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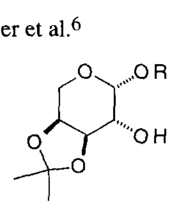
Sugarometallic Chemistry: Aglycone-chromium Complex as Chiral Auxiliary in Asymmetric Diels-Alder Reaction

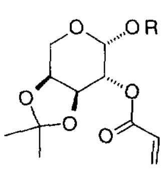
Tony K. M. Shing,* Hak-Fun Chow,* and Ivan H. F. Chung
Department of Chemistry, The Chinese University of Hong Kong, Shatin, Hong Kong

Abstract: *The diastereoselectivity of the Diels-Alder reaction of* η^6*-(4'-methylbenzyl 2-O-Acryloyl-3,4-O-isopropylidene-β-L-arabinopyranoside) tricarbonylchromium(0) 5 with isoprene, butadiene, cyclopentadiene, and furan were studied, and the best selectivity was 95:5 (with isoprene), whereas the diastereoselectivity of the same reaction with the noncomplexed chiral auxiliary-acrylate 6 was only 78:22. The absolute configuration of the newly generated stereogenic center was found to be R in each case.* Copyright © 1996 Elsevier Science Ltd

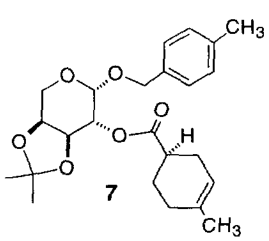
Among a plethora of natural molecules from the chiral pool,[1] carbohydrates probably play an unsurpassed role as chiral auxiliaries in asymmetric synthesis regarding optical purity, number of stereogenic centres, availability, and economics.[2] Following the pioneer work of David and Lubineau et al[3] in 1978 on the use of carbohydrates as enantiopure auxiliaries for asymmetric Diels-Alder reactions, there has since been burgeoning interests on the development of new sugar-derived auxiliaries that would achieve excellent diastereocontrol.[4] Most of the auxiliaries studied have been derived from D-glucose that is inexpensive and available in large quantities. On the other hand, however, the scarcity and the prohibitive cost of L-glucose diminish its attractiveness as the enantio-complement. In our own quest for an efficient stereodirector from sugars, we decided to explore arabinose as a possibility since it is inexpensive and readily available commercially in both enantiomers. Thus, several years ago, by varying the steric demand of the aglycone, we reported[5] that benzyl and methyl 3,4-*O*-isopropylidene-β-L-arabinopyranosides **1** and **2** were *si*-face directing auxiliaries in their acrylates, and the asymmetric inducing capability of **1** was higher than that of **2** in Diels-Alder reactions. Subsequently, a report on very similar chemistry (using D- instead of L-arabinose as the chiral auxiliary), but without citing our work, was described by Nouguier et al.[6]



1 R = Benzyl; **2** R = Methyl;
3 R = η^6-(*p*-methylbenzyl)Cr(CO)$_3$;
4 R = *p*-methylbenzyl



5 R = η^6-(*p*-methylbenzyl)Cr(CO)$_3$
6 R = *p*-methylbenzyl



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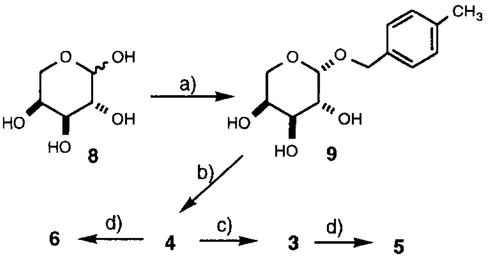
Recently, there has been increasing interests in amalgamating carbohydrate and transitional metal chemistry, which is now coined as sugarometallic chemistry. For examples, novel homochiral metallocenes carrying carbohydrate substituents have been synthesized.[7] Titanium, hafnium, and zirconium complexes containing sugar moieties as alkoxy ligands have been employed for enantioselective addition of alkyl/allyl groups and of ester enoates to aldehydes.[8] Non-carbohydrate (η^6-arene)chromium tricarbonyl complexes have also been used as chiral auxialiaries in asymmetric Diels-Alder reactions.[9] This paper presents our contribution to sugarometallic chemistry in which we describe the preparation of arabinose-chromium(0)[10] tricarbonyl complex **3** as a chiral auxiliary and shows that **3** is superior to the uncomplexed counterpart **4** with respect to stereodirecting capacities in asymmetric Diels-Alder reactions.



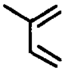
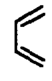
Scheme 1. Syntheses of dienophiles **5** and **6**: a) *p*-methylbenzyl alcohol, cat. HCl, 65 °C, 3 days, 83%; b) 2,2-dimethoxypropane, cat. (±)-camphorsulfonic acid, acetone, rt, 12 h, 87%; c) $Cr(CO)_6$, dibutyl ether/THF v/v 10/1, refluxed, 36 h, 93%; d) acryloyl chloride, *N,N*-diisopropylethylamine, cat. DMAP, CH_2Cl_2, 0 °C, 1 hr, 89% for **5**, 85% for **6**.

