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RESEARCH ARTICLE

Highly Regioselective Cobalt-Catalyzed Hydroboration of Internal Alkynes

Yan-Dong Zhang[1], Xiao-Yu Li[1], Qian-Kun Mo[1], Wen-Bin Shi[1], Jia-Bao Zhao[1], Shou-Fei Zhu*[,1,2]

Dedicated to the 60th anniversary of Institute of Elemento-Organic Chemistry at Nankai University.

[1] Frontiers Science Center for New Organic Matter, the State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China.
[2] Haihe Laboratory of Sustainable Chemical Transformations, Tianjin 300192, China.
[*] Email: sfzhu@nankai.edu.cn

Abstract: Herein, we report the development of new Co complexes that have cyclopropane-based diphosphine ligands and can catalyze highly chemo-, regio-, and stereoselective hydroboration reactions of unsymmetrical internal alkynes. These reactions exhibited unusual regioselectivity: specifically, reactions of aryl alkyl internal alkynes showed excellent *cis*-β-addition selectivity, and reactions of dialkyl internal alkynes gave excellent *cis*-α-addition selectivity. Highly regioselective hydroboration of unsymmetrical dialkyl internal alkynes cannot be achieved by other known methods. The reactions described herein are highly synthetically useful, particularly for the stereoselective synthesis of trisubstituted alkenylborates and alkenes. Mechanistic studies indicate that a Co(I)-H species is a plausible active catalyst and the rigid structure of the cyclopropane skeleton of the ligands and the crowded reaction pocket were responsible for the unprecedented regioselectivity.

Introduction

Organoboron compounds are widely used in organic synthesis, medicinal chemistry, and materials science.[1] In particular, alkenylboron compounds are important synthetic building blocks for Suzuki coupling,[2] Chan–Lam coupling,[3] and Petasis reactions,[4] among others; and such reactions can be used to realize stereoretentive transformation of C–B bonds to C–C and C–X (X = N, O, S, Cl, Br, I, etc.) bonds. Traditional methods for preparing alkenylborates include boration of alkenyl metallic reagents[5] and Pd-catalyzed Miyaura boration reactions of halides and pseudohalides.[6] These two methods have some drawbacks in that the structural diversity of the substrates is limited or they require prefunctionalized starting materials. Therefore, the development of new, efficient methods for the preparation of alkenylboron compounds is important.

One such method is alkyne hydroboration, which uses readily available starting materials and proceeds under mild, tunable reaction conditions.[7] Hydroboration of internal alkynes, combined with subsequent transformations of the C–B bond of the products, is an important method for synthesizing trisubstituted alkenes with defined configurations. However, compared with terminal alkynes, internal alkynes are more sterically hindered and thus generally less reactive; and their hydroboration reactions tend to be less chemoselective and to give only moderate yields.[8] Owing to isomerization and other related processes, hydroboration of internal alkynes can also exhibit unsatisfactory stereoselectivity, giving mixtures of *cis*- and *trans*-addition products (Scheme 1a).[9]

In addition, for unsymmetrical internal alkynes, regioselective catalytic hydroboration (α addition vs β addition, Scheme 1a) is a significant challenge (Scheme 1b).[7b] Depending on the type of substrate, *cis*-α-addition reactions of aryl alkyl internal alkynes (in which the B and H atoms add to the same side of the triple bond and the B adds to the aryl end) can be achieved with Cu catalysts bearing diphosphine or *N*-heterocyclic carbene ligands.[10] However, *cis*-β-addition reactions of aryl alkyl internal alkynes (in which B and H add to the same side of the triple bond and B adds to the alkyl end) have not been thoroughly explored. *cis*-β-Hydroboration has been achieved with the uncommon hydroboration reagent HBdan (1,8-diaminonaphthalatoborane)[11] and with Lewis acid catalysts, but the latter method requires alkynes with certain characteristics.[12] *cis*-β-Addition reactions of aryl alkyl internal alkynes can be realized by means of Cu-catalyzed protoboration,[10a,10b,13] but the need to use diboron reagents and proton sources reduces the atom economy of the reaction. Selective hydroboration reactions of unsymmetrical dialkyl internal alkynes depend mainly on substrate characteristics (e.g., steric bulk or the presence of a directing group). There have been sporadic reports of *cis*-β-addition reactions of dialkyl internal alkynes (in which B and H add to the same side of the triple bond and B adds to the end bearing the smaller alkyl group), but the regioselectivity of these reactions depends on the difference in steric bulk between the alkyl substituents.[14] Currently, there is no general way to access the products of *cis*-α-addition to dialkyl internal alkynes (in which B and H add to the same side of the triple bond and B adds to the end bearing the larger alkyl group). Only one example of such a reaction has been reported: Cu-catalyzed hydroboration of functionalized internal alkynes bearing O or N atoms in the propargylic position.[10a] It is worth mentioning that during the preparation of this manuscript, Breit reported[15] a method for Co-catalyzed hydroboration of alkynes, but for most of the unfunctionalized internal alkynes that were tested, the regioselectivity was only modest (regioisomeric ratios [rr] were generally 3:1), and the yields were unsatisfactory. Therefore, the development of new catalysts, and base metal catalysts in

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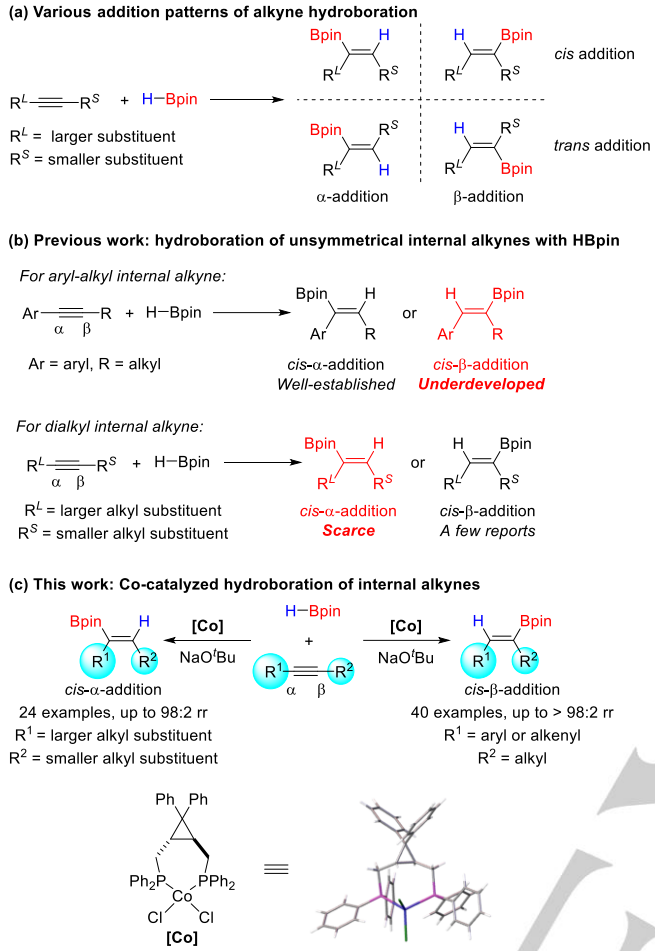
particular, for regioselective hydroboration of unsymmetrical internal alkynes would be of great value.



