Intermolecular Stereoselective Alkenylation of Chiral
N-Acylpyrrolidinium Ions

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Vinylation of the three cyclic, optically active N-acetylpyrrolidinium ions 5, 8 and 12 with the vinylcopper reagent 2-methyl-1-propenylcopper displays a moderate-to-high trans selectivity with respect to the ring substituents. The absolute configuration of the vinylated products has been confirmed by ozonolysis of the double bond and subsequent degradation to the known amino acids (2S,5S)-pyrrolidine-2,5-dicarboxylic acid, trans-4-hydroxy-L-proline, and trans-3-hydroxy-D-proline.

N-Acyliminium ions are useful intermediates in organic synthesis. The reaction of such nitrogen-stabilized cations with various nucleophiles has been used as the key carbon–carbon bond forming step in the synthesis of many naturally occurring nitrogen-containing compounds, in particular alkaloids. However, synthetic approaches to amines containing a β-hydroxy function, as exemplified by the naturally occurring substances slaframidine (1), swainsonine (2) and castanospermine (3) require a nucleophile containing an oxygen functionality on the nucleophile carbon if the amidokylation strategy is to be applied. Our interest in the synthesis of alkaloids using the amidokylation strategy in an intermolecular fashion prompted us to explore the possibility of using an α-functionalized nucleophile as an entry into the above alkaloids. Few such nucleophiles have been used; one example has been reported by Yamamoto and coworkers who used a γ-oxygenated allyltin reagent as the nucleophile to produce β-aminooalcohols.

After some consideration we selected the vinyl group since it, if it can be introduced as the nucleophile, can easily be transformed into the desired oxygen functionality. Intermolecular amidokylation using olefinic nucleophiles generally requires vigorous reaction conditions often incompatible with highly functionalized, chiral N-acyliminium ions. On the other hand, intramolecular vinylation

has been performed under less strenuous reaction conditions, using olefinic nucleophiles carrying cation-stabilizing groups such as a dithioacetal or a silyl group. One example involving an intermolecular vinylation was recently published by Ley and coworkers who reported on the facile vinylation of α-benzencesulfonyl amides using vinylzinc reagents. Another example of a functionalized nucleophile used in an intermolecular fashion is bis(trimethylsilyl)acetylene, reported by Hacksell and coworkers.

Of vital importance for the amidokylation to be a practical synthetic tool in the synthesis of complex molecules, is the control, or at least predictability of the stereoselective outcome of the reaction. We recently reported on the stereoselective alkylation of N-acyliminium ions using vinylcopper reagents. In this report we show that vinylcopper reagents are equally efficient and selective nucleophiles. The stereoselectivity of addition of vinylcopper reagents was studied using the chiral N-acyliminium ions 5, 8 and 12 as substrates. Nucleophilic addition to these

N-acyliminium ions (R = TBDMS) has been reported to give predominantly cis addition using traditional α-nucleophiles such as allyltrimethylsilane with varying degrees of stereoselectivity. In contrast, nucleophilic addition to 12 (R = Ac) has been reported to give selectively trans addition. Alkylation of 5 with vinylcopper reagents also proceeds with a high degree of trans selectivity.

Results and discussion

2-Methyl-1-propenylcopper (4) was chosen as the vinyl component because of its ease of preparation from the corresponding organolithium compound and its relative
Table 1. Stereoselectivity in the reaction of 5 with various nucleophiles.

