Palladium-Catalyzed Asymmetric Diene Cyclization/ Hydrosilylation Employing Functionalized Silanes and Disiloxanes

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Pentasubstituted disiloxanes and silanes of the form $HSiMe_2CH_xPh_{3-x}$ (x = 1 or 2) reacted with dimethyl diallylmalonate (**1**) and other functionalized 1,6-dienes in the presence of a catalytic 1:1 mixture of (N−N)Pd(Me)Cl [N−N = (*R*)-(+)-4-isopropyl-2-(2-pyridinyl)-2-oxazoline] [(*R*)-**2**] and $NaBAr_4$ [Ar = 3,5-$C_6H_3(CF_3)_2$] to form the corresponding silylated cyclopentanes in good yield with high diastereoselectivity. The enantioselectivity of cyclization/hydrosilylation of **1** with disiloxanes and functionalized silanes at −20 °C increased in the following order: $HSiMe_2OSiMe_3$ (75% ee) < $HSiMe_2OSiMe_2$-*t*-Bu (80% ee) < HSi(*i*-Pr)$_2$OSiMe$_3$ (86% ee) = $HSiMe_2Bn$ (86% ee) < $HSiMe_2OSi$-(*i*-Pr)$_3$ (89% ee) < $HSiMe_2OSiPh_2$-*t*-Bu (91% ee) < $HSiMe_2CHPh_2$ (93% ee). Silylated cyclopentanes derived from $HSiMe_2OSiMe_3$ were oxidized with excess KF and peracetic acid at room temperature for 48 h to form the corresponding hydroxymethylcyclopentanes in good yield (82−95%). Silylated cyclopentanes derived from $HSiMe_2OSiPh_2$*t*-Bu were oxidized with a mixture of tetrabutylammonium fluoride and either H_2O_2 or peracetic acid to form the corresponding alcohols in 48−76% yield. Silylated carbocycles generated from benzhydryldimethylsilane were oxidized with a mixture of TBAF/$KHCO_3$/H_2O_2 in 71−98% yield. Asymmetric cyclization/hydrosilylation/oxidation employing benzhydryldimethylsilane tolerated allylic and terminal olefinic substitution and a range of functional groups.

Introduction

Functionalized carbocycles are one of the most common components of naturally occurring and biologically active molecules.[1] As a result, considerable effort has been directed toward the development of efficient methods for the construction of carbocyclic compounds. In this area, transition metal-catalyzed procedures have enjoyed considerable success,[2] particularly with respect to the formation of five-membered rings. However, the majority of these transition metal-catalyzed carbocyclization protocols either generate no new asymmetric centers or do so with low enantioselectivity.[3] A notable exception is the Pd-catalyzed intramolecular asymmetric Heck reaction.[4] Other examples of asymmetric carbocyclization include Rh-[5] and Co-catalyzed[6] [4 + 2] cycloaddition, Ti-catalyzed enyne cyclocarbonylation,[7] and Rh-catalyzed intramolecular hydroacylation,[8] cyclopropanation,[9] and C−H insertion.[10]

Our contribution to the area of catalytic asymmetric carbocyclization has been the enantioselective cyclization/hydrosilylation of functionalized dienes catalyzed by optically active palladium pyridine−oxazoline complexes. For example, reaction of dimethyl diallylmalonate (**1**) and $HSiEt_3$ catalyzed by a 1:1 mixture of (N−N)Pd(Me)Cl

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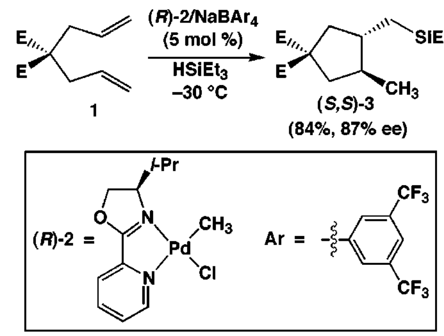
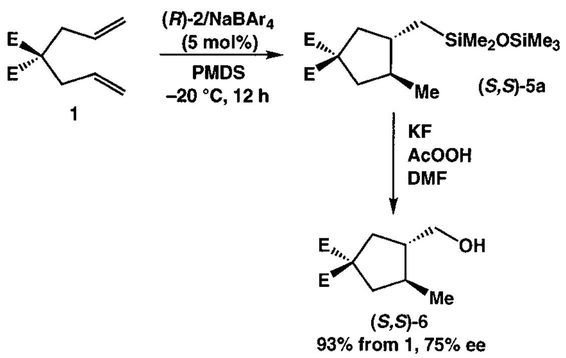
Scheme 1



[N−N = (*R*)−(+)-4-isopropyl-2-(2-pyridinyl)-2-oxazoline] [(*R*)-**2**] and $NaBAr_4$ [Ar = 3,5-$C_6H_3(CF_3)_2$] at −30 °C gave carbocycle (*S*,*S*)-**3** in 84% yield with >95% de and 87% ee (Scheme 1).[11] Asymmetric diene cyclization/hydrosilylation catalyzed by (*R*)-**2** tolerated a range of functional groups as well as allylic and terminal olefinic substitution.[11] Conversely, while efficient and general asymmetric cyclization/hydrosilylation was achieved with trialkylsilanes such as $HSiEt_3$, functionalized silanes of the form $HSiMe_2X$ (X = phenyl, Cl, OEt, allyl, NMe_2, H, or furyl) were ineffective.[12] For example, attempted cyclization/hydrosilylation of **1** with ethoxydimethylsilane led to immediate darkening of the solution without detectable consumption of **1**.

