Cycloaddition Reactions Hot Paper

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Chemodivergent, Regio- and Enantioselective Cycloaddition Reactions between 1,3-Dienes and Alkynes

*Dipshi Singh and T. V. RajanBabu**

Abstract: Alkynes and 1,3-dienes are among the most readily available precursors for organic synthesis. We report two distinctly different, catalyst-dependent, modes of regio- and enantioselective cycloaddition reactions between these classes of compounds providing rapid access to highly functionalized 1,4-cyclohexadienes *or* cyclobutenes from the *same* precursors. Complexes of an earth abundant metal, cobalt, with several commercially available chiral bisphosphine ligands with narrow bite angles catalyze [4+2]-cycloadditions between a 1,3-diene and an alkyne giving a cyclohexa-1,4-diene in excellent chemo-, regio- and enantioselectivities. In sharp contrast, complex of a finely tuned phosphino-oxazoline ligand promotes unique [2+2]-cycloaddition between the alkyne and the terminal double bond of the diene giving a highly functionalized cyclobutene in excellent regio- and enantioselectivities.

Introduction

1,3-Dienes and alkynes are among the most readily available starting materials for organic synthesis, and many of them are marketed as feedstock materials for chemical industry.[1–7] Chemo-, regio- and, especially, enantioselective union of such abundantly available precursors would provide quick access to valuable intermediates for synthesis of compounds of interest to medicinal, agricultural and materials applications, thus adding to our repertoire of environmentally benign processes, especially if reactions are promoted by catalysts derived from earth-abundant metals. For reactions between a 1,3-dienes and alkynes, two types of very powerful cycloaddition reactions, a [2+2]-[8–10] or a [4+2]-[11–13] cycloaddition can be envisioned. These reactions have attracted significant attention because of their ability to forge multiple carbon-carbon bonds in a highly selective and often predictable fashion with minimal waste generation. However, in the realm of alkyne chemistry the full potential of neither of these cycloaddition reactions have been realized. Even though there are examples of metal-catalyzed [2+2]-cycloadditions of alkynes,[10b–g] none of these involve a 1,3-diene reacting chemoselectively as a 2-π-component with an alkyne to give a highly functionalized cyclobutene product with a chiral center bearing an alkenyl group, one of the most useful latent functionalities for further synthetic operations (Figure 1B). As for a chemoselective [4+2]-cycloaddition between an acyclic 1,3-diene reacting as a 4-π-component and an alkyne dienophile, most known enantioselective reactions use cyclic dienes.[14–16] There is one notable exception in a metal catalyzed cycloaddition, that of a single dienophile, dimethyl acetylenedicarboxylate, which gives useful levels of enantioselectivity (Figure 1A).[17] In addition to the limited scope of the dienophile, this reaction uses 10 mol % of prohibitively expensive[18] catalyst, $[(\text{norbornadiene})_2\text{Rh}]^+[\text{BF}_4]^-$ (≈9 turnovers) and 20 mol % of $AgSbF_6$. The best enantioselectivity to date for a related cobalt-catalyzed [4+2]-cycloaddition reaction, which was originally discovered by Hilt in 2001,[19] is an only 71 % *ee*,[20] providing a challenging opportunity to develop this venerable reaction using an earth-abundant metal.

In our search for new applications of the iron-triad metals (Fe, Co, Ni) in organic synthesis, we have recently demonstrated that cationic Co^I complexes[18] of various bisphosphine and phosphino-oxazoline ligands catalyze a number of broadly applicable enantioselective reactions of 1,3-dienes where exquisite control of regio- and enantioselectivities can be realized by the choice of ligands and reaction conditions.[21] These include heterodimerization of dienes with feedstocks such as ethylene,[22] methyl acrylate,[23] and common aldehydes.[24] We recently reported that highly enantioselective hydroboration of prochiral 1,3-dienes with H-BPin can also be effected using similar catalysts in a regiodivergent fashion with boron entering the C1 or C4 of the diene depending on the catalyst.[25,26] No such chemo-/regio- divergent processes are known among the cycloaddition reactions of 1,3-dienes.[27]

We wondered if we could achieve such divergent reactivity in reactions between 1,3-dienes and alkynes, for example, via [2+2] versus [4+2] cycloadditions, and, at the same time retain high yield, regioselectivity and enantioselectivity by appropriate fine-tuning of the catalyst. Indeed, these expectations have been borne out, and in this paper, we report applications of cationic cobalt(I) complexes for chemodivergent, regio- and enantioselective selective [4+2]

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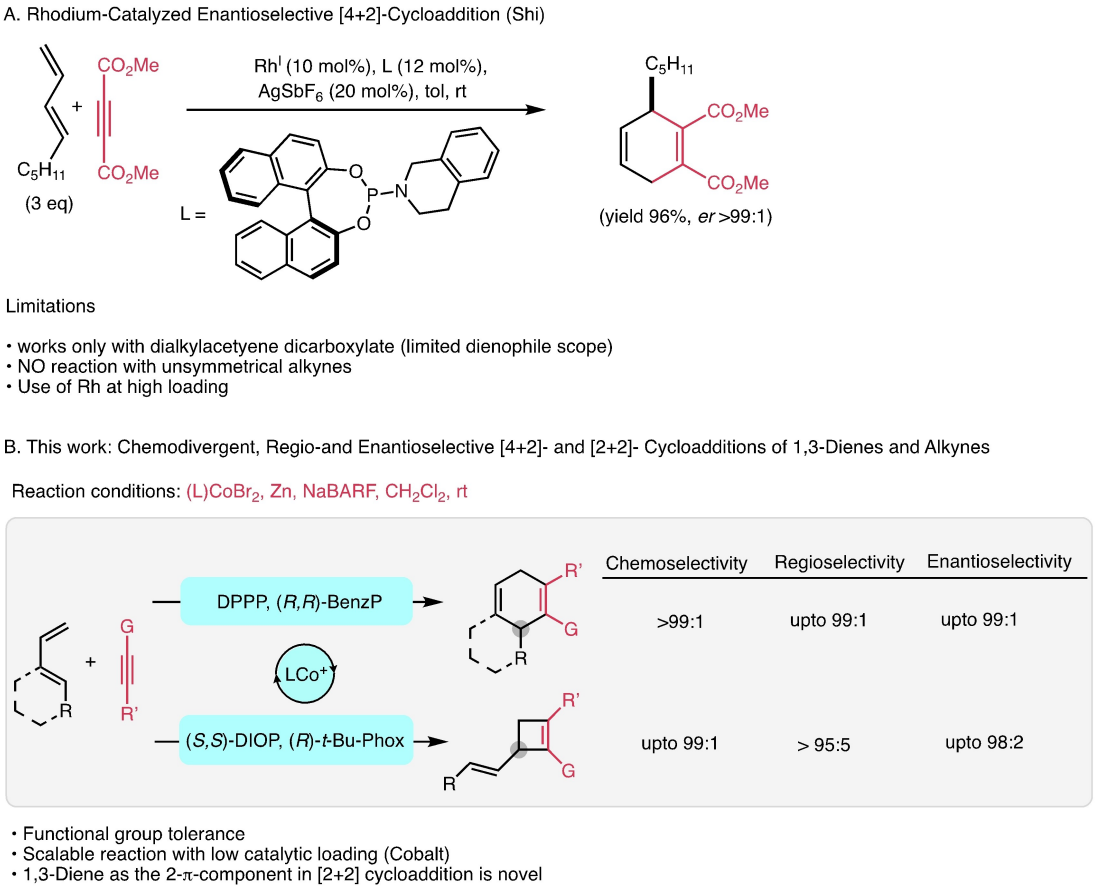


