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Diastereoselective Intramolecular Allyl Transfer from Allyl Carbamate Accompanied by 5-endo-trig Ring Closure**

Oskari K. Karjalainen, Martin Nieger, and Ari M. P. Koskinen*

Pyrrolidin-3-ones, a rare motif in nature, have very few dedicated syntheses. However, substituted pyrrolidinones can easily be envisioned to act as foundations for the construction of organocatalysts, supported organocatalysts, and bioactive molecules.[1] We therefore set out to design as flexible a route as possible to this interesting class of molecules.

The most simplifying disconnection would be the cleavage of one of the C–N bonds to reveal the enone 3 (Scheme 1).

![Scheme 1. Retrosynthetic analysis of substituted pyrrolidin-3-ones.](image)

Although the proposed 5-endo-trig cyclization is disallowed according to the Baldwin rules,[2] we reasoned that suitable activation of the enone moiety could facilitate this ring closure mode. We then realized that an allyl carbamate (Alloc) group would be ideal for this purpose. The masked nitrogen nucleophile can be liberated under neutral conditions, a very important factor considering the sensitive nature of the enone. A related 6-exo heterocyclization has been demonstrated previously by Martin and co-workers, and a 5-exo cyclization through Tsuji et al.[3,4]

The allyl palladium(II) species arising from the cleavage of the allyl carbamate, if sufficiently long lived, might activate the π system towards a formal 5-endo cyclization through several conceivable mechanisms. It is known that hard nucleophiles (such as nitrogen) preferentially attack the palladium center instead of the soft allyl cation.[5] Thus, an intermediate such as 2 (Scheme 1), which could then activate the enone towards amino palladation, might be plausible. Another possible activation mode would be the case where palladium(II) acts as a Lewis acid (or as a π acid) drawing electron density from the π system by coordination to the carbonyl oxygen atom.[6] This activation mode should generate an intermediate (2') with substantial cationic character and allow a pseudo-Nazarov reaction to take place.[7]

Regardless of the mechanism, the allyl group would be trapped by the soft β-ketonitrile nucleophile, thus regenerating palladium(0) and constructing an all-carbon quaternary center.[8] The atom economy of this approach is also considerable. The allyl carbamate is not merely a protecting group but in fact an enabling group whose whole potential is being utilized. During the early stages it acts as a masking group and when cleaved the released CO₂ pays for whatever entropic costs are necessary, and the allyl portion becomes incorporated into the final product. To best of our knowledge, this is an unprecedented reaction, and allows rapid construction of the complex pyrrolidinone scaffold.

The unsaturation in 3 (Scheme 1) would suggest the powerful, yet underused, Knoevenagel condensation[9] to construct it from a wide variety of aldehydes and active methylene compounds (4), which are readily available from amino acids using standard methods for ketone synthesis. All in all, this route would deliver the target compounds in a very step-economic and modular manner.

Initially we used β-ketoesters but despite extensive experimentation we could not identify mild yet effective reaction conditions for the Knoevenagel condensation. Although effective in the cyclization step, we were forced to abandon the ketoesters. After careful consideration, we settled for nitrile as the electron-withdrawing group in 4. The required β-ketonitriles are readily accessible in one step from the corresponding amino acid esters.[10] They also enable smooth Knoevenagel condensations in comparison to β-ketoesters or β-amides. Finally, the nitrile group provides a versatile handle for further transformations.

