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Reagent-Directed Allylic Quadraselection. Chemoselective *Anti*- and *Syn*-Lawton S_N2' Methylation of Seven-Membered Epoxyvinylsulfones

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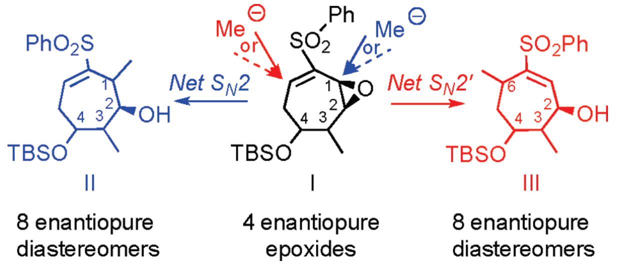
In the course of studying unsymmetrical enantiopure cyclic dienylsulfones,[1] it was desired to establish a **complete set** *of synthetic protocols enabling regio and stereospecific nucleophilic methylation at* **both faces and both termini** *of the allylic functionality*. A previous report featured 1,2-*syn* and 1,2-*anti* additions to four functionalized seven-membered epoxyvinylsulfones **I** which provided stereoselective synthesis of all eight possible homoallylic stereotetrads of the 1,3-dimethyl-2,4-diol moiety **II** (Scheme 1).[2] This communication reveals the complementary 1,4-*syn* and 1,4-*anti* additions to epoxyvinylsulfones **I**, thus completing the first 16-member "quadraset" of reagent-directed stereotetrads **III**.

Scheme 1. Quadraspecific Additions to Stereotetrads **I**



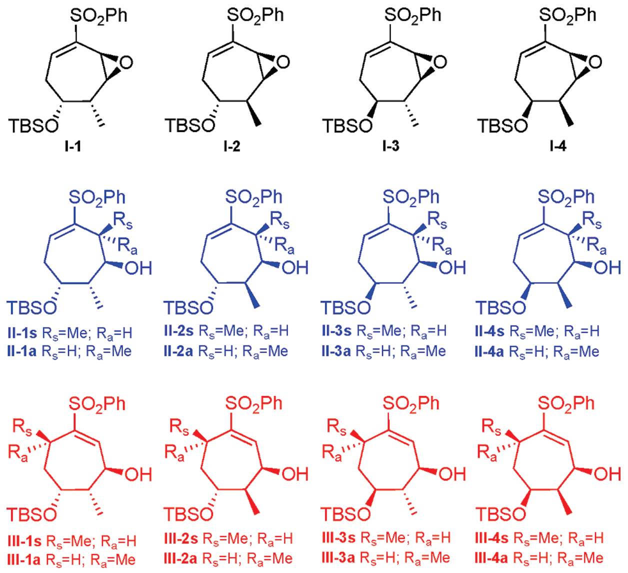
Screening for methyl 1,4-additions to epoxyvinylsulfone **I-1** presented a regioselectivity hurdle rather than one of diastereoselectivity (see discussion and Table A, Supporting Information); however *the previously unknown combination of* Me_2Zn *and catalytic Kochi's reagent* Li_2CuCl_4[3] *in toluene at room temperature remarkably gave a 91% yield of the 1,4-syn product* **III-1s**[4] *as a single diastereomer* (Table 1, entry 1).

The scope and limitations of Me_2Zn/Li_2CuCl_4 were surveyed with other seven-membered epoxyvinylsulfones (Table 1). The new reagent gave high yields and good selectivity for 1,4-*syn*-addition with epoxides **I-1**, **I-2**, and **I-3**.[5] With epoxide **I-4** there was only 39% yield at 50% conversion in a 1.5:1 ratio in favor of **III-4s** (Table 1, gray cell),[6] which apparently reflects an inability to overcome the steric blockade from the β face. However, all-*cis* isomer **III-4s** was easily prepared in 90% overall yield in 14:1 dr by oxidation/DIBAl-H reduction of the enantiomer of **III-1a**.[7]

In reactions with Me_2Zn neither CuI nor CuCN could replace Kochi's reagent, with no reaction observed with the above epoxides, even upon the addition of LiCl.[8] However, as expected, a 2:1 mixture of LiCl and $CuCl_2$ gave identical results with preformed commercial Kochi's reagent.[9]

After establishing 1,4-*syn*-methylation, conditions for 1,4-*anti*-methylation were sought. Treatment of epoxide **I-2** with stoichiometric MeMgBr in the presence of catalytic CuI gave a quantitative 1:4 mixture of regioisomers **II-2a**/**III-2a**. Switching to Li_2CuCl_4 gave identical selectivity. Using catalytic CuCN improved the regioselectivity to 9:1, affording **III-2a** in 73% yield after chromatographic separation. This reaction is stereospecifically *anti* to the epoxide moiety, with no *syn* addition products detectable by high field NMR or TLC.

