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A New Paradigm in Enantioselective Cobalt Catalysis: Cationic Cobalt(I) Catalysts for Heterodimerization, Cycloaddition and Hydrofunctionalization Reactions of Olefins

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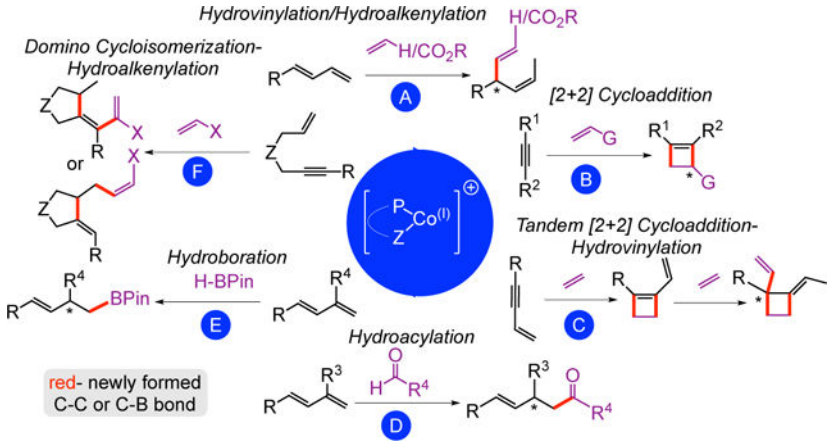

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One of the major challenges facing organic synthesis in the 21st century is the utilization of abundantly available feedstock chemicals for fine chemical synthesis. Regio- and enantioselective union of easily accessible 1,3-dienes and other feedstocks like ethylene, alkyl acrylates and aldehydes can provide valuable building blocks adorned with latent functionalities for further synthetic elaboration. Through an approach that relies on mechanistic insights and systematic examination of ligand and counter ion effects, we developed an efficient cobalt-based catalytic system [(**P~P**)CoX_2/Me_3Al] to effect the first enantioselective heterodimerization of several types of 1,3-dienes with ethylene. In addition to simple cyclic and acyclic dienes, siloxy-1,3-dienes participate in this reaction, giving highly functionalized, nearly enantiopure silyl enolates which can be used for subsequent C-C and C-X bond-forming reactions. As our understanding of the mechanism of this reaction improved, our attention was drawn to more challenging partners like alkyl acrylates (one of the largest volume feedstocks) as the olefin partners instead of ethylene. Prompted by the intrinsic limitations of using aluminum alkyls as the activators for this reaction, we explored the fundamental chemistry of the lesser known (**P~P**)$Co^{(I)}X$ species and discovered that in the presence of halide sequestering agents such as NaBARF or $(C_6F_5)_3B$, certain chiral bisphosphine complexes are superb catalysts for regio- and enantioselective heterodimerization of 1,3-dienes and alkyl acrylates (**A**). We have since found that these cationic Co(I)-catalysts, most conveniently prepared in situ by reduction of the corresponding cobalt (II) halide complexes by zinc in the presence of NaBARF, promote enantioselective [2+2]-cycloaddition between alkynes and an astonishing variety of alkenyl derivatives to give highly functionalized cyclobutenes (**B**). In reactions between 1,3-enynes and ethylene, the [2+2]-cycloaddition between the alkyne and ethylene is followed by a 1,4-addition of ethylene in a tandem fashion to give nearly enantiopure cyclobutanes with an all-carbon quaternary center, giving a set of molecules that maps well into many medicinally relevant compounds (**C**). In another application, we find that the cationic Co(I)-catalysts promote highly selective hydroacylation (**D**) and 1,2-hydroboration (**E**) of prochiral 1,3-dienes. Further, we find that a cationic Co(I)-catalyst promotes cycloisomerization followed by hydroalkenylation of 1,6-enynes to produce highly functionalized carbo- and heterocyclic compounds (**F**). Surprisingly the regioselectivity of the alkene addition depends on whether it is a simple alkene or an acrylate, and, the acrylate addition produces an uncommon *Z*-adduct. This Account will provide a summary of the enabling basic discoveries and the attendant developments that led to the unique cationic Co(I)-complexes as catalysts for disparate C-C and C-B-bond-forming reactions. It is our hope that this account will stimulate further work with these highly versatile catalysts, derived from an earth-abundant metal.

INTRODUCTION

One of the major challenges facing organic synthesis in the 21st century is how to use abundantly available, sustainable feedstocks for fine chemical synthesis. Finding solutions to the dual challenges of activation of thermodynamically stable precursors and their selective reactions with other molecules will have broader implications in catalysis, and, at a practical level, how we synthesize/manufacture chemical intermediates of interest from medicine to materials. Ideally such processes could be environmentally friendly if operated under ambient conditions, use efficient catalysts derived from earth abundant metals, and the reactions involved are optimized for high selectivity in which only the desired product is formed, avoiding costly separation/purification steps. With

these goals in mind, we discovered highly regio- and enantioselective cobalt-catalyzed hydrovinylation 1,3-dienes.[1] As the limitations of the original protocol for this reaction [(**P**~**P**)CoX_2/Me_3Al] became apparent when we switched to methyl acrylate instead of ethylene as a reaction partner for the diene, we recognized that cationic Co(I) species, [(**P**~**Z**)Co]$^+$ [X]$^-$ [(**P**~**Z**) = bisphosphine or phosphinooxazoline ligands] are excellent catalysts for such codimerizations.[2] These complexes have since been found to be equally good catalysts for synthesis of cyclobutenes via enantioselective [2+2]-cycloadditions of alkynes and alkenyl derivatives.[3] Further, these complexes are also applicable for other regio- and enantioselective hydrofunctionalization reactions such as hydroacylations[4] and hydroborations.[5] Most gratifyingly, we find that the cationic cobalt(I) catalysts with appropriate ligands enable tandem reactions of enynes such as cycloaddition-hydrovinylation[6] and cycloisomerization-hydroalkenylation.[7] The cobalt catalysis was originally developed to address the substrate limitations of our hugely successful nickel-catalyzed hydrovinylation of vinylarenes,[8] This Account, which starts with a brief introduction to the nickel chemistry, will chronicle our efforts in the cobalt catalysis area over the past decade. It will cover research published until July 2021.

NICKEL-CATALYZED ASYMMETRIC HYDROVINYLATION

Encouraged by the astonishingly high turnover frequency (>625,000 [propene][Ni]$^{-1}$[h]$^{-1}$) observed for (allyl)Ni(phosphine)X catalysts in the homodimerization of propene (Figure 1 A), which forms the basis of the Dimersol Technology,[9] we made a substantial research investment in developing an enantioselective version of a related heterodimerization between ethylene and other alkenes (hydrovinylation, HV for short), targeting the chiral products. Even though a nickel-catalyzed enantioselective HV of a 1,3-diene(1,3-cyclooctadiene) was one of the first metal-catalyzed asymmetric carbon-carbon bond-forming reactions ever reported (Figure 1 B),[10] until our work,[11] the scope, yield and selectivity for this reaction had remained relatively modest.[12] Our early efforts resulted in the discovery of highly efficient, regio- and enantioselective HV of vinylarenes, strained alkenes and a limited number of configurationally stable *s-cis*-1,3-dienes (Figure 1 C).[8b] Conspicuously absent among the substrates that underwent successful enantioselective HV were linear 1,3-dienes, a large class of readily available substrates which gave unacceptable mixtures of various heterodimerization products (Figure 1 D). Suspecting a facile *s-cis/s-trans*-isomerization that is prevalent in 1,3-dienes to be one source of this poor selectivity, we began to explore the fundamental preparative and catalytic chemistry of the relatively obscure (2008) low-valent Co(I) complexes, which were known to readily form η^4-complexes with dienes[13] even in a high-coordination environment unlike nickel.[14] We reasoned that cobalt might lead to better selectivities in reactions of dienes by reducing the number of possible intermediates in the catalytic cycle (Figure 1 E, see later, Figure 2 B for full details of a possible mechanism). These expectations have been borne out and the explorations that followed have evolved over the past few years as we recognized the unique role of Co(I)-complexes, especially the cationic complexes, in catalyzing not only heterodimerization reactions, but also cycloaddition and hydrofunctionalization reactions of alkenes and alkynes.[15]

COBALT-CATALYZED HETERODIMERIZATION REACTIONS OF 1,3-DIENES

Hydrovinylation of 1,3-dienes—Regio- and enantioselective union of easily accessible 1,3-dienes and other feedstocks like ethylene, alkyl acrylates and aldehydes can provide valuable building blocks adorned with latent functionalities for further synthetic elaboration.[16] Unlike reactions of simple alkenes, reactions of prochiral dienes present additional challenges since a multitude of primary products can be formed even for the simplest of these compounds such as a monosubstitued (*E*)-1,3-diene (Figure 2 A, **1**: $R^1 = R^2 = R^3 = H$; R^4 = alkyl). Thus, in a generic hydrofunctionalization reaction, formation of 1,2/2,1-, 1,4/4,1-, and 3,4/4,3- adducts in addition to geometrical isomers of the residual double bonds in some of the products are possible. Based on several anecdotal observations in the literature,[17] we reasoned that in a catalytic cycle for the reactions of dienes (Figure 2 B), a putative $[\mathbf{L}Co^{(II)}\text{-}H]^+$ species, **2**, may have distinct advantages over the corresponding $[\mathbf{L}Ni^{(II)}\text{-}H]^+$ species, which we had postulated as an intermediate in the HV of vinylarenes.[18] Cobalt is able to coordinate to the diene in an η^4-fashion while also coordinated to chelating ligands (**3**) for better stereochemical control in any coupling reactions. It was known that the Ni-catalyzed HV reaction was inhibited by strongly chelating ligands.[11b] Migratory insertion in **3** would initially give a *syn-anti*-η^3-complex **4** which is poised for insertion of ethylene followed by β-hydride elimination to give the 2,1- or 4,1-HV adducts **5** and **6** respectively. Other geometrical isomers could arise by the π-σ-π-rearrangement of the initially formed η^3-s*yn-anti*-complex **4**. The requisite cobalt hydride would come from treatment of the (**L**)CoX_2 complex with various aluminum alkyls, as postulated in the [pyridine-diimine]Co-catalyzed oligomerization of α-olefins.[17b,19]Accordingly, we initially examined co-dimerization of ethylene in the presence of isolated (**L**)CoX_2 complexes [L = $Ph_2P(CH_2)_nPPh_2$, n = 1–4, X = Cl, Br] and various aluminum alkyl promoters. It was found that 1,4-*bis*-diphenylphosphinobutane (DPPB) with Me_3Al as the promoter (Co:Al = 1:3) yielded the best selectivity for a HV reaction, giving the 4,1-adduct as the major product.[20] Depending on the bis-phosphine and the reaction temperature, various ratios of 2,1- and 4,1-adducts were obtained (Table 1). It should be noted that this catalyst system is different from the linear co-dimerization of a 1,3-diene and a 1-alkene [(**L**)CoX_2/Zn/ZnI_2) originally reported by Hilt[21] and the enantioselective HV of vinylarenes [(**L**)CoX_2/Et_2AlCl/ethylene (30 bar)] reported by Vogt et al.[22] These conditions gave unsatisfactory results in HV of 1,3-dienes under ambient conditions. Notable features of our Co-catalyzed HV reaction are: (i) ligands with large bite-angles (>90°) (DPPP and DPPB) gave almost exclusively the 4,1-(*Z*)-product, whereas ligands with narrow (~72°) bite-angle (e.g., DPPM) gave mostly 2,1-(*E*)-product; (ii) for high selectivity in the 4,1-adduct it is important to keep the temperature low; for a given ligand at higher temperatures, proportion of the (*E*)-isomers increases (entries 2 and 3 in Table 1), presumably via isomerization of the initially formed (*syn-anti*)-η^3-complex **4** to a more stable (*syn-syn*)-isomer (**4'**); (iii) the reaction is compatible with several common functional groups like CO_2Et, OBn, Cl and Ph substitution on the diene; (iv) the products of the reaction are highly valued[23] skipped 1,4-dienes with an alkyl-bearing stereogenic center at the bis-allylic carbon.

