

# First diastereoselective [3+2] cycloaddition of chiral non-racemic alkenyl Fischer carbene complexes with diazomethane derivatives

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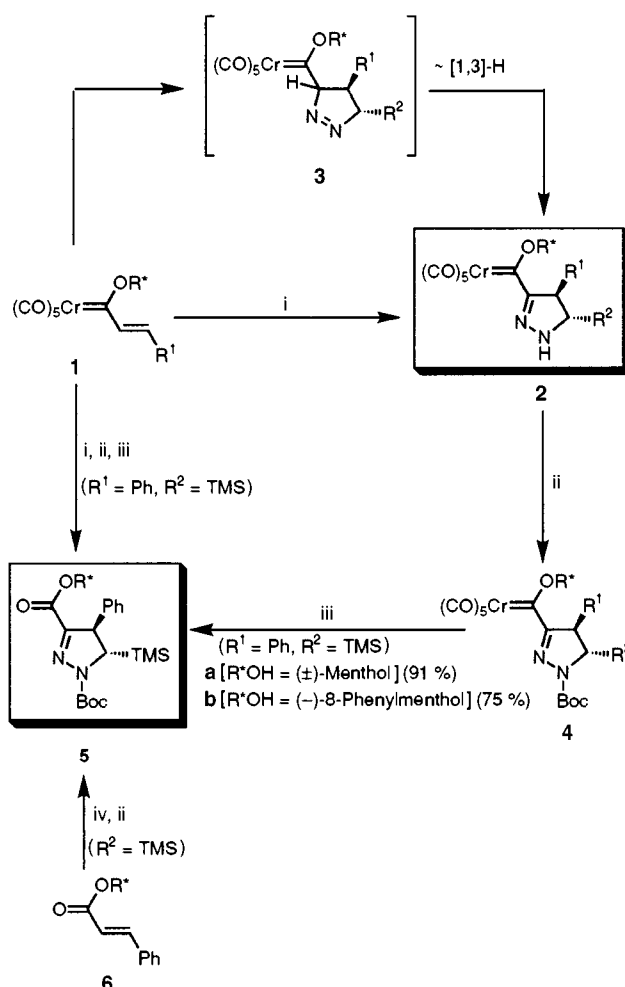
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(-)-8-Phenylmenthol derived pentacarbonylalkenyl(alkoxy)chromium carbene complexes react with diazomethane derivatives to give only one diastereomer of enantiomerically pure 4,5-dihydro-1*H*-pyrazoles; the one-pot synthesis of the corresponding esters is also described.

In the last decade, transition metal Fischer carbene complexes have become a powerful tool in organic synthesis; in particular, the  $\alpha,\beta$ -unsaturated derivatives have been widely used as substrates in cycloadditions.<sup>1</sup> In this sense, we have recently reported several examples where both tungsten and chromium  $\alpha,\beta$ -unsaturated Fischer carbene complexes behave as dienophiles in [4+2] cycloadditions.<sup>2</sup> In contrast, there are few examples of [3+2] cycloadditions of Fischer carbenes with 1,3-dipoles. The first reaction of this type was described by Kreissl *et al.*<sup>3</sup> who obtained low yields of the corresponding cycloadducts in the reaction of pentacarbonyl(ethoxy)phenylethynyltungsten with diazomethane. Chan and Wulff<sup>4</sup> improved this process by introducing a bulky trimethylsilyl (TMS) group on the diazomethane. Alkynyl Fischer carbenes have also been shown to react with nitrones<sup>5</sup> and masked 1,3-dipoles.<sup>6</sup> However, only one case of reaction of alkenyl Fischer carbenes with 1,3-dipoles has been reported to date.<sup>7</sup> Moreover, none of the [3+2] cycloadditions mentioned above involves the use of chiral non-racemic carbene complexes. Therefore, we disclose our preliminary results in the reaction of ( $\pm$ )-menthol and (-)-8-phenylmenthol derived alkenyl(alkoxy)chromium carbenes<sup>8</sup> with diazomethane derivatives.

