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Enantioselective Synthesis

Asymmetric Conjugate Addition of Grignard Reagents to 3-Silyl Unsaturated Esters for the Facile Preparation of Enantioenriched β-Silylcarbonyl Compounds and Allylic Silanes

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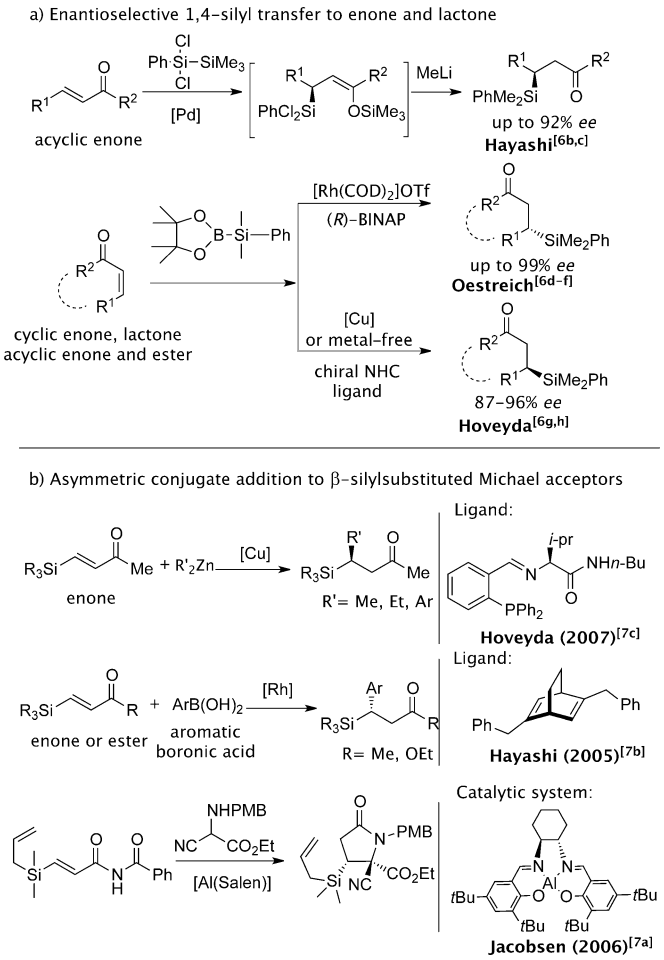
Abstract: A highly enantioselective conjugate addition of Grignard reagents to 3-silyl unsaturated esters to deliver synthetically useful chiral β-silylcarbonyl compounds was developed. The synthetic value of this methodology was further illustrated by the synthesis of enantioenriched β-hydroxyl esters and the facile access granted to various α-chiral allylic silanes. A plethora of diastereoselective transformations of β-silylenolates were also investigated and afforded manifold organosilanes that contained contiguous stereogenic centers with excellent enantioselectivity.

Introduction

Enantioenriched organosilanes have received tremendous attention as versatile building blocks due to their substantial utility in the construction of an enormous number of natural products and pharmaceutical agents.[1] In particular, chiral β-silylcarbonyl compounds[2] have been considered one of the most fascinating synthetic targets due to the potential role of the C–Si bond as a hydroxyl precursor (accessed by stereospecific Fleming–Tamao[3,4]oxidation) and its unique ability to induce a great number of stereoselective organic transformations at neighboring prostereogenic sites.[5] Over the past few decades, several pioneering breakthroughs in the synthesis of enantioenriched β-silylcarbonyl compounds were established by the groups of Hayashi,[6b,c,7b] Hoveyda,[6g,h,7c] Oestreich,[6d–f] Riant,[6i] Córdova,[6j] Jacobsen,[7a] and Lipshutz,[8] which could be classified as follows:

1) Enantioselective C–Si bond formation by transition-metal-catalyzed silyl conjugate addition to α,β-unsaturated carbonyl compounds (Scheme 1 a).[6]
2) Asymmetric C–C bond formation by 1,4-addition of organozinc reagents, organoboronic acids, or stabilized carbanions to β-silylsubstituted Michael acceptors (Scheme 1 b).[7]
3) Asymmetric hydrosilylation of trisubstituted olefins with



Scheme 1. Selected examples for the synthesis of chiral β-silylcarbonyl compounds. COD = 1,5-cyclooctadiene, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, Salen = 6,6′-((1*E*,1′*E*)-((1*S*,2*S*)-cyclohexane-1,2-diylbis(azanylylidene))bis(methanylylidene))bis(2,4-di-tert-butylphenol), PMB = 4-methoxybenzyl.

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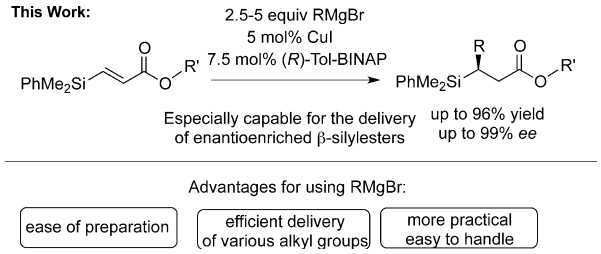
β-silylesters.[8]

Despite these remarkable achievements, efforts to explore novel, efficient, and practical catalytic systems to deliver enantioenriched β-silylcarbonyl compounds in excellent enantioselectivity with wider substrate scope still attract increasing attention among synthetic chemists.

In this article, we describe a highly efficient strategy that uses catalytic CuI and commercially available (*R*)-(+)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl [(*R*)-Tol-BINAP] to promote the enantioselective Michael addition of Grignard reagents to 3-silyl unsaturated esters to afford enantioenriched β-silylcarbonyl compounds in considerable yields (65–96%) and excellent enantioselectivity [92–99% enantiomeric excess (*ee*)]. Notably, this methodology is compatible with a variety of easily accessible alkylmagnesium reagents, which renders this protocol an attractive and robust option for the preparation of synthetically important enantioenriched β-silylesters with various aliphatic functional moieties, which are versatile building blocks for a plethora of organic transformations (Scheme 2).