Figure 1. A) Best reported inter-molecular enantioselective [4+2]-cycloadditions between 1,3-dienes and alkynes use expensive Rh-catalyst and has limited substrate scope. B) Finely tuned cobalt catalysts promote two distinct modes of highly regio- and enantioselective cycloadditions between 1,3-dienes and alkynes. For the structures of ligands see, Figures 2 and 3.

and [2+2] cycloadditions between a broad range 1,3-dienes and functionalized alkynes (Figure 1B).[28] The products of these reactions, 1,4-cyclohexadienes, cyclobutanes and cyclobutenes are very common structural motifs in many biologically relevant compounds including natural products.[9,29,30]

Results and Discussion

Our studies started with an examination of the reaction between a prototypical 1,3-diene, (*E*)-1,3-nonadiene, and various alkynes, under conditions known to generate a cationic $[(L)Co^{I}]^{+}$ species.[23] Initial attempts to affect the reaction between unactivated internal alkynes and typical 1,3-dienes led to unacceptable mixtures of products. Keeping in mind that electronically different partners might be more suitable for this reaction that presumably proceed through an oxidative dimerization mechanism (vide infra), for further optimization studies, we turned to an activated alkyne, methyl hex-2-ynoate (**2a**) for reactions with a relatively electron-rich (*E*)-1,3-nonadiene [See Eq. in Table 1].

In initial optimization studies we examined the effect of ligands, counter ions, and solvents on this reaction (see Supporting Information for details, p. S12–S17), which produced varying amounts of [4+2]- and [2+2]-cycloaddition products (**3a** and **4a**) depending on the ligand and reaction conditions. The most salient results from these studies on the ligand effects are shown in Table 1.

Identification of Ligands for Chemodivergent [4+2]- or [2+2]-Cycloadditions between 1,3-Dienes and Alkynes

Initially we examined two types of cobalt complexes that were previously found to be useful in C–C and C–B bond-forming reactions, chelating bisphosphines possessing different bite angles, and easily tunable 2-[(2-dialkyl or 2-diaryl)phosphinoaryloxazolines (PHOX) ligands (Table 1, see also Supporting Information p. S15–S16). In Table 1, the bisphosphine ligands are arranged approximately in order of increasing natural bite angle.[31,32] As shown in entries 1–6 the proportion of the [4+2]-adduct **3a** steadily diminishes as the bite angle of the ligand is increased. Ligands with the smallest bite angles DPPM, DPPP, and BINAP having the angles below 93° (entries 1–3) gave almost exclusively the

Diels–Alder product, whereas ligands DPPB and DPPF with bite angles 94° and 99° gave a mixture of [4+2]- and [2+2]-adducts (entries 4 and 5). DIOP, another ligand with a relatively large bite angle (98°) gave exclusively the [2+2]-cycloaddition product **4a** (entry 6). Complexes of other ligands with even larger bite angles (DPPPent, DPEPhos, Xantphos and BISBI, entries 7–10) altogether failed to affect the reaction. Differing compositions of the [4+2] and [2+2]-products within ligands of a narrow bite angle, for example, entries 3 and 4 [BINAP (93°), DPPB (94°)] and entries 5 and 6 [DPPF (99°), DIOP (98°)], suggest that although bite angle can be used as an approximate measure, it alone does not totally control the reactivity or selectivity of these reactions.

Selectivities of the phosphino-oxazoline complexes are less predictable, yet preparatively useful, with the parent 2-(2-diphenylphosphino)phenyloxazoline ligand (**L1a**, Figure 2) with no substituent in the 3- or 4-position of the oxazoline giving [4+2]-adduct as the major product (entry 11). Substitution at the 3-position of the oxazoline with an aryl group (ligands **L1b**, **L2**, **L3**, Figure 2) brings about notable changes in the regioselectivity of the reaction: the 2-diphenylphosphinophenyl oxazoline derivative (**L1b**) gave 1:2 mixture of [4+2] and [2+2] adducts (entry 12), while **L2** with a larger *P*-aromatic gave ≈1:5 mixture of the two adducts with the [2+2]-adduct as the major product (entry 13) with *er* of 80:20. The corresponding 2-dicyclohexylphenyl-3-phenyl oxazoline (**L3**) gave exclusively [2+2]-cycloadduct with no trace of the [4+2]-adduct (entry 14). But the [2+2] adduct was formed with only an *er* of 54:46. However, upon changing the substitution at the 3-position of the oxazoline from an aryl group to *t*-butyl group (**L4**) drastically increased the enantioselectivity, giving an *er* of 98:2 (entry 15). The unpredictability of substituent effects is attested by a related ligand **L5**, which gave high chemoselectivity, but low *er* (entry 16, Table 1). Finally, it was noted that the flexibility of tuning in the PHOX-system enabled the discovery of ligand **L4** that gives exceptionally high *er's* in 10 products (*er* >95:5, vide infra, Table 3, column 8).

