## Vinylogous Aldol Products from Chiral Crotylsilanes Obtained by Enantioselective Rh(II) and Cu(I) Carbenoid Si-H Insertion

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Enantioenriched homoallylic ethers containing a  $\alpha_{,\beta}$ -unsaturated ester (*syn*-vinylogous aldol products) were directly accessed by Lewis acid catalyzed crotylation utilizing chiral silane 2. The reagents were prepared by enantioselective Si-H insertion to an  $\alpha$ -diazovinylacetates using Davies' Rh<sub>2</sub>(DOSP)<sub>4</sub> catalyst or chiral Cu(I) Schiff base complex.

The asymmetric allylation and crotylation of aldehydes utilizing chiral allyl- and crotylmetal reagents as carbon nucleophiles remains an important and useful transformation in orgainc chemistry.<sup>1</sup> In that context, allylsilanes are widely used owing to their versatility, ease of handling, and low toxicity.<sup>2</sup> Well-documented studies from our laboratory have established chiral crotylsilane **1** as carbon nucleophiles in

highly diastereo- and enantioselective reactions with acetals and aldehydes to construct homoallylic ethers with an isolated E-olefin subunit (Scheme 1).<sup>3</sup>

Homoallylic ethers linked to an  $\alpha,\beta$ -unsaturated functional group can be further elaborated to construct amides, acids, and lactones. These "building blocks" possess extended functionality and therefore are likely to have utility in natural product and complex molecule synthesis.<sup>4</sup> Despite recent advances toward the synthesis of polypropionate-like subunits, reagents used to gain access to these structural types

## ABSTRACT



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have limited substrate scope.<sup>5</sup> In efforts to continue the development of chiral silane reagents capable of delivering useful levels of asymmetric induction, we report the synthesis of *syn*-homoallylic ethers linked to an  $\alpha$ , $\beta$ -unsaturated ester (vinylogous aldol products). The crotylation takes place with useful dr and ee utilizing chiral silane **2** (Scheme 1).

This study was initiated by establishing a reproducible asymmetric Si-H metal carbenoid insertion to synthesize chiral silane 2a. The known and readily available  $C_2$ symmetric copper(I) diimine complexes<sup>6</sup> were evaluated for their effectiveness in insertions to  $\alpha$ -diazovinylacetates. Although the idea of Cu(I) catalysis has been used to promote Si-H insertions prior to the application of rhodium catalysis,<sup>7,8</sup> the field remains underdeveloped, and few cases of asymmetric variants have been reported.<sup>9</sup> In that regard, we reported earlier useful levels of selectivity with  $\alpha$ -diazophenylacetates<sup>10</sup> and anticipated that we could extend the Cu(I) catalysis to  $\alpha$ -diazovinylacetates (Table 1, entries 1 and 2), thereby complementing Landais and Davies' earlier contributions,<sup>11</sup> who were the first to describe examples of Rh(II)promoted asymmetric Si-H insertion to α-diazovinylacetates. In this paper we report an efficient synthesis of chiral allylic silanes with C-centered chirality, and these experiments also allow a comparison of chiral Cu(I) vs Rh(II) catalysis. Consistent with Davies' studies, the Rh<sub>2</sub>(DOSP)<sub>4</sub> [(R)-6 and (S)-6] catalyst provided both enantiomers of crotylsilane **2a** in excellent ee (entry 3).<sup>12</sup>

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(12) For reaction modification and optimization, see Supporting Information.

**Table 1.** Preparation of (R)-2a Bearing a Dimethyl Phenyl Silyl Group<sup>c</sup>

	Me COOMe .	PhMe <sub>2</sub> SiH catalyst	Me ∕∕	COOM ŠiMe <sub>2</sub> Ph ( <b>R)-2a</b>	le
entry	catalyst	temp (°C)	solvent	yield $(\%)^a$	ee (%) <sup>b</sup>
1	( <b><i>R</i>,<i>R</i>)-5a</b> (5 mol %)	0	benzene	44 - 51	70-73
2	( <b><i>R</i>,<i>R</i>)-5b</b> (5 mol %)	0	benzene	45 - 55	78
3	(S)-6 (1–5 mol %)	-78	hexane	65 - 70	88 - 97

<sup>*a*</sup> Isolated yields were determined after purification over silica gel. <sup>*b*</sup> Based on HPLC data of silane alcohol, which was obtained from ester **2a** by LAH reduction. <sup>*c*</sup> When (S,S)-**5a** or (R)-**6** Rh<sub>2</sub>(R-DOSP)<sub>4</sub> was used, the opposite enantiomer was obtained in comparable yield and ee.



