Catalytic Enantioselective Heterodimerization of Acrylates and 1,3-Dienes
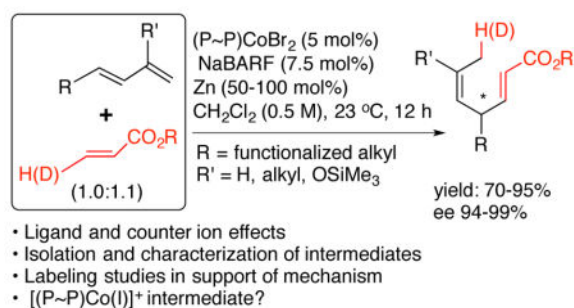
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Abstract

1,3-Dienes are ubiquitous and easily synthesized starting materials for organic synthesis and alkyl acrylates are among the most abundant and cheap feedstock carbon sources. A practical, highly enantioselective union of these two readily available precursors giving valuable, enantio-pure skipped 1,4-diene esters (with two configurationally defined double bonds) is reported. The process uses commercially available cobalt salts and chiral ligands. As illustrated by the use of 20 different substrates including 17 prochiral 1,3-dienes and 3 different acrylates, this heterodimerization reaction is tolerant of a number of common organic functional groups (e.g., aromatic substituents, halides, isolated mono- and di-substituted double bonds, esters, silyl ethers and silyl enol ethers). The novel results including ligand, counter ion and solvent effects uncovered during the course of these investigations show a unique role of a possible cationic Co(I) intermediate in these reactions. The rational evolution of a mechanism-based strategy that led to the eventual successful outcome and the attendant support studies may have further implications for the expanding use of low-valent group 9 metal complexes in organic synthesis.

Graphical abstract

Introduction

Studies aimed at the development of highly efficient and enantioselective methods for the preparation of various classes of organic compounds are among the most active areas of research in modern organic synthesis.[1] Successful outcome of such research, especially when it involves catalytic reactions between readily available starting materials and feedstock carbon sources,[2] can greatly impact the design, synthesis and manufacture of molecules of interest from medicine to materials.[3] Development of enantioselective versions of coupling reactions (heterodimerizations) between two different, stable alkenes for the synthesis of chiral intermediates has huge potential, yet presents significant challenges on two fronts, activation of the relatively unreactive molecules *and* selectivity (chemo- regio- and enantioselectivity) in the reactions between them.[4] In this context, we have reported highly enantioselective heterodimerization between ethylene and activated alkenes using nickel catalysts (Eq 1),[5a] and, between ethylene and 1,3-dienes using cobalt catalysts (Eq 2).[6a,b] While the reactions of ethylene are highly efficient and selective, and, applicable for the syntheses of several biologically important molecules (e. g., 2-arylpropionic acids,[7a] steroid analogs,[7b] pseudopterosins,[7c] trikentrins[7d]) the utility of this reaction would be vastly enhanced if instead of ethylene a functionalized alkene such as methyl acrylate can be used. Even though acrylates are among the largest volume feedstocks (> 2,000,000 metric tons annual production), they are seldom used in catalytic enantioselective reactions, and, for known dimerization reactions involving acrylates and other alkenes, the reported substrate scope, yields and selectivities are somewhat limited.[8] In the best example in the literature of an enantioselective codimerization of an alkyl acrylate and a diene, Hirano et al reported obtaining 31% yield and 58% ee in the reaction between 1,2,3,4-tetramethylbutadiene and *t*-butyl acrylate in the presence of 10 mol% of a Ru(0)-complex. A less substituted butadiene gave mixture of three products (total yield 73%) in ee's in the range of 10–29%.[8f] Since our protocols for ethylene/1,3-diene heterodimerization that uses cobalt/alkylaluminum (Eq 2) failed to work for the Lewis basic acrylate, a new catalystsystem had to be developed. In this article we report the development of a practical, and highly regio- and enantioselective catalytic reaction that combines a range of 1,3-dienes with alkyl acrylates (1:1.1 ratio, 23 °C) in the presence of 1–5 mol% of readily available *bis*-phosphine cobalt halide complexes (Eq 3b) and an activator, sodium *tetrakis*-3,5-*bis*-(trifluromethylphenyl)borate (NaBARF). The products are nearly enantio-pure, conjugated 1,4-diene esters (**5**) bearing a chiral center between the configurationally defined double bonds. Since these double bonds have distinctly different reactivities we expect these chiral synthons to be of significant value for further synthetic applications. Reactions of 20 different substrates including 17 different prochiral dienes giving yields in the range of 70–90% and enantiomeric excesses up to 99% are reported. Mechanistic studies including isolation and characterization of intermediates (multi-nuclear NMR, X-ray crystallography), solvent and counter-anion effects, and isotopic labeling studies suggest the unique role of cationic Co(I) intermediates in these reactions.

Nickel-catalyzed asymmetric hydrovinylation of alkenes

(1)

Cobalt-catalyzed asymmetric hydrovinylation of 1,3-dienes
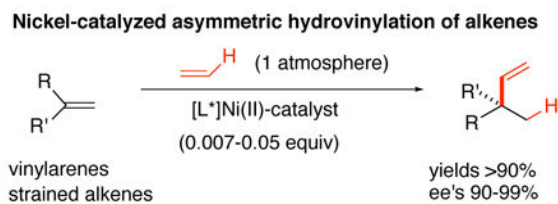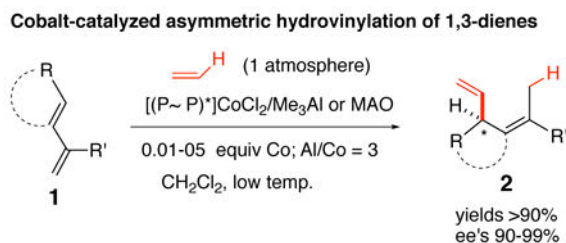
(2)

Cobalt(I)-catalyzed heterodimerization of 1,3-dienes and acrylates

- Ligand and counter ion effects
- Isolation and characterization of intermediates
- Labeling studies in support of mechanism
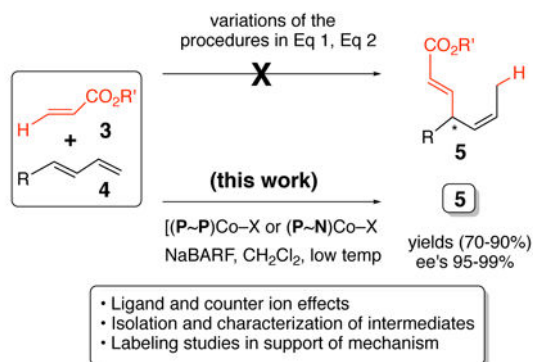
(3a), (3b)

Results and Discussion

A mechanistic proposal

In detailed scouting studies (See Table S1 in Supporting Information for details) we found that our broadly applicable original procedures for hydrovinylation of dienes using various *bis*-phosphine complexes (P~P)CoX$_2$ and an activator trimethylaluminum or methyl aluminoxane (MAO), led to very low conversions to the desired adducts **5** (Eq 3a).

