

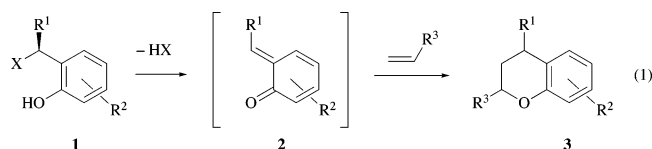
Traceless Stereoinduction in the One-Pot Assembly of All Three Rings of Hexahydrodibenzopyrans

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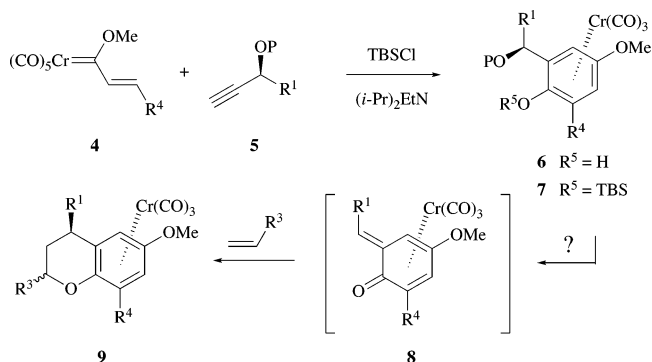
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The chemistry associated with *o*-quinone methides is quite extensive and includes a diverse array of cleverly designed tactics for their generation, a host of elegant applications in the total synthesis of natural products, their natural role as key intermediates in biosynthetic pathways, and as reactive intermediates, the focal point of a range of both natural and intelligently designed bioactivity.¹ The Diels–Alder reactions of *o*-quinone methides with alkenes represents a well-established method for the synthesis of chromanes.¹ For *o*-quinone methides bearing a substituent on the methide carbon (**2**, R¹ ≠ H), the stereochemistry at that carbon in the precursor is lost and the cycloadduct is produced in racemic form (eq 1). Asymmetric Diels–Alder reactions of *o*-quinone methides that produce an asymmetric carbon at the benzylic position are essentially nonexistent, which is undoubtedly a function of the high reactivity of these fleeting intermediates. The one prominent success was reported by Pettus and co-workers and involves an auxiliary-mediated asymmetric cycloaddition of a chiral ether.² The high diastereomeric excess that was observed was presumably enabled by the low-temperature method for *o*-quinone methide generation developed by the Pettus group.³



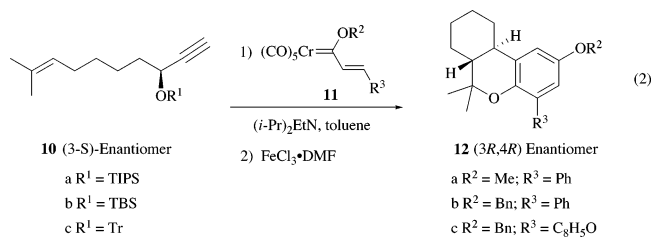
We had previously found that the reactions of Fischer carbene complexes with propargylic ethers in the presence of *t*-BuMe₂SiCl and a base provided good yields of TBS-protected phenol chromium tricarbonyl complexes of the type **7** in which the chromium tricarbonyl unit was installed with high diastereoselectivity relative to the existing propargylic chiral center (Scheme 1).⁴ This reaction presumably proceeded via the phenol complex **6**, which was then silylated to give the ultimate product **7**. The question that arises is if the reaction of complex **4** and propargyl ether **5** is performed in the presence of base without a silylating agent, would elimination occur to give the *o*-quinone methide complex **8**, which is not known but likely exists as an η⁶-complex?^{5b} Metal complexes of *o*-quinone methides are known for osmium (η²),⁶ tungsten (η²),⁷ rhodium, and iridium (η⁴).⁸ Interestingly, the *o*-quinone methide in the Cp*Ir complex has inverted reactivity and displays a nucleophilic methide carbon although this would not be expected for the chromium tricarbonyl complex **8**. There is one example of the generation of an *o*-quinone methide from the reaction of a chromium carbene complex with a propargyl ether where a dimerization of the *o*-quinone methide was observed.⁹ However, it was not established whether the Diels–Alder reaction that led to the dimer involved the cycloaddition of a chromium complexed or metal free *o*-quinone methide. If in fact the chromium complex **8** would undergo a Diels–Alder reaction before the chromium is lost then the product **9** should contain the stereochemical information present in the propargyl ether **5** via a relay to the planar center of chirality present in the phenol complex **6** and the *o*-quinone complex **8**. The absolute stereochem-