The preparative value of the remarkable ligand effects across two well-known classes notwithstanding, a satisfactory rationalization of the variation of chemoselectivities should wait our on-going mechanistic and computational studies (vide infra). While the results with bisphosphines indicate some dependance on the bite-angle of the ligand, no such relation exists in the PHOX series.

Enantioselective [4+2]-Cycloadditions

Having identified small bite-angle as a key feature of possible ligands for the control of regioselectivity of the cycloaddition, we turned to optimization of enantioselectivity in the Diels–Alder reaction. The results of [4+2]-cycloaddition reactions conducted under the optimized conditions [Eq. in Table 1] using selected chiral ligands are shown in Table 2. A more complete list of ligands that we examined is included in the Supporting Information as well as in Figure 3 (Table ST2, p. S15–S16).

As can be seen in Table 2, chiral chelating bisphosphines with relatively small bite angle (<93°) are the best ligands for the formation of the Diels–Alder product. For consideration of the bite angles we have used the (P≈P)$CoBr_2$ complexes, for which we have complete data, from either the literature or from our own work (Supporting Information, Table ST5, p. S19–S20). Thus, the cobalt(II)-complex

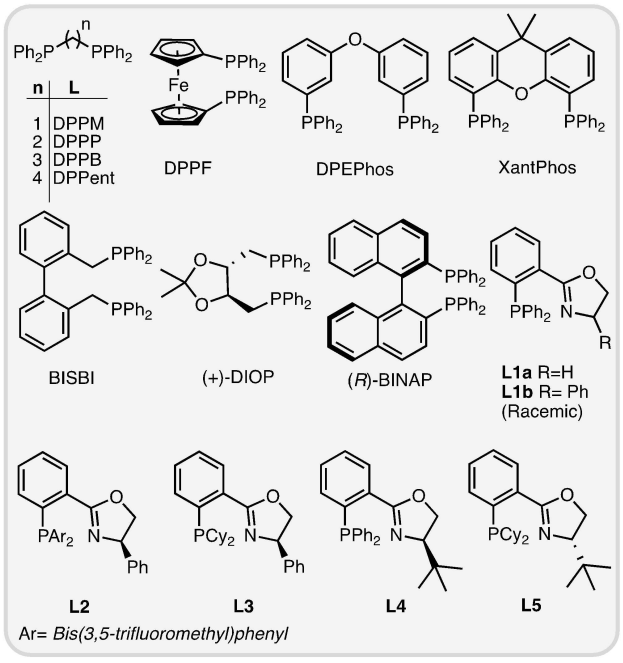


Figure 2. Structures of selected ligands used for optimization of [4+2]- and [2+2]-cycloadditions between 1,3-dienes and alkynes. See Supporting Information (p. S16) for a more complete list.

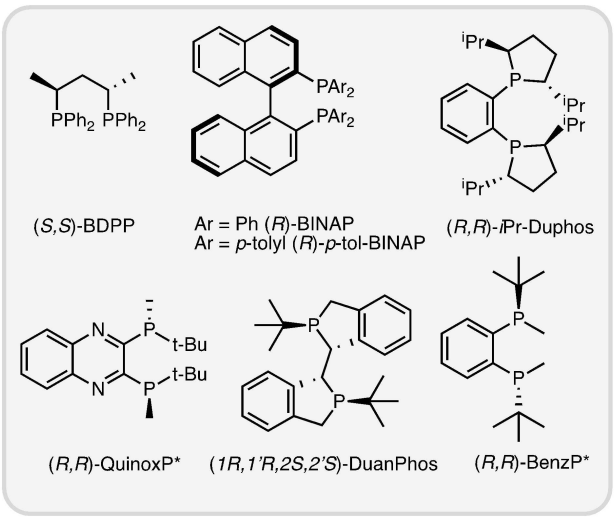
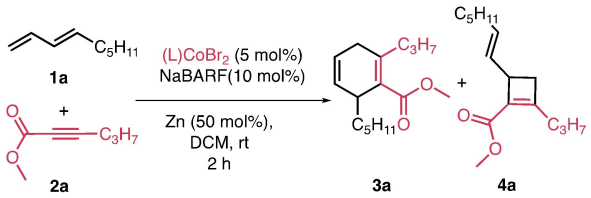


Figure 3. Partial list of chiral ligands explored for enantioselective [4+2]-cycloadditions of 1,3-dienes and alkynes. See Supporting Information for a more complete list (Figure SF4, p. S16).

Table 1: Cobalt-catalyzed reactions between (*E*)-1,3-nonadiene and methyl hex-2-ynoate. Optimization of ligands for [4+2]- and [2+2]-cycloadditions.[a]



Entry	Ligand[b]	Bite angle[c]	Conv.[d]	**3a** [%]	**4a** [%]	Others
Bisphosphine ligands						
1	DPPM	73	89	76	–	34
2	DPPP	91	100	74	–	36
3	(*R*)-BINAP	93	100	91	–	9
4	DPPB	94	100	63	37	–
5	DPPF	99	100	65	35	–
6	(*S*,*S*)-DIOP	98	100	–	95	–
7	DPPPent	–[c]	5	–	–	sm
8	DPEPhos	104	0	–	–	sm
9	XantPhos	108	5	–	–	sm
10	BISBI	122	0	–	–	sm
Phosphino-oxazoline ligands						
11	PHOX **L1a**	–	82	89	–	11
12	Ph-PHOX **L1b**[e]	–	100	30	60	10
13	Bis-CF_3-Ph-PHOX **L2**	–	100	16	84[f]	–
14	Cy_2P-Ph-PHOX **L3**	–	100	–	93[g]	–
15	(*R*)-t-Bu-PHOX **L4**	–	100	38	50[h]	12
16	(*S*)-t-Bu-PCy_2 -PHOX **L5**	–	100	9	91[i]	–

