Catalytic Enantioselective Synthesis of Cyclobutenes from Alkynes and Alkenyl Derivatives

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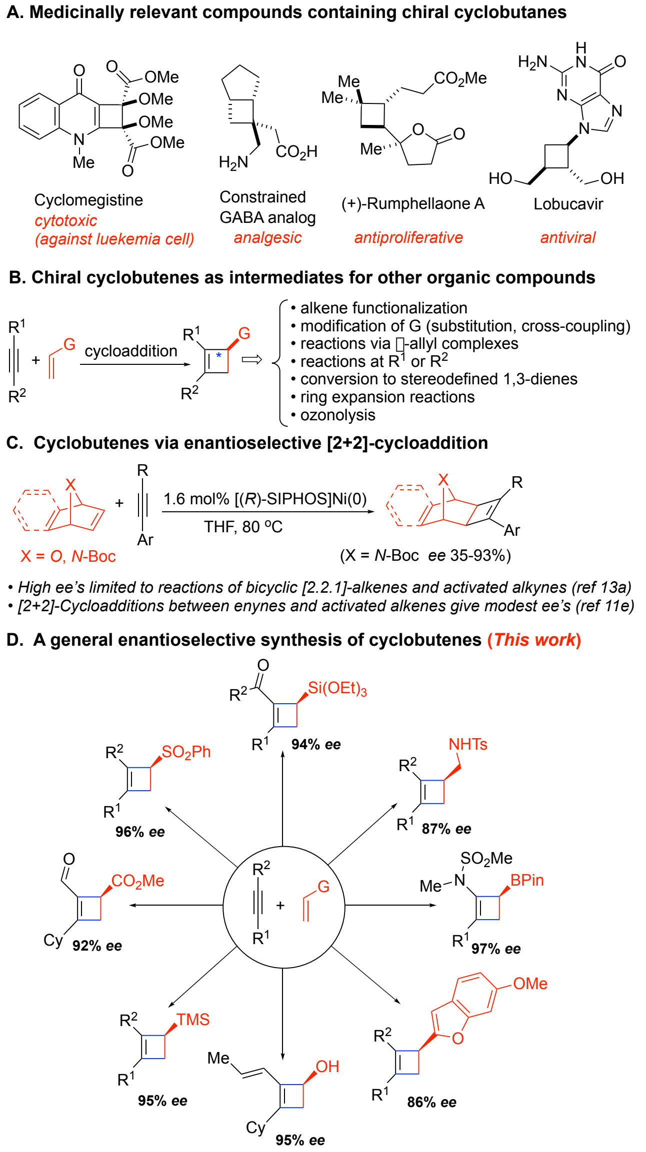
Supporting Information

ABSTRACT: Discovery of enantioselective catalytic reactions for the preparation of chiral compounds from readily available precursors, using scalable and environmentally benign chemistry, can greatly impact their design, synthesis and eventually manufacture on scale. Functionalized cyclobutanes and cyclobutenes are important structural motifs seen in many bioactive natural products and pharmaceutically relevant small molecules. They are also useful precursors for other classes of organic compounds such as other cycloalkane derivatives, heterocyclic compounds, stereo-defined 1,3-dienes and ligands for catalytic asymmetric synthesis. The simplest approach to make cyclobutenes is through an enantioselective [2+2]-cycloaddition between an alkyne and an alkenyl derivative, a reaction which has a long history. Yet known reactions of this class that give acceptable enantioselectivities are of very narrow scope and are strictly limited to activated alkynes and highly reactive alkenes. Here we disclose a broadly applicable enantioselective [2+2]-cycloaddition between wide variety of alkynes and alkenyl derivatives, two of the most abundant classes of organic precursors. The key cycloaddition reaction employs catalysts derived from readily synthesized ligands and an earth-abundant metal, cobalt. Over 50 different cyclobutenes with enantioselectivities in the range of 86-97% ee are documented. With the diverse functional groups present in these compounds, further diastereoselective transformations are easily envisaged for synthesis of highly functionalized cyclobutanes and cyclobutenes. Some of the novel observations made during these studies including a key role of a cationic Co(I)-intermediate, ligand and counter ion effects on the reactions, can be expected to have broad implications in homogeneous catalysis beyond the highly valuable synthetic intermediates that are accessible by this route.

INTRODUCTION

Recent incisive analyses of reactions[1] and molecules[2] of interest to medicinal chemists have validated the notion that molecular complexity, measured by fraction of saturated carbons (Fsp3) and *the presence of chiral centers,* correlate with success as compounds move from discovery, through clinical testing, to drugs. About a third of the compounds whose biological assays were analyzed had at least one chiral center.[1] The improved clinical efficacy has been ascribed to solubility, diminished promiscuity towards receptors, and occasionally, to better transport properties across biological barriers. Practical considerations in the preparation and screening of large and diverse array of structures, and, eventually manufacturing of the successful candidates from readily available precursors, provide strong justification for research into efficient and enantioselective synthetic methods.[3] Functionalized cyclobutanes and cyclobutenes are important structural motifs seen in many bioactive natural products and pharmaceutically relevant small molecules (Figure 1, **A**).[4] They are also useful precursors for other classes of organic compounds such as other cycloalkane derivatives, heterocyclic compounds, stereo-defined 1,3-dienes and ligands for catalytic asymmetric synthesis.[5] Even though direct synthesis of suitably functionalized cyclobutane precursors from readily available starting materials has been the subject of a burgeoning area of research,[6] there is considerable room for improvement with respect to diversity of functional groups on the ring and stereoselectivity associated with the ring formation. In this regard, a class of compounds with enormous potential for diversification are the chiral 3-substituted cyclobutenes (Figure 1, **B**), which allow further modification of the small ring through a myriad of ways involving the double bond,[7] the G group,[8] or through activation of the ring C-H bonds.[9] The simplest approach to making cyclobutenes is through an enantioselective [2+2]-cycloaddition between an alkyne and an alkenyl derivative, a reaction with a long history, starting with mostly addition of reactive alkynes to bicyclic[10] or activated[11] alkenes with the notable exceptions of additions of activated alkynes to cyclopentene (Hilt)[12a] and a variety of styreneyl alkenes to enynes (Ogoshi),[12b] both giving racemic products. Thus, there are no examples in the literature of a broadly applicable enantioselective version of this [2+2]-cycloaddition process. Reactions that give acceptable enantioselectivities are limited to specialized substrates, most often strained alkenes or activated alkynes (example: Figure 1, **C**).[13] Here we disclose a broadly applicable enantioselective [2+2]-cycloaddition between wide spectrum of alkenyl derivatives and alkynes (Figure 1, **D**).



