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Vinylogous Aldol Products From Chiral Crotylsilanes Obtained By Enantioselective Rh(II) and Cu(I) Carbenoid Si-H Insertion

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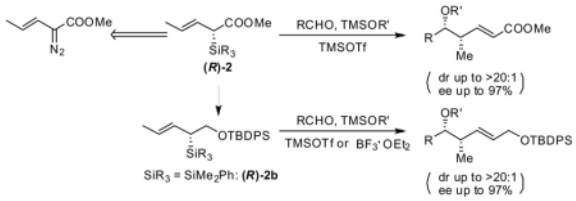
Abstract



Enantioenriched homoallylic ethers linked to an *α*,*β*-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 *α*-diazovinylacetates using Davies' $Rh_2(DOSP)_4$ 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. [1] In that context, allylsilanes are widely used, owing to their versatility, ease of handling and low toxicity. [2] 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). [3]

Homoallylic ethers linked to an *α*,*β*-unsaturated functional group can be further elaborated to construct amides, acids, and lactones. These "building blocks" possess exended functionality and therefore are likely to have utility in natural product and complex molecule synthesis.[4] Despite recent advances toward the synthesis of polypropionate-like subunits, reagents used to gain access to these structural-types have limited substrate scope.[5] 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 *α*,*β*-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 complexs[6] were evaluated for their effectiveness in insertions to *α*-diazovinylacetates. Although the idea of Cu(I) catalysis has been used to promote Si-H

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

insertions prior to the application of rhodium catalysis, [7, 8] the field remains under developed and few cases of asymmetric variants have been reported.[9] In that regard, we reported earlier that useful levels of selectivity with α-diazophenylacetates [10] and anticipated that we could extend the Cu(I) catalysis to α-diazovinylacetates (Table 1, entries 1 and 2), thereby complementing Landais and Davies' earlier contributions, [11] 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 $Rh_2(DOSP)_4$ [**(*R*)-6** and **(*S*)-6**] catalyst provided both enantiomers of crotylsilane **2a** in excellent ee (entry 3).[12]

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 [13] suggested that TMSOTf and dicloromethane were the optimal choices. The crotylation generally resulted in high yields but moderate diastereoselectivity (Table 2). Ee measurements 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.

As anticipated, the reaction favored the *syn* product, consistent with the well established *anti*-S_E' mode of addition,[3] where the steric destablizing 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 (*o*, *m*, *p*) 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.[11b] As such, *p*-tolualdehyde and *p*-bromobenzaldehyde were chosen respectively as representative activated and deactivated aldehydes. As shown in Table 3, reaction of anisyl derivative, which was reported to have greater stability and enhanced nucleophilicity (compared to Ph),[14] 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** to **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 [15] were used, higher levels of selectivity were obtained. At −78 °C, reactions with triphenyl silane **2i** and *Tris*TMS 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 prepared enantioenriched silane reagents **2f** to **2j**. Comparable selectivity was achieved with tributylsilane compared with dimethylphenyl silane (Table 4, entry 1). In contrast, Rh_2(*S*-DOSP)$_4$ afforded only moderate ee of **2j**[16] (entry 2). Owing to the poor solubility of $SiPh_3H$ in pentane, the rhodium catalyst was ineffective for preparing enantioenriched **2i** (entry 3). Alternatively, our preliminary results showed that using $Cu(MeCN)_4BF_4$ and diimine ligand

