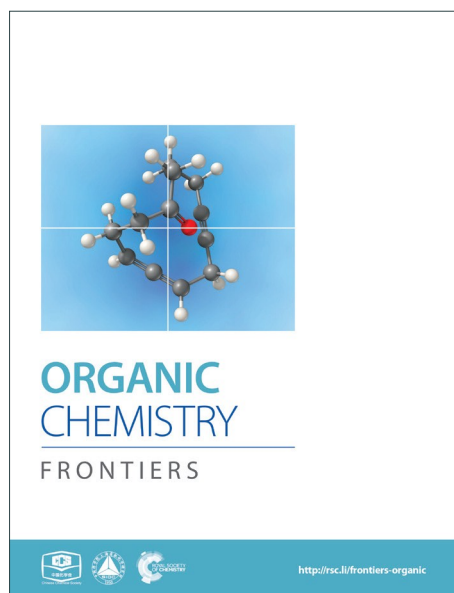
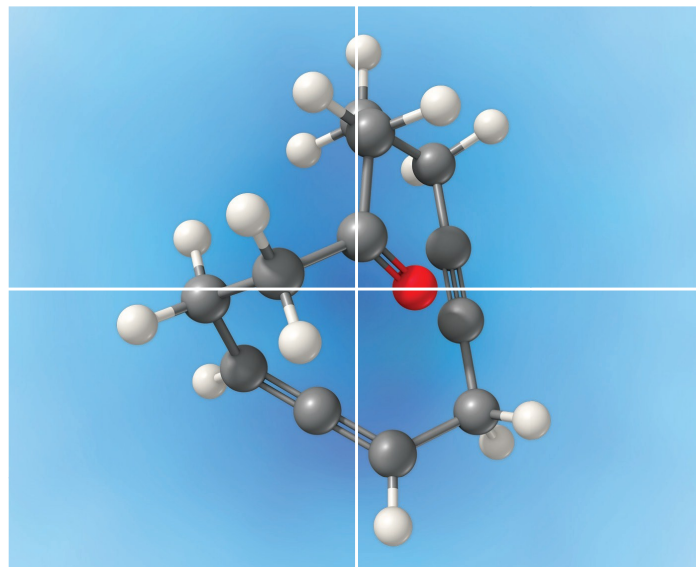


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## Research Article

# Epoxy and aziridinyl enolsilanes in diastereoselective inter- and intramolecular Friedel-Crafts alkylation†

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**The Friedel-Crafts alkylations of epoxy enolsilanes with arenes occur under silyl triflate catalysis at low temperatures. Intermolecular alkylations with optically-enriched epoxides occur with conservation of ee. Intramolecular reactions give rise to cyclized products with high diastereoselectivity in good yields. Aziridinyl enolsilanes also undergo selective inter- and intramolecular Friedel-Crafts reactions in a similar manner.**

## Introduction

The reactions of epoxides and aziridines with  $\pi$ -nucleophiles have been a topic of a longstanding synthetic interest.<sup>1</sup> There are numerous examples of such reactions with heteroaromatic compounds such as indoles, which are more electron-rich and allow such reactions to proceed under milder conditions.<sup>2</sup> In comparison, there are far fewer examples of intermolecular reactions of epoxides/aziridines with arenes.<sup>3</sup> This latter group of Friedel-Crafts reactions has been promoted by strong Lewis and protic acids, and proceeds in moderate to good yields. It is a useful strategy to alkylate and install functionality and chirality proximate to arenes, and there are more examples of the intramolecular version of this reaction than the intermolecular.<sup>4</sup> In addition to the traditional strong Lewis and protic acids for Friedel-Crafts reactions, this reaction has also been promoted with H-mordenite,<sup>5</sup> Sc(OTf)<sub>3</sub>,<sup>3a</sup> AuCl<sub>3</sub>/AgOTf,<sup>6</sup> Ag(PF<sub>6</sub>),<sup>7</sup> InCl<sub>3</sub>,<sup>4e</sup> B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub><sup>8</sup> and silica gel,<sup>9</sup> in solvents including hexafluoroisopropanol<sup>4d</sup> and water,<sup>4d</sup> with a range of stereoselectivities. Cyclizations to generate 5- to 8-membered rings have been observed.