The use of a silyl moiety as a masked hydroxyl group has become an important strategy in the synthesis of complex alcohols due to the development of efficient procedures for both the incorporation and unmasking of the silyl group and due to the stability of silanes to varied reaction conditions and chromatography.[13] However, only functionalized organosilanes, most commonly phenyl-[14] and alkoxysilanes,[15,16] but also allyl-,[17] amino-,[18] furyl-,[19] and H-substituted[20] silanes undergo efficient oxidation. Because of this, the trialkylsilylmethyl carbocycles generated via palladium-catalyzed asymmetric cyclization/hydrosilylation were unreactive toward oxidation, which limited the synthetic utility of the procedure. We have therefore sought to identify silanes which would undergo efficient and general asymmetric cyclization/hydrosilylation to form silylated carbocycles which could be oxidized under mild conditions. Here, we report a full account of our studies in this area.[21]

Scheme 2



Results and Discussion

Pentamethyldisiloxane. Hexaethyldisiloxane is formed as a byproduct of palladium-catalyzed cyclization/hydrosilylation employing triethylsilane, presumably from reaction of the silane with adventitious moisture.[11] In contrast to ethoxydimethylsilane, hexaethyldisiloxane appeared to have no detrimental effect on cyclization/hydrosilylation, attesting to the compatibility of the Si−O−Si functionality with the palladium catalyst.[22] Based on this observation, we considered that pentasubstituted disiloxanes ($HSiR_2OSiR_3$) might also be compatible with the cationic palladium catalyst and undergo asymmetric diene cyclization/hydrosilylation. It also appeared likely that the silylated carbocycles generated from pentasubstituted disiloxanes would be reactive toward oxidation as Tamao reported the oxidation of an unspecified disiloxy group ($-SiMe_2OSiMe_2R$) in 72% yield by acid hydrolysis followed by treatment with 30% H_2O_2.[16]

Pentamethyldisiloxane (PMDS) was initially selected for use in palladium-catalyzed asymmetric diene cyclization/hydrosilylation due to its commercial availability. Reaction of **1** and PMDS catalyzed by a 1:1 mixture of (*R*)-**2** and $NaBAr_4$ (5 mol %) at −20 °C for 12 h led to complete consumption of diene to form (*S*,*S*)-**5a** as the exclusive (≥95%) product by GC analysis (Scheme 2). Although chromatography of the concentrated reaction mixture led to partial decomposition, treatment of (*S*,*S*)-**5a** (88% pure) obtained after chromatography with excess KF and peracetic acid in DMF at room temperature for 2 days formed hydroxymethylcyclopentane (*S*,*S*)-**6** in 93% yield from **1** with 75% ee (Scheme 2).[23] In addition to diene **1**, dienes which possessed homoallylic trimethyl-

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(12) Of these silanes, only dimethylphenylsilane led to any detectable cyclization/hydrosilylation. Reaction of **1** with dimethylphenylsilane in the presence of (*R*)-**2**/$NaBAr_4$ (10 mol %) formed 1,1-dicarbomethoxy-3-dimethylphenylsilylmethyl-4-methylcyclopentane in low yield (38%, 80% ee at −18 °C).[11b] However, dimethylphenylsilane failed to react with any dienes other than **1**.

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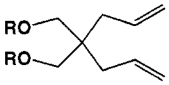
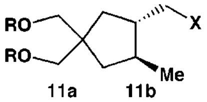
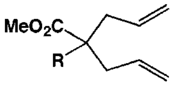
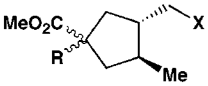
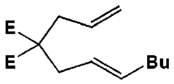
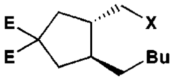
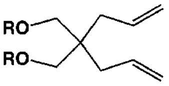
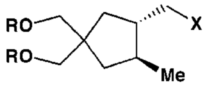
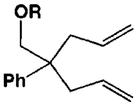
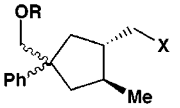
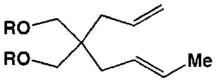
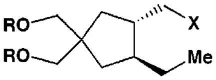
(22) This contention was confirmed by running the cyclization/hydrosilylation of **1** and $HSiEt_3$ in the presence of excess hexaethyldisiloxane.

(23) The overall yield of the conversion of **1** to **6** was higher than the purity of **5a** obtained after chromatography. This observation indicates that the decomposition products resulting from silica gel chromatography of **5a** are also reactive towards oxidation. One likely candidate is the carbocyclic silanol generated from hydrolysis of the $-OSiMe_3$ group.

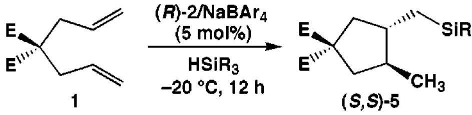
Table 1. Asymmetric Cyclization/Hydrosilylation of Dienes Employing PMDS and $HSiMe_2OTBDPS$ Catalyzed by a 1:1 Mixture of (*R*)-2 and $NaBAr_4$ (5 mol %) at − 20 °C in CH_2Cl_2 for 12 h Followed by Oxidation

entry	diene	disiloxane[a]	oxidation conditions[b]	carbocycle X = SiR_3	X = OH	yield cyclization (%)[c]	yield oxidation (%)[c]	overall yield (%)[c]	dr (%)[d]	ee (%)
										
1	7 (R = Piv)	PMDS	A	11a	11b	—[h]	—[h]	85	>50:1	82[f]
2		$HSiMe_2OTBDPS$	B	11c	11b	99	73	72	>50:1	95[f]
										
3	8 (R = Ph)	PMDS	A	12a	12b	—[h]	—[h]	79	5.6:1	75[e]
4	9 (R = $CONMe_2$)	PMDS	A	13a	13b	—[h]	—[h]	83	5.6:1	79[e]
										
5	10 (E = CO_2Me)	PMDS	A	14a	14b	—[h]	—[h]	82	35:1	76[e]
										
6	16 (R = Bn)	$HSiMe_2OTBDPS$	C	20a	20b	82	76	62	>50:1	94[f]
7	17 (R = Me)	$HSiMe_2OTBDPS$	C	21a	21b	79	76	60	>50:1	85[g]
										
8	18 (R = Piv)	$HSiMe_2OTBDPS$	B	22a	22b	90	69	62	1.3:1	92[f]
9	19 (R = Me)	$HSiMe_2OTBDPS$	C	23a	23b	85	70	60	1.5:1	91[f]
										
10	24 (R = Piv)	$HSiMe_2OTBDPS$	B	25a	25b	92	71	65	39:1	89[f]

