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Diastereoselective Spiroketalization: Stereocontrol Using An Iron(0) Tricarbonyl Diene Complex

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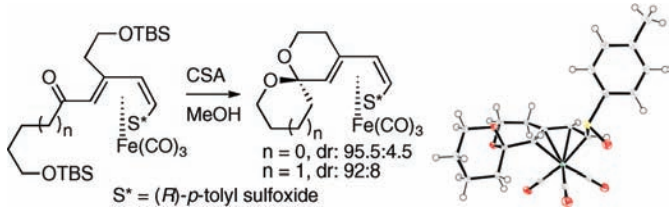
ABSTRACT



It has been demonstrated that an element of planar chirality can influence the formation of an adjacent spiroketal stereocenter. Appropriately functionalized enantiomerically pure 1- and 2-sulfinyl 1,3-dien-5-ones and their corresponding iron(0) tricarbonyl complexes (7, 17) have been prepared, and the derived spiroketals (8, 18) are made in good to excellent diastereoselectivity. A preliminary exploration of the combined effects of planar and central chirality upon the diastereoselectivity revealed matched and mismatched combinations (14).

The preparation of spiroketals and the ability to control the absolute stereochemistry of the spiroketal stereocenter remain important challenges for the synthetic organic chemist. It has been suggested that the spiroketal motif is a *privileged pharmacophore*,[1] and much effort has been made not only toward the total synthesis of spiroketal-containing natural products[2] but also in preparing truncated versions as well as non-natural hybrid constructs in the search for novel bioactive agents.[3] The stereochemistry at the spiroketal carbon is typically dictated by a combination of the thermodynamic preference resulting from the so-called anomeric effect[4] and any inherent steric or electronic factors that the substrate may possess. The conformational preference of the spiroketal oxygen atoms to be mutually axial is stereoelectronically favored; additional steric or electronic biases may either enhance or reduce this preference, and the balance of these factors would be expected to impact the stereochemical outcome of any spiroketalization process.

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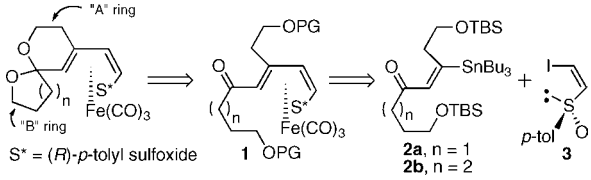
While numerous avenues to stereoselective spiroketal synthesis have been explored it was surprising to discover that no planar chiral π-organometallic complex of any type has ever been reported to be the stereodirecting element in the synthesis of a spiroketal. Since we have prepared a number of enantiomerically pure sulfinyl diene iron(0) tricarbonyl complexes and have reported diastereoselective synthetic transformations along the periphery of the $Fe(CO)_3$ diene units of such compounds,[5] we next considered if appropriately functionalized analogs would undergo diastereoselective spiroketalizations. Herein we report our preliminary results of this study.

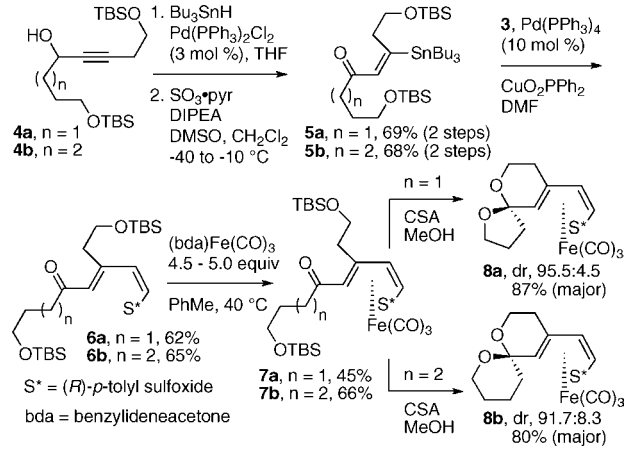
Adapting our previously reported synthetic approach,[5d] we chose the classic method of dehydrative cyclization of a dihydroxyketone for the spiroketal synthesis; the ketone would be placed along the periphery of an enantiomerically pure sulfinyl diene iron(0) tricarbonyl complex (**1**, Scheme 1). Our approach required the synthesis of β-stannylenones

