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Iron-Catalyzed Cross-Coupling of Unactivated Secondary Alkyl Thio Ethers and Sulfones with Aryl Grignard Reagents

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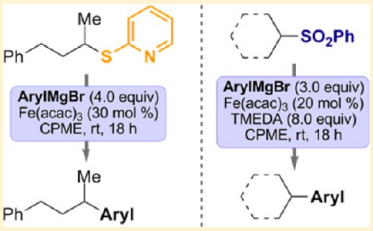
Supporting Information

ABSTRACT: The first systematic investigation of unactivated aliphatic sulfur compounds as electrophiles in transition-metal-catalyzed cross-coupling are described. Initial studies focused on discerning the structural and electronic features of the organosulfur substrate that enable the challenging oxidative addition to the C(sp^3)−S bond. Through extensive optimization efforts, an Fe(acac)$_3$-catalyzed cross-coupling of unactivated alkyl aryl thio ethers with aryl Grignard reagents was realized in which a nitrogen "directing group" on the S-aryl moiety of the thio ether served a critical role in facilitating the oxidative addition step. In addition, alkyl phenyl sulfones were found to be effective electrophiles in the Fe(acac)$_3$-catalyzed cross-coupling with aryl Grignard reagents. For the latter class of electrophile, a thorough assessment of the various reaction parameters revealed a dramatic enhancement in reaction efficiency with an excess of TMEDA (8.0 equiv). The optimized reaction protocol was used to evaluate the scope of the method with respect to both the organomagnesium nucleophile and sulfone electrophile.

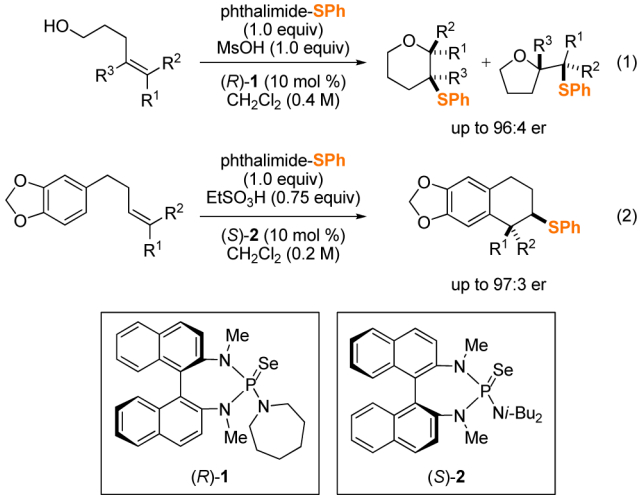


1. INTRODUCTION

The formation of carbon−carbon bonds via the union of unactivated aliphatic electrophiles with organometallic reagents under transition-metal catalysis has long been regarded as one of the most challenging classes of cross-coupling reaction.[1] Principal difficulties include the relatively slow oxidative addition of alkyl electrophiles to transition-metal centers[2] (at least via 2-electron pathways most common with palladium), the proclivity of the derived alkyl metal intermediates to decompose via rapid β-hydride elimination, and the slower reductive elimination of C(sp^3) versus C(sp^2) moieties.[3] Although these hurdles are not necessarily insurmountable under palladium catalysis,[4] complexes based on first-row transition metals such as nickel,[5] cobalt,[6] iron[7,8] and copper[5b,9] are fast emerging as the most efficient catalysts for such transformations.

In continuation of our longstanding research program on the "Lewis base activation of Lewis acids",[10] we have recently reported the first catalytic, enantioselective thiofunctionalizations of unactivated alkenes, including sulfenoetherification[11] (Scheme 1, eq 1) and carbosulfenylation[12] (Scheme 1, eq 2) protocols. During the course of these studies, we became keenly aware of a relative dearth of methods for the constructive elaboration of the C(sp^3)−SPh motif in the thio ether products into C(sp^3)−C bonds and considered the potential for cross-coupling reactions analogous to those developed for other unactivated[13] aliphatic electrophiles (e.g., halides and sulfonates). We describe herein our studies on the use of unactivated, secondary alkyl sulfur electrophiles in transition-metal-catalyzed cross-coupling, culminating in a reaction protocol for the cross-coupling of unactivated, secondary alkyl phenyl sulfones with aryl Grignard reagents under iron catalysis.

Scheme 1



Background. *1.1. Existing Methods for Constructive Elaboration of Unactivated C(sp^3)−SPh Bonds.* The use of unactivated[13] C(sp^3)−SPh bonds as a locus for C(sp^3)−C bond formation is rare in chemical synthesis, at least in a direct fashion, and most manipulations of C(sp^3)−SPh bonds serve either to remove an unwanted thio ether group by desulfurization[14] or transform it to a more versatile functional group such as an alkene (via elimination of the sulfoxide[15]) or a

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carbonyl compound/equivalent (Pummerer rearrangement[16]). Although alkyl phenyl thio ethers can be converted to the corresponding alkyllithium species by means of reductive lithiation followed by trapping with carbon electrophiles, this method is incompatible with substrates containing β-heteroatoms (with the exception of β-lithiooxy groups) because of rapid β-elimination.[17] Additionally, the scope of carbon electrophiles able to react productively with alkyllithium reagents is relatively narrow, being mostly limited to simple alkylations and additions to carbonyl compounds. Although oxidation of an alkyl phenyl thio ether to the corresponding sulfone followed by α-alkylation and desulfurization[18] is a possible alternative, this strategy suffers from the same general limitations.