complex **(*R,R*)-5a** afforded **2i** with good selectivity (>70% ee), which could be improved to 97% ee by recrystallization (2x) 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 slightly higher selectivity than silane **2a** in the crotylation. Branched aliphatic aldehydes **3h-3l** gave the homoallylic ethers with higher selectivity than 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 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[17a] 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 α-diazovinylacetates, resulting in the formation of crotylsilanes bearing C-centered chirality with high enantioenrichment. The silanes described in this work complement our earlier work to afford vinylogous-aldol products (*syn*-polypoprionate building blocks) with high levels of diastereo- and enantioselectivity. Presently, the Davies' catalyst $Rh_2(DOSP)_4$ provides slightly higher levels of selectivity, 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 latter time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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12. For reaction modification and optimization, see Supporting Information.
13. TMSOTf, $BF_3{\cdot}OEt_2$, $Sc(OTf)_3$, $In(OTf)_3$, $TiCl_4$ were screened as Lewis acid in the reaction with benzaldehyde and silane **(*R*)-2a**. Solvents screening included DCM, toluene, pentane and THF.
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16. Freeze pump thaw degassed pentane was required to avoid oxidation of TTMSSH.
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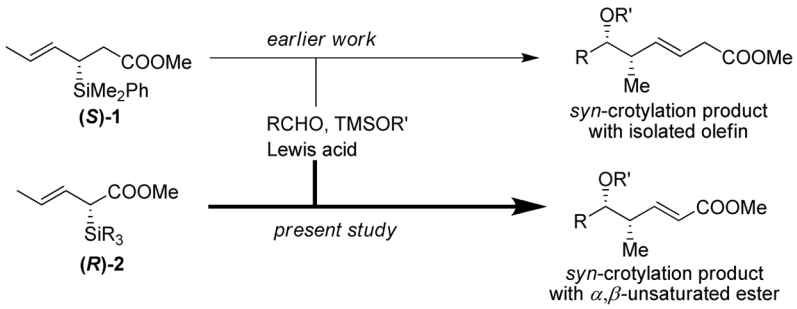
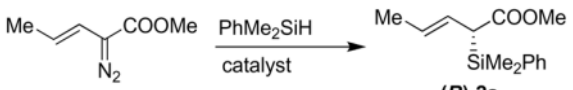


Scheme 1.
Complementary Chrial Silane Reagents

Table 1

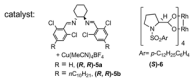
Preparation of **(*R*)-2a** Bearing Dimethyl Phenyl Silyl Group[c]



(*R*)-2a

entry	catalyst	temperature (°C)	solvent	yield (%)[a]	ee (%)[b]
1	**(*R*, *R*)-5a** (5 mol %)	0	benzene	44–51	70–73
2	**(*R*, *R*)-5b** (5 mol %)	0	benzene	45–55	78
3	**(*S*)-6** (1–5 mol %)	−78	hexane	65–70	88–97

catalyst:



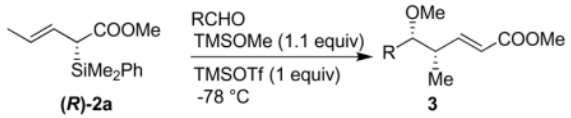
[a]Isolated yields were determined after purification over silica gel.

[b]Based on HPLC data of silane alcohol, which was reduced from ester **2a** by using LAH.

[c]When **(*S*, *S*)-5a** or **(*R*)-6** Rh_2(*R*-DOSP)$_4$ was used, the opposite enantiomer was obtained in comparable yield and ee.

Table 2

Crotylation Using Silane **(*R*)-2a**



entry	aldehyde	dr[a]	yield (%)[b]	ee (%)[d]	product 3
1	benzaldehyde	3.5:1	79	ND	**3a**
2[c]	2,5-dimethoxybenzaldehyde	2.5:1	88	ND	**3b**
3	*p*-tolualdehyde	3.0:1	73	ND	**3c**
4	*o*-bromobenzaldehyde	18:1	81	97	**3d**
5	*p*-bromobenzaldehyde	4.2:1	83	ND	**3e**
6	*o*-nitrobenzaldehyde	16:1	61	95	**3f**
7	hydrocinnamaldehyde	4.0:1	71	91[e]	**3g**
8	cyclohexanecarboxaldehyde	5.0:1	63	ND	**3h**

[a] Diastereomeric ratios (dr) were determined by ^{1}H NMR analysis on crude material.