We reasoned that the failure of this reaction involving various alkyl aluminum promoters might be related to the incompatibility of these reagents with the reactive, Lewis basic alkyl

acrylate substrate (**3**), vis-à-vis ethylene that was used in the successful reactions depicted in Eq 2. We wondered if we could circumvent the use of aluminum alkyls in this protocol by exploiting a discrete and identifiable Co(I)/Co(III)-redox cycle (Figure 1) as a possible pathway for this reaction that maybe approached differently by modifying the reaction conditions. This would involve an oxidative dimerization of the two olefins assisted by the low-valent cobalt species (**3 + 4 + 6 —> 7**), a mechanistic possibility that has been advanced before in other ruthenium-[9] and cobalt-[10] catalyzed heterodimerization reactions, but without much supporting evidence. Even though low-valent cobalt phosphine complexes have been used extensively in catalytic carbon-carbon bond-forming reactions,[11] these reagents are almost invariably generated in situ in the presence of excess reducing agents and other metal salts, and the oxidation state of cobalt and the nature of the intermediates (radicals or low-valent organometallic C-Co species) in many of these reactions are often open to speculation. A dearth of reports on well-characterized phosphine-Co(I) complexes as it relates to its catalytic properties and reaction chemistry has also been recognized in the literature by others.[12] Thus we decided to examine the role of discrete well-characterized Co(I)-complexes for the heterodimerization reactions of 1,3-dienes with the goal of overcoming the limitations of our original procedure.

Development of a modified protocol for the hydrovinylation of 1,3-dienes

To test the viability of an oxidative route (Figure 1) for the dimerization, we prepared and characterized several well-defined Co(I)-complexes (Figure 2) and examined their utility in the catalyzed heterodimerization reactions between (*E*)-1,3-dodecadiene and ethylene as a test reaction (Eq 4, Table 1). Details of the preparation and characterization of the compounds listed in Figure 2 are described in the Supporting Information.
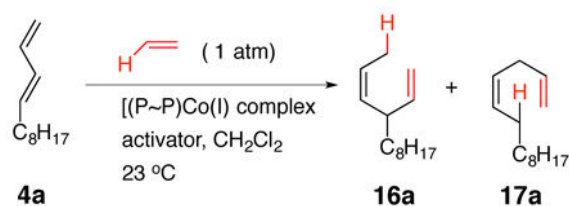

(4)

The most significant findings from the initial scouting experiments are shown in the Table 1. More extensive details describing the effect of ligands and activators on this reaction can be found in the Supporting Information (Table S2). Not surprisingly, the coordinately saturated complex (dppe)$_2$CoH (**9**)[13] or the Co(I) complexes **11a**, **12a**, **12b**, **13a**, **14, 15a** do not catalyze the dimerization reaction under ambient conditions in the absence of an activator (entry 1). However, in the presence of a Lewis acid, various Co(I)-complexes become viable catalysts for this reaction (entries 2–14). Thus fully characterized Co(I) complexes, (dppe)$_2$CoH (**9**)[13] and [(dppp)$_3$Co$_2$Br$_2$] (**11a**), are an excellent catalysts for this dimerization reaction in the presence of (C$_6$F$_5$)$_3$B (entries 2, 3). Sodium *tetrakis*-3,5-(*bis*-3,5-trifluromethylphenyl)borate (NaBARF) is also an excellent activator of **11a** (entry 4). This complex is readily prepared by reduction of the corresponding (P~P)CoBr$_2$ (**10a**) with

EtMgBr, activated Zn or Mn. The identity of the starting (dppp)CoBr$_2$ (**10a**) and the reduced species (**11a**) derived from reactions of **10a** with various reagents (EtMgBr, Zn) were established by X-ray crystallography since NMR spectra often resulted in broad peaks and generally not reliable, presumably because of the presence of traces amounts of Co(II) species and/or high-spin Co(I) species in the mixture. The unit cell parameters of crystals obtained from reduction of the (dppp)CoX$_2$ with EtMgBr and Zn are identical. High-resolution MALDI-mass spectra of the compounds **10a**, (used for the scouting experiments and the preparation of all racemic products in Table 4), **10d** (used to prepare the nearly enantio-pure products described in Table 4), **11a** and **12a** (mechanistically relevant, putative Co(I) complexes) are also especially useful for further characterization of these key compounds.[16] The solid-state structure of a sample obtained from reduction of **10a** with EtMgBr revealed the presence of an additional dppp ligand linking two cobalt centers (**11a**), where each cobalt has 16-electrons. The Zn-reduced complex, represented as '(dppp)CoBr' (**12a**), when activated by (C$_6$F$_5$)$_3$B or NaBARF, catalyzed a quantitative heterodimerization of (*E*)-1,3-dodecadiene and ethylene to give products **16a** and **17a** (entries 5 and 6). The corresponding (dppp)cobalt(I) chloride complex **12b** is equally effective for this reaction using either (C$_6$F$_5$)$_3$B or NaBARF as an activator (entries 7, 8). Entries 9 and 10 illustrate the use of ZnCl$_2$ and ZnI$_2$ as activators for this reaction even though they are not nearly as effective as NaBARF at comparable concentration levels. These activators are also moderately effective in the use of (dppb)cobalt(I) chloride (**13a**) as a catalyst (not shown). We recognized that the complex (COD)Co(η^3-cyclooctenyl) (**14**)[14] is an excellent source of well-defined of (P~P)Co(I)(η^3-cyclooctenyl) complexes (**15a**–**15e**). The application of three such complexes (**15b**, **15c** and **15d**) for the hydrovinylation reaction are shown in entries 12–14 in Table 1. The enantioselectivity observed for the adduct **16a** using the chiral, enantiopure complexes **15c** and **15d** (entries 13 and 14) are comparable to what was previously observed in our original reaction using Me$_3$Al as the activator (Eq 2),[15] validating the hypothesis that Co(I) intermediates may indeed be involved in these reactions carried out under disparate conditions. Most gratifyingly we find that this new protocol for heterodimerization *that avoids the use of near stoichiometric amounts of trimethylaluminum* (Eq 2) has broader scope for the alkenes, including for the use of alkyl acrylates as reaction partners.