Enantioselective HV of acyclic 1,3-dienes—Among the ligands that were evaluated, the best results were achieved with the simplest chiral analogs of DPPP and DPPB that are commercially available: (*S,S*)-2,4-*bis*-diphenylphosphinopentane [(*S,S*)-BDPP,

L1] and (*R,R*)-(2,2-dimethyl-1,3-dioxalane-4,5-diylbismethylene)-*bis*-diphenylphosphine [(*R,R*)-DIOP, **L2**], respectively (Figure 3 A).[20] Under the optimized conditions, a series of linear 1,3-(*E*)-dienes gave nearly quantitative yields of HV products with high regio- (4,1-*Z*-HV) and enantioselectivities (Figure 3 A, Table 2). During these synthetic studies, we characterized several chiral [bis-phosphine]CoX_2 complexes by X-ray crystallography; among them, (*S,S*-BDPP)$CoCl_2$ complex and a corresponding ligand-bridged Co(I)-complex, [(*S,S*)-BDPP]$_3Co_2Cl_2$. In addition to the applications in our own work, the (BDPP)Co(II)-complex has since attracted significant attention for other cobalt-catalyzed enantioselective reactions.[24]

Enantioselective HV of 1-vinylcycloalkenes—In sharp contrast to the Ni-catalyzed HV reaction (using **L3**) where both 1-vinylcycloalkenes and benzannulated 1,3-dienes undergo almost exclusive 2,1-addition (Figure 1 C, Figure 3 B),[18] under cobalt catalysis, the major product is formed by 4,1-addition (Figure 3 B).[25] Reaction of racemic 4-*t*-butyl-1-vinylcyclohexene (**7**) is typical. The (DPPP)$CoCl_2$/Me_3Al-mediated reaction gave mostly 4,1-adducts **9a** and **9b** (*cis*- and *trans*-isomers) in a ratio of 81:17 (ratio of 2,1:4,1-adducts, **8**:**9** = 2:98) in 96% yield. Reactions catalyzed by [(*S,S*)-BDPP]$CoCl_2$ and Me_3Al gave a lower proportion of the 4,1-HV adducts [**8:9** = 13:87] compared to the achiral catalyst; but both **9a** and **9b** were formed with an ee of >98%. This exceptionally high enantiomeric ratio of two diastereomeric products from a chiral racemic substrate **7** is an example of a rare, yet fast growing list of efficient enantiodivergent parallel kinetic resolutions.[26] This Co-catalyzed 4,1-HV is a broadly applicable reaction giving excellent ee's (>96%) for the 4,1-adducts in a broad spectrum of substrates.

Enantioselective HV of siloxydienes. Synthesis of functionalized chiral silyl enolates—A successful enantioselective HV of a siloxydiene would lead to a catalytic route to enantiopure silyl enol ethers, potentially valuable nucleophilic synthons.[27] The closest precedent for a catalytic reaction that results in a regio- and stereoselective synthesis of a silyl enol ether uses a transition metal-catalyzed asymmetric conjugate addition of alkenyl metal to α, β-unsaturated carbonyl compounds followed by, a difficult *in situ* silylation of the metal-enolate using several equivalents of a silylating reagent, base and other additives.[28] We found that 2-trialkylsiloxy-1,3-dienes undergo facile regioselective 4,1-hydrovinylation under the modified reaction conditions using [(*S,S*)-BDPP)]$CoCl_2$ (0.01 mol%!) with MAO as the activator (Figure 4) giving nearly enantiopure silyl enol ethers bearing a vinyl group on a stereogenic carbon at the β-position.[1] Key to success here was identifying the weaker Lewis acidic activator, methylaluminoxane (MAO), which played the dual role of a reducing agent and a halogen sequestering agent in the catalytic cycle without affecting the sensitive silyl enol ether group. Most gratifyingly, the methodology has a broad scope including linear and cyclic trialkylsiloxy-1,3-dienes, as illustrated in Figure 4 A and Figure 4 B. We also realized (Figure 4 B.1) excellent reagent control in the HV of a chiral, (−)-citronellal-derived siloxydiene, which gave diastereomeric products in excellent enantioselectivities depending on which ligand (*S,S*)- or (*R,R*)-DIOP was used for the reaction [at C_4 (*R*, dr 97:3) and C_4 (*S*, dr 96:4) respectively]. Aryl-conjugated dienes exclusively gave achiral 1,4-adducts (**B**.2). A highly functionalized silyl enolate with

a methyl-bearing α-stereogenic center (**B**.3**)** is a key intermediate in our plans for a short synthesis of Callistatin A.

The nearly enantio-pure β-vinyl silyl enol ethers formed from the asymmetric HV reactions provide a direct route to many different types of carbonyl compounds including valuable β-vinyl ketones by simple hydrolysis of the enol ethers (Figure 5 A, B). Few preparatively useful catalytic enantioselective methods currently exist[29a] for synthesis of such *vinyl* compounds, especially in the acyclic series, even though *alkenyl* additions are more well-precedented.[29b-f] The nucleophilic silyl enol ethers also undergo several typical reactions with electrophiles at the α-carbon including diastereoselective α-bromination, α-hydroxylation, Lewis-acid-catalyzed alkylation, aldol, Michael and Mannich reactions[30] Another application is for the synthesis of enol triflates (Figure 5, C, D), which undergo traditional cross-coupling reactions to give enantiopure skipped dienes.[30]

ENANTIOSELECTIVE HETERODIMERIZATION OF ACRYLATES AND 1,3-DIENES. DISCOVERY OF THE ROLE OF A CATIONIC Co(I) CATALYST

Even though acrylates are among the largest volume feedstocks, no useful enantioselective heterodimerization involving these compounds was known when we initiated our efforts to couple 1,3-dienes and methyl acrylate.[31] The protocols that worked for the heterodimerization of ethylene and 1,3-dienes [(**P**~**P**)CoX_2/$AlMe_3$ or MAO)] gave very poor yields of the expected products when ethylene was replaced by methyl acrylate. We reasoned that this failure might be related to the incompatibility of the aluminum reagents (see Figure 2 B) with the reactive, Lewis basic/electrophilic alkyl acrylate.[2] We wondered if we could circumvent the use of aluminum alkyls by exploiting a discrete Co(I)/Co(III) redox cycle as a possible pathway for this reaction rather than relying on a hydride route. Mechanistically this would involve an oxidative dimerization of the two alkenes at a low-valent Co(I)-center followed by a β-hydride elimination and a subsequent reductive elimination as elementary steps (Figure 6 A). To test the viability of such an oxidative cyclization route, we prepared and characterized several well-defined Co(I) complexes (Figure 6 B) and examined their utility in the heterodimerization reactions of (*E*)-1,3-dodecadiene ethylene and methyl acrylate.[2] Interestingly, none of the Co(I) complexes either isolated, or, generated in situ from (**L**)CoX_2 with Zn (Figure 6 B) catalyzed the dimerization reaction under ambient conditions in the absence of an activator. In the presence of a Lewis acid, the Co(I) complexes became viable catalysts for the codimerization of both ethylene and methyl acrylate with (*E*)-1,3-dodecadiene giving high chemo- and regioselectivity (Figure 6 C). Among the activators NaBARF (BARF = *tetrakis*-[*bis*-(3,5-trifluoromethyl)phenyl]borate was found to be most effective (Figure 6 E).[32] Subsequent experiments established that this reaction is most easily carried out by in situ generation of the [(**P**~**P**)Co(I)]$^+$ [BARF]$^-$ complex by reduction of the corresponding (bis-phosphine)CoX_2 complex with Zn in the presence of NaBARF (Figure 6 C). We found that DIOP, BDPP and ferrocene-based ligand Josiphos-1 (**L4**) gave the best selectivities for the 4,1-addition of acrylate across various 1,3-dienes. As shown in Figure 6 C, very good to excellent yields and enantioselectivities for the 4,1-adducts are obtained and the reaction is compatible with many common organic functional groups including silyl ethers. Recently completed mechanistic studies including isotopic labeling studies (Figure 6 D, E) are

consistent with an oxidative dimerization route for this reaction.[33] Since diene-ethylene and diene-acrylate codimerizations are catalyzed equally well by the cationic cobalt complexes[2], it is conceivable that the former reaction also involves Co(I)/Co(III)-redox cycle rather than the hydride mechanism proposed earlier as a working hypothesis at the beginning of our investigations (Figure 2). However, we do not yet have sufficient evidence to discount the hydride route in the diene-ethylene reaction.

ENANTIOSELECTIVE [2+2]-CYCLOADDITION BETWEEN ALKYNES AND ALKENYL DERIVATIVES

Functionalized cyclobutanes and butenes are important structural motifs seen in many biologically important compounds[34] One of the simplest approaches to cyclobutenes is through a [2+2]-cycloaddition between an alkyne and an alkenyl derivative (Figure 7 A).[35] We wondered if a putative Co(III)-metallacycle (**10**, Figure 7 A) formed by an oxidative cyclization between the alkyne and the alkene, could serve as a source of a cyclobutene (**11**) by a direct reductive elimination from **10** with C_{sp2}-C_{sp3}-coupling. A possible complication would be a β-hydride elimination in **10** followed by reductive elimination with the formation of a C_{sp2}-H bond which would result in simple coupling (**12**) akin to a linear heterodimerization. Could these diverse pathways be controlled by choice of ligands? We started our optimization studies with a conjugated 1,3-enyne and methyl acrylate and, as anticipated, quickly realized that indeed the challenge was to suppress the formation of the linear product.[3] Various bis-phosphines such as DPPE, DPPB and chiral analogues (*S, S*)-BDPP, *R*-BINAP did give the cyclobutene as the major product, but, invariably contaminated with 2–20% of **12** and in low enantioselectivities for **11**. We hypothesized that electron-deficient phosphinooxazoline ligands (Figure 7 B) might favor reductive elimination from **10** over β-hydride elimination and might suppress the side-product formation. To our delight, simple achiral 2-(2-diphenylphosphino)phenyl-1,3-oxazoline (PHOX) ligand **L5** gave a very high yield of **11** with excellent selectivity for cyclobutene and none of **12**.[3] Next we examined a number of different chiral PHOX ligands for the cyclobutene formation (Figure 7 B) using the standard procedure for the formation of a cationic Co(I)-intermediate (Figure 7 C). Examining the electronic effect of the arylphosphines, we found that the electron-deficient ligand **L8** gave the best enantioselectivity. Interestingly, more electron rich and sterically encumbered PCy_2-PHOX ligand **L9** also gave nearly identical enantioselectivity (82%) in CH_2Cl_2 as a solvent. We observed dramatic improvements in enantioselectivities upon switching to toluene as a solvent for ligands **L7**-**L9**. The optimized conditions were used for expansion of the substrate scope (Figure 7 C). Variations in both substrates showed excellent functional group compatibility.

Allyl derivatives show a striking ligand effect.—Cycloadditions with allyl derivatives also revealed a remarkable ligand effect. While the cycloaddition reactions carried out using the ligand (**L9**) gave excellent yields of the [2 + 2]-cycloaddition (Figure 7 D, **13**) with outstanding regioselectivity, the $(DPPP)CoBr_2$ complex gave adducts (**14**), corresponding to a formal ene reaction.[36] Mechanistically **14** could arise via a linear codimerization (1,2-addition to the alkyne) followed by a hydrogen migration to the more stable alkenyl Z-derivative.

While attempting to extend the cycloaddition reaction to less reactive alkynes (Figure 8 A) it was found that the simple achiral ligand **L5** (Figure 7 B)or the corresponding 4-phenyloxazoline **L7** proved unsatisfactory. The electron-rich ligand **L9** was found to give excellent selectivity for the formation of the cyclobutenes, especially when a trifluoroethyl acrylate was used as the alkenyl component and the reaction was carried out in toluene at slightly elevated temperatures. The reactivity and selectivity could be improved further with a novel ligand **L10**, readily synthesized from (1*S*,2*R*)-norephedrine, which gave unprecedent yields and enantioselectivities (ee > 90%) for a broad range of alkenyl derivatives and simple alkynes (Figure 8 B).