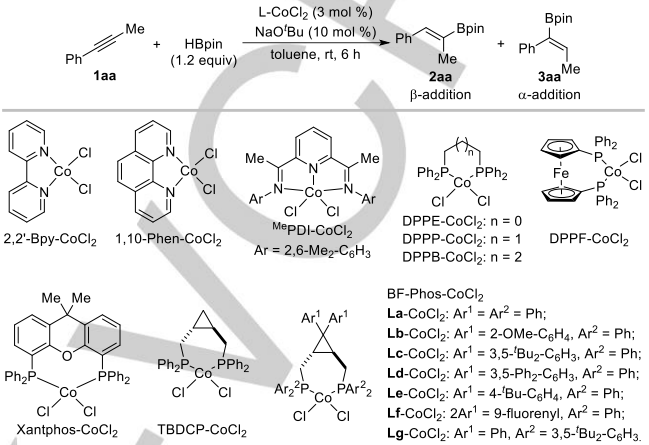
Scheme 1. Hydroboration of unsymmetrical internal alkynes.

As part of our continuing studies on base-metal-catalyzed reactions,[16] we have now developed a method for highly regioselective hydroboration of internal alkynes catalyzed by Co complexes bearing newly developed diphosphine ligands with a cyclopropane scaffold (Scheme 1c). When aryl alkyl internal alkynes were used as substrates, excellent *cis*-β-addition selectivity (up to >98:2 rr) was achieved; and with dialkyl internal alkynes substrates, unprecedented *cis*-α-addition selectivity (up to 97:3 rr) was realized. This new method allowed for efficient synthesis of alkenylborates, some of which cannot be prepared by known methods, and we were able to use the method to synthesize several functional compounds with greater efficiency than that achieved with literature methods. Detailed mechanistic studies clearly demonstrate the effects of the ligands on the Co catalyst and may inspire the development of new Co catalysts and Co-catalyzed reactions.

Results and Discussion

We initiated our study by using 1-phenyl-1-propyne (**1aa**) as a model substrate and commercially available HBpin as a hydroboration reagent, and we evaluated the effects of ligands, metal salts, activating reagents, and solvents on the yields and rr values (see Tables S3–S5 for details). Preliminary experiments showed that the ligand markedly influenced the yield and selectivity of this hydroboration reaction (Table 1). When a dinitrogen ligand such as 2,2'-bipyridine or 1,10-phenanthroline was used, the yield was poor (entries 1 and 2). In contrast, tridentate nitrogen ligand ^{Me}PDI gave an excellent yield but poor regioselectivity (entry 3).

Table 1. Co-catalyzed hydroboration of alkyne **1aa** with HBpin: evaluation of ligands.



Entry	L-$CoCl_2$	Conv. (%)	Yield (%)	rr (**2aa**/**3aa**)
1	2,2'-Bpy-$CoCl_2$	20	15	83:17
2	1,10-Phen-$CoCl_2$	63	23	82:18
3	^{Me}PDI-$CoCl_2$	98	97	67:33
4	$(PPh_3)_2$-$CoCl_2$	57	40	76:24
5	DPPE-$CoCl_2$	14	8	70:30
6	DPPP-$CoCl_2$	87	59	65:35
7	DPPB-$CoCl_2$	61	41	58:42
8	DPPF-$CoCl_2$	68	20	73:27
9	Xantphos-$CoCl_2$	>98	98	81:19
10	TBDCP-$CoCl_2$	>98	93	82:18
11	**La**-$CoCl_2$	>98	98	92:8
12	**Lb**-$CoCl_2$	>98	98	88:12
13	**Lc**-$CoCl_2$	>98	98	72:28
14	**Ld**-$CoCl_2$	>98	98	91:9
15	**Le**-$CoCl_2$	>98	98	91:9
16	**Lf**-$CoCl_2$	95	90	90:10
17	**Lg**-$CoCl_2$	76	64	93:7

[a] Reaction conditions: **1aa** (0.2 mmol), HBpin (0.24 mmol), L-$CoCl_2$ (3 mol %), NaO^{t}Bu (10 mol %), in toluene (1 mL) at rt for 6 h. The conversion, yield, and rr were determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

Systematic evaluation of phosphine ligands (entries 4–8) revealed that diphosphine ligands with large bite angles,[17] such as Xantphos (bite angle 112°) and TBDCP[18] (bite angle 108°), gave promising yields and selectivities (entries 9 and 10). Because of the unique electronic structure and rigidity of cyclopropane, changing a substituent on any one of the carbon atoms of the ring will affect the conformation of the substituents on the other two carbons, so we modified TBDCP by introducing various geminal diaryl moieties. Because single-crystal X-ray analysis revealed that the resulting ligands had a butterfly shape, we designated them as butterfly Phos (BF-Phos). These ligands were prepared by means of a simple, efficient route from commercially available benzophenone hydrazones. For example, air- and moisture-stable ligand **La** could be obtained on a scale of more than 15 g (59% overall yield) by means of the five-step

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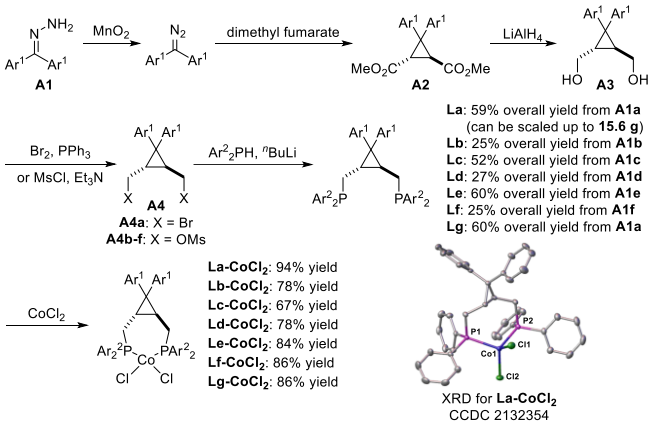
procedure shown in Scheme 2. Complexation of **La** with $CoCl_2$ yielded a blue powder, and single-crystal analysis[19] of the powder showed bidentate chelation between **La** and $CoCl_2$. The four atoms coordinated to the Co atom formed a distorted tetrahedron with a P–Co–P bite angle of 109°.