With respect to the electrophiles, many of these reactions involve the more reactive, aryl-substituted epoxides and aziridines, which are attacked at the benzylic position via S<sub>N</sub>1-like transition states. The reactions of vinyl epoxides are complicated by nucleophilic attack via S<sub>N</sub>2 and S<sub>N</sub>2' pathways. Epoxides bearing electron-withdrawing substituents are opened at the distal position by nucleophiles. Varying degrees of inversion have been recorded for optically-enriched epoxides, depending on the substituents on the epoxide.<sup>10</sup>

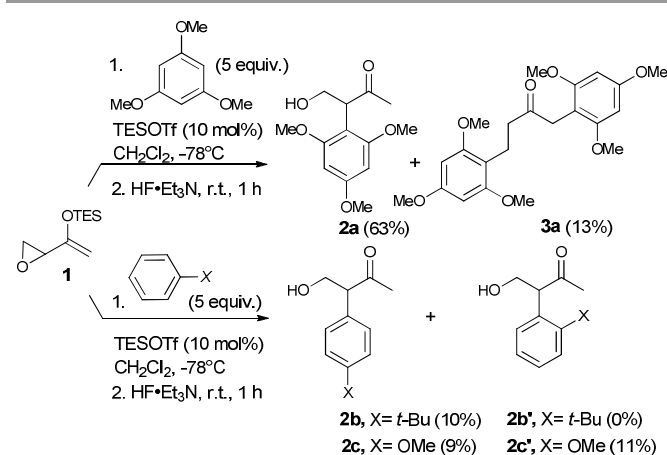
The conversion of an epoxyketone to an epoxy enolsilane has the overall effect of transforming the electron-withdrawing carbonyl group into a nucleophilic moiety, promoting carbon-carbon bond formation at the allylic position. Recently, a related umpolung strategy has been employed by MacMillan et al to induce nucleophilic attack of  $\alpha$ -haloketones under basic and ionizing conditions, by heteroatomic nucleophiles and indoles via the intermediacy of oxyallyl cations.<sup>11</sup>

We have investigated extensively the reactions of epoxy enolsilanes with  $\pi$ -nucleophiles such as furans and dienes, which, under silyl triflate catalysis, are predominantly (4+3) cycloadditions.<sup>12</sup> Side products arising from an arrested cycloaddition, undergoing deprotonation instead of a second carbon-carbon bond formation, and culminating in a Friedel-Crafts process, have been observed as minor products. Our computational studies showed that furan forms carbon-carbon bonds with the activated epoxide via a backside attack, and not through the putative oxyallyl cation intermediate of typical (4+3) cycloadditions.<sup>13</sup> This explains why the cycloadditions proceeded with high levels of inversion and conservation of ee. It occurred to us

that we could also engage the activated epoxide in Friedel-Crafts chemistry, to further exploit the high fidelity of the transfer of chiral information conferred by this intermediate.

## Results and Discussion

As expected, with arenes as  $\pi$ -nucleophiles, the Friedel-Crafts pathway predominated. Under silyl triflate catalysis at very low temperatures (the same conditions optimized for (4+3) cycloadditions with dienes), electron-rich 1,3,5-trimethoxybenzene underwent an  $S_N2$ -like ring opening of *rac*-**1** to give rise to  $\beta$ -hydroxy- $\alpha$ -arylketone *rac*-**2a** as the major product (Scheme 1). Doubly arylated product **3a** was also isolated as a minor product in 13% yield, which was deduced to have been obtained from an initial  $S_N2'$  addition of **1** by the arene. Benzene was apparently not electron-rich enough to react efficiently as the nucleophile (0% yield), and even mono-activated arenes such as *t*-butylbenzene and anisole reacted to give Friedel-Crafts products in  $\leq 20\%$  yield.