[a] PMDS = $HSiMe_2OSiMe_3$; TBDPS = $SiPh_2$-*t*-Bu. [b] Oxidation conditions: A = KF/AcOOH/DMF, 25 °C, 48 h; B = TBAF/KF/$KHCO_3$/H_2O_2/THF/MeOH, 25 °C, 72 h; C = TBAF/$KHCO_3$/H_2O_2/THF/MeOH, reflux, 24 h. [c] Yields refer to the isolated material of >95% purity. [d] Diastereomeric ratio determined by capillary GC analysis of the crude reaction mixture. [e] Enantiomeric excess determined by ^1H NMR spectroscopy employing $Eu(hfc)_3$ as a chiral shift reagent. [f] Enantiomeric excess determined by ^{19}F NMR analysis of the corresponding Mosher ester. [g] Enantiomeric excess determined by chiral GC. [h] Silylated carbocycle was oxidized without isolation.

acetoxymethyl (**7**), phenyl (**8**), or dimethylcarbamoyl (**9**) groups or a terminal olefinic butyl group (**10**) underwent asymmetric cyclization/hydrosilylation/oxidation to form carbocyclic alcohols **11b**−**14b**, respectively, in good yield with moderate enantioselectivity (75−82% ee) (Table 1, entries 1 and 3−5).

Table 2. Asymmetric Cyclization/Hydrosilylation of 1 with Disiloxanes, $HSiMe_2CH_2Bn$, and $HSiMe_2CHPh_2$ Catalyzed by a 1:1 Mixture of (*R*)-2 and $NaBAr_4$ in CH_2Cl_2 at −20 °C for 12 h



entry	$HSIR_3$	cyclopentane	yield[a] (%)	ee[b] (%)
1	$HSiMe_2OSiMe_2$-*t*-Bu	**5b**	99	80
2	HSi(*i*-Pr)$_2$OSiMe$_3$	**5c**	99	86
3	$HSiMe_2OSi$(*i*-Pr)$_3$	**5d**	99	89
4	$HSiMe_2OSiPh_2$-*t*-Bu	**5e**	100	91
5	$HSiMe_2CHPh_2$	**5f**	98	93
6	$SHiMe_2CH_2Ph$	**5g**	91	86

[a] Yield refers to isolated material of >95% purity. [b] Enantiomeric excess determined by ^1H NMR spectroscopy employing $Eu(hfc)_3$ as a chiral shift reagent.

1-*tert*-Butyl-3,3-dimethyl-1,1-diphenyldisiloxane. Pentamethyldisiloxane reacted efficiently with functionalized dienes in the presence of (*R*)-**2**/$NaBAr_4$ to form silylated cyclopentanes that were oxidized in good yield under mild conditions. Unfortunately, the enantioselectivity of cyclization/hydrosilylation employing PMDS (75−82% ee) was significantly lower than the enantioselectivity of the analogous transformations employing $HSiEt_3$ (85−91% ee).[11] In addition, the silylated carbocycles generated from PMDS were sensitive to silica gel chromatography. We considered that both of these limitations could be ameliorated through the use of more sterically hindered disiloxanes. We had previously observed that the enantioselectivity of asymmetric cyclization/hydrosilylation increased with the increasing steric bulk of the silane.[11] Likewise, the reactivity of silyl ethers toward hydrolysis is known to decrease with the increasing steric bulk of the silyl group.[24] Consistent with our expectations, reaction of **1** with $HSiMe_2OSiMe_2$-*t*-Bu catalyzed by (*R*)-**2**/$NaBAr_4$ at −20 °C for 12 h led to the isolation of **5b** in 99% yield with 80% ee after chromatography (Table 2, entry 1).

In addition to $HSiMe_2OSiMe_2$-*t*-Bu, the sterically hindered disiloxanes HSi(*i*-Pr)$_2$OSiMe$_3$, $HSiMe_2OSi$(*i*-Pr)$_3$,

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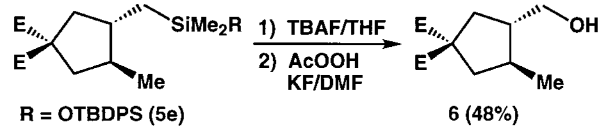
Scheme 3

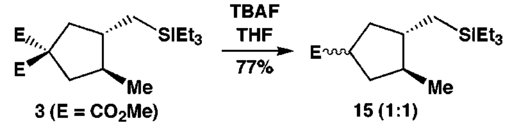


and HSiMe$_2$OTBDPS (TBDPS = SiPh$_2$-*t*-Bu) reacted with **1** in the presence of a catalytic amount of (*R*)-**2**/NaBAr$_4$ at −20 °C to form carbocycles **5c**−**e** in near-quantitative yield with 86, 89, and 91% ee, respectively (Table 2, entries 2−4). Because reaction of **1** with HSiMe$_2$OTBDPS displayed particularly high enantioselectivity, the oxidation of the resulting carbocycle **5e** was investigated. Unfortunately, attempted oxidation of **5e** employing the conditions used to oxidize **5a** led to no detectable formation of **6** after 2 days at room temperature.

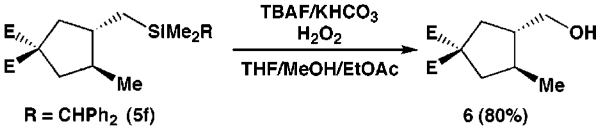
The rate of oxidation of alkoxysilanes decreases with the increasing steric bulk of the silane.[13,25] Therefore, it appeared likely that the resistance of **5e** toward oxidation was due to the excessive steric bulk of the OTBDPS group. Based on this assumption, we reasoned that cleavage of the OTBDPS group would activate the remaining silyl fragment toward oxidation.[26] Tetrabutylammonium fluoride (TBAF) is known to cleave the Si−O bond of TBDPS ethers,[24] and has been previously employed to facilitate the oxidation of hindered disilyl[27] and triphenylsilyl[28] groups via Si−Si and Si−Ph bond cleavage, respectively. In our case, reaction of the **5e** with TBAF for 19 h at room temperature followed by oxidation with a mixture of KF and peracetic acid in DMF at room temperature for 7 h led to the isolation of alcohol **6** in 48% yield (Scheme 3).

