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Exploiting π-shielding interactions: a highly selective chiral auxiliary derived from a biogenic building block

Longfei Xie and Graham B. Jones*

Bioorganic and Medicinal Chemistry Laboratories, Department of Chemistry & Chemical Biology,
Northeastern University, Boston, MA 02115, USA

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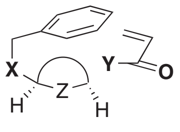
Abstract—A chiral auxiliary template, designed on the basis of π-shielding capability has been prepared from readily available L-proline. Cycloaddition to an acrylate derivative gave high *endo* preference, and diastereoselectivity as high as 99% was attainable. The electronic factors contributing to selectivity were probed, and the technology successfully applied to a polymer supported variant.

Of the many tactics employed to achieve facial selectivity in asymmetric cycloadditions, π-shielding of one face of the dienophile to attack has become a common and effective strategy.[1] Examples include both chiral catalysts and auxiliaries, where the interaction of the chiral controller and dienophile range from passive (steric shielding) through active (π–π stacking).[1] We have been engaged in the design of auxiliaries and catalysts where a pendant aryl substituent interacts with a proximal acrylate to establish a high degree of facial selectivity in cycloaddition viz., **1**.[2] We further demonstrated that variation of the electronic interactions between aryl and vinyl groups can be modulated via the corresponding arene chromium carbonyl complexes, where mixed ligand derivatives provide access to a range of π basic through π acidic characteristics **2**.[3,4] The basic criteria for two entities to engage in a π stack are satisfied when π clouds interact through space at a distance between 3 and 3.5 Å, with optimal overlap at ≈3.4 Å.[5] Based on this criterion we wished to apply the concept of face selection in a readily available auxiliary derived from the chiral pool, and surveyed a variety of inexpensive building blocks. We ultimately decided to pursue derivatives of *N*-benzyl prolinol **3** based on the fact that: (a) molecular modeling analysis suggested that derived acrylate esters could position at π-stacking distance from the aryl; (b) the ligand itself is commercially available and is also easily accessible from proline;[6] (c) both enantiomeric forms are available; and (d) the electronics of the benzyl group could be modulated at ease.



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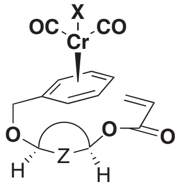

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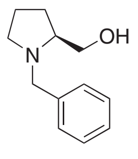

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To establish proof-of-principle, L-proline **4** was converted to its prolinol derivative and a variety of benzyl chlorides **5** were used to introduce the *N*-aryl substituents **6** (Scheme 1).[7] Conversion to the corresponding acrylates **7** allowed us to probe the efficiency and stereoselectivity of cycloaddition, investigated using a series of Lewis acids with cyclopentadiene. Initial results (Table 1) confirmed the viability of the design criteria with moderate to good *endo* selectivity achieved and appreciable diastereocontrol. Chemical yields ranged from poor to excellent, and the auxiliary could be recovered in good (~90% yield) by reduction of the ester linkage. In all cases, the major product obtained was the *endo* *R* isomer, confirmed by comparison with authentic material.[8] The most striking results were observed with 4-substituted derivatives of **7** where a strong correlation between diastereoselectivity and electron donor ability of the substituent X emerged. As the same trends were

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Keywords: Diels–Alder; Cycloaddition; π-shielding; Chiral auxiliary.

* Corresponding author. Tel.: +1 617 373 8619; fax: +1 617 373 8795; e-mail: gr.jones@neu.edu

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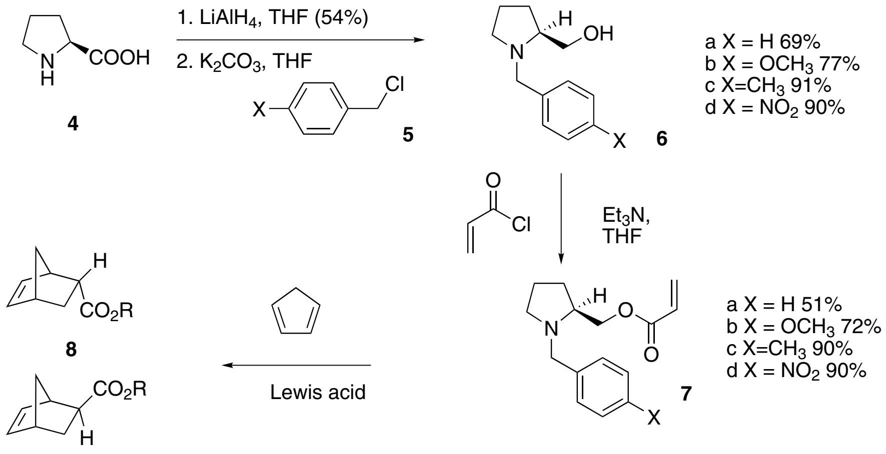


Scheme 1. Synthesis and cycloaddition to *N*-benzyl-prolinol acrylates.

