Reversing the Regioselectivity of Asymmetric C–H and N–H Bond Annulation with Bromoalkynes Under Cobalt(III)-Catalysis

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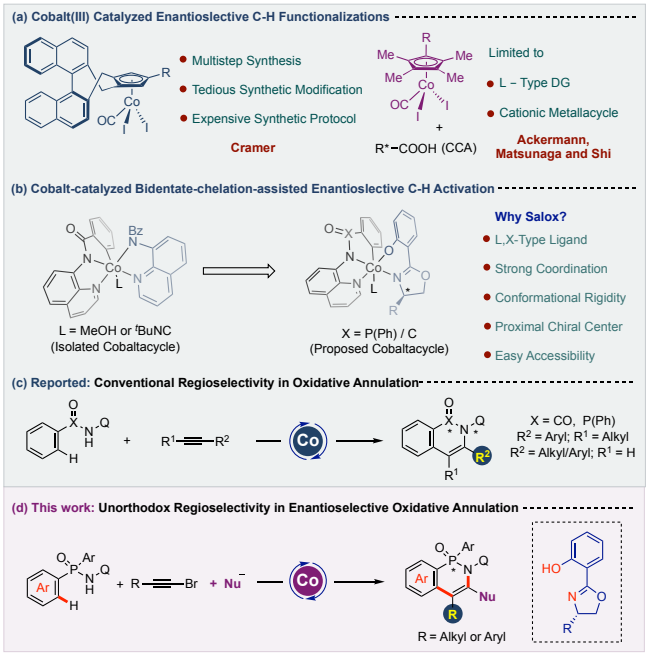
Abstract: Metal-catalyzed C-H bond annulation strategy offers a versatile platform, allowing the construction of complex p-chiral molecules through atom- and step-economical fashion. However, regioselective insertion of π-coupling partner between M-C bond and high enantio-induction remain elusive. Using commercially available Co(II) salt and chiral-salox ligands, we demonstrate an unorthodox protocol for the regio-reversal, enantioselective C-H bond annulation of phosphanamide with bromoalkyne through asymmetric desymmetrization. This method was accomplished by sequentical C-H bond activation, regioselective migratory insertion, reductive elimination, and ligand exchange with carboxylate, which resulted in the formation of novel p-stereogeneic compounds with good substrate scope and high ee (up to 99% ee). The isolation of reactive intermediates involved in the catalytic cycle and the outcomes of control experiments provide support for a plausible mechanism.

Synthesis of organic molecules with high optical purity is essential for synthetic chemists due to the prevalence of chiral components in the pharmaceutical and agrochemical industries.[1] As a result, enantioselective catalysis has made tremendous strides forward over the course of the years; however, the effort to design chiral systems that are more effective in producing high levels of enantioinduction continues unabated.[2] In enantioselective catalysis, the transition-metal-catalyzed, ubiquitous, but inert C-H bond functionalization has been found to be of great benefit in recent decades due to its intrinsic atom and step-economic and environmentally benign nature.[3] In the early stages of development, the primary focus has been placed on catalysts that were derived from 4d and 5d metals.[4] In spite of the notable developments with 4d and 5d metals, and in light of the alarming depletion of those metals in the earth's crust, a surge has recently been realized in the carrying out of enantioselective C-H functionalization with sustainable 3d metal catalysis.[5] In this regard, high-valent cobalt catalysis has been shown to be of significant interest among other 3d metals due to its distinct reactivity in comparison to that of 4d and 5d metals.[6]

In this context, a couple of exciting strategies for enantioselective C-H functionalizations using high-valent cobalt(III) catalysis were developed (Scheme 1a).[7-9] Cramer and co-workers developed tailor made chiral cyclopentadienyl-based

cobalt(III) catalysts for the enantioselective annulation of *N*-chlorobenzamides with alkenes in 2019, and the strategy was further extended to enantioselective C-H alkylation.[7] Parallely, groups led by Ackermann,[8] Matsunaga[9] and Shi[10] independently developed a hybrid catalytic system that combines chiral carboxylic acid (CCA) with an achiral Cp*Co(III) catalyst. It has been shown that enantioselective C(sp^2)-H and C(sp^3)-H functionalizations can be achieved with both chiral cyclopentadienyl and hybrid catalytic strategies. However, there are still barriers to their widespread use, such as the time-consuming and laborious multistep synthesis for the former, and the latter necessitates the generation of cationic cobaltacycle in hybrid strategies involving CCA.