The reaction of chromium carbene complexes **1** with a slight excess of the corresponding diazomethane derivative in THF at temperatures ranging from  $-78^\circ\text{C}$  up to room temperature led, after a few hours, to the 4,5-dihydro-1*H*-pyrazole carbenes **2** as single regioisomers in moderate yields (Scheme 1, Table 1).<sup>†</sup> These results can be explained by considering the initial formation of the 4,5-dihydro-3*H*-pyrazoles **3** which undergo a sigmatropic [1,3]-hydrogen shift leading to the thermodynamically more stable 4,5-dihydro-1*H*-pyrazoles **2**. The diastereoselectivity was moderate when the reaction was carried out with ( $\pm$ )-menthol derived carbenes (Table 1, entries 2, 5); however only one diastereomer was detected when (-)-8-phenylmenthol derived carbenes were used (Table 1).<sup>‡</sup> The *trans* relative stereochemistry of **2** was unequivocally established by NOE experiments. The absolute configuration proposed for **2** should be the one depicted in Scheme 1 based on the model that assumes that in (-)-8-phenylmenthol derived carbene complexes **1** the phenyl ring shields the front face of the double bond in such a way that the dipole attacks selectively from the back.<sup>9</sup>

4,5-Dihydro-1*H*-pyrazole carbenes **2** are stable enough for



**Scheme 1** Reagents and conditions: i,  $\text{R}^2\text{CHN}_2$  (1.5 equiv.), THF, 2–9 h,  $-78^\circ\text{C}$  to room temp.; ii,  $(\text{Boc})_2\text{O}$ ,  $\text{Et}_3\text{N}$ , DMAP, THF, 1 h,  $-78^\circ\text{C}$ ; iii, pyridine *N*-oxide, THF, 12 h, room temp.; iv,  $\text{R}^2\text{CHN}_2$  (1.5 equiv.), THF, 6–8 days,  $67^\circ\text{C}$

their characterization by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy but slowly furnish the corresponding pyrazole derivatives by exposure to air. To avoid this problem they were transformed into the corresponding *N*-Boc derivatives **4** by treatment with  $(\text{Boc})_2\text{O}$  and  $\text{Et}_3\text{N}$ -DMAP. Subsequent oxidation of the metal-carbon double bond with pyridine *N*-oxide led to the corresponding esters **5** (Scheme 1). The overall yields of the transformation **1**→**5** were greatly improved by the one-pot procedure (Table 2, entries 1, 2). Esters **5** can also be prepared from the *trans*-cinnamates **6** but at higher temperatures and longer reaction times with much poorer diastereoselectivities (Table 2, entries 3, 4). These results clearly show the rate and diastereoselectivity enhancement of the metal pentacarbonyl moiety over the oxygen atom in the [3+2] cycloaddition process with diazomethane derivatives.

<sup>†</sup> When disubstituted diazomethane derivatives ( $\text{Ph}_2\text{CN}_2$ ) or diazomethane derivatives containing electron-withdrawing groups ( $\text{R}^2 = p\text{-NO}_2\text{-C}_6\text{H}_4\text{-}$ ,  $\text{EtO}_2\text{C-}$ ) were used the cycloadducts were not detected.

<sup>‡</sup> Diastereoselectivities were determined by  $^1\text{H}$  NMR (300 MHz) of the crude residues. All compounds were fully characterized and gave the expected spectral and analytical data.

**Table 1** [3+2] Cycloaddition of **1** with diazomethane derivatives<sup>a</sup>

Entry	N-H Adduct	Yield (%) <sup>b</sup>	N-boc Adduct	Yield (%) <sup>b</sup>	R <sup>1</sup>	R <sup>2</sup>	Diastereomeric ratio
1	<b>2a</b>	29			Ph	H	>95:5
2	<b>2b</b>	52	<b>4b</b>	60	Ph	TMS	>95:5 (75:25) <sup>c</sup>
3	<b>2c</b>	33	<b>4c</b>	61	Ph	Ph	>95:5
4	<b>2d</b>	47	<b>4d</b>	69	Ph	CH <sub>2</sub> =CH	>95:5
5	<b>2e</b>	38	<b>4e</b>	68	2-Furyl	TMS	>95:5 (67:33) <sup>c</sup>

<sup>a</sup> R\*OH = (–)-8-Phenylmenthol. <sup>b</sup> Isolated yields. <sup>c</sup> R\*OH = (±)-Menthol.

