Asymmetric Synthesis

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Stereoselective Dearomatizing Addition of Nucleophiles to Uncomplexed Benzene Rings: A Route to Carbocyclic Sugar Analogues**

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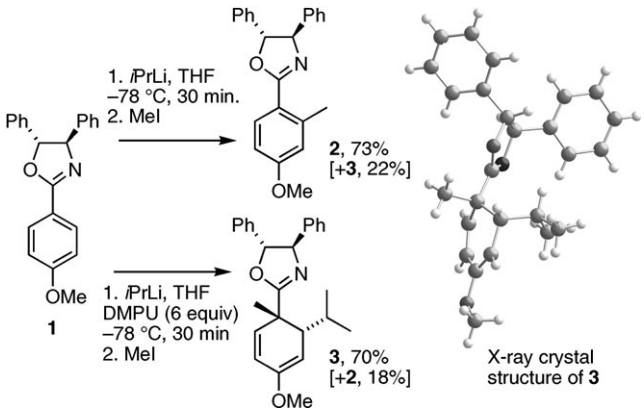
Here we report reaction conditions which enable for the first time the stereoselective dearomatizing addition of organolithium reagents to simple, uncomplexed benzenoid aromatic rings. Dearomatizing nucleophilic addition reactions to arenes provide an efficient way of making complex synthetic intermediates from simple inexpensive precursors.[1,2] As a strategy, dearomatization marries the regioselectivity of aromatic electrophilic substitution with the stereoselectivity achievable upon the conversion of an arene into a cyclohexane derivative.

The seminal work of the Meyers research group[3] showed the importance of oxazolines in promoting dearomatizing addition reactions of organometallic reagents to naphthalene and pyridine derivatives. However, benzene rings are much more difficult to dearomatize: the addition of nucleophiles to uncomplexed phenyloxazolines has previously led to deprotonation or attack at the oxazoline C=N bond.[4] Current solutions to the problem adding nucleophiles stereoselectively addition of nucleophiles to simple substituted phenyl rings involve stoichiometric coordination to Cr, Mn, or Os.[2a–e] Racemic dearomatized products may also be obtained from addition reactions to hindered benzamides[2f,g] or to carbonyl compounds coordinated to aluminum tris(2,6-diphenylphenoxide) (ATPH).[2h–j]

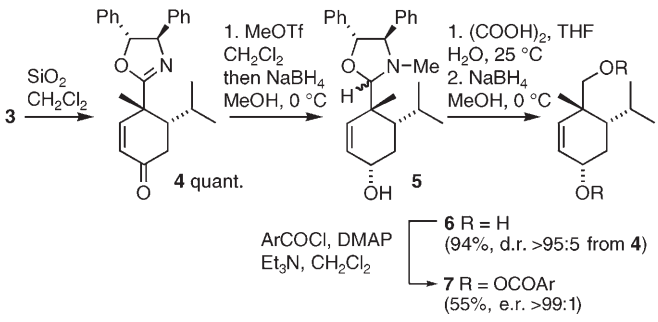
We have found that the previously unexplored 2-aryl *trans*-4,5-diphenyloxazolines promote stereoselective nucleophilic attack on simple benzenoid rings without metal complexation, provided *N*,*N*′-dimethylpropyleneurea (DMPU) is used to activate the organolithium nucleophile (Scheme 1). Upon lithiation with *i*PrLi in THF and quenching with methyl iodide, oxazoline **1**[5] was converted principally into the expected[6] product **2** of *ortho* lithiation. However, this product was accompanied by a dearomatized adduct **3**, which is formed through the attack of *i*PrLi on the *p*-methoxyphenyl ring. When DMPU[7] is first mixed with the starting material (in an optimal ratio of 6:1), the cyclohexadiene **3** becomes the major product. Compound **3** was isolated as a single diastereoisomer (with configuration assigned by X-ray crystallography[8]) in 70% yield.[9]



Scheme 1. DMPU-promoted dearomatization of a 4,5-diphenyloxazoline.

The oxazoline group in **1** functions as a chiral auxiliary.[9] It could be removed from enone **4**, the hydrolysis product of **3**, by the alkylation–reduction–hydrolysis–reduction sequence shown in Scheme 2.[10] The enantiomeric purity (e.r. > 99:1) of the allylic alcohol **6** was established by HPLC analysis of its bis-*p*-bromobenzoate **7**.

Carbocyclic sugars and their alkylated, hydroxylated, and aminated analogues are an important class of natural and



Scheme 2. Removal of the oxazolinyl auxiliary. Ar = *p*-BrC_6H_4; DMAP = 4-dimethylaminopyridine, Tf = trifluoromethanesulfonyl.

