Asymmetric Construction of 4*H*-Carbazol-4-one Intermediates via the Cyclohexadienone Annulation of Chiral Carbene Complexes

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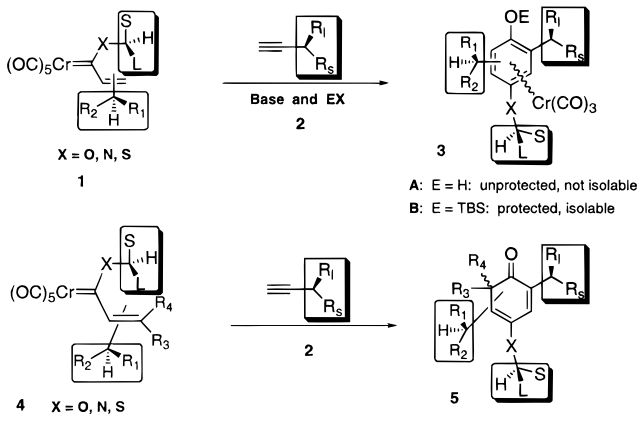
Summary: The quaternary carbon in a 4H-carbazol-4-one can be introduced with high stereoprecision in the cyclohexadienone annulation of a 2-indolyl chromium carbene complex bearing an imidazolidinone chiral auxiliary. The chiral complex ***12*** *was found to exist as atropisomers that were readily separated, and each was found to react with the same alkyne to give opposite configurations at the quaternary carbon in the 4H-carbazol-4-one product.*

In the last few years, we have become interested in the asymmetric reactions of Fischer carbene complexes with alkynes to produce six-membered rings.[1] There are three possibilities for this in the benzannulation reaction, where the planar center of chirality of the chromium tricarbonyl group in **3** can be induced from an existing chiral center in one of the reagents as indicated in Scheme 1. High selectivity can be obtained with chiral alkynes if propargyl ethers are employed as substrates.[2] A few examples have also appeared which reveal that chiral centers in the unsaturated carbene complex substituent can lead to significant induction depending on the position of the chiral center.[3] The incorporation of a chiral center in the heteroatom stabilizing substituent of the carbene complex has also been investigated, and it appears that significant induction can be obtained only in special cases; it is thought that the lack of selectivity is due to the degrees of freedom available to the appended chiral alcohol or amine.[4] There are also three possibilities for induction in the cyclohexadienone annulation where the configuration of the newly formed quaternary carbon of the cyclohexadienone ring in **5** may be influenced by existing chiral centers in either the alkyne or the carbene complex. We have previously reported that high induc-

Scheme 1



tions are possible with either chiral alkynes[5] or with carbene complexes bearing chiral centers in the unsaturated carbene carbon substituent.[3c,6] We report here the first examples of asymmetric induction in a cyclohexadienone annulation from a carbene complex bearing a chiral heteroatom stabilizing substituent.

The cyclohexadienone annulation of indole complexes is attractive for the synthesis of indole alkaloids. Indole carbene complexes of the type **6** bearing a methoxy group can be easily prepared and will undergo reaction with a number of different alkynes to give high yields of the 4*H*-carbazol-4-ones **7**, Scheme 2.[7] In considering asymmetric versions of this reaction, where a chiral center was incorporated into the heteroatom stabilizing substituent, we were attracted to 1,5-dimethyl-4-phenyl-2-imidazolidinone as a chiral auxiliary since it has made high enantioselectivites possible for aldol, Michael, and Diels−Alder reactions of Fischer carbene complexes.[8] There was some concern as to whether complexes of this type would undergo efficient annulation since it is known that substitution of an oxygen heteroatom stabilizing substituent of a Fischer carbene complex by a nitrogen substituent can lead to a decrease in the yield of six-membered ring products.[9] However, Dötz and co-

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(2) Hsung, R. P.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 6449.

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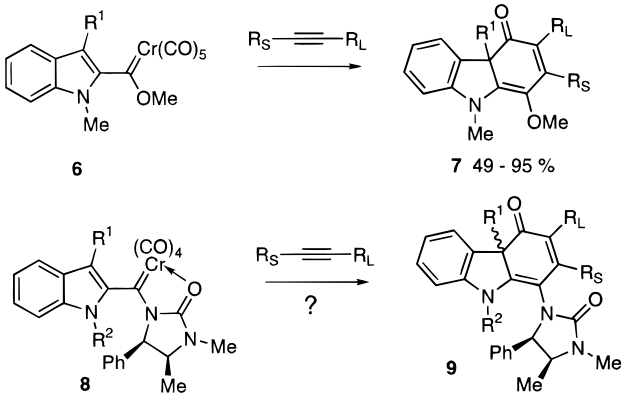
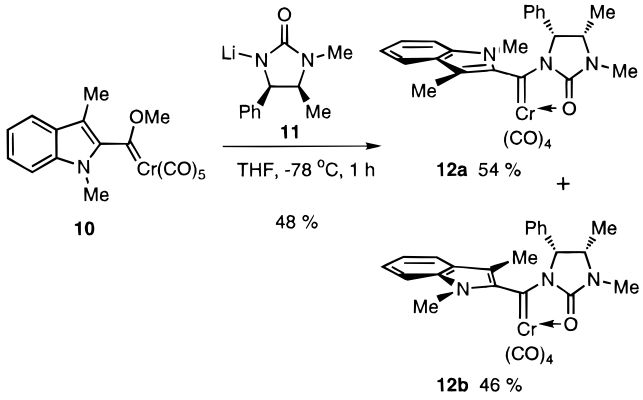
Scheme 2



