Pergamon

Tetrahedron Letters 41 (2000) 4695–4699

TETRAHEDRON
LETTERS

Exploiting π shielding interactions in a η^6 arene-complexed chiral auxiliary

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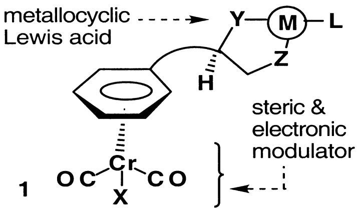
Received 12 April 2000; revised 1 May 2000; accepted 2 May 2000

Abstract

The origin of asymmetric induction in a chiral auxiliary derived from isomannide was probed using a series of η^6 arene chromium carbonyl complexes. Diastereoselectivity as high as 99% was attainable, and subsequent spectroscopic analysis shed light on the role of π–π interactions. © 2000 Elsevier Science Ltd. All rights reserved.

Arene chromium(0) carbonyl complexes are versatile components of the synthetic arsenal, a consequence of the broad range of chemical and stereochemical properties they possess.[1] On complexation to an arene ring, significant changes to its chemistry occur, including increased susceptibility to nucleophilic attack,[2] increased acidity of ring protons,[3] enhanced solvolytic properties,[4] in addition to introduction of the stereodirective capacity of the metal carbonyl tripod.[5] Due to the ability of arene chromium carbonyl complexes to influence the electronic properties of both ring substituents and the π orbitals of the arene, we have become interested in developing chiral controller systems which harness these effects, as depicted in **1**.



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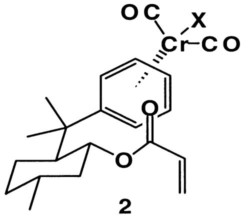

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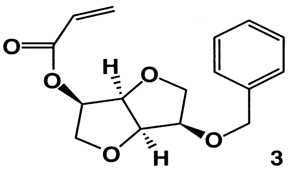

3

We previously demonstrated that mixed ligand complexes of 8-phenylmenthol acrylates **2** exert electronic influence on the diastereoselectivity of cycloadditions to the acrylate, presumably via modulation of aryl-vinyl π–π stacking interactions, and that the process can be tuned by appropriate selection of ligand X.[6] To investigate the scope of such modulation, we sought to demonstrate the

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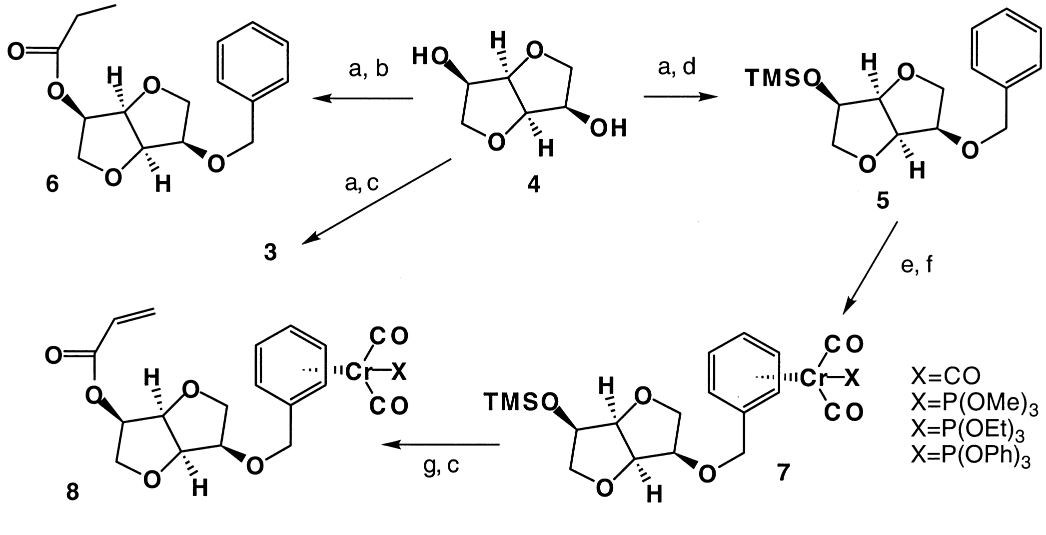
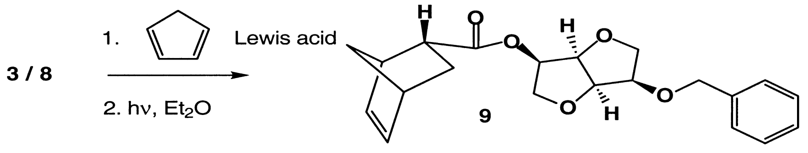
PII: S0040-4039(00)00713-9