Tandem [2+2]-cycloaddition/hydrovinylation for functionalized cyclobutanes with an all-carbon quaternary center: Recognizing the remarkable catalytic activity of cationic Co(I) species in disparate reactions like heterodimerizations and [2+2]-cycloadditions, we wondered if a tandem sequence could be executed. For this we turned to reactions of 1,3-enynes with ethylene (Figure 9). Most remarkably, a highly ligand-dependent reaction ensued giving either a simple [2+2]-addition to a vinylcyclobutene (**16**) or a product (**17**) derived from the subsequent hydrovinylation of **16** (Figure 9 A)[6, 37] Among the Co-complexes of 1,n-diphenylphosphinoalkanes, DPPP and DPPF were most active, selectively yielding almost exclusively the cycloaddition product **16** (for R = *n*-Bu) at low temperature, but yielding **17** on prolonged reaction time. Among the chiral phosphines, phosphinooxazolines showed the best selectivity with the reaction proceeding even at −20 °C when the catalyst was activated with either trimethyl aluminum, MAO or Et_2AlCl. As the examples in Figure 9 C show, a reaction using a simple protocol [(**L7**)$CoCl_2$/ Et_2AlCl/CH_2Cl_2, ethylene (balloon), 0 °C] is quite general for the synthesis of various analogs of functionalized cyclobutane **17** with a chiral all-carbon quaternary center in high enantioselectivity.

REGIODIVERGENT HYDROALKENYLATION OF 1,6-ENYNES AND AN UNCOMMON *β*-C–H ACTIVATION FOR *Z*-SELECTIVE COUPLING OF ACRYLATES

We imagined that different carba- and heterocycles could be accessed by incorporation of feedstock alkenes into other enynes, for example, a 1,6-enyne (**18**, Figure 10). The reactions with ethylene under conditions known to generate a $[LCo(I)]^+$ $[BARF]^-$, a product (**19a**), formally equivalent to a cycloisomerization of the enyne followed by a HV, is formed (Figure 10 A).[7] This reaction in which ethylene is inserted into the Co-C_{sp2} bond of the presumed metallacycle intermediate (**20**, Figure 10)[38] is quite general and various the alkyne substituents (**18**, R = aromatic, heteroaromatic, alkyl, 2-alkenyl) are tolerated (Figure 10 B). When an unsubstituted alkyne is involved, the reaction takes an alternate course (Figure 10 D), and an uncommon [3.1.0]bicyclohexane (**21**, Figure 10 D) is formed. Electron-rich vinyl phthalimide gives aza-bicyclo[4.3.0]-nonane (**22**) similar to a product seen in the Rh-catalyzed [2+2+2]-cycloaddition between a 1,6-enyne and *N,N*-dimethyl acrylamide.[39]

When methyl acrylate was used as the alkene component, a different reaction ensued, now the bond-formation taking place at the C_5 location of the metallacycle (**23**, Figure 10 A, C), and, most remarkably the only product formed (**23**) has the *Z*-configuration (confirmed by X-ray crystallography of products derived from MMA and methyl (*E*)-crotonate). Since

such a stereochemical outcome (*Z*) is quite uncommon in the couplings of acrylates, including Heck-type addition reactions (where almost invariably a *E*-product is observed),[40] we initiated a mechanistic investigation of the reaction, the details of which have been published.[7] Computational studies provide support for our experimental observations that the turnover-limiting step in this reaction involves a *cis*-C-H activation of the acrylate from the cobaltacycle intermediate (**24**, Figure 10 E). We explain the exclusive formation of the *cis*-adduct (**23**) by invoking a metal-assisted σ-bond-metathesis in **24** followed by reductive elimination from the resulting (*Z*)-vinyl-Co species **25** (Figure 10 E). The calculated energies of the transition states and intermediates involved in these steps are consistent with this facile reaction. For example, the more well-precedented sequence for the coupling viz., coordination of the acrylate, insertion and β-hydride elimination, was found to be kinetically inaccessible (40 kcal/mol), whereas the largest $\Delta G^{\neq}$ for a step involving C-H activation starting from **20** via σ-bond-metathesis was only 23.5 kcal/mol. As would be expected from such a mechanism, the reaction fails for methyl *Z*-crotonate, where there is no hydrogen *syn* to the $-CO_2Me$ group. A kinetic isotope effect of 2.1 observed in reactions with methyl methacrylate-d_2 also supports a key C-H/D cleavage in the turnover-limiting step. Other viable substituted methyl acrylates include methyl methacrylate, *E*-2-methoxyacrylate and *E*-methyl crotonate (Figure 10 C).

REGIO- AND ENANTIOSELECTIVE HYDROACYLATION OF 1,3-DIENES

Hydroacylation of alkenes is a very powerful method for the synthesis of ketones from two of the most readily available precursors, alkenes and aldehydes, many of them available as feedstocks.[41] Even though hydroacylations have been carried out with many transition metals, most successful *enantioselective intermolecular* reactions have relied on rhodium, an expensive and relatively rare metal, and, the scope of the substrates are limited to those carrying chelating groups[42] or to those possessing increased reactivity due to strain.[43] Absent among the alkene substrates that have been subjected to enantioselective hydroacylation reactions are 1,3-dienes.[24c, 44] We wondered if the cationic complexes, $[(\mathbf{L})Co]^+ [BARF]^-$, that have been found to effect oxidative dimerizations between alkenes via mechanism involving a Co(I)/Co(III) cycle (vide supra), might also be suitable for the hydroacylation reactions. In 2014, Dong reported the first examples of a racemic version of the cobalt-catalyzed hydroacylation of 1,3-dienes, and showed that regioselectivity (1,2- versus 1,4- addition) could be controlled by the steric and electronic properties of the chelating phosphines.[45] After an extensive search for ligands and optimized reaction conditions, we have identified the best conditions for regio- and enantioselective hydroacylations of 2- and 4-monosubstituted, and 2,4-disubstituted 1,3-dienes.[4] The results of these studies are summarized in Figure 11 (2- mono- and 2,4-disubstituted 1,3-dienes giving predominantly 1,2-adduct) and Figure 12 (4-substituted 1,3-dienes giving 4,1- or 4,3-adducts depending on the nature of the aldehyde). Particularly noteworthy are the use of two feedstock dienes, isoprene and myrcene in these reactions. Examination of various chiral ligands revealed that (*S,S*)-Ph-BPE (**L11**) was the ligand of choice for the highest regio- and enantioselectivities, with (*R,R*)-*i*-Pr-DUPHOS (**L12**) serving as an alternative for some cases. Since isoprene is one of the cheapest feedstock dienes ($ 1.4/kg) we probed this substrate to establish the tolerance of various aldehydes and the results are shown in entries 5–12, Figure 11. As noted, aromatic, heteroaromatic and α,β-unsaturated aldehydes

are suitable precursors for this reaction (entries 7–12). Enantioselective hydroacylation of isoprene with isobutyraldehyde (entry 5) gives (*S*)-Dihydrotagetone, a flavoring agent in 92% ee.[46]

As shown in Figure 12 A, highly enantioselective hydroacylation reactions can also be carried out on 4-substitued 1,3-dienes, which gave either 4,1-adduct (entries 1–4) or 4,3-adduct (entries 6–8) depending on whether an aliphatic or aromatic aldehyde was used. 1,3-Butadiene gave mostly 1,2-addition irrespective of the nature of the aldehyde (entries 5 and 9).

Two special applications of the new reaction are shown in Figure 12 B and C. A 2-step, gram-scale synthesis of the anti-inflammatory agent (*S*)-Flobufen starts with isoprene and a commercial aromatic aldehyde to get an intermediate ketone which was further oxidized to the final product in overall 92% yield and >98% ee.[47] A silyl enol ether derived from methyl vinyl ketone, 2-trimethylsiloxy-1,3-butadiene, undergoes surprisingly efficient enantioselective hydroacylation under our conditions (Figure 12 C) to give valuable silyl-protected aldol products in excellent enantioselectivities, even though the regioselectivity needs further improvement. A hydroacylation route to aldols has not been disclosed before. We find that isolated cationic Co(I) complexes (e.g., **26**) have a distinct advantage in this reaction because the competitive Mukaiyama aldol reaction (presumably catalyzed by the byproduct $ZnBr_2$) is minimized with this single component catalyst derived from a DUPHOS ligand.

REGIO- AND ENANTIOSELECTIVE HYDROBORATION OF 1,3-DIENES

In 2017 when we first disclosed[48] the Co-catalyzed enantioselective hydroboration of prochiral acyclic 1,3-dienes, there were no reports of such a reaction among this class of compounds.[49] Shortly thereafter, Mazet published a Cu-catalyzed addition of *bis*-pinacolborane in protic solvents to get high enantioselectivity for the 1,2-hydroboration products from prochiral 1,3-dienes[50] and this area has since received a lot of attention.[51] Our work[5] started with the assumption that the cationic Co(I) catalysts would also be effective for the regio- and enantioselective hydroboration of 1,3-dienes. The initial optimization studies were carried out on the hydroboration of a prototypical 1,3-diene, (*E*)-1,3-nonadiene with HBPin (Pin = 2,3-dimethylbutane-2,3-dioxy) in the presence of 5 mol% of (**L**)CoX_2 [X = Cl, Br, **L** = 1,n-*bis*-diphenylphosphinoalkane, n =1–5 or phosphinooxazolines) and various activators (Figure 13, A).[52] It was quickly established that [(DPPP)$CoCl_2$ activated with methylaluminoxane (MAO) gave the best selectivity for the 1,2-addition (ratio of 1,2-:1,4-adddition = 95:5). Complexes of bis-phosphine ligands with narrow bite angle (e.g., (*bis*-diphenylphosphino)methane) and PHOX ligands (e.g., **L7**) gave predominantly the 1,4-hydroboration product with (*E*)-1,3-nonadiene. Several examples of 1,2-hydroboration of 1,3-dienes, including isoprene, myrcene, are shown in Figure 13, B. In the case of isoprene and myrcene, significant amounts of 1,4-products were formed even with the DPPP-complex, and, this product constituted the major isomer (~98%) when the ligand **L7** was used.

For an enantioselective version, we turned to 2,4-disubstituted 1,3-diene and 1-(2-alkenyl)cycloalkenes, which gave mostly 1,2-regioselectivity using both (DPPP)$CoCl_2$ and

PHOX ligands (Figure 13 C), with boron entering the least hindered C_1-position. Chiral bis-phosphines are much less regioselective, giving 1,2-, 1,4-, or even 4,3-hydroboration with 2,4-disubstituted 1,3-dienes. However, a reaction catalyzed by the substituted PHOX ligands is broadly applicable for the 1,2-adducts, and, in general, good to excellent regio- and enantioselectivities are observed (Figure 13 C), including for 1,3-dienes carrying useful functional groups on the C_4 chain. Excellent regioselectivity is observed in 1,3-cyclohexadiene depending on the ligand even though the enantioselectivity for the 1,2-addition (ee = 38%) remains a challenge.

ROLE OF CATIONIC Co(I) IN HETERODIMERIZATION, HYDROACYLATION AND HYDROBORATION REACTIONS

Although it is conceivable that (**L**)$Co^{I}X$ or a cationic versions of such a complexes, [(**L**)Co^{I}]$^{+}$[Y]$^{-}$, might have been involved even in the earliest known cobalt-mediated reactions,[17a,20a,53] unequivocal evidence for the involvement of a cationic Co(I)-catalyst was lacking until our investigation into the details of the enantioselective heterodimerization of 1,3-dienes and acrylates.[2] During these studies we discovered that reduction of (DPPP)$CoBr_2$ with Zn or EtMgBr gave a discrete Co(I) complex (Figure 6 B), which crystallized as a ligand bridged dimer, (DPPP)(Br)Co^{I}(μ-DPPP)Co^{I}(Br)(DPPP) (**27**,Table 3, entry 1). Isolation and full characterization by X-ray crystallography of this complex (for an ORTEP, see Figure 6 B), and, the corresponding (*S,S*)-BDPP-complex, (BDPP)(Cl)Co^{I}(μ-BDPP)Co^{I}(Cl)(BDPP) [prepared via reduction of the Co(II) complex[5] with1,4-*bis*-trimethylsilyldihydropyrazine[54]], allowed us to examine the viability of these *neutral* complexes as catalysts for heterodimerization, hydroacylation and hydroboration reactions of 1,3-dienes. The results are shown in Table 3, entries 1–10. We find that neither the isolated, neutral Co(I)-complex **27** (entries 2 and 4), nor an in situ prepared complex [Zn + (DPPP)$CoBr_2$] was competent to effect heterodimerization reactions of 1,3-dienes with ethylene or acrylate. Addition of various Lewis acids or halogen sequestering agents, in particular, NaBARF or $(C_6F_5)_3B$, converts these unreactive Co(I)-complexes into excellent catalysts (entries 1 and 3). Further support for the intermediacy of a cationic Co(I) species in heterodimerization comes from the isolation, identification and enantioselective catalysis by a discrete cationic Co(I)-complex of the ligand (*R*)-QuinoxP* (**28**, Table 3, entry 5). This single component catalyst (1 mol%) produces the 1,4-co-dimer of 1,3-nonadiene-and methyl acrylate in 93% isolated yield with an enantioselectivity of 94% ee.

