ORGANIC LETTERS

2003
Vol. 5, No. 3
309−312

Simultaneous and Stereoselective Formation of Planar and Axial Chiralities in Enantiopure Sulfinyl Iron Diene Complexes

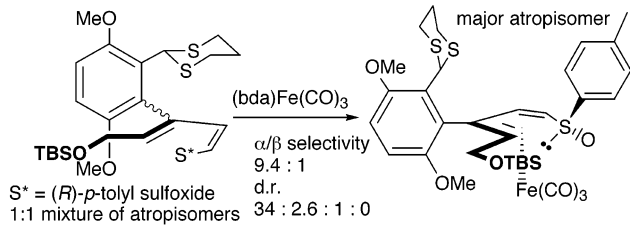
Robert S. Paley,* Jane M. Liu, Bruce R. Lichtenstein, Vanessa L. Knoedler, Toby T. Sanan, Drew J. Adams, Jorge Fernández, and Paul R. Rablen

Swarthmore College, Department of Chemistry, Swarthmore, Pennsylvania 19081

rpaley1@swarthmore.edu

Received November 19, 2002

ABSTRACT



Enantiopure (1*Z*,3*E*)-1-sulfinyl dienes bearing an *o*-dithianylphenyl group can be prepared and complexed with (bda)Fe(CO)$_3$ to afford the corresponding sulfinyl diene iron(0) tricarbonyl complexes. This diastereoselective complexation introduces planar and axial chirality simultaneously, with a high degree of facial selectivity as well as atropselectivity. Dynamic kinetic resolution is likely to be the origin of the atropselectivity.

There continues to be great interest in the preparation and use of molecules that possess an axis of chirality as a result of the success of biaryl systems in asymmetric catalysis, as well as the presence of chiral axes in complex natural products such as vancomycin. On the other hand, compounds possessing an element of planar chirality have been demonstrated to be highly useful synthetic intermediates in addition to also finding success as asymmetric catalysts. The simultaneous formation of planar and axial chiralities is still quite rare; indeed, we are aware of only two prior reports of such a process. Wulff[1] reported that the reaction of Fischer chromium carbene complexes and aryl alkynes proceeded with a high degree of diastereoselectivity to afford racemic biaryls with restricted rotation resulting from a single η^6-Cr(CO)$_3$ arene complex. Uemura and Bringmann[2] have described the synthesis of enantiopure biaryls that have restricted rotation and a planar chiral arene ruthenium Cp$^+$ complex. In this report, we describe additional examples of simultaneous formation of planar and axial chiralities, as the diastereoselective complexation of enantiopure 3-(*o*-dithianylaryl)-1-sulfinyl dienes with an iron tricarbonyl fragment also controls the axial stereochemistry about the aryl-C3 bond.

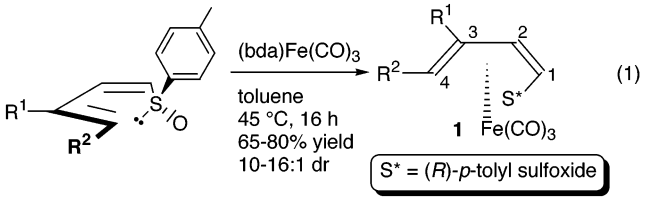
We have previously reported[3] that enantiopure (1*Z*,3*E*)-1-sulfinyl dienes can be transformed into the corresponding planar chiral iron tricarbonyl complexes, **1**, with a high degree of diastereoselectivity (eq 1). The origin of this selectivity is assumed to be due to 1,3-allylic strain, forcing the aromatic sulfoxide substituent into a conformation that effectively blocks one diene face. Typically the major α

(1) Fogel, L.; Hsung, R. P.; Wulff, W. D.; Sommer, R. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2001**, *123*, 5580.

(2) Kamikawa, K.; Furusyo, M.; Uno, T.; Sato, Y.; Konoo, A.; Bringmann, G.; Uemura, M. *Org. Lett.* **2001**, *3*, 3667.

(3) 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. For related complexes, see: Ibbotson, A.; Reduto dos Reis, A. C.; Saberi, S. P.; Slawin, A. M. Z.; Thomas, S. E.; Tustin, G. J.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1251−1259.