Scheme 1. Overview of Ligand enabled Co(III) catalysis and asymmetric C-H bond functionalizations.

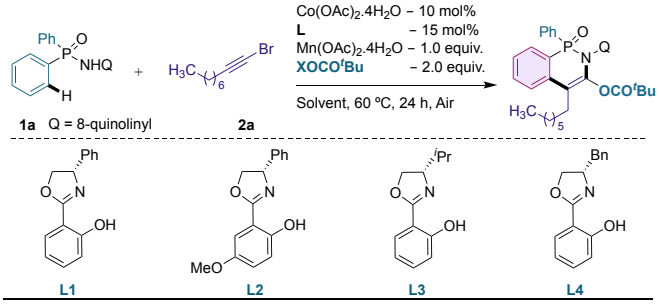
Meanwhile, a Cp*-free bidentate-chelation-assistance approach that was pioneered by Daugulis and co-workers has displayed widespread application over the years owing to the use of commercially available Co(II) and Co(III) salts as precatalysts.[11] However, mechanistic aspects such as the coordination environment around the naked cobalt were a subject of intense speculation until the octahedral cobaltacycle was isolated by the Maiti and Sundararaju groups.[12] It was discovered that the process of functionalization requires the participation of two 8-aminoquinoline moieties as L,X-type ligand bound to cobalt. One of these moieties is present in the substrate and brings the metal in close-proximity to the C-H bond, while the other acts as a spectator ligand. The resultant cobalt(III)-metallacycle obtained in octahedral geometry where the sixth coordination site is bound with solvent (Scheme 1b). By understanding the coordination environment of the in situ-generated octahedral cobaltacycle and our experience of L,X type ligands in Cp*Co(III)-catalysis,[13],[14] we hypothesized that substituting a suitably designed L,X-type chiral ligand in place of the spectator monoanionic aminoquinoline moiety may provide a suitable

chiral environment around the cobalt center for enantioselective C-H bond functionalization. Considering the easy accessibility, similar coordinating nature of the quinolyl moiety, conformational rigidity, and presence of chiral center in proximity to the coordinating atom, salicyloxazoline (Salox) ligand has recently been recognized as the excellent chiral L,X system for enantioselective C-H bond functionalizations using commercially available cobalt salts.[15]

Enantiopure organophosphorus compounds are commonly used as ligands in catalysis and have important biological applications.[16] As a result, the creation of new P-stereogenic scaffolds with high optical purity is desirable. The recently reported cobalt-catalyzed asymmetric C-H annulation reactions with alkynes follow the traditional regioselective annulation mechanism, in which the aryl group of the aryl/alkyl internal alkyne and the substituent attached in the terminal alkyne prefer to be close to the 'N' atom of the amide (Scheme 1c). We hypothesised that by changing the polar groups attached to the alkyne stem, we could reverse the regioselective migratory insertion, resulting in an inverse-regioselective annulation product. To test our hypothesis and continue our efforts to develop cobalt catalysed C-H functionalizations,[17] we attempted to access such scaffolds via cobalt(II)/Salox catalysed desymmetrization of phosphinamides *via* oxidative annulation with bromoalkynes, which were primarily investigated for C-H alkynylation. It is hoped that using bromoalkyne as a coupling partner will change the regioselectivity of the conventional oxidative annulation of amide. Furthermore, the bromo functionality may engage with suitable nucleophile in situ, resulting in the formation of a complex molecular framework in a single step.

Our investigation of the untapped potential of bromoalkynes in enantioselective oxidative annulation began with the reaction of P,P-diphenyl-N-(quinoline-8-yl)phosphinic amide **1a** with 2-bromonon-1-yne **2a** in TFE (0.2 M) at 60°C for 24 hours in the presence of 10 mol percent $Co(OAc)_2.4H_2O$, 15 mol% Salox (**L1**) (Table 1). C3-oxygenated P-stereogenic product 3aa with perfect inverse regioselectivity was produced as a single regioisomer with 39% yield and 59% ee as intended (Entry 1). It is crucial to note that no C-H alkynylation product is observed with bromoalkyne 2a. To improve enantioselectivity and yield, solvents and Salox ligands were screened (entries 2-7). Among the several solvents examined, tert-butanol was found to be the most effective for desymmetrization (entries 1-4). In tert-butanol, various stereo-electronically modified chiral Salox ligands derived from optically pure amino acids[18] were then examined (entries 4-7). Initiating the process of desymmetrization, the better-coordinating **L2** ligand performed poorly (entry 5). When the isopropyl derivative (**L3**) was used in place of the phenyl derivative (**L1**), the enantioselectivity (98% ee) and yield of the expected product were enhanced. (entry 6). Additional screening with **L4** led to a 72% yield of the **3aa** without significantly diminishing its enantioselectivity (entry 7). Finally, the catalyst loading was increased to 20 mol%, and the target product **3aa**, was produced with a 92% yield and a 98% ee (entry 8). The best conditions failed to provide results when pivalic acid was used instead of sodium carboxylate (entry 9). Control experiments revealed that in the absence of the catalyst, base, oxidant, or ligand, the reaction failed to yield the desired outcome (Entries 10-13). The reaction was performed at a scale of 1.0 mmol to evaluate the scalability of the developed protocol, and it produced the intended product with a yield of 74% and an ee of 99.9%. (Entry 14). The structure of **3aa** was determined using X-ray crystallography.[19]