Once reproducible conditions for the insertion were found, our efforts turned to the use of the enantioenriched silane reagents in Lewis acid promoted reaction with in situ derived oxonium ions. Lewis acid and solvent screening results<sup>13</sup> suggested that TMSOTf and dicloromethane were the optimal choices. The crotylation generally resulted in high yields but moderate diastereoselectivity (Table 2). Measurements of ee

Table 2. Crotylation Using Silane (R)-2a

$\checkmark$	COOMe	RCHO TMSOMe (1	.1 equiv)	OMe		DOMe
	ŠiMe₂Ph ( <b>R)-2a</b>	TMSOTf (1 e -78 °C	equiv)	۰۰۰ <u>آ</u> 3	e	
entry	aldehyde		dr <sup>a</sup>	yield (%)	<sup>b</sup> ee (%) <sup>d</sup>	produc
1	benzaldehyde		3.5:1	79	ND	3a
<b>2</b> <sup>c</sup>	2,5-dimethoxyb	enzaldehyde	2.5:1	88	ND	3b
3	<i>p</i> -tolualdehyde		3.0:1	73	ND	3c
4	o-bromobenzak	dehyde	18:1	81	97	3d
5	<i>p</i> -bromobenzak	dehyde	4.2:1	83	ND	3e
6	o-nitrobenzalde	hyde	16:1	61	95	3f
7	hydrocinnamald	lehyde	4.0:1	71	91 <sup>e</sup>	3g
8	cyclohexanecar	boxaldebyde	5.0.1	63	ND	36

<sup>*a*</sup> Diastereomeric ratios (dr) were determined by <sup>1</sup>H NMR analysis on crude material. <sup>*b*</sup> Isolated yields after purification over silica gel. <sup>*c*</sup> Using 0.2 equiv of TMSOTf. <sup>*d*</sup> Selected data based on chiral HPLC, ND = not determined. <sup>*e*</sup> Using silane (S)-2a.

were carried by HPLC analysis, and select examples showed that the enantioenrichment of the silane reagent was fully transferred into vinylogous-aldol products and were obtained in up to 97% ee when the (*R*)-2a was used.

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<sup>(13)</sup> TMSOTf, BF<sub>3</sub>·OEt<sub>2</sub>, Sc(OTf)<sub>3</sub>, In(OTf)<sub>3</sub>, and TiCl<sub>4</sub> were screened as Lewis acid in the reaction with benzaldehyde and silane (R)-2a. Solvents screening included DCM, toluene, pentane, and THF.

As anticipated, the reaction favored the *syn* product, consistent with the well-established *anti*- $S_E'$  mode of addition,<sup>3</sup> where the steric destabilizing interaction between the aldehyde substituent and the vinyl methyl group on the allyl silane is minimized in an open transition state model. However, the magnitude of selectivity was dependent on the aldehyde type; activated aromatic aldehydes were less selective than those containing deactivating substituents (Table 2, entries **3b**, **3c** vs **3d**, **3e**, **3f**). Additionally, the position of substituents (*ortho*, *meta*, *para*) influenced the magnitude of diastereoselectivity; aldehydes containing an *ortho* deactivating group afforded excellent *syn/anti* ratios (**3d**, **3f**). In terms of aliphatic aldehydes, the branched substrate (**3h**) gave higher selectivity than the straight chain system (**3g**).

