Published in final edited form as:

Angew Chem Int Ed Engl. 2015 February 9; 54(7): 2142–2145. doi:10.1002/anie.201410228.

Regiodivergent Addition of Phenols to Allylic Oxides: Control of 1,2 and 1,4-Additions for Cyclitol Synthesis**

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Abstract

Control of 1,2- and 1,4-addition of substituted phenols to allylic oxides is achieved by intercepting palladium π -allyl complexes. The interconversion of palladium complexes results in the total synthesis of MK7607, cyathiformine B type, streptol, and a new cyclitol.

Keywords

carbasugar; regiodivergence; synthesis; catalysis; palladium

Carbasugars,¹ owing to their biomimicry of carbohydrates, possess a wide range of biological activity from antitumor to antibiotic to antifungal, and therefore are attractive targets for synthesis. Several classes of carbasugars, including MK7607, streptol, and cyathiformines, have been isolated as enantiopure products or racemates (Scheme 1). The contiguous array of stereogenic hydroxyls has relegated current syntheses to diastereocontrol beginning from the chiral pool (carbohydrates, quinic acid, tartrates), enzymatic benzene dihydroxylation, or Diels-Alder cycloaddition.¹ With more than 140 known carbasugars, a strategy for enantio-, diastereo-, and regioselective access from a common synthon could afford access to the gamut of biologically active carbasugars.

The majority of the carbasugars have syn- or anti-1,2- and 1,4-cyclohexendiol motifs. The four possible regioisomers (syn-1,2; syn-1,4; anti-1,2; anti-1,4) are notable for their relationship to a single precursor, an allylic oxide (Scheme 1). Ideally, a single synthon would provide all possible stereoisomers and streamline the preparation of several carbasugars. We propose the term allylic oxide regio-resolution (AORR) for this process of resolving a racemic allylic oxide to regioisomeric products using the Tsuji-Trost reaction.^{2–3} Regioselective substitution⁴ of enantioenriched allylic acetates with malonates has been investigated with chiral molybdenum⁵ and palladium⁶ complexes, resulting in regioisomeric

**The project described was supported by Award Number T32GM008500 (MJM) from the National Institute of General Medical Sciences and generously supported by Cornell University. We thank Anthony Condo for mass spectra collection, and Ivan Keresztes for NMR assistance.

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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.2014xxxxx>.

products of 1,2- and 1,4-additions. Our efforts resulted in a catalyst-controlled AORR that delivers asymmetric 1,2- and 1,4-addition products that can be relayed to carbasugar natural products (see Scheme 1).

We began with a simplified carbasugar synthon (**1**) to study the influence of catalyst structure, substrate, and nucleophile for AORR. Racemic allylic oxide **1** was exposed to $\text{Pd}_2(\text{dba})_3$ and PPh_3 with *p*-cresol, which favored syn-1,4-addition (50% yield; Table 1, entry 1) over syn-1,2 addition (15%). The regioselectivity proved to be phosphine-dependent, and (*R*)-BINAP was gauged ineffectual (entry 2). The Trost ligand² (**4**) provided high enantioinduction in lower isolated yields (entry 3) compared with those obtained with the Van Vranken–Trost diphenylethylenediamine (DPEN) ligand **5** (entry 4).⁷ The high-conversion and enantioinduction of **2** and **3** and the absence of kinetic resolution of **1** (57:43 enantiomeric ratio [er] after reaction) suggested that each epoxide enantiomer proceeds to a different regioisomer. To test this hypothesis, we examined each enantioenriched epoxide of **1** under optimized conditions to gauge the “match”⁸ to a single enantiomer of ligand **5** and confirm the anticipated selectivity toward either syn-1,2- or 1,4-addition (entries 5 and 6). As predicted, the enantioenriched oxides smoothly converted to the syn products in an improved er. Notably, the (+)-oxide matched the *S,S* ligand to provide 1,2:1,4-addition products in an 8.5:1 ratio (entry 5), and the (–)-oxide switched the selectivity for a 1:4.6 ratio (entry 6). The recovered oxide showed no changes in enantiopurity for either entry (5 or 6). 4-Hydroxy anisole⁹ (entry 7) provided high levels of regiocontrol, enantioinduction, and conversion. The oxidative removal of 4-hydroxy anisole liberates the stereogenic hydroxyl and is vital to carbasugar preparation via AORR (vide infra; Scheme 2).