Malonic esters undergo dealkoxycarbonylation in the presence of simple salts such as NaCl or KCN in wet DMSO.[29] Because of this, we considered that competitive dealkoxycarbonylation of **5e** by TBAF might be responsible for the moderate yield of **6** obtained in the oxidation of **5e**. Unfortunately, no dealkoxycarbonylation products could be unambiguously identified from the reaction of **5e** and TBAF due to the complexity of the crude reaction mixture.[30] In an effort to establish the TBAF-mediated dealkoxycarbonylation of a *gem*-dicarbomethoxy-substituted cyclopentane, a solution of the triethylsilyl-substituted carbocycle **3** and TBAF in THF was stirred at room temperature and monitored periodically by GC analysis. After 15 h, 66% of **3** had undergone dealkoxycarbonylation to form **15** as the exclusive product as a 1:1 mixture of diastereomers (Scheme 4). After 2 days, **3** had been completely consumed to form **15** in 77% isolated yield.

Scheme 4



Scheme 5



Identification of dealkoxycarbonylation as a competing pathway in the TBAF-mediated oxidation of **5e** suggested that carbocycles which did not possess gem-dicarbomethoxy groups should better tolerate the conditions required to oxidize the −SiMe$_2$OTBDPS group. Consistent with this hypothesis, cyclization/hydrosilylation/oxidation of diene **7** with HSiMe$_2$OTBDPS led to the isolation of alcohol **11b** in 72% overall yield with 95% ee (Table 1, entry 2).[31] In addition to dienes **1** and **7**, 1,6-dienes that possessed homoallylic benzyloxymethyl, methoxymethyl, and phenyl groups (**16**−**19**) underwent cyclization/hydrosilylation/oxidation employing HSiMe$_2$-OTBDPS to form the corresponding carbocyclic alcohols (**20b**−**23b**) in 60−62% overall yield with 85−94% ee (Table 1, entries 6−9).[31] Similarly, cyclization/hydrosilylation/oxidation of **24**, which possessed a terminal olefinic methyl group, formed alcohol **25b** in 65% yield with 89% ee (Table 1, entry 10).[31]

Benzhydryldimethylsilane. In the asymmetric cyclization/hydrosilylation/oxidation of dienes employing disiloxanes, increasing the steric bulk of the disiloxane increased the enantioselectivity of cyclization/hydrosilylation but decreased the efficiency of oxidation. Because of these competing factors, identification of an effective disiloxane for asymmetric cyclization/hydrosilylation/oxidation appeared unlikely and we began to consider alternative approaches. Near this time, we became aware of several recent reports describing the oxidation of benzyl-,[32] benzhydryl-,[33] and trityl-substituted silanes,[34] which suggested the employment of these silanes in the asymmetric cyclization/hydrosilylation/oxidation of dienes. To this end, reaction of **1** and benzhydryldimethylsilane catalyzed by (*R*)-**2**/NaBAr$_4$ at −20 °C led to the isolation of carbocycle **5f** in 98% yield with 93% ee (Table 2, entry 5). Reaction of **1** with benzyldimethylsilane formed carbocycle **5g** in good yield but with diminished enantioselectivity (Table 2, entry 6), while reaction of **1** with dimethyltritylsilane was prohibitively sluggish.[35] Treatment of **5f** with a mixture of TBAF, KHCO$_3$, and 50% H$_2$O$_2$ in THF/MeOH/EtOAc at room temperature for 21 h led to the isolation of hydroxymethylcyclopentane **6** in 80% yield (Scheme 5).

Dienes that possessed homoallylic carbobenzyloxy (**26**), trimethylacetoxymethyl (**7**), benzyloxymethyl (**16**), or methoxymethyl (**17**) groups underwent cyclization/hydrosilylation/oxidation to form the corresponding car-

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[25] *Protective Groups in Organic Synthesis*; Greene, T. W., Wuts, P. G. M., Eds.; John Wiley & Sons: New York, 1991.

[26] Cleavage of either the TBDPS or OTBDPS group from **5e** would render the remaining carbocyclic silanol or silyl fluoride, respectively, reactive towards oxidation.[13]

[27] Suginome, M.; Matsunaga, S.-I.; Ito, Y. *Synlett* **1995**, 941.

[28] Knölker, H.-J.; Wanzl, G. *Synlett* **1995**, 378.

[29] Krapcho, A. P. *Synthesis* **1982**, 805.

[30] The complexity of the reaction mixture may be due to dealkoxycarbonylation combined with both −TBDPS and −OTBDPS cleavage pathways. Therefore, competitive dealkoxycarbonylation from **5e** and the −TBDPS and −OTBDPS cleavage products of **5e** could form three different dealkoxycarbonylation products, each of which would likely be formed a mixture of two diastereomers.

[31] Hydrogen peroxide (50%) was used as the stoichiometric oxidant.

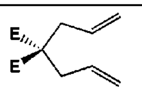
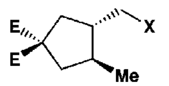
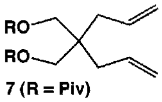
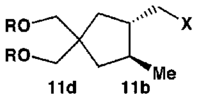
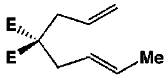
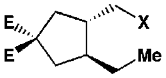
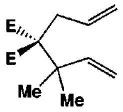
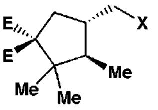
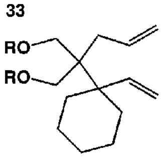
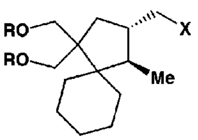
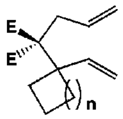
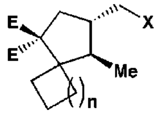
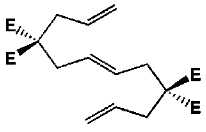
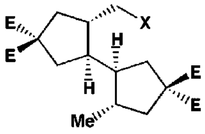
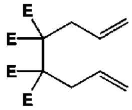
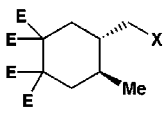
[32] Miura, K.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *Org. Lett.* **2000**, *2*, 385.

[33] Peng, Z. H.; Woerpel, K. A. *Org. Lett.* **2000**, *2*, 1379.