Similar experiments have been carried out with enantioselective hydroacylation of isoprene (entries 6–10)[4] Isolated neutral Co(I) complex (**29**) derived from *i*-PrDUPHOS ligand (entry 7) or an in situ prepared ‘Zn-reduced’ Co(I)-Br derived from the corresponding $CoBr_2$ complex (entry 10) itself does not affect the hydroacylation reaction. Addition of NaBARF turns these into excellent catalysts (entries 6 and 9). Cationic single component catalyst (**26**) gives high enantioselectivity (ee 96%) for the chiral 1,2-addition product (entry 8). A cationic diene-aldehyde complex (**30**) is also a good catalyst for the hydroacylation.[4] A similar sequence of reactions have also confirmed the intermediacy of a cationic Co(I) species in enantioselective hydroboration of 1,3-dienes, where there is a significant acceleration of the reaction when [BARF]$^{-}$ is present, even though a slow reaction can be observed without added Zn as long as NaBARF is present.[5]

CONCLUSIONS AND OUTLOOK

Cobalt is one of the most abundant transition metals with a prolific usage in the history of catalysis thanks in part due to its rich coordination chemistry and accessibility to varied oxidation states. The metal's unique ability to support both closed and open shell pathways in catalytic cycles enables transformations that are otherwise difficult to execute. It is not yet clear if open shell intermediates play any role in the highly selective reactions we have studied. It appears that the highly dissociated counter ions (e.g., $BARF^-$) impart special reactivity to the cationic cobalt species, whose redox activity, can be easily manipulated by the ligands. Together these two properties provide unprecedented opportunities for discovery of new reactions or to demonstrably improve selectivities of well-known reactions. The cationic nature and the attendant Lewis acidity, in conjunction with the redox properties of the metal, provide special reactivity such as seen in the hydroacylation of a silyl enol ether (Figure 12 C) where the expected Mukaiyama reaction is minimized in favor of a hydroacylation. Likewise, knowing the details of the ligation around Co(III) that enabled the $H–C_{sp2}$ activation in the unprecedented *cis*-selective acrylate addition (Figure 10 C) could lead to new Heck-type reactions. Cobalt(III) intermediates with distinct Co–C bonds are ubiquitous in much of the chemistry we discussed, and it should be possible to exploit the weak Co-C bonds in such intermediates to make new bonds. Effect of hemilabile ligands to improve the lifetimes of catalysts[11b, 55] is an area that we are beginning to pay attention to. It has also been amply demonstrated that chemo-, regio- and enantioselectivities in reactions of a polyfunctional molecules such as dienes and allylic derivatives can be controlled by appropriate choice of ligands. Much of the synthetic work so far has relied on empirical choices of ligands and additives, since clear relationships between their discernable properties and any specific catalytic activities are only beginning to be understood. Recruiting powerful tools from computational chemistry might alleviate some of the hurdles here. Going forward, the areas of new cycloaddition, cross coupling and multicomponent cyclization reactions, reactions that rely on base-metal photochemistry and reactions that forge C-O, C-N, C-S, C-P and C-X (F, Cl) bonds are sure to attract increasing attention. Applications of the emerging reactions for polymer synthesis can also be envisaged.

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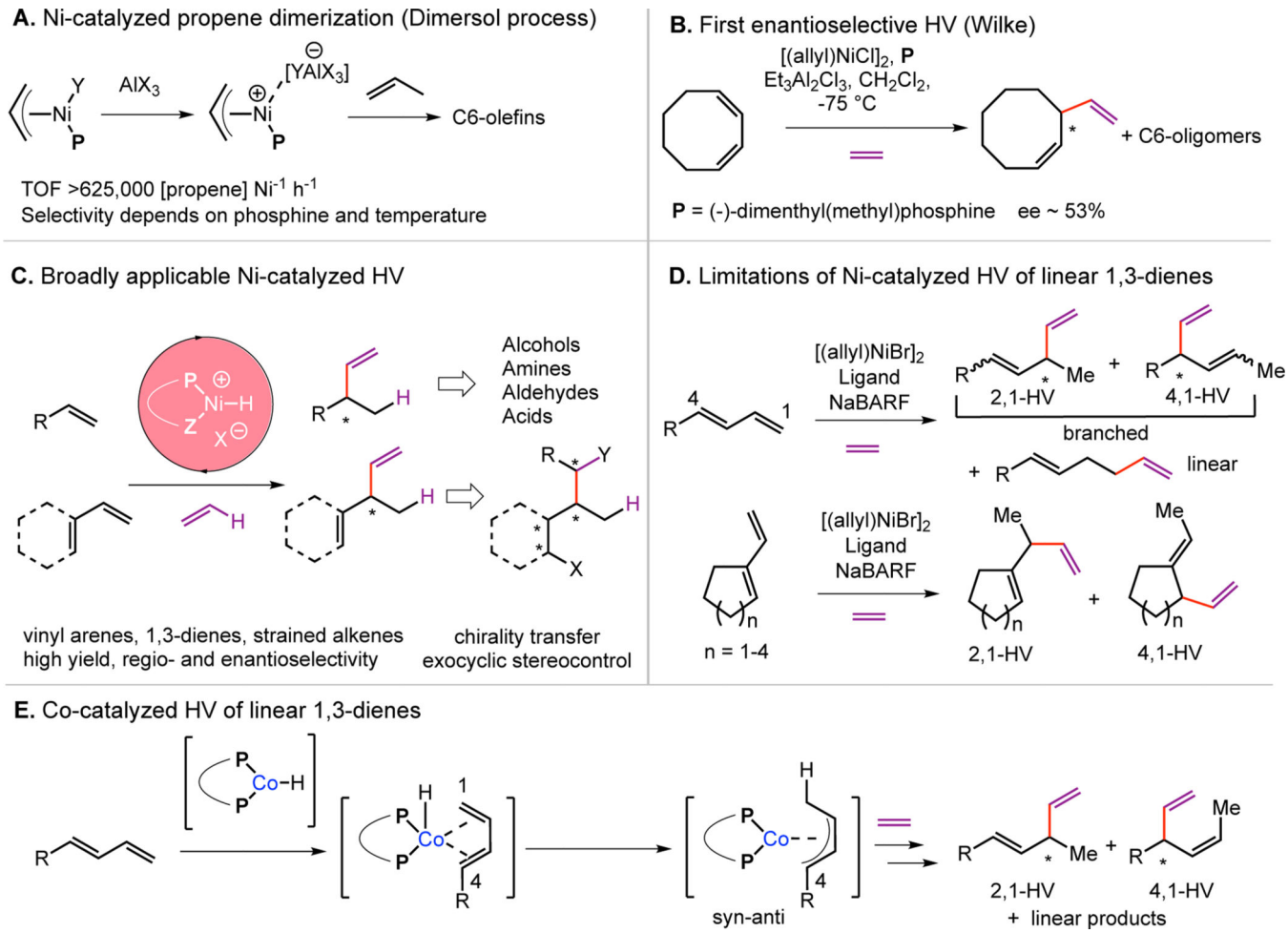


Figure 1.
Nickel and cobalt-catalyzed hydrovinylation reactions

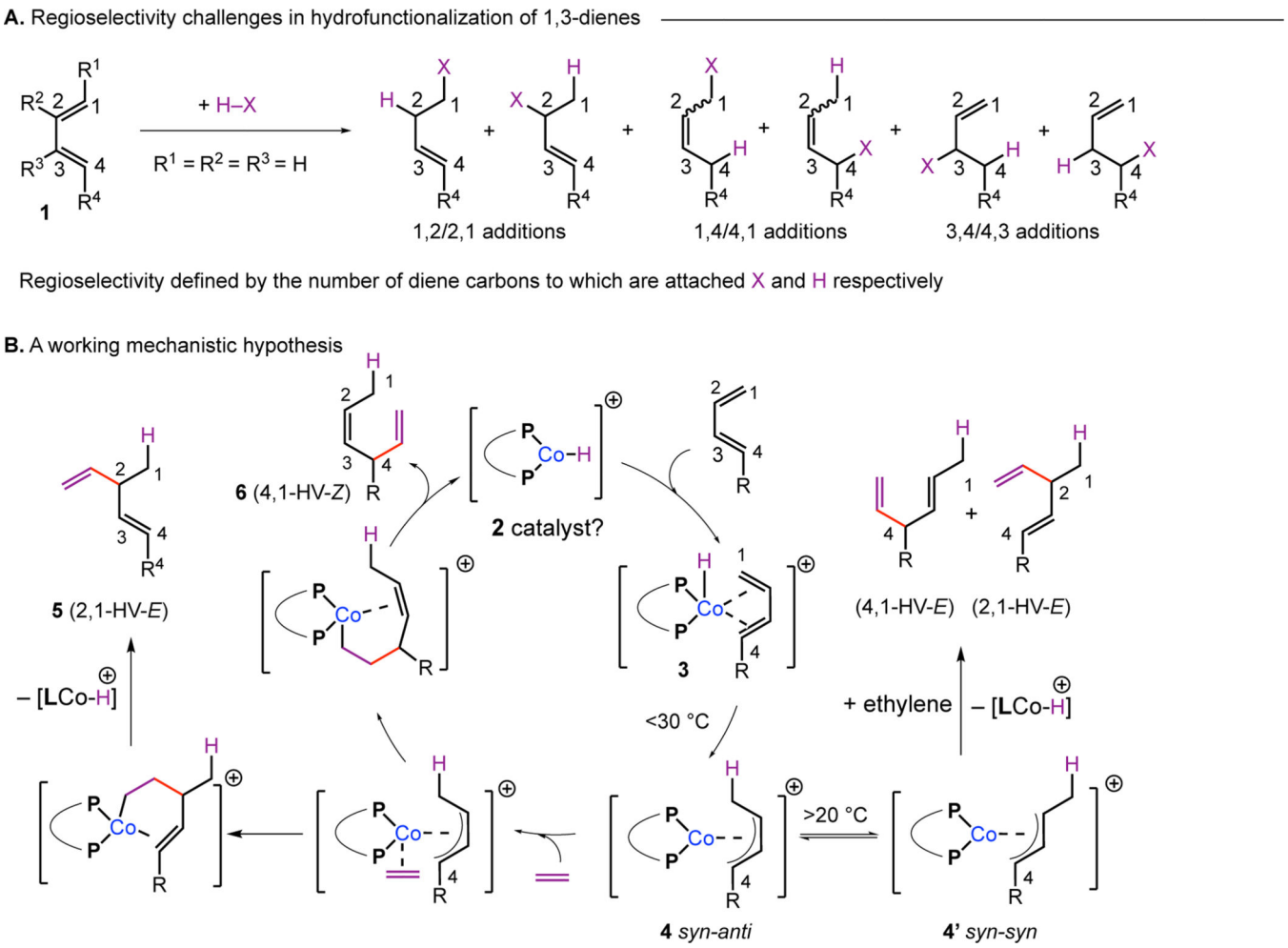


Figure 2.

