic analysis.

A plausible reaction pathway was proposed in Figure 5C. In the key intermediate **Int-2-1**, the C4-substituent of oxazoline moiety direct the coordination of 7-Oxabenzonorbornadiene **2a**. **Int-2-1** underwent an enantioselective migratory insertion to form the seven-membered cobaltacycle **Int-2-2**, which underwent diastereoselective intramolecular nucleophilic attack onto the *Re*-face of imine affords the complex **Int-2-3**. Chiral [3+2] annulation product **5aa** was obtained after reductive elimination, and the Co(I) intermediate is regenerated to active trivalent cobalt species under aerobic condition.

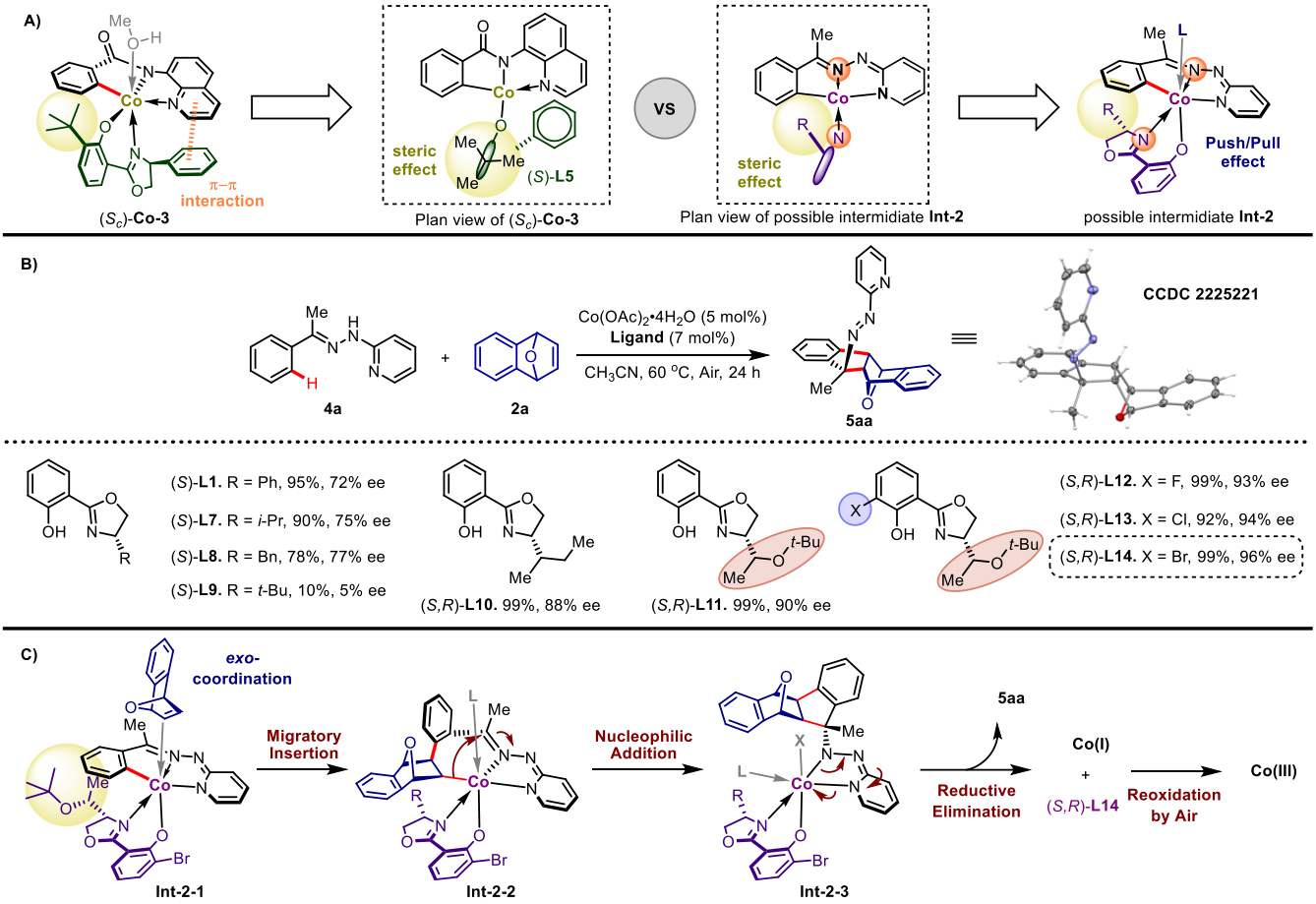

Figure 5. Enantioselective C–H activation/nucleophilic [3+2] annulations of aryl hydrazones. (**A**) The rational design for coordination frameworks of trivalent cobalt. (**B**) Prove the concept through the investigation of Salox ligands. (**C**) Plausible reaction pathway.