Scheme 1. Retrosynthetic Approach to Sulfinyl Diene Spiroketal Complexes



of type **2**, which were to be coupled to enantiomerically pure (*Z*)-iodo vinyl sulfoxide **3**.[5d] For these substrates, β-stannylenone synthesis was straightforward, being readily accomplished by regioselective hydrostannylation of propargylic alcohols[6] **4** followed by subsequent oxidation[7] to β-stannylenones **5** (Scheme 2). The Stille coupling of the two electron-poor coupling partners **3** and **5** was not routine, but the transformation was effected in reasonable yield using the modification recently revealed by Fürstner.[8] Indeed, we have simplified this modification by using $Pd(PPh_3)_4$ with just a single reagent (commercially available CuO_2PPh_2)[9] rather than the two reagents used by Fürstner (CuTC and

Scheme 2. Synthesis of Unsubstituted Spiroketals



$Bu_4NO_2PPh_2$). With enantiopure sulfinyl dienes **6** in hand, diastereoselective complexation[10] using excess $(bda)Fe(CO)_3$ proceeded normally to afford the desired sulfinyl iron(0) diene complexes **7** which set the stage for exploration of the spiroketalizations. Acid-catalyzed methanolysis of the silyl ethers effected deprotection and concomitant dehydrative cyclization to afford the target spiroketals **8** in high yield and excellent diastereoselectivity (11.8:1 for the [6,6]-spiroketal, and 21.4:1 for the [6,5]-spiroketal) as evaluated by integration of the ^1H NMR spectra of the unpurified product mixtures. Furthermore, the diastereomeric spiroketals were readily separable by chromatography and the major isomers were each solids that were crystallized to afford samples suitable for analysis by X-ray crystallography.[11] This allowed the unequivocal stereochemical assignment of the spiroketal stereocenter as well as suggesting a rationale for the origin of the reaction stereoselectivity: a thermodynamic preference presumably places the pseudoaxial oxygen in a conformation that maximizes the stereoelectronic benefit of the anomeric effect while minimizing any dipole interactions with the carbonyl ligands of the $Fe(CO)_3$ unit.

We sought computational support for our rationalization that the thermodynamically favored spiroketal was indeed the major diastereomer observed. Thus the relative energies of the four possible spiroketal conformers for the major *and* the minor spiroketal **8b** were evaluated using electronic structure theory.[12] It was verified that the mutually axial oxygen atom conformations were the most stable in each case (by 3.1 kcal/mol for the major spiroketal and by 2.5 kcal/mol for the minor spiroketal). A comparison of the relative energies of these most

(5) (a) Paley, R. S.; Berry, K. E.; Liu, J. M.; Sanan, T. T. *J. Org. Chem.* **2009**, *74*, 1611–1620. (b) Paley, R. S.; Estroff, L. A.; Gauguet, J.-M.; Hunt, D. K.; Newlin, R. C. *Org. Lett.* **2000**, *2*, 365–368. (c) Paley, R. S.; Estroff, L. A.; McCulley, D. J.; Alfonso Martínez-Cruz, L.; Jiménez Sánchez, A.; Cano, F. H. *Organometallics* **1998**, *17*, 1841–1849. (d) Paley, R. S.; de Dios, A.; Estroff, L. A.; Lafontaine, J. A.; Montero, C.; McCulley, D. J.; Rubio, M. B.; Ventura, M. P.; Weers, H. L.; Fernández de la Pradilla, R.; Castro, S.; Dorado, R.; Morente, M. *J. Org. Chem.* **1997**, *62*, 6326–6343. (e) Paley, R. S.; Rubio, M. B.; Fernández de la Pradilla, R.; Dorado, R.; Hundal, G.; Martínez-Ripoll, M. *Organometallics* **1996**, *15*, 4672–4674.

(6) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857–1867.

(7) Juhl, M.; Monrad, R.; Søtofte, I.; Tanner, D. *J. Org. Chem.* **2007**, *72*, 4644–4654.

(8) Fürstner, A.; Funel, J.-A.; Tremblay, M.; Bouchez, L. C.; Nevado, C.; Waser, M.; Ackerstaff, J.; Stimson, C. C. *Chem. Commun.* **2008**, 2873–2875. It is worth noting that strictly 1:1 molar ratios of our coupling partners were used in these reactions.

