

Asymmetric Conjugate Nucleophilic Addition of Organolithiums to Chromium (Menthylxy)(aryl)carbene Complexes

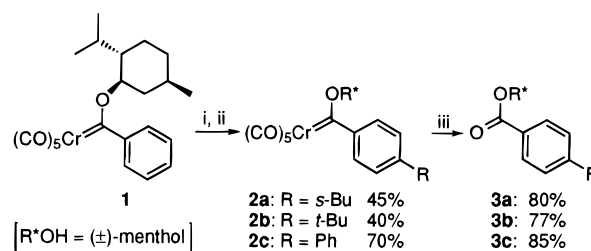
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Nucleophilic aromatic addition and substitution reactions have been essentially achieved with electron-deficient arenes,¹ such as nitroarenes,² 2-aryloxazolines,³ or η^6 -arene transition metal complexes, mainly arenetricarbonyl chromium complexes.⁴ More recently, conjugate-type additions of organolithiums to 2,6-di-*tert*-butyl-4-methoxyphenyl naphthalenecarboxylates (BHA esters)⁵ or to aromatic aldehydes and ketones in the presence of aluminum tris(2,6-diphenylphenoxide) (ATPH)⁶ have been reported. These aromatic derivatives contain, as an electron-withdrawing group, a sterically hindered carboxyl or carbonyl functionality, respectively, which prevents nucleophilic attack to the carbonyl carbon. Given the strong electron-withdrawing ability of the pentacarbonyl metal fragment of Fischer carbene complexes,⁷ the aromatic ring of alkoxy(aryl)carbene complexes should be activated toward nucleophilic attack. However, thus far, all of the experimental evidence known confirms that the addition of nucleophiles takes place at the carbene carbon. Indeed, the nucleophilic addition of heteroatomic nucleophiles (alcohols, amines, thiols) at the carbene carbon has found wide application in the modification of carbene ligands.⁸ Similarly, organolithium reagents and other carbon nucleophiles⁹ add to Fischer arylcarbene complexes in a 1,2-fashion, leading to

Scheme 1^a



^a (i) RLi, THF, -78 °C to rt, 12 h; (ii) Silica gel; (iii) Air, light, hexane, rt, 36 h.

different reaction products depending on the nature of the organolithium, temperature, or workup conditions. The reaction of group 6 pentacarbonylaryl- or heteroaryl(methoxy)carbene complexes with aryl- and heteroaryl lithium compounds gave non-heteroatom-stabilized Fischer diarylcarbene complexes when the reaction was carried out at low temperature¹⁰ and 1,2-dimethoxy-1,1,2,2-tetraarylethanes, among other products, when the reaction was warmed to room temperature.¹¹ On the other hand, the reaction of the same type of carbene complexes with vinyl- and alkyl lithiums afforded a mixture of two vinyl ethers¹² or a pentacarbonyl(π -olefin)tungsten complex;¹³ in addition, treatment with chloromethyl lithium generated in situ led, after hydrolysis of an enol ether intermediate, to aryl methyl ketones.¹⁴ A feature common to all these reactions is the presence of a small alkoxy group attached to the carbene carbon. We thought that a bulky alkoxy derivative could inhibit nucleophilic attack at the carbene carbon (1,2-addition) and direct it to an aromatic ring carbon (1,4- or 1,6-addition). This turned out to be the case, and we report herein the first examples of the regioselective conjugate addition of organolithiums to the aromatic nucleus of sterically demanding alkoxy(aryl)carbene complexes.¹⁵

Treatment of carbene complex **1**¹⁶ with *sec*-butyl-, *tert*-butyl-, or phenyllithium (molar ratio 1:1) at -78 °C provided, on warming to room temperature (rt) overnight and after chromatographic workup, the corresponding aromatic products of *para* substitution (**2**, Scheme 1).¹⁷ These carbene complexes **2** were characterized by NMR spectroscopy and further oxidized with air and light to the corresponding carboxylic esters **3**, where 1,4-disubstitution of the aromatic ring was clearly established. Compounds **2a** and **3a** each showed a single set of NMR signals. The nucleophilic addition of organolithiums to the aromatic ring of complex **1** occurs within minutes at -78 °C, and the initially formed 1,6-adducts can be trapped before the spontaneous aromatization takes place. Thus, as shown in Scheme 2, quenching the reaction (after 5 min of stirring between -78 °C and rt with subsequent removal of THF under reduced pressure

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(17) The reaction with a primary alkyl lithium such as BuLi under the same experimental conditions took place at the carbene carbon (1,2-addition) affording a mixture of butyl phenyl ketone (20%) and its corresponding (\pm)-menthyl enol ether (40%).

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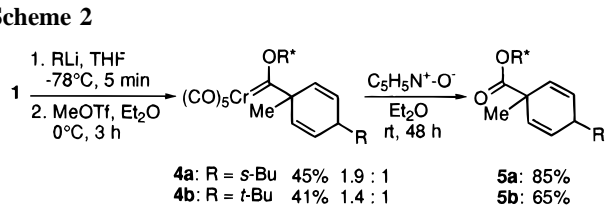
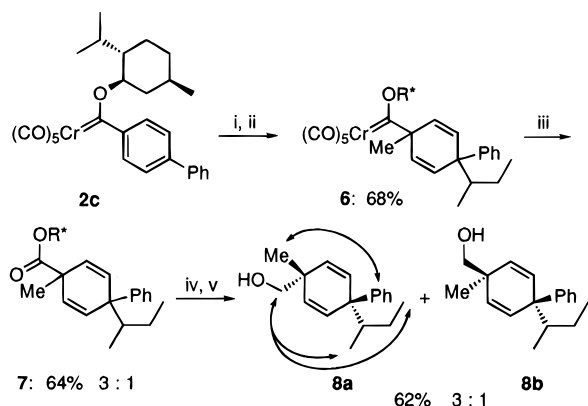
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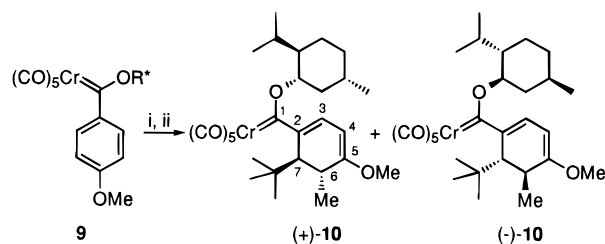
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Scheme 2

