Phenyl Sulfones: A Route to a Diverse Family of Trisubstituted Cyclohexenes from Three Independent Nucleophilic Additions

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Abstract: A novel process is described for the synthesis of di- and trisubstituted cyclohexenes from an arene. These compounds are prepared from three independent nucleophilic addition reactions to a phenyl sulfone ($PhSO_2R$; R = Me, Ph, NC_4H_8) dihapto-coordinated to the tungsten complex {WTp(NO)(PMe_3)}(Tp = trispyrazolylborate). Such coordination renders the dearomatized aryl ring susceptible to protonation at a carbon ortho to the sulfone group. The resulting arenium species readily reacts with the first nucleophile to form a dihapto-coordinated sulfonylated diene complex. This complex can again be protonated, and subsequent nucleophilic addition forms a trisubstituted cyclohexene species bearing a sulfonyl group at an allylic position. Loss of the sulfinate anion forms a π-allyl species, to which a third nucleophile can be added. The trisubstituted cyclohexene can then be oxidatively decomplexed, either before or after substitution of the sulfonyl group. Nucleophiles employed include masked enolates, cyanide, amines, amides, and hydride, with all three additions occurring to the same face of the ring, anti to the metal. Of the twelve novel functionalized cyclohexenes prepared as examples of this methodology, nine compounds meet five independent criteria for evaluating drug likeliness. Structural assignments are supported with nine crystal structures, DFT studies, and full 2D NMR analysis.

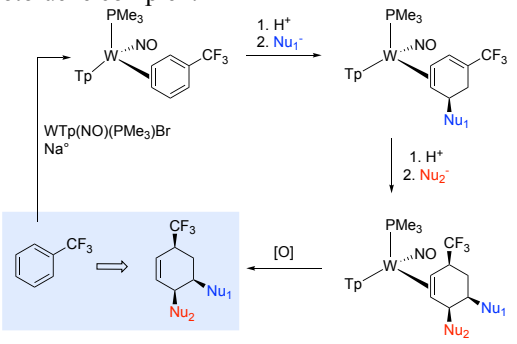
INTRODUCTION

As medicinal chemists seek to expand the structural complexity of molecular libraries through their efforts in diversity-oriented synthesis [DOS],[1] new synthetic methods are desired that access underrepresented regions of druggable chemical space.[2, 3] Carbocycles are considered to be ideal scaffolds for polar substituents in biologically active molecules,[4-6] with the most common being six-membered rings.[4] Here we report a potentially valuable new platform for discovery chemists: The syntheses of highly functionalized cyclohexenes are described accommodating fragments of esters, nitriles, amides, nitrogen heterocycles, and sulfones, functional groups that are ubiquitous in pharmaceuticals. These molecules are assembled without the aid of precious metals or organohalides.

A valuable tool for accessing six-member alicyclic molecules is dearomatization of functionalized benzenes.[7-11] Over the years, our group has focused on a global dearomatization strategy in which a benzene is bound through two of its carbons to a π-basic metal fragment ({$Os(NH_3)_5$}$^{2+}$,[12] {ReTp(CO)(MeIm)},[13] {MoTp(NO)(DMAP)},[7, 13] {WTp(NO)(PMe_3)}).[7] Such action activates the unbound portion of the benzene ring toward electrophilic addition and cycloaddition reactions.

While we have conducted several studies on arenes bearing π-donor groups,[14-23] it was not until recently that organic manipulations of electron-deficient η^2-benzene complexes were explored.[24, 25] Most functional groups that are electron-withdrawing (e.g., benzoates, benzonitrile, phenones) have π-bonds that compete with the aromatic ring for metal coordination.[26, 27] However, in the complexes MoTp(NO)(DMAP)(η^2-trifluorotoluene) and WTp(NO)(PMe_3)(η^2-trifluorotoluene), the metal binds exclusively to the benzene ring.[24, 25, 28] Despite the electron-withdrawing nature of the CF_3 group, protonation of the η^2-trifluorotoluene ligand can be achieved, ortho to the CF_3 group. The resulting η^2-benzenium complex then undergoes reaction with a nucleophile at an adjacent ring carbon, resulting in a 1,5-disubstituted η^2-1,3-cyclohexadiene complex (Scheme 1). The η^2-diene complex can then undergo another protonation/nucleophilic addition sequence to provide a trisubstituted cyclohexene containing up to three new stereocenters.[24]

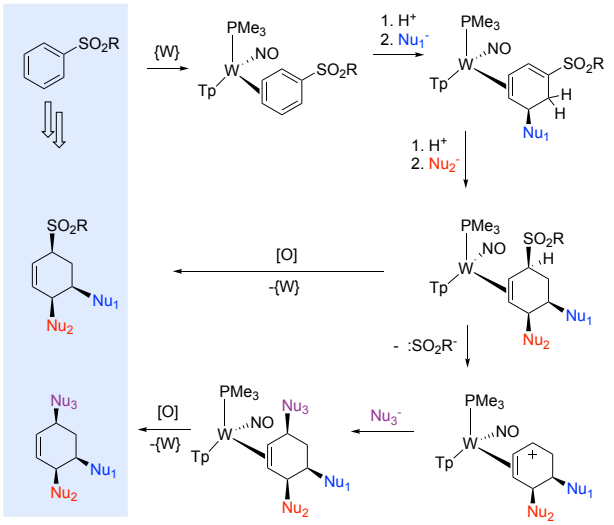
Scheme 1. Reactivity pattern of a dihapto-coordinated trifluorotoluene complex.



A recent study evaluated the scope and binding selectivity of complexes prepared from other electron-deficient arenes.[29] That investigation revealed that sulfones were well-tolerated by the {WTp(NO)(PMe_3)} fragment. Sulfones and sulfonamides are attractive functional groups to leverage in the dearomatization of benzene. Sulfur is the third most common heteroatom in marketed pharmaceuticals behind nitrogen and oxygen.[30, 31] Further, sulfones and sulfonamides are prevalent in a variety of antibiotics, cancer therapeutics, COX-2 inhibitors,

diuretics, and ulcer preventitives.[31, 32] We postulated that the reactivity of η^2-phenyl sulfone complexes would follow a reaction pattern similar to their trifluorotoluene analog. Further, unlike the CF_3 group, sulfinates ($:SO_2R^-$) can act as leaving groups for nucleophilic substitution and elimination reactions.[24, 33-40] The replacement of the sulfonyl group by other substituents could significantly expand the diversity of the anticipated trisubstituted cyclohexene products beyond sulfone and sulfonamide derivatives (Scheme 2).

