

## Completely Regioselective $\gamma$ -Addition in Aldol Reaction of the Conjugate Base of the Pentacarbonyl(Propenylpyrrolidinocarbene)Chromium(0) Complex with Aldehydes

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**Abstract:** The conjugate base of the pentacarbonyl(propenylpyrrolidinocarbene)chromium(0) complex reacts with aldehydes giving the corresponding aldols in good to excellent yields and in a completely  $\gamma$ -regioselective manner. © 1997 Elsevier Science Ltd.

It is known that the reactions involving the conjugate base of tertiary crotonamides ("dienolates") with electrophiles almost exclusively occur at the  $\alpha$ -position: no method has yet been described that is capable of overcoming this natural tendency and forcing simple electrophiles such as organic halides or aldehydes to react with the  $\gamma$ -position.<sup>1</sup> Only with dienolates of secondary  $\alpha,\beta$ -unsaturated amides is it possible to observe appreciable  $\gamma$ -regioselectivities, under particular experimental conditions (in the presence of copper salts).<sup>1</sup>

Fischer-type carbene complexes **1** are now routinely used as synthetic equivalents of esters or amides<sup>2</sup> and, from this point of view, the corresponding  $\alpha,\beta$ -unsaturated analogues **2**<sup>3</sup> can also be considered as synthetic equivalents of the corresponding  $\alpha,\beta$ -unsaturated esters or amides (Figure 1).

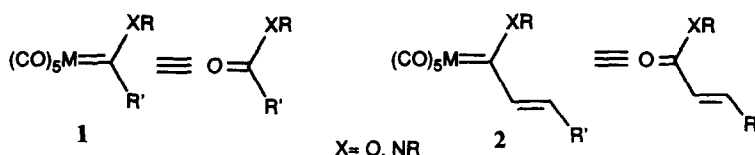


Figure 1

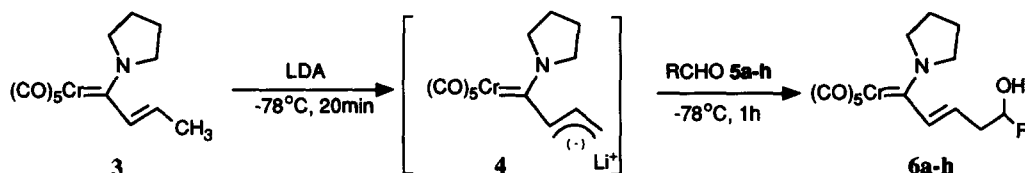
We have recently reported<sup>4</sup> that the propenylpyrrolidinocarbene complex **3** can be easily deprotonated with LDA or *t*-BuLi to the corresponding dienolate **4** (tertiary crotonamides need the presence of HMPA to favour the deprotonation vs 1,4-Michael addition process<sup>5</sup>). We have also reported the results of a study on the reactivity of **4** towards electrophiles, aimed at investigating the effect of the Cr(CO)<sub>5</sub> group on regioselectivity. Good yields were obtained from the reactions of **4** with simple organic halides, with  $\gamma$ -regioselectivity, ranging from 17-100%.<sup>4</sup> The  $\gamma$ -regioselectivity was, in our case, always better than that obtained in a similar reaction using dienolate of tertiary crotonamides (less than 5%).<sup>1</sup>

As a continuation of this work, we have now investigated the reaction of dienolate **4** with a series of aldehydes **5a-h**. Due to their greater electrophilic properties, aldehydes react faster than organic halides and the reactions were almost complete after 1h at -78 °C.<sup>6</sup> <sup>1</sup>H NMR spectrum analysis of the crude mixture

demonstrated that the reaction product came from the addition of the aldehydes at the  $\gamma$ -position of **4** and no traces of  $\alpha$ -adducts could be detected.

The chemical yields of aldols **6a-h** were excellent: over 90% with aromatic or heteroaromatic aldehydes **5f,h** and chromium tricarbonyl benzaldehyde complex **5g**; always over 70% with enolizable and  $\alpha,\beta$ -unsaturated aldehydes **5a-c** and **5d,e**. The aldehydes **5d,e** only afforded 1,2-addition products **6d,e** (Scheme 1, Table 1).

Scheme 1

Table 1. Reaction of propenylpyrrolidino carbene complex **3** with aldehydes **5a-h**

<b>5 / R</b>	<b>% yield of 6</b>
<b>a:</b> Me	79
<b>b:</b> n-C <sub>6</sub> H <sub>13</sub>	80
<b>c:</b> Ph(CH <sub>2</sub> ) <sub>2</sub>	77
<b>d:</b> CH <sub>3</sub> CH=CH	72
<b>e:</b> PhCH=CH	72
<b>f:</b> 2-Thienyl	94
<b>g:</b> $\eta^6(\text{C}_6\text{H}_5)\text{Cr}(\text{CO})_3$	98
<b>h:</b> 3,4(OCH <sub>2</sub> O)C <sub>6</sub> H <sub>3</sub>	95

