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# A two-step synthesis of allylic *syn* 1,3-diols via an intramolecular oxa-Michael reaction followed by a modified Julia olefination

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ABSTRACT

A two-step process for the synthesis of allylic *syn* 1,3-diols is developed. An intramolecular oxa-Michael reaction onto vinyl heteroaromatic sulfones allows the diastereoselective formation of 1-sulfonyl 2,4-diols protected as benzylidene acetals. These sulfones are then engaged in a modified Julia olefination to furnish the olefins contiguous to the benzylidene acetal ring with good *E*/*Z* selectivity.

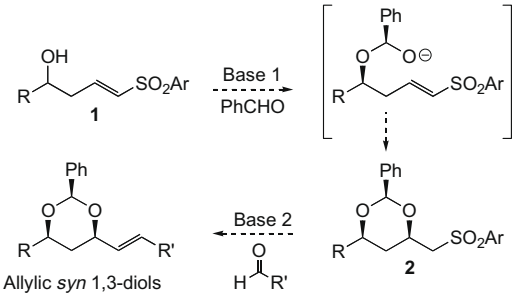


The *syn* 1,3-diol motif flanked by an olefin is found in numerous natural products. In the course of our studies on intramolecular oxa-Michael reactions,[1] we wanted to develop a new access to such a motif by the sequence shown in Scheme 1. The protected *syn* 1,3-diol **2** would be installed via an intramolecular oxa-Michael addition of a hemiacetal anion, prepared in situ from homoallylic alcohol **1** in the presence of benzaldehyde and a sub-stoichiometric amount of base, onto a vinyl sulfone. The resulting sulfone would then be engaged in a Julia olefination[2] to give the required alkene.

We have previously reported such a conjugate addition on tolyl vinyl sulfones **1** (Ar = Tol), which led to the corresponding β-oxygenated sulfones **2** in good yields.[3] Since the addition of aryl sulfones onto aldehydes is reversible, direct condensation of these substituted β-oxygenated sulfones with aldehydes is not possible because of a competing retro-Michael reaction. In order to avoid this side-reaction, the benzylidene acetal was reduced to free the proximal hydroxy group. Addition of the dianion of the β-hydroxy sulfones to aldehydes was successful, but an additional two steps (acetate or benzoate formation, and reductive elimination) were required to form the alkene, with the issue of differentiating the two hydroxy groups in the first step.[3]

In this Letter, we report a two-step synthesis of protected allylic *syn* 1,3-diols from hydroxy vinyl heteroaromatic sulfones **1** (Ar = heteroaromatic). The one-pot olefination first described by S. Julia for benzothiazolyl and pyridinyl sulfones,[4] and later extended to phenyltetrazolyl and *tert*-butyltetrazolyl sulfones by Kocienski[5] would allow direct conversion of the intermediate β-oxygenated heteroaromatic sulfones **2** into the protected allylic diols.[6] The challenge of this sequence is the careful selection of the reaction conditions (especially the base) for both steps. In the oxa-Michael reaction, an unwanted subsequent olefination product could result from further condensation with benzaldehyde, and the retro-Michael reaction has to be avoided during the olefination step.

We first studied the intramolecular oxa-Michael reaction with benzothiazolyl sulfone **3a**[7] (Eq. 1, Table 1). Treatment of this compound with excess benzaldehyde and a catalytic amount of potassium *tert*-butoxide at 0 °C, which are the conditions that had been optimized for phenyl sulfones,[3a] led to the desired benzylidene acetal in only 24% yield (due to poor conversion), with no diastereoselectivity. We assumed that this conjugate addition is under thermodynamic control, as is the case for phenyl vinyl sulfones, thus we tried to displace the equilibrium in favor of the product by performing the reaction at higher temperature. Raising the temperature to 20 °C slightly improved the conversion and the selectivity, but the result was still disappointing. Switching to KHMDS[8] improved the conversion, but not the selectivity. In addition, with KHMDS at 20 °C the olefination side-product resulting from the condensation of **4a** with benzaldehyde was isolated in 20% yield. Changing the base counterion to lithium greatly improved both the conversion and the *syn*/*anti* ratio.[9] Gratifyingly,