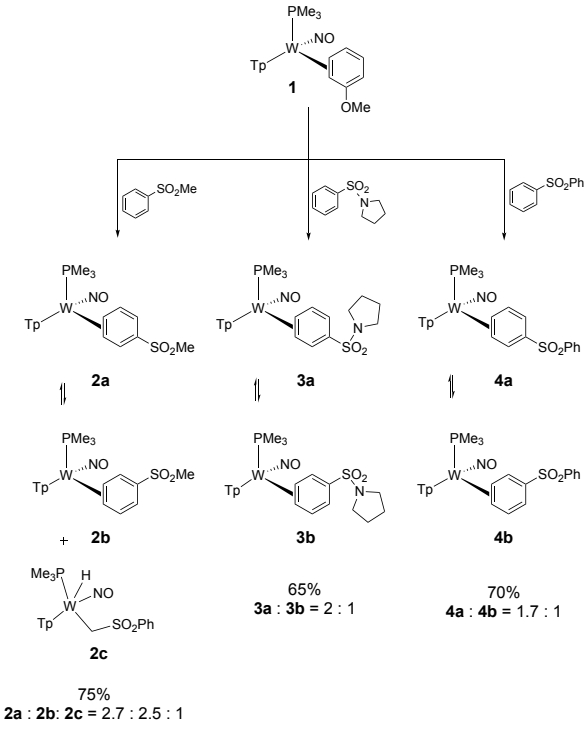
Scheme 2. Proposed syntheses of functionalized cyclohexenes from sulfones (R = Me, Ph) or sulfonamides ($R = NC_4H_8$).

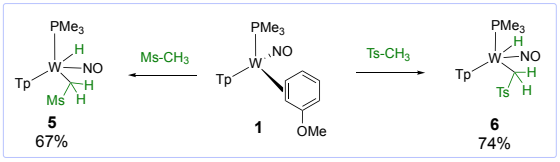


RESULTS and DISCUSSION

Complexes of the form WTp(NO)(PMe_3)(3,4-η^2-$PhSO_2R$) (R= -Me (**2**), -Ph (**4**), $-NC_4H_8$ (**3**)) were prepared by ligand exchange from the precursor complex WTp(NO)(PMe_3)(η^2-anisole) (**1**; Scheme 3).[28] The diphenyl sulfone complex **4** exists in solution as an equilibrium ratio of coordination diastereomers (cdr = 1.7 : 1), differing by which face of the prochiral ring is coordinated. This interconversion of diastereomers (e.g., **4a** and **4b**) is assumed to occur via a C-H oxidative-addition/ reductive-elimination mechanism.[29] The sulfonamide derivative **3** similarly equilibrates in solution, with a cdr of 2 : 1. However, the methyl phenyl sulfone ligand exchange reaction yielded three isomers of **2** in a ratio of 2.7 : 2.5 : 1. The ring-bound isomers **2a** and **2b** partially precipitate out of the reaction mixture if the ligand exchange is conducted in THF solvent (Figure 1).[29] The minor component of the mixture (**2c**) was determined to be a tungsten hydride species that is formed as a result of the metal inserting into the methyl C-H bond.[29] The proposed hydride **2c** has distinguishing spectroscopic features that include a diastereotopic methylene group with resonances at 3.14 and 1.88 ppm, and a corresponding hydride signal at 9.03 ppm, characterized by a J_{PH} = 114.9 Hz and ^{183}W satellites (J_{WH}= 9.3 Hz). To further support the assignment of **2c** as an alkyl hydride, the anisole complex **1** was also combined with dimethyl sulfone and 4-(methylsulfonyl)toluene to yield **5** and **6** (Scheme 3), respectively. In both cases, the only complex formed was the expected sulfonylmethyl hydride, the net product of a tungsten insertion into the methyl CH bond. Previously, the {WTp(NO)(PMe_3)} system has been observed to insert into N-H,[19] O-H,[26] C-H,[41] and C-F[42] bonds, but to our knowledge this is the first example we have encountered involving an sp^3 carbon. We note, however, that seminal work by the Legzdins group includes many such examples for the {WCp*(NO)} system.[43, 44]

Scheme 3. Preparation of dihapto-coordinated phenyl sulfone complexes of {WTp(NO)(PMe_3)} and the C-H insertion of methyl sulfones (insert).





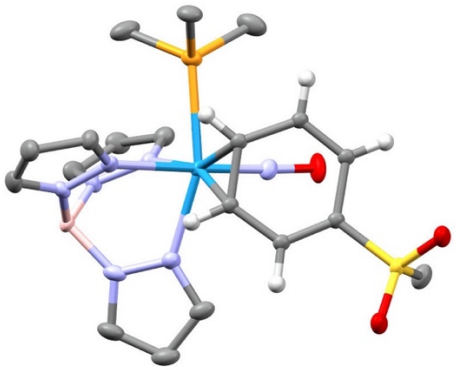


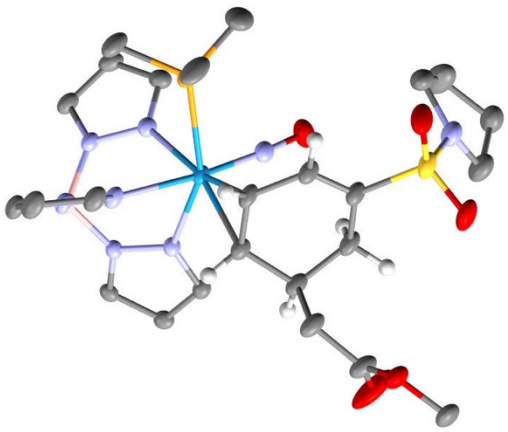
Figure 1. SC-XRD molecular structure determination (50% ellipsoids) of the η^2-phenyl methyl sulfone complex (**2a**; full report in SI of reference 29).