effects in a more readily accessible system, and selected isomannide acrylates **3** for our study. Loupy has reported that cycloaddition to this acrylate may be influenced by π-stacking interactions, helping account for the good levels of asymmetric induction observed.[7] The basic criteria for two entities to engage in a π stack are satisfied when π clouds interact through space at a distance of between 3–3.5 Å, with optimal overlap at approximately 3.4 Å.[8] To investigate this system further, and attempt modulation of the π–π interactions, ligand **4** was transformed into a monobenzylated common precursor, which could be converted to **3** or control substrate **6** as desired (Scheme 1). Alternatively, η^6 complexation followed by ligand substitution of TMS ether **5** gave ligand precursors **7**, which were deprotected and converted to give a family of acrylates **8**. [9] Surprisingly, although acrylates **8**, [X = CO, $P(OMe)_3$, $P(OEt)_3$] were stable, the bulkier triphenylphosphite analog [X = $P(OPh)_3$] was not isolable, resulting in decomplexation even under a variety of conditions. Cycloaddition of the acrylates **3** and **8** was conducted using cyclopentadiene, and various Lewis acid combinations (Scheme 2). Following decomplexation, the de of the cycloadduct **9** was assessed using chiral HPLC (OD column), yielding some important findings (Table 1). As had been reported,[7] appreciable de is obtained with **3**, which could be improved further by an appropriate choice of Lewis acid (entries 1 and 5). In all cases examined the *endo-R* enantiomeric cycloaddition product predominated. Since π–π interactions were reasoned to contribute to diastereocontrol in substrate **3**,[7] it was surprising to find that in the case of the π deficient **8**, X = CO, diastereocontrol is enhanced, contrary to that observed in the analogous 8-phenylmenthol acrylate **2**, X = CO.[6] The more electron-rich mixed ligand systems performed even better, the trend seemingly reflecting steric rather than electronic factors (Table 1).



Scheme 1. Preparation of mixed ligand η^6 arene isomannide acrylates. *Reactions and conditions*: (a) BnCl, LiH, DMF, 68%; (b) CH_3CH_2COOH, HOBt, EDAC, THF, 94%; (c) $ClCOCH{=}CH_2$, 2,6-lutidine 30–40%; (d) TMSCl, imidazole, DMF 99%; (e) $Cr(CO)_6$, nBu$_2$O, THF, 125°C, 16 h, 95%; (f) X, $h\nu$, PhH 75–90%; (g) K_2CO_3, MeOH 90–95%

In an attempt to rationalize these findings, a number of spectroscopic studies were undertaken using ligands **3**, **6** and **8**. Assuming *s-trans* enoate geometry is adopted in the Lewis acid catalyzed cycloaddition, a π–π stacked model (A) does not account for the observed *endo-R* cycloadduct, which would require addition to the (π-shielded) upper face, and which also imposes unfavorable



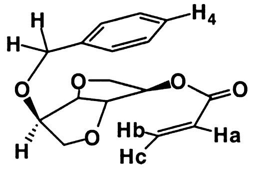
Scheme 2. Diastereocycloaddition of isommanide acrylates

Table 1

Cycloaddition of acrylates **3** and **8** with cyclopentadiene. All cycloadditions conducted in CH_2Cl_2. Cycloadducts were decomplexed in Et_2O, then analyzed by chiral HPLC (Chiracel OD, 10% 2-propanol:90% hexanes as eluent, 1 mL/min flow rate) using a racemic *endo*-**9** prepared by alternate methods as both an internal and external control (t_R *endo-S* = 18.9 min *endo-R* = 20.2 min)

