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Asymmetric Catalysis with Ethylene. Synthesis of Functionalized Chiral Enolates

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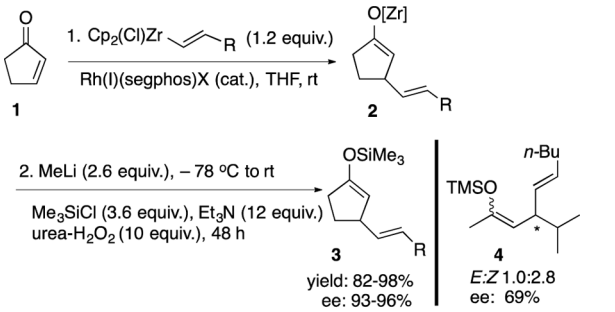
Supporting Information

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 atm) 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, stereodefined trisubstituted alkene intermediates not easily accessible by current methods. Examples of Kumada, Stille, and Suzuki coupling reactions are illustrated.

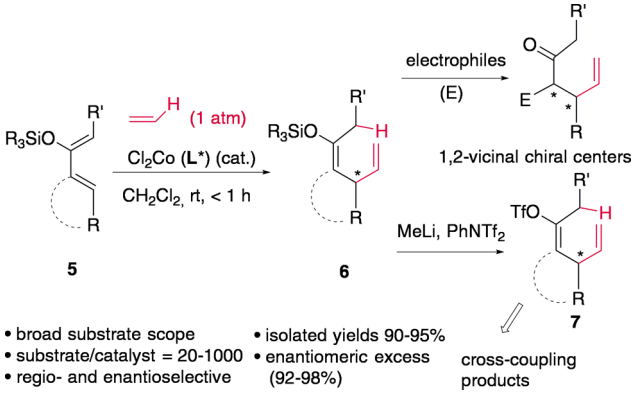
Trialkylsilyl enol ethers are among the most widely used nucleophilic reagents in organic synthesis because of the ease of their preparation and the facile reactions they undergo with a broad range of electrophiles to form highly functionalized carbonyl compounds.[1] Many of these reactions exhibit exquisite 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 four reagents, long reaction times) *in situ* silylation of the weakly reactive zirconium-enolate **2** (see step 2).[3] The reaction shows poor selectivity for the preparation of acyclic derivatives (e.g., **4**).[3] While similar catalytic asymmetric conjugate alkenylation of enones using alkenyl boronates[4a,b] and alkenyl aluminum reagents[4c,d] is known, no such reaction has been reported for simple vinyl ($H_2C{=}CH-$) 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

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



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

Scheme 2. Co(II)-Catalyzed Asymmetric Hydrovinylation of Siloxydienes (this work)



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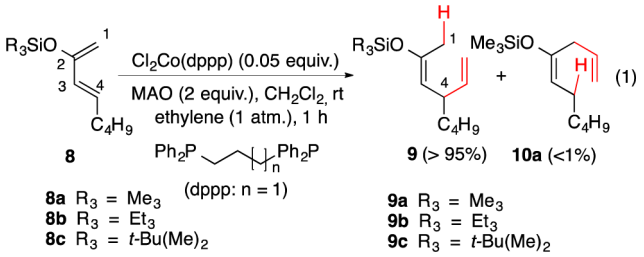
exceptionally high enantioselectivity (92−98% ee). The silyl enolates can be readily converted into nearly enantiopure vinyl triflates (**7**), which are potentially valuable precursors for a variety of cross-coupling reactions.

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 previously,[7] gave unacceptable yields of the expected hydrovinylation product (**9a**). Alternate procedures using Zn/ZnI_2 in place of the aluminum reagents[8] 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, $(dppp)CoCl_2$ [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).

