



Published in final edited form as:

J Am Chem Soc. 2015 November 18; 137(45): 14268–14271. doi:10.1021/jacs.5b10364.

Asymmetric Catalysis with Ethylene. Synthesis of Functionalized Chiral Enolates

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Abstract

Trialkylsilyl enol ethers are versatile intermediates often used as enolate surrogates for the synthesis of carbonyl compounds. Yet there are no reports of broadly applicable, catalytic methods for the synthesis of chiral silyl enol ethers carrying latent functionalities useful for synthetic operations beyond the many possible reactions of the silyl enol ether moiety itself. Here we report a general procedure for highly catalytic (substrate:catalyst ratio up to 1000:1) and enantioselective (92% to 98% major enantiomer) synthesis of such compounds bearing a vinyl group at a chiral carbon at the β -position. The reactions, run under ambient conditions, use trialkylsiloxy-1,3-dienes and ethylene (1 atmosphere) as precursors, and readily available (*bis*-phosphine)-cobalt(II) complexes as catalysts. The silyl enolates can be readily converted into novel enantiopure vinyl triflates, a class of highly versatile cross-coupling reagents, enabling the syntheses of other enantiomerically pure, stereo-defined trisubstituted alkene intermediates not easily accessible by current methods. Examples of Kumada, Stille and Suzuki coupling reactions are illustrated.

Trialkylsilyl enol ethers are among the most widely used nucleophilic reagents in organic synthesis because of the ease of their preparation and the facile reactions they undergo with a broad range of electrophiles to form highly functionalized carbonyl compounds.¹ Many of these reactions exhibit exquisite reagent- and catalyst-dependent selectivities at every level – chemo-, regio-, and stereoselectivity – in the bond-forming processes.² Development of highly efficient and enantioselective protocols for the synthesis of functionalized silyl enol ethers would considerably expand the utility of these venerable intermediates. The closest precedent for a catalytic reaction that results in the regio- and stereoselective synthesis of a silyl enol ether involves a Rh(L*)-catalyzed enantioselective conjugate addition (Scheme 1) of an alkenylorganozirconium reagent to a cycloalkenone (**1**) followed by a difficult (large excess of 4 reagents, long reaction times) *in situ* silylation of the weakly reactive zirconium-enolate **2** (see step 2).^{3a} The reaction shows poor selectivity for the preparation of acyclic derivatives (e. g., **4**).^{3b} While similar catalytic asymmetric conjugate alkenylation of enones using alkenyl boronates^{4a,b} and alkenyl aluminum reagents^{4c,d} are known, no such reaction

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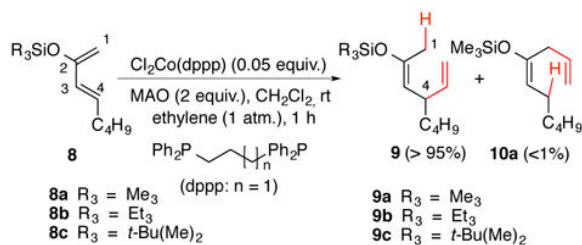
The authors declare no competing financial interest.

Supporting Information

Experimental procedures for the scouting experiments, typical reaction conditions for the hydrovinylation reactions. Chromatographic and spectroscopic data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>

has been reported for simple vinyl ($\text{H}_2\text{C}=\text{CH}-$) additions. In all these cases, the products of addition are almost invariably the ketones, and not the more synthetically useful, regioselectively trapped enolates. Highly specialized silyl enolate products are formed, but never isolated, in some asymmetric metal-catalyzed reactions including hetero-Diels-Alder reactions of siloxy-1,3-dienes.⁵ Here we report a general procedure for highly catalytic, chemo-, regio- and enantioselective synthesis of silyl enol ethers that carry a vinyl-bearing chiral center at the β -position (**6**, Scheme 2). The reactions, which proceed under ambient conditions, couple siloxy-1,3-dienes (**5**) and ethylene (1 atm), use as little as 0.001 – 0.05 equiv. of readily available cobalt complexes, and give products in high yield (>90%) and exceptionally high enantioselectivity (92-98% ee). The silyl enolates can be readily converted into nearly enantiopure vinyl triflates (**7**), which are potentially valuable precursors for a variety of cross-coupling reactions.