[a] See Equation above and Supporting Information (p. S9) for details of the procedures. [b] See Figure 2 for structures of the ligands. For a more complete list see Supporting Information, Figure SF4. p. S16. [c] From ref. [32]. Bite angle is not reported for DPPPent (entry 7) but is expected to be higher than that of DPPB. [d] Determined by GC. [e] $CoCl_2$ complex. [f] *er* for [2+2] product = 80:20. [g] *er* for [2+2] = 54:46. [h] *er* for [2+2] adduct = 98:2. [i] *er* for [2+2] = 59:41. sm: starting material.

of (*S*,*S*)-BDPP,[33] a chiral analog of DPPP, gave good yields of the expected product **3a** as a single regioisomer, albeit with only low enantioselectivity (entry 1). 2,2′-Diarylphosphino-1,1′-biaryls, including (*R*)-BINAP and its analog (*R*)-*p*-tol-BINAP (entries 2 and 3) are also good ligands for the [4+2]-addition, but giving unacceptably low enantioselectivities. (*R*,*R*)-*i*Pr-Duphos, a ligand that was found to give excellent enantioselectivities in other low-valent Co-mediated reactions including hydroacylation reactions of 1,3-dienes[24] also failed to give useful level of enantioselectivity (entry 4). Entries 5–7 show 3 commercially available ligands (QuinoxP*, DuanPhos and BenzP*) that gave very good to excellent enantioselectivities for the test reaction. Among the three ligands, BenzP* gave the best overall yield and enantioselectivity and this ligand was chosen for further optimization and expansion of the scope of this reaction.

It was quickly established that methylene chloride was the solvent of choice and as an activator NaBARF was

Table 2: Enantioselective [4+2]-cycloaddition reaction of 1,3-diene and alkyne.[a]

Entry	Ligand[b]	Bite angle in **L**$CoBr_2$[c]	Conv.[d]	**3a** [%]	Others [%][d]	Er **3a**[d]
1	(*S*,*S*)-BDPP	97	98	98	2	63:37
2	(*R*)-BINAP	93	100	91	9	77:23
3	(*R*)-p-tol-BINAP	–	100	100	–	80:20
4	(*R*,*R*)-iPr-Duphos	88	100	92	8	68:32
5	(*R*,*R*)-QuinoxP*	91	100	92	8	93:7
6	(1*R*,1′*R*,2*S*,2′*S*)-DuanPhos	88	90[e]	93	7	95:5
7	(*R*,*R*)-BenzP*	86	100	90	10	95:5

[a] See Eq. in Table 1 and Supporting Information for typical procedure (Supporting Information, p. S9–S10). [b] See Figure 3 for structures of the ligands. [c] Calculated from solid-state structures of the Co^{II} complexes, see Supporting Information. p. S19–S20. [d] Determined by GC. [e] In 24 h. The major side-product is a trimer of the alkyne (Supporting Information, p. S60, **2aa**). No regioisomer of **3a** was detected.

superior to other activators like ZnI_2, $AgSbF_6$ and $InBr_3$ (Supporting Information Table ST3, p. S17). We have since found that most reactions can be carried out with as little as 5 mol % zinc. The reactivity and selectivities are not drastically affected in the prototypical reaction shown in Figure 4 with the test substrates and ligands DPPP and (*R*,*R*)-BenzP* (Scheme 1, See Supporting Information Table ST4, p. S17).

We have also established that cationic cobalt(I) is crucial for the cycloaddition reaction. A reaction carried out with

