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Stereoselective synthesis of *trans*-olefins by the copper-mediated S_N2' reaction of vinyl oxazines with Grignard reagents. Asymmetric synthesis of D-*threo*-sphingosines

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Abstract—The S_N2' reaction of 6-vinyl-5,6-dihydro-4*H*-[1,3]oxazines with Grignard reagents in the presence of CuCN was studied, and high trans selectivity for the formation of double bond was observed with a variety of RMgX. The S_N2' reaction, coupled with regioselective asymmetric aminohydroxylation reaction, provided a highly efficient route for the asymmetric synthesis of D-*threo*-*N*-acetylsphingosine.

2-Vinyloxiranes,[1] 5-vinyloxazolines/oxazolidinones,[2] and 2-vinylaziridines[3] are versatile synthetic intermediates in organic synthesis, and have been extensively studied. These compounds have been shown to undergo a variety of different reactions, depending upon their structures, the nature of reagents used, and reaction conditions. For example, 2-vinyloxiranes react with alkyl lithiums in the presence of $BF_3{\cdot}OEt_2$[1f] or Grignard reagents[1k] to give the S_N2 products, whereas their reactions with organocopper reagents afford the S_N2' products.[1i] Also known is that 2-vinyloxiranes and 5-vinyloxazolines/oxazolidinones can react with transition metal complexes to form transition metal–π-allyl intermediates, which in turn react with nucleophiles to furnish 'branched' and 'linear' products.[1d,j,2]

We recently reported a convenient route for the asymmetric synthesis of 6-vinyl-5,6-dihydro-4*H*-[1,3]oxazines **I**.[4] By comparing the structures of **I**, 2-vinyloxiranes, and 5-vinyloxazolines/oxazolidinones, it was noticed that they all shared two common structural features, the terminal vinyl group and the good leaving ability at the allylic position, and thus should exhibit similar reactivity patterns (reaction paths c–g, Fig. 1). In addition, after deprotonation by a base, **I** can react with an electrophile to give a higher homolog (reaction path a in Fig. 1).[5] Compound **I** may also undergo a formal [3,3]-rearrangement to *N*-acetyl protected piperidine derivatives under appropriate reaction conditions (reaction path b in Fig. 1).[6] Despite such synthetic versatility, the chemistry of the vinyl oxazine **I** has not been explored much to date. In this Letter, we report the novel S_N2' reaction of vinyl oxazines **I** with Grignard reagents in the presence of CuCN, which proceeds with high trans selectivity for double bond formation.[7] Also reported is an efficient asymmetric synthesis of D-*threo*-*N*-acetyl-sphingosine, which utilizes the developed S_N2' reaction and regioselective asymmetric aminohydroxylation reaction[8] to stereoselectively introduce the requisite

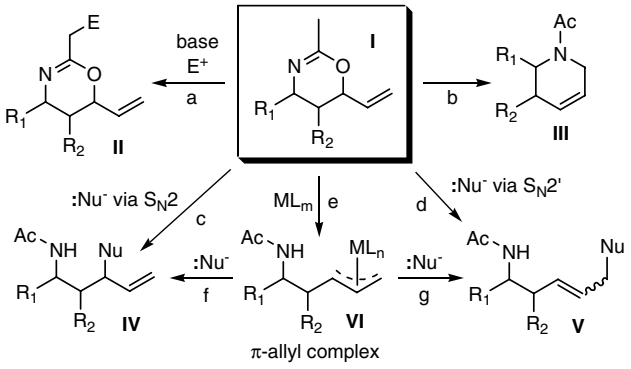

Figure 1. Potential reactions of the 6-vinyl-5,6-dihydro-4*H*-[1,3]oxazines **I**.

Keywords: Sphingosine; Regioselective asymmetric aminohydroxylation; Oxazine; S_N2' Reaction; Grignard reagents.
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trans double bond and vicinal aminoalcohol functionalities, respectively.

As shown in Figure 2, the vinyl oxazines may exist in two conformers **I** and **I′**. Assuming that the reaction of the vinyl oxazines with soft nucleophiles proceeds through S_N2' mechanism, conformer **I** should lead to trans double bond formation, while cis double bond formation is expected from conformer **I′**. Due to steric repulsion between the terminal $=CH_2$ group and R_2 in conformer **I′**, conformer **I** would be more stable and thus more abundant in the equilibrium. Furthermore, attack of a soft nucleophile on conformer **I′** would be kinetically less favorable due to the steric hindrance between the R_2 and the incoming nucleophile. Therefore, trans selectivity is anticipated from the reaction between the vinyl oxazines and soft nucleophiles such as Grignard reagents in the presence of CuCN.