Then, with this set of conditions, we proceeded to evaluate the scope of hydrazone derivatives (Figure 6). In general, aryl hydrazones **4** bearing both electron-donating and -withdrawing groups at the *para*-position were compatible with this reaction, affording the desired products in high yields with excellent enantioselectivities (**5ba**, **5ea**-**5la**, **5na**). *Meta*-methyl-substituted hydrazone (**4c**) and *meta*-chloro-substituted hydrazone (**4m**) furnished a regioisomeric mixture of products (**5ca**:**5ca'** = 7:1, **5ma**:**5ma'** = 3:1) in high yields with excellent enantioselectivities. However, the reaction of *ortho*-substituted hydrazones **4d** and **4g** became sluggish where the yield of **5da** and **5ga** were decreased to 56% and 43% respectively, despite high ee values. Thiophene derived hydrazone, (*E*)-2-(2-(1-(Thiophen-2-yl)ethylidene)-hydrazinyl)pyridine (**4o**), also reacted smoothly to give the desired product **5oa** in 42% yield with 96% ee. The reaction efficiency is inversely correlated with the bulkiness of the alkylidene group, thus, variation from ethylidene (**4p**) and propylidene (**4q**) to benzylidene (**4r**) leads to a dramatically decrease in yield from >95% to 53%, but still with excellent enantioselectivity. The reactivity can be partially recovered by using fused substrate **4s**, giving the desired product **5sa** with multiple fused ring in 72% yield with 95% ee. The structure of **5sa** was confirmed by single-crystal X-ray diffraction analysis (CCDC 2225222). We further examined the enantioselective domino [3+2] annulation reaction with hydrazones derived from the core structures of functional molecule (Ferrocene, **4t**), drug molecule (Gemfibrozil, **4u**), and natural product (Geraniol, **4v**). All of the desired chiral bridged bicylic products were obtained in good yield with high enantiomeric excess (70% to 85% yield and 96% to 98% ee).