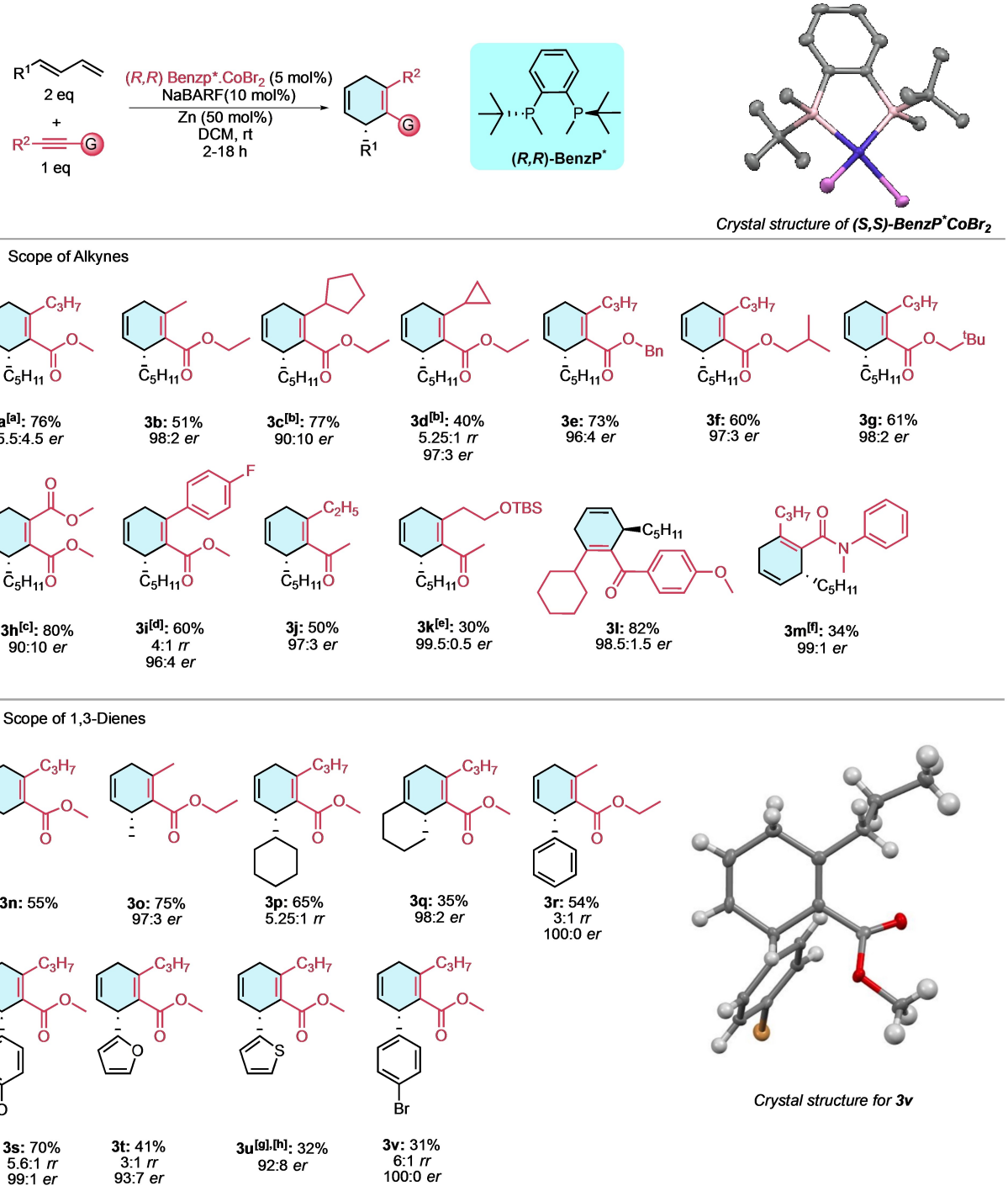


Figure 4. A) Scope of alkynes in [4+2]-cycloaddition reaction. B) Scope of 1,3-dienes in [4+2]-cycloaddition reactions. [a] *Er* reported on a product in which the isolated double bond was reduced (**3a′**), see Supporting Information p. S10, S23. [b] Reaction was heated at 40 °C. [c] [(*R*,*R*)BenzP*]$CoBr_2$ (10 mol %), NaBARF (20 mol %), Zn (1 equiv.) used. [d] [(1*R*,2*S*)-DuanPhos]$CoBr_2$ (10 mol %), NaBARF (20 mol %), Zn (1 equiv.) used. [e] Incomplete reaction, rest starting material. [f] 33 % [2+2] product in crude GC, yield reported for isolated [4+2] product. [g] [(*R*,*R*)-QuinoxP*]$CoBr_2$ (5 mol %), NaBARF (10 mol %), Zn (0.5 equiv.) used. [h] Yield reported for isolated compound.

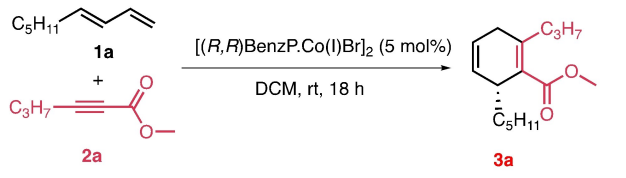
Ligand	Zn loading	% conversion	Product (GC%)
DPPPCoBr$_2$	5 mol%	100	86
(*S*,*S*)-BenzPCoBr$_2$	5 mol%	100	85

Scheme 1. Effect of Zn loading.

isolated complex [(BenzP*)Co^{I}Br]$_2$ alone showed no sign of Diels–Alder reactivity. However, a combination of this complex and NaBARF gave 100 % conversion to the [4+2] product with excellent regioselectivity (Scheme 2, See experimental details and GC supporting the conclusion in the Supporting Information, p. S18).

Scope of Alkynes in [4+2]-Cycloaddition Reaction with 1,3-Dienes

The scope of the alkynes in the enantioselective Diels–Alder reaction with (*E*)-1,3-nonadiene with various functionalized alkynes was examined and structures of the [4+2]-adducts formed are shown in Figure 4A. The progress of the reaction was monitored by GC and showed no other cycloaddition products including regioisomers of **3**.[34] The only byproduct seen in some cases was identified as arising from the trimerization of the alkyne (Supporting Information p. S60). Methyl and ethyl alkynoates with simple alkyl substituents at C3-position gave the corresponding 1,4-cyclohexadienes (**3a**–**3d**) in good yields and excellent regio- and enantioselectivities (*er* > 95:5). Variations on the propiolate ester include those derived from primary, secondary and benzyl alcohols (**3e**–**3g**), all giving excellent regio- and enantioselectivities. Acetylene dicarboxylate underwent the reaction giving a product, **3h** (*er* = 90:10), a compound that had been reported in the literature.[17] Acetylenic ketones also proved to be good substrates (**3j**–**3l**) giving excellent



catalyst	% conversion
[(*R*,*R*)-BenzP.Co(I)Br]$_2$ (5 mol%)	0
[(*R*,*R*)-BenzP.Co(I)Br]$_2$ (5 mol%) + NaBARF (10 mol%)	100

Scheme 2. Role of cationic Co^{I} complex in cycloaddition reactions. Neutral Co^{I} complex is an ineffective catalyst for the cycloaddition reactions.

enantioselectivities, even when the C3-alkyl substituent carried a TBS-protected alcohol (**3k**). Functional group such as an amide (**3m**) was also tolerated well giving the expected product with excellent enantioselectivity (*er* = 99:1) and good yield of isolated Diels–Alder product. The regioselectivities in several cases were established by 2D NOESY and the absolute configurations of the products were deduced by comparison to **3v** (Figure 4B), whose structure was determined by X-ray crystallography.[35] Also, to assess the feasibility of this method on preparative scale, compound **3a** was synthesized on large scale (5 mmol) giving 60 % isolated yield using catalyst loading as low as 2.5 mol % (For details see Supporting Information, p. S11).

Scope of 1,3-Dienes in [4+2]-Cycloaddition Reaction with Functionalized Alkynes

Next, the scope of the 1,3-diene in the [4+2]-cycloaddition with alkyl propiolate was explored and the structures of the adducts formed are shown in Figure 4B. This reaction showed surprisingly broad generality with alkyl, aryl as well as heteroaryl-substituted 1,3-dienes taking part in the reaction giving very good to excellent enantioselectivity (*er* = 92:8 to > 99:1). The product of addition of 1,3-butadiene (**3n**), 2,4-pentadiene (**3o**) and 1-cyclohexylbuta-1,3-diene (**3p**) are formed in good yields with 1-cyclohexylbuta-1,3-diene alone giving two regioisomeric products in 5:1 ratio. Cyclic diene containing an endocyclic double bond, 1-vinylcyclohex-1-ene, gave bicyclic product (**3q**) in high enantioselectivity and modest yield. We have noticed lower yields of the product when the diene is less reactive. Products from difficult substrates such as aromatic dienes, 1-phenyl-1,3-butadiene (**3r**), 1-(4-methoxyphenyl)-1,3-butadiene (**3s**) and 1-(4-bromophenyl)-1,3-butadiene (**3v**) are formed in exceptionally high enantioselectivity (> 99:1) and good regioselectivity with minor amounts of other regioisomer. The absolute configuration of the [4+2]-adduct **3v** was determined from X-ray crystallographic analysis as mentioned before. Heteroaromatic dienes, 1-(1-furanyl)buta-1,3-diene (**3t**) and 1-(1-thiophenyl)butadiene (**3u**) also gave very good enantioselectivity, with 1-(1-furanyl)buta-1,3-diene (**3t**) formed in 3:1 ratio of two regioisomers, where the major isomer was formed with an *er* of 98:2. 1-(1-Thiophenyl)butadiene gave a product 1,4-cyclohexadiene (**3u**) in good yield with a better *er* of 92:8 using (*R*,*R*)-QuinoxP* as compared to (*R*,*R*)-BenzP*. We note that the aromatic dienes are the only ones that gave any notable amounts of the regioisomers.