With this plan in mind we set out to prepare the required β-ketonitriles (Scheme 2). The commercial amino ester salts 5 were benzyl protected by reductive amination using a modified literature procedure,[11] and the crude reaction mixture was reacted with allyl chloroformate to provide the bis(N-protected) amino acid esters in good to excellent yields and excellent purity. Condensation with lithiated acetonitrile[12] provided the necessary β-ketonitriles in good yield. In most cases the crude reaction mixture was pure enough to carry on to the next step after silica gel filtration to remove the
CH$_2$Cl$_2$ gives the best diastereoselectivity (entries 1–3; 1,2-dichloroethane behaves in identical manner). Aryl phosphine ligands other than PPh$_3$ have little effect on the outcome (entries 4–7), whereas alkyl phosphines are completely ineffective. Palladium(II) sources were found to be as effective as palladium(0) (entries 8, 10, and 12), but gave cleaner reaction profiles. We finally settled on [Pd(AllylCl)$_2$] as it was effective even at lower temperatures and gave higher selectivities (entry 13). Inconsistent diastereoselectivities between 6 and 12:1 were initially observed from run to run. After testing various additives (Brønsted acids, Lewis acids, and various bases) secondary amines were found to affect the diastereoselectivity. Most likely the residual morpholine from the Knoevenagel condensation was the culprit. We investigated this aspect by varying the amount of morpholine and temperature (Table 2). Temperature affects the d.r. surprisingly little (entries 1–3). When a catalytic amount of morpholine was added a large increase (2–3-fold) in reaction rate was observed as well as improved selectivity (entry 4). The effect is more pronounced at lower temperatures (entries 5–7) and it is evident that while the selectivity increases, the yield drops. This suggests that morpholine is able to intercept the allyl cation, thus leading to enrichment of the major newly formed double bond have a major impact on the electronic properties of the product. The results of a rudimentary reaction conditions screen are presented in Table 1. As can be seen, apparently polymeric and highly colored baseline impurities. The products had ee values greater than or equal to 97% as determined by HPLC using chiral stationary phase, thus confirming the mildness of the sequence.

Knoevenagel condensation of 7a (chosen as the model substrate) with benzaldehyde in ethanol and catalytic pyrrolidine gave the desired product in near quantitative yield, however, with some racemization. After some investigation morpholine was found to be both nonracemizing and an efficient catalyst for the reaction. NMR spectroscopy and HPLC indicated that 8a was obtained as single double bond isomer.

In a preliminary experiment, when 8a was treated with a palladium(0) source ([Pd(PPh$_3$)$_4$], CH$_2$Cl$_2$, RT, 15 min) the pyrrolidinones 9a and 9a’ were isolated in near quantitative yield as an inseparable mixture. The relative stereochemistry was established using nOe experiments. Notably, the reaction produces the thermodynamically less stable diastereomer 9a as the major product. The results of a rudimentary reaction conditions screen are presented in Table 1. As can be seen, Scheme 2. a) PhCHO, NaHCO$_3$, MeOH, RT, then NaBH$_4$, 0°C;
b) AllocCl, NaHCO$_3$, acetone/H$_2$O (2:1), RT; c) MeCN, BuLi, THF, −78°C; 1.1 equiv PhCHO, cat. morpholine, 4 Å M.S., CH$_2$Cl$_2$. Alloc = allyloxycarbonyl, Bn = benzyl, M.S. = molecular sieves.

The substrate scope was probed with electronically diverse aryl aldehydes and several amino acids (Table 3) using our optimized reaction conditions. We also incorporated the Knoevenagel and cyclization steps into a one-pot procedure, thus reducing the stress on the fragile enone, and eliminating one isolation step. Electronic properties of the newly formed double bond have a major impact on the reaction performance. The cyclizations become progressively slower as the substrate becomes more electron deficient. In fact, with p-nitro substitution the reaction only proceeds at