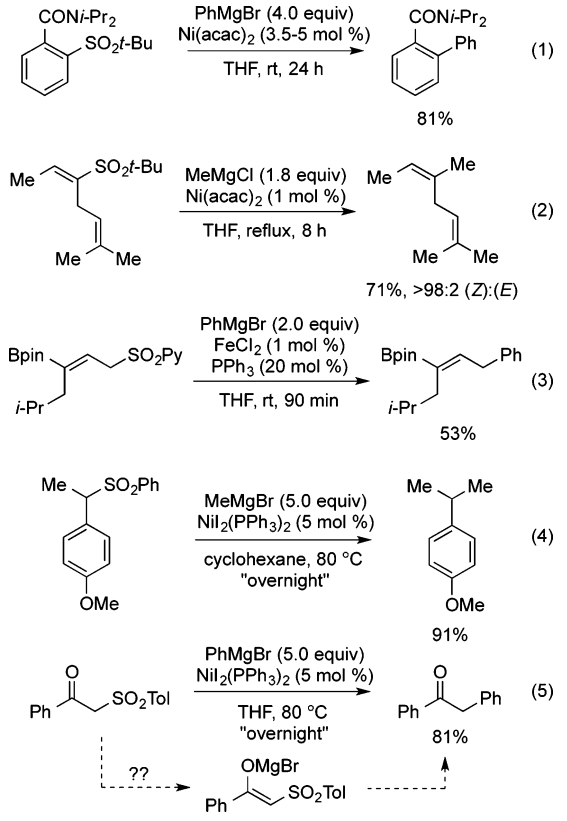
Another strategy to effect the conversion of C(sp^3)−SPh to C(sp^3)−C bonds would be to generate a carbon-centered radical from the thio ether and trap it with radicophilic alkenes, a process that should be tolerant of β-heteroatomic groups.[19] Although it is certainly possible to generate carbon-centered radicals from unactivated C(sp^3)−SPh bonds with Bu_3SnH, the process is considerably less facile than for the corresponding bromides, iodides, or selenides.[20] In most cases, this procedure is limited to simple reductions, which are often slow (the reduction of *i*-PrSPh with Bu_3SnH in refluxing benzene required 110 h).[21] As with alkyl halides, the rate of radical formation from alkyl thio ethers increases with the stability of the incipient carbon radical in the order 3° > 2° > 1° > Me.[20,21] Notably, only a handful of examples of the intramolecular olefinic trapping of radicals generated from unactivated alkyl thio ethers are on record,[21,22] and, to the best of our knowledge, no examples of similar intermolecular reactions are known, a probable consequence of the low rate of radical generation from unactivated thio ethers relative to undesired side reactions with the radicophilic alkene trap.[23]

1.2. Cross-Coupling of Organosulfur Electrophiles: State of the Art. Although halides and sulfonates have traditionally served as the electrophilic coupling partners in transition-metal-catalyzed cross-coupling reactions, a resurgence in the use of organosulfur compounds in cross-coupling has sparked new interest in this long overlooked class of electrophiles.[24] The first use of organosulfur coupling partners is found in the work of Takei[25] and Wenkert[26] on nickel-catalyzed Kumada−Corriu cross-coupling of aryl and alkenyl sulfides in the early 1970s through the mid-1980s. Since these early contributions, the cross-coupling of aryl, heteroaryl, alkenyl, alkynyl, allyl, benzyl, and acyl C−S electrophiles has recently undergone a renaissance, and sulfides, sulfoxides, sulfones, sulfoximines, and sulfonium salts have all been exploited as competent electrophiles.[27] Organomagnesium, organozinc,[28] organotin,[29] and organoboron[30] reagents have all been successfully employed as nucleophiles, and catalysis by both first-row (nickel, cobalt, and iron) and second-row (palladium and rhodium) transition metals has been achieved.

In the context of the present work, it should be noted that methods for the nickel- or iron-catalyzed cross-coupling of both aryl sulfones[25a,31] (Scheme 2, eq 1) and alkenyl sulfones[32] (Scheme 2, eq 2) with alkyl and aryl Grignard reagents are already on record. Moreover, allylic sulfones have also served as competent electrophiles in copper-[33] and iron-catalyzed[34] displacements with Grignard reagents (Scheme 2, eq 3), nickel-[35] and palladium-catalyzed[36] alkylations with stabilized enolates, Lewis acid-mediated substitutions with organoalanes,[37] and alkylations with lithium dialkylcuprates.[38]

Recently, Li and co-workers described an isolated example of a nickel-catalyzed cross-coupling of a benzylic sulfone with MeMgBr (Scheme 2, eq 4) as well as the nickel-catalyzed cross-coupling of α-keto sulfones with Grignard reagents (Scheme 2, eq 5).[39] Although not discussed by the authors, the coupling of the α-keto sulfones is likely proceeding by initial enolization of the substrate by the basic Grignard reagent (pK_a $PhCOCH_2SO_2Ph$ = 11.4 in DMSO[40]) so that the β-oxido vinyl sulfone is the active electrophile; this would also account for the lack of Grignard reagent addition to the keto group.