Our studies started with an examination of the hydrovinylation of a prototypical trimethylsiloxy-1,3- diene, **8a**, under conditions described in eq 1, which was arrived at in initial optimization studies. In these experiments,⁶ carried out using cobalt (II) chloride-complexes of 1,*n*-*bis*-diphenylphosphinoalkane ligands and various promoters, we recognized that trimethylaluminum, a Lewis acidic alkylating agent which we had successfully used previously⁷ gave unacceptable yields of the expected hydrovinylation product (**9a**). Alternate procedures using Zn/ZnI_2 in place of the aluminum reagents⁸ also gave unsatisfactory results. The major product in these reactions arises from simple decomposition of the sensitive silyloxydiene **8a** to regenerate the enone from which this substrate was prepared. On the other hand, a relatively weaker alkylating agent, methylaluminoxane (MAO), which is an easily handled solid reagent,⁹ gave excellent yields of the addition products. In all cases, the major product was identified as the branched 1,4-adduct, (*E*)-**9**.¹⁰ A minor side-product that is observed in some of the reactions is the linear 1,4-adduct **10a**. Among the cobalt complexes, $(\text{dppp})\text{CoCl}_2$ [dppp = 1,3-*bis*-diphenylphosphinopropane], gave an exceptionally clean reaction to yield the product (*E*)-**9a** in quantitative yield. Likewise, the corresponding triethylsilyl and *t*-butyldimethylsilyloxy dienes, **8b** and **8c**, also gave the respective adducts (**9b** and **9c**) in excellent yields and exquisite *E*-selectivity (eq 1).



(1)

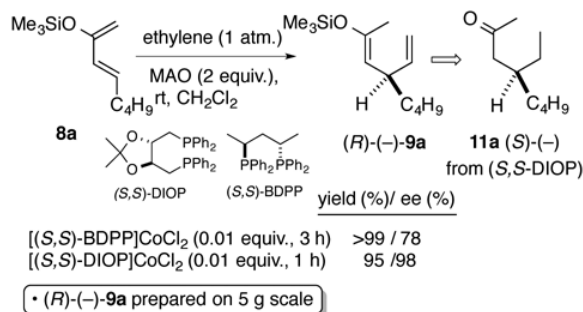
The hydrovinylation reaction has a broad scope as illustrated by the examples **8a-8p** in Table 1. Under the optimized conditions, the reactions of the 2-trimethylsilyloxydienes **8a-8p** proceed at room temperature giving excellent yields of the hydrovinylation products.

In all cases except **8k**(entry 9), the hydrovinylation favors the branched product in which the hydrogen is attached to the terminal, unsubstituted carbon, C₁, and the vinyl group to ^a Supporting Information for details. ^b No other products the C₄ of the original diene. When the trialkylsiloxy group is on C₃ (e.g., **8h**, compared to **8a** where it is on C₂ by this detected by GC. ^c After hydrolysis to ketone. ^d Only a 1,4-numbering scheme), proportionally more linear product **10h** (up to 25%) is also formed (entry 6). Dienes with bulkier substituents (R) at the C₄ position (**8f**, R = *t*-Bu and **8g**, R = *i*-Pr) take up to 20 h to give moderate yields of the products. An enantiopure siloxydiene derived from (–)-citronellal, **8j**, undergoes the reaction giving excellent yield of the expected product as a mixture of 1:1 diastereomers (at C₄) with the achiral (dppp)CoCl₂ complex (entry 8). A diene with a phenyl substituent in the C₄-position (**8k**) does not give any of the expected products. Instead a linear 1,4-adduct, (*Z*)-6-phenyl-1,4-hexadiene (**10k**), is formed in 80% yield (entry 9). Entries 10-14 show a class of substrates where one of the double bonds of diene is embedded in a cycloalkene, which allows for the regio- and stereoselective preparation of 1,2-dialkylated cycloalkanes. The substrates for these reactions are readily prepared from the corresponding cycloalkanones in two steps using the Meyer-Schuster rearrangement¹¹ as the key step.¹⁰ The siloxydienes **8l-8p**, derived from C₆ – C₈ cycloalkanones, lead to exclusive formation of the branched 1,4-hydrovinylation products (**9l-9p**) with the vinyl group attached to a ring carbon. No trace of the alternate achiral linear 1,4-adduct or the 1,2-adduct was observed in any of the reactions. As shown in entries 12 and 13, the triethylsiloxy- and *t*-butyldimethylsiloxy- derivatives (**8n** and **8o**) engage in the reaction just as well as the trimethylsiloxy derivative (**8m**), giving comparable yields of the expected products. The *t*-butyldimethylsiloxy-adduct, **9o**, is hydrolytically stable and is readily purified by column chromatography on silica gel.