Scheme 1 describes the asymmetric synthesis of vinyl oxazines **4**–**6**, which commenced with achiral α,β-unsaturated ester **1**. Compound **1** was converted to the common synthetic precursor **2** for vinyl oxazines **4**–**6** according to the literature procedure, which included a four step reaction sequence of regioselective asymmetric aminohydroxylation, PMB-protection, DIBAL reduction, and vinylation.[4] Alcohol **2** was obtained as a 5:1 mixture of **3** and its C3 epimer. Treatment of **2** with mesyl chloride in the presence of excess triethylamine at 0 °C directly afforded oxazine **4**.

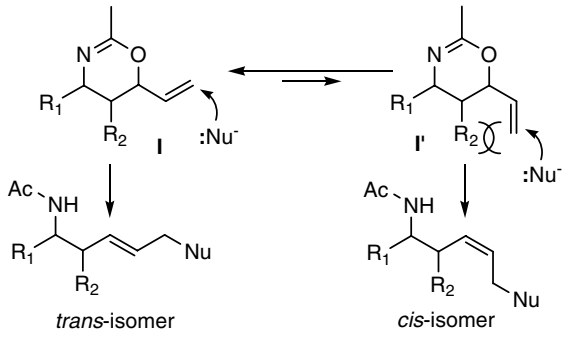
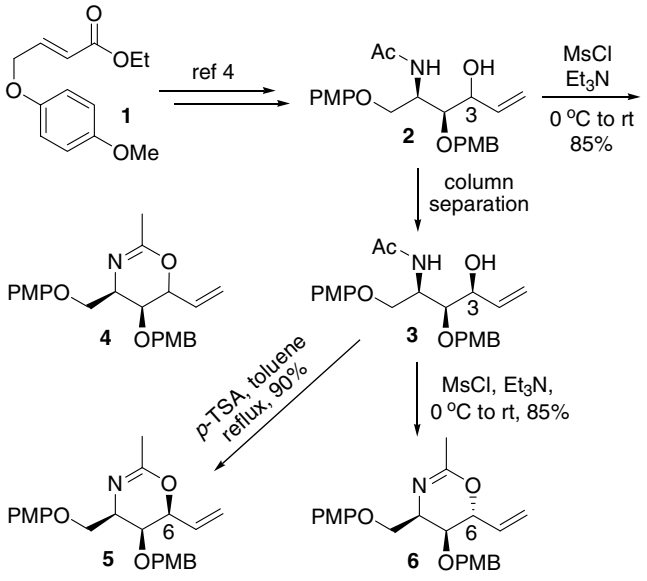


Figure 2. Cis and trans selectivities of the S_N2' reaction.



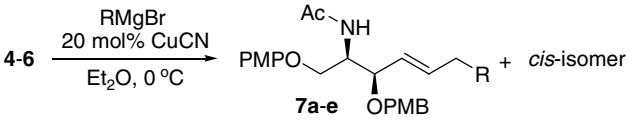
Scheme 1. Asymmetric synthesis of vinyl oxazines **4**–**6**.

As a proof of our approach, the reaction of oxazine **4** with dodecylmagnesium bromide in the presence of 20 mol % (relative to the amount of the Grignard reagent used) CuCN was attempted. Gratifyingly, the reaction proceeded well to provide the protected D-*threo*-C_{18}-sphingosine **7a** in a good yield and with a high trans:cis selectivity (~10:1) (Table 1, entry 1).[9] CuCN was found to be crucial for the reaction, since no reaction was observed in the absence of CuCN.

Next, it was reasoned that the stereochemistry at the allylic position (C6 of the oxazine ring) might also influence on the stereochemical outcome of the reaction. Thus, the optically pure vinyl oxazines **5** and **6** were prepared from alcohol **3**, which was obtained from **2** by column separation (Scheme 1). Refluxing **3** in the presence of a catalytic amount of *p*-toluenesulfonic acid in toluene furnished vinyl oxazine **5** with retention of the configuration at C6.[4] On the other hand, treatment of **3** with mesyl chloride and excess Et_3N generated vinyl oxazine **6** with the inverted C6 configuration.[4] When vinyl oxazines **5** and **6** were subjected to the above reaction conditions, indeed, they showed different trans:cis selectivities in the formation of the protected D-*threo*-C_{18}-sphingosine product, with **5** being more trans selective (>15:1) than **6** (~8:1) (Table 1, entries 2–3).