Scheme 2



However, despite extensive studies performed on the cross-coupling of C(sp^2)−S electrophiles and, to a lesser extent, on allylic,[26e,33−38,41] benzylic,[39,42] or α-carbonyl-activated[39,43] C(sp^3)−S electrophiles, the use of unactivated C(sp^3)−S electrophiles remains uncharted territory. To the best of our knowledge, only two reports of the use of simple alkyl sulfur electrophiles in transition-metal-catalyzed cross-coupling are known, and in neither case is the reaction believed to occur by oxidative addition of the metal to the C(sp^3)−S bond. First, Vogel and Volla have described an iron-catalyzed desulfinylative cross-coupling of alkyl sulfonyl chlorides with Grignard reagents in which the oxidative addition step is believed to occur at the S−Cl bond followed by an extrusion of SO_2 gas (Scheme 3, eq 1).[44] Second, Nakamura and co-workers have developed a nickel-catalyzed alkenylative cross-coupling of alkyl phenyl thio ethers with Grignard reagents in which the oxidative addition is thought to occur at the S−Ph bond (Scheme 3, eq 2).[45] To date, there have been no reports on a cross-coupling of unactivated C(sp^3)−S electrophiles in which oxidative addition occurs to the C(sp^3)−S bond, a necessary

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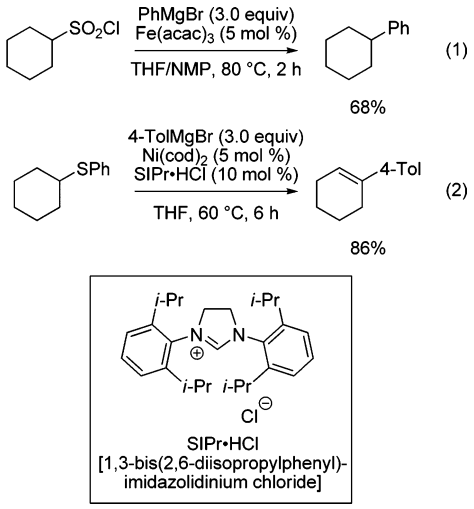
Scheme 3



requirement for the alkylative cross-coupling of alkyl aryl organosulfur compounds.

1.3. Challenges. Besides the usual difficulties encountered with alkyl electrophiles, the cross-coupling of alkyl sulfur electrophiles presents two additional challenges regarding the crucial oxidative addition step: (1) compared to alkyl halides, the C(sp^3)−S bond is relatively unpolarized ($\chi_S-\chi_C$ = 0.03[46]) with a higher energy σ^*_{C-S} orbital and (2) the divalent sulfur atom necessarily bears two C−S bonds that must be distinguished in the oxidative addition step. Point 2 is of particular concern, as documented examples of oxidative addition of low-valent transition metals to alkyl aryl thio ethers[47] and sulfones[31a,b] involve selective insertion into the C(sp^2)−S bond such that the compounds behave as aryl, and not alkyl, electrophiles.

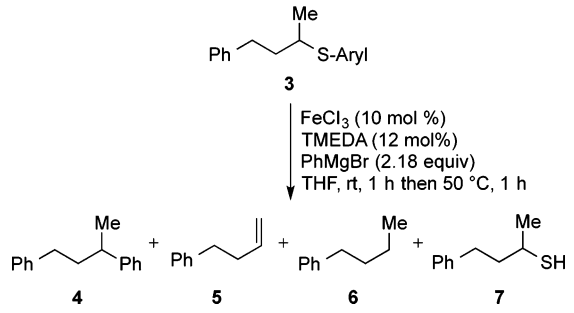
1.4. Objectives of this Study. The principal objectives of the current study are (1) to discern the structural/electronic features of the unactivated alkyl sulfur electrophile (e.g., aryl group, sulfur oxidation level) that best facilitate the difficult oxidative addition to the C(sp^3)−S bond, (2) to identify a suitable metal precatalyst for which the active, low-valent catalytic species produced in situ will undergo selective oxidative addition to the C(sp^3)−S bond, and not the C(sp^2)−S bond, of an alkyl aryl electrophile, (3) to deduce the stereochemical course of the reaction as an insight into the nature of the oxidative addition step, and (4) to establish the scope and limitations of the reaction from the point of view of the alkyl sulfur electrophile and the nucleophile, particularly with respect to the tolerance of β-heteroatomic groups on the substrate.

2. RESULTS

To address objective 1, initial studies focused on the use of alkyl aryl thio ether substrates bearing electron-poor aryl groups in an effort to polarize the C(sp^3)−S bond and to facilitate oxidative addition. With regard to objective 2, a first-row transition-metal catalyst was sought to encourage oxidative addition via a one-electron as opposed to a two-electron pathway.[48] With the knowledge that low-valent nickel species undergo oxidative addition to alkyl aryl thio ethers at the undesired C(sp^2)−S bond,[47] iron salts were selected as catalysts for the initial experiments. PhMgBr was chosen as the nucleophile on the basis of its successful use in a large number of iron-catalyzed cross-couplings of alkyl halides.

2.1. Cross-Coupling of Alkyl Aryl Thio Ethers. *2.1.1. Initial Studies.* Orienting experiments employed alkyl aryl thio ethers **3a**−**d** as the substrates, PhMgBr (2.18 equiv,[49] 1.09 M solution in THF) as the nucleophile, $FeCl_3$ (10 mol %) as the catalyst, and THF as the reaction solvent (Table 1). Each experiment was conducted in a GC vial under an argon atmosphere (without stirring) at room temperature for 1 h followed by heating at 50 °C for a further 1 h. Although several different ligands were surveyed (dppm, dppe, PCy_3, TMEDA, 2,2′-bipy, SI*i*-Pr·HCl (1,3-diisopropylimidazolidinium chloride)), only the results for TMEDA (12 mol %) as the ligand are reported (the results with the other ligands were almost identical within experimental error; see the Supporting Information). The product distribution in each case was assessed by GC analysis, employing tetradecane (0.5 equiv) as an internal standard, and the observed retention times of products **4**−**7** were compared to those of their authentic samples.[50] Whereas phenyl thio ether **3a** and 4-trifluoromethylphenyl thio ether **3b** were unreactive, pentafluorophenyl thio ether **3c** and 2-pyridyl thio ether **3d** both gave detectable (3 to 4%) amounts of the desired product **4**, albeit with relatively larger amounts of undesired alkene **5** and alkane **6**. Biphenyl, resulting from oxidative homocoupling of PhMgBr, was observed in all cases.[51] Because of difficulties in quantifying unreacted pentafluorophenyl thio ether **3c** by GC, 2-pyridyl thio ether **3d** was selected as the substrate for further optimization studies.