10.1021/ol027306q CCC: $25.00
Published on Web 01/09/2003



(1)

product of this kinetically controlled process is easily separated from the minor β isomer by chromatography and then can be utilized in strategies to control the stereochemistry of incipient chiral centers along the diene periphery. As a result of our efforts to expand the synthetic applications of these complexes, we sought to prepare a series of C4-substituted sulfinyl dienes additionally possessing an *ortho*-substituted aryl unit at C3. Molecular models suggested that the iron diene complexes obtained from such compounds might display restricted rotation about the aryl-C3 single bond provided that the *ortho*-substituent was of a sufficient size. Thus, four diastereomers could be produced by complexation of these substrates; each facial isomer could exist as diastereomeric atropisomers, as shown in Figure 1.

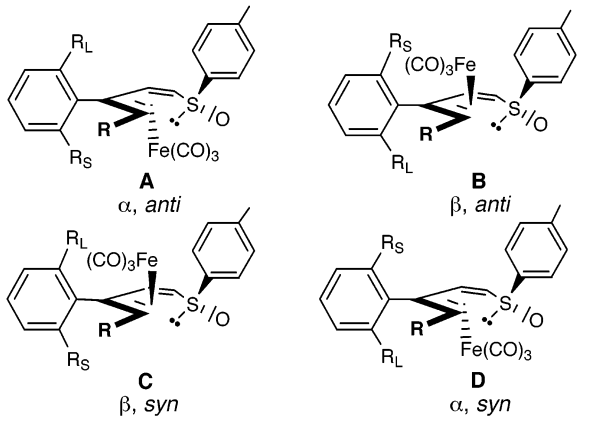
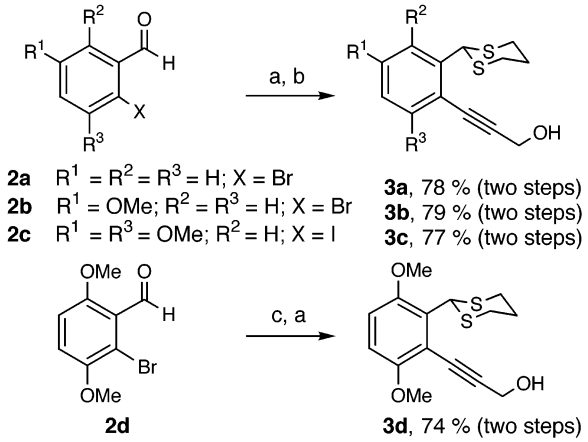


Figure 1. Possible diastereomers formed upon complexation of (1*E*,3*Z*)-1-sulfinyl-3-(*o*-substituted)-aryl dienes with an iron tricarbonyl fragment. The syn or anti notation refers to the relative positions of the $Fe(CO)_3$ unit and R_L; the α or β nomenclature refers to the location of the $Fe(CO)_3$ unit relative to the sulfoxide.

The preparation of the required 3-aryl-1-sulfinyl dienes, each equipped with a dithiane as the bulky aryl *ortho*-substituent (R_L), was initiated with bromoaldehydes **2**. Conversion to the corresponding dithianes followed by Sonogashira-type coupling[4] with propargyl alcohol proceeded smoothly for **2a**−**c**[5] to produce aryl alkynes **3a**−**c**. On the other hand, the sterically demanding **3d** was more efficiently prepared from aldehyde **2d**[6] by $PdP(t\text{-}Bu_3)_2$-catalyzed Stille coupling[7] followed by one-pot dithiane formation and THP deprotection (Scheme 1). Vinylic stannanes **4a**−**d** were then prepared by a highly regioselective palladium-catalyzed hydrostannylation;[8] none of the regioisomeric vinyl stannanes were ever observed (Scheme 2).

Scheme 1[a]



[a] Reagents and conditions: (a) $HS(CH_2)_3SH$, Amberlyst-15 resin, THF, rt. (b) $H-C\equiv C-CH_2OH$, 5 mol % $Pd(PPh_3)_4$, pyrrolidine, 80 °C (50 °C for **2c**). (c) $Bu_3Sn-C\equiv C-CH_2OTHP$, 3 mol % $Pd(P\text{t-}Bu_3)_2$, PhMe, rt.

The required 3-aryl-1-sulfinyl dienes **5a**−**d**, **5c**′, and **5d**′ were prepared by our previously reported approach via Stille coupling of an enantiopure (*Z*)-iodovinyl sulfoxide and the corresponding vinyl stannane (Scheme 2).[3] It is interesting to note that we were unable to effect Stille coupling of aryl vinyl stannanes with *ortho*-substituents that did not contain a benzylic sulfur, suggesting a favorable interaction between the palladium and sulfur atoms that accelerates transmetalation.[9] The ^1H NMR spectra of sulfinyl dienes **5a** and **5b** demonstrated significant broadening at room temperature (presumably a result of slow, but not completely restricted, rotation about the aryl-C3 single bond on the NMR time scale). However, sulfinyl dienes **5c**, **5c**′, **5d**, and **5d**′ had sharply resolved absorbances in their NMR spectra; indeed, **5c**′, **5d**, and **5d**′ were each obtained as atropisomeric mixtures that could be separated by chromatography.