Co-catalyzed HV of 1,3-dienes. Challenges and a possible mechanism

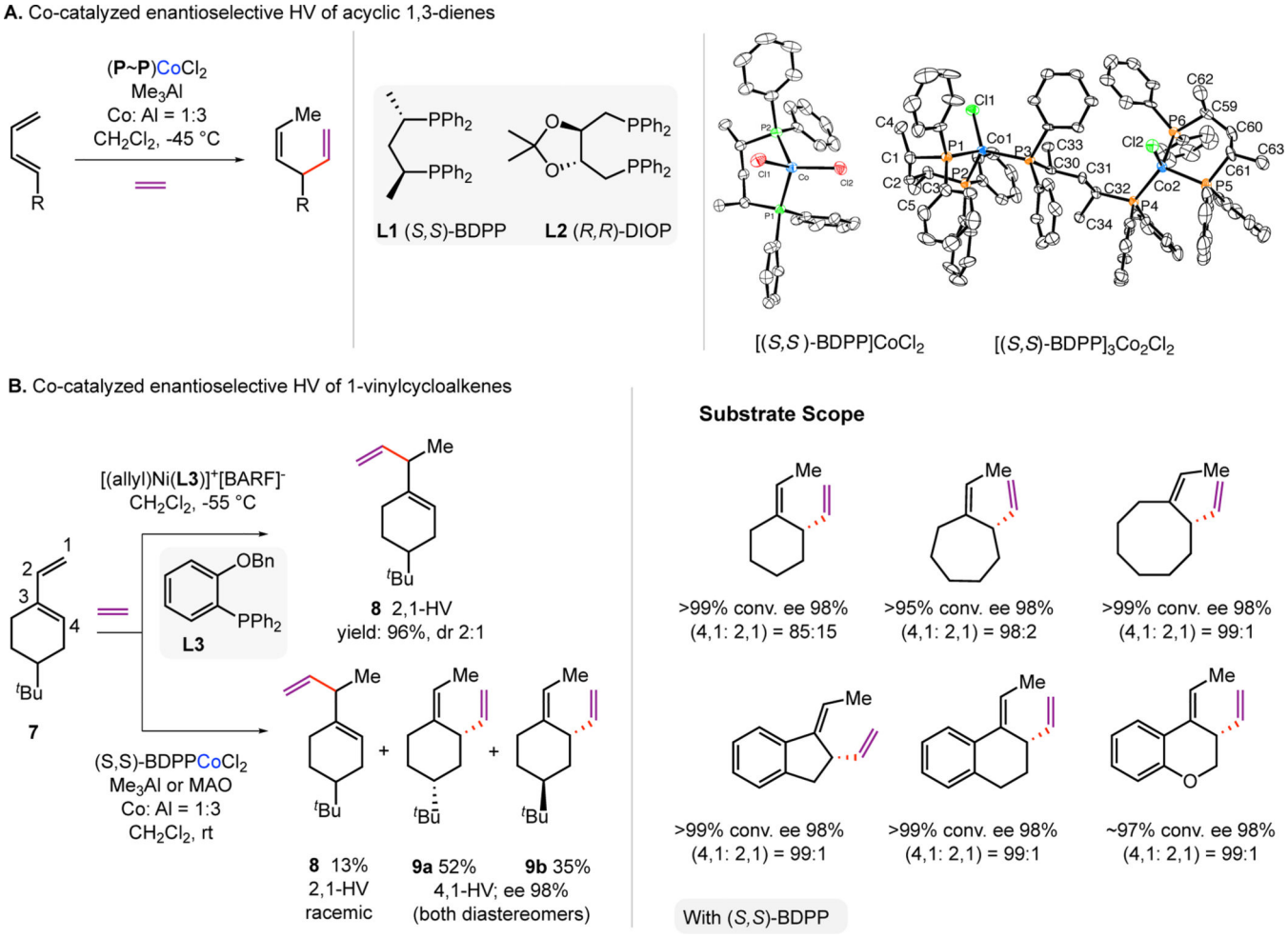


Figure 3.

A. Cobalt-catalyzed HV of acyclic 3-dienes (Table 2). **B**. Comparison to nickel.

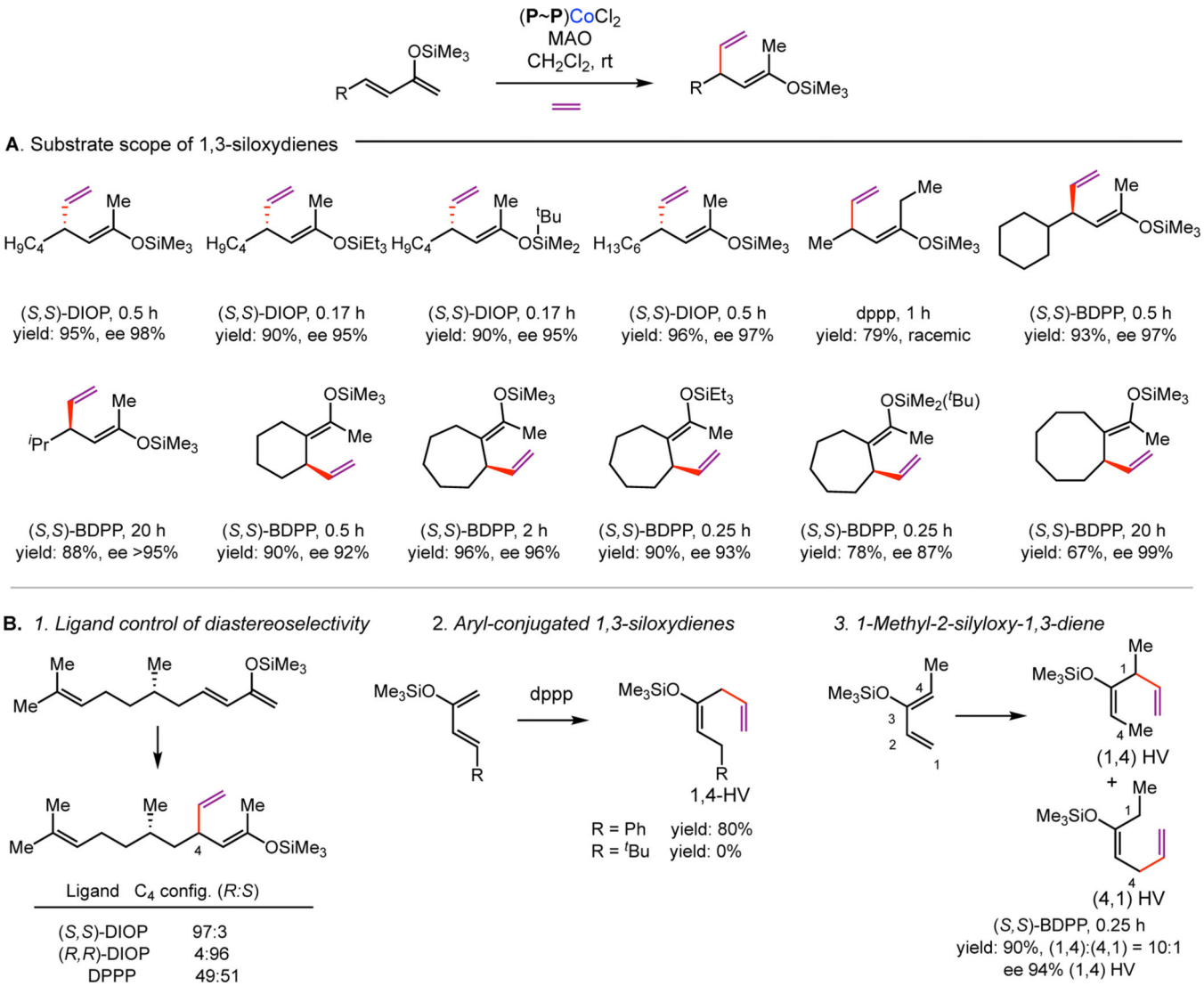


Figure 4.

Enantioselective HV of siloxydienes. Chiral β-Vinyl silyl enol ethers

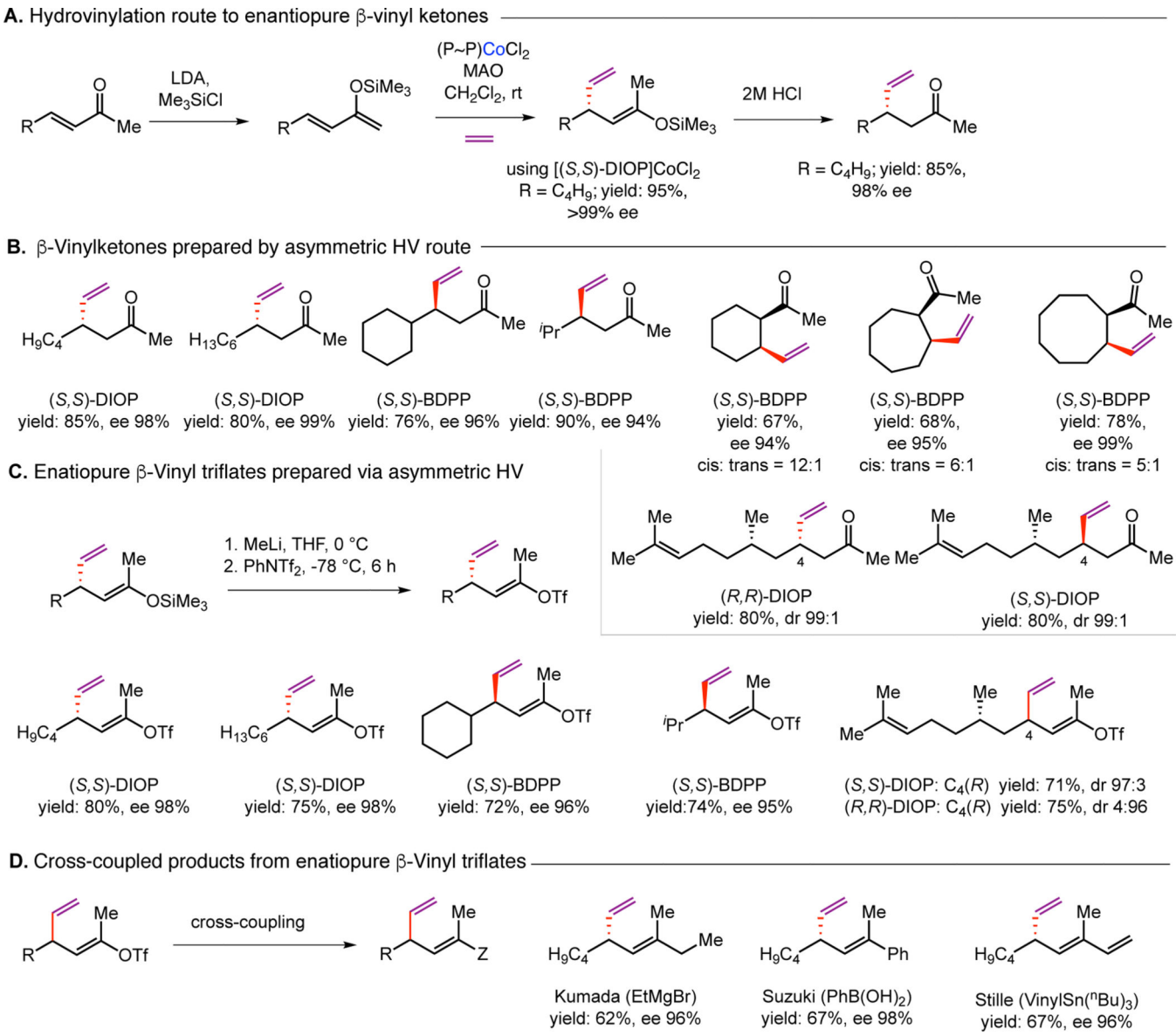


Figure 5.