**Scheme 1.** Synthesis of allylic *syn* 1,3-diols via oxa-Michael addition followed by Julia olefination.

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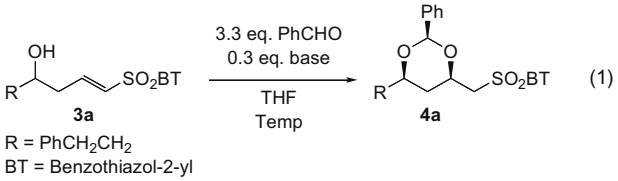
**Table 1**
Optimization of the oxa-Michael reaction with **3a**



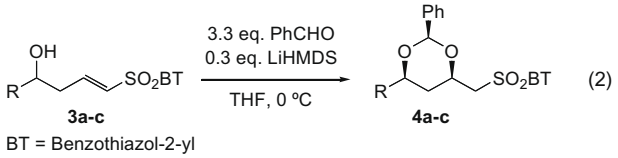

| Entry | Base | *T* (°C) | Yield (%) | *syn*/*anti* |
|---|---|---|---|---|
| 1 | *t*-BuOK | 0 | 24 | 50:50 |
| 2 | *t*-BuOK | 20 | 35 | 75:25 |
| 3 | KHMDS | 0 | 50 | 50:50 |
| 4 | KHMDS | 20 | 54 | 50:50 |
| **5** | **LiHMDS** | **0** | **80** | **90:10** |
| 6 | LiHMDS | 20 | 62 | 90:10 |

no unwanted olefination product was observed. In this case, the yield was lower when the reaction was performed at 20 °C, because of partial decomposition of the product, and with no gain in selectivity.

These optimized conditions (LiHMDS, 0 °C)[10] were then applied to sulfones **3b** and **3c** (Eq. 2, Table 2). The *syn*/*anti* ratio was deduced from analysis of the $^1$H NMR spectrum of the unpurified products; it was lower in the case of the hindered *i*-Pr substituent. In all cases, this ratio was improved after recrystallization (the yields in Table 2 refer to recrystallized products).

Having established the feasibility of the oxa-Michael reaction, we next examined the one-pot Julia reaction with compound **4c**. Only a few examples of modified Julia olefination with a sulfone bearing a β-oxygenated substituent have been reported. In some cases the reaction is straightforward, such as the olefination employed in the synthesis of phorboxazole between a β-methoxy sulfone and an unsaturated aldehyde.[11] However, this reaction can be plagued by β-elimination, leading to poor yields,[12] or by epimerization of the β-center resulting from a β-elimination/oxa-Michael sequence.[13] Reaction between **4c** and benzaldehyde (Eq. 3, Table 3) was slow in the presence of LiHMDS, and the conversion was moderate (less than 50%). The use of NaHMDS improved the yield of **5a**, but the conversion was still not complete. The best yields were obtained with KHMDS, and the *E*/*Z* ratio was higher in DMF as a solvent. This reaction was also performed with success in the presence of NaH in THF, leading to excellent *E* selectivity.[14] This selectivity in favor of the *E*-isomer in the one-pot olefination with aromatic aldehydes had been observed by S. Julia and co-workers.[2,4c] It is worth noting that in all cases, no β-elimination or epimerized side-products were observed, meaning that even if the β-elimination occurs, the oxa-Michael/retro-Michael equilibrium occurs faster than the olefination reaction.

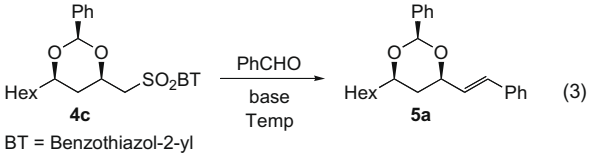
**Table 2**
Oxa-Michael reactions with benzothiazol-2-yl sulfones **3a–c**




| Entry | R | Product | Yield (%) | *syn*/*anti* |
|---|---|---|---|---|
| 1 | $PhCH_2CH_2$ | **4a** | 80 | 90:10 (94:6)[a] |
| 2 | *i*-Pr | **4b** | 82 | 75:25 (90:10)[a] |
| 3 | Hex | **4c** | 75 | 90:10 (92:8)[a] |

[a] After recrystallization.