Scheme 2. Asymmetric conjugate addition of Grignard reagents to 3-silyl unsaturated esters.

Results and Discussion

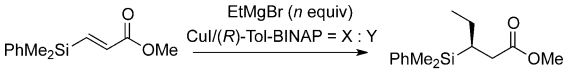
Asymmetric conjugate addition of Grignard reagents to 3-silyl unsaturated esters

Interestingly, although Grignard reagents are one of the most commonly used organometallic reagents, their role as nucleophiles in copper-catalyzed asymmetric conjugate addition (ACA) reactions has only received considerable attention in the past decade,[9] with several significant contributions established by the groups of Feringa,[10] Alexakis,[11] Hall,[12] Tomioka,[13] Schmalz,[14] and our group.[15]

Guided by our previous success when the CuI/Tol-BINAP system was used to promote ACA of Grignard reagents to α,β-unsaturated esters, the reaction of EtMgBr with 3-silyl unsaturated methyl ester **1a** catalyzed by this system was investigated to ascertain the optimal reaction conditions (Table 1). The optimal ratio of CuI/Tol-BINAP was found to be 1:1.5, in agreement with our previous reports.[15a]

After scrutiny of the effects of solvents, temperature, and amount of Grignard reagent, we determined that the reaction performed in CH_2Cl_2 at −78 °C gave the optimal combination of yield and enantioselectivity (Table 1, entry 8). Moreover,

Table 1. Optimization of the reaction conditions.[a]



1a **2a**

	Solvent	*T* [°C]	X/Y	*n*	*t* [h]	Yield [%][b]	*ee* [%][c]
1	*t*BuOMe	−40	1:1	5.0	20	51	81
2	*t*BuOMe	−40	1:1.5	5.0	16	73	83
3	*t*BuOMe	−40	1:1.5	2.5	16	61	87
4	*t*BuOMe	−60	1:1.5	2.5	20	75	89
5	Et_2O	−60	1:1.5	2.5	16	67	97
6	CH_2Cl_2	−60	1:1.5	2.5	24	96	89
7	CH_2Cl_2	−70	1:1.5	2.5	30	91	93
8	CH_2Cl_2	−78	1:1.5	2.5	30	88	97
9	*t*BuOMe/CH_2Cl_2 (2:1 *v/v*)	−40	1:1.5	2.5	16	80	95

[a] Reaction conditions: **1** (0.4 mmol), RMgBr (2.5 equiv), CuI (5 mol%), (*R*)-Tol-BINAP (7.5 mol%) in solution under argon, unless otherwise described. [b] Isolated yield. [c] Determined by chiral HPLC analysis with a Daicel Chiralcel OD-H column. The absolute configuration was determined by comparison of the optical rotation of the products with those reported in the literature (see ref. [6g]).

when 2:1 *t*BuOMe/CH_2Cl_2 was employed as the solvent, the reaction proceeded efficiently at −40 °C, with a shortened reaction time, to give the desired product in considerable yield and enantioselectivity, which made this method more appealing for practical application (Table 1, entry 9).

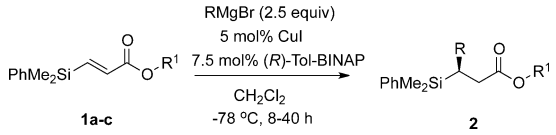
With the optimized conditions in hand, a variety of alkyl Grignard reagents were employed for the conjugate addition to **1** to investigate the scope of this methodology; the results are summarized in Table 2.

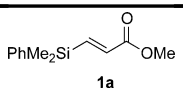
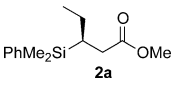
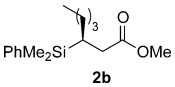
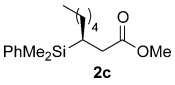
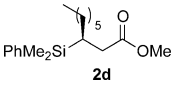
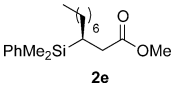
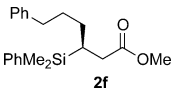
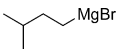
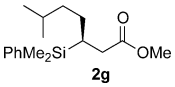
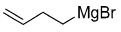
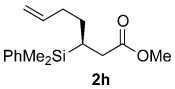
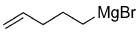
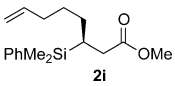
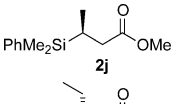
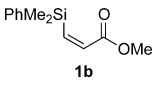
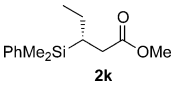
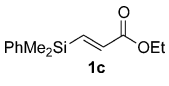
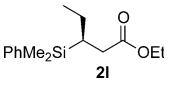
Gratifyingly, for the unbranched alkyl Grignard reagents examined, the reaction proceeded smoothly to give the desired products with excellent yields and enantioselectivities (Table 2, entries 1–6). Relatively bulkier Grignard reagents were also well tolerated and afforded the corresponding products with excellent yields and enantioselectivities (Table 2, entries 7 and 8). Notably, Grignard reagents with alkenyl moieties could also participate in the ACA reaction successfully without any loss of enantioselectivity (Table 2, entries 9 and 10). For the notoriously less-reactive reagent MeMgBr, the target product could also be isolated in moderate yield and high enantioselectivity by employing *t*BuOMe as the solvent and switching the addition sequence of the Grignard reagent and substrate (Table 2, entry 11). To our delight, the catalyst loading could be further decreased to as low as 2 mol% of CuI and 3 mol% of (*R*)-Tol-BINAP without compromising the reactivity or enantioselectivity (Table 2, entry 2).