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd source</th>
<th>Ligand</th>
<th>Solvent</th>
<th>d.r.</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Pd(dba)$_2$]</td>
<td>PPh$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>5.7</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>[Pd(dba)$_2$]</td>
<td>PPh$_3$</td>
<td>toluene</td>
<td>4.0</td>
<td>N.I.</td>
</tr>
<tr>
<td>3</td>
<td>[Pd(dba)$_2$]</td>
<td>PPh$_3$</td>
<td>THF</td>
<td>3.0</td>
<td>N.I.</td>
</tr>
<tr>
<td>4</td>
<td>[Pd(dba)$_2$]</td>
<td>P(4-OMeC$_6$H$_4$)$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>5.2</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>[Pd(dba)$_2$]</td>
<td>PPh$_3$P(NEt$_2$)$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>4.6</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>[Pd(dba)$_2$]</td>
<td>P(Cy)$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>6.0</td>
<td>N.I.</td>
</tr>
<tr>
<td>7</td>
<td>[Pd(Bu)$_2$]</td>
<td>–</td>
<td>CH$_2$Cl$_2$</td>
<td>6.0</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>[Pd(OAc)$_2$]</td>
<td>PPh$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>6.0</td>
<td>N.I.</td>
</tr>
<tr>
<td>9$^b$</td>
<td>[Pd(OAc)$_2$]</td>
<td>PPh$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>6.0</td>
<td>N.I.</td>
</tr>
<tr>
<td>10</td>
<td>[Pd(TFA)$_2$]</td>
<td>PPh$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>6.0</td>
<td>95</td>
</tr>
<tr>
<td>11$^b$</td>
<td>[Pd(TFA)$_2$]</td>
<td>PPh$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>6.0</td>
<td>N.I.</td>
</tr>
<tr>
<td>12</td>
<td>[Pd(AllylCl)$_2$]</td>
<td>PPh$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>5.9</td>
<td>94</td>
</tr>
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<td>13$^b$</td>
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<td>PPh$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>5.9</td>
<td>94</td>
</tr>
</tbody>
</table>

[a] Pd (3 mol %) together with the corresponding ligand (6 mol % Pd or 12 mol % Pd) was added to a solution of 8a (100 mg) in CH$_2$Cl$_2$ at RT under argon. After reaction completion the products were absorbed onto silica gel and chromatographed. [b] Reaction performed at 0°C. TFA = trifluoroacetate, dba = dibenzylidenacetonate, THF = tetrahydrofuran.

Table 1: Initial reaction conditions screening.$^b$

Table 2: The effect of morpholine on reaction performance.$^{b,c}$

These results confirm the mildness of the sequence.
elevated temperatures accompanied by severe decomposition. In all but select few cases the same trans/trans isomer 9 was obtained as the major product. Deviations from a neutral electronic state (when Ar = Ph), regardless of the direction, result in a reduced selectivity. However, we found a clear exception to this trend, that is, 2,6-disubstitution provides the cis/trans isomer 9 exclusively and the reactions are fast (< 1 h) regardless of electronics (entries 5 and 6), thus suggesting a change in mechanism. The effect of amino acid side chain was investigated with and without added morpholine. Alanine (R = Me; 7b) proved less than ideal, thereby exhibiting poor selectivity with one additional diastereomer being evident and low response to the added morpholine (entries 18 and 19). We also reacted 7b with 2,6-dichlorobenzaldehyde, and consistent with the result in entry 6, a single diastereomer was obtained (2,6-Cl-9b), albeit completely racemic! A crystal structure confirmed the nOe assignments (Figure 1). [12,13] Leucine (R = iBu; 7c) showed selectivity similar to phenylalanine without added morpholine (6.5:1) but excellent response to morpholine with full selectivity (entries 20 and 21). Valine (R = iPr; 7d) gave complete selectivity under both sets of reaction conditions (entries 22 and 23). Other benzyl protecting groups can be used, as exemplified in entry 24 with p-methoxybenzyl, but they do affect the reaction in subtle ways most likely because of the changed electronics. Aliphatic aldehydes are not good substrates because of their unwillingness to participate in Knoevenagel condensation under the mild reaction conditions reported herein.

This data suggested to us that the reaction is kinetically controlled. Otherwise, morpholine would not have any effect on the diastereoselectivity. A Hammett plot would clarify these seemingly random results. [14] To our surprise, when we constructed the Hammett using our the data, very clear trends manifested (Figure 2).