Efforts to improve the *syn*-selectivity of the crotylation by modification of the silane group were achieved, and eight racemic silane reagents with different nucleophilicities were prepared by carbene insertion.<sup>11b</sup> As such, *p*-tolualdehyde and *p*-bromobenzaldehyde were chosen as representative activated and deactivated aldehydes, respectively. As shown in Table 3, reaction of the anisyl derivative, which was

Table 3	Effect	of a	Silvl	Group	on	Simple	Diastereoselection
Table 5.	Littet	or a	Ollyr	Oroup	on	Simple	Diastereosciection

_	$\sim$	соом	e RCH TMS	10 SOMe (	OM 	e CO(	ОМе
	ŠiF <i>rac-</i>	R <sup>1</sup> R²R <sup>3</sup> 2	TMS -70	SOTf (1 °C	equiv)	/le <b>:-3</b>	
entry	silane	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	aldehyde c	onversion (%	o) <sup>a</sup> dr <sup>a</sup>
1	rac-2c	Me	Me	anisyl	p-tolualdehyde	100	2.8:1
2	rac-2c	Me	Me	anisyl	p-bromobenzaldehyd	e 80	3.0:1
3	rac-2d	Me	Me	TMS	p-tolualdehyde	100	3.2:1
4	rac-2d	Me	Me	TMS	p-bromobenzaldehyd	e 100	4.7:1
5	rac-2e	Me	TMS	TMS	<i>p</i> -tolualdehyde	100	3.0:1
6	rac-2e	Me	TMS	TMS	p-bromobenzaldehyd	e 100	3.5:1
7	rac-2f	Et	Et	Et	p-tolualdehyde	45	4.2:1
8	rac-2f	Et	Et	Et	p-bromobenzaldehyd	e 90	4.4:1
9	rac-2g	Bu	Bu	Bu	<i>p</i> -tolualdehyde	45	3.7:1
10	rac-2g	Bu	Bu	Bu	p-bromobenzaldehyd	e 91	4.1:1
11	rac-2h	hexyl	hexyl	hexyl	p-tolualdehyde	40	3.8:1
12	rac-2h	hexyl	hexyl	hexyl	p-bromobenzaldehyd	e 90	4.5:1
13 <sup>b</sup>	rac-2i	Ph	Ph	Ph	p-tolualdehyde	93	5.2:1
14 <sup>b</sup>	rac-2i	Ph	Ph	Ph	p-bromobenzaldehyd	e 95	6.8:1
15 <sup>b</sup>	rac-2j	TMS	TMS	TMS	<i>p</i> -tolualdehyde	95	>20:1
16 <sup>b</sup>	rac-2j	TMS	TMS	TMS	p-bromobenzaldehyd	e 98	>20:1

 $^a$  Conversion and syn/anti ratio were based on crude  $^1\rm H$  NMR.  $^b$  Reaction was carried out at -60 °C.

reported to have greater stability and enhanced nucleophilicity (compared to that of Ph),<sup>14</sup> led to slightly lower selectivity (entries 1 and 2). Increasing the nucleophilicity of silane by incorporating additional TMS groups showed no improvement (entries 3–6). For the cases of silane 2f-2h, the size of the silicon group did not alter the magnitude of selectivity, as three different alkyl silanes afforded similar levels (entries 7–12), although slightly enhanced with respect to silane **2a**. Gratifyingly, when silane reagents with decreased reactivity<sup>15</sup> were used, higher levels of selectivity were obtained. At –78 °C, reactions with triphenyl silane **2i** and trisTMS silane **2j** afforded less than 10% conversion after two days. However, increased temperature or concentration drove the reactions to completion with good selectivity (entries 13–16).