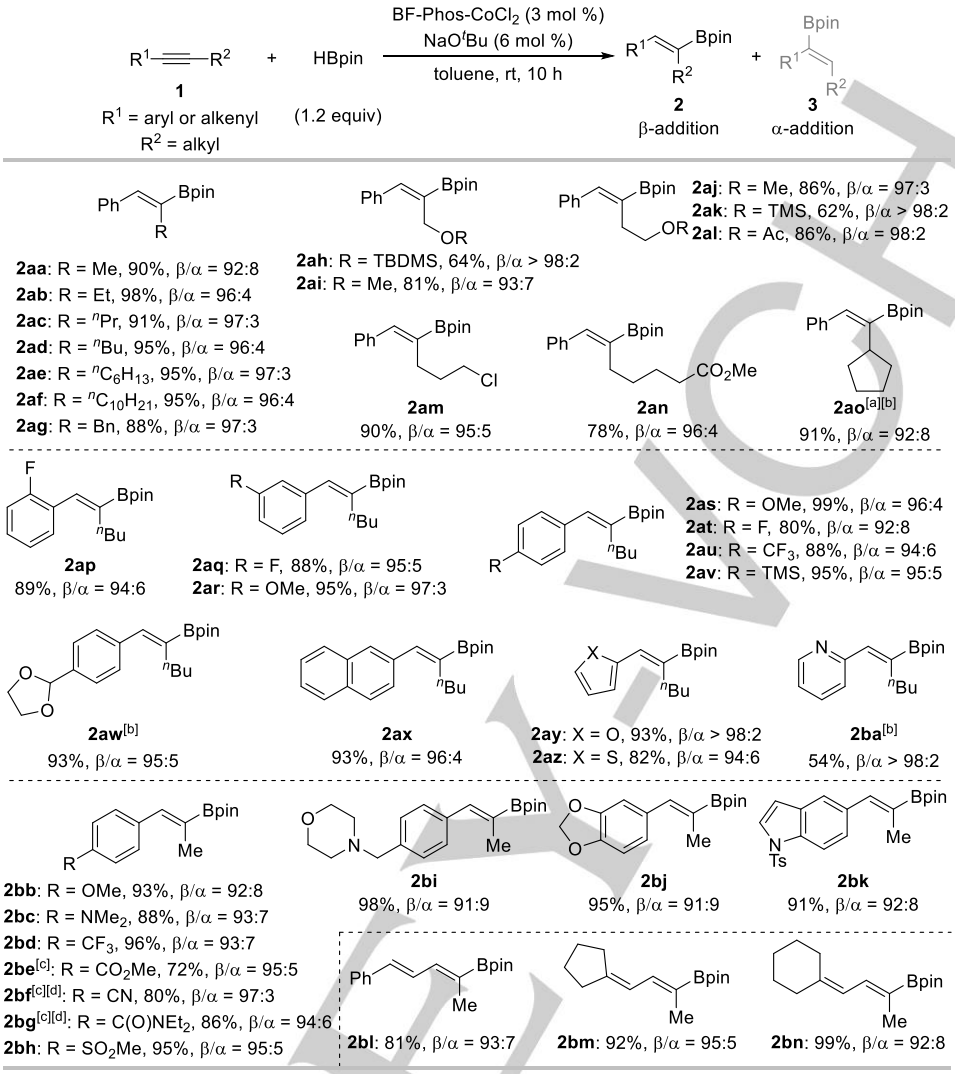


Scheme 2. Synthesis and molecular structure of BF-Phos-$CoCl_2$. Selected bond lengths [Å] and angles [°]: Co1-P1 2.3701(5), Co1-P2 2.3632(5), Co1-Cl1 2.2204(5), Co1-Cl2 2.2068(5); P1-Co1-P2 108.997(19), Cl1-Co1-Cl2 117.22(2). Hydrogen atoms and solvent, DCM were omitted for clarity.

When **La-**$CoCl_2$ was used in the hydroboration of **1aa**, the regioselectivity was indeed markedly better than that with TBDCP-$CoCl_2$ (92:8 rr vs 82:18 rr; Table 1, entries 11 and 10, respectively), which confirmed that introduction of the *gem*-diphenyl moiety changed the ligand properties. In an attempt to further improve the selectivity of the reaction, we synthesized BF-Phos ligands with various other *gem*-diaryl substituents on the cyclopropane skeleton (**Lb**–**Lf**). We observed that variation of the substituents did indeed affect the regioselectivity of the reaction (entries 12–16). When **Lc-**$CoCl_2$ was the catalyst, the selectivity dropped to 72:28 (entry 13), and none of the other tested catalysts showed better regioselectivity than that achieved with **La-**$CoCl_2$. We also evaluated how changing the phosphine substituents of the BF-Phos-$CoCl_2$ catalysts affected the regioselectivity. Specifically, when the phenyl groups on the phosphine were replaced with more sterically hindered 3,5-di-*tert*-butylphenyl groups (**Lg**), the regioselectivity increased to 93:7, but the yield dropped to 64% (entry 17). Control experiments showed that the ligand, metal, and activating reagent were all indispensable for this reaction; and changing the metal salt, the activating reagent, or the solvent did not further improve the reaction outcome (see Tables S3–S6 for details).

Under the optimized conditions (Table S6, entry 8), a wide range of aryl alkyl internal alkynes **1** underwent regio- and stereoselective hydroboration (Scheme 3). First, we evaluated the effect of the alkyl substituents on the reaction outcome. Substrates with linear alkyl substituents ranging from ethyl to *n*decyl smoothly afforded desired products **2ab**–**2af** in yields of >90% with >95:5 rr. Moreover, it is worth noting that the catalyst could distinguish between phenyl and benzyl groups, as indicated by the fact that β-addition product **2ag** was obtained with excellent regioselectivity (97:3 rr). The reaction was not affected by an ether group: a TBDMS-protected propargyl alcohol afforded β-addition product **2ah** with >98:2 rr, a result that contrasts sharply with the result obtained with the catalytic system reported in the literature.[20] Investigation of the influence of other functional groups revealed that an alkyl chain bearing a silyl ether, a chlorine atom, or an ester smoothly afforded corresponding hydroboration products **2ai**–**2an** in high yields with ≥95:5 rr. The reaction of a phenyl cyclopentyl internal alkyne (that is, an alkyne bearing a secondary alkyl substituent) also showed good regioselectivity (**2ao**, 92:8 rr) when the bulkier catalyst **Lg-**$CoCl_2$ was used. Next, we tested aryl *n*butyl and aryl methyl internal alkynes as substrates to investigate how substituents on the aryl ring affected the reaction outcome. The results of these experiments showed that neither the position of the substituent (*ortho*, *meta*, or *para* [**2ap**–**2at**], ≥92:8 rr) nor its electronic properties (**2as**–**2av**, ≥92:8 rr) markedly affected the reaction outcome. The hydroboration method was compatible with a number of functional groups, including ester (**2be**), cyano (**2bf**), amide (**2bg**), sulfonyl (**2bh**), and acetal (**2aw**). In terms of heterocyclic substituents, the reaction was compatible with morpholine (**2bi**), indole (**2bk**), furan (**2ay**), thiophene (**2az**), and pyridine (**2ba**). Moreover, conjugated enynes were suitable substrates: conjugated dienyl borates **2bl**–**2bn** were obtained in good yields with good regioselectivities. [21]