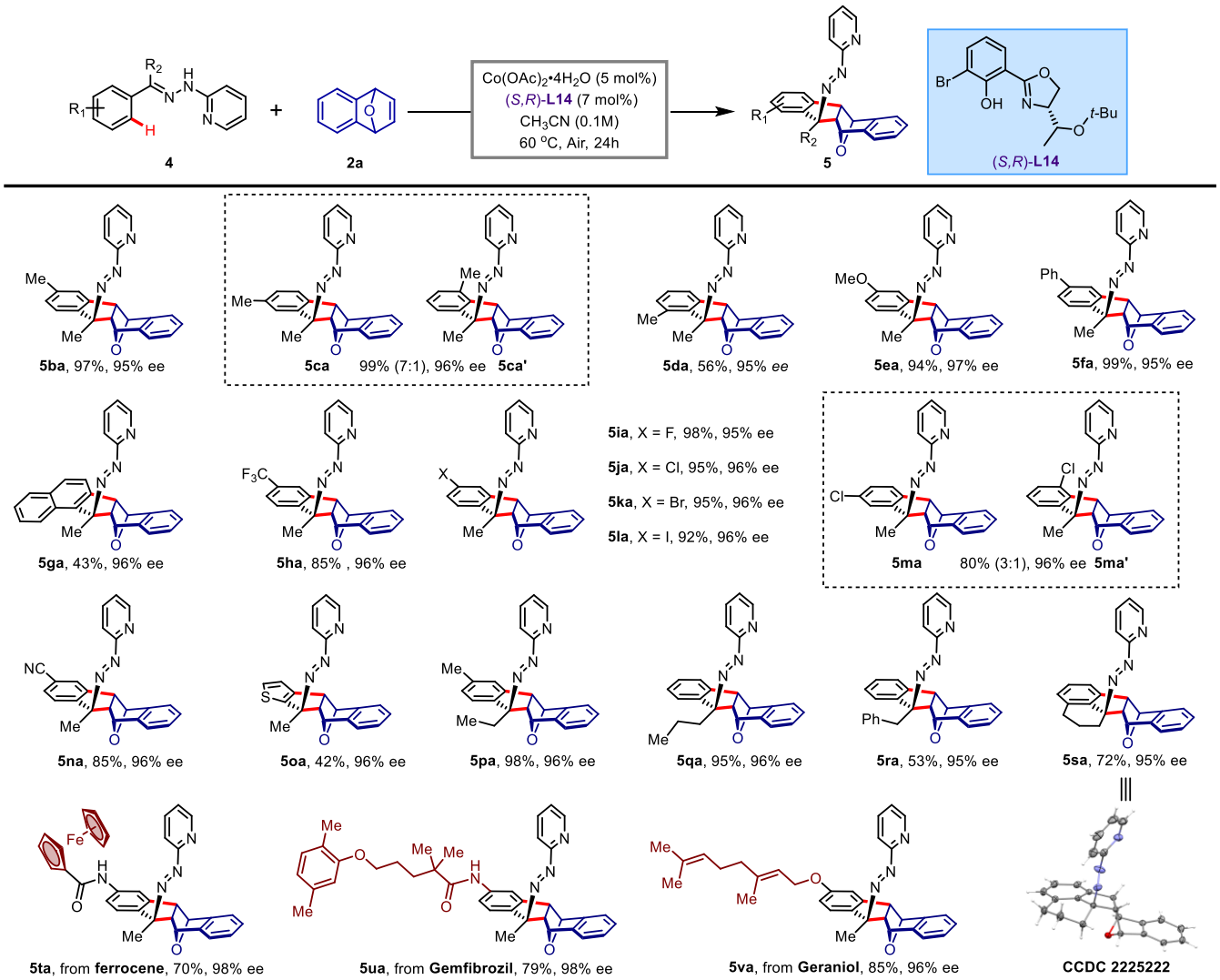

Figure 6. Scope of enantioselective transformation of aryl hydrazones. Reaction conditions: **4** (0.1 mmol), **2a** (1.2 eq, 0.12 mmol), $Co(OAc)_2•4H_2O$ (5 mol%), (*S,R*)-**L14** (7 mol%), CH_3CN (0.1 M, 1.0 mL), 60 °C, under air atmosphere for 24 hours. Isolated yield. The ee value was determined by chiral HPLC.

Synthetic Transformations The study was advanced with evaluating the preparative utility of this chemistry (Figure 7). First, the reduction of optical pure compound **3aa** (>99% ee after recrystallization) with $LiAlH_4$ gave alcohol **6** bearing five contiguous stereogenic centers in quantitative yield with high diastereoselectivity (>20:1 dr), and chirality transfer has occurred with perfect retention of the enantioenrichment. The absolute configuration of **6** (CCDC 2225223) was confirmed by X-ray analysis, showing a *syn*-configuration between the oxhydryl- group and bicyclo unit. The late-stage esterification of drug molecules (**7**, Naproxen; **8**, Probenecid) and material molecule (**9**, DTT-2,6-dicarboxylic acid) with alcohol **6** was then conducted.

As shown in Figure 7B, gram-scale (5.0 mmol) synthesis of chiral bridged bicycle **5aa** could be accomplished in undiminished yield (93%) and enantioselectivity (95% ee) under slightly modified conditions. The azo bond of **5aa** was reduced by employing Raney Ni and hydrazine hydrate in MeOH solvent at 70 °C to produce the chiral amine **10** in quantitative yield.[16] In view of the significance of chiral [2,2,1] bridged bicycles in pharmaceuticals, the synthetic utility of the protocol was further elaborated by the condensation of **10** with (*S*)-Ibuprofen, *N*-Boc-*D*-valine and (+)-mebthyl Chlorofomate to generate molecular complexity.

CONCLUSION

In summary, we have reported the unprecedent cobalt/Salox-catalyzed enantioselective C–H activation/nucleophilic [3+2] annulation with bridged bicyclic alkenes. A broad range of chiral molecules bearing [2,2,1]-bridged bicyclic cores were prepared in good yields with excellent enantioselectivities using two elaborated Salox ligands. Mechanistic studies revealed the chiral pockets for alkenes, which are generated by self-assembly construction of chiral coordination environment, are responsible for the specific orientation of the olefins and the excellent enantioselectivities. We anticipate that this research might boost the earth-abundant 3d-metal-catalyzed asymmetric C–H functionalization reactions.