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Lewis acid</th>
<th>cis : trans</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allyltrimethylsilane</td>
<td>TiCl₄</td>
<td>72 : 28</td>
<td>74</td>
<td>10</td>
</tr>
<tr>
<td>Isopropenyl acetate</td>
<td>BF₃·Et₂O</td>
<td>70 : 30</td>
<td>65</td>
<td>10</td>
</tr>
<tr>
<td>Propylocopper</td>
<td>BF₃·Et₂O</td>
<td>3 : 97</td>
<td>75</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>BF₃·Et₂O</td>
<td>6 : 94</td>
<td>83</td>
<td>This work</td>
</tr>
</tbody>
</table>

stability. Treatment of 5a with 2 equiv. each of 4 and BF₃ at −78 °C gave a 94:6 mixture of the vinyl compounds 6a and 6b (Table 1). After purification by column chromatography, the stereochemistry of the major product 6a was determined by conversion into the known amino acid 7c (Scheme 1). Thus, ozonolysis of 6a gave the aldehyde 7a in 92% yield. Sequential treatment of 7a with pyridinium dichromate (PDC) in DMF and aqueous 6 M HCl gave trans-2,5-pyrrolinedicarboxylic acid 7c in enantiomerically pure form.

The N-acyliminium ion 8 undergoes highly selective cis addition of nucleophiles, in particular if the O-protective group is a silyl group (TBDMS). The corresponding O-acetyl compound shows a somewhat lower degree of cis selectivity. Although the origin of this high selectivity is not entirely understood, it is interesting to note that the N-acyliminium ion 8 shows the same 1,3 spatial relationship between the reacting center and the substituent, in this case a protected alcohol, as the N-acyliminium ion 5.

In the light of the proposed mechanism for the addition of alkylcopper reagents to N-acyliminium ions, substrate 8 provides an interesting probe into the factors governing the selectivity of nucleophilic addition to N-acyliminium ions. The results, shown in Table 2 reveal that the acetoxy group in 8a gives almost no facial selectivity, whereas the OTBDMS group leads to moderate degree of trans selectivity. The absolute stereochemistry of the major product 10a was deduced as before by its conversion into the naturally occurring amino acid trans-4-hydroxy-L-proline 11c with the correct optical rotation (Scheme 2).

Table 2. Stereoselectivity in the reaction of 8 with various nucleophiles.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Nucleophile</th>
<th>Lewis acid</th>
<th>cis : trans</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>Me₂SiCN</td>
<td>TiCl₄</td>
<td>91 : 9</td>
<td>a</td>
<td>12</td>
</tr>
<tr>
<td>8a</td>
<td>4</td>
<td>BF₃·Et₂O</td>
<td>45 : 55</td>
<td>a</td>
<td>This work</td>
</tr>
<tr>
<td>8b</td>
<td>Allyltrimethylsilane</td>
<td>TiCl₄</td>
<td>97 : 3</td>
<td>75</td>
<td>11</td>
</tr>
<tr>
<td>8b</td>
<td>4</td>
<td>BF₃·Et₂O</td>
<td>15 : 85</td>
<td>89</td>
<td>This work</td>
</tr>
</tbody>
</table>

*Not determined. *Isolated yield.

Table 3. Stereoselectivity in the reaction of 12 with various nucleophiles.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Nucleophile</th>
<th>Lewis acid</th>
<th>cis : trans</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a</td>
<td>Allyltrimethylsilane</td>
<td>BF₃·Et₂O</td>
<td>21 : 79</td>
<td>64*</td>
<td>13</td>
</tr>
<tr>
<td>12a</td>
<td>4</td>
<td>BF₃·Et₂O</td>
<td>30 : 70</td>
<td>b</td>
<td>This work</td>
</tr>
<tr>
<td>12b</td>
<td>Allyltrimethylsilane</td>
<td>BF₃·Et₂O</td>
<td>77 : 23</td>
<td>69*</td>
<td>13</td>
</tr>
<tr>
<td>12b</td>
<td>4</td>
<td>BF₃·Et₂O</td>
<td>5 : 95</td>
<td>89</td>
<td>This work</td>
</tr>
</tbody>
</table>