Heterodimerization between (*E*)-1,3-diene and methyl acrylate

Table 2 summarizes the results of optimization of a heterodimerization between methyl acrylate and a prototypical diene, (*E*)-1,3-dodecadiene, using the new protocol (Eq 5). As expected none of Co(I)-complexes (Figure 1) catalyze the reaction *in the absence of activators* under ambient conditions (e. g., entry 1). However, we find that several Co(I)-complexes, among them, (dppp)CoBr (**12a**), (dppp)CoCl (**12b**), (dppb)CoCl (**13a**) and (dppe)CoBr, efficiently catalyze this reaction in the presence of various activators (entries 2–10). Among the activators, NaBARF (BARF = *terakis*-[*bis*-(3,5-trifluromethylphenyl)borate] was found to be the most generally applicable, facilitating the reactions of a wide range of Co(I)-complexes. Among the other activators that were examined, relatively inexpensive ZnCl$_2$ is also found to be acceptable (entry 5) even though stoichiometric amounts of this reagent are needed to complete the reaction. Surprisingly, Me$_3$Al and (C$_6$F$_5$)$_3$B were found to be much less effective (entries 6, 7), as were several others (AlCl$_3$, Zn(OTf)$_2$, AgOTf,

methylaluminoxane, Et_2Zn).[16] Both $AgSbF_6$ and ZnI_2 were usable, but with low conversions even at higher concentrations.[16]

* [shown results with (dppb)CoBr (5 mol%) and activator NaBARF (10 mol%)]
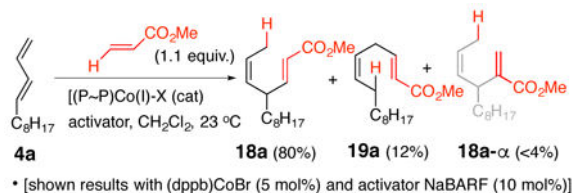
(5)

Further optimizations (see Supporting Information Table S3a–S3e) revealed that the reaction can be accomplished at near 1:1 stoichiometry of the alkenes, with lower catalyst loading (0.05 equiv), and, chlorinated solvents methylene chloride and dichloroethane were the most optimal. In these solvents for most substrates the reaction is best carried out at 0.5–0.6 M to effect complete conversion in 30 min with 5 mol% of the catalyst and 15 mol% of NaBARF (entry 3, Table 2). Oxygenated solvents such as THF, ether or ethyl acetate gave no conversion (entry 4). An important practical consideration related to this solvent effect is that in the preparation of the Co(I)-halide via Zn-reduction of the (P~P)CoX$_2$ complex, which is best carried out in THF, the residual THF should be completely removed after reduction for best results.[16] Hydrocarbons, where the catalyst has low solubility, showed very low conversion.

Cobalt(I) complexes of chiral ligands, [(*S,S*)-BDPP]CoBr and [**L3a**]CoBr (5) also are competent for the heterodimerization reaction, giving up to 97% ee in the former case (Table 2, entry 11). However, in subsequent experiments we realized that the in situ generation of the Co(I) complex (vide infra, Scheme 1) provided an exceptionally facile way of scouting the ligands for higher enantioselectivity for this exacting reaction, and these efforts are described in the next section. It should be noted that except for the counter ion, this procedure resembles the original Hilt conditions for heterodimerization of 2,3-dimethylbutadiene and 1-alkenes.[17]

Enantioselective heterodimerization reactions

Next we turned our attention to enantioselective heterodimerization reactions. Following the optimizations described thus far as a guide, heterodimerization of (*E*)-1,3-dodecadiene (**4a**) and methyl acrylate was carried out under two slightly different protocols, either using the *isolated* Co(I)-complexes (P~P)CoX (X = Br, Cl, COE-, COE- = η^3-cyclooctenyl) of various chiral ligands (Eq 5) or, by generating the Co(I) complexes in situ from the corresponding Co(II)X$_2$ complexes (Scheme 1). Most gratifyingly both conditions for the reaction gave the expected branched product **18a**, with, typically, less than 6% of the achiral linear product **19a**, and only traces (<1%) of the branched product **18a**-α. Even though the use of the isolated cobalt(I) complexes (Eq 5) helped to delineate novel aspects of this reaction, including the role of various activators and solvent effects, the latter procedure (Scheme 1) is more convenient and more efficient from a practical perspective. Therefore the ligand effects

in the enantioselective version of this reaction were examined in greater detail using this protocol. The results of these studies are documented in Table 3.

As is revealed by the entries in the Table 3, four classes of cobalt complexes, those carrying DIOP (**L1**, entry 1), BDPP (**L2**, entries 2, 3, 5, 6), 2-(2-diarylphosphino)phenyl oxazolines (Helmchen's ligands, entries 4, 7, 8, 9), and Josiphos (**L4**, entry 10) ligands were found to be viable for this demanding reaction, with DIOP, BDPP and JOSIPHOS giving outstanding regio- and enantioselectivities, the latter up to 97% ee. (For a complete list of ligands and their effect on selectivities, see, Supporting Information Figures S1 and S2). Entries 1–4 in Table 3 show applications of pre-reduced Co(I)-complexes (Eq 5). The complex (DIOP)CoBr, while giving high ee (entry 1), gave only modest chemical yields. As alluded to earlier, reactions with the (P~P)CoBr$_2$ complexes with zinc as a reducing agent is the most convenient and practical way to effect this reaction (Scheme 1) and the yields obtained for **18a** using this procedure are substantially higher (entries 5–10). Under these conditions nearly quantitative conversion of the diene is observed giving the 1,4-(*Z*)-adduct **18a** along with varying amounts (1–5 %) of a linear adduct (**19a**) and only traces, if any, of the isomeric **18a**-α. Thus, most gratifyingly, the enantioselective version of the reaction offers significantly higher regioselectivity for the reaction. Fine-tuning of the phosphinooxazoline (**L3**) leads to slight improvements in ee's (entries 7, 8 and 9), but even the best of these ligands, the *bis*-cyclohexylphopsphino-ligand **L3f** does not match the results obtained from the BDPP (entries 5, 6), or, the JOSIPHOS (entry 10) ligand, which gave >97% ee and yields in excess of 95% of the desired 1,4-addition product **18a**.

