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Tandem Catalysis for Asymmetric Coupling of Ethylene and Enynes to Functionalized Cyclobutanes

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Summary.

A cobalt catalyst promotes [2+2] cycloaddition followed by enantioselective hydrovinylation for synthesis of cyclobutanes with chiral all-carbon quaternary centers.

Abstract

Transformation of simple precursors into structurally complex cyclobutanes, present in many biologically important natural products and pharmaceuticals, is of considerable interest in medicinal chemistry. Starting from 1,3-enynes and ethylene, both exceptionally inexpensive starting materials, we report a cobalt catalyzed route to vinylcyclobutenes, as well as the further enantioselective addition of ethylene to these products to form complex cyclobutanes with all-carbon quaternary centers. These reactions can proceed in discrete stages, or in a tandem fashion to achieve three highly selective carbon-carbon bond formations in one pot using a single chiral cobalt catalyst.

Development of highly efficient and enantioselective routes to chemical intermediates for the preparation of medicinally relevant compounds has been among the most active areas of research in modern organic synthesis.(1, 2) Especially attractive in this area are catalytic reactions that combine readily available precursors and feedstock materials, which in turn can impact the way we synthesize and manufacture fine chemicals.(3-10) In this context, enantioselective methods for the synthesis of cyclobutanes have attracted substantial attention(11, 12) because of their widespread occurrence in medicinally relevant natural products and pharmaceuticals (Fig. 1 A).(13-19) The chiral all-carbon quaternary centers present in many of these molecules often prove challenging to install efficiently.(20) Cyclobutane derivatives have also found broad use as intermediates for the synthesis of more advanced target structures such as stereo-defined 1,3-dienes, cyclopentanes and ligands for catalytic applications.(21, 22) Most routes to cyclobutane derivatives rely on two strategies for the installation of the stereogenic centers: either enantioselective ring closure (Fig. 1 B,

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Data and materials availability: X-ray crystallographic data for compound [L8a]CoCl₂ are available free of charge from the Cambridge Crystallographic Data Center under CCDC 1562422. Full experimental details for the preparation of all new compounds, and their spectroscopic and chromatographic data can be found in the supplementary material.

C), most often via [2+2] cycloadditions with few notable exceptions,(23-25); or enantioselective functionalization of prochiral cyclobutane/cyclobutene intermediates (Fig. 1 D). Cycloadditions of alkenes and alkynes proceed photochemically(26, 27) or via Lewis acid or transition metal catalysis.(28) Except for a single example (29) of an Fe(0)-catalyzed reaction between butadiene and ethylene (to give achiral vinylcyclobutane) no use of ethylene [annual production 130 million metric tons(30)] for a practical synthesis of cyclobutanes has been reported. Although few enantioselective functionalizations of preformed cyclobutane derivatives using organocatalytic methods are known,(12) the more versatile transition metal catalyzed reactions are rare and the reported routes use precursor cyclobutane carboxylic acid derivatives that have to be synthesized in several steps.(31-33) Here we report cobalt catalysis of a [2+2]-cycloaddition between readily available 1,3-enynes and ethylene followed by an enantioselective hydrovinylation of the resulting vinylcyclobutene (Fig. 1, E) to give highly functionalized cyclobutanes carrying a chiral, all-carbon quaternary center in the ring.