Each of the sulfinyl dienes, **5a**−**5d**, **5c**′, and **5d**′, were subjected to our usual conditions for complexation (using a 4- to 5-fold excess of $(bda)Fe(CO)_3$ in toluene at 45 °C) to afford the sulfinyl iron diene complexes **6a**−**d**, **6c**′, and **6d**′ (Scheme 3). Sulfinyl diene **5a** and **5b** each afforded only two of the four possible diastereomeric complexes of **6a** and **6b**; for dienes **5c**, **5c**′, **5d**, and **5d**′, three diastereomers were obtained. For each set of complexes, facial and axial

(4) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403.

(5) Compound **2c** is available in one step from the corresponding benzyl alcohol: Swindell, C. S.; Fan, W. *J. Org. Chem.* **1996**, *61*, 1109.

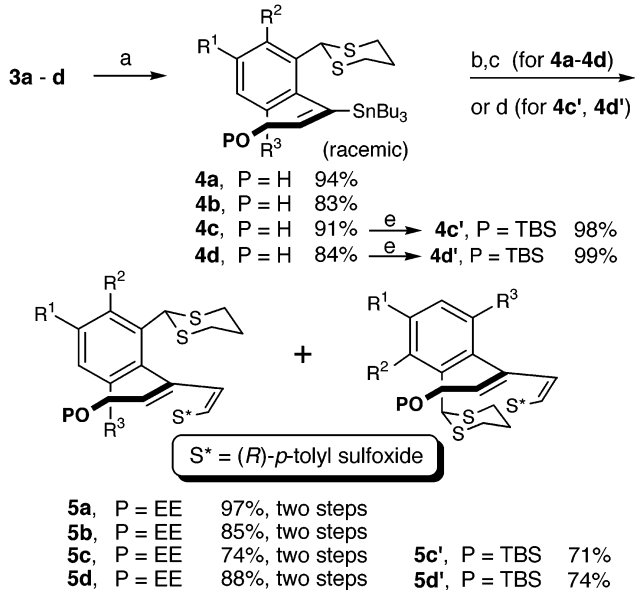
(6) Clive, D. L. J.; Sannigrahi, M.; Hisaindee, S. *J. Org. Chem.* **2001**, *66*, 954.

(7) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343.

(8) Liron, F.; Le Garrec, P.; Alami, M. *Synlett* **1999**, 246.

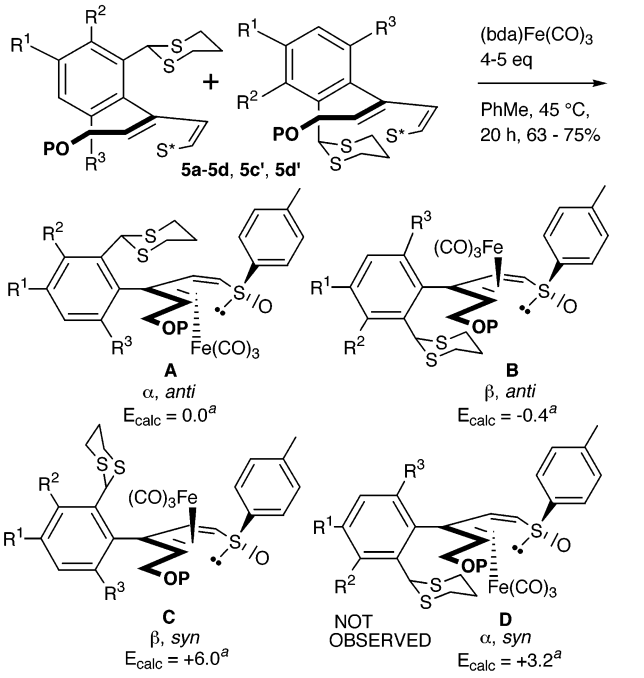
(9) (a) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 8773. (b) Crisp, G. T.; Gebauer, M. G. *Tetrahedron Lett.* **1995**, *36*, 3389. (c) Vedejs, E.; Haight, A. R.; Moss, W. O. *J. Am. Chem. Soc.* **1992**, *114*, 6556.