Preparation of compounds 12a and 12b by anodic methoxylation of the N-protected (3R)-pyrrolidin-3-ol has been published by us.\textsuperscript{13} In this case, the carbon bearing the substituent is situated vicinally to the N-acyliminium ion. We showed,\textsuperscript{2} as indicated in Table 3, that the stereoselectivity of the addition of a π-nucleophile to the N-acyliminium ion 12 can be controlled by the O-protective group to give cis:trans ratios varying from 77:23 to 21:79.\textsuperscript{14} When treated with 4 and BF\textsubscript{3}, both the O-acetyl (12a) and the O-TBDMSC compound (12b) gave preferentially the trans-vinylated products 13a and 14a, respectively, although the O-acetyl group in compound 12a gave a less satisfactory selectivity (Table 3). The products 14a and 14b were separated by column chromatography and 14a was subjected to degradation as above to the amino acid trans-(3R)-3-hydroxyproline 15c with the correct optical rotation (Scheme 3). Complexes have been suggested as intermediates in the conjugate addition of organocuprates to α,β-unsaturated carbonyl compounds.\textsuperscript{17} Selective trans attack by another RCu moiety on this complex would then account for the observed selectivity.

We have also investigated the vinylation of the disubstituted methoxy compound 17a prepared by anodic oxidation of the N-protected amino acid 16a.\textsuperscript{15,16} Both the O-acetyl and the O-TBDMSC derivatives of 17a failed to react with the copper reagent 4 in the presence of BF\textsubscript{3} and could be recovered almost quantitatively. Since the substituents on the N-acyliminium ion have been demonstrated to exert a profound effect on the selectivity of the vinylation, compound 17b [the C(4) epimer of 17a] would be expected to give an unambiguous trans-directing effect. We have previously reported on the preparation of (2S,4S)-N-acetyl-4-hydroxy-L-proline\textsuperscript{26} by epimerization of (2S,4R)-N-acetyl-trans-4-hydroxy-L-proline and this method was successfully adopted to prepare 16b. Anodic methoxylation then gave 17b as a mixture of diastereomers. However, both the O-acetyl and the O-TBDMSC derivatives of 17b were recovered almost quantitatively after treatment with 4-BF\textsubscript{3}; Et\textsubscript{3}O. The reason for this failure to react is at present unknown; one might speculate that formation of the N-acyliminium ion in these cases is, for some reason, unusually slow which would lead to decomposition of the organocupper reagent before reaction could occur.

The selective formation of the trans adduct, as has been observed in most cases in this report, is consistent with the suggested mechanism which involves an intermediate, facially biased RCu π-complex as shown in Fig. 1.\textsuperscript{9} Such complexes have been suggested as intermediates in the conjugate addition of organocuprates to α,β-unsaturated carbonyl compounds. Selective trans attack by another RCu moiety on this complex would then account for the observed selectivity.

In conclusion, we have shown that the intermolecular vinylation of the N-acyliminium ion 5 can be carried out using the vinylcupper reagent 4 in the presence of BF\textsubscript{3} with little or no loss of selectivity compared with alkylcupper reagents.\textsuperscript{9} There is a strong possibility, that similar selectivities reported in this paper for the vinylation of the N-acyliminium ions 8 and 12 will be found with other organocupper reagents. Thus, it seems possible that the stereoechemistry of the nucleophilic addition to the N-acyliminium ions 5, 8 and 12 can be controlled from ≥ 85% trans to ≥ 70–80% cis addition by appropriate selection of the reagent and the O-protective group. The generality and the predictability of the reaction of organocupper reagents with chiral N-acyliminium ions should guarantee its preparative usefulness, e.g. in synthetic approaches to mono- and bi-cyclic alkaloids such as 1, 2 and 3.