Enantioselective hydrovinylation of 2-trialkylsilyloxydienes and applications of the resulting silyl enol ethers

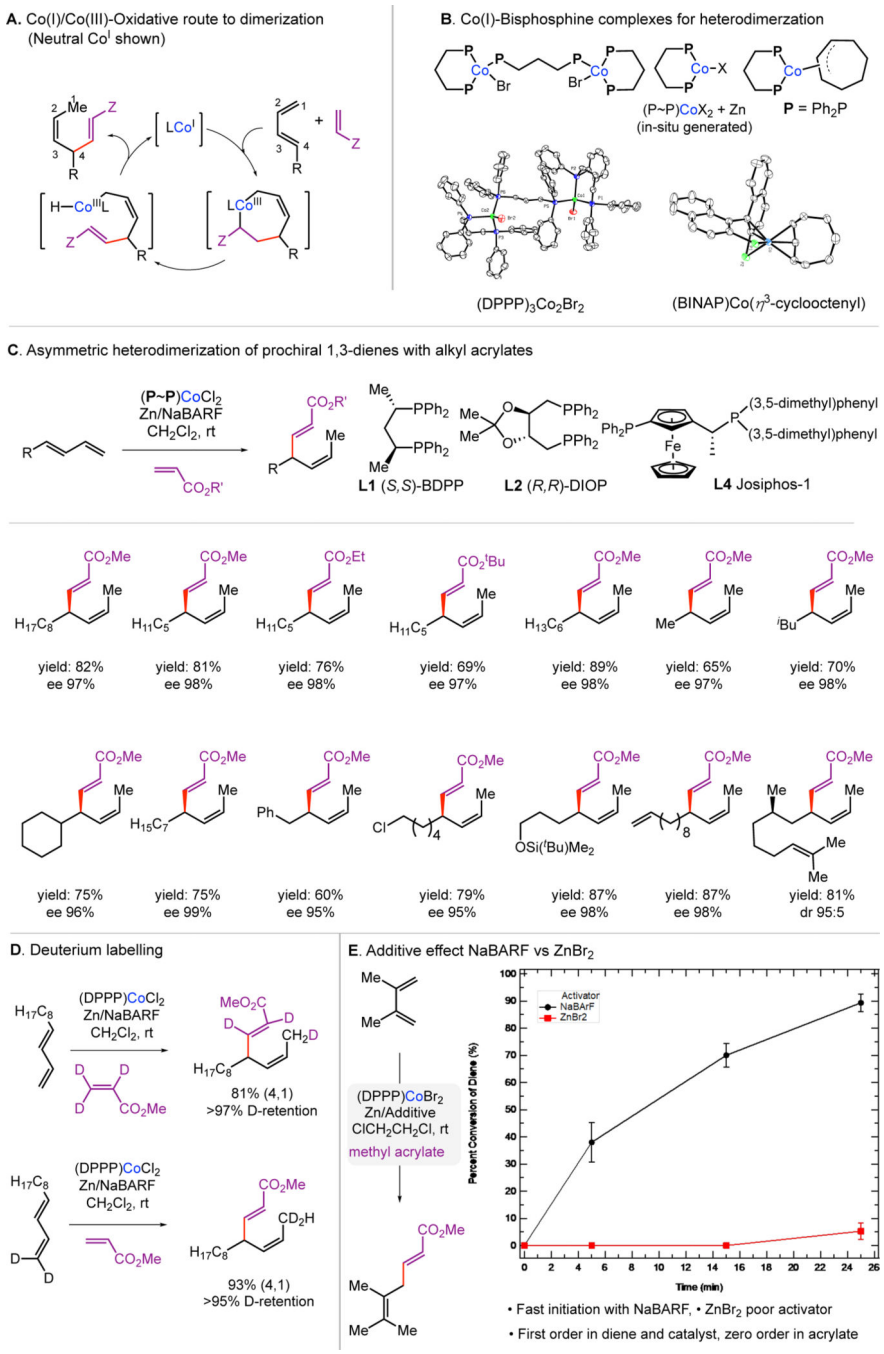


Figure 6.
Cobalt-catalyzed heterodimerization between 1,3-dienes and alkyl acrylates

