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Synthesis of 6-Carbon Termini-Differentiated Stereotriads via Symchiral 2-Trifloxy-1,3-cyclohexadiene monoepoxide[1]

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Abstract: Jacobsen epoxidation of 2-trifloxy-1,3-cyclohexadiene provides a valuable asymmetric monoepoxide product that can be readily manipulated to efficiently provide highly-functionalized symchiral cyclic and acyclic synthons.

Since their introduction by Stang nearly thirty years ago vinyl triflates have received much attention as precursors for vinyl cations and alkylidene carbenes.[2,3] More recently, vinyl and aryl triflates have been seen as readily available partners for a wide variety of organometallic coupling reactions. [4] This methodology has become more accessible largely because of important contributions by Farina *et al.* regarding improvements in catalyst ligand choice, ultimately leading to milder reaction conditions.

We showed in an earlier publication that 2-phenylsulfonyl-1,3 cycloalkadienes were spectacular substrates for epoxidation under catalytic Jacobsen conditions.[5] In order to extend the findings made in the sulfone series, we chose to investigate cyclohexadienyl triflates as potential substrates for the Jacobsen epoxidation. Using the mild triflating reagent described previously by Comins[6], dienyl triflate **1** was prepared in 85% yield from 2-cyclohexen-1-one. This substrate underwent epoxidation utilizing standard Jacobsen conditions to provide vinyl triflate epoxide **2**[7] (Figure 1) in moderate yield[8] with excellent enantioselectivity.[9] The highly-reproducible, key functionality-extending reaction involves treatment of **2** with LiHMDS in the presence of HMPA to generate new cross-conjugated dienyl triflates **3a,b**[10] (functionalized "benzene hydrates") after addition of water or TBSCl, respectively. Compounds **3a,b** serve as central pivots, enabling increased chemical diversity to be expressed through a second olefin functionalization step (epoxidation in this example).[11] It can be seen that both desired epoxides are readily obtained via control from the single homoallylic oxygen center present in dienes **3a,b**. With the exception of a single report by Danishefsky involving Pd(0) coupling,[12] functionalization reactions of epoxy vinyl triflates are unknown. However, the reactions of the related epoxy enolates of Wender[13] and the epoxy silylenol ethers of Marino[14] have provided an important point of departure for our studies.

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Figure 1

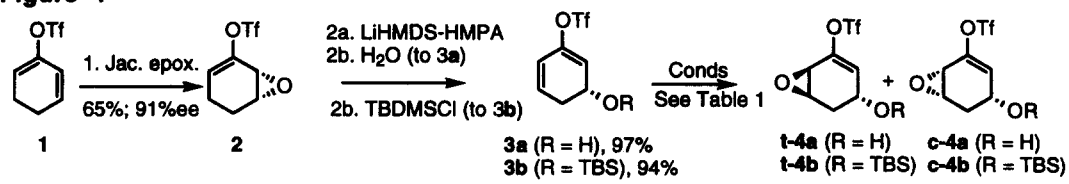
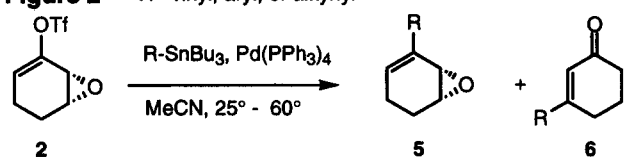


Table 1. Epoxidation Stereocontrol.

SM	Reagent	Yield	Ratio t/c
3a	cat trifluoroacetone/oxone	85%	1:1
3b	cat trifluoroacetone/oxone	88%	15:1
3a	mCPBA/CH_2Cl_2	79%	1:16
3b	.005% methyl trioxorhenium, H_2O_2	94%	13:1

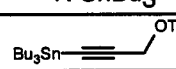
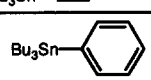
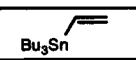
These asymmetric epoxy vinyltriflates offer considerable flexibility in that they are potential substrates for a wealth of Pd[0] chemistry. The first coupling reaction that we chose to explore with epoxide **2** was the Stille reaction[15], because of the easy accessibility of a wide variety of stannanes.[16] Unfortunately, initial attempts to utilize this methodology were plagued by the formation of enone **6** (Figure 2) which often accounted for half of the isolated yield.