The absolute configuration of the major product **18b** derived from (*E*)-1,3-nonadiene and methyl acrylate using [(*S,S*)-BDPP]CoBr$_2$ has been established as (*R*) by the transformations shown in Scheme 2. Hydrovinylation of (*E*)-1,3-nonadine using (*S,S*)-BDPP is known to give the (*S*) adduct, **20b**.[15] This adduct (**20b**) was transformed into a mixture of epoxy esters [**22a + 22b**], by reaction with *m*CPBA, followed by treatment of the product epoxide [**21a+21b**] with Grubbs generation II metathesis catalyst in the presence of 5 equivalents of methyl acrylate. This diastereomeric pair is identical (chiral stationary phase chromatography, NMR) to the epoxides derived from the product of enantioselective heterodimerization of (*E*)-1,3-nonadiene and methyl acrylate using [(*S,S*)-BDPP]Co-complex. The assignments of the configurations of the other structurally related products (Table 4) were made by analogy. Retention behaviors of enantiomers of the adducts in chiral stationary phase GC is also consistent with the assignments across all products.[16]

Scope of the reaction

The optimized conditions were applied to a variety of 1,3-dienes and the results obtained are shown in Table 4. A full Table listing all starting materials and product distribution is included in the Supporting Information (Table S6). C$_4$-Substituted 1,3-dienes giving products **18a**–**18q** are among the best substrates for this reaction. This substituent can bear a number of functional groups, among them, an aromatic moiety (**18h** and **18i**), a chlorine (**18j**), a silyl ether (**18k**), and, mono-, di or tri-substituted alkene (**18l**, **18m**). Substituents at the C$_2$ and C$_3$ positions are tolerated as exemplified by products **18n**–**18t**. The C$_2$-substituent can be a chain carrying a remote alkene, such as in β-myrcene (**18t**) or even a

trimethylsiloxy substituent (**18n**). Several examples show the use of methyl, ethyl and *t*-butyl acrylate.

Even though we have not optimized the yield of all substrates shown, especially for the synthesis of the racemic series of products, the isolated yields of the branched product (**18x**) are generally very good to excellent (70~85%). Varying amounts of the linear product (**19x**, Scheme 1) are also observed in these reactions, especially for mono-substituted 1,3-dienes. Products from 1,3-disubstitued dienes including a trimethylsiloxy diene (**18n**) and from 2,3-dimethylbutadiene (**18s**) generally constitute a single branched adduct. 2-Alkyl dienes, as expected, give two linear 1,4-adducts (e. g., **18r/19r** and **18t/19t**).

Most significantly, enantioselectivities in excess of 95 %ee are obtained for most prochiral dienes. To our delight we also find that the regioselectivities in the enantioselective reactions are much superior to the achiral version of the reaction. Thus, except for two substrates that carry a remote aromatic ring (entries **18h** and **18i**) and one with a branching at the allylic position (18f) less than 6% of the linear product (**19x**) is formed in these reactions (For details, see Supplementary Material, Table S6).

A chiral product **18m** derived from citronellal-derived diene gave a 1:1 diastereomeric ratio of the adducts upon reaction with the achiral catalyst system, (dppp)CoBr$_2$/NaBARF/Zn. The reaction with either enantiomer of the BDPP-CoBr$_2$ complex gives an unusually selective reaction, overcoming the inherent selectivity of this chiral substrate. The two expected products (**18m**) are obtained in excellent diastereomeric ratios (>93:7 at C$_8$) depending on which enantiomer of the chiral catalyst is used.

Mechanism of heterodimerization

All available evidence indicates that neither bis-phosphine complexes derived from CoX$_2$ (X = Br, Cl, I), (P~P)CoX$_2$, or the corresponding reduced species (P~P)CoX (X = Br, Cl or η^3-cyclooctenyl) in themselves are competent to effect this reaction (Table 1, entry 1). Cobalt(I)-complexes, either isolated, or in situ generated *under conditions where no Lewis acid* is present, showed no reactivity. Activation by a Lewis acid [typically NaBARF, (C$_6$F$_5$)$_3$B or Zn salts] is essential for the success of the reaction (Table 1, entries 2–14). The most useful reactions (Table 1), especially the enantioselective versions (Tables 3 and 4), are best carried out using the [BARF] counter ion. BARF is unique and a cationic Co(I) complex cleanly generated from (*S,S*)-(BDPP)Co(η^3-octenyl) complex and [H(OEt)$_2$]$^+$[BARF]$^-$ is competent to effect the reaction, albeit in only a modest 22% yield (Table 3, entry 3). However, the (*Z*)-selectivity of the internal double bond derived from the 1,3-diene in the products **18a** and **19a** (Tables 2, 3), and the overall enantioselectivity of the reaction are the same for a given ligand (e.g., (*S,S*)-BDPP, **L2**) irrespective of which protocols is used (Table 3, entries 2, 3 or 5), strongly suggesting that the intermediates involved in these reactions are identical. Reduction of the Co(II)-salts either by Mn or Zn showed no effect on the overall selectivity (regioselectivity or enantioselectivity) of the reaction. An examination of the activators indicates that a synergy between Lewis acidity of the metals and the properties of the counter ion is important. Significant variations in the yield and selectivity of the reaction upon use of assorted Zn and Ag salts support this contention (See Supporting Information,

Table S3f). Methyl aluminoxane and trimethyl aluminum, which perform exceedingly well for simple co-dimerization of dienes with ethylene, totally fail with methyl acrylate. Diethylaluminum chloride leads to a number of side-products including Diels-Alder reactions between the diene and acrylate (Table S1). These observations suggest that a cationic species is essential for success, and, simple redox mechanism involving neutral Co(I)/Co(III)-cycle is not operating under the reaction conditions. The role of the cationic intermediates is further supported by the remarkable solvent effect seen in this reaction (Supporting Information, Table S3d). Coordinating solvents such as THF, ether, ethyl acetate completely inhibit the reaction. Hydrocarbon solvents are also not suitable, presumably because of insolubility of the putative cationic species. Finally, the configuration of the diene-derived double bond in both major products **18** and **19** is *Z*, suggesting a strong η^4-coordination of the 1,3-diene or a metallacycle intermediate (vide infra, Figure 3).