[b] Isolated yields after purification over silica gel.

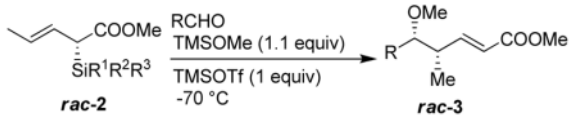
[c] Using TMSOTf 0.2 equiv.

[d] Selected data basded on chiral HPLC.

[e] Using silane **(*S*)-2a**.

Table 3

Effect of Silyl Group on Simple Diastereoselection



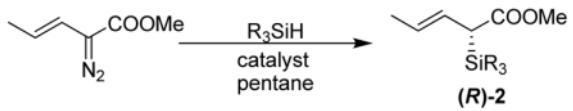
entry	silane	R^1	R^2	R^3	aldehyde	conversion (%)[a]	dr[a]
1	***rac*-2c**	Me	Me	anisyl	*p*-tolualdehyde	100	2.8:1
2	***rac*-2c**	Me	Me	anisyl	*p*-bromobenzaldehyde	80	3.0:1
3	***rac*-2d**	Me	Me	TMS	*p*-tolualdehyde	100	3.2:1
4	***rac*-2d**	Me	Me	TMS	*p*-bromobenzaldehyde	100	4.7:1
5	***rac*-2e**	Me	TMS	TMS	*p*-tolualdehyde	100	3.0:1
6	***rac*-2e**	Me	TMS	TMS	*p*-bromobenzaldehyde	100	3.5:1
7	***rac*-2f**	Et	Et	Et	*p*-tolualdehyde	45	4.2:1
8	***rac*-2f**	Et	Et	Et	*p*-bromobenzaldehyde	90	4.4:1
9	***rac*-2g**	Bu	Bu	Bu	*p*-tolualdehyde	45	3.7:1
10	***rac*-2g**	Bu	Bu	Bu	*p*-bromobenzaldehyde	91	4.1:1
11	***rac*-2h**	hexyl	hexyl	hexyl	*p*-tolualdehyde	40	3.8:1
12	***rac*-2h**	hexyl	hexyl	hexyl	*p*-bromobenzaldehyde	90	4.5:1
13[b]	***rac*-2i**	Ph	Ph	Ph	*p*-tolualdehyde	93	5.2:1
14[b]	***rac*-2i**	Ph	Ph	Ph	*p*-bromobenzaldehyde	95	6.8:1
15[b]	***rac*-2j**	TMS	TMS	TMS	*p*-tolualdehyde	95	>20:1
16[b]	***rac*-2j**	TMS	TMS	TMS	*p*-bromobenzaldehyde	98	>20:1

[a] Conversion, *syn*/*anti* ratio were based on crude ^{1}H NMR.

[b] Reaction was carried out at −60 °C.

Table 4

Enantioselective Si-H Insertion



(*R*)-2

entry	catalyst	R_3SiH	temperature (°C)	product	yield (%)[a]	ee (%)[b]
1	**(*S*)-6**	$n Bu_3SiH$	−78	**(*R*)-2g**	48	86
2	**(*S*)-6**	TMS_3SiH	−40	**(*R*)-2j**	30	40
3	**(*S*)-6**	Ph_3SiH	0	**(*R*)-2i**	NR	NR
4[c]	**(*R*,*R*)-5a**	Ph_3SiH	0	**(*R*)-2i**	41/25[d]	70/97[d]

[a] Isolated yields were determined after purification over silica gel.

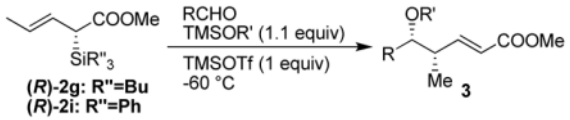
[b] Based on HPLC data of silane alcohol, which was reduced from ester by using LAH.

[c] Reaction run in benzene.