**Table 2** One-pot synthesis of **5** from **1** and **6**

Entry	Starting material	R*OH	<i>t</i> <sup>a</sup>	<i>T</i> °C <sup>a</sup>	Compound	Yield (%) <sup>b</sup>	Diastereomeric ratio
1	<b>1</b>	(±)-Menthol	2 h	0	<b>5a</b>	68 (24) <sup>c</sup>	75:25
2	<b>1</b>	(–)-8-Phenylmenthol	9 h	Room temp.	<b>5b</b>	73 (23) <sup>c</sup>	>95:5
3	<b>6</b>	(±)-Menthol	6 days	67	<b>5a</b>	76	55:45
4	<b>6</b>	(–)-8-Phenylmenthol	8 days	67	<b>5b</b>	65	60:40

<sup>a</sup> Reaction time and temperature for each [3+2] cycloaddition process; times monitored by TLC. <sup>b</sup> Isolated yields. <sup>c</sup> Overall yields in the stepwise procedure.

The one-pot transformation described here represents an expeditious route to 4,5-dihydro-1*H*-pyrazole esters **5** in a highly diastereoselective manner starting from (–)-8-phenylmenthol derived Fischer carbene complexes **1**, a [3+2] cycloaddition being the key step. Work directed to explore the synthetic potential of **5**§ as well as to ascertain some mechanistic aspects of the [3+2] cycloaddition of **1** with diazomethane derivatives and other 1,3-dipoles is under way.

## Experimental

### Preparation of **5b** from **1**. (Typical procedure)

1.5 Equiv. of TMSCHN<sub>2</sub> (0.75 ml; 2.0 M in hexane) were added dropwise to a solution of **1** (1 mmol) in 6 ml of THF at 0 °C and the reaction was stirred at room temperature for 9 h. The reaction mixture was then cooled to –78 °C and (Boc)<sub>2</sub>O (2 mmol, 444 mg), NEt<sub>3</sub> (1 mmol, 0.14 ml) and DMAP (1 mmol, 120 mg) were successively added. After 1 h, the reaction was complete (TLC monitored until disappearance of **2b**). Pyridine *N*-oxide (2 mmol, 182 mg) was added to the reaction and the flask was removed from the cooling bath. After 12 h no intermediate carbene **4** was observed by TLC. The solvent was evaporated under reduced pressure and the residue was chromatographed over silica gel. Sequential elution with hexane–AcOEt 50:1, 20:1 and 9:1 gave pure 4,5-dihydro-1*H*-pyrazole ester **5b** in 73% yield.

**Selected data for **5b**.** *R*<sub>f</sub> = 0.55 (hexane–AcOEt, 9:1); δ<sub>H</sub> (200 MHz; CDCl<sub>3</sub>; *J*/Hz) 7.39–7.22 (10 H, m), 4.84 (1 H, m), 4.37 (1 H, d, *J* 6.0), 3.93 (1 H, d, *J* 6.0), 2.36–0.79 (17 H, m), 1.59 (9 H, s), 0.20 (9 H, s); δ<sub>C</sub> (50 MHz, CDCl<sub>3</sub>) 161.1 (C), 151.5 (C), 149.9 (C), 147.9 (C), 141.5 (C), 128.9 (2 CH), 127.8 (2 CH), 127.4 (CH), 127.0 (2 CH), 125.7 (2 CH), 125.2 (CH), 82.2 (C), 76.5 (CH), 60.9 (CH), 52.7 (CH), 50.3 (CH), 41.4 (CH<sub>2</sub>), 40.2 (C),

34.2 (CH<sub>2</sub>), 31.2 (CH), 30.5 (CH<sub>3</sub>), 28.1 (3 CH<sub>3</sub>), 27.1 (CH<sub>2</sub>), 23.1 (CH<sub>3</sub>), 21.5 (CH<sub>3</sub>), –2.9 (3 CH<sub>3</sub>); *m/z* 576 (M<sup>+</sup>), 377, 235, 163 [Calc. for C<sub>33</sub>H<sub>45</sub>N<sub>2</sub>O<sub>4</sub>Si (M – 15), 561.3148. Found: *M*, 561.3149]; [α]<sub>D</sub><sup>25</sup> –16.0, 10<sup>–1</sup> deg cm<sup>2</sup> g<sup>–1</sup> (*c* 1.04, CHCl<sub>3</sub>).

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§ Preliminary results indicate that compounds **5** are easily transformed into enantiomerically pure 2,4-diamino alcohols. Results from this work will be reported in due course.

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