**Experimental**

_General._ All chemicals used were of highest commercial quality and used without further purification with noted exceptions. Light petroleum (b.p. 60–80°C) and ethyl acetate, used for chromatography, were distilled before use. BF\textsubscript{3}; Et\textsubscript{3}O was distilled from CaH\textsubscript{2} before use. CuBr·Me\textsubscript{3}S was prepared according to the method described by House.\textsuperscript{18} 2-Methyl-1-propenyl lithium (4) was prepared from 1-bromo-2-methyl-1-propene and lithium powder in Et\textsubscript{3}O at −20°C. The concentration of the alkyl lithium solution (usually around 0.5 M) was determined by titration as described by Watson and Eastham.\textsuperscript{19} Reaction mixtures were analyzed by capillary GLC using a Varian 3400 chromatograph equipped with a Varian 4270 integrator on a 25 m × 0.25 mm OV 1701 column and by TLC on commercially available silica gel/aluminum foil plates. Flash chromatography was performed on TLC grade silica gel...
according to Taber. \textsuperscript{20} \textsuperscript{1}H NMR spectra were recorded in CDCl\textsubscript{3} on a Varian XL 300 instrument unless otherwise stated, \( \delta \) being given in ppm downfield from Me\textsubscript{4}Si. Coupling constants, \( J \), are given in Hz. Optical rotations were determined on a Perkin-Elmer 241 MC instrument. High resolution mass spectra [MS(br)] were obtained using a Jeol SX 102 instrument, direct inlet.

**General procedure for vinylation using 4.** To a suspension of CuBr-Me\textsubscript{3}S (1.51 g, 7.4 mmol) in dry diethyl ether (20 ml) was added a solution of 2-methyl-1-propenyl lithium (14.8 ml of a 0.50 M solution in diethyl ether) at \(-40^\circ\text{C}\) under an argon atmosphere. After being stirred for 30 min, the solution was cooled to \(-70^\circ\text{C}\) and BF\textsubscript{3}-Et\textsubscript{2}O (0.93 ml, 7.4 mmol) was added. After 5 min, a solution of the methoxy compound (3.69 mmol) in dry ether (3.0 ml) was added. The reaction mixture was allowed to attain ambient temperature and a 1:1 mixture of a saturated solution of NH\textsubscript{4}Cl and concentrated aqueous ammonia was added. After being stirred for 30 min, the mixture was extracted with dichloromethane (3 \times 20 ml) and the organic phase was dried over MgSO\textsubscript{4}. The organic phase was concentrated under reduced pressure to leave a clear oil.

**3(5S)-1-Methoxycarbonyl-5-(2-methyl-1-propenyl)-1-proline methyl ester (6a).** Vinylation of 5a according to the general procedure followed by purification by column chromatography (ethyl acetate-light petroleum 1:2) gave pure 6a (55%) and a mixture of 6a and 6b (28%). \textsuperscript{1}H NMR (300 MHz): 5.1 (t, J 7.8, 1 H), 4.76 (t, J 9.0, 0.5 H), 4.69 (t, J 9.0, 0.5 H), 4.41 (d, J 8.4, 0.5 H), 4.36 (d, J 8.4, 0.5 H), 3.73, 3.72, 3.66, 3.63 (4s, 1:1:1:1, 6 H) 2.07-2.39 (m, 2 H), 1.93-2.07 (m, 1 H) 1.56-1.80 (m, 7 H). [\( \alpha \)]\textsubscript{D}\textsuperscript{23} = -7.2\textdegree (c 1.0, MeOH). MS (hr): 241.1321. Calc. for C\textsubscript{13}H\textsubscript{20}NO\textsubscript{4}: 241.1314.

**3(5S)-1-Methoxycarbonyl-5-formyl-1-proline methyl ester (7a).** A solution of 6a (465 mg, 1.93 mmol) in methanol (10 ml) was cooled to \(-70^\circ\text{C}\) and treated with a stream of oxygen–ozone until the blue color persisted. The mixture was purged with a stream of argon until colorless and Me\textsubscript{3}S (1.0 ml) was added. The mixture was stirred overnight and allowed to attain ambient temperature. After evaporation, the reaction mixture was purified by column chromatography (ethyl acetate–light petroleum 2:1) to give 7a (380 mg, 92% yield). \textsuperscript{1}H NMR (300 MHz): 9.64, 9.64, 9.58, 9.58 (4 s, 1:1:1:1, 1 H), 4.51-4.58 (m, 1 H), 4.40-4.50 (m, 1 H), 3.76, 3.74, 3.71 (3 s, 1:1:2, 6 H), 1.96-2.30 (m, 4 H). [\( \alpha \)]\textsubscript{D}\textsuperscript{23} = -95.7\textdegree (c 1.0, MeOH). MS (hr): 186.0764. Calc. for C\textsubscript{7}H\textsubscript{12}NO\textsubscript{2} – CHO: 186.0766.