[d] Yield and % ee before and after recrystallization from petroleum ether.

Table 5

Crotylation Using Chiral Silane **(*R*)-2g** and **(*R*)-2i**



entry	silane	aldehyde	TMSOR′	dr[a]	yield (%)[b]	ee (%)[d]	product 3
1	**(*R*)-2g**	hydrocinnamaldehyde	TMSOMe	5.3:1	57	ND	**3g**
2	**(*R*)-2g**	cyclohexanecarboxaldehyde	TMSOMe	7.6:1	61	ND	**3h**
3	**(*R*)-2g**	isobutyraldehyde	TMSOMe	6.6:1	41[c]	ND	**3i**
4	**(*R*)-2g**	isobutyraldehyde	TMSOBn	7.0:1	63	ND	**3j**
5	**(*R*)-2g**	trimethylacetaldehyde	TMSOMe	11:1	39[c]	ND	**3k**
6	**(*R*)-2g**	trimethylacetaldehyde	TMSOBn	15:1	79	85	**31**
7	**(*R*)-2i**	benzaldehyde	TMSOMe	6.3:1	79	97	**3a**
8	**(*R*)-2i**	benzaldehyde	TMSOBn	6.4:1	68	ND	**3m**
9	**(*R*)-2i**	*p*-tolualdehyde	TMSOMe	5.2:1	75	ND	**3c**
10	**(*R*)-2i**	*p*-bromobenzaldehyde	TMSOMe	6.8:1	67	ND	**3e**
11	**(*R*)-2i**	*o*-bromobenzaldehyde	TMSO	15:1	75	ND	**3n**

[a] Diastereomeric ratios were determined by ^{1}H NMR analysis on crude material.

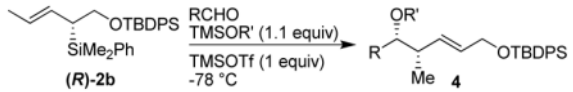
[b] Isolated yields after purification over silica gel.

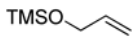
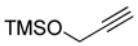
[c] Low yields due to volatility of products.

[d] Selected data basded on chiral HPLC, ND = not determoned.

Table 6

Crotylation Using Chiral Silane **(*R*)-2b**



entry	aldehyde	TMSOR′	dr[a]	yield (%)[b]	ee (%)[e]	product 4
1[c]	2,3-dimethoxybenzaldehyde	TMSOMe	>20:1	92	ND	**4a**
2[c]	2,5-dimethoxybenzaldehyde	TMSOMe	8:1	91	ND	**4b**
3	*p*-tolualdehyde	TMSOMe	11:1	79	ND	**4c**
4	benzaldehyde	TMSOMe	15:1	77	ND	**4d**
5	*p*-bromobenzaldehyde	TMSOMe	16:1	55	ND	**4e**
6	*o*-bromobenzaldehyde	TMSOMe	>20:1	58	ND	**4f**
7	2-naphthaldehyde	TMSOMe	10:1	73	ND	**4g**
8[c]	2,5-dimethoxybenzaldehyde	TMSOBn	>20:1	87	ND	**4h**
9	benzaldehyde	TMSOBn	11:1	51	97	**4i**
10[d]	cyclohexanecarboxaldehyde	TMSOMe	>20:1	76	ND	**4j**
11[d]	valeraldehyde	TMSOMe	>20:1	61	ND	**4k**
12[d]	hydrocinnamaldehyde	TMSOMe	16:1	47	ND	**4l**
13	benzaldehyde		>20:1	72	ND	**4m**
14	benzaldehyde		ND	trace	ND	**4n**

[a] Diastereomeric ratios were determined by ^{1}H NMR analysis on crude material.

[b] Isolated yields after purification over silica gel.

[c] Using TMSOTf 0.2 equiv.

[d] Using excess TMSOMe, see Supporting Information.

[e] Selected data basded on chiral HPLC, ND = not determined.