[34] (a) Brengel, G. P.; Rithner, C.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 5144. (b) Brengel, G. P.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 3230. (c) Groaning, M. D.; Brengel, G. P.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 5517.

[35] The half-life for reaction of **1** and dimethyltritylsilane catalyzed by (*R*)-**2**/NaBAr$_4$ at −20 °C was approximately 6 days.

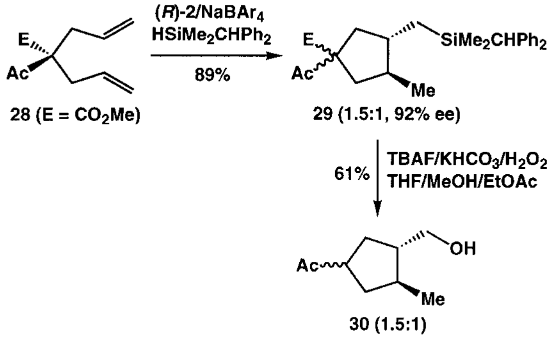
Table 3. Asymmetric Cyclization/Hydrosilylation of Dienes Employing Benzhydryldimethylsilane Catalyzed by a 1:1 Mixture of (*R*)-2 and NaBAr$_4$ (5 mol %) in CH_2Cl_2 at −20 °C Followed by Oxidation with Excess TBAF, $KHCO_3$, and H_2O_2 in THF/MeOH/EtOAc (2/1/0.1) at Room Temperature for 24 h (Diastereoselectivity Was ≥50:1 and E = CO_2Me unless Otherwise Noted)

entry	diene	carbocycle		yield silylation (%)[a]	yield (%) oxidation (%)[a]	overall yield (%)[a]	ee (%)
		X = SiR_3	X = OH				
1	 26 (E = CO_2Bn)	 27a	27b	87	88	77	94[c]
							
2	7 (R = Piv)	11d	11b	96	87[g]	84	95[c]
3	16 (R = Bn)	20c	20b	89	73[g]	65	95[c]
4	17 (R = Me)	21c	21b	81	72[g]	58	88[d]
5	 31	 32a	32b	87[e]	76	66	90[b]
6	 33	 34a	34b	89	93	83	87[b]
7	 35 (R = Piv)	 38a	38b	81	71[g]	58	93[c]
							
8	36 (n = 1)	39a	39b	100	82	82	86[b]
9	37 (n = 2)	40a	40b	98	98	96	88[b]
10	 41	 42a	42b	97[f]	85	82	66[c]
11	 43 (E = CO_2Et)	 44a	44b	67	80	54	20[c]

[a] Yield refers to isolated material of >95% purity. [b] Enantiomeric excess determined by ^1H NMR analysis employing Eu(hfc)$_3$ as a chiral shift reagent. [c] Enantiomeric excess determined by ^{19}F NMR of the corresponding Mosher ester. [d] Enantiomeric excess determined by chiral GC. [e] 19:1 mixture of diastereomers. [f] 10 mol % catalyst employed. [g] EtOAc was not present in the oxidation mixture.

bocyclic alcohols **27b**, **11b**, **20b**, and **21b**, respectively, in 58−84% yield with up to 95% ee (Table 3, entries 1−4). Although the *gem*-dicarbomethoxy groups of **5f** were stable under oxidation conditions (Scheme 5), particularly sensitive substrates remained susceptible to dealkoxycarbonylation. For example, cyclization/hydrosilylation of 4-acetyl-4-carbomethoxy-1,6-heptadiene (**28**) and benzhydryldimethylsilane catalyzed by (*R*)-**2**/NaBAr$_4$ gave cyclopentane **29** in 89% yield as a 1.5:1 mixture of diastereomers with 92% ee (Scheme 6). Attempted oxidation of **29** led to oxidation/dealkoxycarbonylation to form **30** in 61% isolated yield as a ∼1.5:1 mixture of diastereomers (Scheme 6).

Scheme 6



Asymmetric diene cyclization/hydrosilylation/oxidation employing benzhydryldimethylsilane tolerated both allylic and olefinic substitution. For example, diene **31**, which possessed a terminal olefinic methyl group, underwent cyclization/hydrosilylation/oxidation to form alcohol **32b** in 66% overall yield with 90% ee (Table 3, entry

5). Similarly, diene **33** underwent cyclization/hydrosilylation/oxidation to form alcohol **34b** in 83% overall yield with 87% ee (Table 3, entry 6). Toleration of allylic substitution allowed the synthesis of hydroxymethylspirobicycles **38b**−**40b** in good yield with high enantioselectivity (Table 3, entries 7−9). Similarly, toleration of olefinic substitution allowed the asymmetric cascade cyclization/hydrosilylation of triene **41** to form tethered bicyclopentane **42b** in 82% overall yield, albeit with diminished enantioselectivity (66% ee) (Table 3, entry 10). Although 4,4,5,5-tetracarbethyloxy-1,7-octadiene **43** underwent cyclization/hydrosilylation/oxidation to form hydroxymethylcyclohexane **44b** in 54% overall yield (Table 3, entry 11), enantioselectivity was considerably diminished relative to cyclopentane formation.

Conclusions

Pentamethyldisiloxane (PMDS) reacted with functionalized 1,6-dienes catalyzed by (*R*)-**2**/$NaBAr_4$ to form silylated carbocycles that were oxidized in the presence of excess KF and AcOOH to form the corresponding hydroxymethylcyclopentanes in good yield (79−93% from diene) with moderate enantioselectivity (75−82% ee). In comparison, $HSiMe_2OTBDPS$ reacted with functionalized 1,6-dienes catalyzed by (*R*)-**2**/$NaBAr_4$ to form silylated carbocycles which were oxidized with a mixture of TBAF and either H_2O_2 or peracetic acid to give the corresponding hydroxymethylcyclopentanes in moderate yield (48−72% from diene) with good enantioselectivity (85−95% ee). In general, asymmetric cyclization/hydrosilylation/oxidation employing PMDS suffered from low enantioselectivity while asymmetric cyclization/hydrosilylation/oxidation employing $HSiMe_2OTBDPS$ suffered from sluggish oxidation and limited substrate scope.