Scheme 3



workers have shown that high selectivity can be achieved for six-membered ring products if the nitrogen atom is electronically deactivated as a carbamate.[10] The cyclic urea complex **8** should also be electronically deactivated relative to a simple alkylamino complex but, on the other hand, would be expected to be slightly more electronic-rich than a carbamate complex. Thus, it would be impossible to predict with any certainty whether complex **8** would give high selectivity for the cyclohexadienone product **9**.

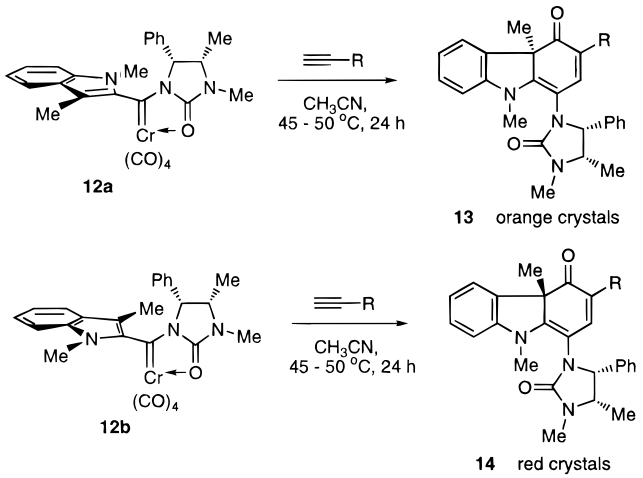
After examination of a number of different methods, it was found that the best way to introduce the imidazolidinone chiral auxiliary was the direct reaction of a methoxyindole carbene complex with the lithium salt of the imidazolidinone. The reaction of the (4*R*,5*S*) lithium salt **11**[11] with the 1,3-dimethyl-2-indolyl carbene complex **10** gave a 48% percent overall yield of the imidazolidinone carbene complex **12**, Scheme 3. Interestingly, it was found that imidazolidinone carbene complex **12** was produced as a nearly equal mixture of atropisomers that do not interconvert. These atropisomers can be completely separated by a single pass on a silica gel column (R_f = 0.43 and 0.30 in 1:1 EtOAc:hexane) to give each compound as lustrous black crystals. These isomers could not be interconverted thermally. When complex **12a** was heated in a deoxygenated benzene solution for 24 h at 80 °C, it was recovered in essentially quantitative yield with no detectable isomerization to **12b** or no detectable decomposition. However, when heated at 110 °C in deoxygenated toluene-d_8 for prolonged periods, only substantial decomposition of **12a** was observed.

Table 1. Asymmetric Induction in Cyclohexadienone Annulation of Indole Complexes[a]

entry	carbene complex	*M*[b]	R	yield of **13**[c]	yield of **14**[c]	% de
1	**12a**	0.05	*n*-Pr	40	≤0.8	≥96
2	**12a**	0.01	*n*-Pr	50	≤1.0	≥96
3	**12a**	0.005	*n*-Pr	61[d]	≤1.2	≥96
4	**12b**	0.05	*n*-Pr	≤0.6	22	≥95
5	**12b**	0.01	*n*-Pr	≤0.9	35	≥95
6	**12b**	0.005	*n*-Pr	≤0.9	33[e]	≥95
7	**12b**	0.01	Ph	≤1.0	40	≥95

[a] Reactions carried out in acetonitrile at the indicated concentration in carbene complex with 1.5 equiv of alkyne. [b] Concentration of carbene complex. [c] Isolated yield after purification on silica gel (hexane:EtOAc, 1:1). Upper limit on minor product determined by ^{1}H NMR. [d] Yields for this reaction ranged from 54 to 70%. [e] Yields for this reaction ranged from 26 to 48%.