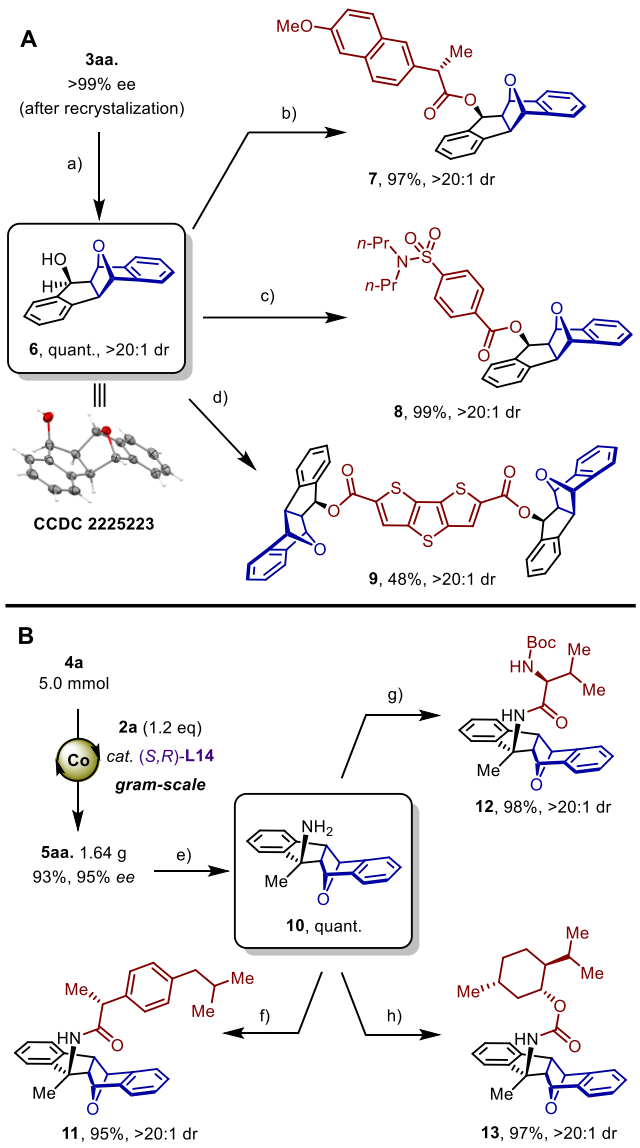

Figure 7 Synthetic transformation of products. a) $LiAlH_4$, in THF, 0 °C to rt under N_2. b) Naproxen, DCC, DMAP, in DCM, rt. c) Probenecid, DCC, DMAP, in DCM, rt. d) DTT-2,6-dicarboxylic acid, DCC, DMAP, in DCM, rt. e) Raney Ni, N_2H_4•H_2O, 70 °C in MeOH under H_2. f) (*S*)-Ibuprofen, BPO, DIPEA, in DCM, rt. g) N-Boc-D-Valine, BPO, DIPEA, in DCM, rt. h) (+)-Menthyl chlorofomate, DIPEA, DCM, 0 °C. See supplementary materials for specific reaction details.

ASSOCIATED CONTENT

This material is available free of charge via the Internet at http://pubs.acs.org.

Detailed experimental procedures, characterization of new compounds, spectroscopic data and crystallographic data (PDF)

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Accession Codes

CCDC 2225227 [(R_c)-**Co-1**], 2225215 (**3aa**), 2225216 (**3oa**), 2225218 (**3ld**), 2225219 (**3le**), 2225221 (**5aa**), 2225222 (**5sa**) and 2225223 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For selected examples, see: (a) Liu, Z.-S.; Hua, Y.; Gao, Q.; Ma, Y.; Tang, H.; Shang, Y.; Cheng, H.-G.; Zhou, Q. Construction of axial chirality via palladium/chiral norbornene cooperative catalysis. *Nat. Catal.* **2020**, *3*, 727-733. (b) Shi, H.; Herron, A. N.; Shao, Y. Shao, Yu, J.-Q. Enantioselective remote *meta*-C–H arylation and alkylation via a chiral transient mediator. *Nature*, **2018**, *558*, 581-585. (c) Brown, M. K.; Corey. E. J. Catalytic Enantioselective Formation of Chiral-Bridged Dienes Which Are Themselves Ligands for Enantioselective Catalysis. *Org. Lett.* **2010**, *12*, 172-175. (d) Demuth, M.; Raghavan, P. R.; Carter, C.; Nakano, K.; Schaffner, K. Photochemical High-yield Preparation of Tricyclo [3.3.0.0^{2,8}]octan-3-ones. Potential Synthons for Polycyclopentanoid Terpenes and Prostacyclin

Analogs. Preliminary Communication. *Helv. Chim. Acta.* **1980**, *63*, 2434-2439. (e) Ma, X.; Lai, H. W. H.; Wang, Y.; Alhazmi, A.; Xia, Y.; Pinnau, I. Facile Synthesis and Study of Microporous Catalytic Arene-Norbornene Annulation–Tröger's Base Ladder Polymers for Membrane Air Separation. *ACS Macro Lett.* **2020**, *9*, 680-685. (f) Yamamoto, K.; Fuchi, Y.; Okabe, M.; Osawa, T.; Ito, Y.; Hari, Y. New Cleavable Spacers for Tandem Synthesis of Multiple Oligo-nucleotides. *Synthesis* **2021**, *53*, 4440-4448. (g) Stockdale, T. P.; Williams, C. M. Pharmaceuticals that contain polycyclic hydrocarbon scaffolds. *Chem. Soc. Rev*. **2015**, *44*, 7737-7763. (h) Sharma, N.; Carlson, K. E.; Nwachukwu, J. C.; Srinivasan, S.; Sharma, A.; Nettles, K. W.; Katzenellenbogen, J. A. Exploring the Structural Compliancy versus Specificity of the Estrogen Receptor Using Isomeric Three-Dimensional Ligands. *ACS Chem. Biol*. **2017**, *12*, 494-503.