Table 1. Attempted Cross-Coupling of Thio Ethers 3 with PhMgBr



			GC yield (%)[a]				
entry	thio ether	aryl	3	4	5	6	7
1	**3a**	C_6H_5	99				
2	**3b**	4-$CF_3C_6H_4$	104				
3	**3c**	C_6F_5	n.d.[b]	3	7	5	
4	**3d**	2-pyridyl	69	4	10	9	

[a]Measured against tetradecane (0.5 equiv) as an internal standard. [b]The compound was not detected by FID-GC.

A brief survey of established reaction conditions used for the iron-catalyzed cross-coupling of alkyl halides with Grignard reagents was next conducted,[8a,e,f] but all of these returned mainly starting material **3d** and gave product **4** in a mere 1−6% yield (GC). The first sign of promise came with a slight modification (extended reaction time) of the protocol reported by Hayashi et al. for the cross-coupling of unactivated alkyl bromides with aryl Grignard reagents, which employs Fe(acac)$_3$ (5 mol %) as the catalyst and 2.0 equiv of the requisite aryl Grignard reagent in Et_2O at reflux.[8b] Thus, the treatment of 2-

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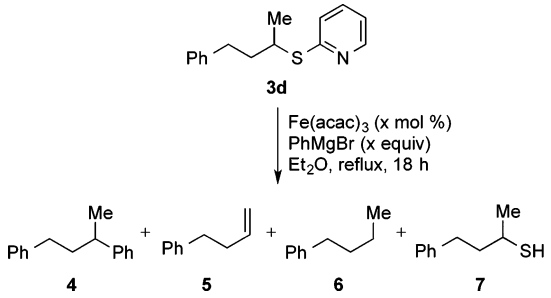
pyridyl thio ether **3d** with PhMgBr (2.0 equiv, 2.91 M solution in Et_2O) and $Fe(acac)_3$ (5 mol %) in Et_2O at reflux for 18 h led to a 24% conversion of **3d** to afford **4** as the major product in 13% yield (GC) in addition to **5**, **6**, and **7** as minor products (Table 2, entry 1). Further optimization of the amounts of PhMgBr and $Fe(acac)_3$ showed that 4.0 equiv of PhMgBr and 30 mol % of $Fe(acac)_3$ led to the formation of desired product **4** in 49% yield (GC) (Table 2, entry 13), and these conditions were selected as an appropriate starting point for a more focused optimization study.

Table 2. Optimization of the Amounts of $Fe(acac)_3$ and PhMgBr



entry	$Fe(acac)_3$ (mol %)	PhMgBr (equiv)	GC yield (%)[a] 3d	4	5	6	7
1	5	2.0	76	13	4	5	2
2	10	2.0	68	16	5	6	2
3	20	2.0	78	17	7	n.d.[b]	1
4	5	3.0	48	27	6	6	3
5	10	3.0	56	22	7	7	2
6	20	3.0	41	31	11	5	2
7	30	3.0	20	38	19	5	1
8	50	3.0	47	26	16	n.d.[b]	2
9	70	3.0	55	22	15	n.d.[b]	2
10	5	4.0	54	21	7	7	2
11	10	4.0	37	32	12	6	2
12	20	4.0	15	42	14	7	2
13	30	4.0	0	49	21	6	1
14	50	4.0	22	40	23	n.d.[b]	3
15	70	4.0	37	32	20	n.d.[b]	3
16	30	5.0	0	48	16	7	1
17	50	5.0	0	52	19	4	0
18	70	5.0	0	46	29	n.d.[b]	4

[a]Measured against tetradecane (0.5 equiv) as an internal standard. [b]The peak in the GC trace was obscured by peaks for small amounts of other unidentified compounds.

2.1.2. Survey of Metal Salts as Catalysts. A variety of metal salts as catalysts were next surveyed using *n*-Bu_2O as the reaction solvent (because of volatility issues with Et_2O on a small scale) (Figure 1). For consistency with previous reactions carried out in Et_2O, a temperature of 45 °C was employed in all cases. Interestingly, iron salts proved uniquely effective in this transformation, and $Ni(acac)_2$ or $Co(acac)_x$ (x = 2 or 3) produced only traces (2 to 3%) of **4** in addition to significant quantities of alkyl thiol **7** derived from $C(sp^2)$–S bond cleavage. Notably, $Ru(acac)_3$ was completely ineffective in the reaction. Of all the iron salts tested, $Fe(acac)_3$ provided the highest yield (58% by GC) of **4** and consequently this metal salt was employed as the catalyst in all further studies.