To account for the experimental observations, we suggest the mechanism shown in Figure 3 based on literature precedents and our initial hypothesis (Figure 1), but slightly modified to accommodate the effects of the Lewis acids, solvents and the counter ions. Thus the cobalt (I)-complex (P~P)CoX (**6**), which is readily formed from the corresponding Co(II) precursor under the reduction conditions, reacts with the Lewis acid or NaBARF to produce the highly reactive cationic species **23**. Subsequent oxidative dimerization (via insertion of the acrylate into the Co–C_4 bond of **24a/24b**) gives **25**, which undergoes β-hydride elimination to give **26**. Reductive elimination from the Co(III) species **26** leads to the major product **18** with regeneration of the catalyst **23**. Such elimination could be assisted by other ligands such as the diene or the acrylate giving a less coordinately unsaturated species formally represented as **23**. Similar insertion of acrylate into Co–C_1, would lead to the minor product **19** via **27**.

While we have identified and fully characterized several catalytically active Co(I) species (Figure 2) including (dppp)$_3$Co$_2$Br$_2$ (**11a**) and (*S,S*-BINAP)Co(η^3-cyclooctenyl) (**15e**), we were unsuccessful in characterizing any of the cationic intermediates beyond **6** in the catalytic cycle. The ^{1}H and ^{31}P NMR spectra obtained upon treatment of **6** with 1,3-dienes in the presence of NaBARF or various Lewis acids are largely unintelligible with broad peaks.

To gain further insight into the mechanism of the reaction, we have carried out the heterodimerization reaction using (2,3,3)-d$_3$ methyl acrylate and (*E*)-1,3-dodecadiene (Eq 6a) and examined the incorporation of deuterium atoms in the product(s). The products of the reaction **18a**-d$_3$ and **19a**-d$_3$ are readily identified by ^{1}H, ^{2}H and ^{13}C NMR spectroscopy. The incorporation of D can be estimated quantitatively by ^{13}C[^{1}H,^{2}H] NMR spectroscopy employing inverse-gated decoupling experiments since substitution by D for H moves the chemical shifts of the C_{sp2}-**CH$_3$**-group in **18** to slightly higher field (in this case by ~ 0.3 δ).[18] Exceptionally high fidelity in the transfer of D from the methyl acrylate-d$_3$ to the product provides strong support for the mechanism proposed. A corresponding experiment with (1,1)-d$_2$-dodecadiene and methyl acrylate (Eq 6b) further supports the mechanistic conclusions.
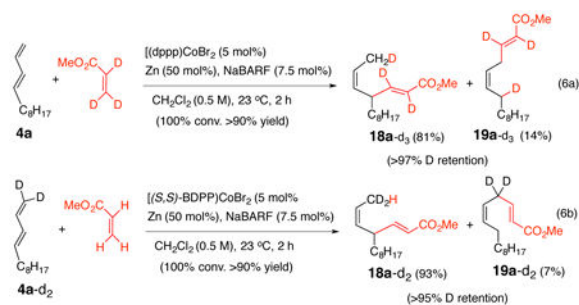
(6a), (6b)