The different trans selectivities of two C6 epimeric vinyl oxazines **5** and **6** in the S_N2' reactions may be rationalized by considering the equilibriums between conformers **VII** and **VII′** for **6**, and between conformers **VIII** and **VIII′** for **5** (Fig. 3). Due to steric repulsion caused by the *endo* terminal $=CH_2$ group, conformers **VII** and **VIII** will be more stable than conformers **VII′** and

Table 1. S_N2' Reactions of vinyl oxazines **4**–**6** with Grignard reagents in the presence of CuCN in ethyl ether at 0 °C



Entry	Oxazines	Product	R=	Yields (%)	Trans:cis[a]
1	**4**	**7a**	$-(CH_2)_{11}CH_3$	82	~10:1
2	**6**	**7a**	$-(CH_2)_{11}CH_3$	80	8:1
3	**5**	**7a**	$-(CH_2)_{11}CH_3$	85	>15:1
4	**5**	**7b**	$-CH_2CH_3$	50	>15:1
5	**5**	**7c**	$-(CH_2)_4CH_3$	80	>15:1
6	**5**	**7d**	$-(CH_2)_9CH_3$	82	>15:1
7	**5**	**7e**	$-(CH_2)_{13}CH_3$	82	>15:1
8	**5**	—	$-CH(CH_3)_2$	NR[b]	

[a] The ratio of trans:cis was determined by the ^1H NMR of the reaction mixture.

[b] NR: no reaction.

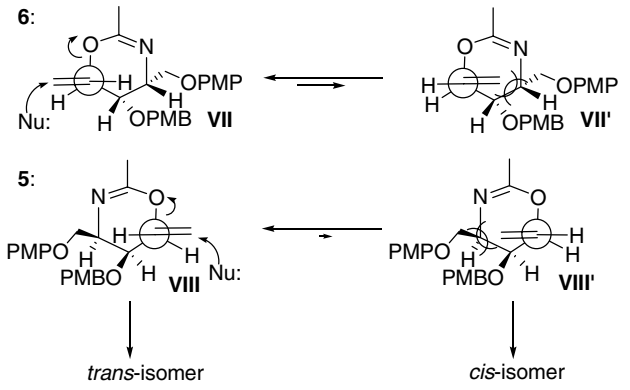
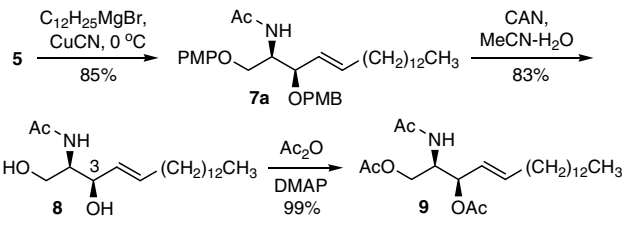


Figure 3. A plausible explanation for the trans selectivity of the S_N2' reaction of the vinyl oxazines **5** and **6**.

VIII′. Such steric hindrance will be particularly severe in conformer **VIII′**, where both $PMPOCH_2$- and PMBO-groups are in close proximity to the *endo* terminal $=CH_2$ group. This will shift the equilibrium for **5** toward conformer **VIII** more relative to the equilibrium for **6**. Moreover, approach of the nucleophile to conformers **VII′** and **VIII′** for the S_N2' reaction would be severely retarded due to the steric hindrance between the incoming nucleophile and the oxazine ring, and the up-stereochemistry of both $PMPOCH_2$- and PMBO-groups in conformer **VIII′** would further disfavor such approach of the nucleophile. Therefore, **5** should be more trans selective than **6**.