Scheme 2[a]



[a] Reagents and conditions: (a) Bu_3SnH, 2 mol % $Pd(PPh_3)_2Cl_2$, THF, rt (for **3a**−**c**) or 50 °C (for **3d**). (b) (*Z*)-(*R*)-I−CH═CH−S*, 4 mol % $Pd(MeCN)_2Cl_2$, DMF, rt. (c) CH_2═CH−OEt (10 equiv), 20 mol % PPTS, DCM. (d) (*Z*)-(*R*)-I−CH═CH−S*, 5 mol % Pd(P-*t*-$Bu_3)_2$, PhMe, 35 °C. (e) TBDMSOTf, 2,6-lutidine, CH_2Cl_2.

Scheme 3



	R^1	R^2	R^3	P	% yield[b]	α/β selectivity	axial selectivity[c]	ratio **A**:**B**:**C**
6a	H	H	H	EE	68	3.2:1	3.2:1	3.2:1:0
6b	MeO	H	H	EE	73	3.2:1	3.2:1	3.2:1:0
6c	MeO	H	MeO	EE	75	3.2:1	5.5:1	9.4:1.9:1
6d	H	MeO	MeO	EE	73	9.4:1	12:1	45:3.8:1
6c'	MeO	H	MeO	TBS	67	4.2:1	6.5:1	13.4:2.2:1
6d'	H	MeO	MeO	TBS	63	9.4:1	13.5:1	34:2.6:1

[a] Relative energies (kcal/mol) for P = H. [b]Combined yield of diastereomeric complexes. [c]Relative to the sulfoxide chiral center.

stereochemistries were assigned on the basis of the ^{1}H NMR chemical shift data.[10] It is worth noting that in each of the latter four cases, the major complex was readily separable by column chromatography from the minor diastereomers.

We also explored the complexation of indole analogues of the aryl dithianes.[11] The synthesis of the required indolyl vinyl stannanes began with known 2-bromo-3-formylindole **7**[12] (Scheme 4). Conversion of the aldehyde to the dithiane and subsequent protection of the indole nitrogen proceeded uneventfully; Sonogashira coupling with propargyl alcohol to give **8** required modification of the Buchwald−Fu conditions[13] and proceeded only with the indole nitrogen protected. Hydrostannylation gave the corresponding vinyl stannane, and as with the aryl dithianes, only a single regioisomer was produced. Removal of the TEOC protecting group was required in order to effect Stille coupling with the enantiopure (*Z*)-iodovinyl sulfoxide. Sulfinyl diene **9** was obtained as a single compound that was purified after protection of the alcohol; subsequent reprotection of the indole nitrogen afforded BOC-derivative **10a** as a 3:1 mixture of atropisomers or the tosyl sulfonamide **10b** as a 1:1 atropisomeric mixture. In both of these cases, the atropisomeric compounds possessed significantly different R_f values but could not be chromatographically separated because of rapid equilibration at room temperature. Complexation produced the corresponding sulfinyl iron diene complexes **11a** and **11b** with 8:1 and 4:1 diastereomeric ratios.[10]

The complexation diastereoselectivities described here merit discussion. Earlier results from our laboratories[3] indicated that facial selectivities obtained during complexation under these conditions were a reflection of kinetic preferences; typical α/*β* selectivities were 10:1, and this ratio was also observed for the complexation of a simple 3-phenyl-1-sulfinyl diene[14] lacking the *ortho* dithiane substituent. The presence of the dithiane in sulfinyl dienes **5a** and **5b** caused a decrease in α/*β* selectivities to 3.2:1; similar selectivities were obtained for the complexation of **5c** and **5c′** (Scheme 3). However, facial selectivities were markedly enhanced (9.4:1) for substrates **5d** and **5d′**. Additionally, significant

(10) For complexes previously prepared in our laboratories, the chemical shift of H2 has consistently appeared more upfield for the major α isomer than for the corresponding minor *β* isomer (see Table S1, Supporting Information). The syn axial stereochemical assignments are based on the chemical shifts of the dithiane methine; the syn diastereomers (i.e., general type **C** in Figure 1) show a significant downfield shift. For a related example, see Kamikawa, K.; Tachibana, A.; Sugimoto, S.; Uemura, M. *Org. Lett.* **2001**, *3*, 2033.