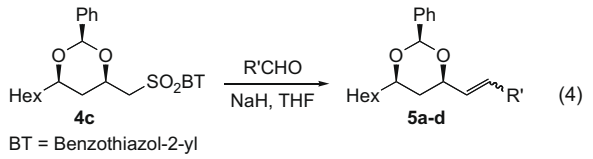
**Table 3**
Optimization of the modified Julia olefination with **4c**




| Entry | Base | Solvent | *T* (°C) | Yield (%) | *E*/*Z* |
|---|---|---|---|---|---|
| 1 | LiHMDS | THF | −78 to 20 | 41[a] | 5:1 |
| 2 | NaHMDS | THF | −78 to 20 | 75[b] | 5:1 |
| 3 | KHMDS | THF | −78 | 81 | 3:1 |
| **4** | **KHMDS** | **DMF** | **−60** | **78[c]** | **7:1** |
| **5** | **NaH** | **THF** | **20** | **71** | **33:1** |

[a] 52% recovered sulfone.
[b] 10% recovered sulfone.
[c] 7% recovered sulfone.

**Table 4**
Modified Julia reactions with benzothiazol-2-yl sulfone **4c**



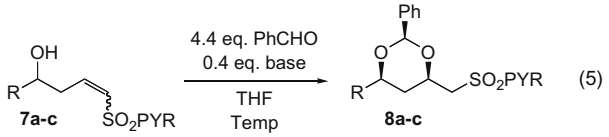

| Entry | R′ | Product | Yield (%) | *E*/*Z* |
|---|---|---|---|---|
| 1 | Ph | **5a** | 71 | 33:1 |
| 2 | PhCH=CH | **5b** | 93 | 1.8:1 |
| 3 | $PhCH_2CH_2$ | **5c** | 70 | 1:3 |
| 4 | *i*-Pr | **5d** | 60 | 1:3 |

The modified Julia reaction was then extended to a range of aldehydes (Eq. 4, Table 4). With saturated aldehydes such as hydrocinnamaldehyde and *iso*-butyraldehyde, alkenes **5c** and **5d** were obtained as 3:1 mixtures of isomers favoring the *Z*-olefin.[2,5b] We tried to improve the selectivity by running the reaction in toluene,[15] but unfortunately sulfone **4c** was not reactive in this solvent. Reaction with cinnamaldehyde led to alkene **5b** with poor selectivity. This tends to prove that the behavior of unsaturated aldehydes in the modified Julia olefination with benzothiazolyl sulfones is intermediate between those of aromatic and saturated aldehydes.

The oxa-Michael reactions were next investigated with pyridinyl sulfones **7a–c**.[16] Reaction of **7a**[17] with LiHMDS and benzaldehyde proceeded smoothly at either 0 °C or 20 °C to give the expected benzylidene acetal **8a** with excellent selectivities[9] (Eq. 5, Table 5). Surprisingly, the conjugate addition of the same substrate with KHMDS at 20 °C was even more diastereoselective, and no olefination side-product was detected. The *syn*/*anti* ratio was very high for **8b** and **8c** as well.

Next, we examined the Julia olefination with sulfone **8a**. Once again, the reaction conditions that had been optimized for the benzothiazolyl sulfones could not be directly transposed to the pyridinyl sulfones. Reaction of **8a** with benzaldehyde in the presence of NaH in THF at 20 °C only furnished traces of the desired alkene **5e** (Eq. 6, Table 6). When the same reaction was performed in DMF, the yield improved to 50%. Similar yields were obtained with KHMDS, with the best *E* selectivity observed in dichloromethane. In all these reactions, conversion of the starting sulfone **8a** was complete. The moderate yields stemmed from the formation of polar side-products that could not be isolated, possibly due to retro-Michael side-reactions.