Now with the right C6 stereochemistry and reaction conditions established, the generality of the S_N2' reaction was examined with vinyl oxazine **5** and Grignard reagents with different chain length (C_2–C_{14}) in the presence of 20 mol % CuCN. As shown in Table 1, all linear chain Grignard reagents produced the corresponding protected D-*threo*-sphingosines (**7a**–**e**)[10] with excellent trans selectivities and good reaction yields (entries 3–7). However, a branched Grignard reagent failed to react (entry 8), and PhMgBr and vinyl-MgBr did not react under the conditions. Use of other cuprate reagents such as Gilman's and higher-order cuprates, which contain branched alkyl groups, also proved to be fruitless.[11]

The developed S_N2' reaction can be easily applied to the asymmetric synthesis of sphingosines, which are ubiquitous membrane constituents of eukaryotic cells and have been reported to exhibit a variety of structural and regulatory functions.[12,13] Scheme 2 describes the asymmetric synthesis of D-*threo*-*N*-acetyl-C_{18}-sphingosine (**8**). Thus, the trans selective S_N2' reaction of oxazine **5** with



Scheme 2. Asymmetric synthesis of D-*threo*-*N*-acetylsphingosine (**8**).

$C_{11}H_{23}MgBr$ in the presence of 20 mol % CuCN produced **7a**. Deprotection of both PMP- and PMB-groups by ceric ammonium nitrate (CAN)[14] in acetonitrile–water (4:1) provided D-*threo*-*N*-acetyl-C_{18}-sphingosine (**8**), whose structure was confirmed by converting it to triacetate **9** and comparing with the corresponding known compound.[15] Finally, it is worthwhile mentioning that given the fact that the C3 stereochemistry of sphingosines can be easily controlled,[16] the corresponding L-*erythro*-*N*-acetyl-C_{18}-sphingosine should be synthesized by applying the same synthetic route.

In conclusion, we have demonstrated that the reaction of the vinyl oxazines with Grignard reagents in the presence of CuCN proceeded via the S_N2' mechanism, and excellent trans selectivity for the formation of double bond was observed. Also described was that the developed S_N2' reaction, combined with the regioselective asymmetric aminohydroxylation reaction of olefins, could provide an efficient and convenient asymmetric route for the synthesis of sphingosine derivatives. Studies toward other possible reactions of the vinyl oxazines are currently under progress in our laboratory, and will be reported in due course.