Next, we turned our attention to asymmetric variants of these reactions. Asymmetric hydrovinylations of prototypical siloxydienes **8a-c** were attempted using various Co(II)-complexes of several commercially available chiral bisphosphines in the presence of MAO as a promoter. Based on the initial observations, 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-*bis*-(diphenylphosphino)butane (DIOP) and 2,3-*bis*-(diphenylphosphino)pentane (BDPP) were chosen for further study under conditions shown in eq 2. As is the case with the structurally analogous complex (dppp)CoCl₂, the enantioselective reaction of **8a** using the [(*S,S*)-BDPP]CoCl₂ complex is very facile, and proceeds to completion in less than 30 minutes at room temperature with 0.05 equivalents of the catalyst. The configuration of the product was established by converting the adduct **9a** to the known saturated ketone **11a** via hydrolysis of the enol ether to a β-vinylketone and subsequent hydrogenation of the alkene using Wilkinson's catalyst [RhCl(PPh₃)₃(cat) /CH₂Cl₂/ 25 °C/ 16 h)].¹⁰ In a preparative scale reaction (5 g), using 0.01 equivalents of [(*S,S*)-DIOP]-CoCl₂ catalyst, 90% yield of the product (*R*)-**9a** (98% ee) was isolated after bulb-to-bulb distillation. To our delight, we also find that the [(*S,S*)-DIOP] CoCl₂ complex also gave excellent yields (>90%) and enantioselectivities (>95% ee) for the triethylsiloxy- and the *t*-butyldimethylsiloxy dienes **8b** and **8c** (see eq 1 for structures).

Further scope of the enantioselective transformation was explored using the siloxydienes previously listed in Table 1 and the results are shown in Table 2. Since the cobalt(II)-BDPP-

complex gave acceptable yields and enantioselectivities for most of the substrates, our studies were largely limited to this catalyst. However, substrates **8a** and **8d** gave relatively lower selectivities (entries 1 and 5) with this complex. Gratifyingly, asymmetric hydrovinylation of these substrates using the cobalt (II)-DIOP-complex, gave excellent yields and >97% ee for the expected products (Table 2, entries 2 and 6). The sterically demanding 4-*t*-butyl-2-trimethylsiloxy-1,3-butadiene (**8f**) failed to react even under more forcing conditions.



(2)

(Table 2, entries 2 and 6). The sterically demanding 4-*t*-butyl-2-trimethylsiloxy-1,3-butadiene (**8f**) failed to react even under more forcing conditions. The corresponding *i*-propyl-derivative **8g** reacts sluggishly (20 h, 0.05 equiv. of catalyst), yet giving very high ee for the expected product, **9g** (entry 9). The siloxydienes derived from cyclic ketones **8l-8p** (see Table 1 for structures) are also excellent substrates for the asymmetric hydrovinylation, giving excellent yields of the expected product in very high enantioselectivities (entries 11-16). A preparative scale run on 2.5 mmol scale of the substrate **8m** uses only 0.01 equivalents of the catalyst (2 h, rt) to give >90% yield of the product in 96% ee (entry 12). Indeed this reaction can be run with as little as 0.001 equivalent (substrate:catalyst 1000:1, 2.5 mmol scale) of the catalyst (entry 13).¹² Since the enantiopure siloxydiene **8j** showed no inherent selectivity in the formation of the newly created chiral center in the HV reaction with the achiral catalyst [(dppp)CoCl₂] (Table 1, entry 8, diastereomeric ratio 1:1), we examined the reaction of this substrate with enantiomeric [DIOP]CoCl₂ complexes. As shown in entries 17 and 18 the enantiomeric complexes [(*R,R*)-DIOP]CoCl₂ and [(*S,S*)-DIOP]CoCl₂ exert excellent catalyst control in the hydrovinylation reaction, and the adducts are formed in diastereomeric ratios [at C₄ (*S*): C₄ (*R*)] 96:4 and 3:97 in the respective cases.