**Table 5**
Oxa-Michael reactions with pyridin-2-yl sulfones **7a–c**

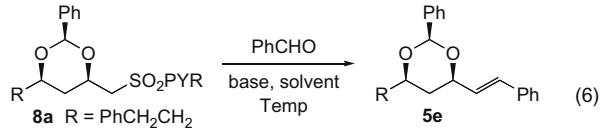



PYR = Pyridin-2-yl

| Entry | R | Product | Base | *T* (°C) | Yield (%) | *syn*/*anti* |
|---|---|---|---|---|---|---|
| 1 | $PhCH_2CH_2$ | **8a** | LiHMDS | 0 | 85 | 92:8[a] |
| 2 | $PhCH_2CH_2$ | **8a** | LiHMDS | 20 | 80 | 94:6[b] |
| **3** | **$PhCH_2CH_2$** | **8a** | **KHMDS** | **20** | **72** | **>98:2** |
| 4 | *i*-Pr | **8b** | KHMDS | 20 | 76 | 94:6 |
| 5 | Hex | **8c** | KHMDS | 20 | 65 | 96:4 |

[a] 97:3 after recrystallization.
[b] 96:4 after recrystallization.

**Table 6**
Modified Julia reactions with pyridin-2-yl sulfone **8a**

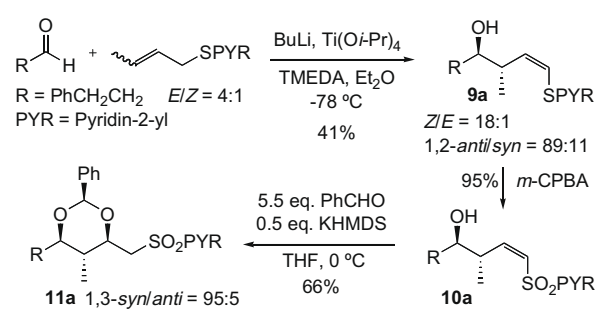



PYR = Pyridin-2-yl

| Entry | Base | Solvent | *T* (°C) | Yield (%) | *E*/*Z* |
|---|---|---|---|---|---|
| 1 | NaH | THF | 20 | Traces | –– |
| 2 | NaH | DMF | 20 | 50 | 8:1 |
| 3 | KHMDS | THF | −78 to 20 | 40 | 5:1 |
| 4 | KHMDS | Toluene | −78 to 20 | 44 | 9:1 |
| **5** | KHMDS | **$CH_2Cl_2$** | −78 to 20 | **47** | **16:1** |

We also performed the oxa-Michael reaction with compound **10a**, which possesses a methyl group at the allylic position. This alcohol was synthesized by regio- and diastereoselective addition of the anion of crotyl pyridinyl sulfide to hydrocinnamaldehyde, followed by *m*-CPBA oxidation (Scheme 2).[16] Formation of **11a** occurred in a good yield and with an excellent diastereoselectivity.

In conclusion, we have developed a straightforward and efficient synthesis of protected allylic *syn* 1,3-diols, in only two steps from hydroxy vinyl heteroaromatic sulfones. Similar good yields and selectivities were observed for the benzothiazolyl and the pyridinyl sulfones during the intramolecular oxa-Michael reaction, but the yields of the modified Julia olefination were significantly higher with the former sulfones. Olefination with aromatic aldehydes led to the *E*-isomer with excellent selectivity, while use of aliphatic aldehydes furnished the *Z*-olefins as the major isomers. This method may be very useful for the synthesis of polyene antibiotics and polyketide natural products, for example.