[2] For selected reviews, see: (a) Kumar, S. V.; Yen, A.; Lautens, M.; Guiry, P. J. Catalytic asymmetric transformations of oxa- and azabicyclic alkenes. *Chem. Soc. Rev.* **2021**, *50*, 3013-3093. (b) Khan, R.; Chen, J.; Fan, B. Versatile Catalytic Reactions of Norbornadiene Derivatives with Alkynes. *Adv. Synth. Catal*. **2020**, *362*, 1564-1601. (c) Lautens, M.; Fagnou, K.; Hiebert, S. Transition Metal-Catalyzed Enantioselective Ring-Opening Reactions of Oxabicyclic Alkenes. *Acc. Chem. Res.* **2003**, *36*, 48-58.

[3] (a) Wang, F.; Yu, S.; Li, X. Transition metal-catalysed couplings between arenes and strained or reactive rings: combination of C–H activation and ring scission. *Chem. Soc. Rev.* **2016**, *45*, 6462-6477. (b) Rayabarapu, D. K.; Cheng, C.-H. New Catalytic Reactions of Oxa- and Azabicyclic Alkenes. *Acc. Chem. Res.* **2007**, *40*, 971-983.

[4] For selected reviews on transition metal-catalyzed enantioselective C-H activation, see: (a) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. Transition metal-catalyzed C–H activation reactions: diastereoselectivity and enantioselectivity. *Chem. Soc. Rev.* **2009**, *38*, 3242-3272. (b) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. Catalytic Enantioselective Transformations Involving C–H Bond Cleavage by Transition-Metal Complexes. *Chem. Rev.* **2017**, *117*, 8908-8976. (c) Saint-Denis, T. G.; Zhu, R.-Y.; Chen, G.; Wu, Q.-F.; Yu, J.-Q. Enantioselective C(sp^3)–H bond activation by chiral transition metal catalysts. *Science* **2018**, *359*, eaao4798. (d) Achar, T.; Maiti, S.; Jana, S.; Maiti, D. Transition Metal Catalyzed Enantioselective C(sp^2)–H Bond Functionalization. *ACS Catal.* **2020**, *10*, 13748-13793. (e) Zhang, Q.; Shi, B.-F. 2-(Pyridin-2-yl)isopropyl (PIP) Amine: An Enabling Directing Group for Divergent and Asymmetric Functionalization of Unactivated Methylene C(sp^3)–H Bonds. *Acc. Chem. Res.* **2021**, *54*, 2750-2763. (f) Liu, C.-X.; Zhang, W.-W.; Yin, S.-Y.; Gu, Q.; You, S.-L.; Synthesis of Atropisomers by Transition-Metal-Catalyzed Asymmetric C–H Functionalization Reactions. *J. Am. Chem. Soc.* **2021**, *143*, 14025-14040. (g) Yoshino, T.; Matsunaga, S. Chiral Carboxylic Acid Assisted Enantioselective C–H Activation with Achiral Cp^xM^{III} (M = Co, Rh, Ir) Catalysts. *ACS Catal.* **2021**, *11*, 6455-6466. (h) Vyhivskyi, O.; Kudashev, A.; Miyakoshi, T.; Baudoin, O. Chiral Catalysts for Pd^0-Catalyzed Enantioselective C–H Activation. *Chem. Eur. J.* **2021**, *27*, 1231-1257. (i) Cong, X.; Huang, L.; Hou, Z. C–H Functionalization with Alkenes, Allenes, and Alkynes by Half-Sandwich Rare-Earth Catalysts. *Tetrahedron* **2023,** *135*, 133323. (j) Liang, H.; Wang, J. Enantioselective C–H bond Functionalization involving Arene Ruthenium(II) Catalysis. *Chem. Eur. J.* **2023**, *29,* e202202461.