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-trimethylsiloxydienes **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, C_1, and the vinyl group to the C_4 of the original diene. When the trialkylsiloxy group is on C_3 (e.g., **8h** compared to **8a** where it is on C_2 by this numbering scheme), proportionally more linear product **10h** (up to 25%) is also formed (entry 6). Dienes with bulkier substituents (R) at the C_4 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 C_4) with the achiral $(dppp)CoCl_2$ complex (entry 8). A diene with a phenyl substituent in the C_4-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−

Table 1. Scope of Hydrovinylation of 2-Siloxy-1,3-dienes[a]

entry	substrate (**8**)	product (**9**, **10** yield %)
1.	**8a** R = C_4H_9	**9a** R = C_4H_9 (99)[b]
2.	**8d** R = C_6H_{13}	**9d** R = C_6H_{13} (93)
3.	**8e** R = cyclohexyl	**9e** R = cyclohexyl (95)
4.	**8f** R = *t*-Bu	**9f** R = *t*-Bu (76)
5.	**8g** R = *i*-Pr	**9g** R = *i*-Pr (91)
6.	**8h**	**9h** + **10h** (4:1, 90)
7.	**8i**	**9i** (79)[c]
8.	**8j**	**9j** [C_4 (1:1), 91]
9.	**8k**	**10k** (80)[d]
10.	**8l**	**9l** (90)
11.	**8m** R_3 = Me_3	**9m** R_3 = Me_3 (91)
12.	**8n** R_3 = Et_3	**9n** R_3 = Et_3 (90)
13.	**8o** R_3 = *t*-Bu$(Me)_2$	**9o** R_3 = *t*-Bu$(Me)_2$ (75)
14.	**8p**	**9p** (68)

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

Schuster rearrangement[11] as the key step.[10] The siloxydienes **8l**−**8p**, derived from C_6−C_8 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,

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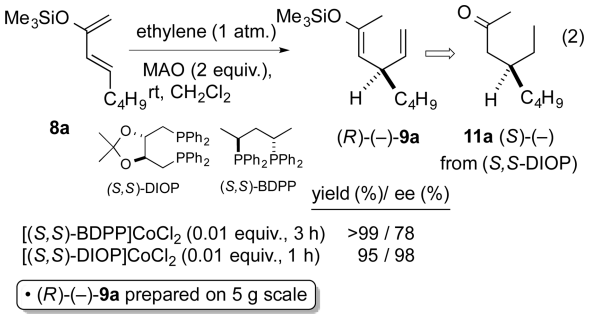
the triethylsiloxy- and *t*-butyldimethylsiloxy derivatives (**8n** and **8o**) engage in the reaction just as well as the trimethylsiloxy derivative (**8m**), giving comparable yields of the expected products. The *t*-butyldimethylsiloxy-adduct, **9o**, is hydrolytically stable and is readily purified by column chromatography on silica gel.

Next, we turned our attention to asymmetric variants of these reactions. Asymmetric hydrovinylations of prototypical siloxydienes **8a**–**8c** 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)$CoCl_2$, the enantioselective reaction of **8a** using the [(*S*,*S*)-BDPP]$CoCl_2$ complex is very facile and proceeds to completion in <30 min at room temperature with 0.05 equiv 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 [$RhCl(PPh_3)_3$(cat)/CH_2Cl_2/25 °C/16 h)].[10] In a preparative scale reaction (5 g), using 0.01 equiv of [(*S*,*S*)-DIOP]-$CoCl_2$ catalyst, 90% yield of the product (*R*)-**9a** (98% ee) was isolated after bulb-to-bulb distillation. To our delight, we find that the [(*S*,*S*)-DIOP] $CoCl_2$ 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. 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 cylic 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 equiv of the catalyst (2 h, rt) to give >90% yield of the product in

Table 2. Asymmetric Hydrovinylation of 1,3-Siloxydienes[a]