Our studies started with attempts to effect a [2+2] cycloaddition reaction between ethylene and an enyne for the synthesis of vinylcyclobutenes. The reported procedures using Zn/ZnI₂ for related processes(34) were limited to racemic product formation from activated and strained alkenes. For example, we found that cobalt-catalyzed cycloadditions with ethylene and a prototypical enyne **1a** with Zn/ZnI₂ led to unacceptably low yields of the product **3a** along with other contaminants including a dimeric product, **2a** (Fig. 2, eq 1). A systematic optimization of the cobalt-catalyzed reaction (see Table S1) led us to Lewis acids containing aluminum as the optimal activators to promote the desired reaction(s). For example, the [2+2]-cycloadditions between a 1,3-enyne (**1a**) and ethylene (balloon) could be carried out under water and oxygen free conditions with excellent yield and selectivity at low temperatures using a variety of chelating bis-phosphine cobalt complexes and trimethylaluminum (TMA) as the activator (Fig. 2, eq 2 and Table S1). This reaction gave not only the cyclobutene (**3a**) but also a hydrovinylated product (**4a**) with an all-carbon quaternary center, at rt and/or slightly longer reaction times. At lower temperatures and shorter reaction times, the [2+2]-adduct **3a** could be isolated in excellent yield. The ligand effects in these cobalt-catalyzed reactions were striking, with complexes of 1,1-*bis*-diphenylphosphinomethane (dppm) and 1,2-*bis*-diphenylphosphinoethane (dppe) giving only modest yields of the products even after prolonged reaction times (Table S1). Cobalt complexes of ligands with larger bite-angles [1,3-*bis*-diphenylphosphinopropane (dppp), 1,4-*bis*-diphenylphosphinobutane (dppb), 1,5-*bis*-diphenylphosphinopentane (dppept), 1,1'-*bis*-diphenylphosphinoferrrocene (dppf) and 2,2'-*bis*-diphenylphosphinobinaphthyl (BINAP)] were more efficient (Table S1), and (dppf)CoCl₂ proved exceptionally active: with 5 mol% of the catalyst, the tandem sequence was complete in less than 2 hours to give nearly quantitative yield of **4a**. Even at -20 °C this complex was competent to carry out the initial [2+2]-cycloaddition. From control experiments it is clear that at least 0.5 equiv. of TMA is needed for the reaction. The reaction was easily scaled up and an isolated yield of 81% (**4a**) obtained on a 5 mmol scale. Further, optimizations revealed that in addition to TMA, methyl aluminoxane (MAO) or Et₂AlCl could be used as activators, and CH₂Cl₂ was the best solvent for carrying out the reaction. With the cobalt-dppf complex, traditional activators such as Zn/ZnI₂, DIBAL-H, EtAlCl₂, LiEt₃BH, Ph₃B and solvents toluene, THF

and *t*-butyl methyl ether were unsatisfactory. No reaction ensued in the absence of either the cobalt catalyst or the activating agent.

The [2+2]-cycloadditions between enynes and ethylene catalyzed by (dppf)CoCl₂/TMA have wide scope as illustrated by the examples in Fig. 2B. At low temperatures and shorter periods the reaction can be carried out selectively to obtain the cyclobutene product, **3** (Fig. 2, B **3a-3r**). Prolonged exposure to the catalyst at room temperature leads to exclusive formation of the cyclobutane, **4** as a mixture of (*E*)- and (*Z*)-isomers (Fig. 2 C; **4a-4h**). In addition to straight chain alkene and cycloalkane substituents (**3a-3f**), chloroalkyl (**3g**), aromatic (**3h-3j**) and cyclopropyl substituents on the enyne were tolerated in these reactions. 1,3-Enynes with a terminal alkyne readily underwent the [2+2]-cycloaddition, but not the subsequent hydrovinylation (**3l**). Products **3m** and **3n** with additional substituents on the alkene also reacted similarly. While unencumbered aromatic substituents on the alkynes were tolerated in the tandem reactions (e.g., **3h** → **4h**), 1-naphthyl derivative **3o** only underwent the initial [2+2]-cycloaddition presumably because of steric effects hindering the subsequent reaction.

Simple dialkyl and diaryl alkynes also underwent the cycloaddition reaction (**3p-3r**) with no complication from other side reactions including further hydrovinylation.

Next we sought to develop an asymmetric version of the tandem process for synthesis of chiral cyclobutanes **4** (Fig. 3 A). Early investigations with prototypical enynes **1a** and **1b** revealed that the ligands (Fig. 3 D) we had successfully used in several other cobalt-catalyzed reactions,⁽³⁵⁾ while giving high yields and excellent *E:Z* ratios of the products, gave unacceptable enantioselectivities (Table S3, entries 1-14). These included *bis*-diphenylphosphino-ligands (*S,S*)-BDPP (**L1**), (*S,S*)-DIOP (**L2**) and JOSIPHOS (**L3a** and **L3b**), BINAP and the *bis*-phospholane ligand **L4** (Fig. 3 D). After an extensive search,⁽³⁵⁾ we identified CoCl₂-complexes of phosphinooxazoline ligands (e.g., **L8-L9**)⁽³⁶⁾ as the most suitable catalysts for this tandem sequence (Tables S3 and S4). Among the activators Et₂AlCl was found to be the most general (Table S4), often giving significantly better enantioselectivities than TMA which was used in initial screening studies. Several other activators including Zn/ZnX₂ (X = Br, I) with complexes of various cobalt halides showed poor catalytic activity.⁽³⁵⁾ To establish the absolute configuration of the product, an authentic sample of (*R*)-**4b** was synthesized from the known ketone (*R*)-**5** (Fig. 3 B) ^(25, 37) Comparison of chiroptical properties and chromatographic behavior on chiral stationary phase GC established the product from the enyne **1b** as (*S*)-**4b**. The configurations of the other products (Fig. 3 E) were assigned by analogy.