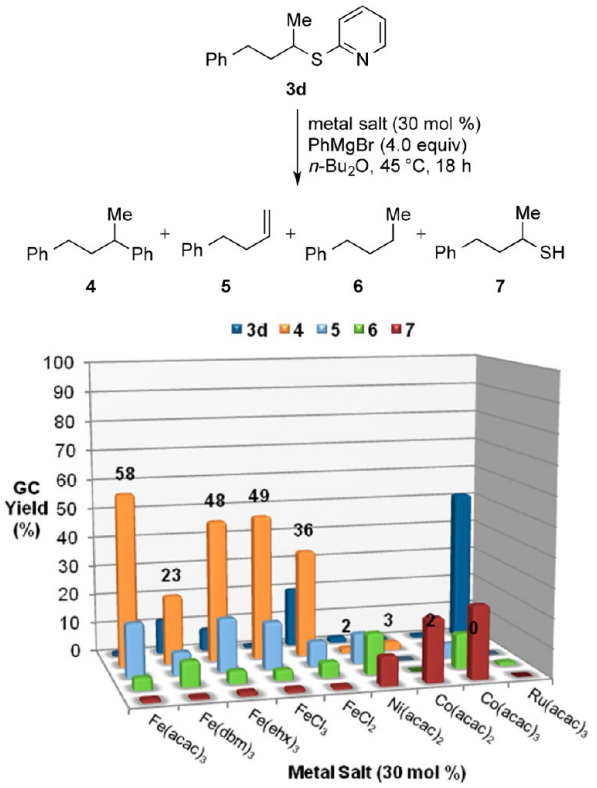


Figure 1. Survey of metal salts as catalysts. All yields were measured against tetradecane (0.5 equiv) as an internal standard. acac, acetylacetonate; dbm, dibenzoylmethane; ehx, 2-ethylhexanoate.

2.1.3. Evaluation of Reaction Solvent. The effect of the reaction solvent on the $Fe(acac)_3$-catalyzed cross-coupling of thio ether **3d** with PhMgBr (4.0 equiv, 2.91 M solution in Et_2O) was next assessed, with all reactions conducted at ambient temperature for the purpose of operational simplicity (Figure 2). Although the reaction generally performed well in dialkyl ether solvents (Et_2O, *n*-Bu_2O, *i*-Pr_2O, MTBE, and CPME), the use of more strongly coordinating THF proved detrimental, affording alkene **5** as the major product. Interestingly, a similar deleterious effect of THF on the $Fe(acac)_3$-catalyzed cross-coupling of aryl Grignard reagents with unactivated alkyl bromides was noted by Hayashi et al.[8b] Ethers bearing more than one donor oxygen atom, such as dioxane, DMM, DME, and diglyme, were also poor reaction media (particularly for the latter two solvents, for which the reaction was largely suppressed). Notably, NMP, which is reportedly a beneficial cosolvent for other iron-catalyzed cross-couplings,[52] strongly inhibited the reaction when employed as a cosolvent (9%) with *n*-Bu_2O. Of all the solvents tested, CPME (cyclopentyl methyl ether)[53] was by far the most effective, delivering **4** in 63% yield (GC), and it was thus selected as the (bulk) reaction solvent of choice for all further optimization. Additionally, with the knowledge that THF is clearly detrimental to the reaction, solutions of PhMgBr in Et_2O were used exclusively for further studies.

2.1.4. Evaluation of Reaction Temperature. The effect of the reaction temperature was also briefly investigated, employing CPME as the reaction solvent (Table 3). At 0 °C, the reaction failed to reach completion after 18 h, and a significant quantity (42%) of starting material **3d** remained (Table 3, entry 1). Alternatively, at 45 °C, almost all of the starting material was consumed (93% conversion), but the yield of **4** was only

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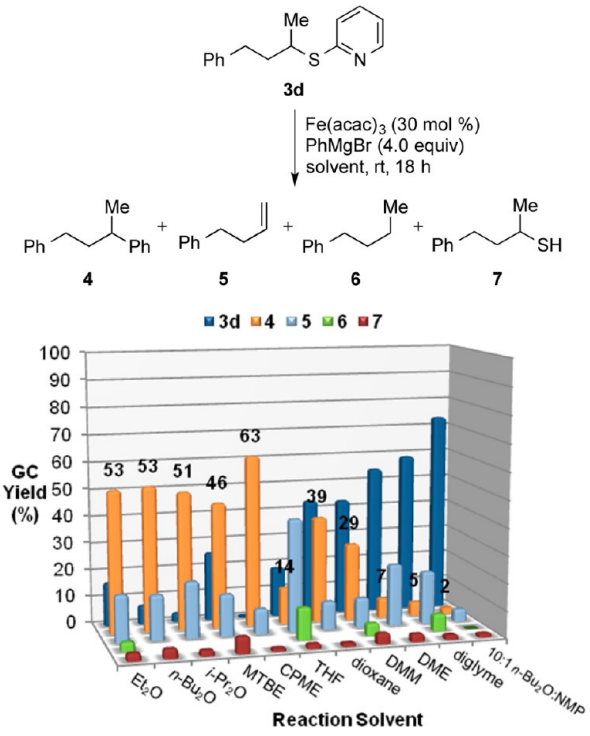
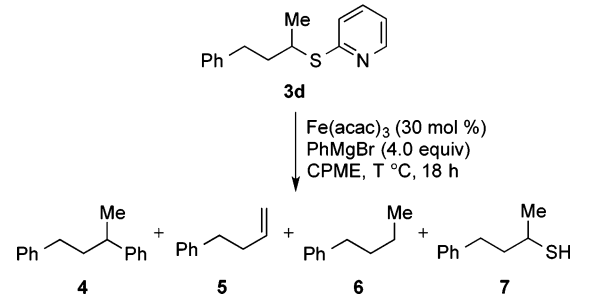


Figure 2. Evaluation of reaction solvent. All yields were measured against tetradecane (0.5 equiv) as an internal standard. MTBE, methyl *tert*-butyl ether; CPME, cyclopentyl methyl ether; DMM, dimethoxymethane; DME, 1,2-dimethoxyethane; and NMP, *N*-methylpyrrolidinone.