Table 1. Reaction optimization[a]

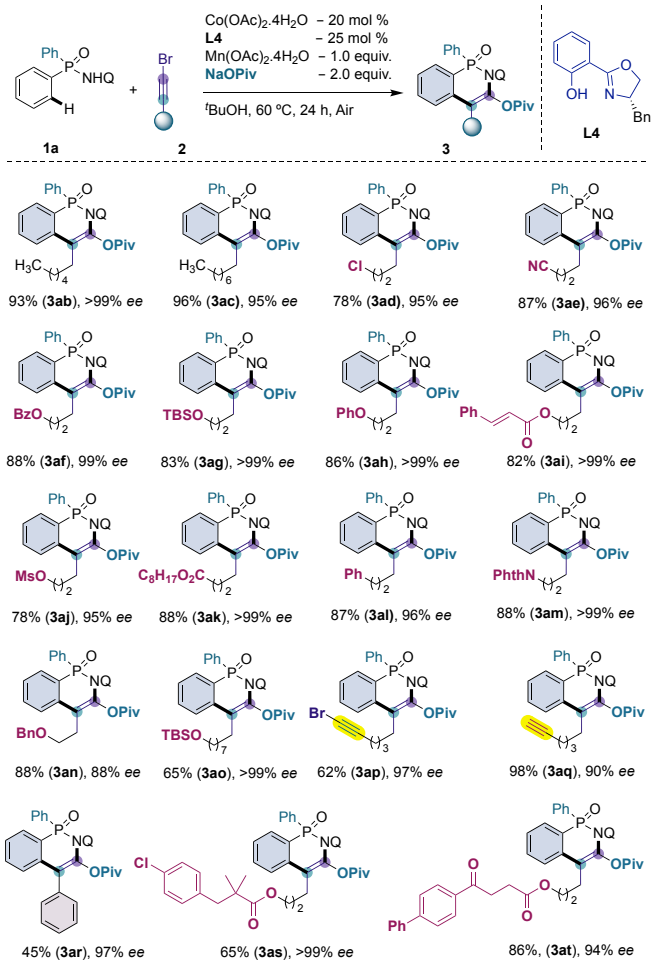


Entry	L	Base	Solvent	Yield (%)[b]	*ee* (%)[c]
1	**L1**	NaOPiv	TFE	39	59
2	**L1**	NaOPiv	EtOH	Trace	n.d.
3	**L1**	NaOPiv	Dioxane	Trace	n.d.
4	**L1**	NaOPiv	^{t}BuOH	93	89
5	**L2**	NaOPiv	^{t}BuOH	Trace	n.d.
6	**L3**	NaOPiv	^{t}BuOH	51	98
7	**L4**	NaOPiv	^{t}BuOH	72	97
8	**L4**	NaOPiv	^{t}BuOH	92	98[d]
9	**L4**	Piv-OH	^{t}BuOH	Trace	n.d.[d]
10	**-**	NaOPiv	^{t}BuOH	n.r.	n.d.[d]
11	**L4**	-	^{t}BuOH	n.r.	n.d.[d]
12	**L4**	NaOPiv	^{t}BuOH	n.r.	n.d.[d,e]
13	**L4**	NaOPiv	^{t}BuOH	n.r.	n.d.[d,f]
14	**L4**	NaOPiv	^{t}BuOH	74	99[d,g]