The extreme sensitivity of this exacting tandem sequence towards the choice of ligand is apparent from the documented results (Table S3) ⁽³⁵⁾. It is notably exemplified by the *bis*-phospholane **L4** and the phosphinooxazoline ligand **L10** (Fig. 3 D). Whereas (**L4**)CoCl₂ is only viable for the second step (asymmetric hydrovinylation, Table S4, entry 5), (**L10**)CoCl₂ catalyzes only the first step, the [2+2]-cycloaddition (Table S4, entry 14). Among the ligands examined, ligands **L8a** (entry 7) and **L8c** (entry 9) gave the best selectivities. Solid-state structure of the most versatile pre-catalyst complex is shown in Fig. 3 C. Substituents on the *P*-aryl groups of the phosphinooxazoline ligands have only marginal effects on the

selectivity except when there is an *ortho*- substituent, which gave inferior results. Aliphatic substituents other than benzyl on the oxazoline moiety gave unsatisfactory results.

The optimized conditions using the readily available complex [L8a]CoCl₂ and Et₂AlCl as an activator were applied to several enynes to examine the scope and limitations of the reaction and the results are shown in Fig. 3 E. Generally the reactions proceeded in very good yield and excellent enantioselectivity to give the products **4**, bearing an all-carbon quaternary center, as the (*E*)-isomer, except in the case **4a** and **4c** where less than 5% of the (*Z*)-isomers were also seen. Primary, secondary and tertiary alkyl substituent on the alkyne is tolerated. The reaction was compatible with a chloroalkyl substituent (**4g**).

The ligand, counterion and solvent effects documented here and in the literature for cobalt-catalyzed olefin dimerization reactions point to a Co(I)/Co(III)-catalytic cycle, not much different from what we proposed recently for the dimerization of 1,3-dienes and methyl acrylate (38). As in the case of that heterodimerization, the tandem sequence disclosed here does not proceed with isolated Co(I) complexes. Specifically, we have attempted to carry out the reaction of **1a** with ethylene (Fig. 3 A) under catalysis by isolated cobalt(I) sources [L8a]CoCl and [L8a]CoEt (38) in the absence of any activators and found no reaction except for decomposition of the starting materials on prolonged time. However, addition of a Lewis acid, B(C₆F₅)₃, resulted in modest yields (up to 50%) of the cyclobutene product **3a**. This result suggests a key role of a cationic Co(I) species in these reactions. We propose the scheme shown in Fig. 4 as a possible mechanism for the overall transformation. At the initial stage of the reaction, an oxidative dimerization of ethylene and the enyne in the coordination sphere of an activated Co(I) species gives a metallacyclopentene **6**, which undergoes reductive elimination to give the cyclobutene **3**. The subsequent hydrovinylation of a diene **3** is possibly initiated by yet another oxidative dimerization between the diene and ethylene to give the metallacycloheptene **8**. β -Hydrogen elimination and reductive elimination from the Co(III) intermediate **9** would lead to the expected product **4**. The sterically encumbered (*Z*)-allyl cobalt(III)-hydride could undergo (*Z*)/(*E*)-isomerization through an η^3 -(allyl) organometallic as shown, which would result in the (*E*)-**4**-isomer as the major product. As expected the isomer ratio depends on the ligands employed and the nature of the substituent R.