Table 3. Evaluation of Reaction Temperature

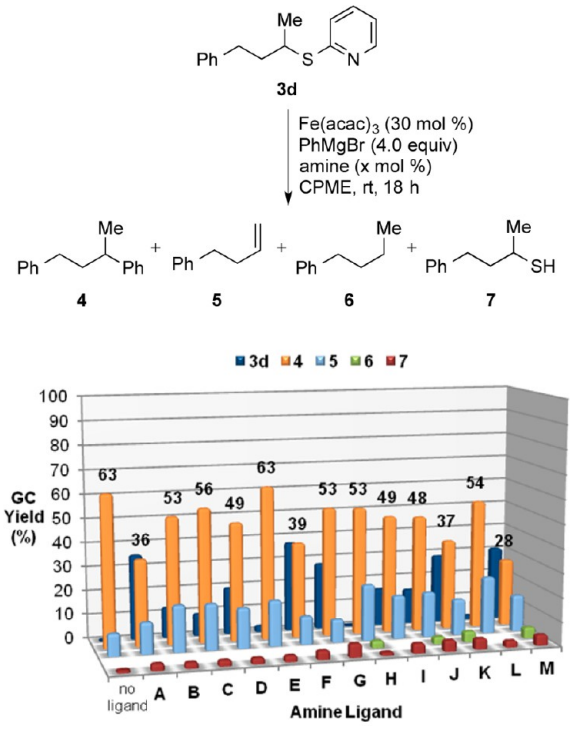


		GC yield (%)[a]				
entry	*T* (°C)	**3d**	**4**	**5**	**6**	**7**
1	0	42	33	16	n.d.[b]	3
2	rt	1	63	9	n.d.[b]	1
3	45	7	44	15	10	2

[a]Measured against tetradecane (0.5 equiv) as an internal standard. [b]The peak in the GC trace was obscured by peaks for small amounts of other unidentified compounds.

44% (GC), and the amounts of undesired products **5**–**7** increased relative to the reaction run at room temperature (Table 3, cf. entries 2 and 3). Accordingly, room temperature was maintained as the temperature of choice for further studies.

2.1.5. Evaluation of Ligands and Additives. Because tertiary amines such as TMEDA,[8a,e,f,i,k,o,w,54] Et_3N,[8f] DABCO,[8f] and HMTA (hexamethylenetetramine)[8k,l] have proved to be effective ligands in the iron-catalyzed cross-coupling of alkyl halides, the effect of amines on the cross-coupling reaction of 2-pyridyl thio ether **3d** was next assessed (Figure 3).



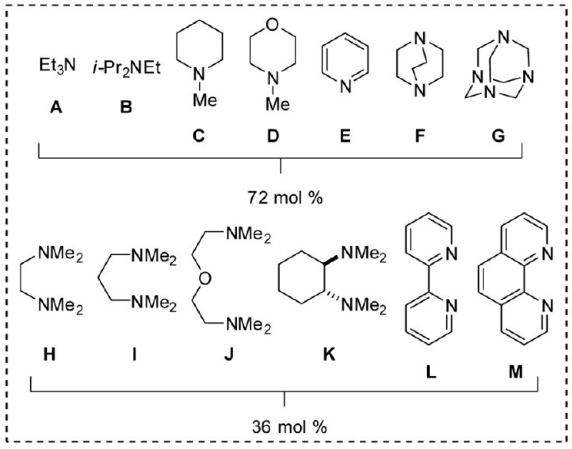


Figure 3. Evaluation of amine ligands. All yields were measured against tetradecane (0.5 equiv) as an internal standard.

Unfortunately, no further enhancement in the yield of product **4** was obtained for any of the amine ligands surveyed, and in many cases the amine proved detrimental to reactivity.[55]

Phosphine,[8h,j,v−x] phosphite,[8h] and NHC[8h,aa] ligands have also found application in the iron-catalyzed cross-coupling of alkyl halides, so a selection of these ligands was next assessed. Unfortunately, bidentate phosphines (dppm, dppe, dppp, dppf, and DPEphos [bis(2-diphenylphosphino)phenyl ether]) and $P(OPh)_3$ strongly suppressed the reaction, and both monodentate phosphines (PPh_3, PCy_3, and *t*-Bu XPhos [2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl]) and NHC ligands (SI*i*-Pr·HCl [1,3-diisopropylimidazolidinium chloride] and IMes·HCl [1,3-bis(2,4,6-trimethylphenyl)-3*H*-imidazol-1-ium chloride]) led to incomplete conversion and an attendant increase in the amount of alkene **5** (see the Supporting Information). Other additives employed in iron-catalyzed cross-coupling, including LiCl,[8t] CsF (as a fluoride source[56]), and 4-

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fluorostyrene,[8t] were also briefly evaluated but gave no enhancement.