With useful levels of diastereoselectivity obtained in the racemic series, we turned to prepare enantioenriched silane reagents 2f-2j. Comparable selectivity was achieved with tributylsilane compared with dimethylphenyl silane (Table 4, entry 1). In contrast, Rh<sub>2</sub>(*S*-DOSP)<sub>4</sub> afforded  $2j^{16}$  with

Table 4. Enantioselective Si-H Insertion

	COOMeN2		R <sub>3</sub> SiH catalyst pentane	→ <sup>√</sup>		
entry	catalyst	$ m R_3SiH$	$temp\;(^{\circ}C)$	product	yield $(\%)^a$	ee (%) <sup>b</sup>
1	(S)-6	$n\mathrm{Bu}_3\mathrm{SiH}$	-78	( <b>R</b> )-2g	48	86
2	(S)-6	$\mathrm{TMS}_3\mathrm{SiH}$	-40	( <b>R</b> )-2j	30	40
3	(S)-6	$\mathrm{Ph}_3\mathrm{SiH}$	0	( <b>R</b> )-2i	NR	NR
$4^c$	( <b>R</b> , <b>R</b> )-5a	$\mathrm{Ph}_{3}\mathrm{SiH}$	0	( <i>R</i> )-2i	$41/25^{d}$	$70/97^d$

<sup>*a*</sup> Isolated yields were determined after purification over silica gel. <sup>*b*</sup> Based on HPLC data of silane alcohol, which was reduced from ester by using LAH. <sup>*c*</sup> Reaction run in benzene. <sup>*d*</sup> Yield and % ee before and after recrystallization from petroleum ether.

moderate ee (entry 2). Owing to the poor solubility of SiPh<sub>3</sub>H in pentane, the rhodium catalyst was ineffective for preparing enantioenriched **2i** (entry 3). Alternatively, our preliminary results showed that using Cu(MeCN)<sub>4</sub>BF<sub>4</sub> and diimine ligand complex (*R*,*R*)-**5a** afforded **2i** with good selectivity (>70% ee), which could be improved to 97% ee by recrystallization  $(2\times)$  from petroleum ether (entry 4).

We next explored the substrate scope with silanes 2i and 2g (Table 5). Crotylation with 2i and aromatic aldehydes gave useful levels of selectivity. However, with less reactive aliphatic aldehydes, only trace amounts of produts were observed spectroscopically. To solve this problem, we evaluated tri-*n*-butyl silane 2g, which exhibited selectivity slightly higher than that of silane 2a in the crotylation. Branched aliphatic aldehydes 3h-3l gave the homoallylic ethers with selectivity higher than that of aliphatic aldehydes 3g.

The parent silane 2a was converted to a primary TBDPS ether  $2b^{17}$  by reduction of the ester group and silylation of the resulting alcohol (two steps, 91% yield) in an attempt to increase selectivity. Subsequent reaction of 2b with a variety

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Table 5. Crotylation Using Chiral Silane (R)-2g and (R)-2i

	( <i>R</i> )-2g ( <i>R</i> )-2i:	COOMe 6iR" <sub>3</sub> : R"=Bu R"=Ph	RCHO TMSOR' (1 TMSOTf (1 -60 °C	.1 equiv) equiv) ►	R	OR'	coo	ЭМе
entr	y silane	aldehyde		TMSOR'	dr <sup>a</sup>	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>	product 3
1	( <i>R</i> )-2g	hydrocinnam	naldehyde	TMSOMe	5.3:1	57	ND	3g
2	( <i>R</i> )-2g	cyclohexane	carboxaldehyde	e TMSOMe	7.6:1	61	ND	3h
3	( <i>R</i> )-2g	isobutyralde	hyde	TMSOMe	6.6:1	41 <sup>c</sup>	ND	3i
4	( <i>R</i> )-2g	isobutyralde	hyde	TMSOBn	7.0:1	63	ND	3j
5	( <i>R</i> )-2g	trimethylace	taldehyde	TMSOMe	11:1	39 <sup>c</sup>	ND	3k
6	( <i>R</i> )-2g	trimethylace	taldehyde	TMSOBn	15:1	79	85	31
7	( <i>R</i> )-2i	benzaldehyd	le	TMSOMe	6.3:1	79	97	3a
8	( <i>R</i> )-2i	benzaldehyd	le	TMSOBn	6.4:1	68	ND	3m
9	( <i>R</i> )-2i	p-tolualdehy	de	TMSOMe	5.2:1	75	ND	3c
10	( <i>R</i> )-2i	p-bromoben:	zaldehyde	TMSOMe	6.8:1	67	ND	3e
11	( <i>R</i> )-2i	o-bromoben:	zaldehyde	гмзо	15:1	75	ND	3n