Similar to Trost’s stereoinduction of allylic acetates and carbonates,² the C_2 -symmetric ligand blocks one of the two sites of the π -allyl, diverting each oxide to a different constitutional isomer of 1,2- or 1,4-addition. The proposed model fits the observed enantioenriched oxide data and provides a predictive basis for new studies of complex allylic oxides in total synthesis.¹⁰

When oxide (+)-**1** is used, the π -allyl of the ester is generated within the complex, resulting in attack at the pro- (*R*) carbon for 1,2-addition (**6**; equation 1, Figure 1a). The 1,4-addition is accessible using the (–)-**1** oxide (**7**; equation 2) via attack at the pro-(*S*) carbon. The selectivity of this addition is consistent with Lloyd-Jones and co-workers’ studies¹¹ of the proposed transition states of the asymmetric allylic alkylation of cycloalkenyl esters.

The predicted and observed enantiomeric ratios can be calculated using the ratio of 1,2:1,4-addition products and the enantiopurity of the oxide (Figure 1b). Beginning with the (+)-oxide (92:8 er), the *S,S* ligand predicts a 1,2-addition with an increase to 99:1 er and a decrease of the 1,4-addition product to 67:33. The observed 1,2-addition product matches a 98:2 er, with a 1,4-addition product er of 68:32. The (–)-oxide (90:10 er) with the *S,S* ligand predicts a 1:99 er of 1,4-addition products and a 40:60 er for the 1,2-addition. The observed 1,4-addition is within error at 4:96, and the 24:76 of the 1,2-addition is reasonable.

The predictive model was then applied to carbasugar frameworks that incorporate additional functionality within the cyclohexenoate. Applying the AORR method to common synthon

8¹² was anticipated to provide syn-1,2-addition (**11**) and syn-1,4-addition (**12**) products originating from the kinetic palladium π -allyl complex **10** (Scheme 2).

The steric demands of the substituted dioxolane may destabilize kinetic π -allyl complex **9**, resulting in conversion to the thermodynamic π -allyl complex **13** via an exogenous Pd⁰ complex, as observed by Bäckvall.¹³ Addition of the nucleophile to complex **14** results in two forms: anti-1,2 (**15**) and anti-1,4 (**16**). Previous efforts by Hudlicky and co-workers¹⁴ have established that anti-1,2-addition of malonates to acetonide allylic oxides is possible but occurs in low yields or as mixtures of diastereomers. Common synthon **8** would be demonstrative of the kinetic to thermodynamic isomerization and would provide access to four classes of carbasugars.

We discovered that three of the four possible regioisomers were formed from synthon **8** with the reaction proceeding to full conversion (Scheme 3a). Anti-1,2-addition product **19** was isolated in 13% yield (93:7 er) and syn-1,4 product **20** in 12% yield (88:12 er). The high stereoselectivity, albeit with low yield, for each isomer reflects the additional constraints the dioxolane imposes on the palladium π -allyl system. The syn-1,2-addition product (**21**) was isolated in 24% yield (91:9 er) with the anti-1,4-addition product (**22**) undetected. The enhanced yield of the syn-1,2 product (**21**) was expected given the sterically encumbered anti-1,4-addition mode under these conditions. The regioisomeric products were then carried forward to three natural products.