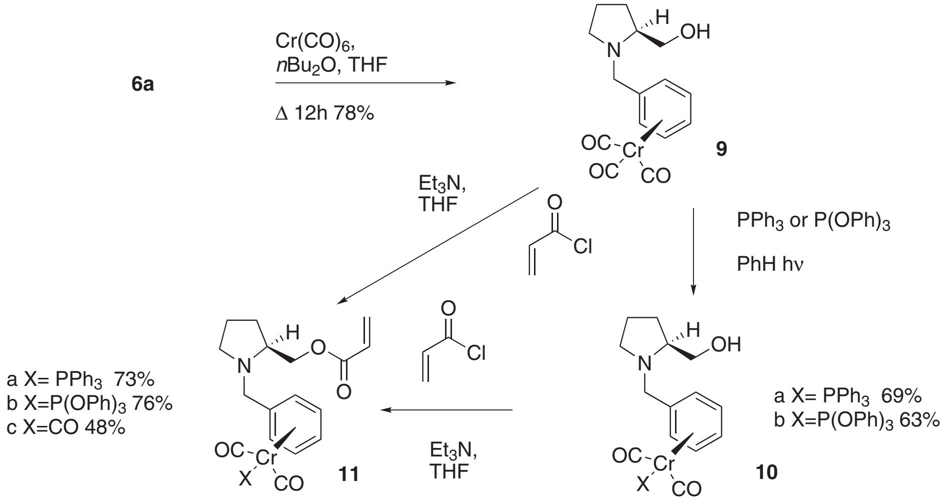
Table 1. Cycloaddition of acrylates **7**/**11** with cyclopentadiene

Entry	Substrate	Lewis acid (equiv)	% **8**	Temp/°C (time/h)	*endo*/*exo*	de (%)
1	**7a**	$BF_3{\cdot}OEt_2$ (1.2)	<1	−78 (48)	—	—
2	**7a**	$BF_3{\cdot}OEt_2$ (1.2)	6	−50 (12)	20:1	95
3	**7a**	$BF_3{\cdot}OEt_2$ (1.2)	57	−25 (6)	8.8:1	55
4	**7a**	$BF_3{\cdot}OEt_2$ (2.0)	24	−25 (6)	5.8:1	81
5	**7a**	$SnCl_4$ (1.2)	23	−25 (6)	1.5:1	21
6	**7a**	$SnCl_4$ (1.2)	10	−50 (12)	3.7:1	81
7	**7a**	$TiCl_4$ (1.2)	<1	−25 (6)	—	—
8	**7a**	$TiCl_2$ (O*i*Pr)$_2$ (1.2)	<1	−25 (6)	—	—
9	**7a**	$AlEt_2Cl$ (1.2)	10	−25 (6)	10:1	93
10	**7a**	$AlEtCl_2$ (1.2)	5	−25 (6)	1:40	80
11	**7b**	$BF_3{\cdot}OEt_2$ (1.2)	90	−25 (12)	39:1	83
12	**7c**	$BF_3{\cdot}OEt_2$ (1.2)	65	−25 (12)	22:1	68
13	**7d**	$BF_3{\cdot}OEt_2$ (1.2)	77	−25 (12)	20:1	22
14	**11a**	$BF_3{\cdot}OEt_2$ (1.2)	99	−25 (24)	35:1	98
15	**11b**	$BF_3{\cdot}OEt_2$ (1.2)	86	−25 (24)	32:1	97
16	**11c**	$BF_3{\cdot}OEt_2$ (1.2)	77	−25 (24)	28:1	96