Previous work with the WTp(NO)(PMe_3)(η^2-trifluorotoluene) complex demonstrated that even though η^2-arene complexes with electron-deficient benzenes exhibit poor coordination diastereoselectivity, protonation of the isomeric mixture at -30 °C followed by treatment with a nucleophile such as a cyanide ion (NaCN) results in the formation of a *single* diastereomer of an η^2-diene complex.[24] Disappointingly, when the methyl phenyl sulfone complex **2** was protonated (HOTf/CH_3CN) and then treated with NaCN at -30 °C, two products (**18a**, **18b**; Table 1, Scheme 4) were formed in roughly a 1 : 2 ratio. Repeating this reaction at room temperature predictably led to a mixture of decomposition products. However, when the reaction was performed at 0 °C a dominant product (**18b**, dr > 20 : 1; later referred to as **18**) could be isolated. When the nucleophile was changed from NaCN to either of the masked ester enolates 1-methoxy-1-trimethylsilyloxy-2-methylpropene (MMTP) or 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (TSME), the ratio of the diene complexes (**10b** : **10a**; **13b** : **13a)** at -30 °C was close to 2:1, but again this ratio improved to > 20 : 1 at 0 °C (Table 1). Finally, when a ^1H NMR spectrum was taken (SI) after the addition of acid to **2** at 0 °C (CD_3CN), one dominant complex (**7b**) was observed that quickly degraded in solution. Key spectroscopic features were similar to those reported for the η^2-arenium species [WTp(NO)(PMe_3)(η^2-$HC_6H_5CF_3$)]$^+$, derived from α,α,α-trifluorotoluene.[24] Taken together, these data indicate that two different η^2-arenium diastereomers (**7-9a**; **7-9b**; Scheme 4) evolve upon protonation of **2** at -30 °C, each derived from a different stereoisomer of the initial arene complex. These arenium species then react with the nucleophile to give two different diene products (*e.g.*, **18a** and **18b**). Repeating the cyanide addition with the other two sulfone derivatives (**3**, **4**) gave similar results, providing diene complexes **19** and **20** respectively. These results are summarized in Scheme 4 and Table 1.

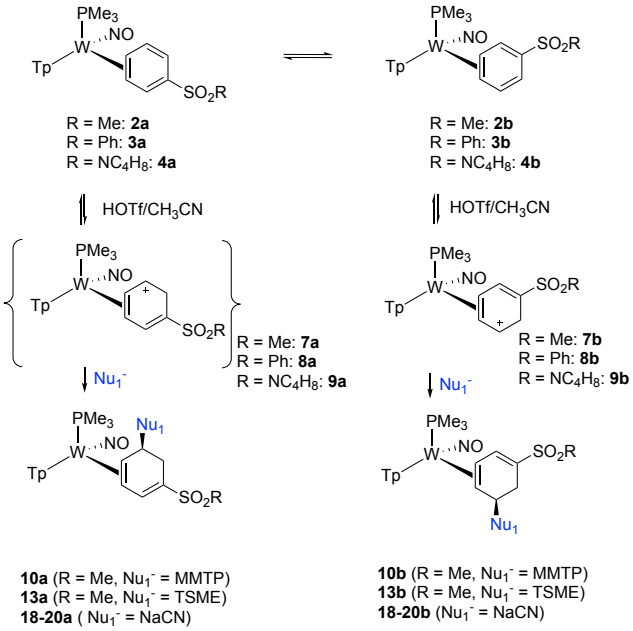
Table 1. Temperature dependence of first nucleophilic addition to η^2-arenium complex.

Nu_1	R	Temperature (°C)	Ratio (b:a)
MMTP	Me (**10**)	-30	1.7:1
		0	>20:1
TSME	Me (**13**)	-30	2:1
		0	> 20:1
NaCN	Me (**18**)	-30	2:1
		0	>20:1
NaCN	Ph (**19**)	-30	1:1
		0	>20:1
NaCN	NC_4H_8 (**20**)	-30	2:1
		0	>20:1

Figure 2. SC-XRD molecular structure determination (50% ellipsoids; mirror image) of the sulfonamide-substituted η^2-diene complex **14**.

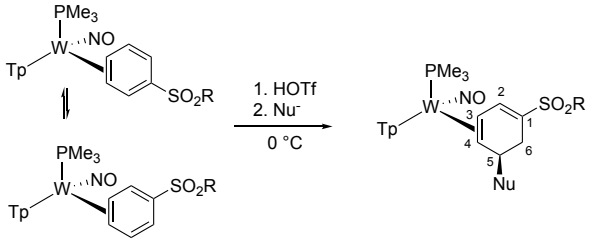


Scheme 4. Protonation of dihapto-coordinated phenyl sulfone ligands followed by nucleophilic addition to generate sulfonylated diene complexes (racemic mixtures).



2D NMR techniques were used to characterize the diene complexes **10**, **11b**, **13b** and **18-20b**, and in all cases, NOE correlations between the protons of the pyrazole ring trans to the PMe_3 ligand and the methine proton of C5 support the conclusion that the nucleophile adds adjacent to the site of arene protonation, and to the face of the bound carbocycle anti to metal coordination. In a similar fashion, other nucleophiles could be selectively added to the η^2-arenium intermediates **7b-9b** including MMTP lithium dimethyl malonate (LiDMM), tetrabutylammonium borohydride (TBAB), and imidazole, all of which react with the η^2-arenium complexes **7b-9b** (prepared in situ) to form η^2-(1-sulfonyl-1,3-diene) complexes (**10-23**) with high levels of regio- and stereocontrol (Table 2; dr > 20:1)).

Table 2. Tandem protonation/nucleophilic addition to η^2-phenyl sulfone complexes (T = 0 °C).