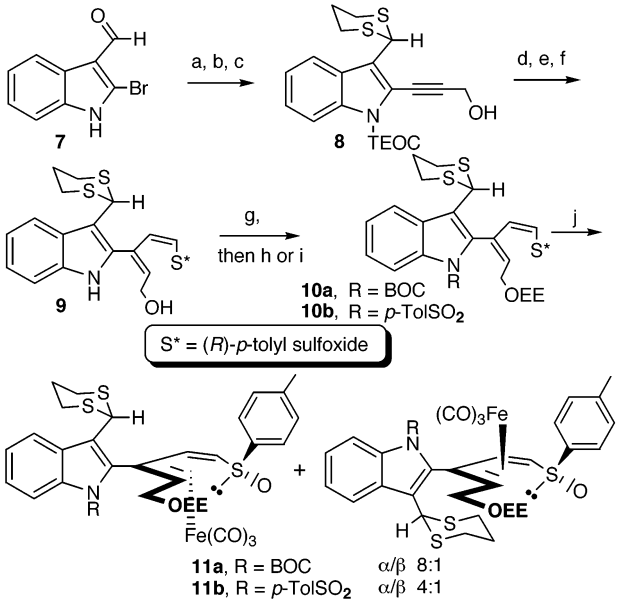
(11) For thiophene analogues, see Supporting Information.

(12) Gilchrist, T. L.; Kemmitt, P. D.; Germain, A. L. *Tetrahedron* **1997**, *53*, 4447.

(13) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729.

(14) See Supporting Information.

Scheme 4[a]



[a] Reagents and conditions: (a) $HS(CH_2)_3SH$, Amberlyst-15 resin, THF, rt, 91%. (b) NaH, THF, 0 °C, then TMS-$(CH_2)_2OCO_2$-*p*-NO_2Ph, 100%. (c) H−C≡C−CH_2OH (3 equiv), $Pd(PhCN)_2Cl_2$ (15 mol %), P(*t*-Bu_3) (33 mol %), CuI (10 mol %), (*i*-$Pr)_2NH$ (1.2 equiv), dioxane, 48−58%. (d) Bu_3SnH, $Pd(PPh_3)_2Cl_2$ (1 mol %), THF, 77%. (e) TBAF, THF, 95%. (f) (*Z*)-(*R*)-I−CH═CH−S*, 4 mol % $Pd(MeCN)_2Cl_2$, DMF, rt. (g) CH_2═CH−OEt (10 equiv), 20 mol % PPTS, DCM; 80%, two steps. (h) BOC_2O, DMAP, THF, 100%. (i) NaH, THF, 0 °C, then TsCl, 70%. (j) (bda)$Fe(CO)_3$ (5 equiv), toluene, 45 °C, 70%.

axial selectivities were also observed in all cases; 1:1 atropisomeric mixtures (or nearly so) were employed for substrates **5c**, **5c′**, **5d**, and **5d′**, yet complexation of these sulfinyl dienes afforded complexes with axial selectivities ranging from 5:1 to 13:1. The origin of this selectivity may be explained by dynamic kinetic resolution;[15] this explanation is supported by the discovery that stirring of each of the chromatographically separated atropisomers of sulfinyl diene **5d** in toluene (45 °C, 18 h) afforded the same (nearly 1:1) atropisomeric mixture. Thus, the atropisomeric sulfinyl dienes are capable of equilibration under the conditions of the complexation; the iron fragment apparently complexes with one atropisomer faster than the other, and the less reactive atropisomer can be equilibrated into the more reactive one. This explanation relies upon the notion that a syn relationship between the dithiane and the $Fe(CO)_3$ fragment is energetically costly. This hypothesis is supported by B3LYP/6-31G* calculations[14] of the relative energies of diastereomers **A**−**D** (Scheme 3); the syn diastereomers **C** and **D** are found to be 3−6 kcal/mol higher in energy than the anti isomers. The marked enhancement of selectivities observed for **5d** and **5d′** is likely due to the presence of the methoxy group *ortho* to the dithiane; because of this more sterically demanding environment around the dithiane, it has fewer conformational degrees of freedom, rendering it effectively larger in size than in the cases lacking an *ortho* methoxy group. This translates into raising the activation barrier for the complexation of the iron fragment to the β face, thus greatly favoring the formation of isomer **A** (α, anti).

We have described the preparation of a new class of enantiopure nonbiaryl atropisomeric compounds.[16] Axial and planar chirality are introduced concurrently and with a high degree of selectivity in a number of cases. Subsequent transformations of these compounds will be reported in due course.

Acknowledgment. R.S.P. thanks the Dreyfus Foundation (Henry Dreyfus Teacher−Scholar Award, 2000), and D.J.A. is grateful to Pfizer, Inc., for a Summer Undergraduate Research Fellowship. P.R.R. acknowledges the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. This work was also supported by Swarthmore College and HHMI.

Supporting Information Available: Full experimental procedures and spectral data for all new compounds, descriptions of the computational procedures, energies in Hartrees, and Cartesian coordinates of optimized geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Clayden, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 949.