It is also notable that when *Z* enoate **1b** was employed, the absolute stereochemistry of the product was totally reversed to afford the enantiomer of **2a** in considerable yield and excellent enantioselectivity (Table 2, entry 12). The plausible decrease of the enantioselectivity ascribed to *Z*–*E* isomerization was not observed in this case.

One of the most important uses of enantioenriched β-silylesters **2** is the synthesis enantiopure secondary β-hydroxyl esters

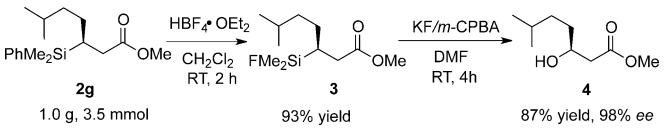
Table 2. Substrate scope for the asymmetric conjugate addition of Grignard reagents to 3-silyl unsaturated esters.[a]



	Substrate	RMgBr	Product	Yield of **5** [%][b]	*ee* [%][c]
1	 **1a**	EtMgBr	 **2a**	88	97
2[d]	**1a**	EtMgBr	**2a**	75	95
3	**1a**	$CH_3(CH_2)_3MgBr$	 **2b**	86	97
4	**1a**	$CH_3(CH_2)_4MgBr$	 **2c**	84	97
5	**1a**	$CH_3(CH_2)_5MgBr$	 **2d**	93	96
6	**1a**	$CH_3(CH_2)_6MgBr$	 **2e**	85	96
7	**1a**	$Ph(CH_2)_3MgBr$	 **2f**	73	99
8	**1a**		 **2g**	89	98
9	**1a**		 **2h**	90	93
10	**1a**		 **2i**	96	97
11[e]	**1a**	MeMgBr	 **2j**	65	93
12	 **1b**	EtMgBr	 **2k**	78	94
13	 **1c**	EtMgBr	 **2l**	91	92

[a] Reaction conditions: **1** (0.4 mmol), RMgBr (2.5 equiv), CuI (5 mol%), (*R*)-Tol-BINAP (7.5 mol%) in CH_2Cl_2 under argon, unless otherwise described. [b] Isolated yield. [c] Determined by chiral HPLC analysis with a Daicel Chiralcel OD-H column. [d] Catalyst loading: CuI (2 mol%)/(*R*)-Tol-BINAP (3 mol%). [e] Reaction conditions: MeMgBr was added dropwise to a solution of CuI/(*R*)-Tol-BINAP complex in *t*BuOMe, then substrate **1a** was added dropwise over 1 h at −40 °C.

by stereospecific transformation of the silyl group into a hydroxyl group by Fleming–Tamao oxidation. The oxidation of enantiopure **2g** could be smoothly executed at gram scale under very mild conditions to give the enantioenriched β-hydroxyl ester **4** in excellent yield with retention of the absolute configuration (Scheme 3). This methodology manifests an alternative approach for the preparation of alkyl-substituted β-hydroxyl esters, which complements existing synthetic methods, for example, oxidation of chiral boronate derivatives[12] or enantioselective acetate aldol and Reformatsky reactions (which are less compatible with aliphatic substrates).[16]



Scheme 3. Stereospecific oxidation of the C–Si bond for the systhesis of β-hydroxyl ester. *m*-CPBA = *meta*-chloroperbenzoic acid.

Enantioselective synthesis of allylic silanes

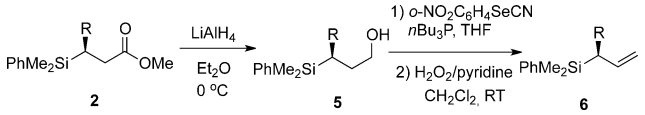
Enantiomerically enriched allylic silanes are increasingly attractive compounds in modern synthetic chemistry as ubiquitous building blocks for the construction of various complex molecules.[17]

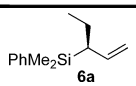
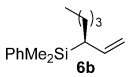
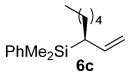
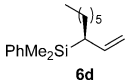
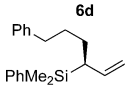
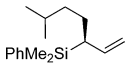
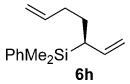
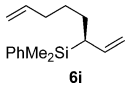
Recently, a large number of synthetic methodologies for the preparation of chiral allylic silanes have been successfully employed.[18] Nevertheless, efforts to develop new strategies to deliver structurally versatile allylic silanes with excellent site- and enantio-selectivities remains highly sought after.

To further illustrate the potential utility of the enantioenriched β-silylester **2** generated by copper-catalyzed ACA of Grignard reagents to 3-silyl unsaturated esters, we demonstrate a facile synthetic route towards a variety of chiral allylic silanes. In this protocol, the chiral β-silylester **2** was converted to the corresponding alcohol **5**, which could successfully undergo Grieco dehydration[19] to give the desired allylic silanes **6** in moderate yield and excellent enantioselectivity (Table 3).