[a] All reactions were carried out under air unless otherwise stated using **1a** (0.1 mmol)/**2a** (0.15 mmol)/$Co(OAc)_2{\cdot}4H_2O$ (10 mol%)/Salox **L** (15 mol%)/ $NaOCO^tBu$ (0.30 mmol) mmol in ^{t}BuOH (0.5 mL) at 60 °C for 24 h. [b] Isolated yield. [c] The *e.e.* values were determined by chiral HPLC analysis. [d] 20 mol% of $Co(OAc)_2{\cdot}4H_2O$ and 25 mol% of **L4** used. [e] without $Co(OAc)_2{\cdot}4H_2O$ [f] without $Mn(OAc)_2{\cdot}4H_2O$ [g] Reaction performed in 1.0 mmol scale. TFE-2,2,2-Trifluoroethanol, n.r. = no reaction, n.d. = not determined.

The scope of bromoalkynes to access P-chiral molecules via asymmetric oxidative annulation was then investigated. As shown in Scheme 2, a broad variety of substituted bromoalkynes **2** were suitable under the given conditions, resulting in the desired products (**3ab**-**3an**) with good-to-excellent yields (78-96%) and a high level of enantioinduction (up to >99.0% ee). Notably, useful functional groups such -Cl, -CN, -OCO_2R, -OPh, and -OTBS were unaffected under the optimised conditions, allowing them to act as an additional handle for post-synthetic modifications. The chain length of bromoalkynes did not alter the enantioselectivity, demonstrating that the approach is applicable to a broad variety of bromoakynes (**3ao** vs **3ag**). Furthermore, selective annulation was achieved with 1,7-dibromohepta-1,6-diyne, yielding **3ap** with excellent enantioselectivity (97% *ee*). Bromoalkyne tethered terminal alkyne underwent selective annulation at the internal alkyne, yielding the desired product **3aq** with high yield (98%) and enantioselectivity (90% *ee*) while leaving the terminal alkyne unaffected. Encouragingly, the challenging phenyl alkynyl bromide **2r** was tolerated, harnessing the product **3ar** with desired

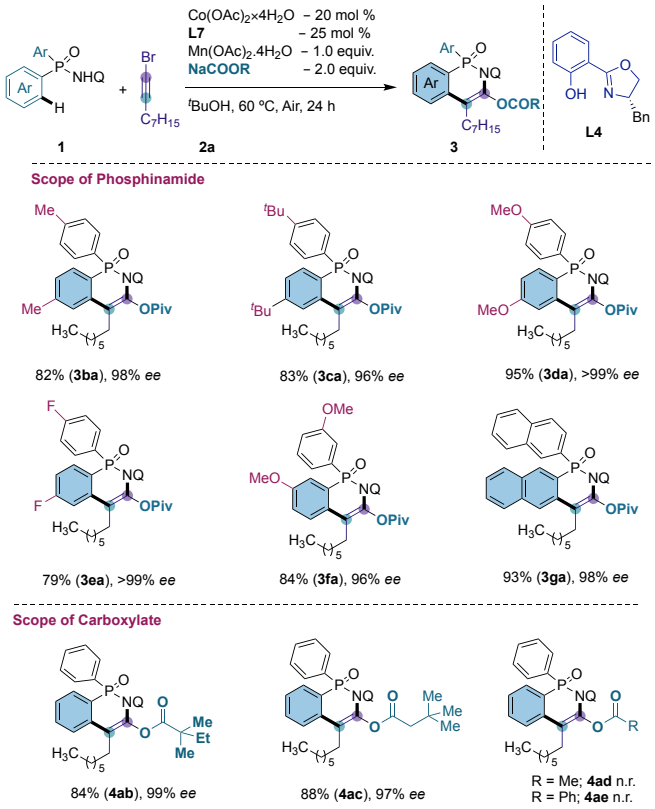
selectivity in acceptable yield and excellent enantioinduction. To further expand the application of the protocol, biologically relevant bromoalkynes (**2s** & **2t**) were synthesized from drugs used to treat high cholesterol and inflammation, such as clofibric acid and fenbufen. The bromoalkynes derived both the molecules furnished the annulated products (**3as** & **3at**) with out compromise in yield and enantioselecitvity (>99% & 94% *ee, respectively*).



Scheme 2. Scope of alkynyl bromides.

