Asymmetric *Exo*-Selective Diels–Alder Reactions of Cyclic BF_2 Adducts of Functionalized Fischer Vinylcarbene Complexes with Chiral 2-Amino-1,3-dienes

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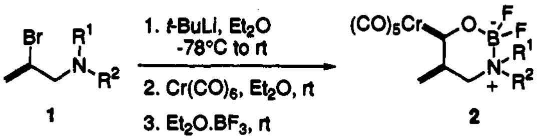
The enantioselective Diels–Alder reaction is a powerful tool for the rapid preparation of cyclohexene derivatives with up to four new and contiguous stereogenic centers generated with absolute stereochemical control.[1] It is well-known that this cycloaddition is generally *endo*-selective, although there are some cases of *exo*-selective Diels–Alder additions with conformationally restricted *s-cis* dienophiles,[2] α-substituted dienophiles,[3] furans or cyclopentadiene derivatives as dienes,[4] or monosubstituted dienophiles (isolated examples).[5] Alkenyl Fischer carbene complexes have been found to be exceptionally reactive, regioselective, and mainly *endo*-diastereoselective dienophiles in Diels–Alder reactions.[6] The first studied alkenylalkoxycarbene derivatives,[7] which are assumed to react in an *s-trans* conformation, led to different *endo*/*exo* product ratios, in which the former is usually the major product.[8] The Diels–Alder reactions of the less reactive alkenylaminocarbene complexes, which are assumed to take place via an *s-cis* conformation of the vinylcarbene unit, have been lately reported to proceed with high *exo* selectivity.[9] Herein we describe a facile one-pot synthesis of a novel type of Fischer vinylcarbene complex with a cyclic BF_2-chelated structure which temporary fixes the *s-cis* conformation of the exocyclic carbon–carbon and carbon–chromium double bonds and also the first examples of asymmetric Diels–Alder reactions of these boron difluoride complexes with chiral 2-amino-1,3-dienes[10] which are highly *exo*-selective. We recently reported the first [4 + 2] cycloadditions of these chiral dienes with conventional vinylalkoxycarbene complexes.[11]

Scheme 1



Compound	R^1	R^2	Yield (%)[a]
2a	Et	Et	39
2b	Et	Ph	38
2c	Me	Ph	35
2d	Me	*p*-Me_3CPh	45
2e	Me	*p*-MeOPh	30

[a] Based on compound **1**

Carbene complexes **2** were prepared as shown in Scheme 1. The appropriate β-amino-functionalized vinylic organolithium reagent[12] was generated from the corresponding 2-bromoallylamine **1** by reaction at low temperature in Et_2O with *tert*-butyllithium (2 equiv) and then was added dropwise to a solution of chromium hexacarbonyl (1 equiv) in Et_2O at room temperature. Subsequent treatment with an excess (3–4 equiv) of boron trifluoride etherate followed by purification by flash column chromatography on silica gel (hexane:CH_2Cl_2, 1:1–2) led to carbenes **2** as perfectly stable dark-red solids,[13,14] though they very slowly decomposed upon standing at room temperature in THF or CH_2Cl_2 solutions. The structures of compounds **2** were determined from their spectral data and unambiguously established by single-crystal X-ray analysis of **2a** and **2b**.[15,16]

Given that *exo* selectivity in Diels–Alder reactions seems to be a general property of conformationally rigid cyclic *cisoid* dienophiles, carbene complexes **2** appeared to us to be attractive

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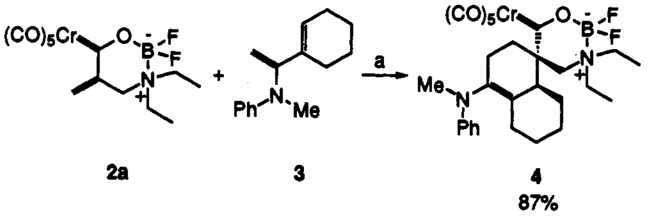
Table 1. *Exo* Enantioselective Diels–Alder-Type Reactions of Metal Carbene **2a** with Chiral Dienes **5**

product	R^3	yield (%)[a]	ee (%)[b]	$[\alpha]_D$[c] (deg)
6a	OMe	39	92	–4.4
6b	OCH_2Ph	39	93	–9.6
6c	$OSiMe_3$	44	90	–24.9

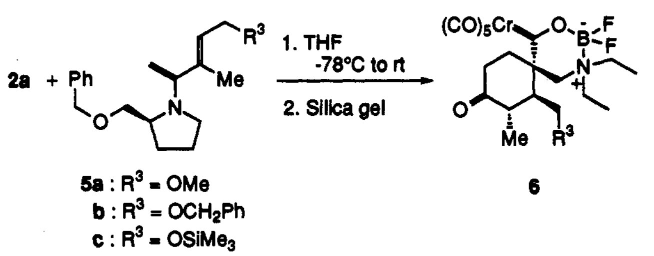
[a] Isolated yields of cycloadducts after flash chromatography based on carbene **2a**. [b] Enantiomer ratios determined by chiral HPLC (Chiralcel OD-H, hexane:THF, 6-12:1) in comparison with the corresponding racemic mixtures. [c] Optical rotations were recorded in $CHCl_3$ at 20–25 °C, c = 0.59 (**6a**), 1.55 (**6b**), and 0.33 (**6c**) g/100 mL.

Scheme 2



[a] Conditions: (a) THF, –78 °C to room temperature.

