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# [4+2] Cyclization reactions of chiral $C_{\beta}$ -substituted Fischer alkenyl carbene complexes: efficient synthesis of enantiopure cyclohexenone and norbornene derivatives

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Abstract—Chiral alkenyl carbene complexes of tungsten(0) **1** and **2**, readily available from the chiral pool, undergo the [4+2] cycloaddition with the Danishefsky diene to provide enantiopure 4-alkenyl-2-cyclohexenone adducts **5** and **7** with high stereoselectivity after treatment of the primary cycloadducts **4** and **6** with TBAF. Cyclopentadiene also cycloadds to carbenes **1** and **2** affording the expected norbornene metal carbene complexes **10** and **12** with remarkable diastereo and face selectivity. Oxidative removal of the metal pentacarbonyl fragment leads to the ester derivatives **11** and **13**. The X-ray structure analysis of two cycloadducts derived from carbenes **1** and **2** has been performed. © 2007 Elsevier Ltd. All rights reserved.

### 1. Introduction

Due to the high electron-accepting power of the pentacarbonylmetal unit, Fischer-type  $\alpha$ , $\beta$ -unsaturated carbene complexes have demonstrated to be excellent partners for different cycloaddition reactions.<sup>1</sup> In particular, the [4+2] cycloaddition of alkenyl carbene complexes toward electronrich dienes,<sup>2</sup> which emerged two decades ago,<sup>3</sup> reveals some advantages over that based on electron-poor, non-metal dienophiles: (i) the reaction occurs under much milder reaction conditions and, therefore, higher selectivity is attained and (ii) the versatile metal carbene functionality is maintained unaltered in the cycloadduct allowing to undertake further elaboration.<sup>4</sup>

On the other hand, the asymmetric version of this process has not been so widely developed.<sup>5</sup> The most relevant contribution has been delivered by Wulff et al. who found that chiral aminoalkenyl carbene complexes of chromium(0) exhibited very high exo- and facial diastereoselectivity toward 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene).<sup>6</sup> In contrast, chiral alkoxyalkenyl carbene complexes, e.g., carbene complexes derived from (–)-menthol, have been shown to induce modest selectivity.<sup>5,7</sup> In a different approach, the cycloaddition reaction of cyclopentadiene and 2,3-dimethyl-1,3-butadiene with methoxyalkenyl carbenes having a monosaccharide unit (arabinose and galactopyranose) attached to the C- $\beta$  carbon has been reported to take place with moderate selectivity.<sup>8</sup> In this context, we have focused recently on the potential of tungsten alkenyl carbenes **1** and **2** containing a chiral group—1,3-dioxolane (**1**) and 1,3-dioxane (**2**)—that are readily available from the chiral pool<sup>9</sup> and, importantly, very promising for further elaboration. This type of chiral carbene complexes has been shown to exhibit high selectivity in Michael–Mukaiyama addition<sup>10</sup> and cyclopropanation (Michael type addition/cyclization)<sup>11</sup> reactions with 2-trimethylsilyloxy and 2-methoxyfuran, respectively (Fig. 1).

On the basis of these findings, we have explored the behavior of carbenes 1 and 2 in the Diels–Alder cycloaddition. We report herein that they undergo the [4+2] cycloaddition reaction with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene and cyclopentadiene with good chemical yield and high selectivity. The transformation of the cycloadducts into metal-free derivatives is also undertaken.

## 2. Results and discussion

First we found that enantiopure tungsten carbene complexes 1 and 2 are highly reactive toward the Danishefsky's diene 3 at low temperature (Scheme 1).<sup>12</sup> Thus, the reaction of the methoxycarbene 1a (R=Me) with 3 (5 equiv) in toluene

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#### Figure 1.

at-35 °C led to the formation of the expected [4+2] cycloadduct **4a** as a mixture of four diastereoisomers. The complex reaction crude was not analyzed, but it could be transformed into a 6:1 epimeric mixture of cyclohexenones by treatment with tetrabutylammonium fluoride (CH<sub>2</sub>Cl<sub>2</sub>, 0 °C), in 79% overall yield. Simple flash chromatographic purification permitted the isolation of the major diastereoisomer **5a** in enantiopure form and in high overall yield (64% yield referred to the starting metal carbene complex).



#### Scheme 1.

Furthermore, the stereoselectivity could be increased by simply using carbene complexes containing a higher steric demanding alkoxy group (Scheme 1). Thus, replacing the methoxy group (carbene 1a) with the isopropoxy group (carbene 1b) and conducting the sequence under the same reaction conditions resulted in the formation of the cyclohexenone adduct as a 15:1 epimeric (81% yield).

In the same way, the [4+2] cycloaddition of the carbene complex **2** with the diene **3** furnished a mixture of cycloadducts **6** (Scheme 2). Further treatment with TBAF afforded a 12:1 mixture of cyclohexenones (84% yield) from which the major stereoisomer **7** was separated by flash column chromatography (63% overall yield from carbene **2**).

The structure of the cycloadducts **5** and **7** is fully consistent with both the NMR spectral data, including 2D experiments (HMBC, HSQC, and NOESY), and the postulated diene–carbene approach (vide infra). The presence of the chiral auxiliary appendage allowed us to undertake further elaboration and to unambiguously determine the structure of the cycloadducts (Scheme 3). Thus, either cycloadduct **5a** or **5b** 



#### Scheme 2.

was stirred with concd HCl in methanol at 0 °C to afford the enantiopure isochromenone **8** in moderate yield (70% from **5a**; 75% from **5b**), after flash chromatographic purification.<sup>13</sup> (Scheme 3).



#### Scheme 3.

Compound **8** could be crystallized from a 10:1 pentane/ethyl acetate mixture and its structure confirmed by an X-ray analysis (Fig. 2).





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