Table 1. 1,4-*Syn*/1,4-*Anti* Ratios and Yields for Organometallic Additions to Enantiopure Epoxyvinyl Sulfones **I**



entry	SM	Me_2Zn +30% Li_2CuCl_4	MeMgBr +30% CuCN or 5% Li_2CuCl_4	Me_3Al + MeCu (1 equiv)	Me_3Al +9% Li_2CuCl_4
1	**I-1**	**III-1s** >50:1 (91%)	**II-1a**/**III-1a**/**III-1s** 1:5:1 (91%)	**III-1s**/**III-1a** 1:20 (92%)	**III-1s**/**III-1a** 1:7 (74%)
2	**I-2**	**III-2s**/**III-2a** 11:1 (85%)	**II-2a**/**III-2a** 1:9 (73%)	**III-2s**/**III-2a** 1:16 (79%)	**III-2s**/**III-2a** 1:10 (88%)
3	**I-3**	**III-3s**/**III-3a** 10:1 (75%)	**III-3a** <1:50 (91%)	**III-3a** <1:50 (92%)	**III-3s**/**III-3a** 1:17(85%)
4	**I-4**	**III-4s**/**III-4a** 1.5:1 (39%)	**III-4a** <1:50 (95%)	**III-4a** <1:50 (87%)	**III-4s**/**III-4a** 1:25 (82%)

In the case of epoxide **I-3**, very high selectivity was achieved with MeMgBr in the presence of catalytic Kochi's reagent or CuI. The reaction was completely regio- and stereospecific with **III-3a** being the only product observed. Epoxide **I-4** reacted similarly and was regio- and stereospecifically converted to the 1,4-*anti* product **III-4a** by treatment with MeMgBr/cat. Li_2CuCl_4.

Copper-catalyzed reactions of Al and Zn reagents have been increasing since Lipshutz and Knochel's reports of 1,4-additions of vinylalanes to enones and S_N2' additions of alkylzinc iodides to vinyl epoxides.[10] Additionally, we had shown in 1981 that parent epoxide **I-5** (see Supporting Information) undergoes 1,4-*anti* methylation to **III-5a** with high regio- and stereoselectivity by Me_3Al/cat. MeCu (See Table B, Supporting Information).[11] Thor-

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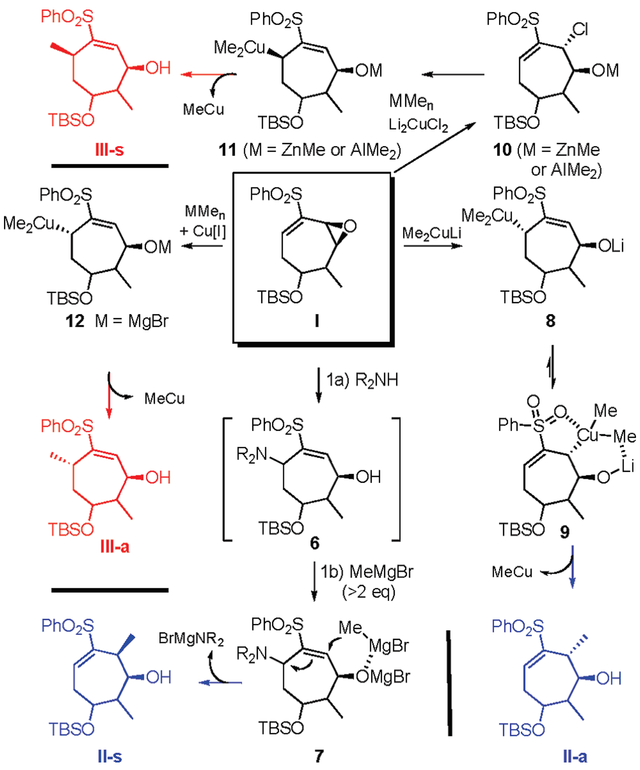
Scheme 2. Mechanism for Reagent-Based Quadraselection



ough screening of this reagent combination revealed that optimal results were achieved by addition of trimethylaluminum (2.2 equiv) to a −78 °C suspension of MeCu (1.0 equiv) followed by addition of a solution of epoxyvinylsulfone **I-3**. The reaction was complete after 2 h at −78 °C and 3 h at 25 °C. This 1,4-*anti* methylation protocol worked exceptionally well for all substrates.[12]