[5] (a) Yang, X.; Zheng, G.; Li, X. Rhodium(III)-Catalyzed Enantioselective Coupling of Indoles and 7-Azabenzonorbornadienes by C–H Activation/Desymmetrization. *Angew. Chem. Int. Ed.* **2019**, *58*, 322-326. (b) Mi, R.; Zheng, G.; Qi, Z.; Li, X. Rhodium-Catalyzed Enantioselective Oxidative [3+2] Annulation of Arenes and Azabicyclic Olefins through Twofold C–H Activation. *Angew. Chem. Int. Ed*. **2019**, *58*, 17666-17670. (c) Duchemin, C.; Smits, G.; Cramer, N. Rh^I, Ir^{III} , and Co^{III} Complexes with Atropchiral Biaryl Cyclopentadienyl Ligands: Syntheses, Structures, and Catalytic Activities. *Organometallics* **2019**, *38*, 3939-3947. (d) Zheng, Y.; Zhang, W.-Y.; Gu, Q.; Zheng, C.; You, S.-L. Cobalt(III)-catalyzed asymmetric ring-opening of 7-oxabenzonorbornadienes via indole C–H functionalization. *Nat. Commun.* **2023**, *14*, 1094. (e) Liao, G.; Chen, H.-M.; Xia, Y.-N.; Li, B.; Yao, Q.-J.; Shi, B.-F. Synthesis of Chiral Aldehyde Catalysts by Pd-Catalyzed Atroposelective C–H Naphthylation. *Angew. Chem. Int. Ed.* **2019**, *58*, 11464-11468. (f) Trifonova, E. A.; Ankudinov, N. M.; Mikhaylov, A. A.; Chusov, D. A.; Nelyubina, Y. V.; Perekalin, D. S. A Planar-Chiral Rhodium(III) Catalyst with a Sterically Demanding Cyclopentadienyl Ligand and Its Application in the Enantioselective Synthesis of Dihydroisoquinolones. *Angew. Chem. Int. Ed.* **2018**, *57*, 7714–7718. (g) Ozols, K.; Jang, Y.-S.; Cramer, N. Chiral Cyclopentadienyl Cobalt(III) Complexes Enable Highly Enantioselective 3d-Metal-Catalyzed C–H Functionalizations. *J. Am. Chem. Soc.* **2019**, *141*, 5675-5680. (h) Ozols, K.; Shunsuke, O.; Łukasz, W.; Cramer, N. Cobalt(III)-Catalyzed Enantioselective Intermolecular Carboamination by C–H Functionalization. *Angew. Chem. Int. Ed.* **2021**, *60*, 655-659. (i) Brandes, D. S.; Sirvent, A.; Mercado, B. Q.; Ellman, J. A. Three-Component 1,2-Carboamidation of Bridged Bicyclic Alkenes via Rh^{III}-Catalyzed Addition of C–H Bonds and Amidating Reagents. *Org. Lett.* **2021**, *23*, 2836-2840.

[6] For selected reviews, see: (a) Zheng, Y.; Zheng, C.; Gu, Q.; You, S.-L. Enantioselective C–H functionalization reactions enabled by cobalt catalysis. *Chem Catal.* **2022**, *2*, 2965-2985. (b) Xu, W.; Ye, M. Enantioselective Cobalt-Catalyzed C–H Functionalization. *Synthesis* **2022**, *54*, 4773-4783. (c) Loup, J.; Dhawa, U.; Pesciaioli, F.; Wencel-Delord, J.; Ackermann, L. Enantioselective C–H Activation with Earth-Abundant 3d Transition Metals. *Angew. Chem. Int. Ed.* **2019**, *58*, 12803-12818. (d) Yoshino, T.; Satake, S.; Matsunaga, S. Diverse Approaches for Enantioselective C–H Functionalization Reactions Using Group 9 Cp^xM^{III} Catalysts. *Chem. Eur. J.* **2020**, *26*, 7346-7357. (e) Woźniak, Ł.; Cramer, N. Enantioselective C-H Bond Functionalizations by 3d Transition-Metal Catalysts. *Trends in Chem.* **2019**, *1*, 471-484.

[7] For selected examples, see: (a) Lee, P.-S. Yoshikai, N. Cobalt-Catalyzed Enantioselective Directed C–H Alkylation of Indole with Styrenes. *Org. Lett.* **2015**, *17*, 22-25. (b) Fukagawa, S.; Kato, Y.; Tanaka, R.; Kojima, M.; Yoshino, T.; Matsunaga, S. Enantioselective C(sp^3)–H Amidation of Thioamides Catalyzed by a $Cobalt^{III}$/Chiral Carboxylic Acid Hybrid System. *Angew. Chem. Int. Ed.* **2019**, *58*, 1153-1157. (c) Liu, Y.-H.; Li, P.-X.; Yao, Q.-J.; Zhang, Z.-Z.; Huang, D.-Y.; Le, M.-D.; Song, H.; Liu, L.; Shi, B.-F. Cp*Co(III)/MPAA-Catalyzed Enantioselective Amidation of Ferrocenes Directed by Thioamides under Mild Conditions. *Org. Lett.* **2019**, *21*, 1895-1899. (d) Whyte, A.; Torelli, A; Mirabi, B.; Prieto, L.; Rodriguez, J. F.; Lautens, M. Cobalt-Catalyzed Enantioselective Hydroarylation of 1,6-Enynes. *J. Am. Chem. Soc.* **2020**, *142*, 9510-9517. (e) Yuan, W.-K.; Shi, B.-F. Synthesis of Chiral Spirolactams via Sequential C–H Olefination/Asymmetric [4+1] Spirocyclization under a Simple Co^{II}/Chiral Spiro Phosphoric Acid Binary System. *Angew. Chem. Int. Ed.* **2021**, *60*, 23187-23192. (f) Y.-B. Zhou, T. Zhou, P.-F. Qian, J.-Y. Li, B.-F. Shi, Synthesis of Sulfur-Stereogenic Sulfoximines via Co(III)/Chiral Carboxylic Acid-Catalyzed Enantioselective C–H Amidation. *ACS Catal.* **2022**, *12*, 9806-9811. (g) N. Jacob, Y. Zaid, J. C. A. Oliveira, L. Ackermann, J. Wencel-Delord, Cobalt-Catalyzed Enantioselective C–H Arylation of Indoles. *J. Am. Chem. Soc.* **2022**, *144*, 798-806. (h) Y. Hirata, D. Sekine, Y. Kato, L. Lin, M. Kojima, T. Yoshino, S. Matsunaga, Cobalt(III)/Chiral Carboxylic Acid-Catalyzed Enantioselective Synthesis of Benzothiadiazine-1-oxides via C–H Activation. *Angew. Chem., Int. Ed.* **2022**, *61*, e202205341.