A. Medicinally relevant compounds containing chiral cyclobutanes

B. Chiral cyclobutenes as intermediates for other organic compounds

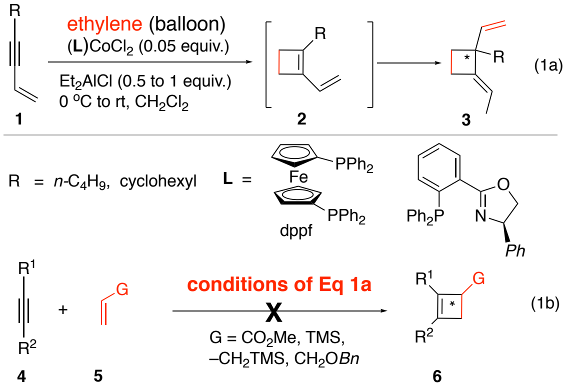
C. Cyclobutenes via enantioselective [2+2]-cycloaddition

D. A general enantioselective synthesis of cyclobutenes (*This work*)

Figure 1. A. Cyclobutane and cyclobutene motifs occur in many medicinally important small molecules and natural products. **B**. Cyclobutenes are excellent precursors for cyclobutanes and other useful intermediates. **C**. Current methods for their direct preparation via [2+2]-cycloaddition are applicable only to activated alkenes and/or activated alkynes. **D**. This work documents a practical, catalytic enantioselective (enantiomeric excess: 86-97%, ~50 examples) approach to the most diverse set of cyclobutenes reported to-date.

RESULTS AND DISCUSSION

For the enantiopure, substituted cyclobutenes (Figure 1, **B**) as the targets, we recognized that none of the existing methods[11c.11e-g.13a] including our own recently disclosed[7a] enantioselective cobalt-catalyzed cycloaddition between an enyne (**1**) and ethylene (Eq 1a) are suitable. The use of ethylene as the 2π-component necessarily leaves two prochiral carbons of the cyclobutene unfunctionalized. An attractive way to circumvent this problem would be to access precursor cyclobutenes (**6**) with the use of alkenyl derivatives (**5**) in place of ethylene (Eq 1b). This further raises the intriguing possibility of preparing these chiral 3-substituted cyclobutenyl derivatives via enantioselective catalysis. However, the application of reaction conditions described in Eq 1a led to complex mixtures with very little of the desired products (Eq 1b), prompting further investigations into a new strategy.



A New Reaction and Optimization Studies. Following many failed attempts to modify the reaction conditions described in Eq 1a, we wondered if the incompatibility of the Lewis bases in the substrates was the problem, and if so, could it be addressed by activation of the reagents by a cationic Co(I) species, an intermediate that was implicated in our recent 1,2-hydroboration of prochiral 1,3-dienes.[14] Initial scouting experiments (Table 1) were conducted with a prototypical alkyne, 4-octyne (**4a**) and two acrylates, methyl acrylate (**5a**) and 1,1,1-trifluoroethylacrylate (**5b**). Concurrently, we also studied the corresponding reaction between a more reactive enyne and methyl acrylate (Table 2). The most pertinent results from these studies are summarized in the Tables 1 and 2.

Details of initial optimization of the reaction conditions, from which the results in Tables 1 and 2 are abbreviated, can be found in the Supporting Information (See Tables S1-S7, pp. S12-S20). These experiments include effects of the following parameters on the efficiency and selectivity of the reactions: (i) cobalt(II) halide (Br or Cl) complexes of 1,n-*bis*-diphenylphosphinoalkanes of varying bite angles [Ph_2P–$(CH_2)_n$–PPh_2, n = 1-5)], including chiral variants such as chiraphos, BDPP, BDPH, DIOP, and other chelates with different backbone motifs such as dppf, biaryl, Josiphos ligands and phosphino-oxazoline ligands [see Figure 2 for structures of the ligands and Figure S1 (p. S12) in the Supporting Information, which contains a complete list of all ligands]; (ii) zinc, manganese, and, various 1,4-*bis*-trimethylsilyldihydropyrazines [14,15] as reducing agents; (iii) activators such as ZnX_2, AgOTf, $AgSbF_6$, $InBr_3$, sodium *tetrakis*-[3,5-(*bis*-trifluoromethyl)phenyl]borate (NaBARF); (iv) solvents, dichloromethane (DCM), 1,2-dichloroethane (DCE), toluene, hexanes, THF, ether, ethyl acetate or acetonitrile; (v) reaction temperature. In general, it was found that the reactions proceed best at or near room temperature in non-coordinating solvents such as DCM, DCE or toluene, with NaBARF as the most suitable activator. As expected, none of the solvents containing heteroatoms were suitable for this reaction. For enantioselective reactions, toluene was found to be a better solvent (giving 5-10% higher enantioselectivities vis-à-vis DCM) in several instances.

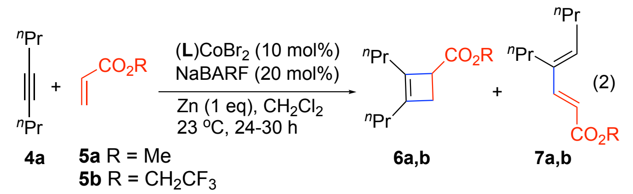


Table 1. Optimization of Co-catalyzed enantioselective [2+2]-cycloadditions between acrylates and an alkyne (4a) [a]

	entry	ligand[b]	conv. (%)	**6a** (%)	**7a** (%)	ee (**6**)
5a	1	dppp	55	36	15	0
	2	dppf [c]	40	35	0	0
	3	(*S*)-BINAP	100	73	23	84
	4	(*S,S*)-BDPP	100	74	22	16
	5	**L1**	5	5	-	0
	6	**L2**	55	25	28	-
	7	**L8** [d]	95	87	0	90
	8	**L9** [e]	100	92	0	91
				6b	**7b**	
5b	9	(*R*)-BINAP	100	47	42	90
	10	**L8** [d]	100	>95	0	84
	11	**L9** [d]	100	>95	0	88

[a] See Eq 2 for a typical procedure. [b] For structures of ligands, see Figure 2. [c] at 50 ºC. [d] in toluene. [e] in toluene at 40 ºC.

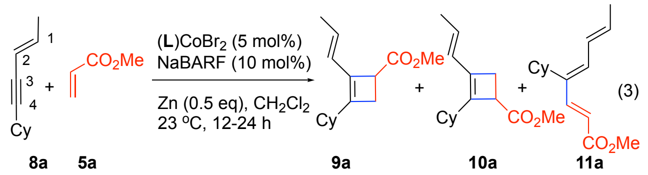


Table 2. Optimization of Co-catalyzed enantioselective [2+2]-cycloadditions between acrylate 5a and an enyne 8a[a]

entry	ligand[b]	conv. (%)	**9a** (%) [c]	**10a** (%) [c]	**11a** (%) [c]	ee (**9a**)
Achiral Ligands						
1	dppp	100	78	3	19	0
2	dppf	36	23	-	-	0
3	dPEPhos	45	45	-	-	0
4	**L1**	100	92	4	-	0
Chiral Ligands						
5	(*S,S*)-BDPP	97	80	3	13	52
6	(*S,S*)-BDPH	100	80	5	10	56
7	Josiphos 1	50	40	40	2	64
8	Josiphos 2	0	0	0	0	0
9	(*S*)-BINAP	100	80	-	16	18
10	**L2**	100	97	2	0	62
11	**L3**	100	93	2	0	54
12	**L4**	100	94	4	0	80
13	*ent*-**L7**	100	82	17	0	10
14	**L8**	100	95	3	0	82
15 [d]	**L8**	100	92	4	0	94
16 [d,e]	**L8**	100	98	<1	0	90
17 [d]	**L9**	100	90	10	0	90

[a] See Eq 3 for typical procedure. [b] See Figure 2 for structures of ligands. [c] Yield determined by internal standard method. [d] Toluene used as a solvent. [e] Trifluoroethylacrylate used instead of methyl acrylate.