Supplementary Material

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References and Notes

- 1Carreira EM, Yamamoto H. , Eds., Comprehensive Chirality (Elsevier, Amsterdam , 2012).
- 2Ojima I, , Ed., Catalytic Asymmetric Synthesis , 3rd Edition. (Wiley , Hoboken, New Jersey , 2010).
- 3Bayeh L, Le PQ, Tambar UK. Catalytic Allylic Oxidation of Internal Alkenes to a Multifunctional Chiral Building Block Nature. 2017; 547:196–200. [PubMed: 28636605]

- 4Shi SL, Wong ZL, Buchwald SL. Copper-Catalysed Enantioselective Stereodivergent Synthesis of Amino Alcohols *Nature*. 2016; 532:353–356. [PubMed: 27018656]
- 5Zhang W. Enantioselective Cyanation of Benzylic C-H Bonds via Copper-Catalyzed Radical Relay *Science*. 2016; 353:1014–1018. [PubMed: 27701109]
- 6Zbieg JR, Yamaguchi E, McInturff EL, Krische MJ. Enantioselective C-H Crotylation of Primary Alcohols via Hydrohydroxyalkylation of Butadiene *Science*. 2012; 336:324–327. [PubMed: 22442385]
- 7Klosin J, Landis CR. Ligands for Practical Rhodium-Catalyzed Asymmetric Hydroformylation *Acc. Chem. Res.* 2007; 40:1251–1259. [PubMed: 17997526]
- 8Wu GG, Chen FX, Yong K. , ‘ Industrial Applications of Metal–Promoted C–C, C–N, and C–O Asymmetric Bond Formations’, in *Comprehensive Chirality* (Elsevier, Amsterdam , 2012), vol. Vol. 9. , pp. 147–208 .
- 9RajanBabu TV. Hydrocyanation of Alkenes and Alkynes *Organic Reactions*. 2011; 75:1–73.
- 10Tokunaga M, Larrow JF, Kakiuchi F, Jacobsen EN. Asymmetric Catalysis with Water: Efficient Kinetic Resolution of Terminal Epoxides by Means of Catalytic Hydrolysis *Science*. 1997; 277:936–938. [PubMed: 9252321]
- 11Xu Y, Conner ML, Brown MK. Cyclobutane and Cyclobutene Synthesis: Catalytic Enantioselective [2+2] Cycloadditions *Angew. Chem. Int. Ed. Engl.* 2015; 54:11918–11928. [PubMed: 26333192]
- 12Secci F, Frongia A, Piras P. Stereocontrolled Synthesis and Functionalization of Cyclobutanes and Cyclobutanones *Molecules*. 2013; 18:15541. [PubMed: 24352013]
- 13Dembitsky VM. Naturally Occurring Bioactive Cyclobutane-Containing (CBC) Alkaloids in Fungi, Fungal Endophytes and Plants *Phytomedicine*. 2014; 21:1559–1581. [PubMed: 25442265]
- 14Berger WT. Targeting Fatty Acid Binding Protein (FABP) Anandamide Transporters – A Novel Strategy for Development of Anti-Inflammatory and Anti-Nociceptive Drugs *PLOS ONE*. 2012; 7:e50968. [PubMed: 23236415]
- 15Wager TT. Discovery of Two Clinical Histamine H³ Receptor Antagonists: trans-N-Ethyl-3-fluoro-3-[3-fluoro-4-(pyrrolidinylmethyl)phenyl]cyclobutanecarboxamide (PF-03654746) and trans-3-Fluoro-3-[3-fluoro-4-(pyrrolidin-1-ylmethyl)phenyl]-N-(2-methylpropyl)cyclobutanecarboxamide (PF-03654764) *J. Med. Chem.* 2011; 54:7602–7620. [PubMed: 21928839]
- 16Blakemore DC. Synthesis and in vivo Evaluation of Bicyclic Gababutins *Bioorg. Med. Chem. Lett.* 2010; 20:461–464. [PubMed: 20005103]
- 17Hughes D, Wheeler P, Ene D. Olefin Metathesis in Drug Discovery and Development—Examples from Recent Patent Literature *Org. Process Res. Dev.* 2017; 21:1938–1962.
- 18Slade J. A Concise Synthesis of a Novel Insulin-Like Growth Factor I Receptor (IGF-IR) Inhibitor *Org. Process Res. Dev.* 2007; 11:825–835.
- 19Singh J. A Practical Asymmetric Synthesis of the Antiviral Agent Lobucavir, BMS-180194 *Org. Process Res. Dev.* 1998; 2:393–399.
- 20Quasdorf KW, Overman LE. Catalytic Enantioselective Synthesis of Quaternary Carbon Stereocentres *Nature*. 2014; 516:181–191. [PubMed: 25503231]
- 21Seiser T, Saget T, Tran DN, Cramer N. Cyclobutanes in Catalysis *Angew. Chem. Int. Ed. Engl.* 2011; 50:77740–77752.
- 22Namyslo JC, Kaufmann DE. The Application of Cyclobutane Derivatives in Organic Synthesis. *Chem. Rev.* 2003; 103:1485–1537. [PubMed: 12683789]
- 23Kim DK, Riedel J, Kim RS, Dong VM. Cobalt Catalysis for Enantioselective Cyclobutanone Construction *J. Am. Chem. Soc.* 2017; 139:10208–10211. [PubMed: 28704053]
- 24Wang YM, Bruno NC, Placeres AL, Zhu SL, Buchwald SL. Enantioselective Synthesis of Carbo- and Heterocycles through a CuH-Catalyzed Hydroalkylation Approach *J. Am. Chem. Soc.* 2015; 137:10524–10527. [PubMed: 26256576]
- 25Kleinbeck F, Toste FD. Gold(I)-Catalyzed Enantioselective Ring Expansion of Allenylcyclopropanols *J. Am. Chem. Soc.* 2009; 131:9178–9179. [PubMed: 19530649]
- 26Poplata S, Tröster A, Zou Y-Q, Bach T. Recent Advances in the Synthesis of Cyclobutanes by Olefin [2+2] Photocycloaddition Reactions *Chem. Rev.* 2016; 116:9748–9815. [PubMed: 27018601]