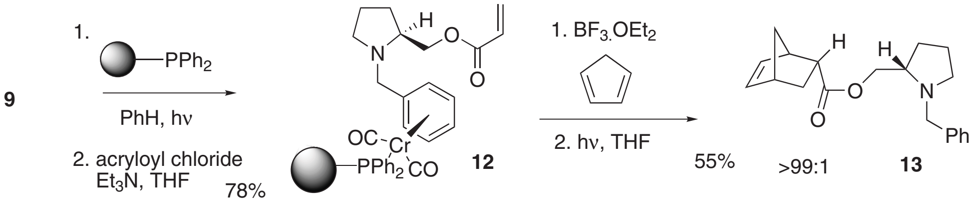
All cycloadditions were conducted in CH_2Cl_2. *exo*:*endo* ratios were determined by GC–MS (HP-5, evap temp. 220 °C; operating temp 60 °C, 5 min then 4 °C/min ramp rate to 145 °C); *endo* **8** 18.32 min *exo* **8** 18.58 min; de was determined by HPLC (Chiralcel OD, 3% 2-propanol:97% hexanes eluent, 1 mL/min flow rate) in comparison to reference standards (t_R *exo* $S = 4.84$ min *exo* $R = 5.48$ min, t_R *endo* $S = 5.95$ min *endo* $R = 6.97$ min). Cycloadducts derived from **11** were decomplexed in Et_2O and then analyzed.

not reflected in *endo*:*exo* ratios, we become interested in preparing alternate variants where through space electronics could be modulated, and turned attention to the arene chromium complexes.[2] Thus, commencing with **6a**, complexation was achieved using conventional conditions to give alcohol **9**, presumably via intramolecular delivery of the $Cr(CO)_3$ tripod from an intermediate oxo–Cr complex (Scheme 2).[3] Ligand exchange was effective without need for masking of the alcohol group, allowing **9**, **10a** and **b** to be converted to the corresponding acrylates **11**. Cycloaddition was efficient with all three substrates (Table 1) and expected correlations between π donor ability and *endo* preference/diastereoselectivity were observed within the series. Clearly, substrate **11c** presents a more electron deficient π face than **7a** suggesting that the steric bulk of the metal carbonyl tripod contributes substantively to diastereoselectivity. A very high degree of diastereoselectivity was obtained in the case of **11a**, suggesting the platform to be suitable for application in other areas. One such avenue of interest to us lies in preparation of solid-supported variants of this system. Promoted by reports from the Semmelhack and Thomas groups,[9,10] we have utilized the 'traceless linker' approach for the preparation of polymer-bound mixed ligand phosphine–chromium arene complexes, and sought to apply in this series.[11] Accordingly, irradiation of **9** in the presence of polystyrene–diphenylphosphine complex resulted in formation of the mixed ligand derivative, which was converted to acrylate ester **12** without incident (Scheme 3). Cycloaddition proceeded with essentially complete diastereoselectivity, and the adduct **13** could be uncoupled from the support merely by exposure to light.

In an attempt to rationalize these findings, spectroscopic studies were undertaken using ligands **7** and **11**. Assuming *s-trans* enoate geometry is adopted in the Lewis acid catalyzed cycloaddition, a π–π stacked/shielded model is consistent with the observed *endo R* cycloadduct, which implies approach of diene with the methylene group anti



Scheme 2. Preparation of η^6-arene chromium carbonyl complexed derivatives.



Scheme 3. Preparation and cycloaddition of polymer supported derivative.

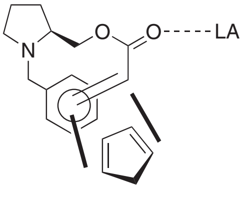


Figure 1.

to the (mobile) benzyl substituent (Fig. 1). However, chemical shift analysis of the acrylate protons in **7** and **11** ($CDCl_3$, 25 °C) revealed only minor perturbations in the presence of Lewis acid. If pronounced π stacking effects were operational, upfield shift of these protons would be expected.[1] Additional NOE experiments were conducted on substrates and in the case of **7c** irradiation of the aryl methyl group resulted in <2% enhancement of the acrylate vinyl protons. Based on these data, a face-to-edge arrangement seems most plausible, a hypothesis which will be investigated with in depth fluorescence quenching studies.

In summary, a chiral auxiliary derived from inexpensive L-proline has been designed and demonstrated excellent selectivity in cycloaddition chemistry. A polymer supported variant has also been produced, extending the versatility of this system. Application in the preparation of chiral synthons is now expected, and the π-shielding design criterion may lead to the development of additional auxiliary and catalyst families.[12]

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