Next, we evaluated the performance of **La-**$CoCl_2$ in hydroboration reactions of dialkyl internal alkynes **4** (Scheme 4). Surprisingly, when a benzyl methyl alkyne was used as the substrate, the B atom selectively added to the end of the alkyne with the larger (benzyl) group to give **5a** (95:5 rr). Again, neither the position of a substituent on the phenyl ring (**5b**–**5e**, ≥92:8 rr) nor its electronic properties (**5e**–**5h**, ≥95:5 rr) had a marked effect on the yield or the selectivity. The configuration of **5i** was confirmed by single-crystal X-ray diffraction analysis.[19] Internal alkynes with a naphthyl group (**5j, 5k**) and a phenylpropyl group (**5l**) were suitable for this reaction. Encouragingly, even 2-pentyne afforded α-addition product **5m** with 91:9 rr, indicating that our catalyst could distinguish between ethyl and methyl groups. When one of the alkyl substituents on one end of the alkyne was fixed as methyl, the regioselectivity of the reaction was unaffected by the length of the alkyl chain on the other end (**5n–5r**, ≥91:9 rr). If the group at the other end of the alkyne was a more sterically hindered isopropyl or cyclohexyl group, the B atom still added to the end near the secondary carbon to afford **5s** and **5t**, respectively. Notably, the hydroboration could be scaled up to a gram scale at a Co catalyst loading of 1 mol % with no decrease in the yield (**5o**). To our knowledge, rr values of >10:1 have not previously been reported for any α-addition hydroboration reactions of simple alkyl methyl internal alkynes.[7] Moreover, the trisubstituted alkenylborates obtained through the hydroboration of dialkyl alkynes is difficult to synthesize by known methods.[22]



Scheme 3. Substrate scope of Co-catalyzed hydroboration of aryl-alkyl internal alkynes. Reaction conditions: **1** (0.5 mmol), HBpin (0.6 mmol, 1.2 equiv), **La**-$CoCl_2$ (3 mol %), and NaO^{t}Bu (6 mol %) in toluene (2 mL) were stirred at rt for 10 h. Isolated yields were given. The regioisomeric ratios (rr, β/α) were determined by ^{1}H NMR. [a] The reaction was performed at 0.2 mmol scale with **Lg**-$CoCl_2$ as catalyst. [b] Reaction time: 24 h. [c] Reaction time: 12 h. [d] Used 0.55 mmol HBpin (1.1 equiv).

Our catalyst could distinguish between a branched alkyl group and a linear alkyl (ethyl or ^{n}butyl) group, and thus the B atom could be selectively added to the more sterically hindered, branched alkyl end of the alkyne (**5u**, **5w**). In addition, the reaction was compatible with protected piperidine rings (**5v**, **5w**), which are found in many FDA-approved pharmaceuticals.[23] When a ^{n}pentyl alkyne with a propargyl ether was used as a substrate, the B atom selectively added to the end of the alkyne bearing the alkyl group (**5x**).

Hydroboration products of dialkyl internal alkynes have only rarely been reported in literature, so we evaluated the utility of these products by carrying out a series of transformations of alkenylborate **5i** (Scheme 5). After **5i** was synthesized on a gram scale (1.55 g, 93% yield, 98:2 rr) using 1 mol % Co catalyst, it could be used to prepare trisubstituted olefin **T1** with retained configuration by means of Pd-catalyzed Suzuki coupling. Conjugated dienyl ester **T2** could be prepared by oxidative Heck coupling of **5i** and ethyl acrylate with no isomerization of the double bond. *γ*,*δ*-Unsaturated ketone **T3** was synthesized by a Rh-catalyzed conjugate addition reaction between **5i** and methyl vinyl ketone. By means of a homologation–oxidation reaction, **5i** could be converted to allyl alcohol **T4** with complete stereoretention. Ketone **T5** was obtained in high yield by the oxidation of **5i**.

Trisubstituted alkenyl halides with defined configurations have important applications in organic synthesis, but they are difficult to prepare.[24] At present, the main route involves hydrometallation (Zr, Al, Mg, Zn)–halogenation of internal alkynes, but the regioselectivity of the addition reactions of simple dialkyl internal alkynes is difficult to control.[25] In contrast, **5i** could be used to synthesize trisubstituted alkenyl halides **T6–T8** with defined configurations. Furthermore, **5i** underwent $CuSO_4$-mediated transformation to trisubstituted alkenyl azide **T9** with stereoretention, which is difficult to accomplish by other methods.[26] In summary, the C–B bond of **5i** could be converted to C–C or C–X bonds (X = N, O, Cl, Br, I) in a stereoretentive manner, demonstrating the potential applications of our hydroboration method.