Conclusions

1,3-Dienes are ubiquitous and easily synthesized starting materials for organic synthesis and alkyl acrylates are among the most abundant and cheap feedstock carbon sources. A practical, highly enantioselective union of these two readily available precursors giving valuable, nearly enantio-pure skipped 1,4-diene esters (with two configurationally defined double bonds) contributes significantly to our repertoire of powerful synthetic methods, especially since the process also uses commercially available cobalt salts and chiral ligands. This atom-economical heterodimerization reaction is tolerant of a number of common organic functional groups as illustrated by the use of 20 different substrates including 17 prochiral 1,3-dienes and 3 different acrylates. The novel results including ligand, counter ion and solvent effects we have uncovered during the course of these investigations show a unique role of a possible cationic Co(I)- intermediate in these reactions. We hope that the rational evolution of a mechanism-based strategy that led to the eventual successful outcome and the attendant support studies will add to the burgeoning organometallic chemistry of cobalt and its applications with further implications beyond the synthetic reactions described in this paper.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
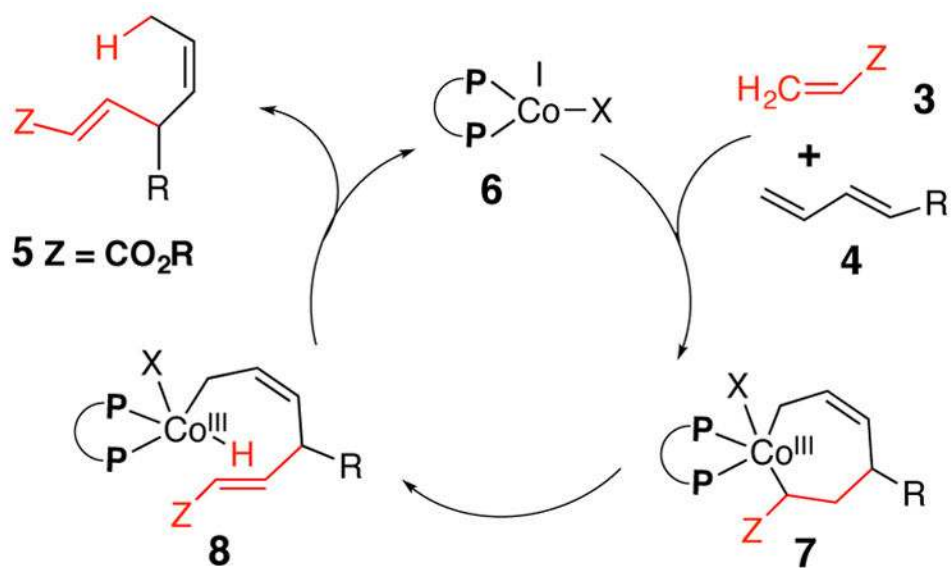Oxidative route to dimerization of alkenes
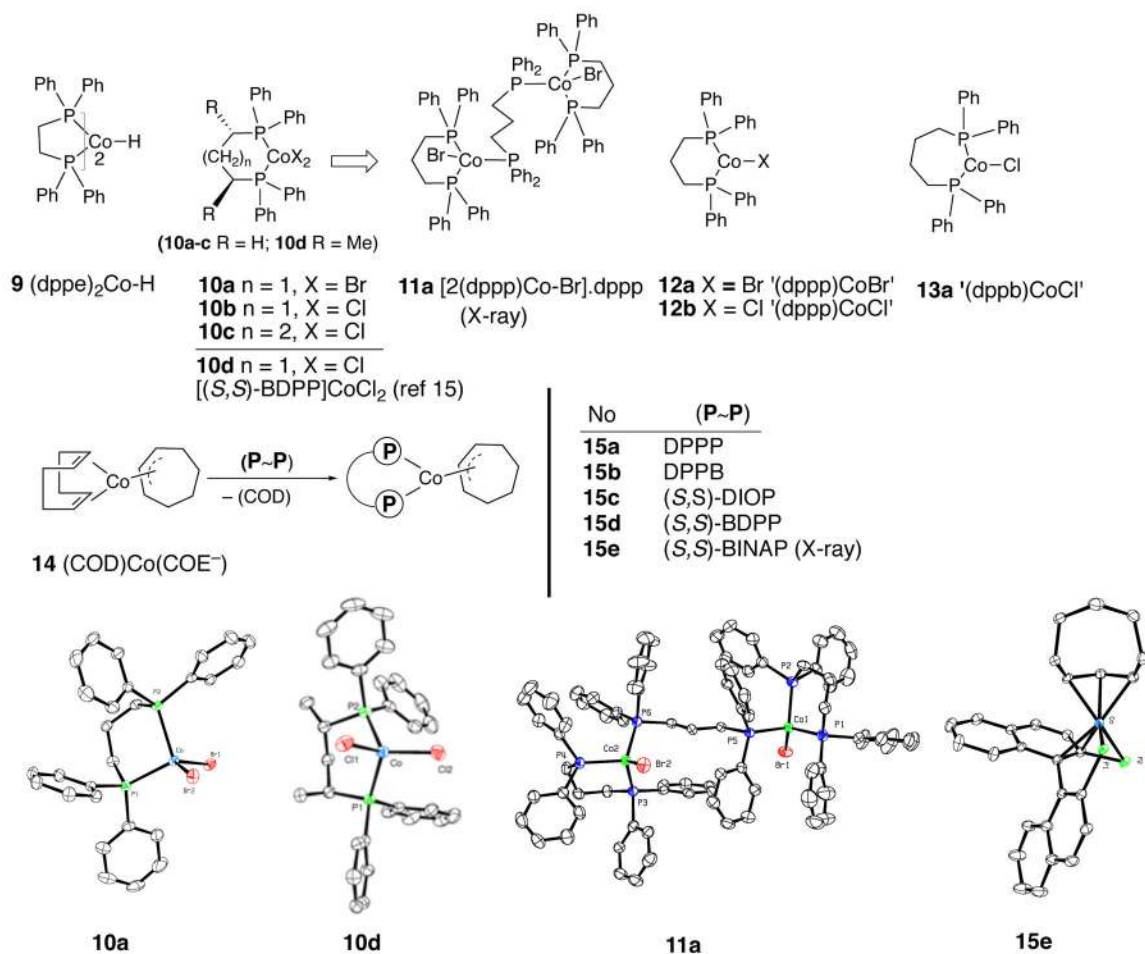
Figure 2.
Cobalt(I) and cobalt (II) *bis*-phosphine complexes for heterodimerization of alkenes. See
Supporting Information page S26 for full structures of ligands.
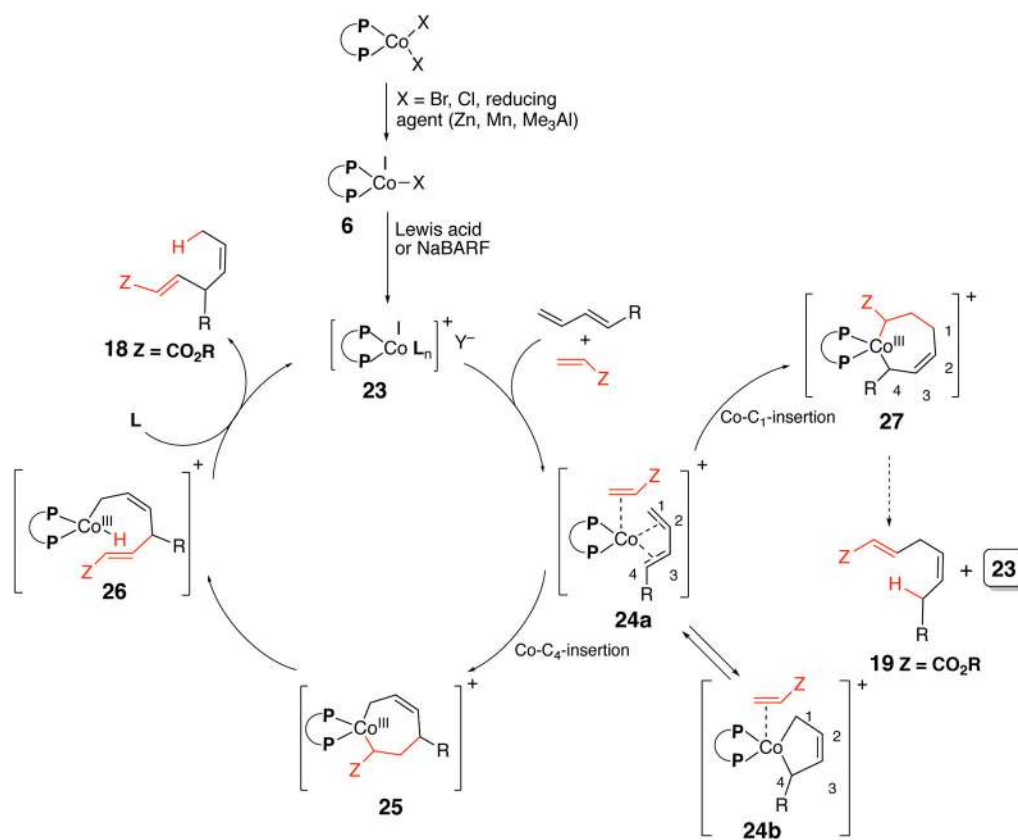
Figure 3.
A plausible mechanism of heterodimerization which accounts for the ligand, counter ion and solvent effects, the configuration of double bonds in the products, and, labeling studies.