Reagent (Nu^-)	R	Product	Yield
OTMS, OMe (MMTP)	Me (**10**) Ph (**11**) NC_4H_8 (**12**)	[W], SO_2R, CO_2Me	54% 67% 53%
OTBS, OMe (TSME)	Me (**13**) NC_4H_8 (**14**)	[W], SO_2R, CO_2Me	54% 53%
MeO, O, OLi, OMe	Me (**15**) Ph (**16**) NC_4H_8 (**17**)	[W], SO_2R, MeO_2C, CO_2Me	65% 61% 62%
NaCN	Me (**18**) Ph (**19**) NC_4H_8 (**20**)	[W], SO_2R, CN	56% 31% 50%
tBu_4NBH_4	Me (**21**) Ph (**22**)	[W], SO_2R, H	62% 68%
H, N, N	Me (**23**)	[W], SO_2R, N, N	43%

[W] = $WTp(NO)(PMe_3)$

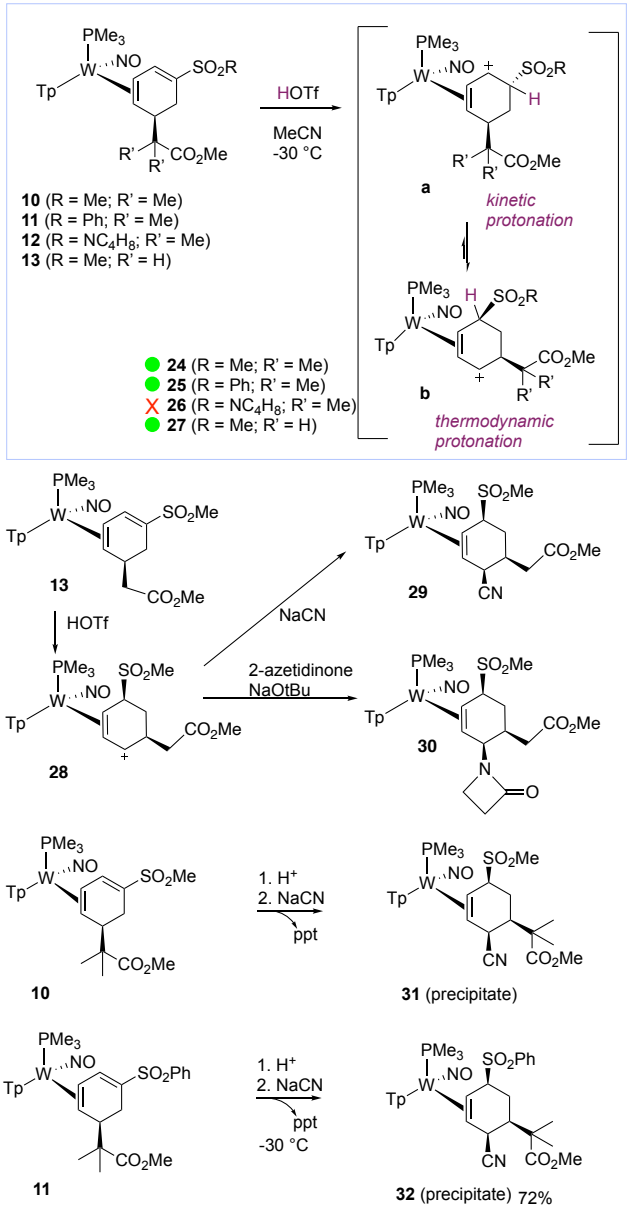
Single-crystal X-ray diffraction studies (SC-XRD; e.g., Figure 2; see SI) provided molecular structures of the diene complexes **11** and **14-17**, all of which are consistent with the assigned stereochemistries.[29] We posit that the high diastereoselectivity (dr >20:1) observed for these diene complexes at 0°C (Table 2 **10-23**) is the result of the reversible isomerization for the η^2-arene coordination diastereomers (Table 1, **a** and **b**) coupled with a greater thermodynamic driving force to form arenium isomer **b**

(e.g., **7a** → **7b**: ΔG = -3.0 kcal/mol; SI). This is analogous to that reported for trifluorotoluene.[24]

The products resulting from the 1,2-addition reactions of the η^2-phenyl sulfones are rare examples of conjugated η^2-diene complexes. The uncoordinated sp^2 carbons are in conjugation with the tungsten dπ orbital, and these complexes are expected to have a basic carbon at the terminus the diene.[24, 45] Protonation of dienes **10**, **11**, and **13** at -30 °C cleanly yield the η^2-allyl complexes **24**, **25**, and **27**). This type of allyl distortion, in which only two of the three allyl carbons are strongly coordinated by the metal is typical for complexes of the form [WTp(NO)(PMe_3)(π-allyl)]$^+$ (*vide infra*).[46] Calculations indicate that having the weakly coordinated carbon (indicated as a carbocation in Scheme 5) distal to the PMe_3 is favored by ~3 kcal/mole over the proximal allyl conformer (**a**) for the parent cyclohexadienium species (SI).[46] This inherent preference also avoids placing the carbocation-like allyl carbon next to the electron-withdrawing SO_2R group (**a** in Scheme 5). NOE correlations between the methine group bound to the sulfone and the PMe_3 group, along with stereochemical determinations of subsequently derived products (vide infra) support the notion that the sulfone group is oriented trans to tungsten. NMR data for **24** - **27** are consistent with what is reported for the trifluorotoluene-derived analogs.[24] As seen with the latter, we suspect that although protonation of the η^2-diene complex under kinetic control likely occurs anti to the metal (**a** in Scheme 5),[41, 47] such an action creates a steric interaction between the sulfone and the PMe_3 and NO ligands. Subsequent deprotonation followed by protonation syn to the metal would provide the observed stereochemistry in which the sulfone group is anti to the metal. In contrast to the sulfonylated diene complexes, attempts to convert the sulfonamide-diene **12** to the corresponding allyl (**26** in Scheme 5) were unsuccessful.

When the sulfonylated η^2-diene complex **10** was protonated (HOTf/CH_3CN) at -30 °C and the resulting solution treated with NaCN, a white precipitate formed. Full 2D NMR analysis of the isolated solid confirmed the formation of the desired trisubstituted η^2-cyclohexene complex (**31**; 65%; Scheme 5). Repeating this reaction at -60 °C increased the yield of the precipitate (**31**) to 82%. NOE and COSY data indicate that the CN^- adds to what was initially the para carbon of the phenyl sulfone, anti to the metal. Analogous reactions successfully converted sulfonylated diene complexes **11** and **13** into trisubstituted cyclohexene complexes (**29**, **32**). Replacing the cyanide with other nucleophiles resulted in a similar reaction sequence. For example, a solution of 2-azetidinone was deprotonated with NaO^{t}Bu then added to allyl **28** to give trisubstituted cyclohexene **30** (Scheme 5).