[8] (a) Yao, Q.-J.; Chen, J.-H.; Song, H.; Huang, F.-R.; Shi, B.-F. Cobalt/Salox-Catalyzed Enantioselective C–H Functionalization of Arylphosphinamides. *Angew. Chem. Int. Ed.* **2022**, *61*, e202202892. (b) Wang, B.-J.; Xu, G.-X.; Huang, Z.-W.; Wu, X.; Hong, X.; Yao, Q.-J.; Shi, B.-F. Single-Step Synthesis of Atropisomers with Vicinal C–C and C–N Diaxes by Cobalt-Catalyzed Atroposelective C–H Annulation. *Angew. Chem. Int. Ed.* **2022**, *61*, e202208912. (c) Chen, J.-H.; Teng, M.-Y.; Huang, F.-R.; Song, H.; Wang, Z.-K.; Zhuang, H.-L.; Wu, Y.-J.; Wu, X.; Yao, Q.-J.; Shi, B.-F. Cobalt/Salox-Catalyzed Enantioselective Dehydrogenative C–H Alkoxylation and Amination. *Angew. Chem. Int. Ed.* **2022**, *61*, e202210106. (d) Si, X.-J.; Yang, D.; Sun, M.-C.; Wei, D.; Song, M.-P.; Niu, J.-L. Atroposelective isoquinolinone synthesis through cobalt-catalysed C–H activation and annulation.

Nat. Synth. **2022**, *1*, 709-718. (e) Yang, D.; Zhang, X.; Wang, X.; Si, X.-J.; Wang, J.; Wei, D.; Song, M.-P.; Niu, J.-L. Cobalt-Catalyzed Enantioselective C–H Annulation with Alkenes. *ACS Catal.* **2023**, *13*, 4250-4260. (f) Yao, Q.-J.; Huang, F.-R.; Chen, J.-H.; Zhong, M.-Y.; Shi, B.-F. Enantio- and Regioselective Electrooxidative Cobalt-Catalyzed C–H/N–H Annulation with Alkenes. *Angew. Chem. Int. Ed.* **2023**, *62*, e202218533. (g) Zhou, G.; Chen, J.-H.; Yao, Q.-J.; Huang, F.-R.; Wang, Z.-K.; Shi, B.-F. Base-Promoted Electrochemical Co^{II}-catalyzed Enantioselective C–H Oxygenation. *Angew. Chem. Int. Ed.* **2023**, *62*, e202302964. (h) Wu, Y.-J.; Chen, J.-H.; Teng, M.-Y.; Li, X. Jiang, T.-Y.; Huang, F.-R.; Yao, Q.-J.; Shi, B.-F. Cobalt-Catalyzed Enantioselective C–H Annulation of Benzylamines with Alkynes: Application to the Modular and Asymmetric Syntheses of Bioactive Molecules. *J. Am. Chem. Soc.* **2023**, *145*, 24499-24505. (i) Münchow, T.; Dana, S.; Xu, Y.; Yuan, B.; Ackermann, L. Enantioselective electrochemical cobalt-catalyzed aryl C–H activation reactions. *Science* **2023**, *379*, 1036-1042. (j) Li, T.; Shi, L.; Wang, X.; Yang, C.; Yang, D.; Song, M.; Niu, J.-L. Cobalt-catalyzed atroposelective C–H activation/annulation to access N–N axially chiral frameworks. *Nat. Commun.* **2023**, *14*, 5271.

[9] (a) Yoshino, T.; Matsunaga, S. (Pentamethylcyclopentadienyl)cobalt(III)-Catalyzed C–H Bond Functionalization: From Discovery to Unique Reactivity and Selectivity. *Adv. Synth. Catal.* **2017**, *359*, 1245-1262. (b) Park, J.; Chang, S. Comparison of the Reactivities and Selectivities of Group 9 [Cp*M^{III}] Catalysts in C–H Functionalization Reactions. *Chem. Asian J.* **2018**, *13*, 1089-1102.