Chemo- Regio- and Enantioselective [2+2]-Cycloaddition. Highly Functionalized Cyclobutenes

Intermolecular [2+2]-cycloaddition reaction between a 1,3-diene and an alkyne to produce a highly functionalized cyclobutene (Figure 5), to the best of our knowledge, has no precedent in the literature. As shown in Table 1, we have identified several ligands, among them (*S*,*S*)-DIOP and

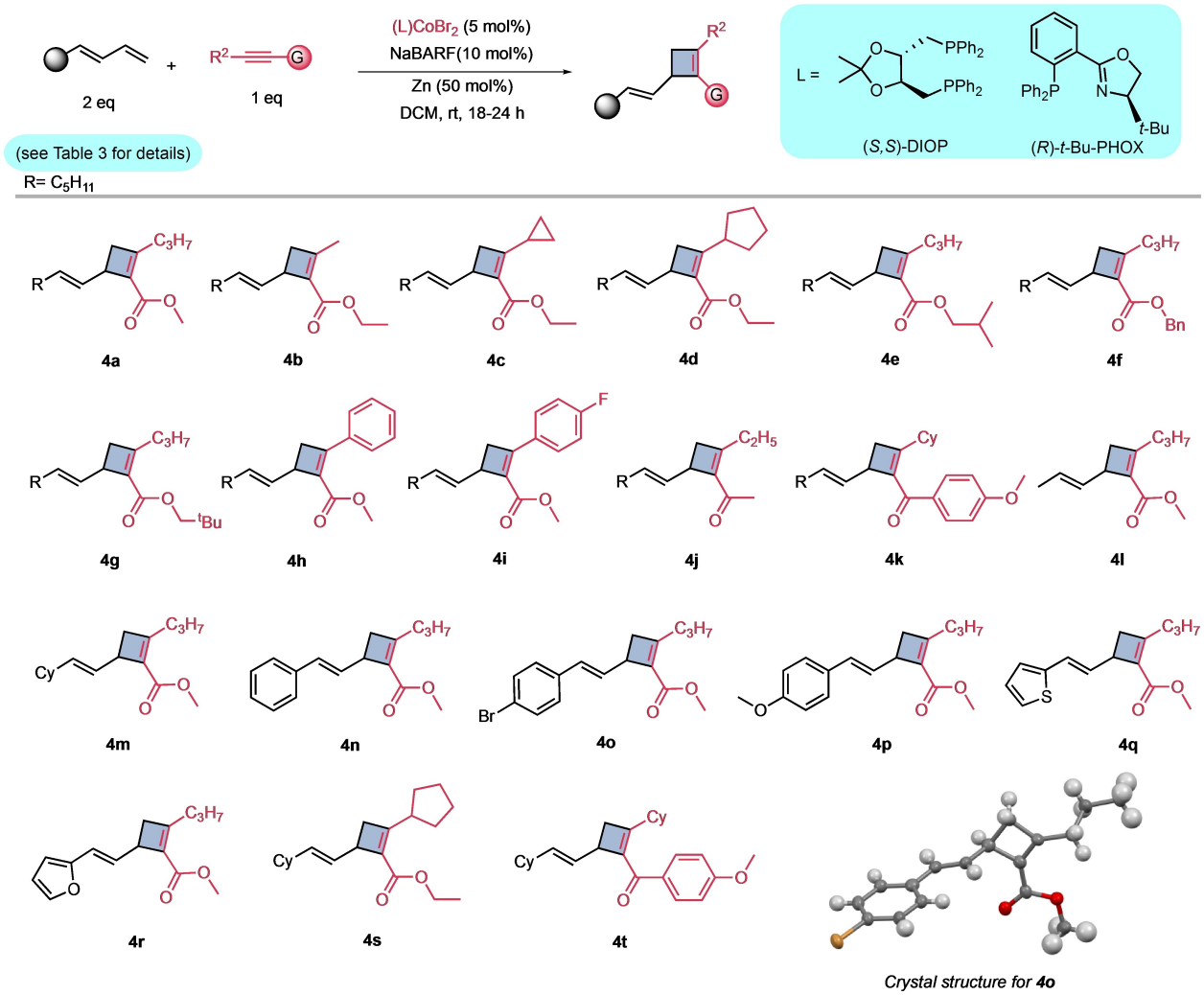


Figure 5. Structures of products in chemo-, regio- and enantioselective [2+2]-cycloaddition reactions between 1,3-dienes and alkynes. See Table 3 for additional details of selectivities as a function of ligands.

modified phosphino-oxazoline ligands (Table 1, entries 6, 14) that gave almost exclusively the [2+2]-cycloaddition. For a more extensive listing of ligands and the selectivities they give, see Table ST2, p. S15 in the Supporting Information.

Among the ligands (*S*,*S*)-DIOP and *t*-Bu-PHOX (**L4**) were chosen for further expansion of the scope of the substrates. The structures of the products formed are listed in Figure 5 with details of the selectivities shown in Table 3. The commercially available (*S*,*S*)-DIOP ligand was found to give good yields and the highest chemo- and regioselectivity (>95:1, mostly >99:1) for the formation of the products **4a**–**4t**. The cyclobutenes were easily separated from the minor side-products formed, including the [4+2]-adducts, which were readily identified by ^{1}H NMR. Careful NMR studies (NOESY) of several of the adducts, and in one case, X-ray crystallography, established regioselectivities in the products as shown. The major enantiomer of one the [2+2]-cycloadducts (**4o**) was recrystallized and analyzed by X-ray crystallography to reveal the regioselectivity and the absolute configuration of the major product **4o** (*R*).[35] Configurations of the other products were assigned by analogy.