Scheme 1.
Enantioselective heterodimerization between (*E*)-1,3- dodecadiene and methyl acrylate

Scheme 2.
Relating the absolute configuration of the heterodimerization product 18b to the known configuration of 20b

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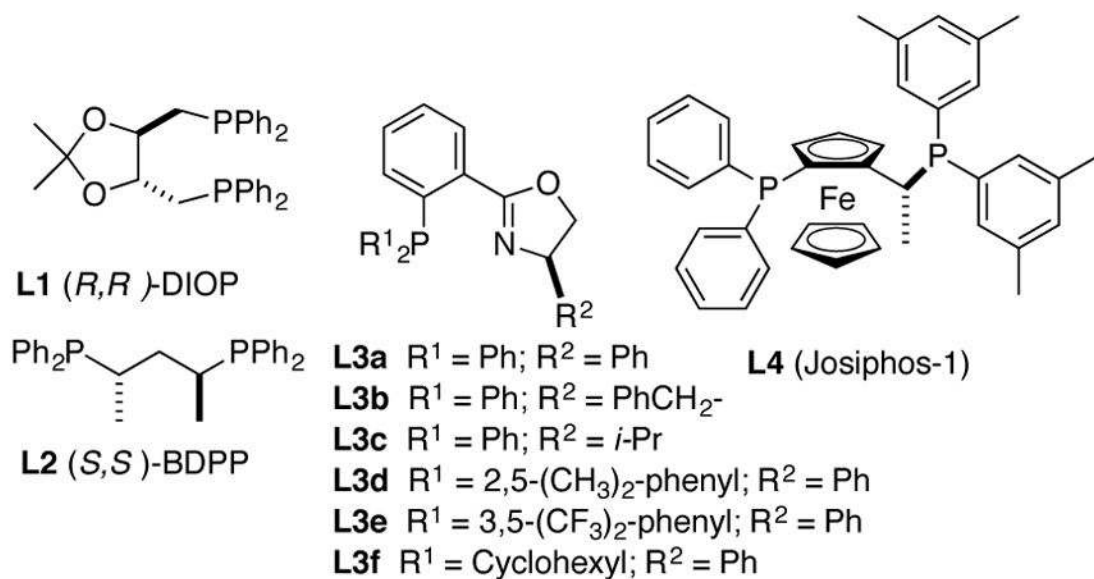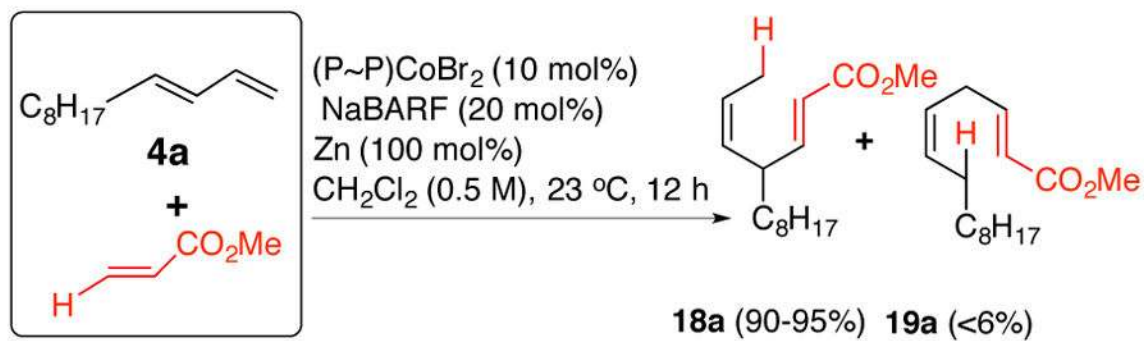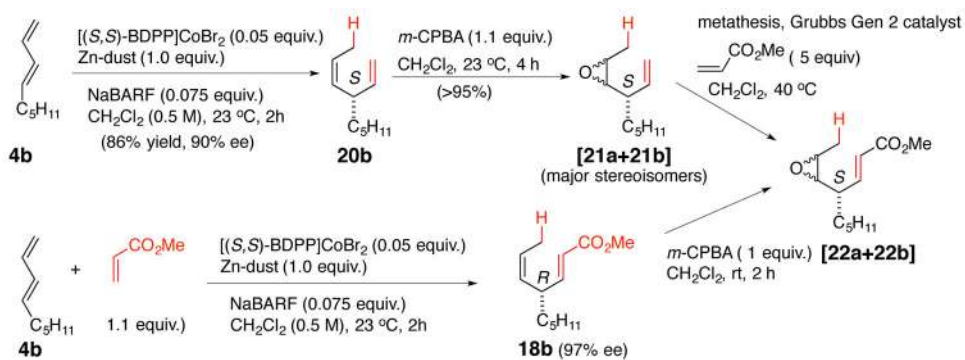
Table 1

Codimerization of (E)-1,3-dodecadiene and ethylene using Co(I) complexes[a]

entry	Co(I) source (mol%)	activator (mol%)	temp (°C) time	conv. (%)	16a/17a
1	**9, 11a, 12a, 12b, 14, 15a**	none	various[a]	<5	--
2	**9** (dppe)₂CoH (20)	$(C_6F_5)_3B$ (20)	23, 4	100	78/20
3	**11a** (dppp)₃Co₂Br₂ (5)	$(C_6F_5)_3B$ (60)	23, 1	100	80/20
4	**11a** (dppp)₃Co₂Br₂ (5)	NaBARF (20)	23, 1	>99	82/17
5	**12a**[b] '(dppp)CoBr' (10)	$(C_6F_5)_3B$ (15)	23, 1	100	80/20
6	**12a**[b] '(dppp)CoBr' (10)	NaBARF (30)	23, 1	100	79/20
7	**12b**[b] '(dppp)CoCl' (10)	$(C_6F_5)_3B$ (30)	23, 1.5	100	76/19
8	**12b**[b] '(dppp)CoCl' (10)	NaBARF (25)	23, 1.5	100	77/17
9	**12b**[b] '(dppp)CoCl' (10)	$ZnCl_2$ (50)	23, 3	90	78/22
10	**12b**[b] '(dppp)CoCl' (10)	ZnI_2 (30)	23, 6	55	40/11
11	**14** (COD)Co(COE-) (10)	$(C_6F_5)_3B$ (30)	23, 12	100	76/11
12	**15b** (dppb)Co(COE-) (10)	$(C_6F_5)_3B$ (30)	23, 1	100	71/3
13	**15c** (S,S)-DIOPCo(COE-) (5)	$(C_6F_5)_3B$ (10)	−20, 12	25	34[c]/5
14	**15d** (S,S)-BDPPCo(COE-) (10)	$(C_6F_5)_3B$ (30)	0 to 23, 2	100	77[d]/21

[a] See Eq 4 and Supporting Information for details. A more detailed list of cobalt(I) sources and corresponding reaction conditions are also included there (Table S2). The conversion and composition of products **16** and **17** (Eq 4) were determined by gas chromatography and confirmed by NMR spectroscopy. See Supporting Information for details.