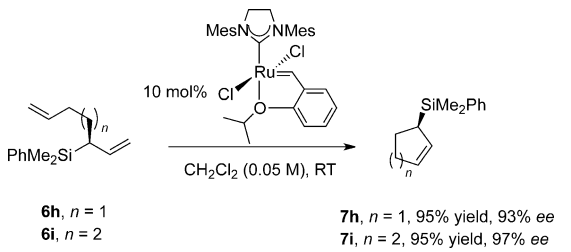
A plethora of enantioenriched tertiary allylic silanes with various aliphatic substituents were obtained with excellent enantioselectivities and moderate yields (Table 3, entries 1–6). In addition, substrates with alkenyl moieties

Table 3. The facile synthesis of enantioenriched allylic silanes.[a]



	Substrate	Product	Yield [%][b]	*ee* [%][c]
1	**2a**	 **6a**	56	97
2	**2b**	 **6b**	60	97
3	**2c**	 **6c**	71	96
4	**2d**	 **6d**	57	96
5	**2f**	 **6f**	63	99
6	**2g**	 **6g**	68	98
7	**2h**	 **6h**	62	93[d]
8	**2i**	 **6i**	64	97[d]

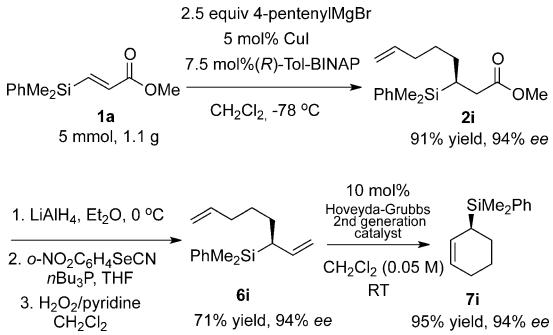
[a] Reaction conditions: **2** (0.3 mmol), $LiAiH_4$ (0.36 mmol), 2-nitrophenyl-selenocyanate (0.36 mmol), P(*n*-Bu)$_3$ (0.36 mmol), pyridine (0.6 mmol), H_2O_2 (3.0 mmol), unless otherwise described. [b] Isolated yield. [c] Determined by chiral HPLC analysis of the corresponding alcohol **5** generated by the hydroboration–oxidation reaction of **6**. [d] Enantioselectivity was determined from the *ee* of the corresponding precursors **2** and **5**.



Scheme 4. The synthesis of cyclic allylic silanes **7h** and **7i** by ring-closing metathesis. Mes = mesityl.

tolerated the oxidative conditions of the Grieco dehydration and gave the target allylic silanes **6** with excellent enantioselectivity (Table 3, entries 7 and 8), which could be readily subjected to ring-closing metathesis[20] to deliver enantiomerically pure cyclic allylic silanes **7h** and **7i** in excellent yield (Scheme 4).

Intriguingly, this approach is suitable for gram-scale synthesis without deterioration of the yield or enantioselectivity (Scheme 5), which allows it to serve as one of the most effi-



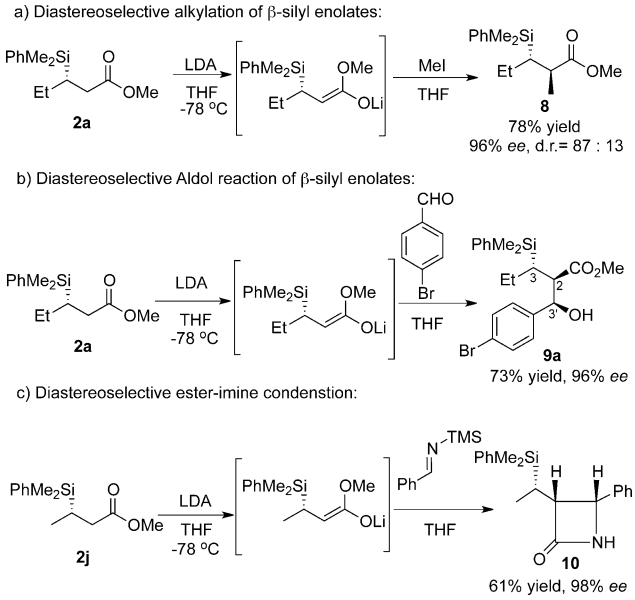
Scheme 5. Gram-scale preparation of cyclic allylic silane **7i**.

cient and robust tools to access chiral cyclic allylic silanes because of the considerable yield and excellent enantioselectivity of the reaction.

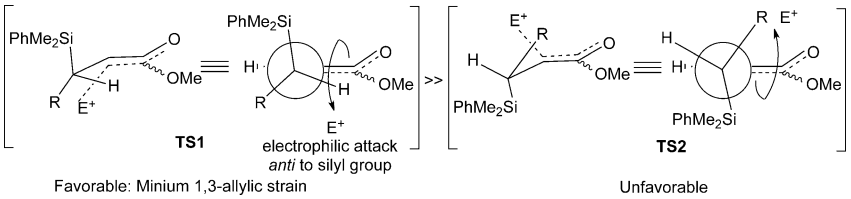
Diastereoselective transformations of enantioenriched β-silylcarbonyls

Aside from its potential capability as a masked hydroxyl surrogate, the phenyldimethylsilyl group in β-silylenolates could also act as a robust tool to induce extraordinary diastereoselective control during electrophilic attack on neighboring prostereogenic carbon centers. Guided by this principle, we proceeded to investigate the utility of enantioenriched β-silylester **2** in a series of diastereoselective transformations, which included diastereoselective alkylation with MeI,[21] aldol reaction with aldehydes,[22] and condensation with imines.[23] Manifold enantioenriched chiral silanes with up to three stereogenic centers were obtained with excellent diastereo- and enantioselectivities (Scheme 6).[24]

In these reactions, the excellent diastereoselectivity between the chiral center that carries the β-silyl group and its neighbor-



Scheme 6. Diastereoselective transformations of enantioenriched β-silylcarbonyl compounds. LDA = lithium diisopropylamide.