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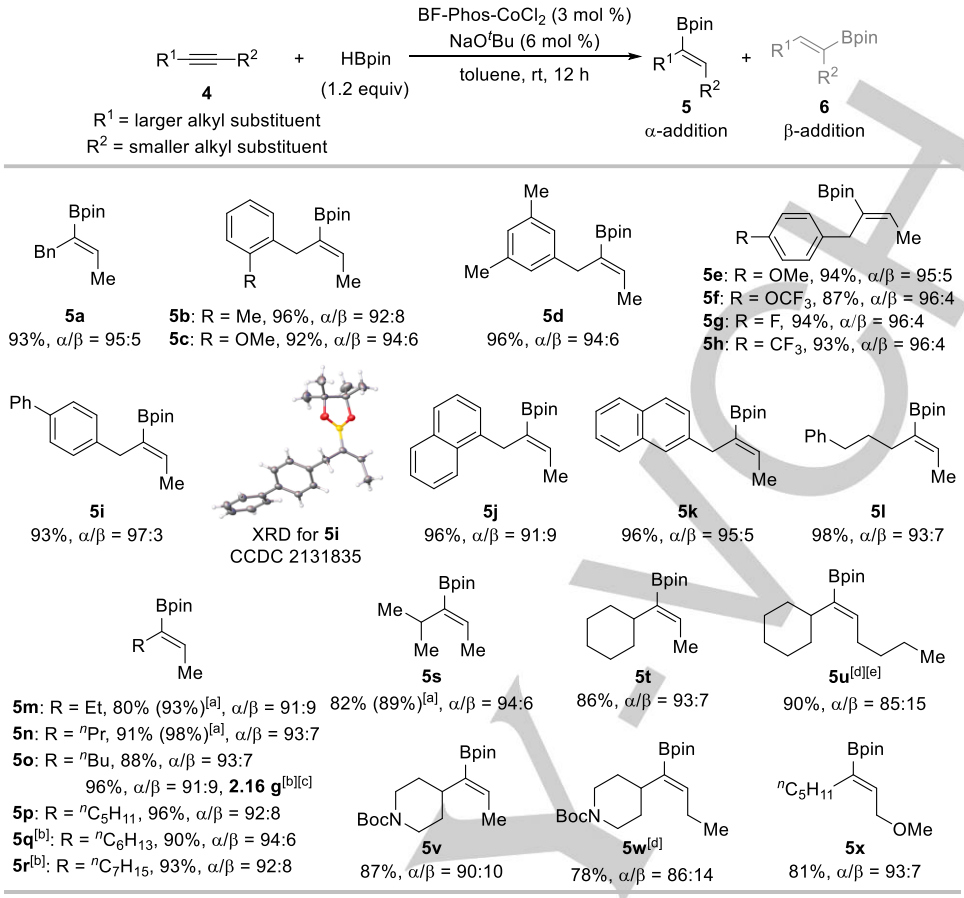
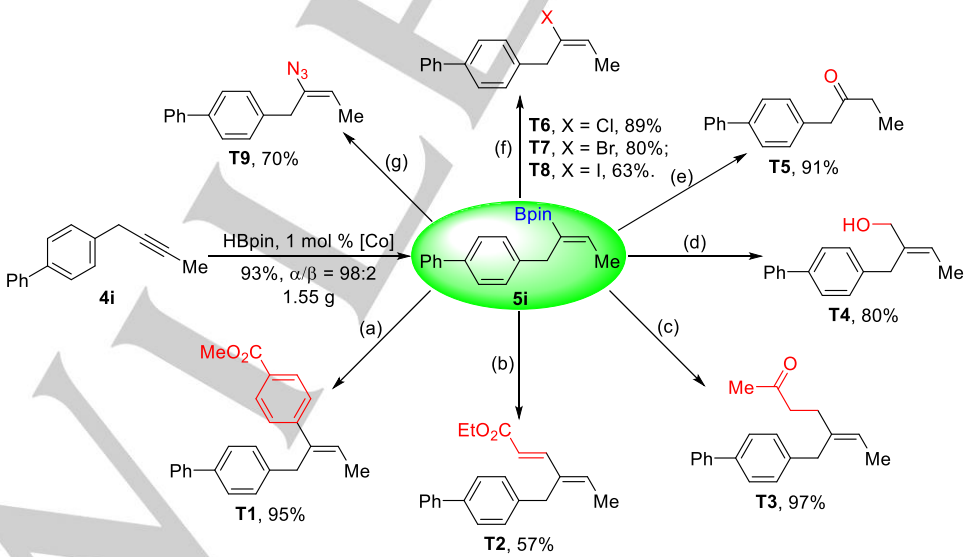


Scheme 4. Substrate scope of Co-catalyzed hydroboration of dialkyl internal alkynes. Reaction conditions: **4** (0.5 mmol), HBpin (0.6 mmol, 1.2 equiv), **La**-$CoCl_2$ (3 mol %), and NaO^tBu (6 mol %) in toluene (2 mL) were stirred at rt for 12 h. Isolated yields were given. The regioisomeric ratios (rr, α/β) were determined by ^1H NMR. [a] Yields determined by ^1H NMR using CH_2Br_2 as an internal standard were given in parentheses. [b] Used 1 mol % BF-Phos-$CoCl_2$ and 2 mol % NaO^tBu. [c] Used 10 mmol **4o**. [d] Reaction time: 24 h. [e] Used 0.4 mmol **4u**.



Scheme 5. Gram-scale synthesis and transformations of dialkyl alkenylborate **5i**. Reaction conditions: (a) methyl 4-bromobenzoate, $Pd(PPh_3)_4$, Cs_2CO_3, THF, 65 ˚C, 12 h; (b) ethyl acrylate, $Pd(OAc)_2$, 1,10-phenanthroline, O_2 balloon, *N*,*N*-dimethylacetamide, 80 ˚C, 12 h; (c) methyl vinyl ketone, $[Rh(COD)Cl]_2$, K_3PO_4, 1,4-dioxane/H_2O, 80 ˚C, 12 h; (d) ICH_2Cl, ^{n}BuLi, THF, -78 ˚C to rt, 10 h; then NaOH (aq., 2M), 30% H_2O_2, 0 ˚C, 2 h; (e) NaOH (aq., 2M), 30% H_2O_2, THF, 0 ˚C, 3 h; (f) for chlorination: $CuCl_2$, THF/MeOH/H_2O, 100 ˚C, 36 h; for bromination: $CuBr_2$, EtOH/H_2O, 100 ˚C, 24 h; for iodination: KI, CuI, 1,10-phenanthroline, MeOH/H_2O, 80 ˚C, 12 h; (g) NaN_3, $CuSO_4$, MeOH, 50 ˚C, 20 h.