2.1.6. Evaluation of the S-Aryl Group. With an optimized protocol in place for the $Fe(acac)_3$-catalyzed cross-coupling of 2-pyridyl thio ether **3d** with PhMgBr, the next phase focused on a reevaluation of the effect of the S-aryl group on the efficiency of the reaction. Thus, a variety of alkyl aryl thio ethers, **3b–m**, bearing a diverse range of aryl groups were combined with PhMgBr (4.0 equiv, either 2.74 or 3.04 M solution in Et_2O) and $Fe(acac)_3$ (30 mol %) in CPME at ambient temperature (Figure 4). For thio ethers **3b**, **3c**, and **3e** bearing simple fluorinated phenyl groups, conversion of starting material was low (≤10%), and the desired product **4** was obtained in yields of only 6–10% (GC). In view of the relatively efficient cross-coupling of 2-pyridyl thio ether **3d**, additional thio ethers **3f–m** bearing proximal nitrogen atoms were also tested under the cross-coupling conditions. Although none outperformed 2-pyridyl thio ether **3d**, all of the nitrogen-containing substrates, **3f–m**, proved superior to the thio ethers **3b**, **3c**, and **3e** bearing fluorinated phenyl groups, affording **4** in yields ranging from 20 to 59% (GC). In several cases, the alkyl thiol **7** derived from undesired cleavage of the $C(sp^2)$–S bond was formed as a significant byproduct.

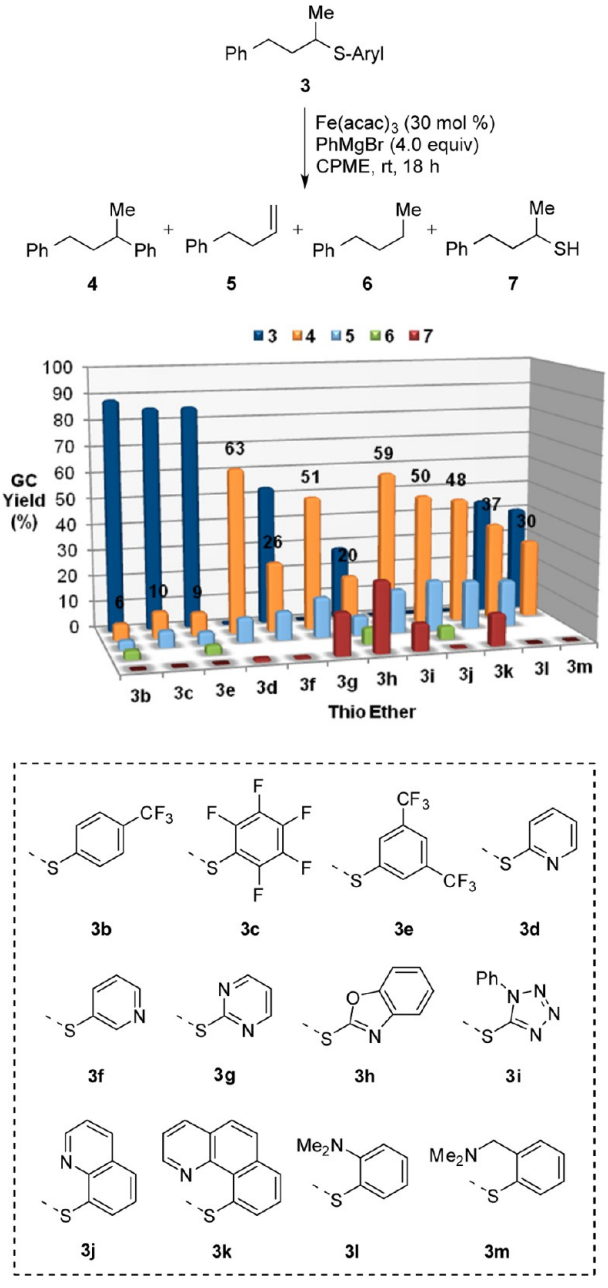

Figure 4. Evaluation of the S-aryl group. All yields were either measured against tetradecane (0.5 equiv) as an internal standard or estimated by integration in the ^1H NMR spectrum of the crude product mixture.

2.1.7. Preparative Scale Cross-Coupling. With the optimization phase complete, the cross-coupling of 2-pyridyl thio ether **3d** was executed on preparative scale (1.0 mmol) to obtain a yield of the isolated, cross-coupled product. To facilitate chromatographic separation of the product from the biaryl byproduct (derived from homocoupling of the Grignard reagent), PhMgBr was replaced with 4-methoxyphenylmagnesium bromide as the nucleophile. Thus, treatment of **3d** with 4-methoxyphenylmagnesium bromide (4.0 equiv, 2.17 M solution in Et_2O) and $Fe(acac)_3$ (30 mol %) in CPME at ambient temperature afforded **8** in 55% isolated yield (Scheme 4).

Scheme 4

2.2. Cross-Coupling of Alkyl Phenyl Sulfones. Although the cross-coupling of alkyl thio ethers developed thus far could potentially find use in the arylative functionalization of alkyl 2-pyridyl thio ethers generated by atom transfer radical additions of PTOC derivatives (PTOC = [(1*H*)-pyridine-2-thione]-oxycarbonyl),[57] we were motivated to remove the somewhat limiting requirement for a 2-pyridyl group on sulfur. Consequently, our attention turned to alkyl phenyl sulfones as alternative alkyl electrophiles, as these are readily accessible via oxidation of the corresponding thio ethers. Moreover, the phenyl sulfonyl group possesses a rich chemistry as an anion-stabilizing group in organic synthesis, facilitating alkylations, conjugate additions, and cycloadditions as well as other useful C–C bond-forming transformations.[58] Although a two-step alkylation–desulfonylation sequence has long been employed as a strategy to effect the net replacement of a sulfonyl group with an alkyl group,[59] the similar introduction of an aryl group cannot be achieved via this strategy. The obvious dilemma with alkyl sulfones as electrophiles for Kumada-type cross-coupling reactions is the possibility for competing deprotonation of the acidic α-protons flanking the $-SO_2Ph$ group [pK_a $PhSO_2Et$ = 31.0 in DMSO[40]] by the strongly basic Grignard reagents.[60]