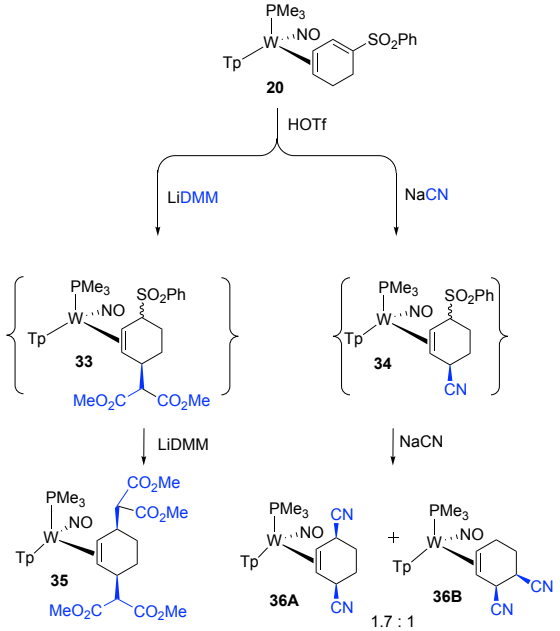
Scheme 5. (top) kinetic and thermodynamic protonation of η^2-(1-sulfonyl-1,3-diene) complexes (**10**, **11**, **13**), and conformational change ("allyl shift"), of the resulting η^2-allyl complex. (bottom) Conversion of sulfonyldiene complexes to sulfonyl-substituted cyclohexene complexes (**29**-**32**) via allyl intermediates (e.g., **28**; all compounds are racemic mixtures).



When sulfonylated diene complex **20** was treated with the nucleophiles LiDMM or NaCN (Scheme 6), the reaction sequence took a different course: Subjecting complex **20** to acid followed by NaCN, two complexes (**36A** and **36B**) resulted from the double addition of cyanide, *with concomitant loss of the sulfone group*. Presumably, the reaction occurs via an intermediate sulfonylcyclohexene **34**.

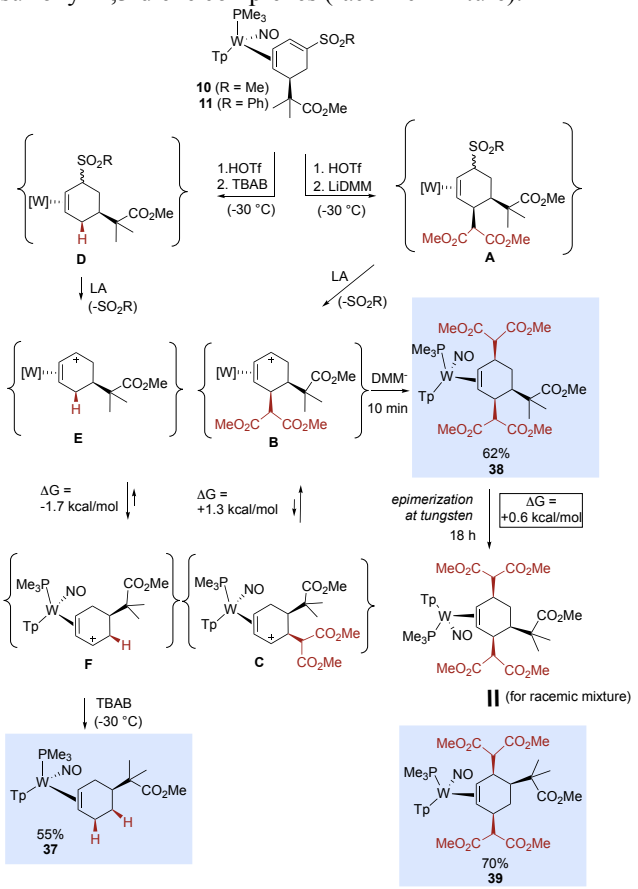
Subsequent loss of the sulfinate anion results in an allyl complex that can react with CN^- with either the distal or proximal conformer of the allyl complex to generate the 3,4-dicyano (**36B**) or 3,6-dicyanocyclohexene species (**36A**), respectively (Scheme 6). Through a similar sequence, the 3,6-disubstituted bis-malonate **35** was generated via the allyl sulfone complex **33**, but in this case, only the 3,6-substitution pattern is observed.

Scheme 6. Second protonation/nucleophilic addition of cyanide to the arene ring (racemic mixture).



Protonation of either diene complex **10** or **11** followed by the addition of TBAB resulted in the monosubstituted cyclohexene complex **37**. In this case the purported cyclohexene **D** (Scheme 7) loses sulfinate then adds the second hydride (i.e., an S_N1 reaction mechanism). Analysis of compound **37** revealed that the alkyl substituent is oriented toward the PMe_3. The proximal allyl conformation (**E** in Scheme 7) is expected to be unstable with respect to the distal form (**F**),[46] and hydride addition occurs with the latter conformer to form **37**. In contrast, when the sulfonylated diene **10** or **11** was treated with acid followed by LiDMM, the trialkylated η^2-cyclohexene complex **38** is produced. Apparently, **10** and **11** undergo the addition of the malonate, but then rapidly lose the sulfinate to form allyl **B** (Scheme 7). Although allyl **B** is expected to be unstable with respect to its conformer **C**, steric interactions apparently inhibit reaction adjacent to the DMM group and the 3,4,6-trisubstituted cyclohexene product **38** forms. Repeating this reaction with only one equivalent of LiDMM generates half an equivalent of product and the parent allyl. This tandem addition and substitution sequence from **10** to **38** occurred in less than 10 minutes. However, if the reaction is allowed to stand overnight, the product undergoes an isomerization to form **39**.

Scheme 7. Double nucleophilic additions to η^2-1-sulfonyl-1,3-diene complexes (racemic mixture).