Scheme 3^a

^a (i) *s*-BuLi, THF, -78°C, 5 min; (ii) MeOTf, Et₂O, 0°C, 3 h; (iii) C₅H₅N⁺·O⁻, Et₂O, rt, 4 d; (iv) LiAlH₄, THF, 0°C to rt, 12 h; (v) 1 N HCl.

Scheme 4^a

9	R*	Product	yield(%) ^b	[α] _D ²⁰ (c) ^c	config. ^d
9a	(±)-menthyl	(±)-10	27	-	-
9b	(+)-menthyl	(+)-10	28	+271.4 (0.07)	6 <i>R</i> , 7 <i>S</i>
9c	(-)-menthyl	(-)-10	31	-267.2 (0.12)	6 <i>S</i> , 7 <i>R</i>

^a (i) *t*-BuLi, THF, -78°C, 5 min; (ii) MeOTf, Et₂O, 0°C, 3 h. ^b Isolated yields after column chromatography based on carbene complexes 9.

^c Optical rotations were measured in CHCl₃; c in g per 100 mL.

^d Absolute configuration of the newly formed stereogenic carbon centers.

at rt and replacement by Et₂O) with methyl triflate at 0 °C produced the 1,4-dialkylated products 4 as a mixture of *Z/E* isomers (ratio determined from the ¹H NMR spectrum) which could not be separated by column chromatography. Carbene complexes 4 were then submitted to oxidative removal of the Cr(CO)₅ fragment with pyridine *N*-oxide yielding esters 5. Significantly, the conjugate addition of *s*-BuLi to the *p*-phenyl-substituted carbene complex 2c occurred smoothly, affording also the 1,6-adduct which was analogously treated with MeOTf to give carbene complex 6 as a 3:1 mixture of *Z/E* diastereoisomers, determined after oxidation to ester 7 as previously described. The stereochemistry of the major isomer was deduced from the 2D NOESY spectrum performed on the 3:1 mixture of primary alcohols 8a/8b, which were obtained after

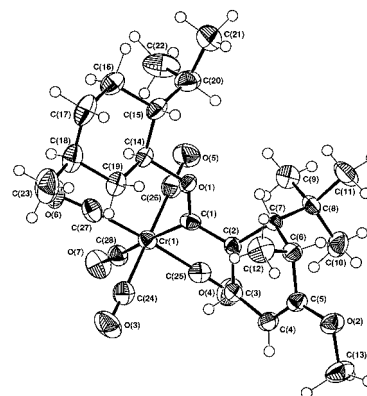


Figure 1. Molecular structure of (+)-10 (Xtal_GX plot).

LiAlH₄ reduction of esters 7 (Scheme 3). The arrows in 8a stand for the observed NOE enhancements. To our delight, the reaction of *t*-BuLi with the *p*-methoxy-substituted racemic 9a or optically active 9b,c carbene complexes, under otherwise similar reaction conditions, occurred in a 1,4-fashion leading, after addition of MeOTf, to the conjugated carbene complexes 10 generated exclusively as a single diastereoisomer enantiomerically pure for (+)-10 and (-)-10, although with low yields (Scheme 4).¹⁸ Confirmation of the structure and relative configuration of compounds 10 and assignment of the absolute configuration were based upon the single-crystal X-ray structure analysis performed on compound (+)-10 (Figure 1).¹⁹

In summary, we have achieved for the first time the regio- and stereoselective nucleophilic aromatic addition of organolithium reagents to (menthyl)oxy(aryl)carbene complexes of chromium, which represents a new dearomatization reaction.^{1,20} Efforts to investigate further structural possibilities as well as to study the reaction chemistry of the novel captodative²¹ dienes 10, having both conjugated metal-carbene and enol ether functionalities and which are readily accessible in either enantiomerically pure form, are currently in progress.

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Supporting Information Available: Experimental procedures, analytical and spectral data for compounds 2–8 and 10, and X-ray crystallographic data of (+)-10 (17 pages). See any current masthead page for ordering and Internet access instructions.

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(18) The structure of compounds 10 was assigned on the basis of ¹H and ¹³C NMR spectra including proton-detected 2D ¹H to ¹³C correlation through one and several bonds (HMQC and HMBC experiments, respectively). A proton–proton coupling constant near zero was observed between the methine ring protons at C(6) and C(7), indicating a *trans* relationship of the two nuclei; see ref 4d.

(19) Crystal data for (+)-10: C₂₈H₃₈CrO₇, red crystal, *M*_r = 538.58, orthorhombic, space group *P*2₁2₁2₁, *a* = 11.976(5) Å, *b* = 14.584(4) Å, *c* = 16.913(5) Å, α = β = γ = 90°, *V* = 2954(2) Å³, *Z* = 4. Final conventional *R* = 0.035 (for 3282 *F*_o > 4σ(*F*_o)). Goodness-of-fit on |*F*|² GOF = 1.050. Flack parameter -0.01(2). Full details are available in the Supporting Information.

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