Scheme 1

We continued to examine this reaction for optically-enriched **1** with electron-rich arenes (Table 1). Indeed, the yields of the intermolecular Friedel-Crafts alkylation increased with increasing electron density of the arenes. In all cases, the Friedel-Crafts reaction proceeded to give **2** with high enantiomeric purity, inferring that a similar activated epoxide was the electrophile, and that the arenes underwent an  $S_N2$ -like, backside attack.<sup>14</sup> It should be noted

Table 1. Intermolecular Friedel-Crafts alkylation of (+)-**1**

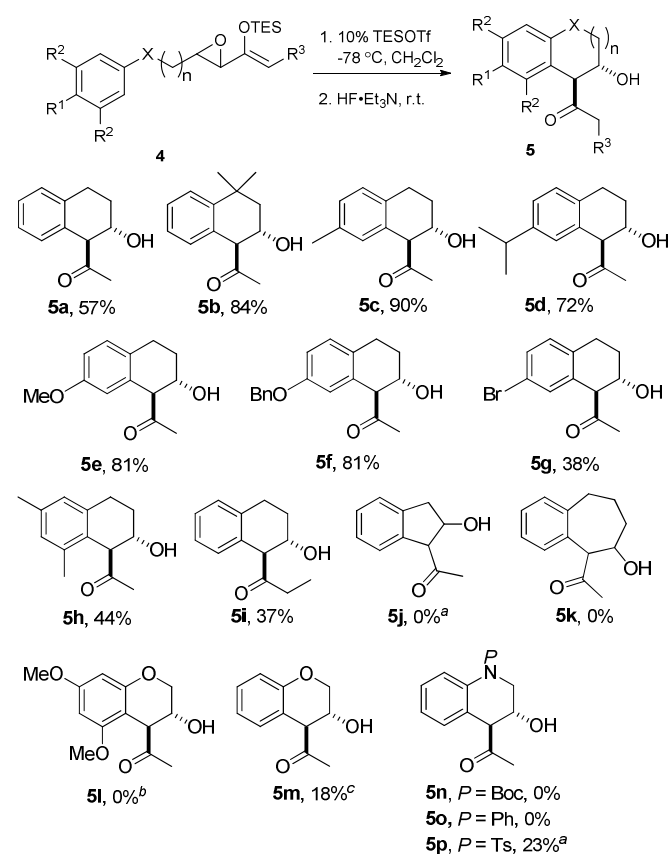
entry	ArH	Yield of <b>2</b>	ee of <b>2</b>
1	1,3,5-trimethoxybenzene	(+)- <b>2a</b> 63%	95%
2	mesitylene	(+)- <b>2d</b> 64%	97%
3	1,4-dimethoxybenzene	(+)- <b>2e</b> 43%	93%
4	<i>p</i> -xylene	(+)- <b>2f</b> 58%	97%
5	<i>m</i> -xylene	(+)- <b>2g</b> 55% <sup>a</sup>	97% <sup>b</sup>

<sup>a</sup> 3:1 mixture of regioisomers. <sup>b</sup> ee of the major 1,2,4-regioisomer.

that asymmetric aldol reactions of arylated ketones with formaldehyde as a strategy to synthesize similar arrays remains a challenge.

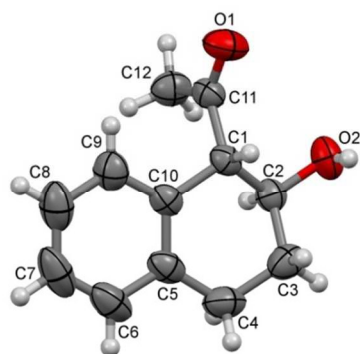
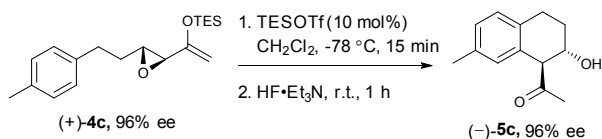
We proceeded to investigate the intramolecular version of this alkylation (Table 2). A series of substrates **4a-k**, each with an arene coupled to an epoxy enolsilane through all-carbon tethers were synthesized. Gratifyingly, substrates that cyclize by a ( $\pi$ -endo)-endo epoxide reaction to generate six-membered rings and yield octalin derivatives, proceeded with high diastereoselectivity. The pseudoaxial methine proton alpha to the acyl group had  $^3J = 8-9$  Hz by coupling with the methine proton at the secondary hydroxyl group, which is consistent with a *trans*-relationship of the protons. The