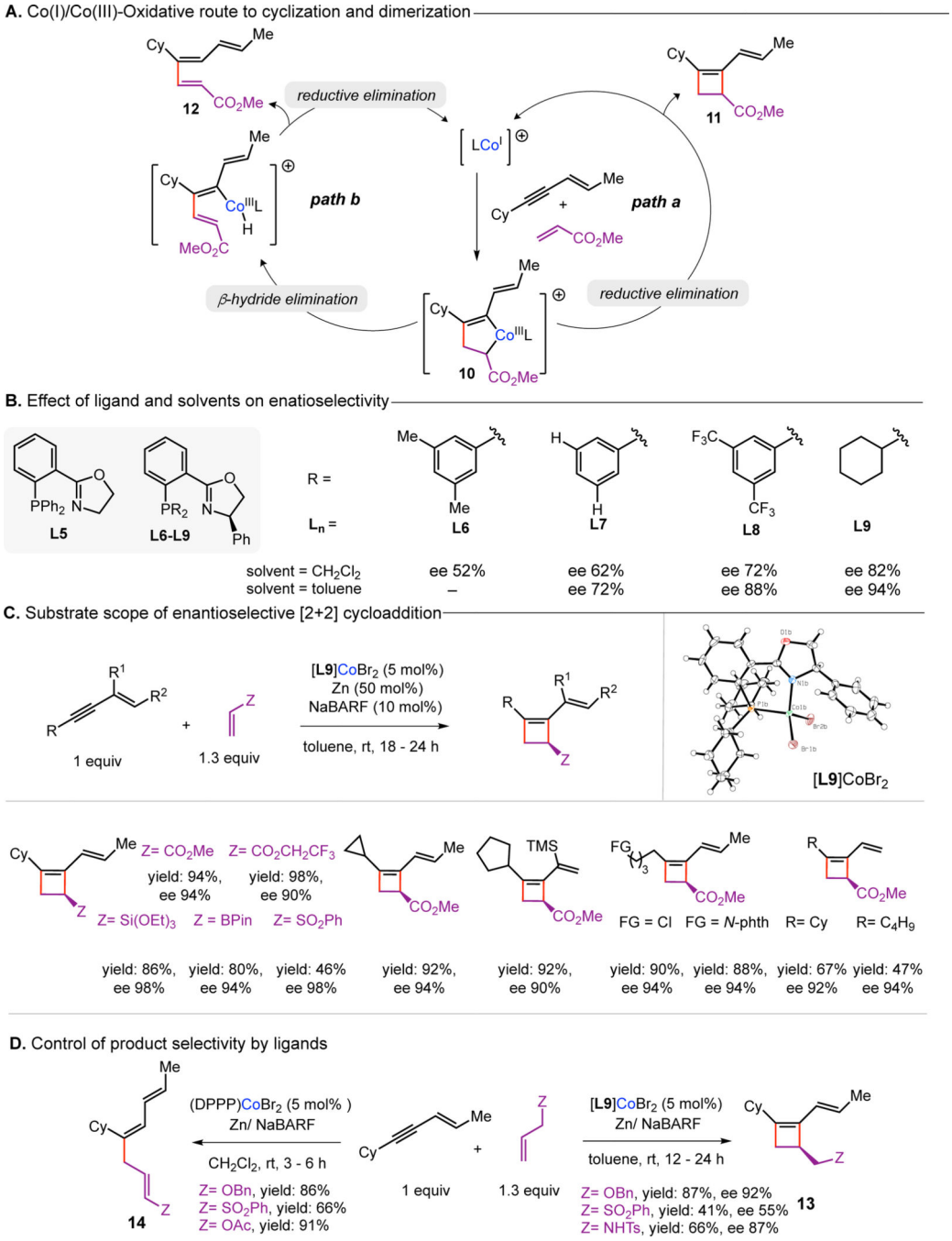


Figure 7.
Enantioselective cobalt-catalyzed [2+2]-cycloadditions

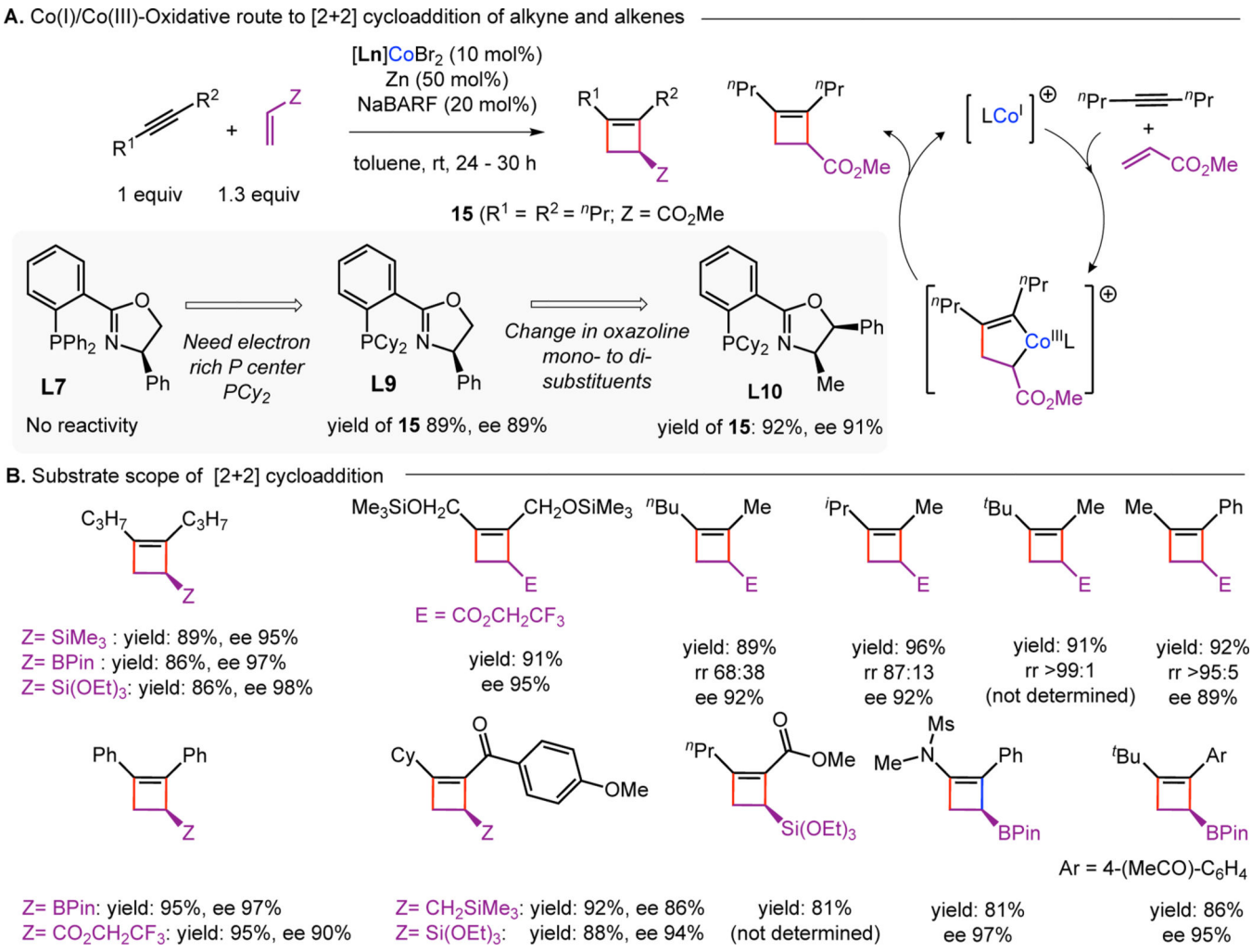


Figure 8.
Fine-tuning of ligands for [2+2]-cycloaddition

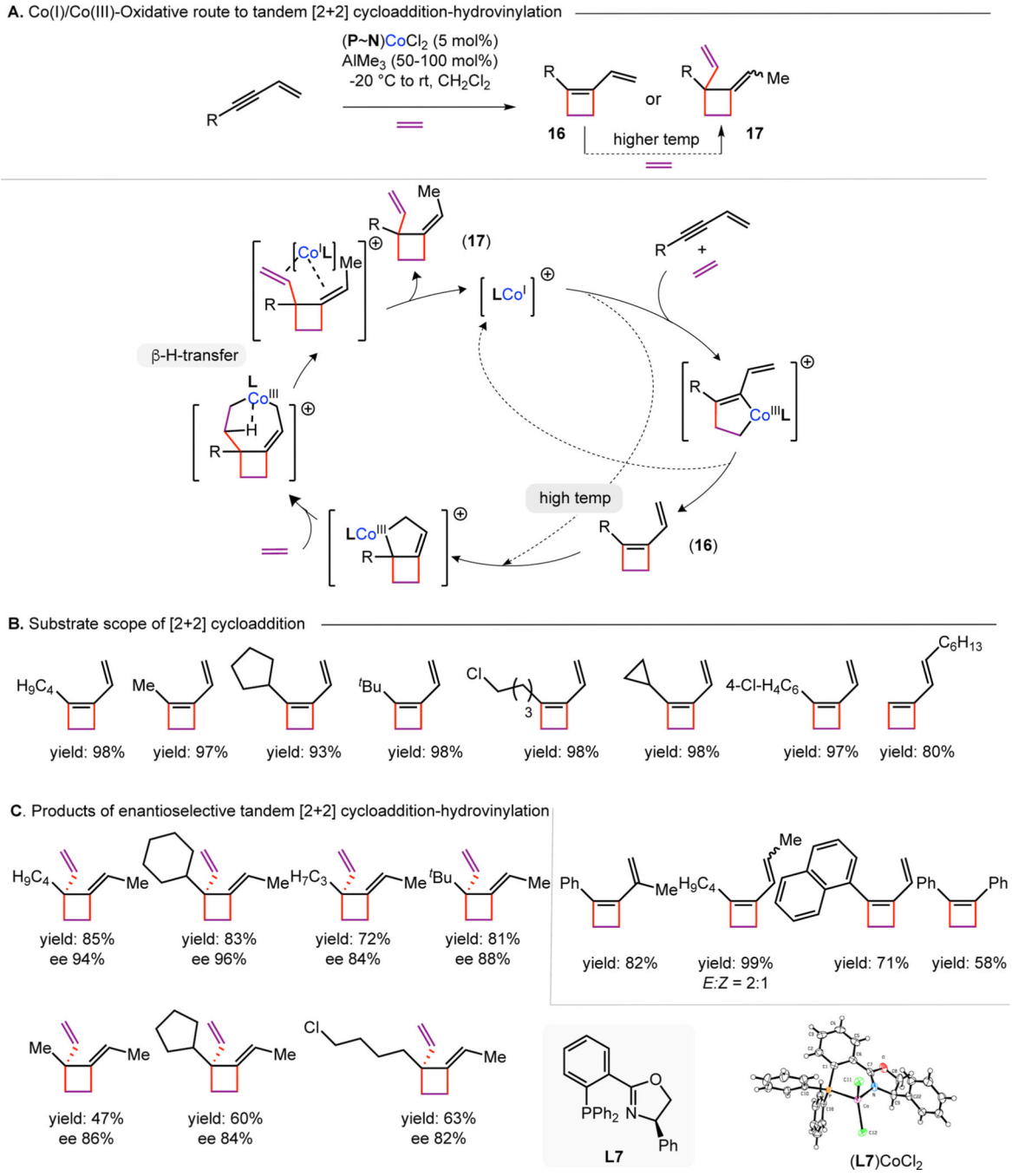


Figure 9.
Cyclobutanes via tandem [2+2]-cycloaddition/hydrovinylation

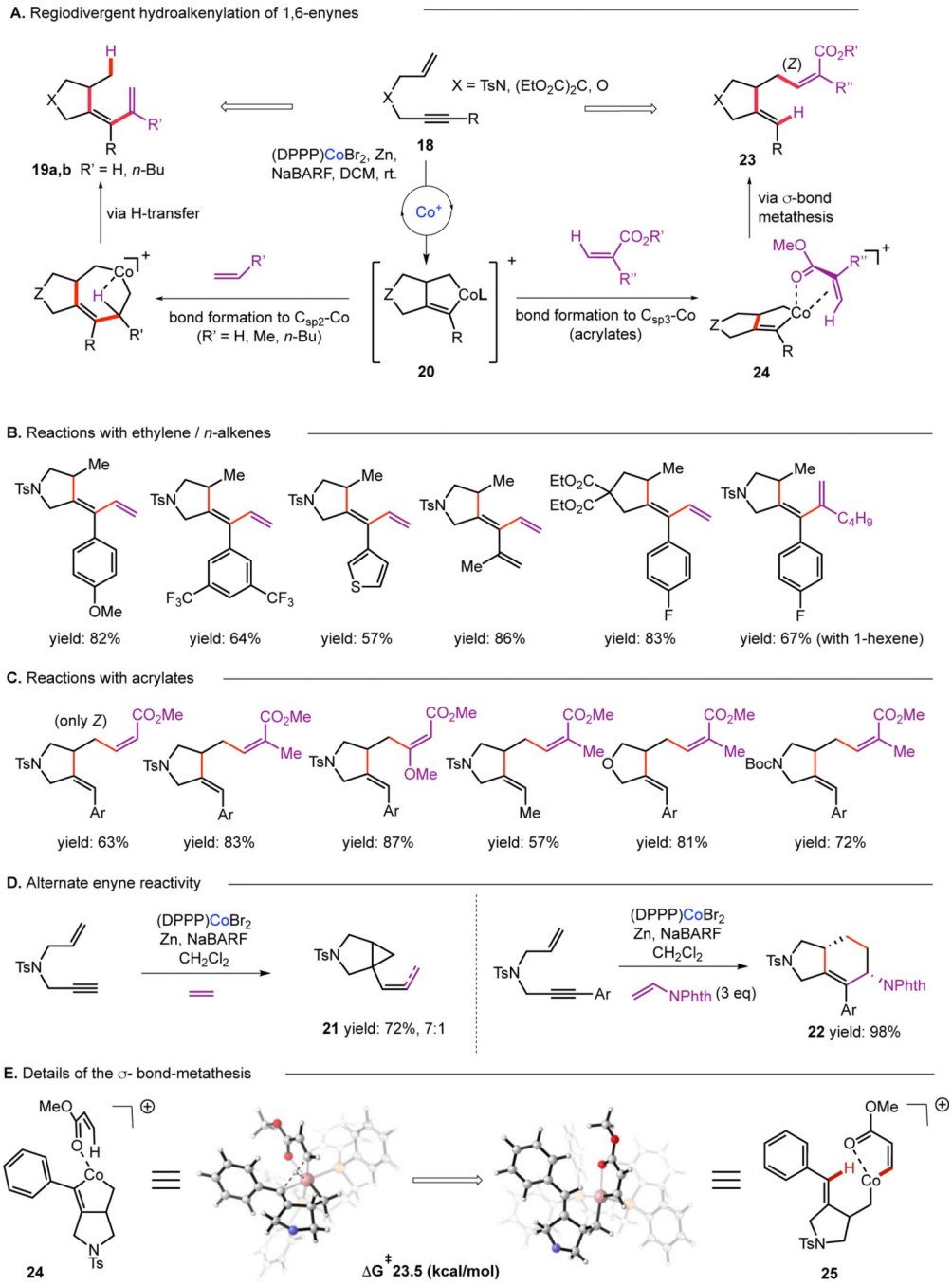
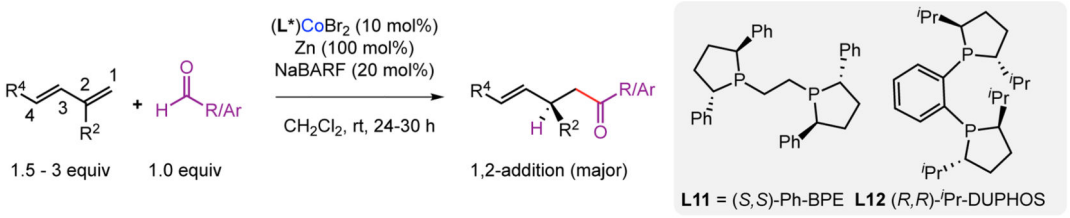
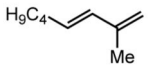
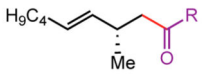
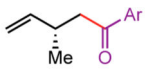
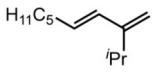
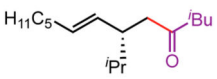
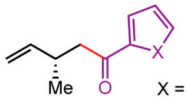
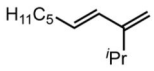
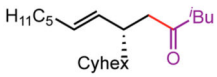
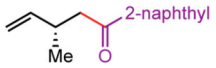
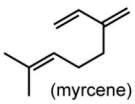
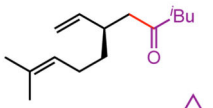
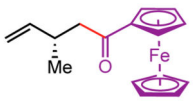
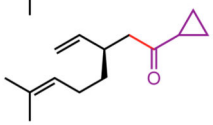
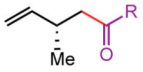
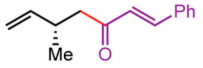
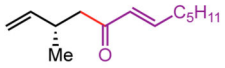


Figure 10.
Cycloisomerization/regiodivergent hydroalkenylation of 1,6-enynes



Dienes and diverse aldehydes					Isoprene and aromatic/alkenyl aldehydes			
no.	diene	adduct	yield/rr	ee (%)	no.	adduct	yield/rr	ee
1.					6.			
		R = ^{i}Pr	75/9:1	94		Ar = Ph	96/7:1	99
		^{n}Bu	63/7:1	84		3,4-(OMe)$_2$C$_6$H$_3$	79/9:1	99
		Cyclopentyl	66/7:1	93		4-CF$_3$-C$_6$H$_4$	98/3:1	99
						4-MeCO$_2$C$_6$H$_4$	94/6:1	80
						4-Br-C$_6$H$_4$	95/4:1	98
2.			66/4:1	94	7.			
						X = O	65/9:1	99
						X = S	76/3:1	97
3.			54/6:1	82	8.		95/3:1	98
4.			84/6:1	>80	9.		85/20:1	98
	(myrcene)		57/9:1	98	10.		26/9:1	98
5.					11.		78/20:1	99
	(isoprene)				12.		72/9:1	nd
	(*S*)-Dihydrotagetone	R = ^{i}Bu	83/16:1	92				
		^{n}Hex	89/7:1	88				
		Cyclopentyl	90/11:1	90				
		Cyclohexyl	84/19:1	92				

(*S*,*S*)-Ph-BPE used as the ligand. rr = ratio of 1,2-adduct to other regioisomers.
For myrcene (*R*,*R*)-^{i}Pr-DUPHOS was used as the ligand.