<sup>*a*</sup> Diastereomeric ratios were determined by <sup>1</sup>H NMR analysis on crude material. <sup>*b*</sup> Isolated yields after purification over silica gel. <sup>*c*</sup> Low yields due to volatility of products. <sup>*d*</sup> Selected data based on chiral HPLC, ND = not determined.

of aliphatic and aromatic aldehydes exhibited good to excellent *syn*-selectivity and typically good yields (Table 6). Notably, even the straight chain aliphatic systems (**4k**, **4l**), which normally gave poor diastereoselectivity, afforded satisfactory *syn/anti* ratios. Aliphatic aldehydes often produced tetrahydrofuran byproducts<sup>17a</sup> that were not observed with silane **2a**. This pathway was minimized by adding excess TMSOMe (3 equiv).

In summary, we have extended the use of Jacobsen's  $C_2$ symmetric copper(I) diimine complexes to carbene insertions with  $\alpha$ -diazovinylacetates, resulting in the formation of crotylsilanes bearing C-centered chirality with high enantioenrichment. The silanes described in this work complement our earlier work, affording vinylogous-aldol products (*syn*-polypoprionate building blocks) with high levels of diastereo- and enantioselectivity. Presently, the Davies' catalyst Rh<sub>2</sub>(DOSP)<sub>4</sub> provides slightly higher levels of Table 6. Crotylation Using Chiral Silane (R)-2b

	OTBDPS ŠiMe <sub>2</sub> Ph ( <b>R)-2b</b>	RCHO TMSOI TMSO <sup>-</sup> -78 °C	R' (1.1 equi Tf (1 equiv)	iv)	QR' R	کمی 4	OTBDPS
entry	aldehyde		TMSOR'	dr <sup>a</sup>	yield (%) <sup>b</sup>	ee (%) <sup>e</sup>	product 4
1 <sup>c</sup>	2,3-dimethoxybenza	aldehyde	TMSOMe	>20:1	92	ND	4a
<b>2</b> <sup>c</sup>	2,5-dimethoxybenza	aldehyde	TMSOMe	8:1	91	ND	4b
3	<i>p</i> -tolualdehyde		TMSOMe	11:1	79	ND	4c
4	benzaldehyde		TMSOMe	15:1	77	ND	4d
5	<i>p</i> -bromobenzaldehy	de	TMSOMe	16:1	55	ND	4e
6	o-bromobenzaldehy	de	TMSOMe	>20:1	58	ND	4f
7	2-naphthaldehyde		TMSOMe	10:1	73	ND	4g
<b>8</b> <sup>c</sup>	2,5-dimethoxybenza	aldehyde	TMSOBn	>20:1	87	ND	4h
9	benzaldehyde		TMSOBn	11:1	51	97	4i
10 <sup>d</sup>	cyclohexanecarbox	aldehyde	TMSOMe	>20:1	76	ND	4j
11 <sup>d</sup>	valeraldehyde		TMSOMe	>20:1	61	ND	4k
12 <sup>d</sup>	hydrocinnamaldehy	de	TMSOMe	16:1	47	ND	41
13	benzaldehyde	TI	MSO	>20:1	72	ND	4m
14	benzaldehyde	TI	мѕо	ND	trace	ND	4n

<sup>*a*</sup> Diastereomeric ratios were determined by <sup>1</sup>H NMR analysis on crude material. <sup>*b*</sup> Isolated yields after purification over silica gel. <sup>*c*</sup> Using 0.2 equiv of TMSOTf. <sup>*d*</sup> Using excess TMSOMe, see Supporting Information. <sup>*e*</sup> Selected data based on chiral HPLC, ND = not determined.

selectivity, and as such, development of more selective Cu(I) catalysts as an effective approach to chiral silane reagents and their use in complex molecule synthesis are currently underway and will be reported at a later time.

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**Supporting Information Available:** Experimental details and new selected spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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