Entry	**Substrate**	**Lewis Acid**(eq.)	**% 9**	**Temp.(Time)**	**Endo/Exo**	**%de**
1	**3**	Et_2AlCl (1.0)	42	-78°C (2h)	>99:1	70
2	**8**, X=CO	Et_2AlCl (1.0)	72	-78°C (2h)	>99:1	80
3	**3**	$EtAlCl_2$ (1.0)	39	-10°C to rt (6h)	>99:1	67
4	**3**	$EtAlCl_2$ (1.0)	66	-40°C (2h)	>99:1	84
5	**3**	$EtAlCl_2$ (1.0)	42	-78°C (2h)	>99:1	88
6	**8**, X=CO	$EtAlCl_2$ (1.0)	81	-78°C (2h)	>99:1	95
7	**8**, X=P(OMe)$_3$	$EtAlCl_2$ (1.0)	53	-78°C (2h)	>99:1	97
8	**8**, X=P(OEt)$_3$	$EtAlCl_2$ (1.0)	71	-78°C (2h)	>99:1	97
9	**3**	$EtAlCl_2$ (0.5)	55	-78°C (2h)	>99:1	86
10	**3**	$EtAlCl_2$ (2.0)	74	-78°C (2h)	>99:1	88
11	**8**, X=CO	$EtAlCl_2$ (2.0)	22	-78°C (2h)	>99:1	94
12	**8**, X=P(OEt)$_3$	$EtAlCl_2$ (1.0)	73	-90°C (2h)	>99:1	99

geometry on the ester function.[10] Fluorescence-quenching studies indicated a concentration-dependent interaction between the acrylate and aryl moieties of **3** in the absence of Lewis acid.[11] No quenching was observed with the analogous arene complexes **8** (or control element **6**), either in the presence or absence of Lewis acid, which may indicate the metal carbonyl tripod either imparts a conformational bias to the benzyl group, or electronically insulates the arene. Chemical shift analysis of the acrylate protons in **3** and **8** ($CDCl_3$, 25°C) did not reveal a trend for upfield shift consistent with π stacking with the phenyl ring,[8] instead giving near uniform values for the entire series, even in the presence of Lewis acid (Table 2). More revealing were NOE studies, which failed to show any NOE between the vinyl group protons and either the aryl moiety or benzylic hydrogens, in both **3** and **8**. However, in the presence of $EtAlCl_2$, NOEs were observed between the phenyl H_4 and the acrylate H_b (5%) and H_c (2%), suggesting that a conformational change ensues when Lewis acid coordinates to the enoate.[12] Taken together, the data is suggestive of a conformation B, where approach of the diene is directed to the underside of the enoate, leading to the observed *endo-R* cycloadduct.



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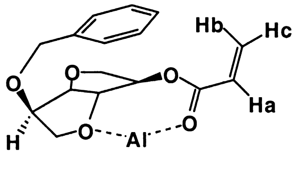

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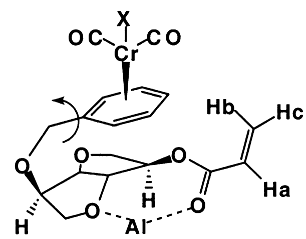

C

Table 2
^{1}H NMR analysis of isomannide acrylates (δ)

Entry	Substrate	Ha	Hb	Hc
1	**3**	6.18	5.87	6.46
2	**3** (+$EtAlCl_2$)	6.10	5.85	6.43
3	**8** X=CO	6.12	5.82	6.40
4	**8** X=$P(OMe)_3$	6.22	5.87	6.54
5	**8** X=$P(OEt)_3$	6.24	5.88	6.57

The correlation of steric bulk with de in the case of derivatives **8**, can be satisfied with structure C, the metal carbonyl group serving to amplify π-shielding of the upper face of the enoate. Other possibilities include interaction of (the metal-complexed) arene with the acrylate by some form of charge transfer process that is not detected by fluorescence quenching,[13] or the participation of the metal carbonyl tripod itself in binding to the Lewis acid.[14]

Given the commercial availability of the ligand **4**[15] and the very high levels of asymmetric induction attainable (Table 1, entry 12), immediate application of this auxiliary can be anticipated, as can the design of catalysts which benefit from such stereodirective elements.[16] The results herein suggest that in systems where arene-vinyl π-shielding plays an intergral role in stereocontrol, metal carbonyl-complexed aryl derivatives may serve to amplify selectivity.

Acknowledgements

We thank the PRF (Administered by the American Chemical Society) for financial support of this work (33920-AC1).

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