**Scheme 2.** Oxa-Michael reaction with a substrate bearing an allylic substituent.

## Acknowledgments

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7. The preparation of sulfones **3a–c** will be reported elsewhere.
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9. Only one of the two possible *anti* diastereomers was observed in all cases. The stereochemistry of the major *syn* isomer was proven by NOE experiments.
10. *Procedure for the oxa-Michael reaction*: To a solution of 700 mg of vinyl sulfone **3a** (1.87 mmol) in 19 mL of anhydrous THF at 0 °C was added 207 μL of freshly distilled benzaldehyde (2.06 mmol, 1.1 equiv) followed by 187 μL of 1 M LiHMDS in THF (0.187 mmol, 0.1 equiv) and the resulting solution was stirred for 15 min at 0 °C. A second portion of benzaldehyde (1.1 equiv) and 1 M LiHMDS (0.1 equiv) in THF was added and after 15 min, a third portion (same amounts) was added. The mixture was then stirred for 1 h and quenched with 10 mL of a saturated aqueous $NH_4Cl$ solution. The aqueous phase was extracted with diethyl ether (3 × 15 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting white solid was recrystallized from $Et_2O$/petroleum ether (20:80) to give 700 mg (80%) of the desired ketal **4a** as a 15:1 mixture of diastereomers. Spectroscopic data for the *syn* diastereomer: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.18 (br d, $J$ = 8.0 Hz, 1H), 7.84 (br d, $J$ = 8.4 Hz, 1H), 7.61 (ddd, $J$ = 8.0, 7.2, 1.2 Hz, 1H), 7.54 (ddd, $J$ = 8.4, 7.6, 1.2 Hz, 1H), 7.30–7.26 (m, 2H), 7.22–7.16 (m, 3H), 7.12–7.06 (m, 1H), 6.96–6.90 (m, 4H), 5.39 (s, 1H), 4.55 (m, 1H), 4.12 (dd, $J$ = 14.8, 8.8 Hz, 1H), 3.81 (m, 1H), 3.53 (dd, $J$ = 14.8, 3.2 Hz, 1H), 2.76 (m, 2H), 2.01–1.92 (m, 1H), 1.85–1.77 (m, 1H), 1.74 (td, $J$ = 13.2, 2.8 Hz, 1H), 1.64–1.58 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 166.3, 152.6, 141.3, 137.2, 136.8, 128.45, 128.4, 127.7, 127.6, 127.4, 125.9, 125.5, 125.3, 122.2, 100.3, 75.2, 71.1, 59.7, 37.0, 35.7, 30.9; IR ($CH_2Cl_2$) $\nu$ 2926, 2810, 1470, 1450, 1400, 1380, 1330, 1315, 1240, 1154, 1105, 1069, 1021 $cm^{-1}$; HRMS (EI) $m/z$ calcd for $C_{26}H_{25}NO_4S_2$ 479.1225; found: 479.1228.
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14. *Procedure for the modified Julia olefination*: To a solution of 50 mg of **4c** (0.11 mmol) and 17 μL of freshly distilled benzaldehyde (0.16 mmol, 1.5 equiv) in 0.4 mL of anhydrous THF at room temperature was added 18 mg of sodium hydride as a 60% dispersion in mineral oil (0.45 mmol, 2.5 equiv) in one portion. The reaction was monitored by TLC, and after 5 h, the reaction was quenched by addition of a saturated aqueous $NH_4Cl$ solution. The aqueous layer was extracted with diethyl ether (3 × 15 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting white solid was purified by flash column chromatography on silica gel ($Et_2O$/petroleum ether 20:80) to give 27 mg (71% yield) of the pure product **5a** as a single diastereomer: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.57–7.55 (m, 2H), 7.40–7.23 (m, 8H), 6.67 (d, $J$ = 16.0 Hz, 1H), 6.22 (dd, $J$ = 16.0, 6.0 Hz, 1H), 5.63 (s, 1H), 4.55–4.51 (m, 1H), 3.90–3.86 (m, 1H), 1.76–1.48 (m, 4H), 1.42–1.25 (m, 8H), 0.90–0.87 (m, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 138.7, 136.6, 130.6, 129.2, 128.6, 128.5, 128.2, 127.6, 126.5, 126.2, 100.7, 77.2, 76.8, 37.1, 35.9, 31.7, 29.2, 24.9, 22.6, 14.0; IR ($CH_2Cl_2$) $\nu$ 3048, 2984, 2957, 2930, 2858, 2685, 2305, 1946, 1737, 1600, 1495, 1451, 1423, 1402, 1335, 1310, 1270, 1214, 1144,1105, 1027 $cm^{-1}$; HRMS (EI) $m/z$ calcd for $C_{24}H_{30}O_2$: 350.2246; found: 350.2245.
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