- 27Du J, Skubi KL, Schultz DM, Yoon TP. A Dual-Catalysis Approach to Enantioselective [2 + 2] Photocycloadditions Using Visible Light Science. 2014; 344:392–396. [PubMed: 24763585]
- 28Fructos MR, Prieto A. 2+2 Cycloaddition Reactions Promoted by Group 11 Metal-Based Catalysts Tetrahedron. 2016; 72:355–369.
- 29Russell SK, Lobkovsky E, Chirik PJ. Iron-Catalyzed Intermolecular $[2\pi + 2\pi]$ Cycloaddition J. Am. Chem. Soc. 2011; 133:8858–8861. [PubMed: 21598972]
- 30Amghizar I, Vandewalle LA, Van Geem KM, Marin GB. New Trends in Olefin Production Engineering. 2017; 3:171–178.
- 31Xiao KJ. Palladium(II)-Catalyzed Enantioselective C(sp³)-H Activation Using a Chiral Hydroxamic Acid Ligand J. Am. Chem. Soc. 2014; 136:8138–8142. [PubMed: 24815880]
- 32Reeves CM, Eidamshaus C, Kim J, Stoltz BM. Enantioselective Construction of α -Quaternary Cyclobutanones by Catalytic Asymmetric Allylic Alkylation Angew. Chem. Int. Ed. Engl. 2013; 52:6718–6721. [PubMed: 23686812]
- 33Misale A, Niyomchon S, Maulide N. Cyclobutenes: At a Crossroad between Diastereoselective Syntheses of Dienes and Unique Palladium-Catalyzed Asymmetric Allylic Substitutions Acc. Chem. Res. 2016; 49:2444–2458. [PubMed: 27797480]
- 34Treutwein J, Hilt G. Cobalt-Catalyzed [2+2] Cycloaddition Angew. Chem. Int. Ed. Engl. 2008; 47:6811–6813. [PubMed: 18720333]
- 35Timsina YN, Sharma RK, RajanBabu TV. Cobalt-Catalyzed Asymmetric Hydrovinylation of 1,3-Dienes Chem. Sci. 2015; 6:3994–4008. For a complete list of cobalt complexes of chiral ligands and activators examined and their associated selectivities, see Table S3. [PubMed: 26430505]
- 36Helmchen G, Pfaltz A. Phosphinooxazolines. A New Class of Versatile, Modular *P,N*-Ligands for Asymmetric Catalysis Acc. Chem. Res. 2000; 33:336–345. [PubMed: 10891051]
- 37See Supplementary Material for further details on the synthesis of authentic (R)-4b.
- 38Jing SM, Balasanthiran V, Pagar V, Gallucci JC, RajanBabu TV. Catalytic Enantioselective Heterodimerization of Acrylates and 1,3-Dienes J. Am. Chem. Soc. 2017; 139:18034–18043. [PubMed: 29120629]
- 39Waser J, Gonzalez-Gomez JC, Nambu H, Huber P, Carreira EM. Cobalt-catalyzed Hydrohydrazination of Dienes and Enynes: Access to Allylic and Propargylic Hydrazides Org. Lett. 2005; 7:4249–4252. [PubMed: 16146399]
- 40Brewitz L, Llaveria J, Yada A, Furstner A. Formal Total Synthesis of the Algal Toxin (-)-Polycavernoside A Chem. Eur. J. 2013; 19:4532–4537. [PubMed: 23418052]
- 41Lee CL. First Total Synthesis of Antrocamphin A and its Analogs as Anti-inflammatory and Anti-platelet Aggregation agents Org. Biomol. Chem. 2011; 9:70–73. [PubMed: 21088769]
- 42Koch G. Synthesis of Chiral (phosphinoaryl)oxazolines, a Versatile Class of Ligands for Asymmetric Catalysis Recl. Trav. Chim. Des Pays-Bas. 1995; 114:206–210.
- 43Sharma RK, RajanBabu TV. Asymmetric Hydrovinylation of Unactivated Linear 1,3-Dienes J. Am. Chem. Soc. 2010; 132:3295–3297. [PubMed: 20163120]
- 44Wu Z, Nguyen ST, Grubbs RH, Ziller JW. Reactions of Ruthenium Carbenes of the Type $(PPh_3)_2(X)_2Ru:CH-CH:CPh_2$ (X = Cl and CF₃COO) with Strained Acyclic Olefins and Functionalized Olefins J. Am. Chem. Soc. 1995; 117:5503–5511.