Table 2 Intramolecular Friedel-Crafts alkylation of epoxy enolsilanes



<sup>a</sup> 1.1 equiv. TESOTf used. <sup>b</sup> 1% 2,6-lutidine added,  $-78$  to  $-40$   $^\circ\text{C}$ . <sup>c</sup> 10% 2,6-lutidine added; refluxed 1 h.

relative stereochemistry was further confirmed by x-ray crystallographic analysis of **5a**.<sup>15</sup> This stereochemical outcome again inferred an  $S_N2$ -like attack on an activated epoxide intermediate, rather than an  $S_N1$ -like transition state resembling a siloxallyl cation. It follows then, that the reaction of optically pure (+)-**4b** generated a single diastereomer of **5b** with high enantiomeric purity also (Scheme 3).<sup>14</sup>

Figure 1. X-ray crystallographic structure of **5a**

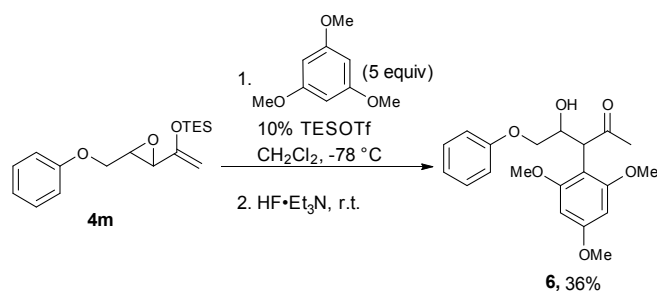
Equation 1

Gem-dimethyl effects in **4** facilitated the cyclization process to give **5** significantly (eg. **4a** vs **4b**). Electron-rich arenes underwent cyclizations with up to 90% yield, whereas the less electron-rich substrates cyclized with moderate yields (eg. **4g**). The para-disubstituted arenes such as **4c-f** underwent cyclization efficiently, whereas cyclizations of meta-substituted arenes such as **5g** were less facile due to steric congestion. When **4i** was substituted at the enolsilane ( $R_3 \neq H$ ), the Friedel Crafts cyclization was also less efficient. The low yield of **5i** may be due to the formation of side products arising from increased oxyallyl cation character in the intermediate.

Substrates **4j-k** were synthesized to explore variations in the length of the tether, but neither reacted significantly in Friedel-Crafts cyclizations.<sup>4a</sup> In fact, **4j** was completely unreactive under the typical conditions and could be essentially completely recovered.

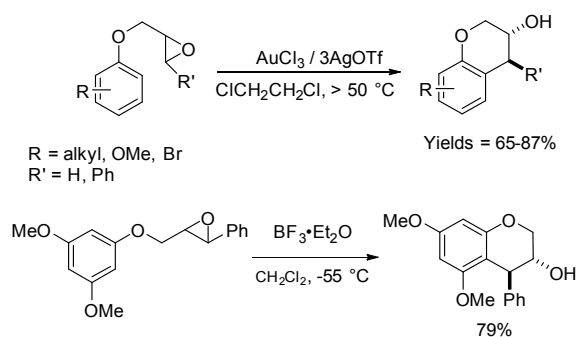
Surprisingly, the oxygen-tethered substrates **4l-m**, as well as the nitrogen-tethered **4n-p**, which are rather electron-rich arene nuclei, failed to undergo any Friedel-Crafts cyclization under the typical reaction conditions. Only under more forcing conditions were some Friedel-Crafts products detected. In the case of **4p**, only when one equivalent of TESOTf was used, the reaction proceeded to give a modest yield of **5p**. The addition of 2,6-lutidine as a proton scavenger allowed some of the reactions to be conducted at elevated temperatures and over longer reaction times, because trace amounts of Brønsted acid promoted the desilylation of the enolsilanes. When the reaction of **4m** was heated in the presence of 2,6-lutidine, a modest 18% yield of **5m** was isolated.