The chiral auxiliary **4** and its chromium(0) complex[11] **3** could be prepared easily and efficiently from L-arabinose **8**, *via* glycoside **9**, on large scales as shown in Scheme 1. Acryloylation of the free hydroxy groups of **3** and **4** afforded the dienophilic acrylates **5** and **6**, respectively, in multigram quantities. The ethylaluminium dichloride catalyzed Diels-Alder reactions of **5** and **6** with a series of dienes were then investigated.[12] In a typical experiment, reaction of **5** with isoprene furnished, after decomplexation with pyridine,[13] a pair of diastereomeric cycloadducts in a ratio of 95:5. Hydrolysis of these adducts to the corresponding carboxylic acids of known configuration[14,15] established the absolute stereochemistry of the major adduct as illustrated in **7**. Examination of the results in Table 1 shows that the present chiral auxiliaries **3** and **4** have *si*-face stereodirecting effect that is in accord with that of our previously evaluated **1** and **2**. All the major cycloadducts have the *R* configuration at the alpha carbon of the ester moiety. Furthermore, introduction of the chromium(0) tricarbonyl moiety to **4** improves the asymmetric induction significantly. We believe that the observed shielding effect of the auxiliaries may be merely ascribable to steric crowding[16] rather than aryl-acrylate π-π orbital overlap[17] since the olefinic protons of the acrylate moiety in **5** and in **6** display no appreciable difference in chemical shifts (^{1}H NMR spectral analysis). Inspection of models shows that the most favourable conformation, illustrated in Figure 1, involves minimum steric interaction between the phenyl ring and the acrylate moiety and hence the phenyl ring would be blocking the *re*-face of the dienophile. The enhanced stereocontrol in the complex **5** may be attributable to the even more restricted rotation along the benzylic carbon-oxygen as well as the carbon-carbon bonds and to the increased size of the blocking group.

It is noteworthy that substituted phenyl derivatives such as **12** and **13** showed inferior diastereoselectivity in the asymmetric cycloaddition reaction with isoprene (d.e. = 40 and 35% respectively) whereas substituted benzyl derivatives such as **14** and **15** decomposed readily under the acidic conditions. These results demonstrated that high asymmetric induction could not be realized by simply introducing more substituents into the aromatic ring and electron releasing substituents destabilized the benzylic ether in the presence of the Lewis acid catalyst.

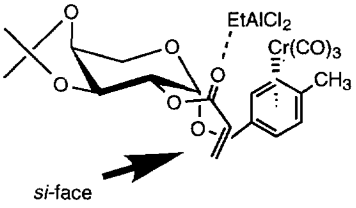
In summary, we have demonstrated a novel application of sugarometallic chemistry in which L-arabinose-chromium tricarbonyl complex **5** displays itself as a superior *si*-face directing stereo-auxiliary in Diels-Alder reactions. Since D-arabinose is also inexpensive and commercially available, enantiomeric pairs of cycloadducts are therefore readily accessible. Work on the development of other sugarometallic complexes and of enantioselective sugarometallic reagents are under active investigation.

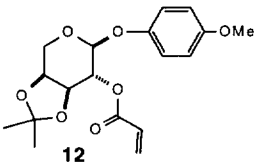
Table 1. $EtAlCl_2$ catalyzed Diels-Alder Reactions of 5^{a} and 6 with dienes.

Diene	Dienophile	*de* ^{b} [%]	*Endo : Exo* ^{c}	Isolated Yield (%)
	**6**	56^{d}	-	60
	5	90^{d}	-	77
	**6**	54^{e}	-	65
	5	70^{e}	-	63
	**6**	*Endo* 66^{d}	>95 : 5	71
	5	*Endo* 84^{d}	>95 : 5	89
	**6**	*Endo* 66^{d} *Exo* 80^{d}	67 : 33	90^{f}
	5	*Endo* 90^{d} *Exo* 92^{d}	67 : 33	90^{g}

a, The ratios of the diastereoselection were determined after decomplexation. b, Authentic standards of 1:1 mixture of diastereomers were synthesized from coupling the chiral auxiliary-alcohol **4** with the corresponding racemic carboxylic acids. The major cycloadduct has the *R* configuration at the α–carbon of the carboxylic acid in each case. c, Determined by ^{1}H NMR spectral analysis. d, Determined by HPLC. e, Determined by ^{13}C NMR spectral analysis. f, Based on 50% recovery of starting material. g, Based on 37% recovery of starting material.

Figure 1





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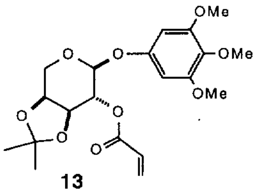

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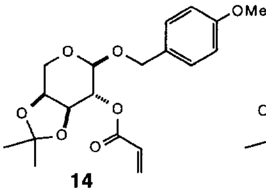

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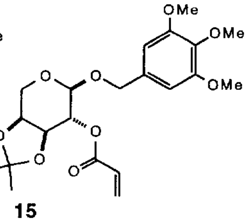

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12. General procedure. To a stirred solution of the dienophile (0.2 mmol) in dry CH_2Cl_2 (10 mL) was added 1M solution of $EtAlCl_2$ (0.2 mmol) in hexanes under an atmosphere of nitrogen at - 20 °C. Then the diene (1.0 mmol) was added dropwise. The resulting solution was stirred at - 20 °C for 8 h and quenched with a drop of sat. NH_4Cl solution. The resulting mixture was filtered through a pad of silica gel and washed with EtOAc (10 mL). The filtrate was concentrated *in vacuo* to give a crude yellow syrup that was purified by flash column chromatography on silica gel to afford the cycloadducts.
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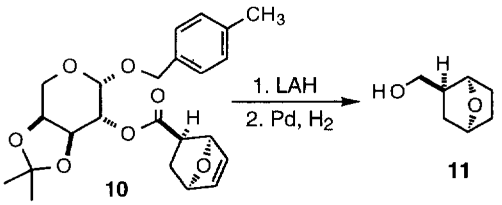

10 **11**

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