Scheme 4



The cyclohexadienone annulation reactions of atropisomeric carbene complexes **12a** and **12b** were carried out independently, and the results are summarized in Table 1. All of these reactions produce the cyclohexadienone product as the only compound which is mobile on silica gel, Scheme 4. The yield of the 4*H*-carbazol-4-one increases with decreasing concentration, suggesting that multiple alkyne incorporation is a competing pathway, as observed in the other examples.[12] The yields in Table 1 for entries 3 and 6 are the average of several runs, where, for example, the range in the yield of **13** is 54−70 % at 0.005 M. In every reaction in Table 1, only a single diastereomer of the product could be observed within the limits of detection by ^{1}H NMR. Interestingly, it was found that the reaction is stereospecific with each atropisomer giving a different diastereomer, one of which was dark orange and the other dark red. The diastereomeric 4*H*-carbazol-4-ones **13** and **14** do not exist as atropisomers, although hindered rotation is evident in their ^{1}H NMR spectra at room temperature. The assignment of the stereochemistry of the diastereomeric 4*H*-carbazol-4-ones **13**

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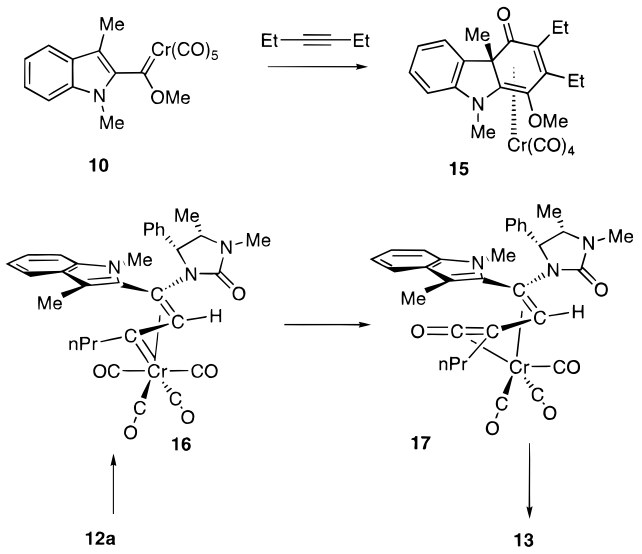
(11) Both the (4*R*,5*S*) and the (4*S*,5*R*) isomers of the 1,5-dimethyl-4-phenyl-2-imidazolidinone are commercially available from Aldrich Chemical Co. or can be conveniently prepared in one step from ephedrine, see: Close, W. J. *J. Org. Chem.* **1950**, *15*, 1131.

(12) Wulff, W. D.; Bax, B. M.; Brandvold, T. A.; Chan, K. S.; Gilbert, A. M.; Hsung, R. P.; Mitchell, J.; Clardy, J. *Organometallics* **1994**, *13*, 102.

Scheme 5



and **14** and the atropisomeric carbene complexes **12a** and **12b** was determined by X-ray diffraction. Single crystals were grown of the less polar atropisomer of the carbene complex (**12a**) and of the orange diastereomer of the 4*H*-carbazol-4-one (**13**). The results of the x-ray diffraction study of **12a** and **13** can be found in the Supporting Information and conclusively show that the atropisomer with the indole nitrogen syn to the phenyl group of the chiral auxiliary gives the 4*H*-carbazol-4-one with an α-disposition of the angular methyl group.

One possible explanation for the stereospecificity of the reactions of complexes **12a** and **12b** is shown in Scheme 5. Rotation about the indole−carbene carbon bond does not occur in carbene complex **12** under the reaction conditions, and if this is also the case for the vinyl carbene complexed intermediate **16** and the vinyl ketene complexed intermediate **17**, then the stereochemistry of **13** can be predicted from **12a** according to the stereochemistry of the intermediates in Scheme 5. Reaction of **12a** with the alkyne would be expected to occur with the chromium and its ligands remaining on the same face of the indole ring to give the vinyl carbene intermediate **16**. Insertion of CO would then give the ketene complex **17**. If the electrocyclic ring closure of ketene complex **17** were to occur with a migration of the methyl group away from the chromium, then the stereochemistry of the observed product **13** could be accounted for. Evidence for this stereochemistry in the electrocyclic ring closure can be found in our earlier observation of the η^4-cyclohexadienone chromium tetracarbonyl complex **15**.[7] Complex **15** is the only example of a complex of this type from the cyclohexadienone annulation. It was isolated as a single diastereomer with the methyl anti to the chromium, although it is not clear that this is the only isomer produced since substantial amounts of the demetalated material was also produced in this reaction. Additional evidence for the *anti*-rotation of the methyl group in the cyclization of **17** comes from our recent studies on 1,4-induction in the cyclohexadienone annulation of chiral alkynes.[5]

Further studies are underway to determine if the high asymmetric induction observed in the cyclohexadienone annulation of the imidazolidinone carbene complex **12** is due to the hindered rotation of the indole substituent about the carbene carbon or if it is due to some other consequence of the presence of the imidizolidinone chiral auxiliary.

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Supporting Information Available: Text giving the experimental procedures and spectral data for all new compounds and tables of atomic parameters, anisotropic thermal parameters, bond distances, and bond angles, and ORTEP diagrams of **12a** and **13** (30 pages). Ordering information is given on any current masthead page.

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