Catalytic 1,4-*anti* methylations were surveyed using epoxyvinylsulfone **I-3** in the presence of 3 equiv of Me_3Al and 0.09 equiv of Cu[I][13] source (Li_2CuCl_4, LiMeCuCN or MeCu) to afford adducts **III-3a/III-3s** with dr 14−17:1 in yields of 82−88% as compared with dr >50:1 using Me_3Al with stoichiometric MeCu (Table 1). The Li_2CuCl_4 catalyzed Me_3Al procedure was successfully applied to epoxides **I-1**, **I-2**, **I-3**, and **I-4** although erosion of diastereoselectivity was seen (Table 1, column 6).

Copper catalysis plays a prominent part in three of the four reagent combinations employed to achieve the quadraselection (Scheme 2). It is interesting to note that while the reaction of Me_3Al/MeCu or Me_3Al/Li_2CuCl_4 with epoxyvinylsulfone family **I** gives the expected[14] S_N2' *anti* coupling product family **III-a** presumably via intermediate **12**, direct reaction of **I** with Me_2CuLi generates the alternative allylic regioisomer **II-a**. A tentative hypothesis for the **II-a/III-a** regiocontrol may lie in the ability of the oxidolithium moiety to stabilize proximal η-1 intermediate **9**, by equilibrating initially formed distal η-1 intermediate **8** via a π-allyl η-3 species (not drawn)[15] prior to reductive elimination to **II-a**. Presumably magnesium alkoxide **12** is not able to achieve satisfactory bidentate chelation (perhaps due preferential formation of higher aggregates), and reductive elimination to **III-a** ensues.

Formation of **III-s** is especially intriguing. Treatment of **I** with Me_2Zn in the presence of catalytic Li_2CuCl_4 was initially expected to form **III-a**; however the product was clearly the *syn*-1,4-adduct **III-s**. A tentative explanation posits that under the required "forcing" reaction conditions (toluene, 12 h, 25 °C), epoxy vinylsulfone **I** suffers S_N2 *anti-addition of chloride anion to give* **10**. While such a species might undergo intramolecular *7-endotrig* methylation to **III-s** (possibly via a π-allyl intermediate), it is hard to argue that such a process would be strongly favored over the intramolecular *5-exotrig* alternative leading to **II-s**. However, *oxidative addition of catalytic dimethylcuprate to* **10** *would be expected to afford* **11** *followed by reductive elimination to* **III-s**. Apparently **11** like **12** does not benefit from bidentate chelation akin to **9**, thus kinetically favoring production of the distal allylic methylation product **III-s** (Scheme 2). Additional experiments support the generation of allylic chloride intermediates in the *syn*-methylation sequence.[4]

In conjunction with the recently reported 1,2-*syn* and 1,2-*anti* additions to **I**[2] this work provides the *first example of a strategy for reagent-controlled quadraselection*, thus giving an enantiopure collection of 16 stereotetrads from four enantiopure epoxyvinylsulfones.

Supporting Information Available: Additional experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) See Supporting Information.
(5) Upon the addition of Me_2Zn to a solution of the epoxide and Li_2CuCl_4 in toluene, the mixture turns bright yellow.
(6) In the case of **I-3 and I-4**, the solvent was a 24:1 mixture of toluene and THF to retard THF-mediated decomposition of the bimetallic complex.
(7) Synthesis of **III-4s** is described in the Supporting Information.
(8) Color change characteristic of Me_2Zn/Li_2CuCl_4 was not observed.
(9) 0.1 M Kochi's reagent in THF from Sigma-Aldrich was employed.
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(12) The yellow solution changes to a greenish suspension during warming.
(13) Me_2Zn (and therefore presumably Me_3Al) is known to reduce Li_2CuCl_4 to Cu[I]. Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055–12056. Wang, M.-C.; Liu, L.-T.; Hua, Y.-Z.; Zhang, J.-S.; Shi, Y.-Y.; Wang, D.-K. *Tetrahedron: Asymmetry* **2005**, *16*, 2531–2534.
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(15) Strong evidence in support of such an equilibrium is seen in: Jiang, W.; Lantrip, D. A.; Fuchs, P. L. *Org. Lett.* **2000**, *2*, 2181–2184.

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