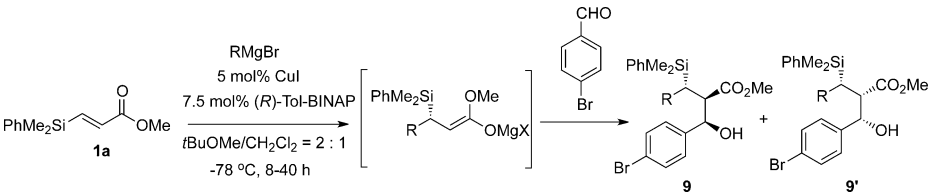
Scheme 7. Transition-state model for the diastereoselective transformation.

ing prostereogenic site could be rationalized by the transition state of the β-silylenolates (Scheme 7).[21] The transition state **TS1** is more favorable than **TS2** because of the minimized $A_{1,3}$-allylic strain. Electrophilic attack would then occur *anti* to the bulky phenyldimethylsilyl group and lead to formation of the desired products in a highly diastereoselective manner.

One-pot catalytic asymmetric 1,4-addition/aldol reactions

Catalytic enantioselective one-pot tandem reactions have attracted increasing attention because of their unique abilities to construct polyfunctionalized molecules with multiple stereogenic centers from simple prochiral building blocks.[25] Among these reactions, the cascade 1,4-addition/aldol reaction represents a particularly attractive category because of its wide-spread application in the synthesis of a number of biologically important natural products.[26] Nevertheless, the construction of multiple stereogenic centers in acyclic systems has proven to be a challenging task due to the difficulty of controlling the geometry of the acyclic enolate intermediates.[26a] Recently, several stunning examples of copper-catalyzed asymmetric domino conjugate-addition/electrophilic-trapping reactions applied to acyclic substrate were disclosed, which afforded a variety of multifunctional compounds that contained contiguous stereocenters with excellent diastereo- and enantio-control.[27–29] Encouraged by these exciting breakthroughs, we proceeded to investigate the one-pot tandem 1,4-addition/aldol reaction by employing β-silylated enoate **1a** as the substrate. We envisioned that the magnesium enolate generated in situ from the Michael addition could be successfully trapped by the aldehyde to construct enantioenriched β-silylcarbonyls **9** with three contiguous stereocenters. The steric hindrance posed by the phenyldimethylsilyl group effectively directed the electrophilic attack of the aldehyde from its *anti* position, which led to good stereocontrol between C2 and C3. On the other hand, the *Z*-configured magnesium enolate, formed preferentially at low temperatures, contributed to the excellent diastereoselectivity between C2 and C3′.[30] To our delight, the tandem 1,4-addition/aldol reaction proceeded smoothly and gave the desired product with three contiguous stereocenters in good yield and excellent enantioselectivity in one pot, rather than by the two-step protocol depicted in Scheme 6b. In addition, eight stereoisomers could be generated in this process but only two were predominantly observed and, in most cases, product **9** was isolated as the major product with moderate-to-good diastereoselectivity (Table 4).

Table 4. The trapping of the magnesium enolate formed in situ by tandem 1,4-addition/aldol reaction.[a]



	RMgBr	Yield [%][b]	Products[c]	d.r.[d] (**9**/**9**′)	*ee* [%][e] **9** (**9**′)
1	EtMgBr	65	**9a** / **9a'**	81:19	99 (99)
2	MgBr	68	**9b** / **9b'**	83:17	94 (94)
3	MgBr	66	**9c** / **9c'**	78:22	98 (98)
4	MgBr	58	**9d** / **9d'**	72:28	99 (99)
5	MgBr	70	**9e** / **9e'**	67:33	98 (98)

[a] Reaction conditions: **1a** (0.4 mmol), RMgBr (2.5 equiv), CuI (5 mol%), (*R*)-Tol-BINAP (7.5 mol%), and 4-bromobenzaldehyde (1.6 mmol) in solution under argon, unless otherwise described. [b] Isolated yield. [c] The relative and absolute configurations were assigned by ^{1}H NMR analysis of the acetonide derivatives (see the Supporting Information for details). [d] Diastereomeric ratio determined from the ^{1}H NMR spectrum of the crude product. [e] Determined by chiral HPLC analysis.

Conclusion

We have outlined a highly efficient enantioselective conjugate addition of Grignard reagents to silylated enoates catalyzed by CuI/(*R*)-Tol-BINAP, which provides an attractive, efficient, and concise route to alkyl-substituted enantioenriched β-silylesters. The potential synthetic value of this methodology was exemplified by a mild C–Si bond oxidation to delivered enantioenriched β-hydroxyl esters and by the facile entry to various synthetically valuable acyclic and cyclic allylic silanes. A plethora of diastereoselective transformations of β-silylcarbonyl compounds, which included alkylation, one-pot tandem 1,4-addition/aldol reaction, and ester–imine condensation were investigated to further highlight the application of this methodology to construct various synthetically important enantiopure organosilanes that contain multiple stereogenic centers.

Experimental Section

General considerations

Unless otherwise stated, experiments that involve moisture and/or air sensitive components were performed in oven-dried glassware under a positive pressure of argon with freshly distilled solvents. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AMX 400 spectrophotometer. Chemical shifts (δ) are reported in parts per million (ppm) downfield from $SiMe_4$ ($\delta = 0.0$). Coupling constants (J) are reported in (Hz). ^{13}C NMR are reported in ppm downfield from $SiMe_4$ ($\delta = 0.0$) and relative to the signal of $CDCl_3$ ($\delta = 77.16$, t). The proportion of diastereomers and geometric isomers was determined by integration of signals in the ^{1}H and ^{13}C NMR spectra. Analytical TLC was performed with Merck 60 F254 precoated silica gel plates. IR spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. HRMS was performed with a Finnigan MAT95XP GC/HRMS instrument. Enantioselectivities were determined by HPLC analysis with a Daicel Chiracel OD-H or Chiralpak AD-H column at 25 °C. Optical rotations were measured in solution in $CHCl_3$ (c = g/100 mL) on a Schmidt+Haensch polarimeter (Polartronic MH8) with a 1 cm cell. The absolute configuration of the products was determined by comparison to previously published data.