The stereochemical assignments for both **38** and **39** are supported by NOESY and COSY correlations between the five methine ring hydrogens. Further, DFT calculations determine that **39** is roughly equal in free energy to its isomer **38** (Scheme 7). Of note, if **38** is isolated, washed with hexanes, and dried before being placed into a solution of acetonitrile, then no epimerization is observed over a period of 48 h, indicating that the epimerization is catalyzed by an impurity in the initial reaction mixture.

In the synthesis of trisubstituted cyclohexene complexes **31** or **32** (see Scheme 5), the η^2-1,3-cyclohexadiene complex **40** was often observed as a biproduct in the filtrate, and its formation was markedly enhanced in the presence of silica. In a similar manner, diene complex **41** was generated in the formation of **29** from **13**, and this diene complex could be made exclusively if the reaction solution was run down silica. X-ray crystal structure determinations (Figure 3) confirm the identity of **40** and the analog **41** as desulfonylated diene complexes.

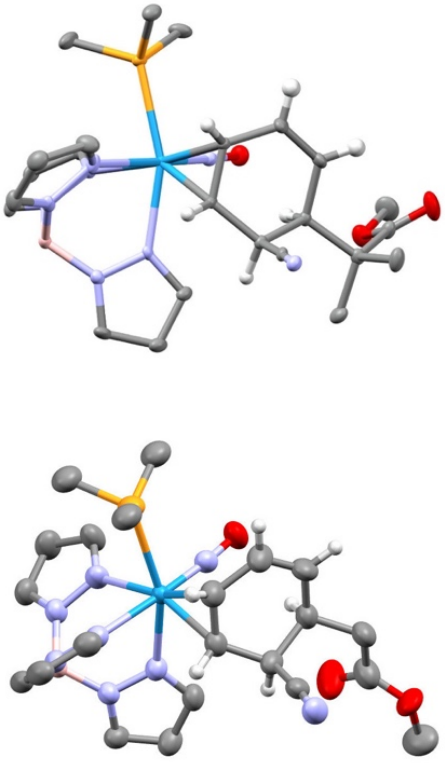
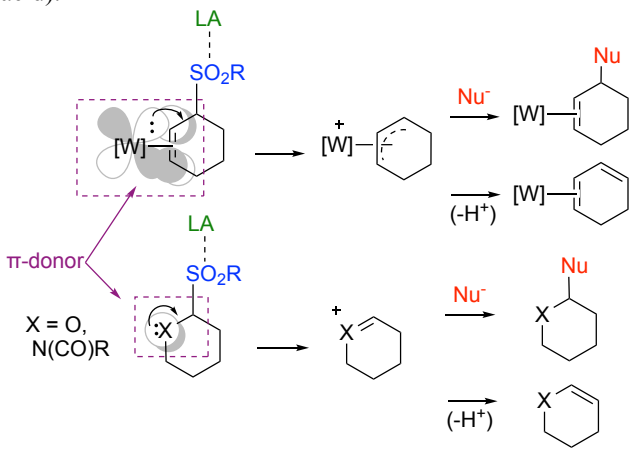


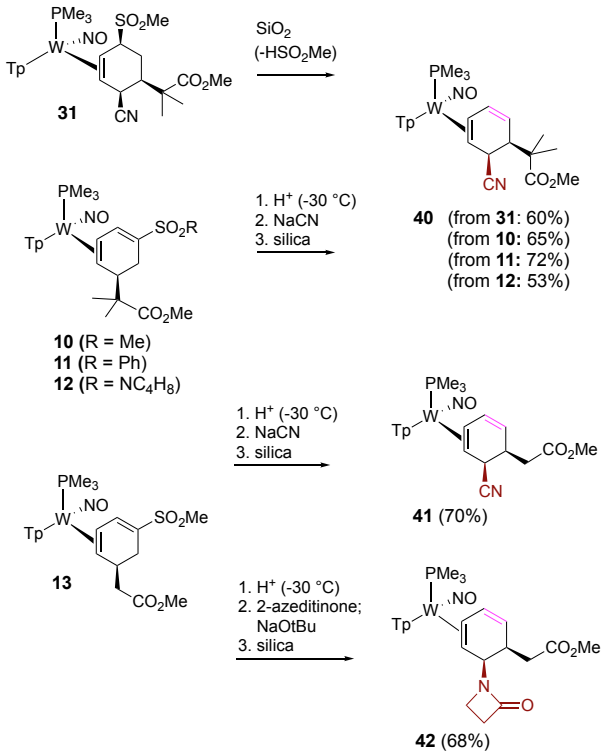
Figure 3. SC-XRD molecular structure determinations (50% ellipsoids) of the η^2-diene complexes (**40**; mirror image and **41**).

Sulfones are generally regarded as robust functional groups, with elimination occurring only at high temperatures (ca. 500 °C) through an intramolecular process (E_i).[34] However, elimination of sulfinic acid was observed to occur on silica for a tosylated glucopyranoside in which the tosylated carbon was attached to an oxygen.[36] Fujita et al. also demonstrated that β-tributylstannyl sulfones undergo elimination on silica to form the corresponding alkene, whereas without the silica, refluxing xylenes was required to achieve elimination.[37] Ley et al. demonstrated that α-sulfonated cyclic ethers or cyclic amides could undergo substitution or elimination with a suitable nucleophile in the presence of a Lewis acid such as $MgBr_2$.[39, 40] This behavior is similar to that observed for the tungsten allyl sulfones of the present report, where the tungsten-bound alkene moiety serves as the π-donor, facilitating loss of a sufinate anion (Scheme 8) in tandem with a Lewis acid. With the tungsten acting as a π donor, exposing **31** to silica promotes the elimination of the sulfinic acid and formation of **40** (Scheme 9). It was also observed that when salts of stabilized carbanions such as NaCN or LiDMM were used, no external Lewis acid was needed (beyond the alkali metal cation). Parenthetically, Pd(0) has been used to catalyze the allylic substitution of allylic sulfones,[48] where one can consider the metal as stabilizing both allyl and sulfonate fragments.

Scheme 8. Sulfone substitution reactions (LA = Lewis acid).



Scheme 9. Formation of disubstituted η^2-diene complexes from sulfonylated cyclohexene or sulfonylated cyclohexadiene complexes (racemic mixtures).