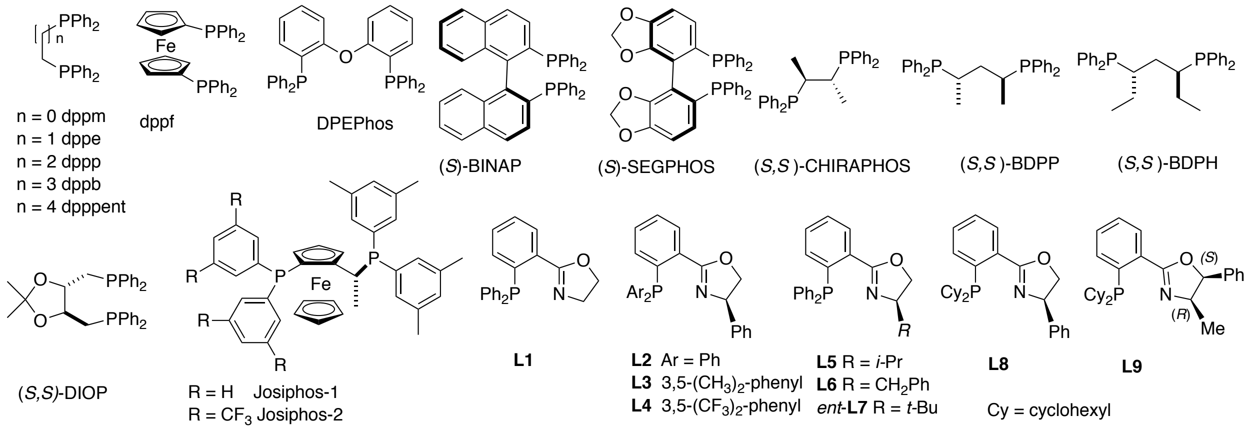
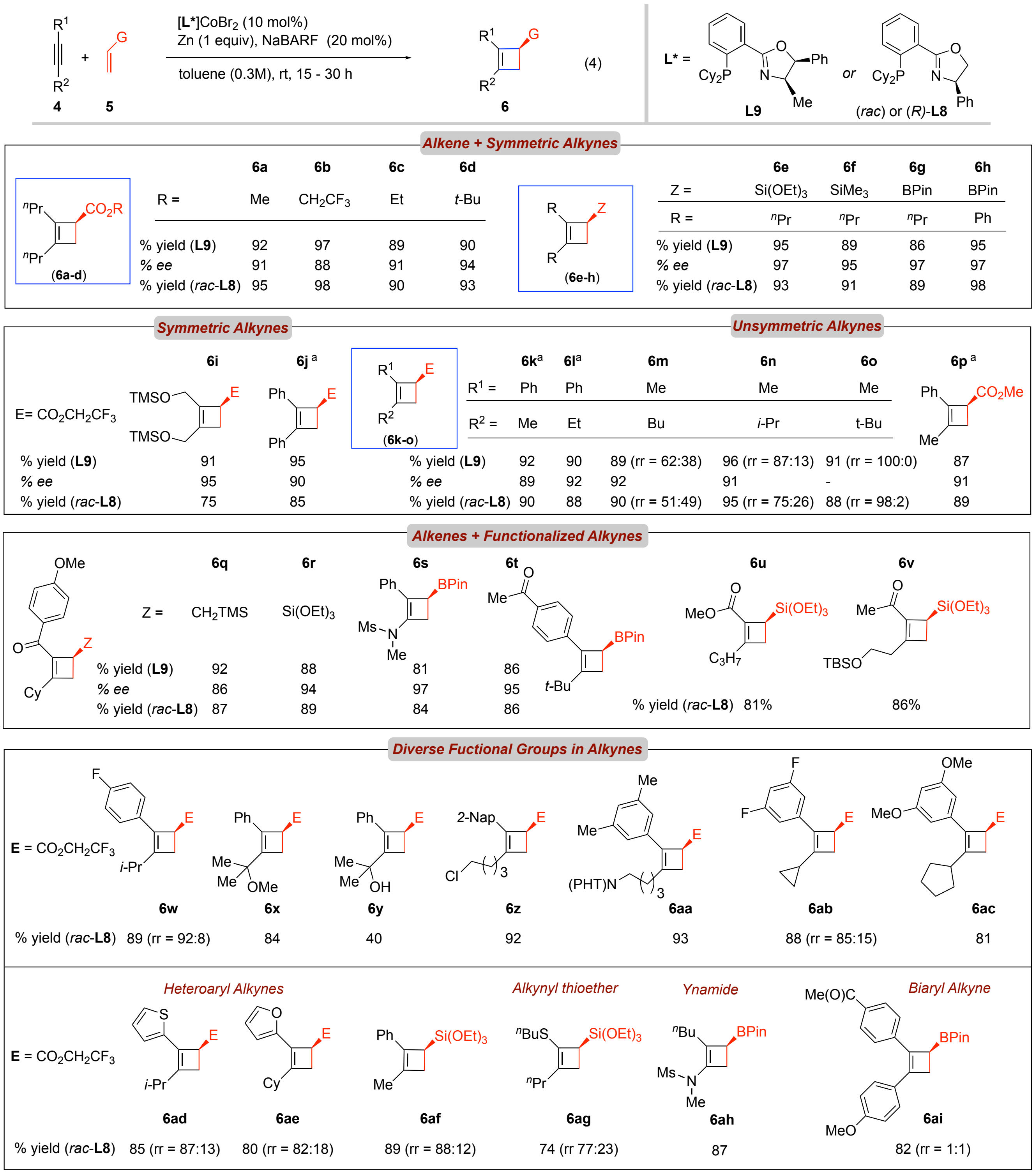


Figure 2. Partial list of ligands examined for cobalt-catalyzed [2+2]-cycloaddition between alkynes and alkenyl derivatives

*[2+2]-Cycloadditions between an alkyne (**4a**) and alkyl acrylates (**5a** and **5b**) (Eq 2, Table 1).* The results for the [2+2]-cycloaddition reactions of a prototypical alkyne, 4-octyne show that for the reaction with methyl acrylate, among the 1,n-*bis*-diphenylphosphino-alkane [Ph_2P-$(CH_2)_n$-PPh_2] ligands, only dppp (n = 3) gave moderate yield of the expected cyclobutene **6a**, the others producing significant amounts of a diene byproduct **7a** [Table 1, entry 1, see also: Supporting Information Table S1 (p. S13) in for a more details]. The byproduct contamination was also a major problem with other commonly used chiral bis-phosphines including (*S*)-BINAP (entry 3) and (*S,S*)-BDPP (entry 4).