A. Medicinally relevant compounds containing cyclobutanes **B. [2+2] Cycloaddition** **C. From acyclic or cyclopropane precursors** **D. Stereoselective reactions of pre-formed cyclobutanes and cyclobutenes** **E. This work:****Tandem [2+2] cycloaddition, asymmetric hydrovinylation** **Figure 1. Background for asymmetric cyclobutane synthesis.**

A. Cyclobutanes in drugs and natural products. Many of these compounds have chiral all-carbon quaternary centers, which pose a major synthetic challenge. **B-C.** Current methods for the synthesis of chiral cyclobutanes from acyclic precursors. **D.** Synthesis from pre-formed cyclobutanes. Location of functionalization shown by the arrows. **(a)** α -functionalization; **(b)** nucleophilic substitution; **(c)** desymmetrization; **(d)** C-H activation/functionalization. **E.** A single cobalt-catalyst for a [2+2]-cycloaddition of ethylene and an enyne to vinylcyclobutene followed by a subsequent asymmetric hydrovinylation.

A. Cobalt-catalyzed reaction between enyne and ethylene

B. Products of [2+2]-cycloaddition

C. Products of tandem [2+2]-cycloaddition/hydrovinylation

Figure 2. Cobalt-catalyzed reaction between 1,3-enyne 1a and ethylene.

A. Use of aluminum based activators dramatically improves the yield, scope and selectivity of this reaction. **B. Scope of cobalt-catalyzed [2+2]-cycloaddition and subsequent hydrovinylation.** dppe ligand and TMA (eq 2) are optimal for both the [2+2]-cycloaddition and the subsequent hydrovinylation. Isolated yields are shown in brackets. See Table S2 for exact reaction conditions for the synthesis of 3 or 4. **B.** Products (3a-3r) of the initial [2+2]-cycloaddition between the enyne and ethylene could be isolated in high yield at low temperature and short reaction times. **C.** Functionalized cyclobutanes (4a-4h) with an all-

carbon quaternary center were products of the tandem sequence obtained at room temperature (rt) and longer reaction times.

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Figure 3. Development of enantioselective version of the tandem cyclization/hydrovinylation.

A. Best protocol uses Et₂AlCl as activator and phosphino-oxazolone ligands. See supplementary material Table S4. **B.** Configuration of product established by comparison to authentic product (*R*)-4b. **C.** Characterization of the structure of the most versatile pre-catalyst by x-ray crystallography in solid-state. **D.** Viable ligands for the tandem sequence. For a more complete set of ligands **L1-L13**, see supplementary material Table S3. **E.** Cyclobutane products with chiral all-carbon quaternary centers. All isolated yields shown.

Figure 4. Possible mechanism of tandem [2+2]-cycloaddition/hydrovinylation.

This mechanism invokes an oxidative dimerization via a cobaltametallacyclopentene (6) for the [2+2]-cycloaddition and a metallacycloheptene (8) for the subsequent heterodimerization of the diene and ethylene.