Conversion of silyl enolates to suitable precursors for cross-coupling would considerably expand the utility of this chemistry. For this we turned to alkenyl triflates which could be formed via the lithium enolates and subsequent trapping by PhN(Tf)₂ (Scheme 3). The conversions of the silyl enolates to the vinyl triflates (**12-17**) and their subsequent cross coupling reactions (typical examples of products: **18-20**) proceed with complete retention of configuration at the double bond and preservation of the vinylbearing stereogenic center. Examples of Kumada, Stille and Suzuki coupling reactions of a prototypical vinyl triflate (**12**) are included in the Supporting Information. The reactivity difference between the

mono-substituted and the stereo-defined trisubstituted double bonds in these 1,4-skipped diene products¹³ should make these almost enantiopure intermediates valuable components for further synthesis. Further applications of the silyl enol ethers and the enol triflates are the subject of on-going investigations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

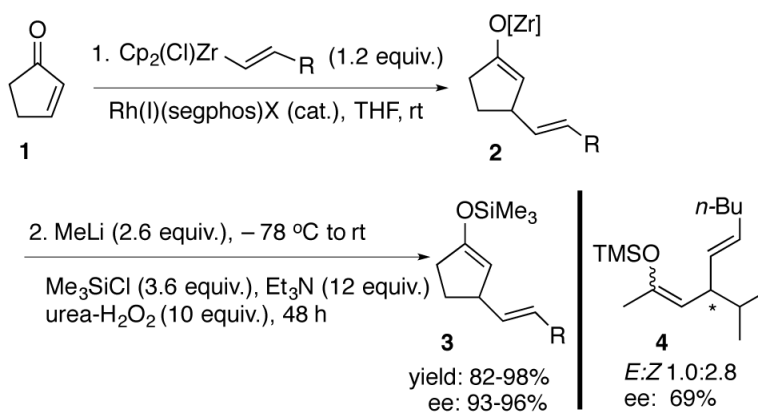
ACKNOWLEDGEMENTS

Financial assistance for this research provided by US NSF (CHE-1057818) and NIH (R01 GM108762) is gratefully acknowledged.

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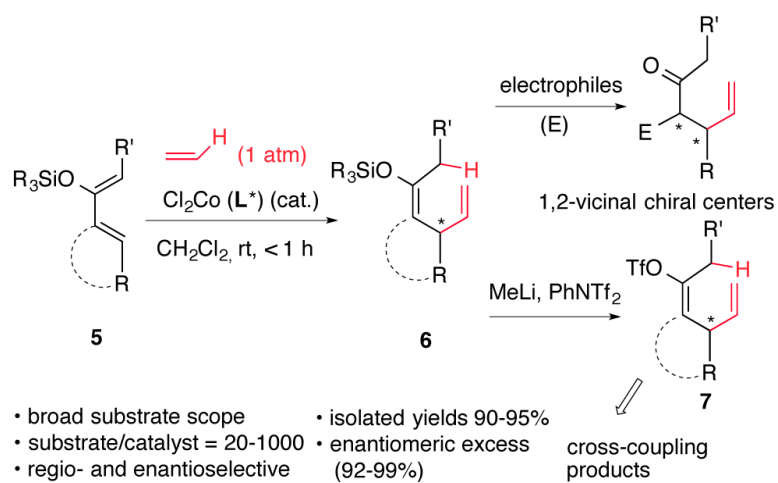
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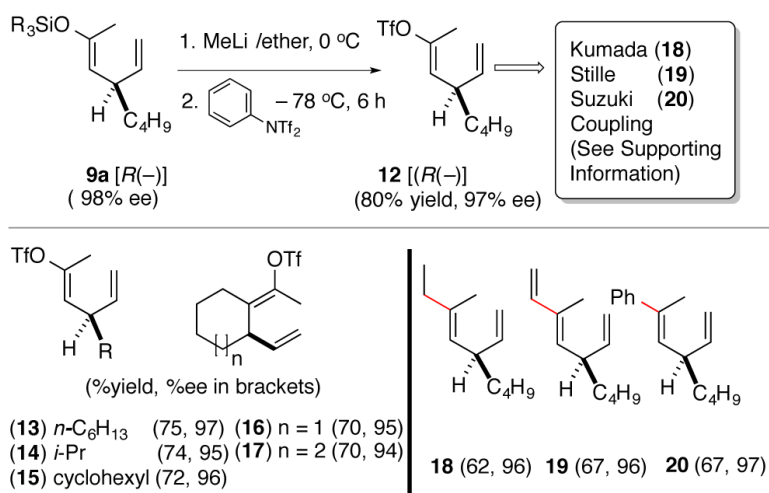
- LOW SELECTIVITY IN REACTIONS OF ACYCLIC ENONES
- NOT APPLICABLE TO ADDITION OF VINYL GROUP