Phosphino-oxazoline Ligands. While these studies were in progress, we were also examining the related [2+2]-cycloaddition of the acrylate **5a** with the enyne **8a** (see: Eq 3, Table 2), where it was found that the phosphino-oxazoline ligands, including the easily synthesized achiral ligand **L1** and chiral ligand **L2** (Figure 2), were much superior in giving the cyclobutene product (**9a**) with very high chemo- and regioselectivity. These observations, along with the highly tunable nature of the phosphino-oxazoline ligands prompted us to examine this ligand system for further detailed investigations. Accordingly, several of phosphino-oxazoline ligands (**L1**-**L9**) were prepared (Figure 2), and their cobalt (II) complexes studied as catalysts for the cycloaddition reaction at room temperature under conditions described in Eq 2. As can been seen in entries 7 and 8 (Table 1), with the new Co-complexes of these ligands, the [2+2]-cycloaddition between 4-octyne and methyl acrylate proceeded to give synthetically useful yield in unprecedented levels of enantioselectivity for the cyclobutene products. Most notably, replacing the *P*-diarylphosphino group in **L2** with a dicyclohexylphosphino group (**L8**) produced a very active Co-catalyst that gave exclusively the cyclobutene adduct **6a** in an enantiomeric excess (ee) of 90% in toluene, *with none of the undesired heterodimerization product 7**a***. With yet another modification, viz., introduction of 4,5-disubstitution on the oxazoline as in the ligand **L9** [readily prepared from (1*S*,2*R*)-norephedrine], further improvements in both the reactivity and selectivity of the reaction were observed (entry 8). With these new ligands and use of an activated trifluoroethyl acrylate **5b**, a quantitative reaction ensued with minimal loss in selectivity (Table 1, entries 10 and 11). For the effects of a more complete set of ligands, see Supporting Information, Table S6 (p. S19).

*[2+2]-Cycloaddition between a 1,3-enyne (**8a**) and methyl acrylate (Eq 3, Table 2).* The cycloadditions of 1,3-enynes presented further challenges, the increased reactivity of the enynes notwithstanding. In the initial investigations, we found that 1- or 2-substituted alkenyl alkynes were the best substrates for this reaction (vide infra). For example, one such substrate, **8a**, with a C_1-methyl substituent (Eq 3, Table 2), gave varying amounts of codimerization product (**11a**) along with regioisomeric mixtures, **9a** and **10a**, of the [2+2]-cycloadducts. Most gratifyingly, these selectivity problems could be readily solved by examination of ligand effects on this reaction. See Supporting Information Tables S2-S5 (p. S14-S18) for complete optimization of reaction conditions. Initially, we found that cobalt-complexes of achiral (entries 1-3) and chiral (entries 5-9) bisphosphine ligands were generally unsatisfactory either because of low reactivity or low selectivity. However, the phosphino-oxazoline (PHOX) ligands, including the achiral ligand **L1**, are excellent ligands for this transformation giving almost exclusively the expected cyclobutene product **9a**. Recall that **L1** was surprisingly ineffective in the cycloadditions of simple alkynes (e.g., Table 1, entry 5). Changing the 4-aryl substituent on the oxazoline moiety in the PHOX ligands to alkyl groups (e. g., from Ph in **L2** to *t*-Bu in **L7**, entries 10-13) led to poorer ligands. In sharp contrast, tuning of the *P*-aryl substituents led to significant improvements in enantioselectivites (the ee's improving from 62% to 80%, entries 10-12). The best results were obtained when the *P*-aryl groups were replaced by cyclohexyl groups as in **L8**, which resulted in the highest yield (98%), regioselectivity (regioisomeric ratio, rr = >95:5), and enantioselectivity (ee = 94%) for this substrate, especially when the reaction was carried out in toluene as the solvent (entries 15 and 16). For an ORTEP representing the solid-state structure of the pre-catalyst, [(*R*)-**L8**]$CoBr_2$, see Figure 4 (**A**). The norephedrine-derived ligand **L9**, also gave high enantioselectivity (ee = 90%), albeit with only modest regioselectivity (**9a**:**10a** = 90:10, entry 17). With the identification of a viable protocol for the reaction and the availability of several useful ligands, the stage is now set for a broader investigation of the scope of vinyl derivatives and the alkynes.



Alkene + Symmetric Alkynes

	6a	6b	6c	6d
R =	Me	CH_2CF_3	Et	t-Bu
% yield (**L9**)	92	97	89	90
% ee	91	88	91	94
% yield (*rac*-**L8**)	95	98	90	93

	6e	6f	6g	6h
Z =	$Si(OEt)_3$	$SiMe_3$	BPin	BPin
R =	^{n}Pr	^{n}Pr	^{n}Pr	Ph
% yield (**L9**)	95	89	86	95
% ee	97	95	97	97
% yield (*rac*-**L8**)	93	91	89	98

Symmetric Alkynes / **Unsymmetric Alkynes** (E= $CO_2CH_2CF_3$)

	6i	6j^a	6k^a	6l^a	6m	6n	6o	6p^a
R^1 =			Ph	Ph	Me	Me	Me	
R^2 =			Me	Et	Bu	*i*-Pr	t-Bu	
% yield (**L9**)	91	95	92	90	89 (rr = 62:38)	96 (rr = 87:13)	91 (rr = 100:0)	87
% ee	95	90	89	92	92	91	-	91
% yield (*rac*-**L8**)	75	85	90	88	90 (rr = 51:49)	95 (rr = 75:26)	88 (rr = 98:2)	89

Alkenes + Functionalized Alkynes

	6q	6r	6s	6t	6u	6v
Z =	CH_2TMS	$Si(OEt)_3$				
% yield (**L9**)	92	88	81	86		
% ee	86	94	97	95		
% yield (*rac*-**L8**)	87	89	84	86	81%	86%

Diverse Fuctional Groups in Alkynes (**E** = $CO_2CH_2CF_3$)

	6w	6x	6y	6z	6aa	6ab	6ac
% yield (*rac*-**L8**)	89 (rr = 92:8)	84	40	92	93	88 (rr = 85:15)	81

	6ad	6ae	6af	6ag	6ah	6ai
% yield (*rac*-**L8**)	85 (rr = 87:13)	80 (rr = 82:18)	89 (rr = 88:12)	74 (rr 77:23)	87	82 (rr = 1:1)

^{a} Ligand **L8** at 40 °C was used. For **6a**, **6c**, **6d**, **6v** to **6ae** reaction performed at 40 °C. For **6e**, **6f**, **6g**, **6m,** and **6n** reaction performed with 5 mol% catalyst loading.

Figure 3. Scope of [2+2]-Cycloaddition between Alkenyl Derivatives and Alkynes. The versatility of the reaction is illustrated by the diverse functional group present in the two coupling partners. In unsymmetrical alkynes regioselectivities of the products (**6**) are >95:5 unless otherwise indicated. The structures shown are for the major regioisomers and the corresponding ee's were determined by using CSP-GC or CSP-HPLC. See the Supporting Information for further details. Yields shown are for isolated products.