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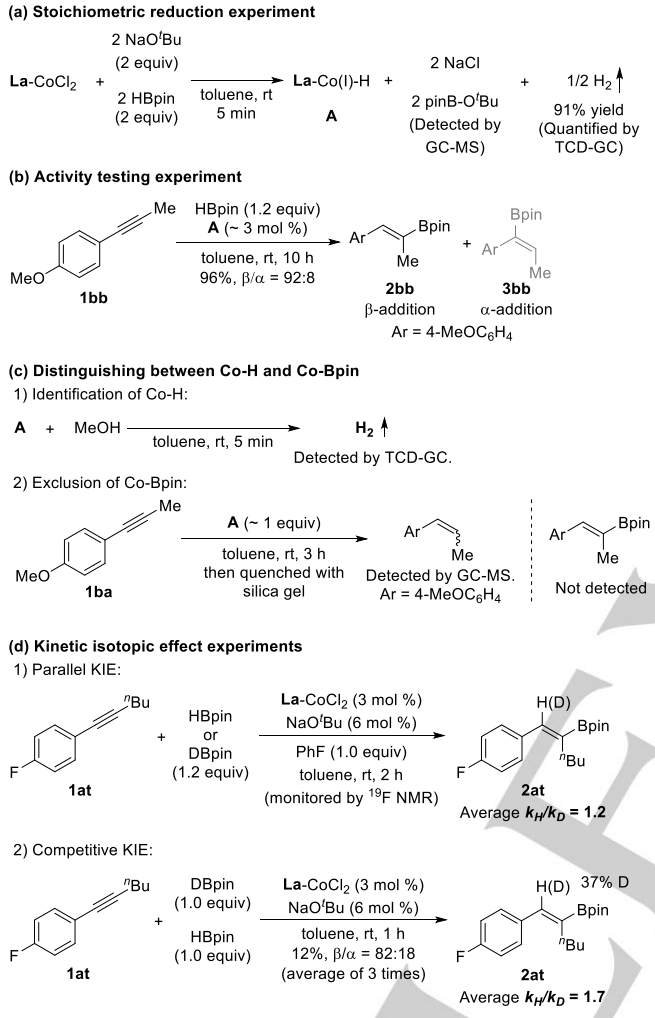
Next, we explored the synthetic applications of our method for Co-catalyzed hydroboration of internal alkynes (Scheme S4). Studies show that several biologically active compounds (temarotene, arotinoid acid, etc.) and key intermediates in the synthesis of natural products (carbazole alkaloids) could be prepared by our protocol. Compared with the reported methods, our protocol has remarkable advantages in overall yields and selectivities.



Scheme 6. Mechanistic studies.

To elucidate the possible reaction mechanism, we conducted a set of control experiments. The addition of a radical scavenger, such as BHT or 1,1-diphenylethylene, had no effect on the hydroboration reaction, and the added scavengers were completely recovered (see Table S8 for details). These results rule out a radical process. We observed that after **La-**$CoCl_2$, NaO^tBu, and HBpin were mixed, bubbles were generated. Qualitative analysis and a stoichiometric experiment (Scheme 6a) showed that hydrogen gas was produced in 91% yield. Analysis of the other components of the reaction mixture revealed the presence of pinB-O^tBu (see the SI for details). ^1H NMR spectrum of the isolated active catalyst **A** exhibited a set of peaks at around -18 ppm, which may refer to the hydride in **A** (see the SI for details).[15,27] Balancing the reaction equation on the basis of the above-described results suggests that the active catalyst (**A**) was a Co(I)-H species. Hydroboration of **1bb** catalyzed by **A** proceeded smoothly and gave results similar to those obtained under the standard conditions (Scheme 6b). Several control experiments were conducted to further discriminate **A** from a Co-H species to a Co-Bpin species. When methanol (a proton source) was added to **A**, hydrogen evolution was detected (Scheme 6c1), indicating that hydride might be present in **A** (which would be consistent with Co-H). When **1bb** was mixed with a stoichiometric amount of **A** and the reaction was subsequently quenched with silica gel, the corresponding alkene was generated, but no alkenylborate was detected (Scheme 6c2), suggesting that **A** was not a Co-Bpin species. Alkene production may have occurred as follows: insertion of the alkyne into Co-H would give an alkenyl Co intermediate, which would subsequently undergo protonolysis. To study the relative rate of the hydride transfer step, we conducted two kinetic isotope effect experiments. The parallel k_H/k_D was 1.2 (Scheme 6d1), and the competitive k_H/k_D was 1.7 (Scheme 6d2). The relatively small kinetic isotope effects (1.2 and 1.7) indicate that hydride transfer may not have been involved in the rate-determining step.

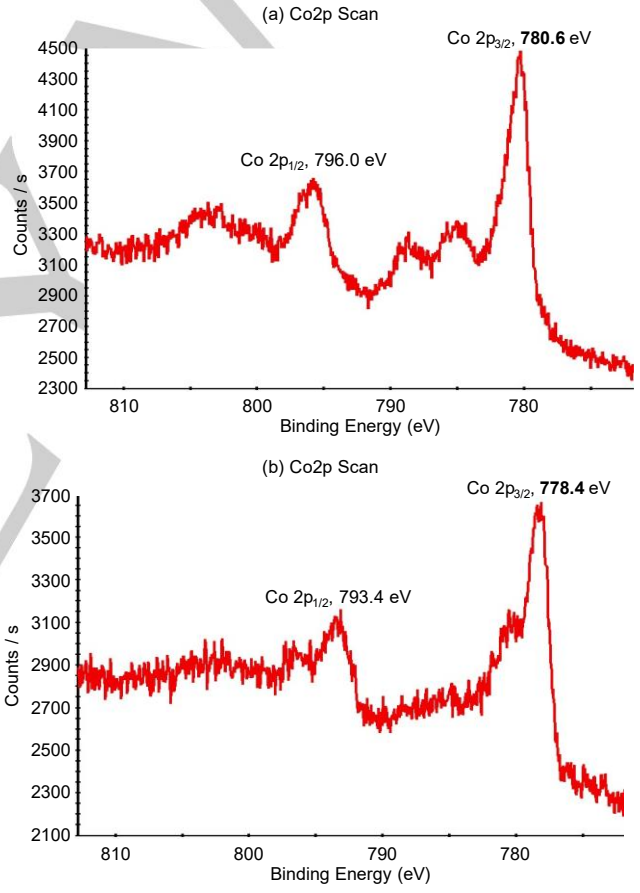
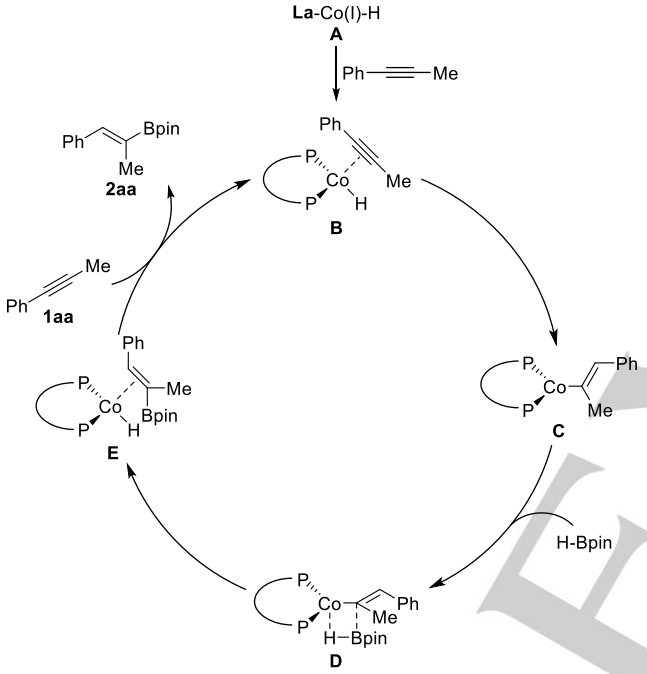


Figure 1. X-ray photoelectron spectroscopy of cobalt catalysts. (a) XPS of **La-**$CoCl_2$; (b) XPS of **A**.