General experimental procedure for asymmetric conjugate addition

CuI (3.8 mg, 0.02 mmol, 5 mol%) and (*R*)-Tol-BINAP (20.4 mg, 0.03 mmol, 7.5 mol%) were added to an oven-dried Schlenk tube under a positive pressure of argon. Anhydrous CH_2Cl_2 (1.0 mL) was added and the solution was left to stir at RT for 30 min. Subsequently, a solution of 3-silyl unsaturated ester **1a** (88.1 mg, 0.4 mmol) in anhydrous CH_2Cl_2 (5.5 mL) was added to the reaction mixture, which was stirred for 10 min then cooled to −78 °C. RMgBr (1.0 mmol, 2.5 equiv) was added to the reaction mixture dropwise over 10 min. After complete consumption of **1a** (monitored by TLC), the reaction was quenched with MeOH (1.0 mL) and NH_4Cl (1.0 M, 4.0 mL) and the mixture was warmed to RT. The layers were separated and the aqueous layer was extracted with Et_2O (3×15 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography (1:80 Et_2O/petroleum ether) to afford the desired product **2** as a colorless oil.

Compound 2a: Colorless oil; 88%; 97% *ee* determined by HPLC: Daicel Chiralcel OD-H column, hexane/isopropanol = 99.8:0.2, flow rate 1.0 mL min^{-1}, $\lambda = 220$ nm, retention time (t_R) = 7.887 (minor), 13.868 min (major); $[\alpha]_D^{20} = +10.1$ ($c = 1.25$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.51$–7.49 (m, 2H; ArH), 7.35–7.34 (m, 3H; ArH), 3.58 (s, 3H; OCH_3), 2.34 (dd, $J = 15.5$, 5.3 Hz, 1H), 2.25 (dd, $J = 15.6$, 8.3 Hz, 1H), 1.56–1.50 (m, 1H), 1.42–1.26 (m, 1H), 0.87 (t, $J = 7.2$ Hz, 3H), 0.29 ppm (s, 6H; 2×$SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.90$, 138.13, 134.05, 129.13, 127.88, 51.55, 34.51, 23.98, 23.23, 13.62, −3.94, −4.18 ppm; IR (KBr): $\tilde{\nu} = 2960$, 2937, 1734, 1459, 1436, 1428, 1354, 1259, 1250, 1198, 1152, 1112, 1016, 812, 701 cm^{-1}; HRMS (ESI): m/z calcd for $C_{14}H_{23}O_2Si$: 251.1467 [M+H$^+$]; found: 251.1461.

Experimental procedure for the stereospecific Fleming–Tamao oxidation (4)

A solution of **2g** (1.02 g, 3.5 mmol) in Et_2O (6.0 mL) was added to an oven-dried Schlenk tube equipped with a stirrer bar. $BF_4{\cdot}Et_2O$ (580 μL) was added at 0 °C. The mixture was warmed to RT over 10 min. After stirring for 2 h at RT, the reaction was quenched with cold water (10 mL). The mixture was extracted with Et_2O (3× 20 mL), the combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the corresponding fluorosilane **3**, which was directly subjected to the next step without further purification. *m*-CPBA (1.5 g, 80% purity) and anhydrous potassium fluoride (470 mg, 8.1 mmol) were added to a solution of crude fluorosilane (766 mg, 3.3 mmol) in freshly distilled DMF (15.0 mL). The suspension was stirred for 3 h at RT and diluted with CH_2Cl_2 (200 mL). The mixture was washed successively with a saturated aqueous solution of $Na_2S_2O_3$ (20 mL), a saturated aqueous solution of $NaHCO_3$ (20 mL), water (10 mL), and brine (10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a viscous oil, which was purified by column chromatography (1:5 Et_2O/pentane) to afford the desired β-hydroxyl ester **4** as colorless oil (81% overall yield?, 98% *ee*); $[\alpha]_D^{20>} = +23.8$ ($c = 1.21$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.01$–3.94 (m, 1H), 3.72 (s, 3H), 2.86 (d, $J = 4.0$ Hz, 1H), 2.53 (dd, $J = 16.4$, 3.1 Hz, 1H), 2.42 (dd, $J = 16.4$, 9.0 Hz, 1H), 1.56–1.48 (m, 2H), 1.46–1.40 (m, 1H), 1.38–1.29 (m, 1H), 1.27–1.14 (m, 1H), 0.90 (d, $J = 1.8$ Hz, 3H), 0.88 ppm (d, $J = 1.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.63$, 68.47, 51.84, 41.24, 34.71, 34.51, 28.10, 22.70, 22.61 ppm; IR (KBr): $\tilde{\nu} = 3584$, 3418, 2957, 2934, 2870, 1738, 1439, 1368, 1259, 1169, 1080, 799 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{19}O_3$: 175.1334 [M+H$^+$]; found: 175.1327.