Scheme 1



istry of **9** derives from the expectation that the cycloaddition should occur *anti* to the metal.⁵

We report here that the reactions of chromium carbene complexes of the type **11** with enynyl propargyl ethers **10** in the presence of base will generate hexahydrodibenzopyrans after an oxidative workup. The involvement of a [4 + 2] cycloaddition of a chromium complexed *o*-quinone methide intermediate is inferred from the high asymmetric induction observed. Since the origins of this stereoinduction cannot be discerned by examination of the product this is termed a traceless stereoinduction.



The reaction of carbene complex **11a** (R² = Me, R³ = Ph) with the 3*S*-enantiomer of the enyne **10a** (R¹ = TIPS) was carried out in toluene in the presence of 5 equiv of Hünig's base. A non-oxidative workup gave inseparable mixtures with non-cyclized products but it was found that **12** could be isolated cleanly upon workup with FeCl₃·DMF complex. Hexahydrodibenzopyran **12a** was obtained in 60% yield with 90% ee (Table 1, entry 2). The stereochemistry of the ring junction was assigned as *trans* on the basis of the ¹H NMR spectrum (of the Cr(CO)₃ complex, see Supporting Information) and thus results from an *exo* transition state in the intramolecular Diels–Alder reaction.¹⁰ The 3*R*,4*R* configuration is assigned assuming that the propargyl ether delivers the Cr(CO)₃ group to the lower face of the *o*-quinone methide **8** as indicated in Scheme 1 and that the olefin participates in a Diels–Alder reaction that involves approach *anti* to the chromium in the *o*-quinone methide complex **8**.^{5,11} These assumptions are supported by the matched/mismatched study discussed below. The asymmetric induction in the formation **12a** was determined by chiral HPLC after the methyl ether was deprotected to give a phenol. The trityl protected enyne

Table 1. Sequential Benzannulation, *o*-quinone Methide Formation, and IMDA Reactions of Carbene Complex **11** and Enynyl Ether **10**^a

R ³	R ²	R ¹	temp (°C)	time (h)	yield 12 ^b	% ee 12 ^c
C ₆ H ₅	Me	TIPS	90	24	42	94
		TIPS	100	48	60	90
		TIPS	110	24	48	92
		TBS	90	24	39	94
		TBS	100	24	39	94
		TBS	100	48	51	92
		TBS	110	24	58	88
C ₆ H ₅	Bn	TIPS	100	48	45	86
		TIPS	100	48	48	93
C ₈ H ₅ O	Bn	TIPS	100	48	40	91

^a All reaction were carried out at 0.03 M carbene complex in toluene with 1.2 equiv of alkyne and 5 equiv of (*i*-Pr)₂EtN under argon for the indicated time and temperature followed by oxidative workup with FeCl₃·DMF. ^b Isolated yield by chromatography on silica gel. ^c Determined by HPLC after either demethylation or debenzoylation to the free phenol.

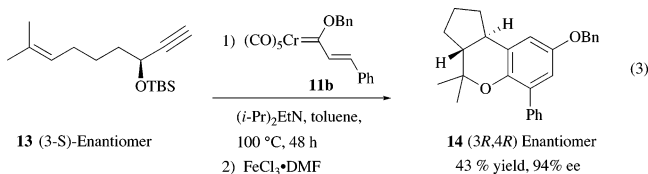
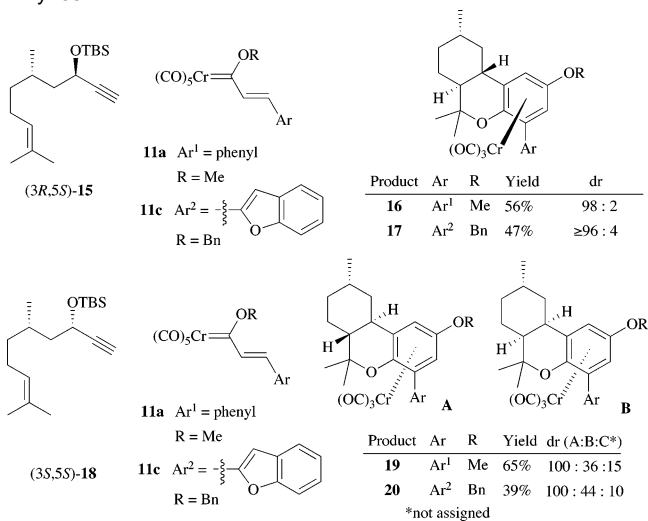