To shed light on the oxidation state of the Co species in active catalyst **A**, we analyzed Co 2p by means of core-level X-ray photoelectron spectroscopy, and the spectra were fitted with spin-orbital split $2p_{1/2}$ and $2p_{3/2}$ components (Figure 1). The analysis showed that the electron binding energies of Co $2p_{1/2}$ and $2p_{3/2}$ in **La-**$CoCl_2$ were 796.0 and 780.6 eV, respectively, and that the corresponding energies of Co $2p_{1/2}$ and $2p_{3/2}$ in **A** were 793.4 and 778.4 eV. The fact that the latter energies are lower than the former indicates that the oxidation state of the Co in **A** was less than +2 (that is, either +1 or 0). Further analysis showed that the

electron binding energy (778.4 eV) of Co $2p_{3/2}$ in **A** was very close to the corresponding electron binding energy (778.3 eV) in a Co(I)-P complex reported in the literature,[28] suggesting that the oxidation state of Co in **A** was +1. On the basis of these results, we deduced that the active catalyst for this Co-catalyzed hydroboration reaction was most likely a Co(I)-H species (in monomer or dimer form).

On the basis of the control experiments and previous reports,[8c,27] a plausible catalytic cycle is proposed in Scheme 7. First, Co(I)-H species **A** is generated by combined interactions between **La**-$CoCl_2$, NaO^{t}Bu, and HBpin. Coordination of the alkyne with **A** followed by insertion of the alkyne into the Co-H bond delivers alkenyl Co intermediate **C**. Then, a σ-bond metathesis reaction between **C** and HBpin gives intermediate **E**. Finally, ligand exchange between alkenylborate and alkyne affords desired product and regenerates intermediate **B**, completing the catalytic cycle.



Scheme 7. Proposed catalytic cycle.

To clarify the origin of the regioselectivity, we performed density functional theory calculations of pathways for the reactions of 1-phenyl-1-propyne (**1aa**, an aryl alkyl internal alkyne) and 1-phenyl-2-butyne (**4a**, a dialkyl internal alkyne) as model substrates (Scheme 8a). We performed the calculations by means of the ωB97XD/def2-TZVPP//ωB97XD/6-31G*/TZVP method in toluene solution (using the SMD model) with the Gaussian 09 program package (see the SI for details). The computational results showed that migratory insertion of the alkyne into the Co-H bond is the turnover-limiting step that determines the regioselectivity of the reaction (see Figure S3 for computed whole catalytic cycle). For 1-phenyl-1-propyne (**1aa**), the energy barrier to the insertion step is 3.3 kcal/mol. The activation barrier of the transition state (via **^{3}ts1a'**) that gives the *cis*-α-addition product is 2.5 kcal/mol higher than that of the transition state (via **^{3}ts1a**) that delivers the *cis*-β-addition product, and this difference is consistent with the experimental finding of good *cis*-β-addition selectivity (β/α = 92:8). For 1-phenyl-2-butyne (**4a**), the activation barrier to the insertion step for *cis*-α-addition is 4.9 kcal/mol, which is 3.1 kcal/mol lower than the activation barrier to the insertion step for *cis*-β-addition (via **^{3}ts1c'**). This difference is also in accordance with the experimental finding of high *cis*-α-addition selectivity (α/β = 95:5).

To gain more insight into the origin of the differences of the energy between the transition states, we conducted independent gradient model (IGM)[29] analysis (Scheme 9b) of the two transition states (**^{3}ts1** and **^{3}ts1'**). The results showed that, for 1-phenyl-1-propyne (**1aa**), the two phenyl rings on the ligand are more stacked in **^{3}ts1a** than in **^{3}ts1a'**, and the corresponding centroid distance was 3.75 Å, which indicates a stronger π–π interaction between these two phenyl groups. In addition, the angle between the hydride H^1 and C^2C^3 of the alkyne ($\angle H^1C^2C^3$) in **^{3}ts1a** is 120.4°, which is closer to 120.0° than $\angle H^1C^2C^3$ in **^{3}ts1a'** (120.6°). This angle is in accordance with the Bürgi–Dunitz angle, that is, the optimal angle for attack of a nucleophile on an sp-hybridized carbon electrophilic center (120.0°).[30] For 1-phenyl-2-butyne (**4a**), there are π–π interactions both in **^{3}ts1c** and **^{3}ts1c'**, but the C–H···π interactions in **^{3}ts1c** further lower the energy of the transition state. Moreover, the value of $\angle H^1C^2C^3$ in **^{3}ts1c** (119.7°) is also closer to 120.0° than is the value of $\angle H^1C^2C^3$ in **^{3}ts1c'** (120.8°). In addition, we found that the dihedral angle between the H^1–C^2–C^3 and Co–C^2–C^3 planes profoundly affects the energy of the transition state. The smaller the dihedral angle is, the larger the overlap of the *s* orbital of H^1 and the antibonding orbital of C^2–C^3 is; and the larger overlap is beneficial for hydride transfer from Co to the alkyne.

To quantify the energy difference between **^{3}ts1** and **^{3}ts1'**, we performed distortion/interaction analysis on the two transition states (Figure S6). Activation energy, $\Delta E^{\ddagger}$, can be written as ΔE_{dis} + ΔE_{int}, where distortion energy ΔE_{dis} is the energy difference that arises from structural changes leading to transition state formation, and interaction energy ΔE_{int} corresponds to the energy difference between the distorted catalyst plus the alkyne and the Co complex in the transition state. This analysis showed that ΔE_{dis} of **^{3}ts1a** is 4.8 kcal/mol higher than ΔE_{dis} of **^{3}ts1a'** owing to structural changes. However, because of the interactions between the ligands around Co, ΔE_{int} of **^{3}ts1a** is 6.4 kcal/mol lower than ΔE_{int} of **^{3}ts1a'** (see Figure S6 for details). Thus, the difference in energy between **^{3}ts1a** and **^{3}ts1a'** derives mainly from interaction energy ΔE_{int}. Similarly, we can draw the same conclusion for **^{3}ts1c** and **^{3}ts1c'** (see Figure S6 for more details), which is also consistent with the analysis results of IGM, bond angle and dihedral angle. In essence, we contend that the origin of the selectivity depends on the structure and properties of the catalyst. As a first-row transition metal, Co has a relatively small atomic radius and a unique open-shell structure. As the smallest carbocycle, cyclopropane has a rigid structure, and its properties are strongly affected by the substituents on the ring. The Co catalyst and the cyclopropane-based diphosphine ligand form a crowded reaction pocket, which can detect slight differences between the substituents at the two ends of the alkyne substrates, which in turn leads to the excellent regioselectivity.