The scope of the alkyne (Figure 5, **4a**–**4k**) parallels the results of the [4+2]-cycloaddition and includes alkyl and benzyl propiolate esters with diverse alkyl and cyclo-alkyl substituents on the C3 carbon of the alkyne (**4a**–**4g**). In addition, 3-aryl substituted propiolates are also tolerated well (**4h**, **4i**). Alkynyl ketones undergo regioselective [2+2] cycloaddition to (*E*)-1,3-nonadiene giving moderate yields of the products (**4j**, **4k**). As for the scope of the dienes (Figure 5, **4l**–**4t**), those bearing alkyl (**4l**), cycloalkyl (**4m**), aryl (**4n**, **4o**, **4p**) and heteroaryl (**4q**, **4r**) substituents at the C4-position undergo this selective reaction producing the [2+2]-product as the sole cycloadduct.

The excellent chemo- and regioselectivity in the formation of the cyclobutenes notwithstanding, the enantioselectivities with the DIOP ligand were typically in the range of only ≈80:20 (*er*) (Table 3, column 5) in cases where we analyzed the enantiomers on chiral stationary Phase HPLC (**4a**, **4c**, **4i**, **4n**, **4o** and **4r**). In order to improve the

Table 3: Enantioselective [2+2]-cycloaddition reaction of 1,3-diene and alkyne.[a]

Entry	[2+2]-adduct	(*S*,*S*)-DIOP[b]			t-Bu-PHOX (L4)[b]		
		Yield [%]	Chemoselectivity (% of [2+2] adduct)[c]	Enantiosel. (er)	Yield [%]	Chemoselectivity (% of [2+2] adduct)	Enantiosel. (er)
1	**4a**	90	94	79:21	95[h]	50	98:2
2	**4b**	90	83[d]	nd	–	–	–
3	**4c**	60	77	85:15	–	–	–
4	**4d**	90	>99	nd	>90[h]	76	95:5
5	**4e**	50	90	nd	99[h]	48	98:2
6	**4f**	70	94	nd	>80[h]	45	96:4
7	**4g**	90	93	nd	91[h]	44	98:2
8	**4h**	90	92[e]	nd	–	–	–
9	**4i**	70	83[f]	79:21	–	–	–
10	**4j**	43	95	nd	–	–	–
11	**4k**	48	>99	nd	–	–	–
12	**4l**	91	>95	nd	>90[h]	57	98:2
13	**4m**	95	>96	nd	>90[h]	65	98:2
14	**4n**	74	>99	82:18	nd	35	94:6
15	**4o**	60	>99	75:25	–	–	–
16	**4p**	62	>99	nd	–	–	–
17	**4q**	42	>99	nd	–	–	–
18	**4r**	65	>99	85:15	–	–	–
19	**4s**	85	>99	nd	87	93	>97:3
20	**4t**	40[g]	>99	nd	40[g]	>99	97:3

[a] See Figure 5. [b] Regioselectivity >95% for the isomer shown, determined by NMR. [c] rest [4+2]-adduct, and unidentified product as indicated (footnotes [d]–[f]). [d] 7% Unidentified. [e] 8% Unidentified. [f] 6% Unidentified. [g] Incomplete reaction, rest starting material. [h] Yields reported are for mixture of isomers (see Supporting Information for details). nd: not determined.

unacceptable levels of enantioselectivities we turned to easily tunable phosphinooxazoline ligands, and, found that a *t*-butyl derivative ligand **L4** gave excellent enantioselectivities for several carefully chosen prototypical cyclobutenes (**4a**, **4d**, **4e**, **4f**, **4g**, **4l**, **4m**, **4n**, **4s**, **4t**). These results are listed in Table 3 (columns 6–8). As noted in the Table under *t*-Bu-PHOX, while the regio- and enantioselectivities of the products continue to be excellent (most >95:5), the chemoselectivities are some-what lower compared to the results obtained from the (*S*,*S*)-DIOP-complex. However, it is hard to envision a more facile approach to the highly functionalized, nearly enantiopure 3-alkenylcyclobutenes without multiple steps. Besides, the discovery of the ligand effects also set the stage for further improvements through ligand tuning. Incidentally, a careful examination of the structures of cyclobutenes produced (especially **4d**, **4m**, **4s**, **4t**) reveals that sterically demanding substituents on the C3-postion of the alkyne or at the C4 position of the diene give high chemoselectivities (>80%), and these structural elements could be useful for obtaining higher overall selectivities for this exacting reaction.

Plausible Mechanisms of the Reactions

Hilt and Frenking[36] have carried out a detailed computational investigation of the cobalt-catalyzed [4+2] cycloaddition between 2-methylbutadiene (isoprene) and phenyl acetylene in an attempt to explain the "para" selectivity seen in this reaction. While the intimate details of this study may not be applicable to the more complex substrates and ligands involved in the present case, some general features of the mechanism might still be applicable (Figure 6), especially since we have been able to establish (Scheme 2, see also: Supporting Information, p. S18) the key role of the cationic $[[(R,R)\text{-BenzP*}]\text{Co}]^+$ $[\text{BARF}]^-$ in these reactions using isolated $[[(R,R)\text{-BenzP*}]\text{Co}^{\text{I}}\text{Br}]_2$. Accordingly, we suggest the initial formation of $[(\text{L})\text{Co}^{\text{I}}\ (\text{diene})(\text{alkyne})]^+$ complex **A** followed by a turn-over limiting oxidative cyclization to form a $[\text{Co}^{\text{III}}]$-metallacycle, **B**. Subsequently, a fast reductive elimination ensues with the formation of a second bond to form a $(\mathbf{L})\text{Co}^{\text{I}}\ (1,4\text{-diene})]^+$ complex (**C**) from which the product is released with liberation of the catalyst.[37] Likewise, the [2+2]-cycloaddition between an alkyne and alkene, might be initiated by formation of a cobaltacycle intermediate similar to **D** (Figure 6), formed by an oxidative cyclization of the alkene and alkyne assisted by the $[(\mathbf{L})\text{Co(I)}]^+$ catalyst as we had previously proposed.[37] A reductive elimination from this intermediate would provide the cyclobutene product. The regioselectivity in the cyclobutene formation might have its origin in the steric repulsion between the C3-alkyl group of the alkyne and the residual double bond with its substituent (R^1) during the C–C bond forming steps.