General experimental procedure for the synthesis of allylic silanes 6

A solution of β-silylester **2** (0.3 mmol) in anhydrous Et_2O (1.0 mL) was added to an oven-dried Schlenk tube equipped with a stirrer bar. $LiAlH_4$ (0.36 mL, 1.0 M in Et_2O, 1.2 equiv) was added dropwise over 10 min at 0 °C. After stirring at 0 °C for 1 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (2.0 mL) and the mixture was allowed to warm to RT. The crude mixture was extracted with Et_2O (3×15 mL) and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under vacuum to give alcohol **5**. Subsequently, **5** and 2-nitrophenylselenocyanate (81.7 mg, 0.36 mmol, 1.2 equiv) were dissolved in anhydrous THF (2.0 mL). Tri-*n*-butyl phosphine (90 μL, 0.36 mmol, 1.2 equiv) was added dropwise and the mixture was stirred for 1 h at RT under argon. The solvent was removed under reduced pressure and the crude selenoxide was re-dissolved in CH_2Cl_2 (2.0 mL). Pyridine

(50 μL, 0.6 mmol, 2.0 equiv) was added. Hydrogen peroxide solution (30% *w/w* in H_2O, 350 μL) was added dropwise over 10 min at 0 °C. The solution was allowed to warm to RT, then stirred for 16 h at RT. The reaction mixture was diluted with water (5.0 mL) and extracted with Et_2O (3×10 mL). The combined organic phases were washed successively with a saturated aqueous solution of sodium hydrogencarbonate (10 mL), a saturated aqueous solution of copper sulfate (10 mL), and brine (10 mL), then dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (1:100 Et_2O/petroleum ether) to afford **6** as colorless oil.

Compound 6c: Colorless oil; 71% yield; $[\alpha]_D^{20}=+12.7$ ($c=1.42$ in $CHCl_3$); 96% *ee* determined by chiral HPLC: Daicel Chiralpak AD-H column, substrate = alcohol **5c** generated by the hydroboration–oxidation reaction of **6c**, hexane/isopropanol = 99:1, flow rate = 1.5 mL min^{-1}, $\lambda=220$ nm, $t_R=8.720$ (major), 9.665 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.51$–7.46 (m, 2H; ArH), 7.36–7.33 (m, 3H; ArH), 5.58 (ddd, $J=17.1$, 10.2, 9.6 Hz, 1H; CHC**H**=CH_2), 4.88 (ddd, $J=10.3$, 2.0, 0.5 Hz, 1H; CH=C**H**H), 4.80 (ddd, $J=17.1$, 2.0, 1.0 Hz, 1H; CH=CH**H**), 1.75–1.69 (m, 2.9 Hz; 1H), 1.43–1.12 (m, 8H), 0.82 (t, $J=7.1$ Hz, 3H; CH_3), 0.26 (s, 3H; $SiCH_3$), 0.25 ppm (s, 3H; $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=140.08$, 138.13, 134.20, 129.01, 127.72, 112.51, 34.56, 31.78, 29.09, 28.54, 22.72, 14.25, −4.30, −5.03 ppm; IR (KBr): $\tilde{\nu}=3397$, 2956, 2924, 2854, 1624, 1466, 1427, 1248, 1113, 895, 835, 698 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{27}Si$: 247.1882 [M+H$^+$]; found: 247.1887.

General experimental procedure for the synthesis of allylic silanes 7

A solution of **6** (0.2 mmol) in CH_2Cl_2 (4.0 mL) and Hoveyda–Grubbs second generation catalyst (12.5 mg, 0.02 mmol) were added to an oven-dried Schlenk tube under argon. The mixture was left to stir for 1 h at RT, then the solvent was evaporated under reduced pressure and the residue was purified by column chromatography to give the cyclic allylic silane **7**.

Compound 7h: Colorless oil; 95% yield; 93% *ee*; $[\alpha]_D^{20}=-107.6$ ($c=0.73$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.53$–7.51 (m, 2H; ArH), 7.36–7.34 (m, 3H; ArH), 5.70–5.68 (m, 1H; C**H**=CH), 5.64–5.62 (m, 1H; CH=C**H**), 2.37–2.28 (m, 1H), 2.21–2.11 (m, 2H), 2.08–1.98 (m, 1H), 1.88–1.80 (m, 1H), 0.25 (s, 3H; $SiCH_3$), 0.24 ppm (s, 3H; $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=138.82$, 133.99, 132.14, 129.01, 128.55, 127.79, 34.15, 33.03, 25.30, −4.50, −4.54 ppm; IR (KBr): $\tilde{\nu}=3051$, 2957, 2928, 2835, 1639, 1427, 1247, 1113, 895, 835, 721, 698 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{19}Si$: 203.1256 [M+H$^+$]; found: 203.1255.

Experimental procedure for the diastereoselective alkylation (8)

A solution of β-silylester **2a** (75.1 mg, 0.3 mmol) in anhydrous THF (3.0 mL) was added to an oven-dried Schlenk tube equipped with a stirrer bar. The solution was cooled to −78 °C and LDA (0.36 mL, 1.0 M in THF/hexanes, 1.2 equiv) was added dropwise over 10 min. After stirring at −78 °C for 30 min, a solution of MeI (75 μL, 1.2 mmol) in THF (1.0 mL) was added dropwise over 5 min, then the mixture was slowly warmed to 0 °C over 3 h and left to stir for an additional 5 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (2.0 mL). The crude mixture was extracted with Et_2O (3×15 mL), then the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (1:100 Et_2O/petroleum ether) to give **8** as colorless oil (78% yield, 96% *ee*). HPLC: Daicel Chiralcel OD-H column, hexane/isopropanol = 99.9:0.1, flow rate = 1.0 mL min^{-1}, $\lambda=220$ nm, $t_R=19.603$ (minor), 21.897 min (major); $[\alpha]_D^{20}=+38.3$ ($c=1.16$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.54$–7.51 (m, 2H; ArH), 7.37–7.33 (m, 3H; ArH), 3.57 (s, 3H; OCH_3), 2.61 (qd, $J=7.1$, 3.4 Hz, 1H), 2.25 (dd, $J=15.6$, 8.3 Hz, 1H), 1.56–1.49 (m, 1H), 1.47–1.39 (m, 2H), 1.06 (d, $J=7.1$ Hz, 3H), 0.83 (t, $J=7.2$ Hz, 3H), 0.33 ppm (s, 6H; 2×$SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=177.81$, 138.96, 134.01, 129.03, 127.88, 51.56, 39.06, 30.82, 19.71, 14.66, 14.04, −2.78, −2.91 ppm; IR (KBr): $\tilde{\nu}=2958$, 2876, 1736, 1733, 1460, 1434, 1428, 1197, 1179, 1111, 811, 735, 703 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{25}O_2Si$: 265.1624 [M+H$^+$]; found: 265.1621.