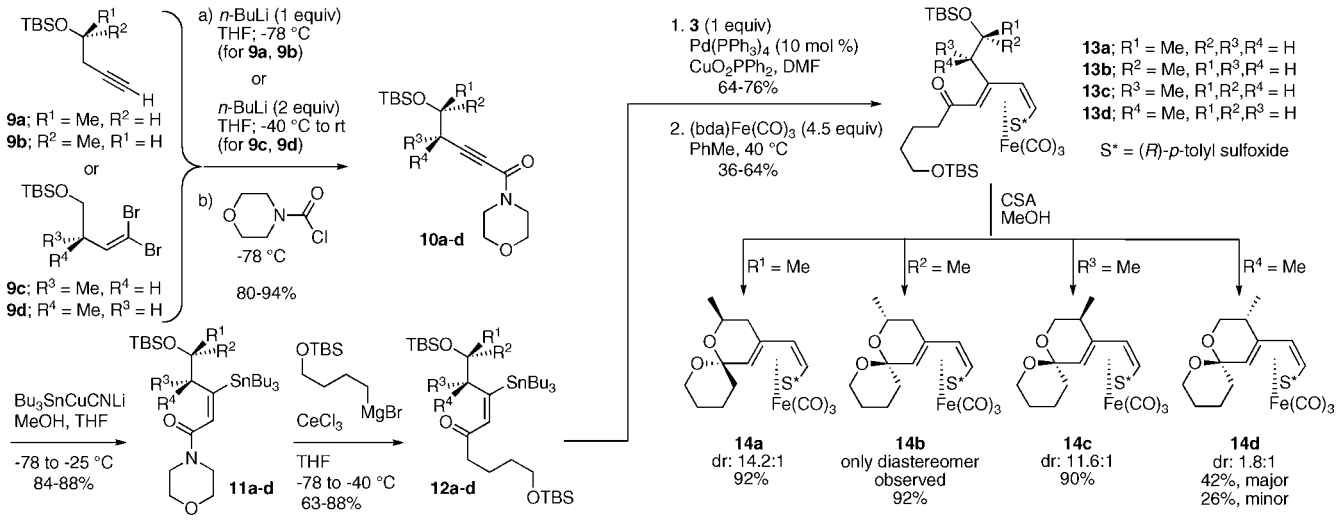
(9) Copper diphenylphosphinate (CuDPP) has been used in the related couplings of aryl- and vinylstannanes with thioesters; see: Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033–3035.

(10) Diastereomer ratios: 6−7:1. For a review of diastereoselective complexation, see: Paley, R. S. *Chem. Rev.* **2002**, *102*, 1493–1524.

(11) See Supporting Information for details.

(12) Energies were computed at B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) and MP2/6-311+G(d,p)//B3LYP/6-31G(d). Energies reported in the text represent averages of these two different methods. Justification for this procedure is provided in the Supporting Information. Both proton NMR chemical shifts and proton−proton coupling constants were calculated using density functional theory. In general, the values calculated for the conformations shown agreed considerably more closely with experiment than did the values calculated for alternative conformations. See the Supporting Information for full details about the computational investigation.

Scheme 3. Synthesis of Substituted [6,6]-Spiroketals



stable conformations revealed a 1.8 kcal/mol thermodynamic preference for the major diastereomer; this correlates to a 95:5 ratio at room temperature, which is similar to the experimentally observed 92:8 ratio.

We next sought to explore the effect on the diastereoselectivity of the spiroketalization if an additional stereocenter was present on the A ring of the spiroketal, and we chose to incorporate a methyl group at either the allylic or homoallylic position. However, synthesis of spiroketals **14a**−**d** (Scheme 3) by the same sequence depicted in Scheme 2 proved to be unsatisfactory, as the additional propargylic or homopropargylic stereocenter rendered the hydrostannylation sluggish and nonregioselective.[13] The option of preparing our targeted precursors, (*E*)-*β*-stannyl enones **12a**−**d**, by stannylcupration of the corresponding alkynyl ketones was ruled out because of the established lack of stereoselectivity.[14] We therefore needed to develop a different approach to prepare **12a**−**d**, and our solution is illustrated in Scheme 3. The key discoveries were that (a) the alkynyl morpholine amides (**10a**−**d**) could be readily prepared from known precursors **9a-d**;[15] (b) these cleanly underwent stannylcupration to afford (*E*)-*β*-stannyl enamides **11a**−**d** as single regio- and stereoisomers;[16] and (c) these enamides could be converted into the required ketones **12a**−**d** by treatment with Grignard-derived organocerium reagents *at −40 °C*.[17] Under these conditions the potentially labile vinylstannane unit was retained, as was the stereochemical integrity of the trisubstituted double bond. Following Stille coupling of **12a**−**d** with **3** and conversion of the resulting enantiopure sulfinyl dienes to the corresponding iron(0) tricarbonyl complexes, **13a**−**d**, spiroketals **14a**−**d** were obtained in good yield but with variable diastereoselectivity. In the case of **14c**, the selectivity was essentially identical to that observed for its unsubstituted analog, **8b**. However, for **14b** the directing effect of the $Fe(CO)_3$ fragment was reinforced by the apparent minimization of presumed diaxial interactions between the methyl substituent and the B ring, resulting in the formation of a single diastereomeric spiroketal. On the other hand the position of the methyl group in **14a**, with a stereocenter of configuration opposite to that of **14b**, apparently induced such a severe strain that the directing effect of the $Fe(CO)_3$ fragment was overwhelmed; the opposite configuration at the spiroketal carbon was greatly favored.[18] Finally, a poor selectivity was observed for the cyclization of **13d** that produced spiroketal **14d**.