In the absence of computational/modeling studies, the origin of the remarkable ligand-dependent chemoselectivities remains speculative. It is conceivable that the relative stabilities/reactivities of the metallacycle intermediates formed by the oxidative dimerization process, **B** and **D**, might be responsible for the observed selectivity. For the chelating bisphosphines, as the bite angle of the ligand is decreased the proportion of the [4+2]-adduct progressively

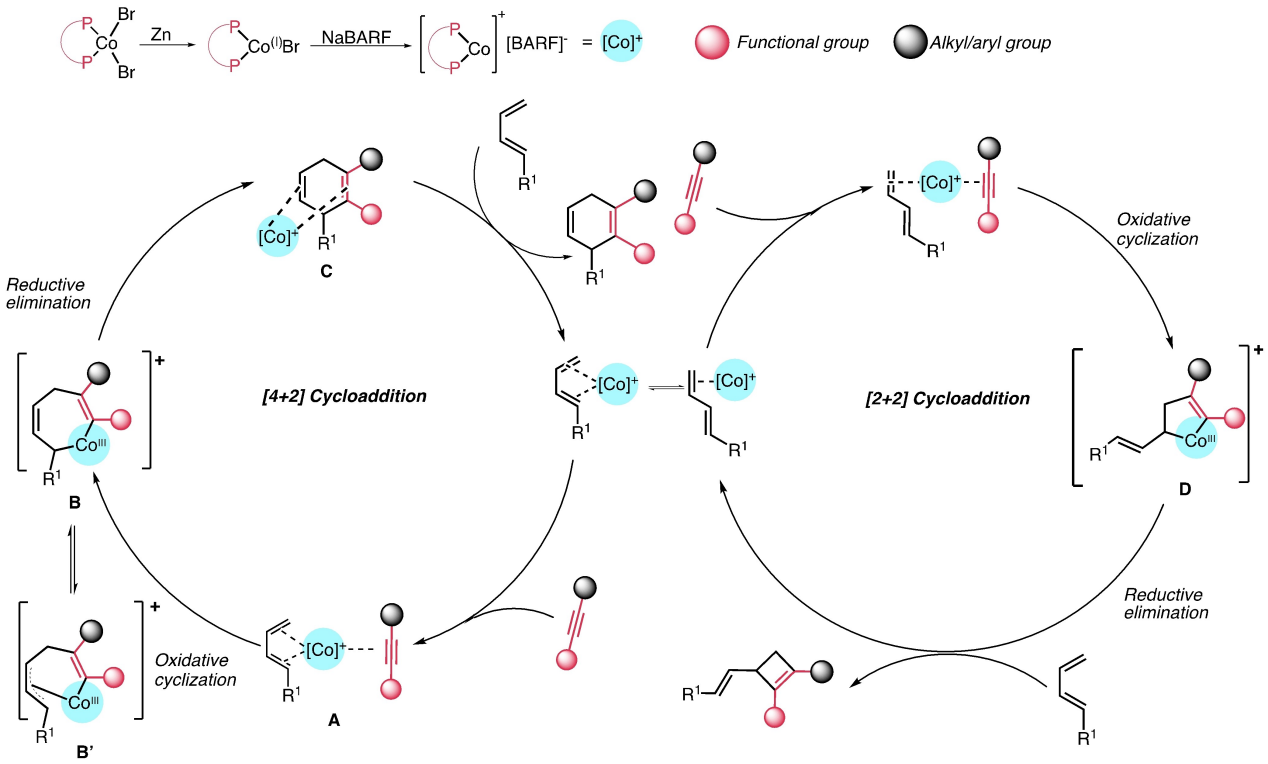


Figure 6. Plausible mechanisms of cycloadditions.

increases (Table 1), which suggests that the cobaltacycloheptadiene **B** becomes more important vis-à-vis cobaltacyclopentene **D**, leading to larger amounts of [4+2]-adducts. This observation formed the basis of our choice of chiral ligands with low bite angles (Table 2, entries 4–7) for enantioselective versions of the [4+2]-cycloadditions. Three of these ligands (entries 5–7, Table 2) including the most optimal ligand (*R*,*R*)-BenzP*, gave excellent chemo- regio- and enantioselectivities for a broad range of substrates in the [4+2]-cycloaddition (Figure 4). As for the PHOX ligands, the situation is much less clear. The available data suggests that an increase in steric effects via substitution at the phosphorus or at the C3 and C4 positions of the oxazoline leads to increase in selectivity for the [2+2]-cycloaddition (ligand **L5**, entry 16, Table 1, which confirms this hypothesis), even though the effects of such substitutions on enantioselectivity remain unpredictable.

Conclusion

We have identified ligands and reaction conditions that promote two distinct modes of $[(\mathbf{L})Co(I)]^+$-catalyzed cycloadditions of readily available 1,3-dienes and alkynes. Cobalt complexes of achiral and chiral bisphosphine ligands with relatively small bite angles ($<93°$) catalyze [4+2]-cycloadditions of 1,3-dienes and 3-alkyl- or 3-aryl-propiolate esters and alkynyl ketones giving excellent chemo-, regio- and enantioselectivities (*er* $>95:5$) for the resulting cyclohexa-1,4-dienes bearing a stereogenic center at the bis-allylic position. In sharp contrast, DIOP ligand (Figure 2) promotes [2+2]-cycloaddition between the terminal double bond of the diene and the alkyne in high chemo-and regioselectivity, but only with modest *er*. Delightfully, the phosphino-oxazoline ligand, *t*-Bu-PHOX (**L4**) gave high enantioselectivities for the [2+2]-cycloadditions. Mechanistic and computational studies to understand the origins of these uncommon ligand-dependent selectivities in these cycloaddition reactions are currently underway.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

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

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