Scope of [2+2]-Cycloadditions between Alkynes and Alkenyl Derivatives. The optimized reaction conditions with minor modifications (Figure 3, Eq 4) were employed in the [2+2]-cycloaddition reactions of a wide variety of alkynes and alkenyl derivatives. The enantioselective reactions were carried out using the ligand **L9** unless otherwise noted, and authentic racemic products were synthesized using the ligand *rac*-**L8**. In general, excellent yields and enantioselectivities were observed for both sets of ligands for a broad range of cyclobutenes carrying many common organic functional groups, originating either from the alkyne or the alkene. Details of the synthesis of each of the specific adducts can be found in the Supporting Information. For the sake of brevity and clarity, the products are classified according to the types of alkyne precursors (**4**), and, within each type, by the alkenyl partners. The simplest alkynes are the symmetric ones (R = *n*-Pr, Ph, CH_2OTMS) leading to products **6a-6j**. The alkenyl derivatives include alkyl and trifluoroethyl acrylates (**6a-6d**), vinyltriethoxysilane (**6e**), vinyltrimethylsilane (**6f**), vinylboronic acid pinacolate (**6g** and **6h**), each giving excellent yields (86-97%) and ee's (88-97%). The trifluoroethyl acrylates were generally more reactive and the reactions proceeded at a faster rate compared to the alkyl acrylates. This permits lower temperatures for the reactions, leading to improved yields but with little change in selectivities. Among the acrylates *t*-butyl acrylate gave the product **6d** with the highest enantioselectivity (94%) with 4-octyne. The hydroxymethyl-bearing product **6i,**was formed in very good yield and excellent ee (95%). Products derived from unsymmetrical alkynes bearing an aryl group and an alkyl group are represented by **6k**–**6t**. 1-Phenylpropyne and 1-phenylbutyne gave high yields of the [2+2]-adducts **6k, 6l** and **6p** upon reaction with the respective acrylates in excellent regioselectivity (rr >95:5) and enantioselectivity (ee >89%), with the ester moiety placed adjacent to the aromatic substituent. Ligand **L8** was found to be the most optimal for these aromatic substrates. The regioselectivity in the products from unsymmetrical dialkyl alkynes depends on the difference in the size of the two alkyl groups. Methyl/butyl and methyl/*i*-propyl combination gave relatively low selectivity (62:38 and 87:13 for **6m** and **6n**), even though the enantioselectivity reached >91% ee for the major product in both cases. Significantly, the norephedrine-derived ligand **L9** gave better regioselectivity compared to **L8**. *t*-Butylmethyl acetylene with a significant size difference between the groups underwent a highly regioselective [2+2]-cycloaddition to give the product **6o**.

Products **6q**-**6ai** derived from functionalized, unsymmetrical alkynes, including some carrying hetero-atoms (*N*, *S*) on the alkynyl carbon (**6s**, **6ag**, **6ah**), demonstrate the vast functional group compatibility of the reaction. The following additional substituents on the alkynes are tolerated: carbonyl group as in a ketone or ester (**6q**, **6r**, **6t**, **6u**, **6v** and **6ai**), electron-rich or electron-poor aryl and heteroaryl groups (**6t**, **6w**, **6x**, **6y**, **6z**, **6aa**, **6ab**, **6ac**, **6ad**, **6ae**, **6af**, **6ai**), alkyl sidechains with -OH (**6y**), -Cl (**6z**), or phthalimido- (**6aa**) groups, cyclopropyl groups (**6ab**). In general, very good to excellent yields of the isolated products were obtained for a wide variety of alkenyl derivatives previously shown to work with simpler symmetric alkyne substrates. The regioselectivity observed was also high (>95:5) except for a few instances (**6m**, **6ag**, **6ai**). Where ever we have carried out the enantioselective reactions (**6a-6t**), the ee's are very high (86-97%).

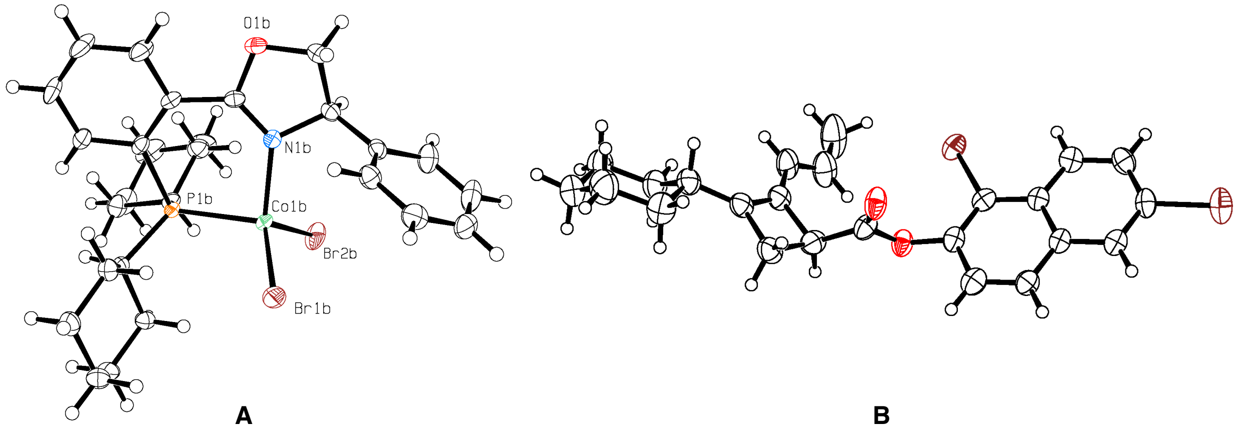


Figure 4. **A.** Solid-state structure (ORTEP) of the pre-catalyst [(*R*)-**L8**]$CoBr_2$ (Cambridge Crystallographic Data Centre CCDC # 1860755). **B.** Absolute configuration (*S*) established by X-ray crystallography of a 1,6-dibromo-2-naphthoate corresponding to cyclobutene **9a** (Cambridge Crystallographic Data Centre CCDC # 1921037). See Supporting Information for details.