The limitations associated with the use of disiloxanes in asymmetric diene cyclization/hydrosilylation/oxidation were largely avoided through the employment of benzhydryldimethylsilane. Benzhydryldimethylsilane reacted with functionalized 1,6-dienes catalyzed by (*R*)-**2**/$NaBAr_4$ to form silylated carbocycles in good (81−100%) yield with high levels of enantioselectivity (86−95% ee). These silylated carbocycles were oxidized in good yield (71−98%) with a mixture of TBAF, $KHCO_3$, and H_2O_2 within 1 day at room temperature. The cyclization/hydrosilylation/oxidation protocol employing benzhydryldimethylsilane tolerated a range of functionality and olefinic and allylic substitution and was applied to the synthesis of spiro and tethered bicyclic compounds.

Experimental Section

General Methods. All cyclization/hydrosilylation reactions were performed under an atmosphere of nitrogen employing standard Schlenk techniques; oxidations were performed under air. NMR were obtained on a Varian spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C in $CDCl_3$ unless otherwise noted. IR spectra were obtained on a Bomen MB-100 FT IR spectrometer. Gas chromatography was performed on a Hewlett-Packard 5890 gas chromatograph equipped with a 25 m poly(dimethylsiloxane) capillary column. Flash chromatography was performed employing 200−400 mesh silica gel (EM). Elemental analyses were performed by E+R Microanalytical Laboratories (Parsippany, NJ). CH_2Cl_2 and 1,2-dichloroethane (DCE) were distilled from CaH_2 under nitrogen. Dimethyl diallylmalonate (Lancaster), benzyldimethylsilane (Aldrich), and pentamethyldisiloxane (Gelest) were used as received. Benzhydryldimethylsilane was prepared according to a published procedure.[36] All dienes except **35** have been previously reported;[37] the synthesis of **35** is included in the Supporting Information.

1-*tert*-Butyl-3,3-dimethyl-1,1-diphenyldisiloxane. 1-*tert*-Butyl-3,3-dimethyl-1,1-diphenyldisiloxane was prepared employing a modified literature procedure.[38] Saturated aqueous $NaHCO_3$ (120 mL) was added to a solution of *tert*-butylchlorodiphenylsilane (13.0 mL, 50.0 mmol) and chlorodimethylsilane (16.6 mL, 150 mmol) in THF (120 mL) at 0 °C, warmed slowly to room temperature, and stirred overnight. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic fractions were washed with 1 N HCl and brine, dried ($MgSO_4$), filtered, concentrated under vacuum, and chromatographed (hexanes−EtOAc = 60:1) to give $HSiMe_2OSiPh_2$-*t*-Bu (12.6 g, 80%) as a colorless oil. ^1H NMR: δ 7.69−7.66 (m, 4 H), 7.42−7.36 (m, 6 H), 4.97 (sep, $J = 2.8$ Hz, 1 H), 1.06 (s, 9 H), 0.27 (s, 3 H), 0.26 (s, 3 H). $^{13}C\{^1H\}$ NMR: δ 136.1, 135.2, 129.7, 127.9, 27.0, 19.7, 1.4. IR (film, cm^{-1}): 3069, 3049, 2957, 2856, 2122, 1958, 1896, 1810, 1589, 1470, 1426, 1251, 1110, 1083, 903. Anal. Calcd (found) for $C_{18}H_{26}OSi_2$: C, 68.73 (68.59); H, 8.33 (8.43).

Disiloxanes $HSiMe_2OSiMe_2$-*t*-Bu,[38] $HSi(i\text{-}Pr)_2OSiMe_3$, and $HSiMe_2OSi(i\text{-}Pr)_3$ were prepared by use of a similar procedure. The spectral and analytical data for these disiloxanes are included in the Supporting Information.

Synthesis and Oxidation of *trans*-1,1-Dicarbomethoxy-3-(1,1,3,3,3-pentamethyldisiloxyl)methyl-4-methylcyclopentane (5a). Dimethyl diallylmalonate (100 mg, 0.47 mmol) and pentamethyldisiloxane (0.29 mL, 1.5 mmol) were added sequentially to a solution of (N−N)Pd(Me)Cl [N−N = (*R*)-(+)-4-isopropyl-2-(2-pyridinyl)-2-oxazoline] [(*R*)-**2**] (8 mg, 0.023 mmol) and $NaBAr_4$ (21 mg, 0.023 mmol) in CH_2Cl_2 (10 mL) at −20 °C, and the resulting pale yellow solution was stirred overnight to form a dark brown solution. Solvent and excess silane were evaporated under vacuum, and the residue was chromatographed (hexanes−EtOAc = 24:1) to give **5a** (170 mg, 100%, 88% pure) as a pale yellow oil. A suspension of diene **5a** (88% pure, 0.63 g, 1.75 mmol), KF (0.81 g, 14.0 mmol), and peracetic acid (32wt % in acetic acid, 5.0 mL, 21.0 mmol) in DMF (14 mL) was stirred at room temperature for 48 h. Water (20 mL) was added, and the resulting suspension was extracted with ethyl acetate. The combined organic extracts were washed with 10% Na_2SO_3 and saturated $NaHCO_3$, dried (Na_2SO_4), concentrated under vacuum, and chromatographed (hexane/EtOAc = 20:1 → 2:1) to give **6** (0.37 g, 93%) as a colorless oil.

For 5a. ^1H NMR: δ 3.70 (s, 6 H), 2.58 (dd, $J = 6.2$, 13.4 Hz, 1 H), 2.49 (dd, $J = 6.2$, 13.4 Hz, 1 H), 1.68 (m, 2 H), 1.45 (m, 2 H), 0.95 (d, $J = 6.0$ Hz, 3 H), 0.87 (dd, $J = 2.4$, 14.8 Hz, 1 H), 0.31 (dd, $J = 10.8$, 14.8 Hz, 1 H), 0.08 (s, 6 H), 0.06 (s, 9 H). $^{13}C\{^1H\}$ NMR: δ 173.8, 58.5, 52.9, 43.7, 43.2, 43.0, 42.5, 22.2, 17.5, 2.3, 1.5. HRMS(EI): calcd (found) for $C_{15}H_{29}O_5Si_2$ ($M^+ - CH_3$) 345.1554 (345.1555).