Because none of the methyl substituted spiroketals could be induced to crystallize, we required computational models to reach a more complete understanding of the interplay between the factors leading to the selectivity (or lack thereof) observed in the spiroketalizations. Therefore energy minimized structures for each of the spiroketals **14a**−**d** and their diastereomers (at the spiroketal stereocenters) were obtained, again using electronic structure theory. Additional calculations were undertaken to evaluate ^{1}H NMR chemical shift as well as coupling constant data for these minimized structures to increase our confidence that these models were reasonably accurate; indeed, the calculated NMR data were in satisfactory agreement with the experimentally obtained data in most cases.[12] Thus the computed models clearly indicate that the methyl substituents in **14b** and **14c** (diastereomeric ratios, 100:0 and 11.6:1, respectively) occupy a pseudoequatorial position on the A ring while

(13) Neither $Pd(PPh_3)_2Cl_2$ nor $Pd(P(o\text{-tol})_3)_2Cl_2$ as a catalyst (see ref 7) was effective.

(14) Barbero, A.; Pulido, F. J. *Chem. Soc. Rev.* **2005**, *34*, 913–920.

(15) For **9a**/**9b**: Selles, P.; Lett, R. *Tetrahedron Lett.* **2002**, *43*, 4621–4625. For **9c**/**9d**: Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535–9544. Mulzer, J.; Berger, M. *J. Org. Chem.* **2004**, *69*, 891–898.

(16) Alkynyl amides have rarely been subjected to stannylcupration. See: Piers, E.; Chong, J. M.; Keay, B. A. *Tetrahedron Lett.* **1985**, *26*, 6265–6268.

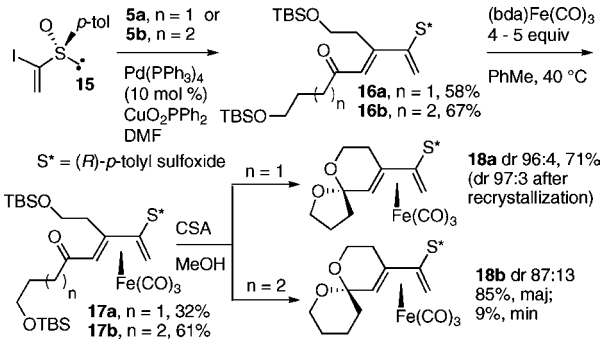
(17) Badioli, M.; Ballini, R.; Bartolacci, M.; Bosica, G.; Torregiani, E.; Marcantoni, E. *J. Org. Chem.* **2002**, *67*, 8938–8942.

(18) ^{1}H NMR spectra for each of the major diastereomeric spiroketals **8a**, **8b**, and **14b**−**d** display a more downfield chemical shift for the proton at C2 of the diene unit than in the corresponding minor diastereomer. Only in the case of spiroketal **14a** does the major diastereomer display a more upfield shift for this proton, suggesting that the configuration at the spiroketal is opposite those of the other compounds. Furthermore, the major diastereomer of **14a** is less polar by TLC than the minor diastereomer; in the other cases the major diastereomer is always more polar.