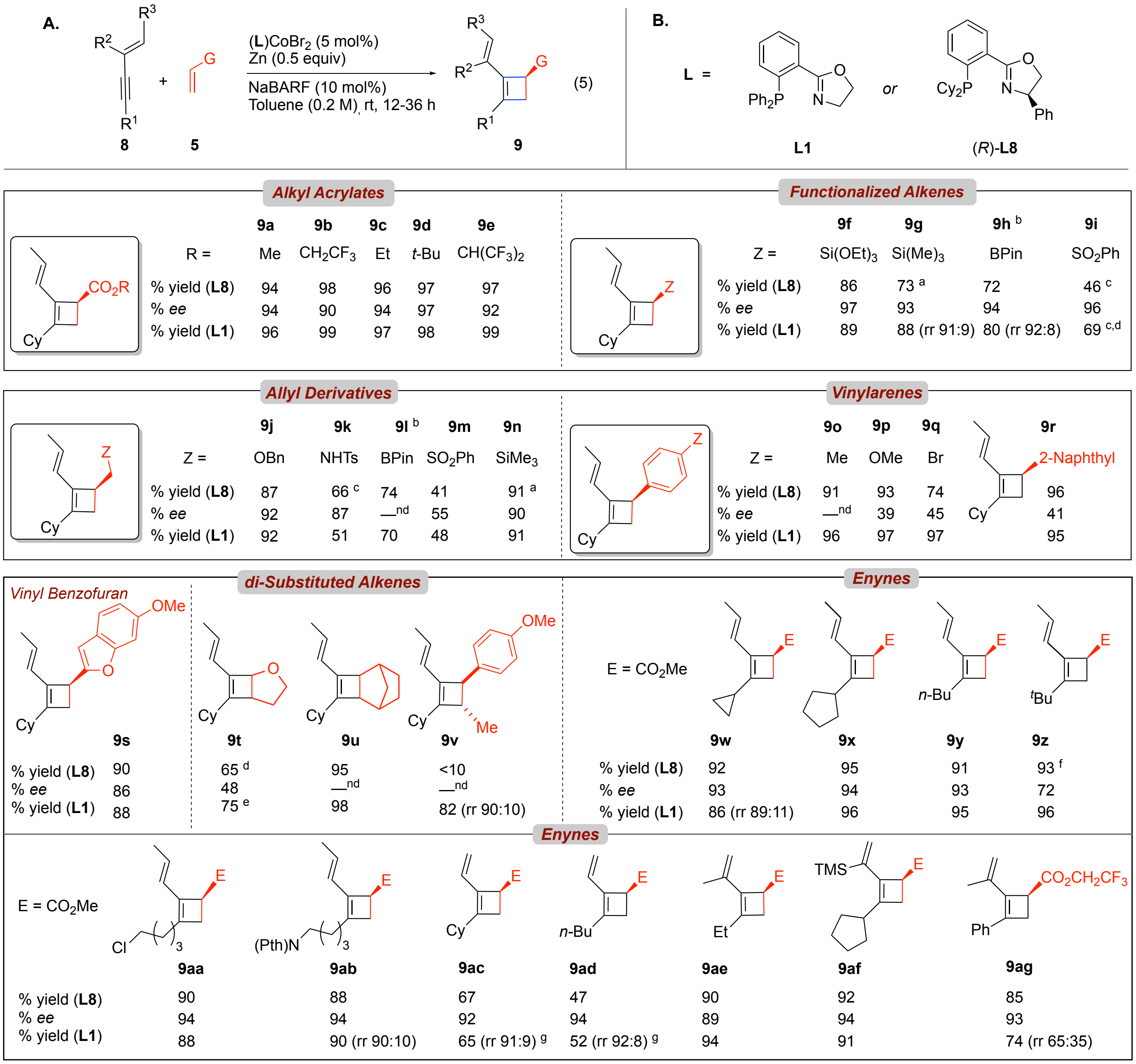
Scope of [2+2]-Cycloadditions between 1,3-Enynes and Alkenyl Derivatives. 1,3-Enynes as the alkyne components in the [2+2]-cycloadditions increase the versatility and applicability of this chemistry by placing yet another functionalizable carbon in the form of an alkenyl substituent on the product cyclobutene (**9,** Eq 5, Figure 5**)**. The (*E*)-1-propenyl moiety was chosen as the optimal substituent on many of the enynes in this study for three reasons: (a) the substrates bearing this group can be easily synthesized in high yield by cross-coupling chemistry; (b) the propenyl derivative can be readily converted into a more versatile cyclobutenyl aldehyde by chemoselective ozonolysis (Figure 6, **A**); (c) 1,3-enynes with no alkenyl substituents require three equivalents of the alkenyl partner to promote efficient [2+2]-

cycloaddition (for example, to prepare **9ac** or **9ad**) and to prevent a competitive co-dimerization of such enynes (example, to give **13ad**, Figure 6, **B**) to 1,6-dialkylvinylaromatic compounds. See Supporting Information Table S7 for further details.

The most general reaction conditions, applicable to the broadest spectrum of substrates, is shown in Eq 5 (Figure 5), and, the corresponding substrate scope is illustrated by the accompanying structures. The electron-rich phosphino-oxazoline ligand **L8** appears to be the best ligand to obtain the highest regio- and enantioselectivity under the previously optimized conditions for this transformation. See also Table 2, and, a more elaborate Table S2 in the Supporting Information (p. S14) for the effect of other ligands, and Table S3 (p. S16) for the effect of solvents. Solid state structure of the most useful $CoBr_2$-complex is shown in Figure 4 (**A**). The authentic racemic products were synthesized using ligand **L1**. The diverse structures of products in Figure 5 validate the broad scope of this [2+2]-cycloaddition reaction with respect to the enynes and the alkenyl derivatives. The absolute configuration of the products is based on the X-ray crystallographic structure of a 1,6-dibromo-2-naphthoate corresponding to the methyl ester **9a** (Figure 4, **B**). Configuration of the other products are assumed by analogy.

For convenience, the products from enynes are classified into six somewhat arbitrary groups, five of them showing the variations in the starting alkenyl components – alkyl acrylates (**9a-9e**), hetero-functionalized alkenes (**9f-9i**: starting from trialkoxyvinylsilane, trialkylvinylsilane, vinylboronate and vinylsulfone), allyl derivatives (**9j-9n**: from allyl ethers, allyl amides, allyl pinacolboronates, allyl sulfones and allyl trialkylsilanes), vinylarenes (**9o-9s**), and disubstituted alkenes such as dihydrofuran (**9t**), norbornene (**9u**) and *trans*-anethole (**9v**). Another group of adducts (**9w – 9ag**) show the variations possible in the enynes.

In most of the adducts derived from alkyl acrylates, the hetero-functionalized alkenes, and the allyl derivatives (**9a-9n**), the major product carries the alkenyl substituent adjacent to the 2-propenyl group of the enyne (>95:5 rr). The enantioselectivities in these instances are also excellent (generally >90% ee), except for the adducts from allyl *N*-tosylamide (**9k,** 87%) and allyl phenyl sulfone (**9m**, 55%). Cycloadditions with allyl derivatives also revealed a remarkable ligand effect. While the cycloaddition reactions carried out using the PHOX ligands (**L1** or **L8**) gave excellent yields of the [2+2]-cycloaddition (**9j-9n**) with outstanding regioselectivity, the (dppp)$CoBr_2$ complex gave adducts corresponding to a formal ene reaction (Figure 6, **C**).[12a] See Supporting Information for other substrates showing similar behavior (Supporting Information Table S8, p. S21). Simple internal alkynes give only ene-products with 1-alkenes irrespective of the ligands.[12c] The vinylarenes (corresponding to the products **9o-9s**) are excellent alkenes for the cycloaddition, even though the enantioselectivities seen are unacceptably low, except for the benzofuranyl compound **9s** (ee 86%). Compatibility of functional groups in the cyclization of enynes is similar to what was previously observed for simple alkynes (Figure 3). Thus, cyclopropyl (**9w**), alkyl (**9x** – **9z**), chloroalkyl (**9aa**), phthalimido-alkyl (**9ab**) or trimethylsilylvinyl (**9af**) groups presented no complications in the reaction. In general, very good to excellent regioselectivities (rr >90:10) and enantioselectivities (> 89% ee) were observed for the corresponding substrates.



	9a	9b	9c	9d	9e
R =	Me	CH_2CF_3	Et	*t*-Bu	$CH(CF_3)_2$
% yield (**L8**)	94	98	96	97	97
% *ee*	94	90	94	97	92
% yield (**L1**)	96	99	97	98	99

	9f	9g	9h [b]	9i
Z =	$Si(OEt)_3$	$Si(Me)_3$	BPin	SO_2Ph
% yield (**L8**)	86	73 [a]	72	46 [c]
% *ee*	97	93	94	96
% yield (**L1**)	89	88 (rr 91:9)	80 (rr 92:8)	69 [c,d]

	9j	9k	9l [b]	9m	9n
Z =	OBn	NHTs	BPin	SO_2Ph	$SiMe_3$
% yield (**L8**)	87	66 [c]	74	41	91 [a]
% *ee*	92	87	—[nd]	55	90
% yield (**L1**)	92	51	70	48	91

	9o	9p	9q	9r
Z =	Me	OMe	Br	2-Naphthyl
% yield (**L8**)	91	93	74	96
% *ee*	—[nd]	39	45	41
% yield (**L1**)	96	97	97	95