Figure 2 R= vinyl, aryl, or alkynyl



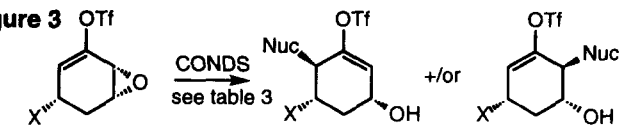
Believing that palladium-catalyzed rearrangement of the vinyl epoxide[17] was the problem, we sought to increase the efficacy of our catalyst by employing a ligand of low donicity, namely $AsPh_3$.[18] This strategy enabled us to adopt milder conditions while increasing reaction rate, thereby minimizing or avoiding entirely, the undesired enone **6**. The results of these coupling experiments are shown in Table 2.

Table 2. Stille coupling of epoxy vinyl triflates with cat $Pd_2(dba)_3$, $AsPh_3$

R-SnBu3	Conditions	Yield 5	ratio 5/6
	MeCN 25°, 9h	64%	>20/1
	MeCN 25°, 16h 5 eq LiCl	69%	12/1
	MeCN 25°, 12h	67%	>20/1

Having established the ability to successfully employ epoxide **2** in Pd[0] coupling reactions, attention was turned to the use of the vinyl epoxide as a source of further functionalization. We have observed that a large variety of nucleophiles can be added to vinyl epoxide **2** in predominantly 1,2 fashion to give a rich array of stereodefined alcohols. Extension of this strategy into the crucial domain of nucleophilic methylation has also been extremely successful, selectively providing 1,2 or 1,4 addition products in good yield (Figure 3/Table 3).[19] Another feature of this class of molecules is the fact that compounds **8a** and **8b** possess an enantiomeric relationship after deprotection, thereby allowing for the development of *enantiodivergent schemes at every stage in this strategy* from a single symchiral epoxyvinyltriflate.

Figure 3



2; X =H
c-4b; X =OTBS

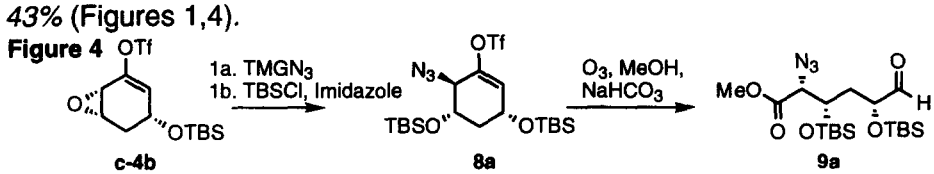
7a X =H **7b**
8a X =OTBS **8b**

Table 3. Epoxide Opening Regiocontrol of **2** and **c-4b**

SM	Reagent	Yield	1,4:1,2 Ratio
2	PhSH, NaH, -78°C to 25°C	88%	>20:1
2	allyl TMS;BF_3•Et_2O, 0°C	73%	>20:1
2	TMSCN;BF_3•Et_2O, 0°C	46%	>20:1
2	$TMGN_3$/CH_3CN, rt, 18h	91%	19:1
2	LiBr, AcOH, THF	88%	8:1
2	LiI, AcOH, THF	86%	8:1
2	MeMgBr, BF_3•Et_2O, THF (Nuc=Br)	95%	>20:1
2	MeCu (cat.);1.2 Me_3Al, THF	86%	94:6
2	10eq Me_3Al; H_20; CH_2Cl_2	85%	1:>20
c-4b	$TMGN_3$/CH_3CN, rt, 18h	95%	>20:1
c-4b	MeCu (cat.);1.2 Me_3Al, THF	84%	6:1
c-4b	10eq Me_3Al; H_20; CH_2Cl_2	87%	1:>20

Completion of the strategy is shown in Figure 4: Azidation and protection of **c-4b** affords **8a** in 91% yield followed by methanolic ozonolysis to quantitatively provide termini-differentiated ester-aldehyde **9a**. *The overall yield for the 6-step process is 43%* (Figures 1,4).

Figure 4



c-4b **8a** **9a**

To the best of our knowledge, this is the first reported example of ozonolytic cleavage of enol triflates and this useful reaction makes available a wealth of highly functionalized, stereodefined acyclic fragments. These compounds can be viewed as immediate precursors to a large variety of natural and unnatural amino acids and an effective complement to the desymmetrization tactics of Hudlicky and Johnson.[20]

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References and Notes

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[7] Compound **22** will undergo polymerization upon standing at 25°C for more than 1.5 hours, but has excellent room temperature stability when stored as a solution.

[8] We typically notice 10-15% of the aromatization byproduct PhOTf (see Ref 5).

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[10] We have unambiguously established the absolute stereochemistry of the analogous sulfone product and will present the stereochemistry of the triflate products in a subsequent full paper.

[11] Such directable reactions include cyclopropanation, dihydroxylation, aminohydroxylation, nucleophilic additions etc. see Hoveyda, A.H.; Evans, D.A.; Fu, G.C. *Chem. Rev.* **1993**, *93*, 1307.

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