Next, the suitability of stereo electronically biased diarylphosphinamides for desymmetrization process was explored (Scheme 3). Various electron-donating and electron-withdrawing *para*-substituted phosphinamides **1b-1d** were found to be amenable to the annulation process with the yield in the ranges of 79-82%, and enantioselectivity of 94– >99% *ee* (**3ba-3ea**). Highly regioselective product **3fa** in good yield (84%) and enantioselectivity (96% *ee*) was obtained at the less hindered site when *meta*-substituted phosphinamide **1f** was employed. Moreover, sterically hindered dinaphthyl phosphinamide **3ga** smoothly underwent the desired annulation at the less hindered site with ease, resulting in a product with good yield and 98% *ee*. Additionally, the extent of the sodium carboxylate additives was examined. Sodium carboxylate derived from 2,2-dimethylbutanoic acid and 3,3-dimethylbutanoic acid underwent annulation smoothly to access the respective products (**4ab**

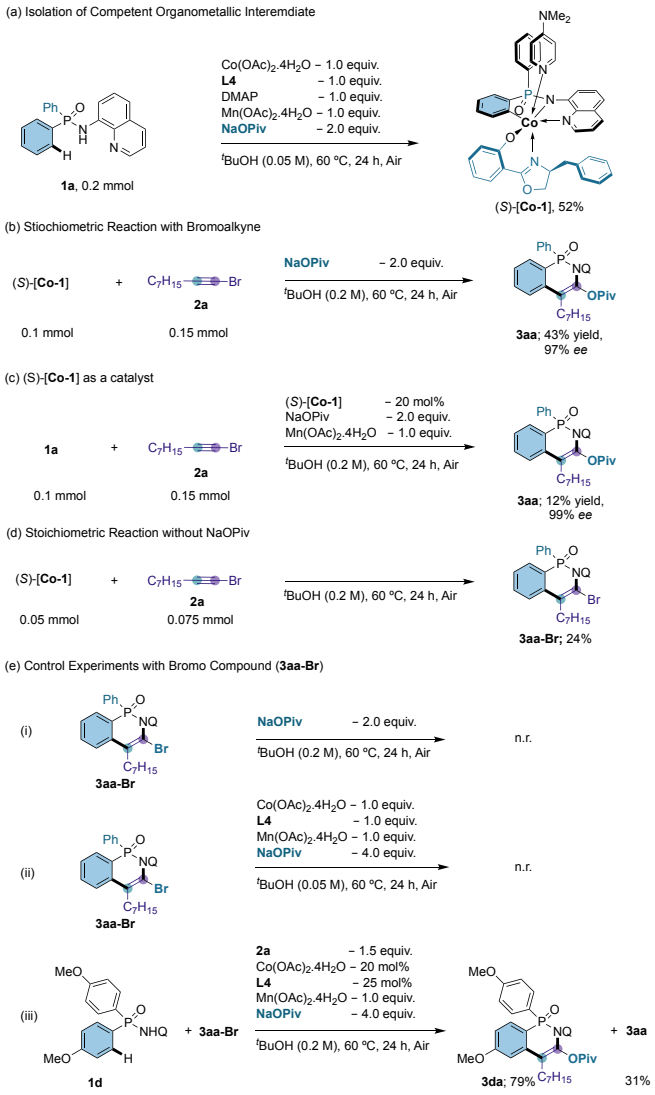
& **4ac**) with good yields (84 & 88%) and excellent enantioselectivities (99 & 97% *ee*). However, the less nucleophilic sodium acetate and sodium benzoate failed to produce the necessary scaffolds (**4ad** & **4ae**).



Scheme 3. Scope of phosphanamides and carboxylates.

Several stoichiometric reactions and control experiments were conducted to understand the reaction pathway (Scheme 4). At first, a stoichiometric reaction was carried out using phosphinamide **1a** with $Co(OAc)_2{\cdot}4H_2O$, $Mn(OAc)_2{\cdot}4H_2O$, **L4**, NaOPiv, and 4-DMAP in ^{t}BuOH under air, furnishing an chiral octahedral cobaltacycle (*S*)-[**Co-1**] (Scheme 4(a)). The chiral octahedral complex (*S*)-[**Co-1**] was then subjected to a stoichiometric reaction with bromoalkynes **2a** in the presence of sodium pivalate in tert-butanol, yielding the desired product **3aa** in 43% yield and 99% *ee* (Scheme 4(b)). Thereafter, the octahedral complex (*S*)-[**Co-1**] was employed as a catalyst, furnishing the desired product **3aa** with 12% yield and 99% *ee* (Scheme 4(c)). The low yield of product **3aa** might be due to the presence of strongly coordinating DMAP ligand. These results collectively suggest the octahedral complex (*S*)-[**Co-1**] as the reaction intermediate in the desymmetrization process. Stochiometric reaction between isolated cobalt complex (*S*)-[**Co-1**] and bromoalkyne **2a** in the absence of NaOPiv in tert-butanol provided a bromo derivative **3aa-Br** suggesting that the reaction proceeds through annulation pathway before exchange carboxylate to deliver the desired product. To understand whether the Br- to OPiv conversion is mediated by metal or not, we performed the reaction with the bromo compound **3aa-Br** under standard conditions or treated solely with sodium pivalate alone without cobalt in ^{t}BuOH at 60°C for 24 hours. As expected, the bromo functionality remains unaffected in both experiments (Scheme 4(e)). In