	9s	9t	9u	9v
% yield (**L8**)	90	65 [d]	95	<10
% *ee*	86	48	—[nd]	—[nd]
% yield (**L1**)	88	75 [e]	98	82 (rr 90:10)

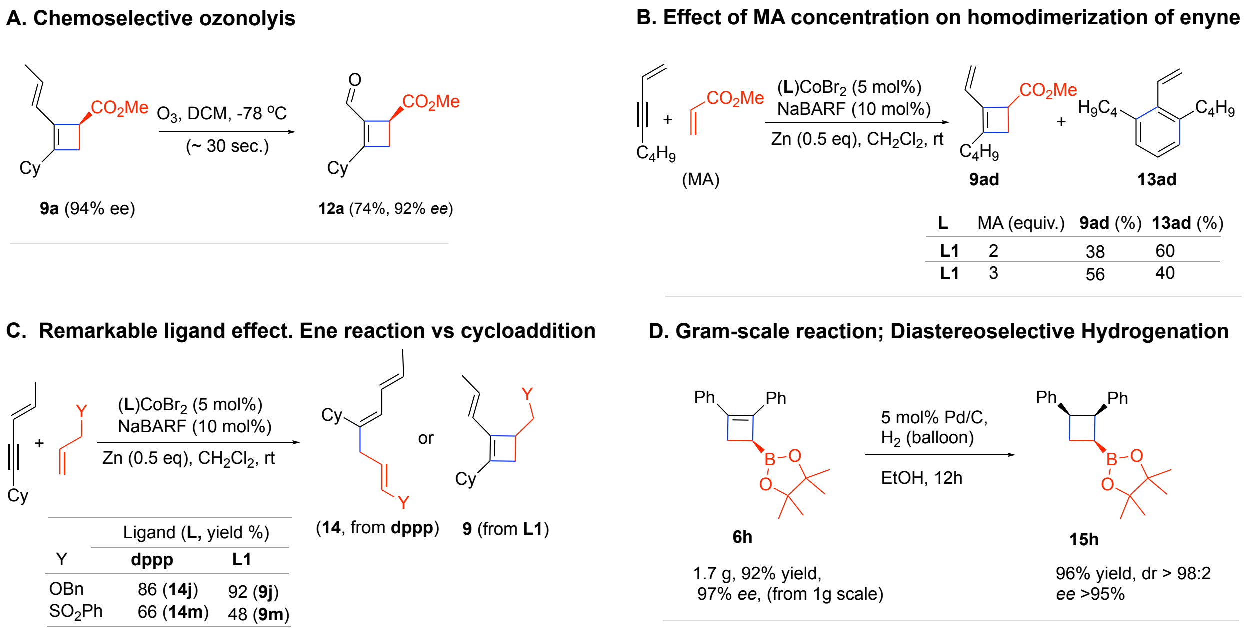
	9w	9x	9y	9z
% yield (**L8**)	92	95	91	93 [f]
% *ee*	93	94	93	72
% yield (**L1**)	86 (rr 89:11)	96	95	96

	9aa	9ab	9ac	9ad	9ae	9af	9ag
% yield (**L8**)	90	88	67	47	90	92	85
% *ee*	94	94	92	94	89	94	93
% yield (**L1**)	88	90 (rr 90:10)	65 (rr 91:9) [g]	52 (rr 92:8) [g]	94	91	74 (rr 65:35)

[a] Ligand **L9** was used. [b] identified as the alcohol (yields over two steps). [c] 10 mol% of catalyst was used. [d] DPPP was used as ligand. [e] (*S*,*S*)-BDPP was used. [f] Ligand **L2** was used. [g] 3 eq methyl acrylate was used, major byproduct: 1-vinyl-2,6-dicyclohexylbenzene (from homodimerization of enyne). [nd] not determined.

Figure 5. Scope of [2+2]-Cycloaddition between Enynes and Alkenyl Derivatives. A. Typical reaction conditions. Broad scope of the reaction is illustrated by diverse functional groups tolerated in the two coupling partners. Regioisomeric ratio of product **9** was >95:5 unless otherwise indicated. The structures shown are for the major regioisomers and the corresponding ee's were determined by using CSP-GC or CSP-HPLC. See the Supporting Information for further details. **B**. Most useful ligands for the [2+2]-additions of 1,3-enynes and alkenyl derivatives.

As alluded to earlier, 1,3-enynes lacking substituents on the C_{sp2}-carbons (R^2 or R^3) gave only modest yields (e.g., 67% for **9ac**; 47% for **9ad**), even though the observed enantioselectivity was very high (92% ee and 94% ee respectively). A competing homodimerization of these enynes to give 1-vinyl-2,6-dialkylbenzenes (Figure 6, **B**) can be avoided by using excess of the alkenyl derivative (up to 3 equivalents in the case of **9ac** and **9ad**). As illustrated by the high yields and selectivities observed for examples **9ae**, **9af**, and **9ag** (*under near stoichiometric ratios of the starting materials*), substitution at the internal C_{sp2} carbon of the enynes also promotes facile [2+2]-cycloaddition without any complication from the homodimerization of the enyne.



A. Chemoselective ozonolyis

B. Effect of MA concentration on homodimerization of enyne

C. Remarkable ligand effect. Ene reaction vs cycloaddition

D. Gram-scale reaction; Diastereoselective Hydrogenation

L	MA (equiv.)	9ad (%)	13ad (%)
L1	2	38	60
L1	3	56	40

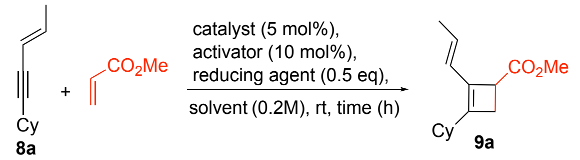
	Ligand (**L**, yield %)	
Y	**dppp**	**L1**
OBn	86 (**14j**)	92 (**9j**)
SO_2Ph	66 (**14m**)	48 (**9m**)

1.7 g, 92% yield,
97% *ee*, (from 1g scale)

96% yield, dr > 98:2
ee >95%

Figure 6. **A**. A propenyl substituent in an enyne (thus in the cycloadduct **9a**) is useful as an aldehyde surrogate. **B**. This group also prevents homodimerization of the enyne to a vinyl aromatic (**13ad**). **C**. Allyl derivatives give [2+2]-cycloadducts with ligand **L1**, but an ene-products with dppp. **D.** A gram-scale reaction and a diastereoselective transformation of a cyclobutene.