For 6. ^1H NMR: δ 3.71 (s, 6 H), 3.69 (dd, $J = 4.0$, 10.8 Hz, 1 H), 3.52 (dd, $J = 6.4$, 10.8 Hz, 1 H), 2.48 (m, 2 H), 2.08 (dd, $J = 9.0$, 13.8 Hz, 1 H), 1.80 (m, 2 H), 1.78 (m, 1 H), 1.74 (s, 1 H), 1.02 (d, $J = 5.6$ Hz, 3 H). $^{13}C\{^1H\}$ NMR: δ 173.6, 173.3, 64.5, 58.8, 52.9, 49.0, 43.0, 37.8, 36.2, 18.6. IR (neat, cm^{-1}): 3412 (O−H) 1723 (C=O). Anal. Calcd (found) for $C_{11}H_{18}O_5$: C, 57.38 (57.02); H, 7.88 (8.06).

The conversion of **7** to **11b**, **8** to **12b**, **9** to **13b**, and **10** to **14b** (Table 1, entries 1 and 3−5) were performed employing a procedure similar to that used for the conversion of **1** to **6**. Spectral and analytical data for these alcohols and the silylated intermediates **11a**, **12a**, **13a**, and **14a** are included in the Supporting Information.

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(36) Olah, G. A.; Rasul, G.; Heiliger, L.; Bausch, J.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1992**, *114*, 7737.

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***trans*-3-(3-*t*-Butyl-3,3-diphenyl-1,1-dimethyldisiloxy)methyl-1,1-dicarbomethoxy-4-methylcyclopentane (5e).** Diene **1** (170 mg, 0.80 mmol) and $HSiMe_2OSiPh_2$-*t*-Bu (0.75 g, 2.5 mmol) were added sequentially to a solution of (*R*)-**2** (15 mg, 0.04 mmol) and $NaBAr_4$ (36 mg, 0.04 mmol) in CH_2Cl_2 (9 mL) under nitrogen at −20 °C and maintained at this temperature for 12 h. Evaporation of solvent and chromatography (hexanes−EtOAc = 55:1 → 25:1) gave **5e** (420 mg, 100%) as a colorless oil. ^1H NMR: δ 7.72−7.61 (m, 4 H), 7.42−7.33 (m, 6 H), 3.69 (s, 3 H), 3.68 (s, 3 H), 2.56 (dd, J = 6.8, 13.6 Hz, 1 H), 2.46 (dd, J = 6.8, 13.6 Hz, 1 H), 1.68 (dd, J = 10.8, 13.6 Hz, 1 H), 1.63 (dd, J = 6.8, 13.6 Hz, 1 H), 1.48−1.39 (m, 2 H), 1.03 (s, 9 H), 0.98 (dd, J = 2.2, 14.8 Hz, 1 H), 0.87 (d, J = 6.0 Hz, 3 H), 0.37 (dd, J = 11.2, 14.8 Hz, 1 H), 0.12 (s, 3 H), 0.11 (s, 3 H). $^{13}C\{^1H\}$ NMR: δ 173.8, 173.6, 136.3, 135.4, 129.7, 127.8, 58.5, 52.9, 43.8, 43.0, 42.9, 42.4, 27.1, 22.5, 19.5, 17.4, 2.0, 1.5. IR (neat, cm^{-1}): 3062, 2953, 2857, 1961, 1888, 1827, 1735, 1428, 1256, 1117, 1047, 839, 819. HRMS (EI): calcd (found) for $C_{28}H_{39}O_5Si_2$ ($M^+ - CH_3$) 511.2336 (511.2344).

The conversion of **1** to **5b**−**g** (Table 2), **7** to **11c**, **16** to **20a**, **17** to **21a**, **18** to **22a**, **19** to **23a**, **24** to **25a** (Table 1, entries 2 and 6−10), **26** to **27a**, **7** to **11d**, **16** to **20c**, **17** to **21c**, **31** to **32a**, **33** to **34a**, **35** to **38a**, **36** to **39a**, **37** to **40a**, **41** to **42a**, **43** to **44a** (Table 3), and **28** to **29** (Scheme 6) were performed employing a procedure similar to that used to synthesize **5e**. Spectral data for these silylated carbocycles are included in the Supporting Information.

Oxidation of 5e. A suspension of **5e** (440 mg, 0.83 mmol) and TBAF (1.0 M in THF, 7.0 mL, 7.0 mmol) was stirred at room temperature for 19 h. Solvent was evaporated, and the resulting viscous oil was dissolved in DMF (5 mL), treated with KF (470 mg, 8.0 mmol) and AcOOH (32wt % in AcOH) (2.6 mL, 12.0 mmol), and stirred at room temperature for 7 h. Water (5 mL) was added and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with 1 N HCl, saturated aqueous $NaHCO_3$, 10% Na_2SO_3/H_2O, and brine, dried ($MgSO_4$), filtered, concentrated under vacuum, and chromatographed (hexane/EtOAc = 20:1 → 2:1) to give **6** (92 mg, 48%) as a colorless oil.

Oxidation of 3-(Benzhydryldimethylsilyl)methyl-1,1-dicarbomethoxy-4-methylcyclopentane (5f). A suspension of **5f** (350 mg, 0.81 mmol), TBAF (1.0 M in THF, 9.7 mL, 9.7 mmol), $KHCO_3$ (160 mg, 1.6 mmol), and H_2O_2 (50wt % in water, 0.94 mL, 16 mmol) in MeOH/EtOAc (10:1, 4.4 mL) was stirred at room temperature for 21 h. Water/EtOAc workup and chromatography (hexanes−EtOAc = 23:1 → 2:1) gave **6** (149 mg, 80%) as a colorless oil. Carbocycles **27a**, **32a**, **34a**, **39a**, **40a**, **42a**, and **44a** were oxidized employing an analogous procedure (Table 3, entries 1, 5, 6, and 8−11). Carbocycles **11d**, **20c**, **21c**, and **38a** were oxidized employing a procedure analogous to that used to oxidize **5f** except that no ethyl acetate was present in the reaction mixture (Table 3, entries 2−4 and 7). Spectral and analytical data for alcohols **11b**, **20b**, **21b**, **32b**, **27b**, **34b**, **38b**, **39b**, **40b**, **42b**, and **44b** are included in the Supporting Information.