Acknowledgements

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9. *General procedure for the copper-mediated S_N2' reaction of vinyl oxazine with Grignard reagents*: A flame dried two-necked flask was charged with cuprous cyanide (8.5 mg, 0.1 mmol) and dry ether (10 mL) under nitrogen atmosphere. The reaction flask was cooled to 0 °C in ice–salt mixture and a solution of Grignard reagent in ether (1 M, 0.5 mL, 0.5 mmol) was added dropwise. After stirring for 10 min, a solution of vinyl oxazine (79 mg, 0.2 mmol) in ether was added dropwise through cannula for 10 min. The reaction mixture was stirred for an additional hour, and then brought to room temperature and stirred for another 1 h. After the complete disappearance of the starting material on TLC, the brownish reaction mixture was quenched with saturated ammonium chloride, extracted with ethyl ether (3×20 mL), washed with water, and dried over anhydrous sodium sulfate. The solvents were removed in vacuo and the residue was purified by flash column chromatography on silica gel (ethyl acetate–hexane, 3:1) to afford the respective protected *N*-acetyl-sphingosines **7a**–**e**.
10. *Characterization data* **7a**: Mp = 62–63 °C; $[\alpha]_D^{25}$ −44.5 (*c* 1.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, 2H, $J = 9.0$ Hz), 6.82–6.81 (m, 6H), 5.86 (d, 1H, $J = 8.6$ Hz), 5.73 (dt, 1H, $J = 7.0$, 16.0 Hz), 5.41 (dd, 1H, $J = 8.0$, 15.6 Hz), 4.53 (d, 1H, $J = 10.5$ Hz), 4.31–4.25 (m, 2H), 4.13 (dd, 1H, $J = 3.0$, 8.0 Hz), 3.97–3.90 (m, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 2.07 (q, 2H, $J = 7.4$ Hz), 1.99 (s, 3H), 1.44–1.35 (m, 2H), 1.26 (s, 20H), 0.88 (t, 3H, $J = 6.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.78, 159.29, 154.05, 152.78, 135.99, 130.29, 129.43, 126.60, 115.64, 114.67, 113.78, 70.04, 66.84, 55.67, 55.14, 52.28, 32.24, 31.84, 29.59, 29.42, 29.14, 23.15, 22.57, 13.93. Compound **7b**: $[\alpha]_D^{25}$ −50.0 (*c* 1.3, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, 2H, $J = 9.0$ Hz), 6.82–6.80 (m, 6H), 5.88 (d, 1H, $J = 8.8$ Hz), 5.73 (dt, 1H, $J = 6.4$, 15.4 Hz), 5.42 (dd, 1H, $J = 7.6$, 15.6 Hz), 4.54 (d, 1H, $J = 11.5$ Hz), 4.32–4.25 (m, 2H), 4.14 (dd, 1H, $J = 3.0$, 8.0 Hz), 3.97–3.91 (m, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 2.08–2.04 (m, 2H), 1.99 (s, 3H), 1.42 (d hexate, 2H, $J = 1.5$, 7.0 Hz), 0.91 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.77, 159.29, 154.05, 152.78, 135.61, 130.29, 129.43, 126.88, 115.64, 114.69, 113.80, 76.69, 70.06, 66.86, 55.69, 55.15, 52.30, 34.29, 23.18, 22.25, 13.49. Compound **7c**: mp = 40–41 °C; $[\alpha]_D^{25}$ −59.7 (*c* 1.3, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, 2H, $J = 8.5$ Hz), 6.82–6.80 (m, 6H), 5.87 (d, 1H, $J = 8.7$ Hz), 5.73 (dt, 1H, $J = 6.5$, 15.4 Hz), 5.41 (dd, 1H, $J = 8.5$, 15.6 Hz), 4.53 (d, 1H, $J = 12$ Hz), 4.32–4.25 (m, 2H), 4.13 (dd, 1H, $J = 3.0$, 8.5 Hz), 3.97–3.90 (m, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 2.11–2.04 (m, 2H), 1.99 (s, 3H), 1.40–1.35 (m, 2H), 1.32–1.25 (m, 6H), 0.89 (t, 3H, $J = 6.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.80, 159.32, 154.10, 152.83, 136.00, 130.35, 129.46, 126.68, 115.69, 114.72, 113.83, 76.77, 70.09, 66.89, 55.72, 55.20, 52.33, 32.27, 31.64, 29.12, 28.79, 23.23, 22.55, 13.98. Compound **7d**: mp = 49–50 °C; $[\alpha]_D^{25}$ −46.89 (*c* 1.22, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, 2H, $J = 8.9$ Hz), 6.82–6.81 (m, 6H), 5.85 (d, 1H, $J = 8.7$ Hz), 5.73 (dt, 1H, $J = 6.0$, 15.5 Hz), 5.41 (dd, 1H, $J = 8.1$, 15.6 Hz), 4.53 (d, 1H, $J = 11.3$ Hz), 4.31–4.25 (m, 2H), 4.13 (dd, 1H, $J = 3.0$, 8.0 Hz), 3.97–3.90 (m, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 2.07 (q, 2H, $J = 7.2$ Hz), 1.99 (s, 3H), 1.41–1.35 (m, 2H), 1.26 (s, 16H), 0.88 (t, 3H, $J = 6.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.97, 159.17, 153.88, 152.63, 136.24, 130.16, 129.53, 129.40, 126.39, 115.49, 114.54, 113.72, 69.93, 66.57, 55.67, 55.19, 52.18, 32.34, 31.90, 29.64, 29.48, 29.35, 29.17, 23.36, 22.67, 14.11. Compound **7e**: mp = 67–68 °C; $[\alpha]_D^{25}$ −40.5 (*c* 1.2, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, 2H, $J = 8.2$ Hz), 6.82–6.81 (m, 6H), 5.84 (d, 1H, $J = 8.5$ Hz), 5.73 (dt, 1H, $J = 6.7$, 15.5 Hz), 5.41 (dd, 1H, $J = 7.6$, 15.6 Hz), 4.53 (d, 1H, $J = 11.0$ Hz), 4.31–4.25 (m, 2H), 4.13 (dd, 1H, $J = 3.0$, 7.5 Hz), 3.97–3.90 (m, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 2.07 (q, 2H, $J = 7.4$ Hz), 1.99 (s, 3H), 1.41–1.35 (m, 2H), 1.26 (s, 24H), 0.88 (t, 3H, $J = 6.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.81, 159.35, 154.12, 152.84, 136.07, 130.37, 129.49, 126.67, 115.70, 114.75, 113.86, 76.79, 70.12, 66.91, 55.75, 55.23, 52.34, 32.32, 31.92, 29.69, 29.50, 29.22, 23.28, 22.67, 14.03.
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