The anti-1,2 product (**19**) comprises the stereoarray of streptol (**23**), a potent plant growth inhibitor.¹⁵ The conversion to streptol **23** was achieved by reducing the ester and protecting the transient acyl followed by cerium ammonium nitrate (CAN) oxidative cleavage of the anisole. The removal of the dioxolane using acetyl chloride and catalytic zinc chloride followed by global acyl cleavage proved uneventful. The syn-1,4 product (**22**) matches the unusual fungal metabolite cyathiformine B (**25**), a chorismic acid derivative.¹⁶ The cyathiformine structure poses potential problems due to its sensitive enol pyruvate that could complicate the oxidative cleavage of the anisole and Lewis-acid mediated dioxolane removal. Proceeding forward, the installation of the diazophosphonate using rhodium acetate was followed by CAN oxidation with surprisingly little degradation. Horner–Wadsworth–Emmons olefination using gaseous formaldehyde provided cyathiformine B type **24**. The dioxolane proved difficult to remove with varying levels of success (not shown). The syn-1,2 product (**21**) mapped to MK7607¹⁷ (**25**) and was targeted next. Following a similar approach to streptol, we prepared MK7607 in five steps.

The missing isomer, anti-1,4 (**22**), was not observed in the regio-resolution of oxide **8**. To carry out all possible additions to the allylic oxide, we determined that two criteria must be met to remove the other three regioisomers (syn-1,2; syn-1,4; anti-1,2): (1) the thermodynamic palladium complex must be formed to eliminate syn-1,2 and syn-1,4, and (2) the ligand must match the enantiopure oxide to eliminate anti-1,2 addition. The first criterion was satisfied via removal of the kinetic π -allyl isomer by increasing the steric crowding proximal to the palladium center. We hypothesized that a switch from a dioxolane to an acetonide would facilitate this population inversion, which was observed when applying racemic **27**¹⁸ to the reaction conditions (see supporting information). The second

criterion was fulfilled by evaluating the predicted model (Figure 1) and observed modes of addition for streptol, cyathiformine B type, and MK7607, which revealed the *S,S* ligand to be optimal. Enantiopure acetone oxide **27**¹⁹ provided the previously unobtainable anti-1,4-product **30** in 44% yield via a predicted interconversion of **28** to **29** and ligand directed addition to the anti-1,4 site (Scheme 3b). Acylation, oxidative cleavage of the anisole and saponification of the acetate followed by acid-mediated hydrolysis of the acetone gave the new cyclitol **31**.²⁰

In conclusion, we developed a regiodivergent, catalyst-controlled, asymmetric addition of phenols to allylic oxides that leads to the synthesis of streptol, MK7607, cyathiformine B type, and a novel cyclitol. The AORR method tolerates complex, fully substituted cyclohexenoates to provide access to the enantiomers of carbasugar natural products. The mechanistic dichotomy of the syn versus anti chiral palladium complexes and the study of complex nucleophiles and allylic oxides will be reported in due course.

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20. Structure **31** may be a member of the rancinamycin family or the pericosines (desmethyl).

a) AORR results - Enantioenriched oxide

b) Predicted and observed enantiomer ratios (er's)

	6 R:S		7 R:S	
	Predicted (er)	Observed (er)	Predicted (er)	Observed (er)
(+)- 1 92:8 e.r.	99:1	98:2	67:33	68:32
(-)- 1 90:10 e.r.	40:60	24:76	1:99	4:96

Figure 1.

Proposed transition states for stereinduction with observed product ratios.

Scheme 1.

Strategic allylic oxide regio-resolution (AORR) to access targeted carbasugar motifs.

Scheme 2.

AORR kinetic and thermodynamic palladium allyl distribution and resulting diastereomers.

a) AORR results - racemic oxide - streptol, cyathiformine B type, and MK7607

b) AORR results - chiral pool - a new cyclitol

Scheme 3.

Applying the AORR approach for the total synthesis of streptol, cyathiformine B type, MK7607, and a new cyclitol.