Oxidation of 3-(3-*tert*-Butyl-3,3-diphenyl-1,1-dimethyldisiloxy)methyl-1,1-bis(trimethylacetoxymethyl)-4-methylcyclopentane (11c). A solution of **11c** (360 mg, 0.57 mmol), TBAF (1.0 M in THF, 5.0 mL, 5 mmol), KF (410 mg, 7.0 mmol), $KHCO_3$ (120 mg, 1.2 mmol), and H_2O_2 (50wt %, 0.70 mL, 12.0 mmol) in MeOH (3 mL) was stirred at room temperature for 3 days. Water/EtOAc workup followed by chromatography (hexanes−EtOAc = 25:1 → 2:1) gave *trans*-1,1-bis(trimethylacetoxymethyl)-3-hydroxymethyl-4-methylcyclopentane (**11b**) (143 mg, 73%) as a colorless oil. Carbocycles **22a** and **25a** were oxidized employing a similar procedure (Table 1, entries 8 and 10). Spectral and analytical data for alcohols **22b** and **25b** are included in the Supporting Information.

For 11b. ^1H NMR: δ 3.93 (s, 4 H), 3.74 (dd, J = 3.8, 10.6 Hz, 1 H), 3.51 (dd, J = 6.2, 10.6 Hz, 1 H), 1.83 (m, 2 H), 1.52 (m, 2 H), 1.50 (s, 1 H), 1.32 (dd, J = 10.2, 13.4 Hz, 1 H), 1.19 (s, 18 H), 1.14 (m, 1 H), 1.01 (d, J = 6.0 Hz, 3 H). $^{13}C\{^1H\}$ NMR: δ 178.8, 68.3, 68.0, 65.3, 49.1, 44.4, 41.8, 39.3, 36.6, 36.1, 27.5, 18.9. IR (neat, cm^{-1}): 3444, 2957, 2870, 1730, 1480, 1397, 1364, 1283, 1152, 1028. Anal. Calcd (found) for $C_{19}H_{34}O_5$: C, 66.63 (66.19); H, 10.01 (9.88).

Oxidation of 3-(3-*tert*-Butyl-3,3-diphenyl-1,1-dimethyldisiloxy)methyl-1,1-bis(methoxymethyl)-4-methylcyclopentane (21a). A suspension of **21a** (325 mg, 0.65 mmol), TBAF (1.0 M in THF, 7.0 mL, 7.0 mmol), $KHCO_3$ (100 mg, 1.0 mmol), and H_2O_2 (50wt % in water, 0.75 mL, 13.0 mmol) in MeOH (3 mL) was refluxed for 24 h. Water/EtOAc workup followed by chromatography gave *trans*-1,1-bis(methoxymethyl)-3-hydroxymethyl-4-methylcyclopentane (**21b**) (100 mg, 76%) as a colorless oil. Carbocycles **20a** and **23a** were oxidized employing a similar procedure (Table 1, entries 6 and 9). Spectral data for alcohols **20b** and **23b** are included in the Supporting Information.

For 21b. ^1H NMR: δ 3.67 (dd, J = 4.0, 10.8 Hz, 1 H), 3.46 (dd, J = 6.4, 10.4 Hz, 1 H), 3.30 (d, J = 1.2 Hz, 6 H), 3.19 (d, J = 3.4 Hz, 4 H), 1.95 (s, 1 H), 1.75 (m, 2 H), 1.64 (m, 2 H), 1.22 (dd, J = 10.0, 13.2 Hz, 1 H), 1.05 (dd, J = 10.0, 12.6 Hz, 1 H), 1.96 (d, J = 6.0 Hz, 3 H). $^{13}C\{^1H\}$ NMR: δ 78.3, 78.1, 65.7, 59.5, 49.2, 45.8, 42.3, 36.8, 36.3, 19.0. IR (neat, cm^{-1}): 3409 (O−H). Anal. Calcd (found) for $C_{11}H_{22}O_3$: C, 65.31 (64.89); H, 10.96 (10.68).

4-Carbomethoxy-1-triethylsilylmethyl-2-methylcyclopentane (15). A suspension of **3** (95 mg, 0.29 mmol) and TBAF (1.0 M in THF, 3.5 mL, 3.5 mmol) was stirred at room temperature for 2 days. Evaporation of solvent and chromatography (hexanes−EtOAc = 50:1 → 25:1) gave **15** (60 mg, 77%) as a pale yellow oil. The ^1H NMR spectrum of **15** was identical to an authentic sample.[37b]

Determination of Enantiomeric Excess and Absolute and Relative Configuration. The enantiomeric excess of carbocycles **5a**−**g**, **12a**, **13a**, **14a**, **29**, **32a**, **34a**, **39a**, and **40a** was determined by ^1H NMR spectroscopy employing $Eu(hfc)_3$ as a chiral shift reagent. The enantiomeric excess of carbocycles **11b**, **20b**, **22b**, **23b**, **25b**, **27b**, **38b**, **42b**, and **44b** was determined by ^1H and ^{19}F NMR analysis of the corresponding Mosher ester. The enantiomeric excess of carbocycle **21b** was determined by chiral GC analysis on a 20 m × 0.25 mm Chiraldex G-TA column (Advanced Separation Technologies). In each case, the peaks corresponding to the enantiomeric pair were identified from the corresponding racemic carbocycle. The relative and absolute stereochemistry of *trans*-(*S,S*)-**6** formed from **5a**, **5e**, and **5f** was established by comparison to an authentic sample.[11b] The absolute stereochemistry of the remaining carbocycles was assigned by analogy to carbocycle *trans*-(*S,S*)-**6**. The relative stereochemistry of the remaining carbocycles was assigned based on the relative stereochemistry of the analogous triethylsilyl-substituted carbocycles.[37]

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Supporting Information Available: Analytical and spectroscopic data for new compounds and experimental procedure for the synthesis of **35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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