Given the tendency of allyl sulfones (e.g., **A** in Scheme 7 or **33** and **34** in Scheme 6) to undergo elimination in the presence of even mild Lewis acids (e.g. sodium salts or silica), we sought to prepare desulfonylated diene complexes to serve as synthons of the allyl sulfone complexes. Curiously, treatment of the sulfonylated cyclohexene **31** (Scheme 9) with acid (HOTf/MeOH, HOTf/CH_3CN, HOTf/acetone, diphenyl ammonium triflate

(DPhAT) or base (triethylamine) alone failed to cause any reaction. However, we were able to prepare diene complexes directly after addition of the second nucleophile simply by treating the solution with silica. Hence, diene complexes **10** - **13** were smoothly converted to their desulfonylated analogs **40** - **42**.

Diene complexes **40** and **42** could then be protonated and treated with a third independent nucleophile to generate trisubstituted cyclohexene complexes **46** and **47**. Alternatively, the sulfone group of **31** could also be directly substituted with other nucleophiles via the diene intermediate **40** with the nucleophilic salts LiDMM, TBAB, or NaCN to form cyclohexenes **43**, **44**, and **45** respectively (Scheme 10; Figure 4). This substitution was accomplished without the need for external acid. However, the sulfone substitution did not proceed in the case of neutral nucleophiles such as methylamine, dimethylamine, or MMTP. To circumvent this, diene **40** was protonated at low temperature to form the purported allyl intermediate, which then cleanly reacts with imidazole to provide the trisubstituted cyclohexene **46** (Scheme 10). The analogous reaction was demonstrated for the ester-azetidinone diene complex **42** and NaCN to form **47**. Of note, several other amines have been shown to add to π - allyl complexes of the form $WTp(NO)(PMe_3)(\eta^2\text{-}C_6H_9)]^+$.[49]

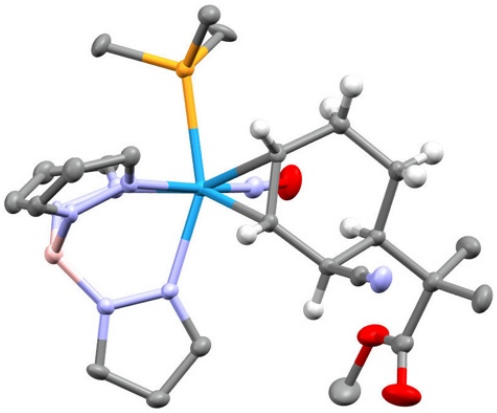
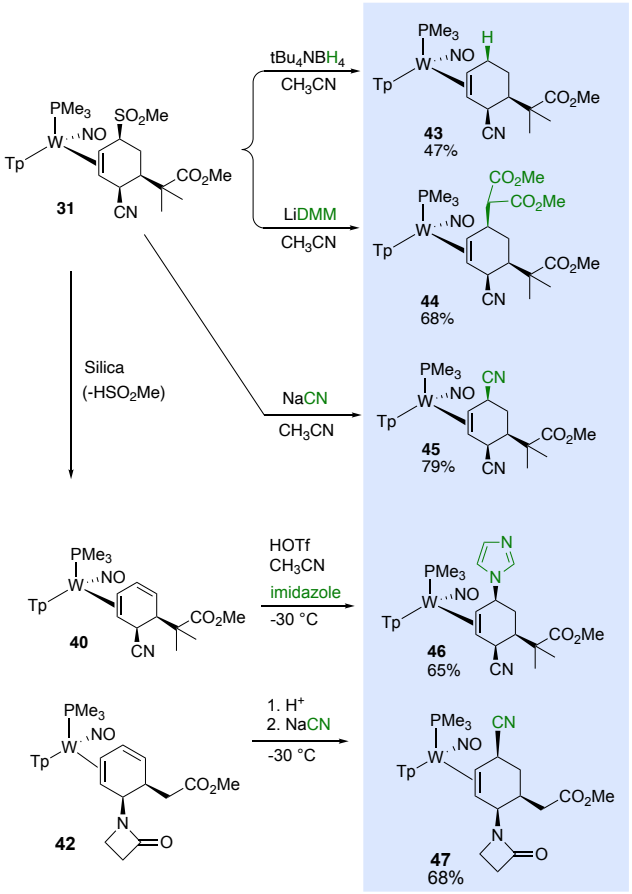


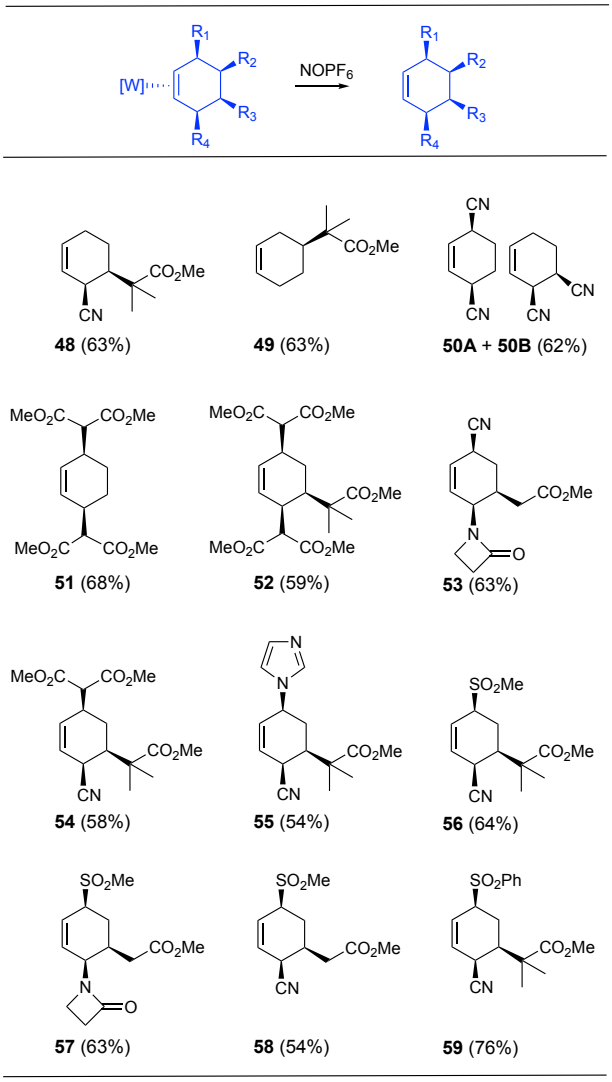
Figure 4. SC-XRD molecular structure determination (50% ellipsoids) of the disubstituted η^2-cyclohexene complex (**43**).