Two distinct regimes of reactivity are evident. Electron-donating and electron-deficient substituents lead to completely different reactivities. The results in the electron-rich domain are consistent with an interrupted Nazarov-type reaction as the reaction rate increases with increasing electron density at the aryl substituent. The loss of selectivity with

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Ar</th>
<th>d.r. (9/9')</th>
<th>Yield [%]</th>
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<tr>
<td>1</td>
<td>Bn</td>
<td>Ph</td>
<td>14.3:1</td>
<td>82</td>
</tr>
<tr>
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<td>Bn</td>
<td>2-MeC₆H₄</td>
<td>11.1:1</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>2-MeOC₆H₄</td>
<td>6.5:1</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>2-CIC₆H₄</td>
<td>3.2:1</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>2,4,6-MeC₆H₄</td>
<td>&gt;1:20</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>Bn</td>
<td>2,6-CIC₆H₄</td>
<td>&gt;1:20</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>Bn</td>
<td>3-MeC₆H₄</td>
<td>8.7:1</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>Bn</td>
<td>3-MeOC₆H₄</td>
<td>7.7:1</td>
<td>80</td>
</tr>
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<td>9</td>
<td>Bn</td>
<td>3-CIC₆H₄</td>
<td>2.6:1</td>
<td>71</td>
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<tr>
<td>10</td>
<td>Bn</td>
<td>3-CNCH₃</td>
<td>1.1:1</td>
<td>51</td>
</tr>
<tr>
<td>11</td>
<td>Bn</td>
<td>3,5-MeOC₆H₄</td>
<td>11.0:1</td>
<td>75</td>
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<tr>
<td>12</td>
<td>Bn</td>
<td>piperonal</td>
<td>12.1:1</td>
<td>75</td>
</tr>
<tr>
<td>13</td>
<td>Bn</td>
<td>4-MeC₆H₄</td>
<td>7.5:1</td>
<td>93</td>
</tr>
<tr>
<td>14</td>
<td>Bn</td>
<td>4-iBuC₆H₄</td>
<td>7.4:1</td>
<td>77</td>
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<tr>
<td>15</td>
<td>Bn</td>
<td>4-MeOCH₃</td>
<td>6.5:1</td>
<td>84</td>
</tr>
<tr>
<td>16</td>
<td>Bn</td>
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<td>5.4:1</td>
<td>81</td>
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<td>17</td>
<td>Bn</td>
<td>furfural</td>
<td>8.8:1</td>
<td>89</td>
</tr>
<tr>
<td>18</td>
<td>Me</td>
<td>Ph</td>
<td>4.9:1:1:1</td>
<td>84</td>
</tr>
<tr>
<td>19</td>
<td>Me</td>
<td>Ph</td>
<td>6.2:1:1:1</td>
<td>70</td>
</tr>
<tr>
<td>20</td>
<td>Me</td>
<td>iBu</td>
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<td>99</td>
</tr>
<tr>
<td>21</td>
<td>iBu</td>
<td>Ph</td>
<td>&gt;20:1</td>
<td>76</td>
</tr>
<tr>
<td>22</td>
<td>iPr</td>
<td>Ph</td>
<td>&gt;20:1</td>
<td>89</td>
</tr>
<tr>
<td>23</td>
<td>iPr</td>
<td>Ph</td>
<td>&gt;20:1</td>
<td>79</td>
</tr>
<tr>
<td>24</td>
<td>iPr</td>
<td>Ph</td>
<td>7.5:1</td>
<td>75</td>
</tr>
</tbody>
</table>