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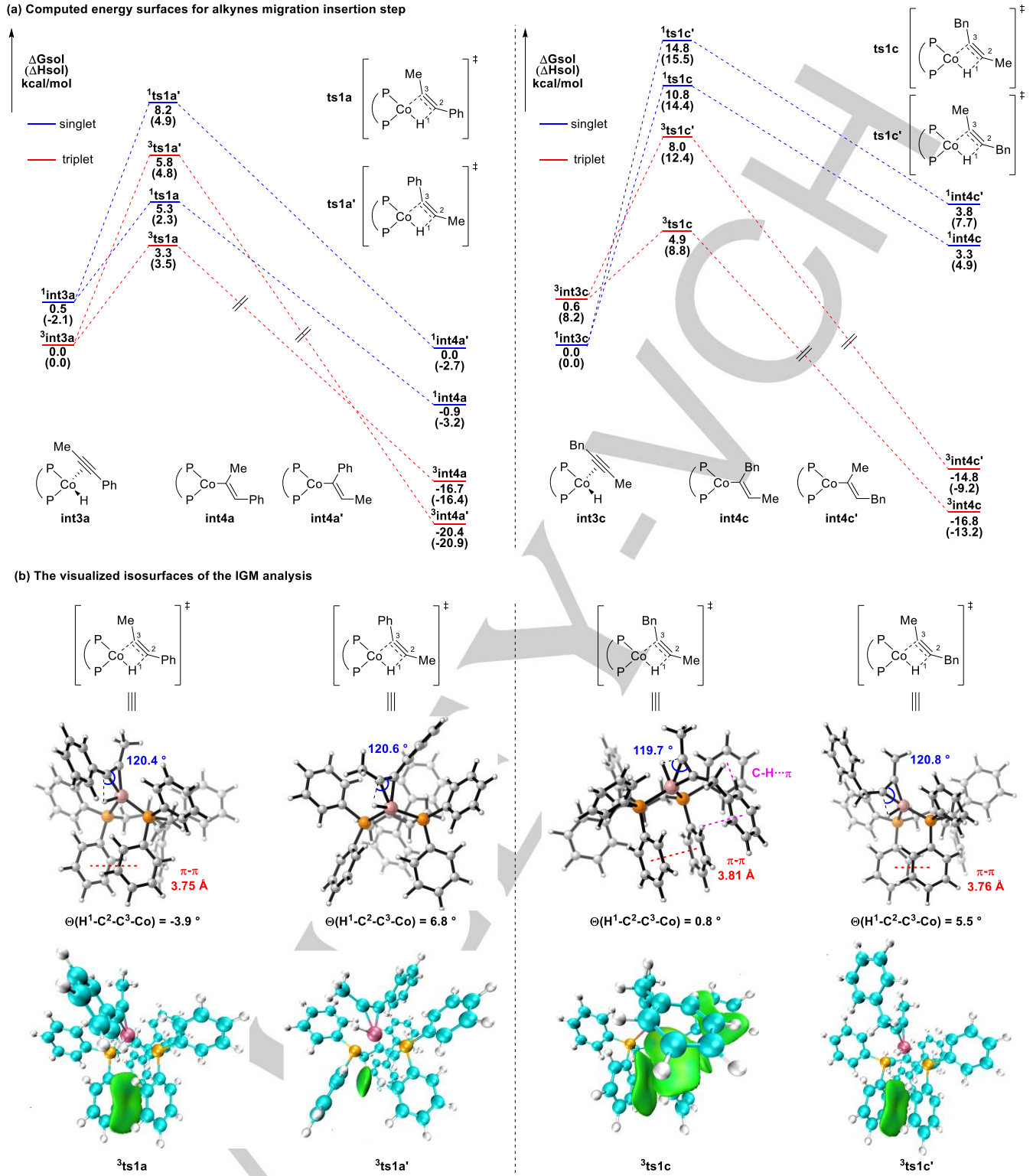

Scheme 8. DFT calculations.

Conclusion

In conclusion, we have developed novel Co catalysts bearing diphosphine ligands with a cyclopropane scaffold, and we used these catalysts to achieve highly chemo-, regio-, and stereoselective hydroboration of unsymmetrical internal alkynes. The catalysts showed excellent *cis*-β-addition selectivity in hydroboration reactions of aryl alkyl internal alkynes and unprecedented high *cis*-α-addition selectivity in reactions of unsymmetrical dialkyl alkynes. These operationally simple reactions had a wide substrate scope and were compatible with various functional groups (e.g., ester, cyano, amide, sulfonyl) and

heterocycles (e.g., furan, thiophene, indole, pyridine). The C–B bonds of the alkenylborate products could be easily transformed into C–C and C–X (X = N, O, Cl, Br, I) bonds with stereoretention. Reactions mediated by these catalysts were used for the synthesis of bioactive molecules and natural product intermediates with better efficiency than the literature methods. Mechanistic studies suggested that a Co(I)-H active catalyst bearing *gem*-diaryl-substituted cyclopropane diphosphine ligands was able to detect slight differences between the substituents at the ends of the triple bonds of the alkynes, thereby ensuring the unique regioselectivity. The development of these new diphosphine ligands with a cyclopropane scaffold and their use with Co catalysts has expanded the scope and deepened our understanding of Co catalysis, in addition to providing a new, efficient protocol for the preparation of trisubstituted alkenylborates, as well as alkenes.

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Keywords: hydroboration • internal alkynes • cobalt catalysis • diphosphine ligands • alkenylborates

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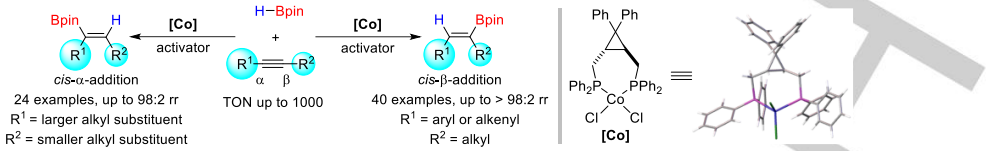

A highly selective hydroboration of unsymmetrical internal alkynes featuring with unique regioselecitivty, broad substrate scope and good functional group compatibility was realized by using cobalt catalysts modified with newly developed cyclopropane-based diphosphine ligands. The current protocol enabled the synthesis of novel alkenyl borates and improved the synthetic efficiency of bioactive compounds.