Scheme 10. Addition of the third nucleophile either via replacement of the sulfone or from addition to the η^2-diene (racemic mixtures).



Previous studies have shown that cyclohexenes can be liberated from the {WTp(NO)(PMe3)} system using a variety of different oxidants, including Ag^+, $[FeCp_2]^+$, DDQ, $NOPF_6$, CAN, and even O_2. Twelve examples are provided in Table 3. These cyclohexenes (**48**-**59**) were liberated from the metal through oxidation with the $NOPF_6$ in yields ranging from 54 to 76 %. As a representative example, compound **57**, which contains acetate, azetidinone, and nitrile fragments, can be prepared in overall 15% yield (5 steps) from the anisole complex **1** (1.0 g of **1** yields 74 mg of **57**). Chiral sulfones are common building blocks found in biologically active compounds, especially where the sulfone bears a stereocenter at the α or β carbon (e.g., Otezla).[31, 50] Of note, chiral sulfonylated cyclohexenes have been explored as anti-sepsis agents.[51]

Table 3. Decomplexation of functionalized cyclohexenes (racemic mixtures).



In recent years there has been an explosion of new methods for dearomatization of benzenes[8] including catalytic hydrogenations[52, 53] enzymatic oxidations,[54] radical cyclizations,[55, 56] photochemical and thermal cycloadditions,[9, 57-60] as well as transition metal mediated methods.[7, 11-13, 61] Regarding the last approach, arenes can be coordinated through two, four, or six carbons, with η^6-arene complexes such as $Cr(CO)_3(\eta^6$-benzene) being the most common method.[11] In such compounds the metal acts as an electron-withdrawing group and the arene is activated toward nucleophilic addition reactions. We note that while methoxy groups and halides are well known as leaving groups for η^6-benzene complexes of $Cr(CO)_3$ and $[Mn(CO)_3]^+$,[62, 63] sulfinates have not been utilized for such purposes, although several examples of η^6-sulfone complexes have been documented.[64-67]

The dihapto-coordinate dearomatization of benzene by π-basic metal fragments has been extensively investigated for arenes containing a π-donor substituent such as anisoles,[15, 21, 68, 69] phenols,[16-18, 70] and anilines.[19, 71, 72] The closest prior example of a reaction sequence *in which a metal mediates three additions* to an aromatic ring was a single example with an osmium anisole derivative.[22] In that case, addition of an electrophile at C4 followed by nucleophilic addition at C3 generated an methoxydiene complex. Subsequent reduction and substitution of the methoxy group provided a trisubstituted cyclohexene.[73] The tungsten complex in the present study is π-basic enough to promote protonation of the arene even in the presence of the electron-withdrawing sulfonyl group. The resulting η^2-arenium complex readily reacts with a broad range of nucleophiles. Because the metal only occupies one double bond of the benzene ring, the entire process can be repeated. The distinguishing feature of the current study is the ability of the EWG substituent to be replaced with a third independent nucleophile. And, as demonstrated above, in addition to using the sulfone or sulfonamide as a leaving group, these medicinally relevant functional groups can be left intact.[74, 75] Of the twelve novel substituted cyclohexenes prepared as examples of this methodology, nine (**48**, **51**, **53** - **59**) meet the criteria of Lipinski's rule of five[76] for evaluating drug likeliness, as well as the criteria of Ghose,[77] Veber,[78] Egan,[79] and Muegge.[80] This indicates that these nine compounds have a high probability of showing desirable biological availability.

CONCLUSION

The coordination of methyl phenyl sulfone, diphenyl sulfone, and phenylsulfonyl pyrrolidine by the π-base $WTp(NO)(PMe_3)$ increases the electron density of the phenyl ring, which enables the selective protonation of the carbon ortho to the sulfone group. The resulting η^2-arenium complexes undergo nucleophilic addition with a range of nucleophiles to yield conjugated η^2-diene species. In turn, these diene complexes can undergo a second protonation and nucleophilic addition, leading to trisubstituted cyclohexenes. The sulfone can then be substituted for a third independent nucleophile. Without exception, this reaction sequence produces a predictable regio- and stereochemical pattern for the cyclohexene ligand, which is liberated from the metal through oxidative decomplexation. Through this methodology, not only can *cis,cis*-3,4,6 trisubstituted cyclohexenes be generated, but through appropriate use of hydride, *cis*-3,4-, and *cis*-3,6-cyclohexene patterns are also achieved. The range of demonstrated nucleophiles includes stabilized enolates, N-heterocycles, and amines, amides. Given that $WTp(NO)(PMe_3)$(benzene) and its derivatives can be prepared in enantioenriched form,[81] the compounds reported herein should be accessible as single enantiomers.[24, 45] Work is currently underway to carry out controlled epimerizations in the cyclohexene ring via a

deprotonation/protonation sequence, in order to achieve trans- substitution patterns for the cyclohexene ring, where the influence of the metal can be leveraged still further.

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Supporting Information Available:

^{1}H and ^{13}C NMR spectra of selected compounds, and crystallographic information for compounds **11**, **14** - **17**, **21**, **40**, **41,** and **43**. This material is available free of charge via the Internet at http://pubs.acs.org CCDC 2088188-2088194 and 2162397-2162398 deposition numbers contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures

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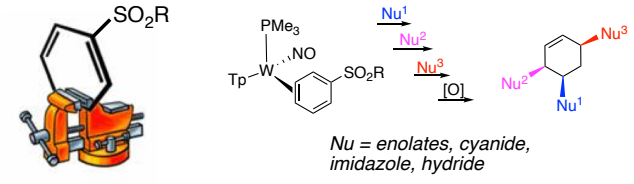
SO2R
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Nu = enolates, cyanide,
imidazole, hydride

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