[a] 4 Å M.S. (100 w%) followed by the aryl aldehyde (120 mol%) and morpholine (23 mol%) were added to a solution of 7 in CH₂Cl₂ (0.5 M) under argon at RT. After complete as determined by TLC the reaction was cooled to 0°C and diluted with CH₂Cl₂ (0.11 M). Then [[PdAllylCl]₂] (3 mol%) was added together with PPh₃ (15 mol%). After reaction completion the products were absorbed on silica and chromatographed. [b] Determined by ¹H NMR spectroscopy. [c] Yield of product isolated after chromatography. [d] No morpholine. [e] Third diastereomer (stereochmistry not assigned) was detected in the product mixture. [f] PMB protecting group instead of Bn. PMB = p-methoxybenzyl.
increasing electron-donor ability can be explained by the high reaction rate: morpholine is simply not quick enough as a trapping agent. The reaction described in entry 15 of Table 3 was repeated at 10°C and indeed an increase in diasteroselectivity was observed (9.6:1 compared to 6.5:1 at 0°C). A further increase in temperature to 20°C gave, again, lower selectivity. Thus, with a judicious choice in trapping agent and reaction temperature, good selectivities should be achievable with most substrates in this regime. The electron-deficient domain appears to be a completely different case. No marked effect in diasteroselectivity was observed as a function of temperature (reaction in entry 16 of Table 3 was investigated). The dramatic decrease in diasteroselectivity cannot be easily explained and would call for a mechanism that would allow for equilibration. To this date we are unable to propose a reasonable mechanism to explain all the effects observed.

Finally, we wanted show that the diastereomers can be separated after a simple reaction, a feat that would render the reaction synthetically useful (Scheme 3). Luche reduction of the carbonyl group gave near-complete control over the newly formed stereocenter. The procedure was easily incorporated into the existing one-pot procedure, thus providing the pyrrolidinols 10 in reasonable yields after purification on silica gel. The optical purity of the products closely match the enantiopurity of the starting materials 7, thus indicating that no enolization takes place towards the amino group during the reaction.

In conclusion, we have developed a novel, synthetically useful reaction cascade able to deliver highly functionalized pyrrolidinones in good yields. In this reaction two new stereocenters, one of which is quaternary, are formed with very high selectivity. The allyl carbamate nitrogen-protecting group of the amino acid derived starting material functions as a very high selectivity. The allyl carbamate nitrogen-protecting group of the amino acid derived starting material functions as a very high selectivity. The allyl carbamate nitrogen-protecting group of the amino acid derived starting material functions as a very high selectivity. The allyl carbamate nitrogen-protecting group of the amino acid derived starting material functions as a very high selectivity. The allyl carbamate nitrogen-protecting group of the amino acid derived starting material functions as a very high selectivity. The allyl carbamate nitrogen-protecting group of the amino acid derived starting material functions as a very high selectivity.

Keywords: allylic compounds - amino acid - asymmetric synthesis - heterocycles - palladium

[12] The crystal structure of 2,6-Cl29b was determined on a Bruker-Nonius APEX-II diffractometer at 123(2) K using Mo-Kα radiation (λ = 0.71073 Å). Direct Methods (SHELXS-97)[2] were used for structure solution. Refinement was carried out using SHELXL-97[2] (full-matrix least-squares on F²), and hydrogen atoms were refined using a riding model. 2,6-Cl29b: colorless blocks, C20H17Cl2N2, M = 399.30, crystal size 0.50 × 0.40 × 0.30 mm, monoclinic, space group P21/c (No. 14), a = 8.9625(1), b = 15.8145(3), c = 13.7667(3) Å, β = 96.625(1)°, V = 1938.26(6) Å³, Z = 4, μ = 1.37 Mg m⁻³, μ(Mo-Kα) = 0.344 mm⁻¹, F(000) = 832, 2Θmax = 55°, 22719 reflections of which 4400 were independent (Rint = 0.017), 244 parameters. R1 = 0.028 (for 4189 I > 2σ(I)), wR2 = 0.070 (all data), S = 1.05, largest diff. peak/ hole = 0.334/–0.205 e Å⁻³. CCDC 910467 (2,6-Cl29b) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.