the mutually axial orientation of the spiroketal oxygen atoms is maintained. For **14d** the diastereomer energies are similar; for the major isomer the A ring slightly distorts from its ideal half-chair conformation so that the methyl substituent minimizes a steric interaction with the nearby $Fe(CO)_3$ fragment while maintaining the stereoelectronic benefit of the anomeric effect. However, this is only a marginal energetic improvement over the minor diastereomer, in which the benefit of an ideal A ring half-chair conformation (with pseudoequatorial methyl) and mutually axial oxygen atoms is compromised by the dipole−dipole interaction between the B ring oxygen atom and the $Fe(CO)_3$ fragment. Finally, for **14a**, in which the major diastereomer has the opposite spiroketal stereocenter configuration from the other three cases, the combination of a favorable equatorial methyl substituent and a favorable anomeric effect along with an unfavorable $O_{B\text{-ring}}$−$Fe(CO)_3$ dipole−dipole repulsion is energetically preferable to the conformation of the minor isomer. In that case, the calculated model reveals a nonanomeric spiroketal; the B ring oxygen occupies a pseudoequatorial conformation, as does the methyl substituent. This apparently is somewhat energetically better than a conformation that maintains the anomeric effect but forces the methyl substituent into an unfavorable axial position. Clearly in this case (**14a**) it is the stereocenter bearing the methyl group that controls the diastereoselectivity of the spiroketalization, not the element of planar chirality.

We were next delighted to discover that the Fürstner modification of the Stille coupling also allowed access to the enantiopure 2-sulfinyl dien-5-ones, **16a** and **16b**, using 2-iodovinyl sulfoxide **15**[5d] (Scheme 4). Conversion of these

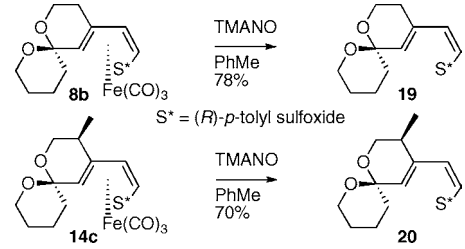
Scheme 4. Synthesis of Enantiopure 2-Sulfinyl Dienes and Derived Spiroketal Iron(0) Diene Complexes



compounds to their corresponding $Fe(CO)_3$ diene complexes (**17**) proceeded with good diastereoselectivity, and as with the isomeric complexes, the major diastereomers could be readily separated by column chromatography. Spiroketal formation also proceeded diastereoselectively, and X-ray crystallography of the major diastereomer of **18b** revealed that the $Fe(CO)_3$ fragment occupied the *opposite* face of the diene unit from the spiroketals derived from the 1-sulfinyl dienes, **6**.[11] The spiroketal stereocenter of **18b** was also opposite in configuration, again a result of the preference to avoid the dipole−dipole interaction between the B ring oxygen atom and the $Fe(CO)_3$ unit.

Finally, a prerequisite for using these results for further manipulations is the removal of the $Fe(CO)_3$ fragment without loss of stereochemical integrity at the spiroketal stereocenter. The use of reagents such as CAN (CH_3CN, −30 °C, with or without K_2CO_3)[19] or $CuCl_2$ (EtOH, rt),[20] did produce partially racemized decomplexed products, as evidenced by the formation of diastereomeric products as observed by ^1H NMR spectroscopy. Fortunately, the use of excess trimethylamine *N*-oxide (TMANO, 10 equiv) afforded the decomplexed products **19** and **20** as single diastereomers (Scheme 5).

Scheme 5. Sulfinyl Diene Spiroketals via Decomplexations



Herein is the first report that a π-bonded metal fragment, acting as an enantiomeric scaffold,[21] can effectively influence the formation of an adjacent spiroketal stereocenter. An additional stereocenter can either reinforce or overwhelm the effect of the planar chirality. We are continuing to investigate this chemistry by examining the effect that stereocenters or other structural variations on the B ring will have on the diastereoselectivity of the spiroketalization. Also, we are examining the elaboration of the sulfinyl diene unit following $Fe(CO)_3$ decomplexation; results will be reported in due course.

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Supporting Information Available: Experimental procedures, spectral data, copies of ^1H and ^{13}C NMR spectra, crystallographic data, and computationally derived models (including complete tabulation of the calculated energies and Cartesian coordinates of the various structures and conformations). This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) For example, see ref 5a and Yasutaka, B.; Saha, G.; Nakao, C.; Tanaka, T.; Ibuka, T.; Ohishi, H.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 81–88.

(20) For example, see: Williams, I.; Reeves, K.; Kariuki, B. M.; Cox, L. R. *Org. Biomol. Chem.* **2007**, *5*, 3325–3329.

(21) Coombs, T. C.; Zhang, Y.; Garnier-Amblard, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2009**, *131*, 876–877, and references therein.