Figure 11.
Enantioselective hydroacylation of 2- and 2,4-disubstituted 1,3-dienes

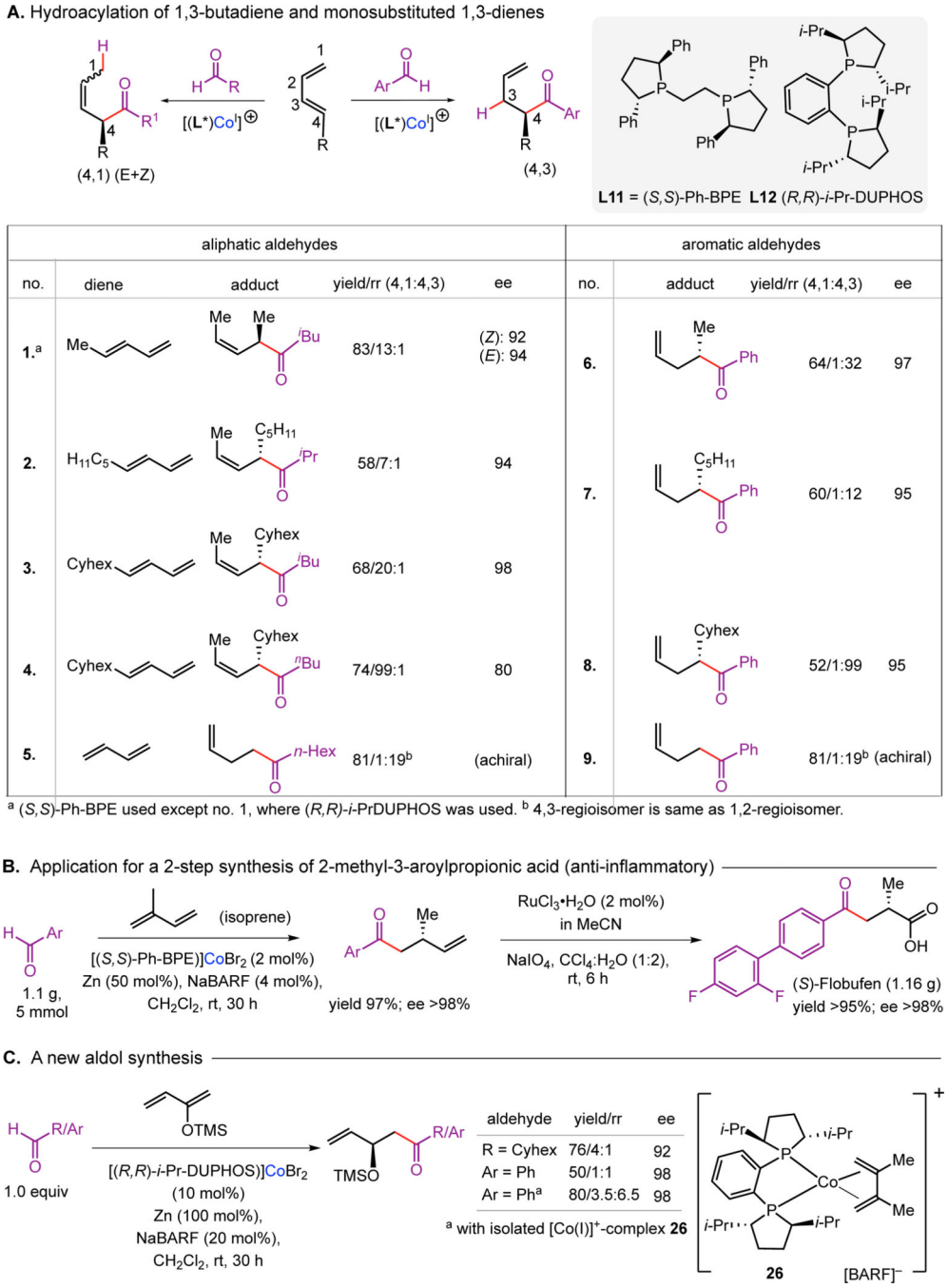


Figure 12.

Enantioselective hydroacylation of 4-substituted 1,3-dienes. Applications of enantioselective hydroacylations

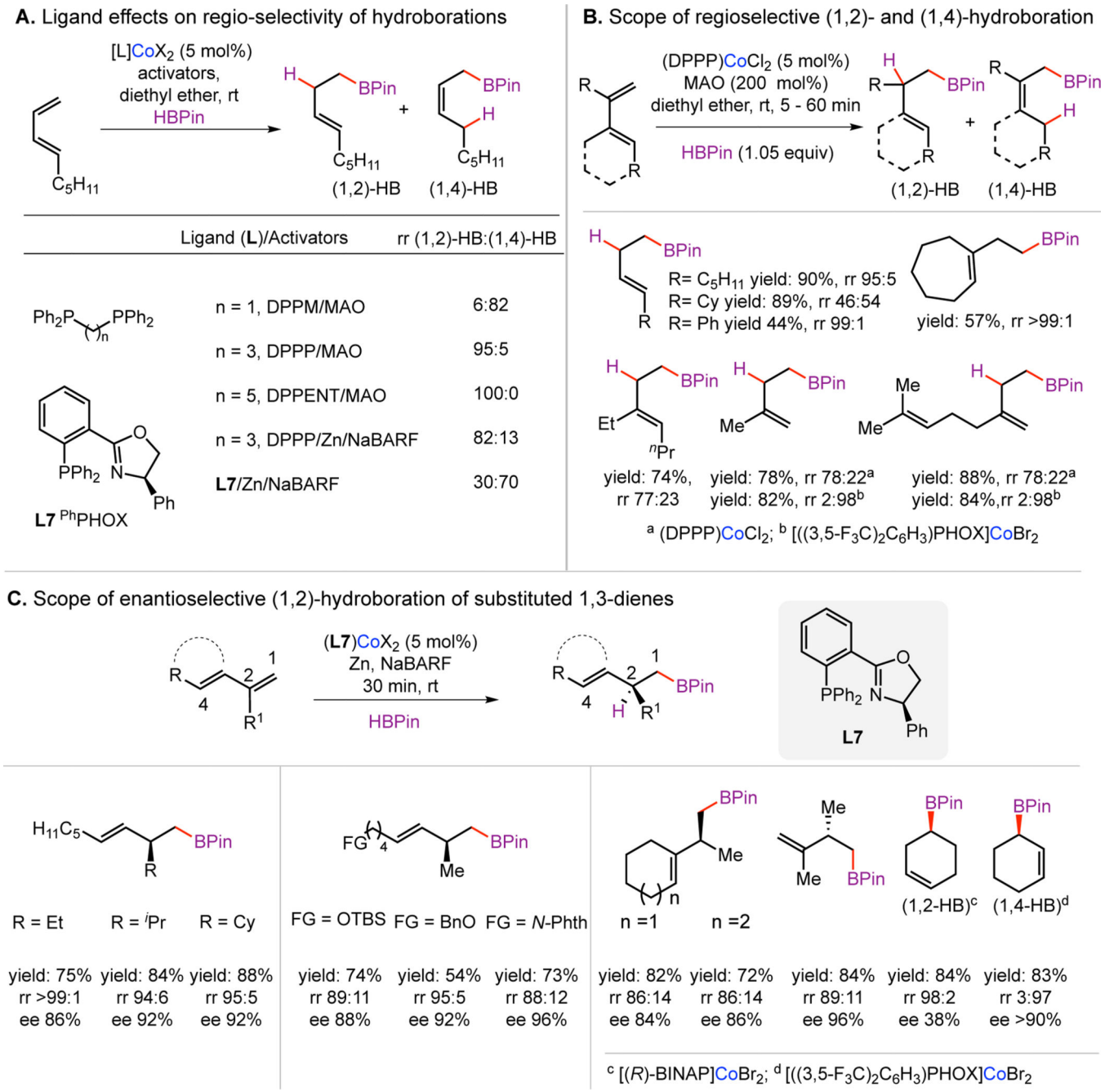
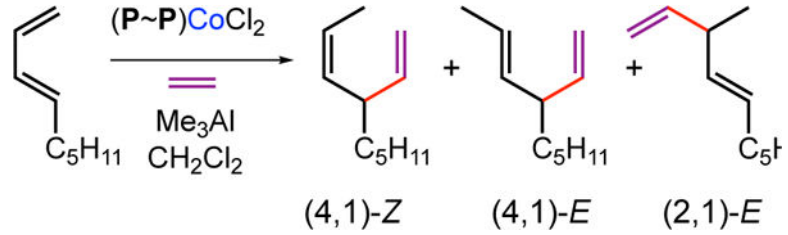


Figure 13.
Enantioselective hydroboration of 1,3-dienes

Table 1.

Ligand Effects in Co-Catalyzed HV of 1,3-Dienes



no.	ligand	*T* (°C)	(4,1)-*Z*	(4,1)-*E*	(2,1)-*E*
1.	DPPB	−20	94	<1	0
2.	DPPP [a]	−20	75	0	0
3.	DPPP	23	0	26	65
4.	DPPM	−20	<2	33	64

[a] + 14% 1,4-linear.

Table 2.

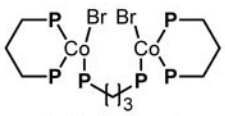
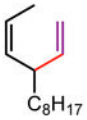
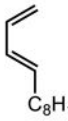
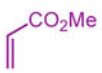
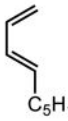
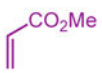
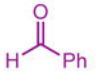
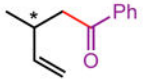
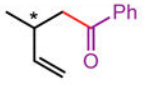
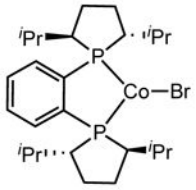
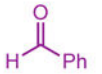
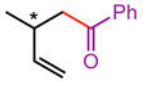
Substrate Scope of Enantioselective HV of 1,3-Dienes

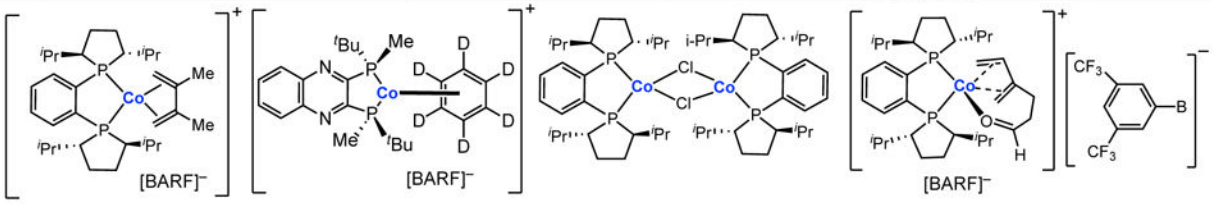
no.	R^4	ligand	yield %	ee % (config.)
1.	Me	(*R,R*)-DIOP	95	95 (*S*)
2.	C_5H_{11}	(*R,R*)-DIOP	95	95 (*S*)
3.	C_5H_{11}	(*S,S*)-BDPP	96	96 (*S*)
4.	CyHex	(*S,S*)-DIOP	49	84 (R)
5.	$BnOCH_2CH_2$	(*S,S*)-BDPP	95	97 (*R*)
6.	$BrCH_2CH_2$	(*S,S*)-DIOP	97	93 (*R*)
7.	$EtOC(O)CH_2$	(*S,S*)-BDPP	84	98 (S)

See Figure 3 A for procedure.

Table 3.

Role of cationic cobalt(I) intermediates in heterodimerization and hydroacylation reactions

no	catalyst	diene	reagent	product	reaction conditions	comments
1.	 **27** (**P** = Ph_2P)		 (1 atm)		[**27**] (5 mol%) NaBARF (20 mo%) DCM, rt, 1 hr	100% conv. 82% yield
2.					[**27**] (10 mol%) NaBARF (0 mol%) DCM, rt, 3 h	no reaction
3.	**27**				[**27**] (5 mol%) NaBARF (15 mol%) CH_2Cl_2, rt, 0.5 h	100% conv. 85% yield
4					NaBARF (0 mol%) DCM, rt, 18 h	no reaction
5.	{[(*R*)-QuinoxP*]Co}$^+$ [η^6-C_6D_6] [BARF]$^-$ **28**				[**28**] (1 mol%) DCM, rt, 10 h (single-component catalyst, **28**)	100% conv. 93% yield 94% ee
6.	{[(*R,R*)-*i*-PrDUPHOS]Co^{I}Cl}$_2$ (**29**)				(**29**) (2.5 mol%) NaBARF (7.5 mol%) ether, 24 h	100% conv. 60% yield 96% ee
7.	{[(*R,R*)-*i*-PrDUPHOS]Co^{I}Cl}$_2$ (**29**)				(**29**) (2.5 mol%) NaBARF (0 mol%) ether, 24 h	no reaction
8.	{[(*R,R*)-*i*-PrDUPHOS]Co (DMBD)]}$^+$ [BARF]$^-$ (**26**)				(**26**) (5 mol%) DCM, 40 h (single-component catalyst) (**26**)	60% conv. 36% yield 96% ee
9.	 **31** 'Zn-reduced (DUPHOS)$CoBr_2$'				[(*R,R*)-*i*-Pr-DUPHOS]Co^{II}Br_2 (5 mol%), Zn (50 mol%) NaBARF (7.5 mol%) DCM, 24 h	93% conv. 56% yield 96% ee
10.					Same as above except NaBARF (0 mol%) DCM, 24 h	no reaction



26 {[(*R,R*)-*i*-PrDUPHOS] Co(DMBD)} **28** [(*R*)-Quinoxp]Co(C_6D_6)] **29** {[(*R,R*)-*i*-PrDUPHOS]Co^{I}Cl}$_2$ **30** {[(*R,R*)-*i*-PrDUPHOS] Co(diene-aldehyde)} BARF$^-$

All structures (**26**– **30**) confirmed by X-ray crystallography.