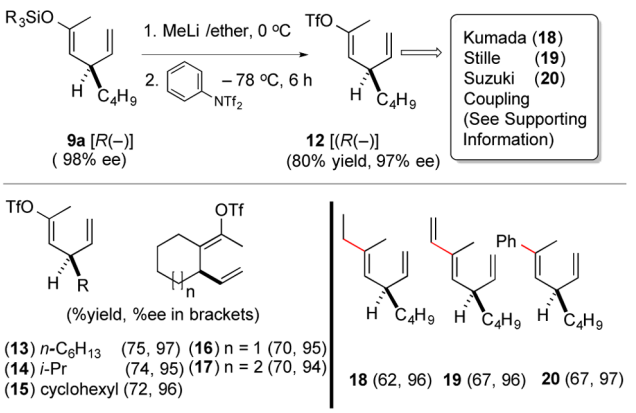
entry	diene[b]	cat. (equiv), time (h)	product	yield (%)	ee (%)[c]
1	**8a**	0.05, 0.5	(*S*)-**9a**	>95	84
2	**8a**	0.05, 0.17[d]	(*R*)-**9a**	95	98
3	**8b**	0.05, 0.17[d]	(*R*)-**9b**	>90	>95
4	**8c**	0.05, 0.17[d]	(*R*)-**9c**	>90	>95
5	**8d**	0.05, 0.5	(*S*)-**9d**	>95	80
6	**8d**	0.05, 0.17[d]	(*R*)-**9d**	96	97
7	**8e**	0.05, 0.5	(*S*)-**9e**	93	97
8	**8f**	0.20, 24	(*S*)-**9f**	0	–
9	**8g**	0.05, 20	(*S*)-**9g**	88	>95
10	**8h**	0.05, 0.25	(*S*)-**9h**[e]	>90	94
11	**8l**	0.05, 0.5	(*R*)-**9l**	90	92
12	**8m**	0.01, 2	(*R*)-**9m**	>90	96
13	**8m**	0.001, 36	(*R*)-**9m**	93	96
14	**8n**	0.05, 0.25	(*R*)-**9n**	>90	93
15	**8o**	0.05, 0.25	(*R*)-**9o**	78[g]	87
16	**8p**	0.05, 20	(*R*)-**9p**	68	98
17	**8j**	0.05, 0.25[d]	**9j** [C_4(*R*)]	91	97:3[h]
18	**8j**	0.05, 0.25[f]	**9j** [C_4(*S*)]	92	96:4[h]

[a]See SI for further details. Using [(*S*,*S*)-BDPP]$CoCl_2$ except entries 2, 3, 4, 6, 17 where the (*S*,*S*)-DIOP complex is used. [b]See Table 1 for structures of siloxydienes and the corresponding products. [c]Determined by CSP GC. [d]Using [(*S*,*S*)-DIOP]$CoCl_2$. [e]**10h** (9%) also formed. [f]Using [(*R*,*R*)-DIOP]$CoCl_2$. [g]Isolated by column chromatography. [h]Diastereomeric (at C_4) ratio.

96% ee (entry 12). Indeed this reaction can be run with as little as 0.001 equiv (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)$CoCl_2$] (Table 1, entry 8, diastereomeric ratio 1:1), we examined the reaction of this substrate with enantiomeric [DIOP]$CoCl_2$ complexes. As shown in entries 17 and 18 the enantiomeric complexes [(*R*,*R*)-DIOP]$CoCl_2$ and [(*S*,*S*)-DIOP]$CoCl_2$ exert excellent catalyst control in the hydrovinylation reaction, and the adducts are formed in diastereomeric ratios [at C_4 (*S*): C_4 (*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).[13] The conversions of the silyl enolates to the

Scheme 3. Synthesis of Enol Triflates and Cross-Coupling Products



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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 vinyl-bearing stereogenic center. Examples of Kumada, Stille, and Suzuki coupling reactions of a prototypical vinyl triflate (**12**) are included in the Supporting Information (SI). The reactivity difference between the monosubstituted and the stereodefined trisubstituted double bonds in these 1,4-skipped diene products[14] 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 ongoing investigations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10364.

Experimental details; typical reaction conditions for the hydrovinylation reactions; chromatographic and spectroscopic data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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