[10] Ikemoto, H.; Yoshino, T.; Sakata, K.; Matsunaga, S.; Kanai, M. Pyrroloindolone Synthesis via a Cp*Co^{III}-Catalyzed Redox-Neutral Directed C–H Alkenylation/Annulation Sequence. *J. Am. Chem. Soc.* **2014**, *136*, 5424–5431.

[11] Gandeepan, P.; Pajamalli, P.; Cheng, C.-H. Diastereoselective [3+2] Annulation of Aromatic/Vinylic Amides with Bicyclic Alkenes through Cobalt-Catalyzed C–H Activation and Intramolecular Nucleophilic Addition. *Angew. Chem. Int. Ed.* **2016**, *55*, 4308-4311.

[12] (a) Daugulis, O.; Roane, J.; Tran, L. D. Bidentate, Monoanionic Auxiliary-Directed Functionalization of Carbon–Hydrogen Bonds. *Acc. Chem. Res.* **2015**, *48*, 1053-1064. (b) Rej, S.; Ano, Y.; Chatani, N. Bidentate Directing Groups: An Efficient Tool in C–H Bond Functionalization Chemistry for the Expedient Construction of C–C Bonds. *Chem. Rev*. **2020**, *120*, 1788-1887. (c) Grigorjeva, L.; Daugulis, O. Cobalt-Catalyzed, Aminoquinoline-Directed C(sp^2)-H Bond Alkenylation by Alkynes. *Angew. Chem. Int. Ed.* **2014**, *53*, 10209-10212. (d) Grigorjeva, L.; Daugulis, O. Cobalt-Catalyzed, Aminoquinoline-Directed Coupling of sp2 C–H Bonds with Alkenes. *Org. Lett.* **2014**, *16*, 4684-4687.

[13] (a) Poater, A.; Ragone, F.; Mariz, R.; Dorta, R.; Cavallo, L. Comparing the Enantioselective Power of Steric and Electrostatic Effects in Transition-Metal-Catalyzed Asymmetric Synthesis. *Chem. Eur. J*. **2010**, *16*, 14348-14353. (b) Falivene, L.; Credendino, R.; Poacter, A.; Petta, A.; Serra, L.; Oliva, R.; Scarano, V.; Cavallo, L. SambVca 2. A Web Tool for Analyzing Catalytic Pockets with Topographic Steric Maps. *Organometallics* **2016**, *35*, 2286-2293. (c) Falivene, L.; Cao, Z.; Petta, A.; Poater, A.; Oliva, R.; Scarano, V.; Cavallo, L. Towards the online computer-aided design of catalytic pockets. *Nat. Chem*. **2019**, *11*, 872-879.

[14] (a) Zhou, S.; Wang, M.; Wang, L.; Chen, K.; Wang, J.; Song, C.; Zhu, J. Bidentate Directing-Enabled, Traceless Heterocycle Synthesis: Cobalt-Catalyzed Access to Isoquinolines. *Org. Lett.* **2016**, *18*, 5632-5635. (b) Dey, A.; Volla, C. M. Traceless Bidentate Directing Group Assisted Cobalt-Catalyzed sp^2-C–H Activation and [4 + 2]-Annulation Reaction with 1,3-Diynes. *Org. Lett.* **2020**, *22*, 7480-7485. (c) Dey, A.; Singh, A.; Volla, C. M. R. Cobalt-catalyzed highly diastereoselective [3 + 2] carboannulation reactions: facile access to substituted indane derivatives. *Chem. Commun.* **2022**, *58*, 1386-1389.

[15] (a) Moulton, C. J.; Shaw, B. L. Transition metal–carbon bonds. Part XLII. Complexes of nickel, palladium, platinum, rhodium and iridium with the tridentate ligand 2,6-bis[(di-t-butylphosphino)methyl]phenyl. *J. Chem. Soc. Dalton Trans.* **1976**, *11*, 1020-1024. (b) Peris, E.; Crabtree, R. H. Key factors in pincer ligand design. *Chem. Soc. Rev.*, **2018**, *47*, 1959-1968; (c) Alig, L.; Fritz, M.; Schneider, S. First-Row Transition Metal (De)Hydrogenation Catalysis Based on Functional Pincer Ligands. *Chem. Rev.* **2019**, *119*, 2681-2751.

[16] Kopecky, K. R.; Mojelsky, T. W.; Gillan, T.; Barry, J. A.; Sastre, J. A. L. Products and stereochemistry of thermolysis of some diazenes containing the 2-phenyl-2-butyl group. *Can. J. Chem*. **1977**, *55*, 1001-1014.

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