For these substrates that failed to cyclize, it was not because the epoxy enolsilane was unreactive: in the presence of 5 equivalents of 1,3,5-trimethoxybenzene, the intermolecular Friedel-Craft alkylation product **6** was obtained at  $-78$  °C, while no **5m** was observed (Scheme 2).



Scheme 2

On the other hand, we noted in the literature that there were examples of related arene substrates in which epoxides were similarly tethered via a phenolic oxygen atom, that underwent Friedel-Crafts reactions successfully, albeit at higher reaction temperatures than those used in our reactions (Scheme 3).<sup>6,16</sup>



Scheme 3

A rudimentary computational study was done to sample the ground state conformations of **4a** and **4m** using MMFF methods.<sup>17</sup> Figure 2 shows the structures of the lowest energy conformers. For **4a**, the two carbons ( $C_1$ ,  $C_2$ ) that would eventually need to approach at a bonding distance were quite close to each other at about 3.8 Å, whereas for the lowest energy conformer of **4m**, the two carbons were much farther apart (5.2 Å). We found that the populations of the two substrates also differed significantly (Tables S1, S2, see Supplementary Information). The majority of the conformers of **4a** was found to have bent carbon tethers, which bring the arene close to the epoxide and place  $C_1$  and  $C_2$  at  $\leq 4.0$  Å proximity. In contrast, the conformers of **4m** possessed tethers that were more linear and directed the epoxide away from the aromatic ring, such that at 298K, fewer than 2% of the sampled population had  $C_1$  and  $C_2$  within 5.0 Å of each other. Based on this, it can be reasoned qualitatively that the transition state of the Friedel-Crafts reaction which has  $C_1$  and  $C_2$  at a bonding distance would be lower in energy for **4a** than **4m**. However, this scenario does not preclude the cyclization of **4m** at higher temperatures. Probably the more extended conformations of the tether of **4m** are due to electron donation from the oxygen atom into the arene ring.

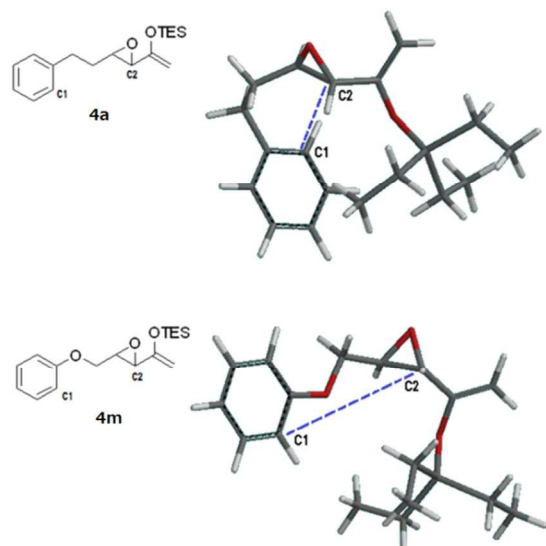
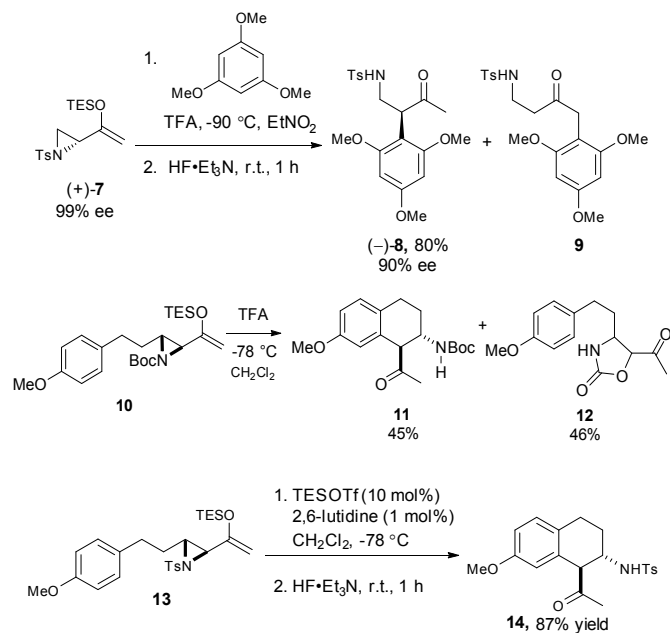