Scheme 3



candidates for diastereoselective [4 + 2] cycloadditions. Thus, we first studied the reaction of **2a** with 2-aminodiene **3**[10a] (molar ratio 1:1, THF, from –78 °C to rt, 12 h), which led after chromatographic purification (basic aluminum oxide, hexane: $Et_2O:CH_2Cl_2$, 8:1:1) to only one diastereo- and regioisomeric cycloadduct **4** as a yellow solid (Scheme 2; the stereochemistry shown has been assumed by analogy from subsequent results). This high selectivity moved us to study the reaction with chiral dienes **5**,[17] and the results are indicated in Scheme 3 and summarized in Table 1. Treatment of chromium carbene **2a** with dienes **5** under the above conditions followed by column chromatography purification (silica gel, hexane:CH_2Cl_2, 1:1.5–2, where hydrolysis of the aliphatic enamine group took place) afforded spiro compounds **6** (yellow solids) as single Diels–Alder adducts with a uniformly high level of enantioselectivity (90–93% ee). As proven by an X-ray structure determination of **6a**[15,18] (Figure 1), the relative and absolute configuration is as depicted in **6**, which corresponds to an *exo* diene–dienophile (C=Cr bond) orientation. Surprisingly, the sense of diastereofacial selectivity, opposite to that initially expected,[10b] would correspond to dienophile addition to the π-face of the chiral diene, which appears to be the sterically more hindered one. Presumably, the reaction takes place in a sequential fashion involving zwitterionic species, with the observed facial selectivity controlled by electrostatic interactions.[19] Finally, the reaction shown in Scheme 4 illustrates a method for transforming cycloadducts **6** to metal-free organic products. Oxidative cleavage of the chromium pentacarbonyl fragment of **6a** with ceric ammonium nitrate (CAN, 2 equiv)[20] afforded BF_2-protected amino acid **7**. Further methanolysis to cleave the boron complex,[21] which unfortunately took place with epimerization of the stereogenic center α to the ketone carbonyl group, gave amino acid **8** as a roughly 2:1 mixture of diastereoisomers.[22]

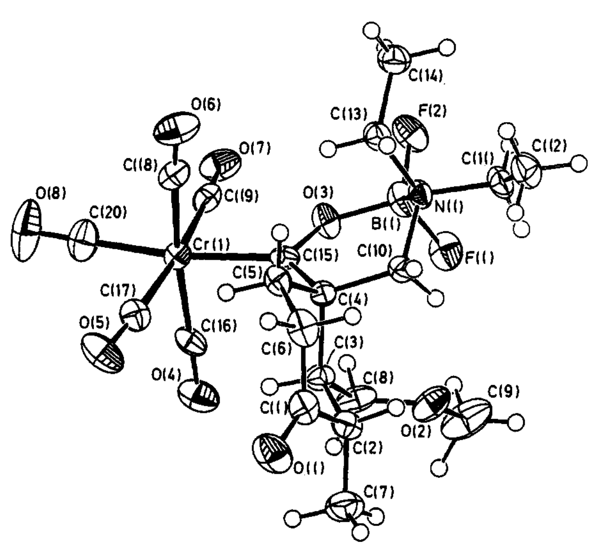
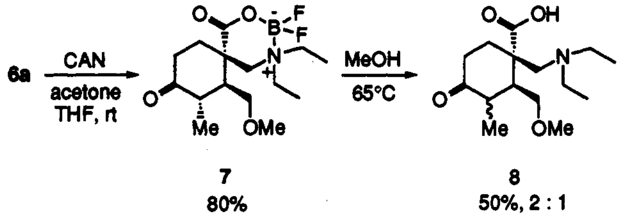


Figure 1. Molecular structure of **6a** (EUCLID plot).

Scheme 4



In summary, we described the preparation of a new type of Fischer vinylcarbene complex that is temporarily locked into *s-cis* conformation by means of an eventually removable BF_2 group. These carbenes behave as dienophiles which are remarkably regio- and *exo*-selective in addition to being highly diastereofacially selective in Diels–Alder reactions with chiral 2-aminodienes.

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Supplementary Material Available: General experimental procedures for **2** and **6**; copies of ^1H, ^{13}C, and ^{19}F NMR spectra of **2a–e**, **4**, **6a–c**, **7**, and **8**; copies of HPLC chromatograms of **6a–c**; tables of X-ray data for **2a**, **2b**, and **6a**; and structural diagrams of **2a** and **2b** (64 pages); listing of observed and calculated structure factors for **2a**, **2b**, and **6a** (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information. The crystal data have been deposited at the Cambridge Crystallographic Data Center.

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(17) Prepared in optically-pure form from commercially available enynes and (*S*)-prolinol. See ref 10.

(18) Absolute configuration checked using the BIJVOET program[23] giving B = 0.984(1) for the 200 strongest Friedel pairs [Flack χ parameter,[24] –0.0135-(206)].

(19) A referee has suggested the possibility of a two-step mechanism and a zwitterion. Assuming an initial *anti* attack of the enamine unit to complex **2**, the face selectivity of the diene can be explained by a greater number of close contacts of the prolinol unit with the metal center than with the vinyl substituent of the enamine. The zwitterion thus formed undergoes final ring closure with the -CH_2R^3 unit positioning itself *anti* to the metal. We acknowledge it.

(20) This oxidation can also be carried out with methyl(trifluoromethyl)-dioxirane (TFMD). We thank A. Messeguer, F. Sánchez-Baeza, and A. M. Lluch for performing the initial experiments.

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