**3(2S,5S)-Pyrrrolidine-2,5-dicarboxylic acid (7c).** Compound 7a (284 mg, 1.32 mmol) dissolved in dry dimethylformamide (DMF) was added to a solution of pyridinium dichromate (1.74 g, 4.62 mmol) in dry DMF (5.0 ml) and the mixture was stirred overnight. After addition of water (50 ml), the mixture was acidified with hydrochloric acid and extracted with diethyl ether (4×20 ml). The ethereal phase was concentrated under reduced pressure to leave crude 7b (220 mg). A sample of crude 7b was heated to reflux in 6 M HCl for 6 h and, after evaporation, purified on an ion-exchange column (Dowex 50×8, 200–400 mesh) using 1.3 M NH\textsubscript{4} as the eluant to give 7c. Spectral data (\textsuperscript{1}H NMR and optical rotation) were in agreement with the reported literature data.\textsuperscript{21}

\textsuperscript{20} \textsuperscript{4}-tert-Butyl(dimethyl)siloxy-1-methoxycarbonyl-2-(2-methyl-1-propenyl)-pyrroldine (10a). Vinylation of 8b (289 mg, 1.0 mmol) according to the general procedure followed by purification by column chromatography (ethyl acetate–light petroleum 1:5) gave 10a (209 mg) and a mixture of 10a and 10b (70 mg) in a total yield of 89% yield. \textsuperscript{1}H NMR (300 MHz): 4.94-5.04 (br d, 1 H), 4.52-4.72 (m, 1 H), 4.32-4.40 (m, 1 H), 3.66 (s, 3 H), 3.28-3.53 (m, 2 H), 1.94-2.05 (m, 1 H), 1.65-1.77 (m, 7 H), 0.87 (s, 9 H), 0.06, 0.06 (2 s, 6 H). [\( \alpha \)]\textsubscript{D}\textsuperscript{23} = +24.5\textdegree (c 1.0, MeOH). MS (hr): 256.1355. Calc. for C\textsubscript{13}H\textsubscript{23}NO\textsubscript{5}Si – CH\textsubscript{3}H\textsubscript{2}: 256.1369.

\textsuperscript{21} \textsuperscript{4}-Acetoxy-1-methoxycarbonyl-2-(2-methylpropenyl)-pyrroldine (9). Vinylation of 8a (215 mg, 0.99 mmol) according to the general procedure gave crude 9 as a 45:55 isomeric mixture. In order to identify the products, 9 was transformed into 10 by treatment with K\textsubscript{2}CO\textsubscript{3} (276 mg, 2.0 mmol) in methanol (10 ml). After completion of the reaction as determined by TLC, the mixture was evaporated and the residue filtered through a silica pad using ethyl acetate as the eluant. The filtrate was evaporated and the residue treated with TBDMSCl (226 mg, 1.5 mmol) and imidazole (136 mg, 2.0 mmol) in dry DMF (5.0 ml). After overnight stirring, CH\textsubscript{2}Cl\textsubscript{2} (25 ml) was added and the mixture was washed with 1 M aq. HCl (20 ml) and satd. aq. NaCl (3×20 ml). The organic phase was dried over MgSO\textsubscript{4} and the products were analyzed by capillary GLC and compared with authentic 10 obtained from 8b.