Table 2. Matched and Mismatched Reactions with *syn* and *anti* Alkynes^a



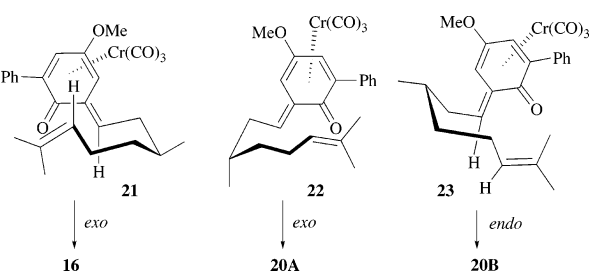
^a Conditions given in Table 1; 80–90 °C, 24–30 h.

10c (R¹ = trityl) gave a slightly lower induction than either the TBS or TIPS ethers, which was not expected on the basis of the diastereoselectivities observed for the complexes **7**.⁴ High asymmetric inductions are also observed for the benzyl protected complexes **11b** (R² = Bn, R³ = Ph) and **11c** (R² = Bn, R³ = C₈H₅O).

The reaction of the 1,7-enyne **13** with carbene complex **11b** gave the 6–6–5 tricyclic compound **14** in 94% ee as a single diastereomer that was determined to have a trans ring fusion (eq 2). This reaction is of interest since the generation of hexahydrocyclopenta-benzopyrans via the intramolecular Diels–Alder reaction of an *o*-quinone methide is limited to four reports, which describe either the formation of the cis-adduct in low yields (12%),^{12a} the formation of cycloadducts with undetermined stereochemistry,^{12b} or the formation of mixtures of cis and trans isomers along with either cycloadducts with inverted regiochemistry^{12c} or products resulting from carbocation rearrangements.^{12d}

The reaction was also investigated with enynes containing a second chiral center in addition to the propargylic ether (Table 2). The (3*R*,5*S*)-enyne **15** is the matched case and gives a 98:2 mixture of diastereomers the major of which was assigned as **16** having a

Scheme 2



trans-ring junction as indicated by ¹H NMR analysis. The formation of **16** is envisioned to occur via the Diels–Alder reaction indicated by the conformation of the *o*-quinone methide intermediate **21** (Scheme 2). It is well-established that a methyl group at the C-9 position of the tether such as in **21** will enforce the formation of a single diastereomer from the Diels–Alder reaction of a metal free *o*-quinone methide and this occurs via a chair transition state for an *exo*-cycloaddition in which the methyl group is in an equatorial position.¹³ Such a chair transition state is possible in **21** with the cycloaddition occurring *anti* to the chromium but not in diastereomer **22**, where the chromium is on the opposite face of the *o*-quinone methide and where the chair transition state for the *exo*-cycloaddition *anti* to the metal has an axial methyl. The ((3*S*,5*S*)-enyne **18** is the mismatched case and gives a mixture of diastereomers, the two most predominate of which are formed via an *exo*-cycloaddition with a chair transition state with an axial methyl (**22**) and an *endo*-cycloaddition with a chair transition state with an equatorial methyl (**23**).

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Supporting Information Available: Experimental procedures, and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (10) The *exo* transition state is observed for the intramolecular Diels–Alder reactions of metal-free *o*-quinone methides in the synthesis of hexahydrocannabinoids; see ref 1, pp 5369–5370.
- (11) The reaction of **10b** and **11a** in the presence of TBSCl gives **7b** (R⁴ = Ph, R¹ = (CH₂)₄CH=(CH₃)₂ in 82% yield as one diastereomer (dr ≥ 96:4) (see Supporting Information). Thus the high selectivity for **12** is not due to selective reactions of the diastereomers of **6**.
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