Figure 2

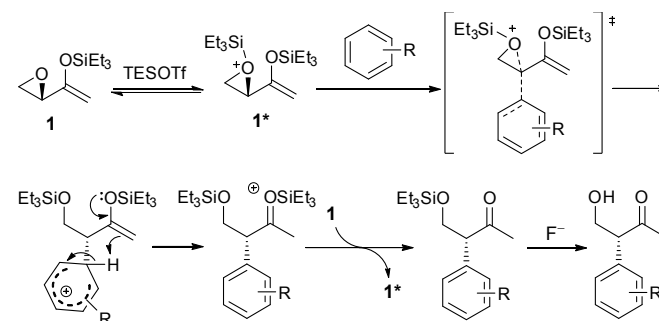
We also examined the Friedel-Crafts reaction of the related aziridinyl enolsilanes. Under acid or Lewis acid activation, they reacted in a similar fashion as the epoxy enolsilanes, to afford the corresponding aminoalkylated arenes. The reaction of optically pure **7** with 1,3,5-trimethoxybenzene produced  $\beta$ -aminoketone **8** in good yield and with conservation of ee, along with some  $S_N2'$  product **9** (Scheme 4). The Friedel-Crafts cyclization of **10** proceeded to afford a single diastereomer of  $\beta$ -aminoketone **11**, along with a carbamate ring expansion product **12** as the major side product.<sup>18</sup> Replacing the carbamate protecting group with a tosyl group in **13** obviated the side reaction and improved the yield of  $\beta$ -aminoketone **14** significantly.



Scheme 4

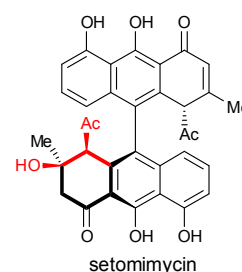
The mechanism of the intramolecular Friedel-Crafts alkylation is proposed to be as depicted in Scheme 5. Epoxide **1** reacted with silyl

triflate to give activated epoxide **1\***, which is subsequently attacked by the arene from the back in an  $S_N2$ -like manner. The aromaticity of the arene is restored by deprotonation, while the enolsilane could react as a proton acceptor to form the activated oxonium species that could then silylate **1** and propagate the reaction. The reaction involving aziridinyl enolsilanes would be expected to be very similar.

Scheme 5. Proposed mechanism of the Friedel-Crafts reaction of **1**.

## Conclusions

In summary, the scope of intermolecular and intramolecular Friedel-Crafts cyclization of epoxy enolsilanes with arenes has been explored. The reaction occurs with high stereoselectivity through the intermediacy of a stereochemically defined chiral activated epoxide, rather than an oxyallyl cation, to give  $\beta$ -hydroxy- $\alpha$ -arylketones in enantiomerically pure forms. Electron-rich arenes underwent the reaction with moderate to high yields. Aziridinyl enolsilanes undergo a similar stereoselective reaction to afford  $\beta$ -amino- $\alpha$ -arylketones. This reaction may offer us a strategy to tackle the synthesis of the differently functionalized anthracenone hemispheres in a natural product such as setomimycin (Figure 3).

Figure 3 Natural product containing a  $\beta$ -hydroxy- $\alpha$ -arylketone substructure.

## Notes and references

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<sup>†</sup>Electronic Supplementary Information (ESI) available: Experimental procedures for synthesis, full characterization of all new compounds, and details of computations. See DOI: 10.1039/c000000x/

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