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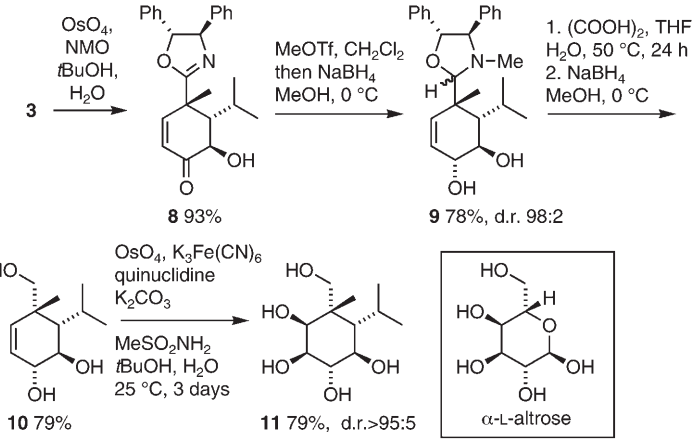
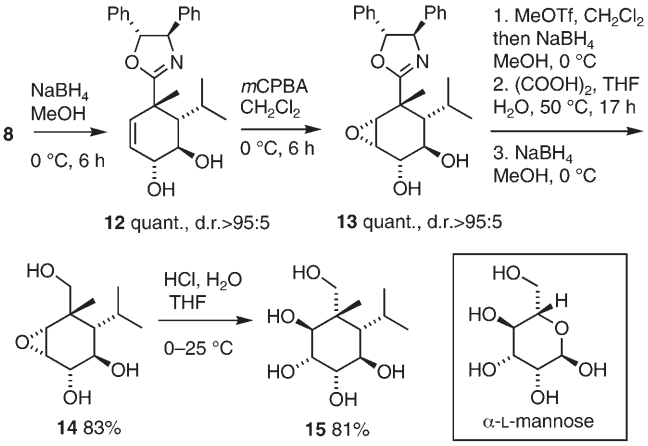
non-natural compounds that possess a range of antibiotic and antiviral biological activity.[11] The cyclohexadiene **3** and cyclohexenone **4** presented themselves as readily available and versatile synthetic intermediates for the synthesis of functionalized cyclohexanes structurally related to these compounds.[12] Schemes 3 and 4 illustrate the conversion of **3** into the alkylated carbocyclic analogues **11** and **15** of L-altrose and L-mannose, respectively, through short, protecting-group-free sequences.

The dienyl ether **3** was prepared by the addition of *i*PrLi to **1** on a 2 g scale, and was oxidized to yield a single diastereoisomer of the base-sensitive hydroxyenone **8** (Scheme 3). The oxazoline substituent was removed by the method used for **4**. Concurrent 1,2-reduction of the enone was fully diastereoselective, and after hydrolysis of the oxazolidine moiety of **9** and further reduction, the triol **10** was obtained as a single diastereoisomer. Diastereoselective[13] dihydroxylation of the alkene[14] yielded a single diastereoisomer of the alkylated carbocyclic analogue **11** of α-L-altrose. The X-ray crystal structure of **11**[8] confirmed its configuration.



Scheme 3. Synthesis of an L-altrose analogue. NMO = 4-methylmorpholine *N*-oxide.

Intermediate **8** from this synthesis was also converted into a carbocyclic analogue of α-L-mannose (Scheme 4). The enone underwent 1,2-reduction to give **12** as a single diastereoisomer, the relative configuration of which was verified by X-ray crystallography.[8] The directed epoxidation of **12** yielded **13**, and removal of the oxazoline moiety by the standard method then afforded the epoxytriol **14**. The treatment of **14** with aqueous acid led to *trans*-diaxial ring opening of the epoxide and provided the α-L-mannose analogue **15** in 81 % yield.[15]



Scheme 4. Synthesis of an L-mannose analogue. *m*CPBA = *m*-chloroperbenzoic acid.

The scope and limitations of the dearomatizing addition were investigated by treating a range of aryl oxazolines **16a–e** with organolithium reagents (1.5–3 equiv; Scheme 5 and Table 1). A deep green or brown solution formed upon the successful addition of an organolithium reagent to **16**; quenching of the presumed azaenolate intermediate **17** with methyl iodide gave a cyclohexadiene **18**. The addition of secondary organolithium reagents generally led to the desired products in moderate to good yields. In each case only a single diastereoisomer and regioisomer of the product was detected, along with remaining starting material and sometimes the rearomatized by-product **19**.[16] The use of *tert*-butyllithium led to the formation of **18a″** in low yield (Table 1, entry 4), and *n*-butyllithium failed to add to the ring (Table 1, entry 1).