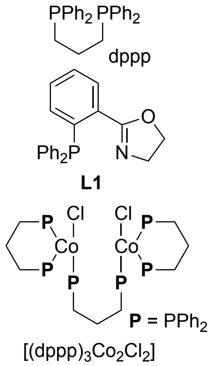
Role of Cationic Cobalt (I) in the [2+2]-Cycloaddition Reaction and a Possible Mechanism of the Reaction. In the initial studies we have recognized a prominent role for a cationic cobalt (I) species in these reactions. Control experiments (Eq 6 and the accompanying Table 3) confirm that no reaction ensues in the presence of isolated Co(I) complex $(dppp)_3Co_2Cl_2$[14] or a Co(I) complex formed by in situ reduction of **L**$CoBr_2$ (**L** = dppp or **L1**) using Zn as a reducing agent (See Supporting Information Table S5 for further details) in the absence of NaBARF (entry 4 and 9 versus 1 and 2). A possible unified mechanism that accounts for all products formed and the various experimental observations is shown in Figure 7. The presence of NaBARF, which presumably generates a cationic Co(I) species (**15**), under these reaction conditions is essential for the success of the reaction. Oxidative dimerization of the alkyne and the alkenyl reactant gives the metallacycle **17**, which could undergo reductive elimination to give the cyclic product **6** or **9**. Alternately, β-hydride elimination followed by reductive elimination could give either **7** or **14** depending upon the substrate. Allylic derivatives with an exo-cyclic CH_2 group (**17**, G = CH_2Y) gives the formal ene-product via **19**. That coordinating solvents such as THF, acetonitrile and even ethyl acetate are not suitable for the reaction also supports the intermediacy of the cationic Co(I) species **15** as a viable catalyst. Thus, this cycloaddition reaction joins a growing list of other alkene functionalization reactions such as diene-acrylate dimerization[16] and HBPin-mediated hydroboration[14] and hydrogenation[17] of prochiral alkenes where cationic Co(I) have been invoked as intermediates.



(6)

Table 3. Role of cationic Co(I) in [2+2]-cycloaddition [a]

entry	catalyst	activator	reductant	solvent.	time (h)	**9a** (%)
1	(**L1**)$CoBr_2$	NaBARF	Zn	CH_2Cl_2	15	96
2	(dppp)$CoBr_2$	NaBARF	Zn	CH_2Cl_2	6	>80
3	(**L1**)$CoBr_2$	NaBARF	none	CH_2Cl_2	24	0
4	(**L1**)$CoBr_2$	none	Zn	CH_2Cl_2	24	0
5	(**L1**)$CoBr_2$	NaBARF	Zn	THF	24	0
6	(**L1**)$CoBr_2$	NaBARF	Zn	CH_3CN	24	0
7 [b]	(dppp)$CoBr_2$	NaBARF	Zn	CH_2Cl_2	6	16
8 [c]	$(dppp)_3Co_2Cl_2$	NaBARF	none	CH_2Cl_2	6	9
9	$(dppp)_3Co_2Cl_2$	none	none	CH_2Cl_2	24	0



[a] See Eq 6 for a typical procedure and SI for further details. Solvent and additive effects support a key role for cationic Co(I)-species in [2+2]-cycloadditions. [b] Additionally, 2.5 mol% dppp was used. Note that addition of extra ligand inhibits the reaction (Table entry 2 vs 7). [c] 2.5 mol% catalyst loading (5 mol% in Co).

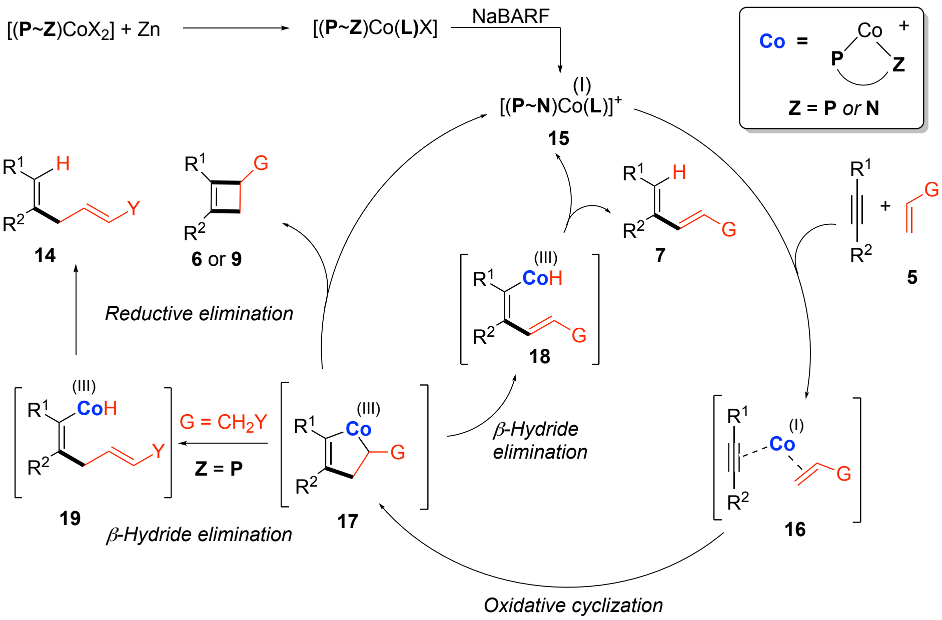


Figure 7. A possible mechanism that accounts for the observed ligand, counter ion and solvent effects.

CONCLUSIONS

Cyclobutanes are important structural motifs in many biologically relevant compounds. We report a practical approach to diverse array of nearly enantiopure cyclobutenes from which these compounds can be easily accessed. Two of the most abundant organic precursors, alkynes and alkenyl derivatives are used in the key enantioselective [2+2]-cycloaddition reaction, which employs catalysts derived from readily available amino-alcohols and an earth-abundant metal, cobalt. These enantioselective cycloaddition reactions are easily scaled up to gram scale. With the diverse functional groups present in the cyclobutenes, further diastereoselective transformations are easily envisaged for synthesis of other useful intermediates including highly functionalized cyclobutanes, cyclopentanes and stereo-defined 1,3-dienes. . Experimental observations implicate a cationic cobalt(I)-

species in the mechanism of this reaction. Such species may have broader applications for other carbon-carbon and carbon-heteroatom bond-forming reactions.

EXPERIMENTAL SUMMARY

In an N_2-filled glovebox, an 8-mL vial equipped with a septum screw cap was charged with a magnetic stirrer bar, [**L**CoBr$_2$] (0.01 mmol, 0.05 equiv), activated zinc-dust (0.1 mmol, 0.5 equiv), NaBARF (0.02 mmol, 0.1 equiv), and toluene (0.20 - 0.25 M). The vial was capped and after stirring the mixture for 5-10 minutes, the alkyne (0.20 mmol, 1 equiv) was added neat using microliter syringe via the septum, followed by the alkenyl derivative (0.22 – 0.30 mmol, 1.1-1.5 equiv). The resulting mixture was stirred at rt. The progress of the reaction was monitored by taking an aliquot using a glass pipette, diluting with ether and filtering through a pad of silica before analyzing via GC-FID or TLC. Upon completion of the reaction (4 h-24 h), the vial was taken out of the box and quenched with ether (5 mL). The resulting mixture was filtered over a short pad of silica eluting with ether. Concentration on a rotary evaporator, and subsequent purification by column chromatography eluting with hexane/ethyl acetate (0 to 20%) afforded the products. Full experimental details, spectroscopic and analytical data including chiral stationary phase chromatograms can be found in the Supporting Information under each new compound.

ASSOCIATED CONTENT

Supporting information

This Information is available free of charge via the Internet at http://pubs.acs.org. Experimental procedures, syntheses and isolation of all intermediates, and Tables with details of several optimization studies. Spectroscopic and chromatographic data showing compositions of products under various reaction conditions (PDF).
Crystallographic Information for complex [(*R*)-**L8**]CoBr$_2$ (CIF)
Crystallographic Information for (*S*)-9-1,6-dibromo-2-naphthoate ester (CIF). Data have been deposited at the Cambridge Crystallographic Data Centre under accession numbers CCDC 1860755 and 1921037 respectively.

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Notes

The authors declare no competing financial interest.

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