General experimental procedure for the one-pot tandem 1,4-addition/aldol reaction

In an oven-dried Schlenk tube, CuI (3.8 mg, 0.02 mmol, 5 mol%) and (*R*)-Tol-BINAP (20.4 mg, 0.03 mmol, 7.5 mol%) were dissolved in anhydrous CH_2Cl_2 (1.6 mL) and the mixture was stirred for 30 min at RT. Subsequently, 3-silyl unsaturated ester **1a** (88.1 mg, 0.4 mmol) dissolved in freshly distilled *t*BuOMe (3.2 mL) was added to the mixture. The solution was cooled to −78 °C and RMgBr (1.0 mmol, 2.5 equiv) was added dropwise over 10 min. Upon complete consumption of **1a** (monitored by TLC), a solution of 4-bromobenzaldehyde (296 mg, 1.6 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise over 5 min at −78 °C. After stirring for an additional 5 min, the reaction was quenched with a saturated aqueous solution of NH_4Cl (4.0 mL). The mixture was extracted with Et_2O (3× 15 mL) and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:60 ethyl acetate/hexane) to afford **9** (the desired major diastereomer) together with **9′** (the minor diastereomer).

Compound 9a: Colorless oil; 65% yield; 99% *ee* determined by HPLC: Daicel Chiralpak AD-H column, hexane/isopropanol = 98:2, flow rate = 1.0 mL min^{-1}, $\lambda=220$ nm; $t_R=12.001$ (minor), 16.909 min (major); $[\alpha]_D^{20}=+13.9$ ($c=2.03$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.64$–7.62 (m, 2H; ArH), 7.39–7.36 (m, 5H; ArH), 7.04–7.02 (m, 2H; ArH), 4.64 (dd, $J=9.6$, 3.4 Hz, 1H), 3.37 (s, 3H; OCH_3), 2.95 (dd, $J=9.6$, 2.9 Hz, 1H), 1.87 (d, $J=3.7$ Hz, 1H), 1.70–1.60 (m, 1H), 1.54–1.50 (m, 1H), 1.48–1.40 (m, 1H), 0.93 (t, $J=$ 7.2 Hz, 3H), 0.42 (s, 3H; $SiCH_3$), 0.36 ppm (s, 3H; $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=174.36$, 142.22, 140.10, 134.30, 131.52, 129.02, 128.55, 127.83, 121.84, 72.48, 53.77, 51.35, 28.55, 21.57, 14.20, −2.56, −2.59 ppm; IR (KBr): $\tilde{\nu}=3385$, 2968, 2930, 1730, 1715, 1427, 1379, 1366, 1248, 1161, 1109, 1011, 951, 831, 818, 773, 735, 703 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{28}O_3Si^{79}Br$: 435.0991 [M+H$^+$]; found: 435.0999.

Experimental procedure for the ester–imine condensation (10)

A solution of β-silylester **2a** (75.1 mg, 0.3 mmol) in anhydrous THF (3.0 mL) was added to an oven-dried Schlenk tube equipped with a stirrer bar. The solution was cooled to −78 °C and LDA (0.36 mL, 1.0 M in THF/hexanes, 1.2 equiv) was added dropwise over 10 min. After stirring at −78 °C for 30 min, a solution of (*E*)-*N*-benzylidene-1,1,1-trimethyl-silanamine (65 mg, 0.36 mmol) in anhydrous THF (0.5 mL) was added dropwise over 5 min. The mixture was stirred at −78 °C for 1 h, the cold bath was removed, and the mixture was allowed to slowly warm to RT. The mixture was stirred for 2 h at RT, then diluted with Et_2O (20 mL) and washed with 1.0 M HCl (3× 10 mL). The combined organic phases were dried over $MgSO_4$, fil-

tered, and concentrated under vacuum. The crude product was purified by flash column chromatography (1:10 ethyl acetate/hexane) to give **10** as white solid (61% yield; 98% *ee*). HPLC: Daicel Chiralpak AD-H column, hexane/isopropanol = 98:2, flow rate = 1.0 mL min^{-1}, $\lambda = 220$ nm, $t_R = 20.798$ (major), 27.731 min (minor); m.p. = 122–123 °C; $[\alpha]_D^{20} = +51.3$ ($c = 0.66$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.56$–7.53 (m, 2H; ArH), 7.39–7.31 (m, 8H; ArH), 5.90 (s, 1H), 4.78 (d, $J = 5.1$ Hz, 1H), 3.31 (ddd, $J = 12.5$, 5.1, 1.3 Hz, 1H), 0.98 (dq, $J = 12.5$, 7.1 Hz, 1H), 0.45 (s, 3H; $SiCH_3$), 0.39 (d, $J = 7.1$ Hz, 3H; CH_3), 0.36 ppm (s, 3H; $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.58$, 137.95, 137.93, 134.52, 128.94, 128.43, 128.33, 127.95, 127.65, 61.70, 55.83, 16.45, 13.71, −2.89, −3.86 ppm; IR (KBr): $\tilde{\nu} = 3406$, 1715, 1255, 1018, 833, 739, 721 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{30}NO_2Si$: 416.2046 [M+H$^+$]; found: 416.2047.

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Keywords: asymmetric synthesis · domino reactions · Grignard reagents · Michael addition · organosilanes

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