**trans-4-Hydroxy-1-proline (11c).** The procedure described for the transformation of 7a into 7b was used starting from 11a (160 mg, 0.56 mmol) to give crude 11b (152 mg, 89% yield). A sample of crude 11b was heated to reflux in 6 M HCl for 6 h. After evaporation the solid residue was purified on an ion-exchange column (Dowex 50×8, 200–400 mesh) using 1.3 M NH\textsubscript{3} as the eluant to give 11c which, after recrystallization from ethanol–water, was obtained as
white needles. Spectral data (¹H NMR and optical rotation) were in agreement with the reported literature data.²²

(2S,3R)-3-tert-Butyl(dimethyl)siloxy-1-methoxycarbonyl-2-(2-methyl-1-propenyl)pyrrolidine 14a. Vinylation of 12b (500 mg, 1.73 mmol) with 4 according to the general procedure gave crude 14a which was purified by column chromatography using ethyl acetate–light petroleum (7:1) as the eluant. Yield: 424 mg, 78%. ¹H NMR (300 MHz): 4.85, 4.81 (2 s, 1 H, 1 H), 4.19–4.42 (m, 1 H, 1 H), 3.96 (br s, 1 H, 3.67 (s, 3 H), 3.40–3.62 (m, 2 H), 1.90–2.05 (m, 1 H, 1.69–1.82 (m, 7 H), 0.87 (s, 9 H), 0.06, 0.05 (2 s, 1:1, 6 H). MS (hr): 313.2065. Calc. for C₃₀H₅₄NO₆Si: 313.2073. [α]D²⁰ = −70.6° (c 1.0, MeOH).

(3R)-Acetoxy-1-methoxy-2-(2-methyl-1-propenyl)-pyrrolidine (15). Vinylation of 12a (217 mg, 1.0 mmol) according to the general procedure gave crude 15a as a mixture of isomers in the ratio 29:71 (260 mg). In order to identify the products, the crude product was transformed into its TBDMS derivative using the procedure described above. Comparison by GLC with an authentic sample of 14 identified the major isomer as being trans.

(2R,3R)-3-tert-Butyl(dimethyl)siloxy-2-formyl-1-methoxy-carbonylpyrrolidine (15a). Oxonolysis of 14a (370 mg, 1.18 mmol) was carried out as above. The crude product was purified by column chromatography using ethyl acetate–light petroleum ether (2:3) as the eluant to give 15a (262 mg, 77%). ¹H NMR (300 MHz): 9.50, 9.51, 9.59, 9.60 (4 s, 1:1:1:1, 1 H), 4.43 (br s, 1 H), 4.04, 4.20 (2 s, 1:1, 1 H), 3.55–3.75 (m, 5 H), 1.82–1.92 (m, 2 H), 0.88 (s, 9 H), 0.10, 0.09 (2 s, 1:1, 6 H). MS (hr): 258.1520. Calc. for C₁₃H₁₄NO₂Si–CHO: 258.1525. [α]D²⁰ = +76° (c 1.0, MeOH).

trans-3-Hydroxy-1-proline (15e). The procedure described for the transformation of 7a into 7b was used starting from 15a (100 mg, 0.35 mmol) to give crude 15b (95 mg). A sample of crude 15b was heated to reflux in 6 M HCl for 6 h and evaporated to leave a solid residue. Purification of this on an ion-exchange column (Dowex 50×8, 200–400 mesh) using 1.3 M NH₃ as the eluant gave 15c which, after recrystallization from ethanol–water, was obtained as white needles. Spectral data (¹H NMR and optical rotation) were in agreement with the reported literature data.²³

(2S,4R)-4-Hydroxy-1-methoxycarbonylproline methyl ester (16a). A solution of trans-4-hydroxy-L-proline (13.1 g, 0.10 mol) in 2 M aq. NaOH (50 ml) were added simultaneously methyl chlorofomate (7.75 ml, 0.10 mol) and 4 M aqueous KOH (25 ml). After being stirred for 1 h the neutral mixture was reduced to 20 ml under reduced pressure and acidified with hydrochloric acid. After evaporation to dryness, the residue was triturated with ethyl acetate and the organic phase was dried with MgSO₄ and evaporated to give crude 4-hydroxy-1-methoxycarbonyl-L-

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References
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