[b] Synthesized by reduction of the corresponding (P–P)CoX₂ by Zn.

[c] 87% ee.

[d] 80% ee.

Table 2

Optimization of 1,3-diene-acrylate dimerization (Ligand and counter ion effects)[a]

entry	Co(I) source[b] (mol%)	activator (mol%)	temp (°C) time (h)	conv. (%)	products (%)[c] 18a	19a
1	**12a** (dppp)CoBr (10)	none	23, 18	0	--	--
2[d]	**12a** (dppp)CoBr (5)	NaBARF (10)	23, 12	100	80	12
3[e]	**12a** (dppp)CoBr (5)	NaBARF (15)	23, 0.5	100	85	10
4[f]	**12a** (dppp)CoBr (5)	NaBARF (15)	23, 12	0	--	--
5	**12a** (dppp)CoBr (10)	ZnCl$_2$ (100)	23, 18	100	79	15
6	**12a** (dppp)CoBr (10)	(C$_6$F$_5$)$_3$B (30)	23, 20	9	-	-
7	**12a** (dppp)CoBr (10)	Me$_3$Al (60)	23, 20	<5	-	-
8	**12b** (dppp)CoCl (10)	NaBARF (30)	23, 12	100	79	13
9	**13a** (dppb)CoCl (10)	NaBARF (30)	23, 12	100	78	13
10	(dppe)CoBr (10)	NaBARF (30)	23, 12	100	86	7
11	[(S,S)-BDPP]CoBr (10)	NaBARF (30)	23, 12 h	56	54[g]	2
12	[**L3a**]CoBr (5)	NaBARF (15)	23, 12	100	87[h]	13

[a]See Eq 5 and Supporting Information for experimental details. More elaborate Tables (Tables S3a–S3e, Table S4a–S4b) describing effect of various parameters used for the optimization of this reaction (activators, solvents, stoichiometries of NaBARF and methyl acrylate) are also included in the Supporting Information.

[b]The Co(I)-bromide complexes were prepared by reduction with activated zinc. See Supporting information for details.

[c]Up to 4% of a regioisomer **18a**-α was also observed.

[d]0.12 M in substrate.

[e]0.60 M in substrate.

[f]in THF.

[g]97% ee, See Scheme 1 below for the structure of the ligand.

[h]60% ee, See Scheme 1 below for the structure of the ligand.

Table 3

Ligand effects in enantioselective heterodimerization of (*E*)-1,3-dodecadiene and methyl acrylate[a]

Entry	Co source (mol%), Zn (mol%) activator (mol%)	time (h)	conv.(%)	18a	
				yield (%)	ee (%)
Cobalt(I) [Eq 5]					
1	(*R,R*)-DIOP(**L1**)CoBr (5), Zn (0), NaBARF (7)	20	<10	<10	93
2	(*S,S*)-BDPP(**L2**)CoBr (10), Zn (0), NaBARF (30)	20	56	53	97
3	(*S,S*)-BDPP(**L2**)Co(COE-) (5), Zn (0), H(EtO)$_2$BARF (5)	20	22	22	93
4	[**L3a**]CoBr (5), Zn (0), NaBARF (15)	12	100	87	60
Cobalt(II) [Scheme 1]					
5	(*S,S*)-BDPP(**L2**) CoBr$_2$ (10), Zn (100), NaBARF (20)	12	100	95	97
6	(*R,R*)-BDPP(*ent*-**L2**) CoBr$_2$ (10) Zn (100) NaBARF (40)	12	100	94	95
7	[**L3a**]CoCl$_2$ (10), Zn (100), NaBARF (20)	12	100	88	60
8	(*ent*-**L3b**)CoBr$_2$(10), Zn (100), NaB-ARF (20)	12	100	68	73
9	(**L3f**) CoBr$_2$(10), Zn (50), NaBARF (40)	12	100	80	77
10	(**L4**) CoBr$_2$(10), Zn (50), NaBARF (40) Josiphos 1	12	99	97	97

[a]For entries 1–4, Eq 5, for entries 5–10 see Scheme 1. For a more complete list of ligands examined, see Supporting Information, Figures S1 and S2.

Table 4

Scope of heterodimerization of 1,3-dienes and acrylates[a]

Chiral Products

	18a-Me	18a-Et	18a-t-Bu	18b-Me	18f-Et	18f-t-Bu	18c-Me	18c-Et	18c-t-Bu
% yield (racemic)	81	80	75	86	91	81	60	60	51
% yield (non-racemic)	82	--	--	81	76	69	65	75	72
% ee	97			98	98	97	97	81	96

	18d-Me	18d-t-Bu	18e-Me	18e-t-Bu	18f-Me	18f-t-Bu	18g	18h-Me	18h-t-Bu
% yield (racemic)	79	79	75	81	72	75	81	65	60
% yield (nonracemic)	89	--	70	-	75	--	75	60	-
% ee	98		98	-	96	--	99	95	-

	18i-Me	18i-t-Bu	18j	18k	18l	18m[b]	18n
% yield (racemic)	76	62	85	78	78	92 (dr 1:1)	85
% yield (nonracemic)	72	--	79	87	87	81, 75	--
% ee	98	--	>95	98	98	dr 95:5; 7:93	--

Products from 2 or 3-substituted 1,3-dienes[c,d]

	18o	18p	18q	18r + 19r	18s-Me	18s-t-Bu	18t + 19t
(% yield)	81	85	79	85 (1:1)	85	79	70 (1:1)

[a]See Scheme 1 and Supporting Information for details of the procedure and full characterization of products. The yield and proportion of the major product (**18x**) is shown. The remaining material is the linear adduct **19x** (see Eq 5). Selectivities were determined by chiral stationary phase gas chromatography. Chromatograms for all products are included in the Supporting Information. For **18a**, >96 % ee (*S*) with (*R,R*)-BDPP CoBr$_2$.

[b]For **18m**, diastereomeric ratio, [C$_8$(*R*): C$_8$(*S*)], with (*S,S*)-BDPP = 95:5; with (*R,R*)-BDPP = 7:93.

[c]For **18n–18q** the % ee was not determined.

[d]Products **18r–18u** are achiral.