Protonation of the extended azaenolate **17** gave a 1,3-cyclohexadiene **20** or 1,4-cyclohexadiene **21** (depending on the substitution pattern) in around 50 % yield, along with the rearomatized by-product **19** and recovered starting material. Treatment of the extended enolate **17** with allyl bromide or benzyl bromide also yielded mixtures of regioisomers.

In conclusion, the dearomatizing reaction provides a new entry into highly functionalized cyclohexene and cyclohexanone derivatives, yielding carbocyclic sugar analogues in six to eight steps and 33–43 % yield from simple aromatic oxazoline derivatives.

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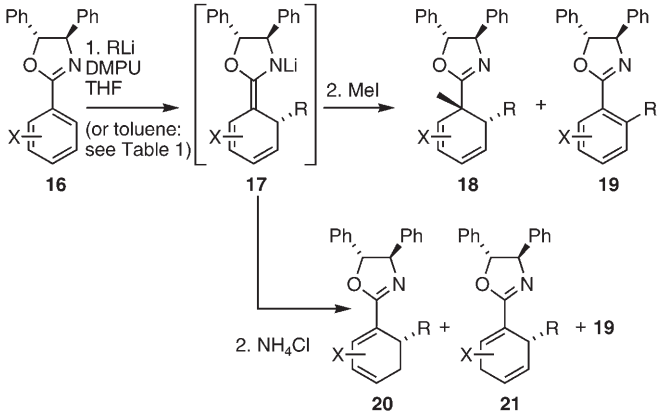

Scheme 5. Dearomatizing functionalization of aryl oxazolines.

Table 1: Addition to aryl oxazolines **16**.

Entry	**16**	X[a]	R[a]	Quench	Product, yield [%]	Yield [%] of **16**;[b] **19**
1	**16a**	H	*n*Bu	MeI	–	95; 0
2	**16a**	H	*i*Pr	MeI	**18a**, 70[c]	12; 0
3	**16a**	H	*s*Bu	MeI	**18a′**, 81[d]	1; 0
4	**16a**	H	*t*Bu	MeI	**18a″**, 17	12; 0[e]
5	**16b**	4-Ph	*i*Pr	MeI	**18b**, 32	12; 30
6	**16c**	3-OMe	*i*Pr	MeI	**18c**, 54[c]	20; 0[f]
7	**16d** (**1**)	4-OMe	*i*Pr	MeI	**3**, 70[c]	6; 0
8	**16d** (**1**)	4-OMe	*s*Bu	MeI	**18d′**, 78	5; 7
9	**16a**	H	*i*Pr	NH_4Cl	**20a**, 47	32; 5
10	**16a**	H	*s*Bu	NH_4Cl	**20a′**, 56	29; 9
11	**16d** (**1**)	4-OMe	*i*Pr	MeOH	**20d**, 30; **21d**, 15	29; 6
12[g]	**16e**	4-F	*i*Pr	NH_4Cl	**21e**, 53	37; 7

[a] See Scheme 5. [b] Recovered starting material. [c] The configuration of the product was confirmed by X-ray crystallography.[8] [d] The product was formed as a 3:1 mixture of diastereoisomers with respect to the exocyclic stereogenic center. [e] Alkylation of the oxazoline ring occurred to provide a further by-product in 17% yield. [f] A further by-product was formed in 9% yield by *ortho* methylation. [g] The reaction was carried out in toluene with racemic **16e**.

Keywords: carbohydrates · dearomatization · diastereoselectivity · oxazolines · pseudosugars

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[8] CCDC 670194 (**3**), CCDC 670195 (**11**), CCDC 670196 (**12**), CCDC 670197 (**18a**), and CCDC 670198 (**18c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] The stereoselectivity of both the dearomatizing addition and the alkylation appears to be greater than 10:1, as no stereoisomeric dearomatized products were observable in the NMR spectrum of the crude reaction mixture. We assume that the configuration of the product arises from coordination of isopropyllithium to the basic nitrogen atom of the oxazoline, followed by 1,4-addition to the 2-position of the *p*-methoxyphenyl ring from the face *anti* to the 4-phenyl substituent of the oxazoline ring. Details of the mechanism are still under investigation; however, preliminary attempted trapping experiments suggest that radical intermediates are not involved.

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[15] The new diaxial relationship in **15** was indicated by $^3J_{H,H}$ coupling constants in the ^{1}H NMR spectrum.

[16] The configuration of the adducts was assigned by analogy with **3**, **18a**, and **18c**.