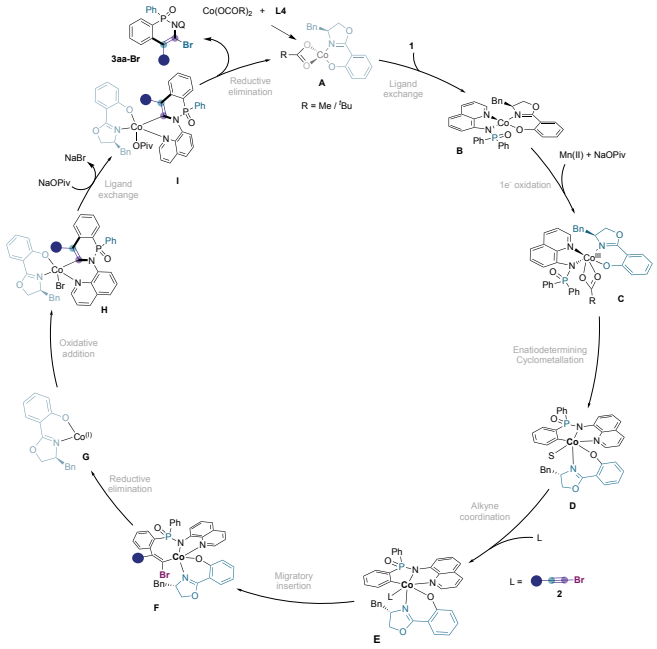
contrast, the bromo compound converted to the corresponding product **3aa** when it was subjected to a catalytic reaction of **1d** with 1-bromonon-1-yne **2a**, providing both **3da** in 79% and **3aa** in 31% (Scheme 4(e)(iii)), suggesting that the in situ-generated low-valent cobalt(I) species generated after reductive elimination helps in the oxygenation of bromo compounds to furnish the expected product.



Scheme 4. Mechanistic investigations.

Based on the control experiments, and literature reports,[12,20-21] we proposed a plausible reaction pathway as depicted in Scheme 5. Initially, the precatalyst undergoes ligand exchange with Salox **L4** to form a Co(II) intermediate **A**, which then chelates with the phosphinamides **1** leading to Co(II) intermediate **B**. Thereafter, manganese (II) promotes facile oxidation of Co(II) complex **B** under air to corresponding Co(III) intermediate **C** and subsequent enantio-determining carboxylate-assisted C-H cleavage to form the chiral octahedral cobaltacycle **D**. Coordination of bromoalkyne **2** and subsequent regiospecific

insertion into the Co-C bond results in the seven-membered metallacycle **F**. Following that, reductive elimination in the intermediate **F** provides the bromo intermediate **3aa-Br** and Co(I) species **G**. The **3aa-Br** undergo oxidative addition with Co(I) species, followed by ligand exchange with carboxylate, and finally reductive elimination to deliver the desired product **3**. The regenerated Co(II) intermediate **A** mediated by manganese is back to the catalytic cycle for the next cycle.



Scheme 5. Plausible catalytic cycle.

In conclusion, we have developed an efficient, inverse regioselective, asymmetric oxidative C-H annulation strategy to provide a new class of chiral phosphorus compounds with excellent enantiopurity using commercially available Co(II) salts and Salox chiral ligand. A complete reversal of regioselectivity complementary to classical oxidative annulation with alkyne is accomplished with diversified bromoalkynes. The mechanistic studies further revealed Co(II)-Co(III)-Co(I) catalytic pathways for the annulation process and Co(I)-Co(III)-Co(I) pathway for the oxygenation step.

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Keywords: Enantioselective C-H Functionalizations • Cobalt • Salox • Inverse Regioselectivity • Asymmetric Catalysis

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