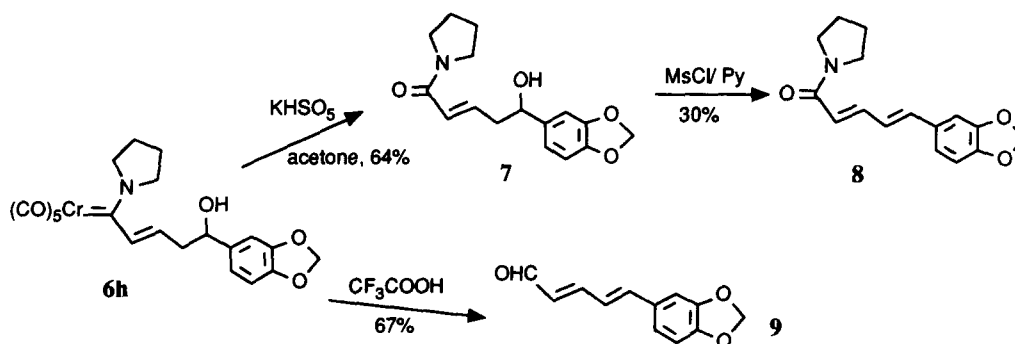
The high degree of  $\alpha$ -regioselectivity observed in the reaction involving the dienolate of tertiary crotonamides is believed to arise from the release of the steric strain existing between the nitrogen substituents and those on the double bond which occurs with its deconjugation in the final  $\alpha$ -addition products. A similar rationale would seem to justify the formation of the  $\alpha$ -adducts in the alkylation reactions of **4** studied by us.<sup>4</sup> Alternatively a rough correlation of the  $\alpha/\gamma$  ratio with the steric interaction between the electrophile and the bulky Cr(CO)<sub>5</sub> group could also be a reasonable hypothesis, which agrees well with the  $\gamma$ -regioselectivity observed when electrophiles with higher steric requirements, such as the aldehydes, are used. As recently suggested by Wulff,<sup>7</sup> the high degree of congestion around the  $\alpha$ -carbon atom to the carbenic centre was taken as explanation for the low stability of the aldol addition product achieved from the reaction of conjugated base of the ethylpyrrolidino carbene complex (a secondary carbanion) with benzaldehyde. Since, in principle, the aldol reaction is a reversible process, in our case the observed complete  $\gamma$ -regioselectivity may have been the result of the transformation of the possible (but less stable for steric reasons) kinetic  $\alpha$ -aldol addition products into more stable  $\gamma$ -adducts. To clarify this aspect an experiment was performed allowing the lithium aldolate of the aldol **6c** (generated with LDA at -78 °C in THF) to react with the aldehyde **6h** for 1h at -78 °C. Quenching the reaction with ammonium chloride at -78 °C, the aldol **6c** was recovered in almost quantitative yield without any formation of the aldol derivative

**6h**.<sup>8</sup> Hence, the  $\gamma$ -regioselectivity arises from a kinetically controlled process and must be controlled by the transition state energy which produces the aldols **6**. Since deuterium-incorporation experiments have shown that the lithium dienolate **4** generated with LDA, does not exist as a monomeric species<sup>4</sup> but in an aggregate form involving the isopropylamine (generated from LDA by the deprotonation process<sup>9</sup>) it is still impossible to formulate any reasonable hypothesis for this transition state.

Among the several methods for detaching the organic ligand from the complexes, the oxidative removal of the  $(\text{CO})_5\text{Cr}$  group in amino carbene complexes allows its recovery as an amide derivative. The oxidation of the aldols **6** would therefore seem to be a synthetically useful entry to the  $\delta$ -hydroxy- $\alpha,\beta$ -unsaturated amides. These latter compounds cannot be obtained by reaction of the conjugated base of tertiary crotonamides with aldehydes since, as previously mentioned, these reactions almost exclusively furnish  $\alpha$ -addition products. Furthermore, the dehydration of the  $\delta$ -hydroxy- $\alpha,\beta$ -unsaturated amides would give conjugated polyunsaturated amides, many of which are natural products.<sup>10</sup> For example, the piperiline **8**,<sup>10b</sup> a spice component found in the seeds of the *piper niger*, has been obtained by us through dehydration of the  $\delta$ -hydroxy- $\alpha,\beta$ -unsaturated amide **7** produced by means of the oxidation of the corresponding aldol **6h**. Many oxidants, including DMSO,  $\text{O}_2/h\nu$ ,  $\text{J}_2$ , peracids,  $\text{Ce}^{+4}$  salts and dimethyldioxirane have been used to transform **6h** into **7** but with yields that do not exceed 50%. Potassium caroate ( $\text{KHSO}_5$ , oxone) has given the best results, allowing the recovery of **7** in 64% yield. Dehydration of **7** to **8** was performed with mesyl chloride in pyridine at room temperature, as already reported in the literature for similar compounds.<sup>1</sup>

Another important transformation of the  $(\text{CO})_5\text{M}=\text{C}-\text{XR}$  moiety in Fischer-type carbene complexes is in a carbaldehyde functionality by means of protonolysis with strong organic or inorganic acids.<sup>11</sup> The complex **6h** was then treated with trifluoroacetic acid leading, to the corresponding conjugated polyunsaturated aldehyde **9** in 67% yield.<sup>12</sup> Dehydration occurs during the protonolysis process. This latter result shows that the propenylpyrrolidino carbene complex **3** can also be considered as a synthetic equivalent of the crotonaldehyde and may be useful in the direct homologation of aldehydes with two conjugated double bonds (Scheme 2).