Scheme 1.

Enantioselective 1,4-Addition as a Route to Chiral Silyl Enol Ethers

**Scheme 2.**

Co(II)-Catalyzed Asymmetric Hydrovinylation of Siloxydienes (this work)

**Scheme 3.**

Synthesis of Enol Triflates and Cross-Coupling Products

Table 1Scope of Hydrovinylation of 2-Siloxy-1,3-dienes^a

entry	substrate (8)	product (9, 10 yield %)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.		
12.		
13.		
14.		
15.		
16.		

^b No other products detected by GC. ^c After hydrolysis to ketone. ^d Only a 1,4-linear product **10k** is formed.^a Supporting Information for details.

Table 2Asymmetric Hydrovinylation of 1,3-siloxydienes^a

entry	diene ^b	cat.(equiv.), time (h)	product	yield (%)	ee (%) ^c
1.	8a	0.05, 0.5	(<i>S</i>)- 9a	>95	84
2.	8a	0.05, 0.17 ^d	(<i>R</i>)- 9a	95	98
3.	8b	0.05, 0.17 ^d	(<i>R</i>)- 9b	>90	>95
4.	8c	0.05, 0.17 ^d	(<i>R</i>)- 9c	>90	>95
5.	8d	0.05, 0.5	(<i>S</i>)- 9d	>95	80
6.	8d	0.05, 0.17 ^d	(<i>R</i>)- 9d	96	>97
7.	8e	0.05, 0.5	(<i>S</i>)- 9e	93	97
8.	8f	0.20, 24	(<i>S</i>)- 9f	0	--
9.	8g	0.05, 20	(<i>S</i>)- 9g	88	>95
10.	8h	0.05, 0.25	(<i>S</i>)- 9h ^e	>90	94
11.	8l	0.05, 0.5	(<i>R</i>)- 9l	90	92
12.	8m	0.01, 2	(<i>R</i>)- 9m	>90	96
13.	8m	0.001, 36	(<i>R</i>)- 9m	93	96
14.	8n	0.05, 0.25	(<i>R</i>)- 9n	>90	93
15.	8o	0.05, 0.25	(<i>R</i>)- 9o	78 ^g	87
16.	8p	0.05, 20	(<i>R</i>)- 9p	68	98
17.	8j	0.05, 0.25 ^d	9j [C ₄ (<i>R</i>)]	91	97:3 ^h
18.	8j	0.05, 0.25 ^f	9j [C ₄ (<i>S</i>)]	92	96:4 ^h

^aSee Supporting Information for further details. Using [(*S,S*)-BDPP]CoCl₂ except entries 2, 3, 4, 6, 17 where the (*S,S*)-DIOP complex is used.^bSee Table 1 for structures of siloxydienes and the corresponding products.^cDetermined by CSP GC.^dUsing [(*S,S*)-DIOP]CoCl₂.^e**10h** (9%) also formed.^fUsing [(*R,R*)-DIOP]CoCl₂.^gIsolated by column chromatography.^hDiastereomeric (at C₄) ratio.