^aReagents and conditions: (a) 10 mol% Pd₂(dba)₃, 30 mol% (*R,R*)-**5**, *p*-OMePhOH (1.2 equiv), PhMe, 23 °C, 48 h (13% **19** (93:7 er), 12% **20** (88:12 er), 24% **21** (91:9 er)); (b) DIBALH (3.5 equiv), DCM, 0.3 h, 38%; (c) Ac₂O (3.0 equiv), DIPEA, DMAP, DCM, 0.3 h; (d) CAN (2.2 equiv), MeCN/H₂O 4:1, 0.20 h, 49% (two steps); (e) (1) AcCl, then ZnCl₂ (0.1 equiv) 0 to 23 °C; (2) H₂O, THF, 0.3 h; (f) NaOMe (1 equiv) MeOH, 16 h, 55% (two steps); (g) Rh₂(OAc)₂, **26**, DCM, 5 h, reflux, 64%; (h) CAN (2.2 equiv), MeCN/H₂O 4:1, 0.20 h, 81%; (i) LiHMDS, CH₂O, THF, 2 h, -78 °C, 71%; (j) DIBALH (3.5 equiv), DCM, 0.3 h 28%; (k) Ac₂O (3 equiv), DIPEA, DMAP, DCM 0.3 h; (l) CAN (2.2 equiv), MeCN/H₂O 4:1, 0.20 h, 21% (two steps); (m) (1) AcCl, then ZnCl₂ (0.1 equiv) 0 to 23 °C; (2) H₂O, THF, 0.3 h, (n) NaOMe (1 equiv) MeOH, 16 h, 57% (two steps), (o) 10 mol% Pd₂(dba)₃, 30 mol% (*S,S*)-**5**, *p*-OMePhOH (1.2 equiv.), PhMe, 23 °C, 48 h, 44% (up to 59% recovered **27**); (p) (1) Ac₂O (3 equiv), DIPEA, DMAP, DCM, 0.3 h; (2) CAN (2.2 equiv), MeCN/H₂O 4:1, 0.20 h, 63%; (q) (1) NaOMe, MeOH 0.1 h, 23 °C, 98%; (2) TFA, MeOH, 40 °C, 7 h, 51%. dba = dibenzylideneacetone, DIBALH = diisobutylaluminum hydride, DIPEA = diisopropylethylamine, DMAP = 4-(dimethylamino)pyridine, CAN = ceric ammonium nitrate, LiHMDS = lithium hexamethyldisilylazide, TFA = trifluoroacetic acid.

Table 1

Regiochemical control of enantioinduction.

entry	oxide 1	ligand	phenol	1 er ^b	2 er ^c	3 er ^c	% yield ^d (1:2:3)
1	(±)	PPh ₃	R = <i>p</i> -Me	–	–	–	20:15:50
2	(±)	(<i>R</i>)-BINAP	R = <i>p</i> -Me	–	–	–	n. d. ^e
3	(±)	(<i>R,R</i>) 4	R = <i>p</i> -Me	40:60	22:78	10:90	35:29:24
4	(±)	(<i>S,S</i>) 5	R = <i>p</i> -Me	57:43	96:4	93:7	2:39:34
5	(+) ^f	(<i>S,S</i>) 5	R = <i>p</i> -Me	92:8	98:2	32:68	31: 34 :4
6	(–) ^g	(<i>S,S</i>) 5	R = <i>p</i> -Me	10:90	24:76	96:4	28: 8 :37
7	(±)	(<i>S,S</i>) 5	R = <i>p</i> -OMe	56:44	85:15	95:5	1:48:35

^a Enantiomers shown are the major enantiomers derived from the *S,S*-ligand (entries 4–7).^b Enantiomeric ratio of recovered epoxides was determined with GC analysis.^c Enantiomeric ratios were determined with liquid chromatography analyses against prepared racemic standards.

^dYield refers to isolated yields following silica gel chromatography.

^eDecomposition of epoxide.

^fEnantiomeric ratio of 92:8 favoring the (+)-**1** isomer.

^gEnantiomeric ratio of 10:90 favoring the (–)-**1** isomer.

dba = dibenzylideneacetone, BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.