Scheme 2



In conclusion the conjugate base of propenylpyrrolidino carbene **3** is reactive towards aldehydes giving good to excellent yields of the corresponding  $\delta$ -aldols in a complete  $\gamma$ -regioselective manner. This behavior makes complex **3** complementary to the tertiary crotonamides, in which similar reactions are almost always completely  $\alpha$ -regioselective. In addition, preliminary experiments have shown the usefulness of complex **3**

as synthetic equivalents of tertiary crotonamides and crotonaldehydes.

Further work is in progress to evaluate the potential of this reactivity and the usefulness of the aldols synthesized **6** as well as their dehydration to the corresponding conjugated polyunsaturated carbene complexes, some of which could show interesting NLO properties.

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- Typical procedure:** To a tetrahydrofuran solution of dienolate **4** [generated by adding 1.3 mmol of commercial 2M LDA (from Merck) to 1 mmol of **3** at -78 °C and keeping the mixture at the same temperature for 20 min], the aldehyde (3eq. for enolizable aldehydes **5a-c** and 1.2 eq. for aromatic, heteroaromatic and  $\alpha,\beta$ -unsaturated aldehydes **5d-h**) was added at -78 °C under inert atmosphere. The mixture was allowed to react at -78 °C and the progress of the reaction was monitored by t.l.c. analysis (eluent CH<sub>2</sub>Cl<sub>2</sub>/light petroleum 1:1). After 1h at -78 °C, the reaction was practically complete. The reaction was quenched by adding 10 ml of saturated ammonium chloride solution, followed by extraction with CH<sub>2</sub>Cl<sub>2</sub> (2 x 50 ml). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by means of dry flash column chromatography (eluent light petroleum/CH<sub>2</sub>Cl<sub>2</sub>, 1:1). All of the new alkenylpyrrolidino-carbene complexes **6a-h** were fully characterized by means of spectroscopic techniques (<sup>1</sup>H, <sup>13</sup>C NMR, I.R., M.S.) and gave a satisfactory elemental analysis. Data for: **6h**: oil; IR (nujol) cm<sup>-1</sup>: 3386 (ν OH), 2055 (ν CO *trans*), 1981-1866 (broad, ν CO *cis*), 1642 (ν C=C) cm<sup>-1</sup>; <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>) δ ppm: 2.10 (m, 5H, CH<sub>2</sub>CH<sub>2</sub>-N<sub>F</sub>-CH<sub>2</sub>CH<sub>2</sub> + OH), 2.56 (t, 2H, J<sub>vic</sub> = 7.0Hz, -CH=CH-CH<sub>2</sub>-), 3.47 (m, 2H, N<sub>F</sub>-CH<sub>2</sub>CH<sub>2</sub>), 4.10 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>-N), 4.72 (td, 1H, J<sub>vic</sub> = 7.0Hz, J = 3.2Hz, CH-OH), 5.16 (dt, 1H, J<sub>trans</sub> = 16.1Hz, J<sub>vic</sub> = 7.0Hz, -CH=CH-CH<sub>2</sub>-), 5.94 (s, 2H, O-CH<sub>2</sub>-O), 6.48 (bd, 1H, J<sub>trans</sub> = 16.1Hz -CH=CH-CH<sub>2</sub>-), 6.83 (m, 3H, arom); <sup>13</sup>C NMR (300MHz, CDCl<sub>3</sub>) δ ppm: 25.5 (N<sub>F</sub>-C-C), 25.8 (C-C-N), 42.9 (-CH=CH-CH<sub>2</sub>), 55.6 (N<sub>F</sub>-C-C), 59.7 (C-C-N), 74.2 (CH-OH), 101.6 (O-CH<sub>2</sub>-O), 106.9 (CH arom.), 108.7 (CH arom), 119.9 (CH arom), 121.3 (Cr=C-CH=CH-CH<sub>2</sub>-), 138.6 (C<sub>q</sub> arom), 144.1 (Cr=C-CH=CH-CH<sub>2</sub>-), 147.7 (C<sub>q</sub> arom), 148.5 (C<sub>q</sub> arom), 218.7 (CO<sub>cis</sub>), 224.1 (CO<sub>trans</sub>), 265.3 (Cr=C-C); MS, m/z = 465 (M<sup>+</sup>, very low intensity), 409 (M<sup>+</sup>-2CO), 381 (M<sup>+</sup>-3CO), 363 (M<sup>+</sup>-4CO), 335 (M<sup>+</sup>-5CO).
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