2.2.1. Orienting Experiments. To ascertain the viability of alkyl phenyl sulfones as alkyl electrophiles for cross-coupling, sulfone **9** was subjected to the reaction conditions previously optimized for 2-pyridyl thio ether **3d**. Gratifyingly, 90% conversion of **9** occurred to give the desired product **4** in 48% yield (GC) in addition to alkene **5** in 19% yield (GC) as the major products (Scheme 5).[50]

2.2.2. Survey of Metal Salts as Catalysts. To determine whether or not $Fe(acac)_3$ is the most efficient catalyst for the cross-coupling of sulfone **9**, a variety of metal salts as catalysts were next surveyed (Figure 5). As for 2-pyridyl thio ether **3d**,

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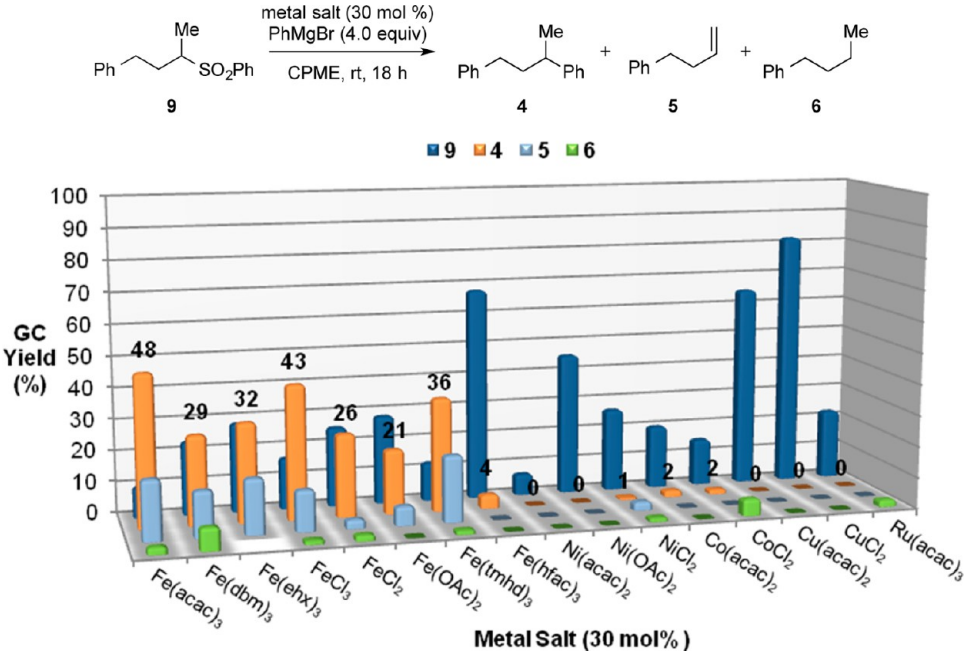
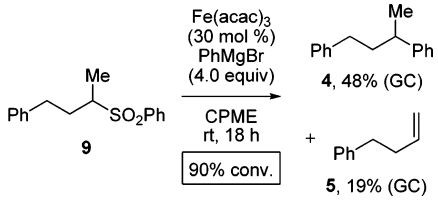


Figure 5. Survey of metal salts as catalysts. All yields were measured against tetradecane (0.5 equiv) as an internal standard. acac, acetylacetonate; dbm, dibenzoylmethane; ehx, 2-ethylhexanoate; tmhd, 2,2,6,6-tetramethyl-3,5-heptanedionate; and hfac, hexafluoroacetylacetonate.

iron salts proved uniquely effective in this transformation, and nickel-, cobalt-, copper-, or ruthenium-based catalysts gave little or no desired product **4**. $Fe(acac)_3$ proved optimal and was thus employed as the catalyst in all further studies.

Scheme 5



2.2.3. Evaluation of Reaction Solvent. The influence of the reaction solvent was also reinvestigated and, as was the case for 2-pyridyl thio ether **3d**, CPME was optimal (Figure 6). Notably, THF again proved detrimental, significantly promoting the formation of alkene **5**.

2.2.4. Evaluation of Amine Additives. Although the inclusion of ligands proved ineffective for the earlier cross-coupling of 2-pyridyl thio ether **3d**, a brief study of amine additives on the cross-coupling of sulfone **9** was next conducted. *N*-Methylmorpholine **10**, pyridine **11**, TMEDA **12**, and PMDETA (*N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine) **13** were selected as representative monodentate (aliphatic and aromatic), bidentate, and tridentate amine ligands, respectively. Thus, sulfone **9** was combined with PhMgBr (4.0 equiv, 2.87 M solution in Et_2O) and $Fe(acac)_3$ (30 mol %) in CPME at ambient temperature in the presence of the corresponding amine additive (at loadings of 1.0, 2.0, 5.0, and 10.0 equiv (wrt **9**)) (Figure 7).

Although *N*-methylmorpholine **10** and pyridine **11** had little influence regardless of loading, the effect of TMEDA **12** as an additive was striking. At lower loadings (1.0 to 2.0 equiv), the addition of TMEDA proved notably deleterious, promoting the

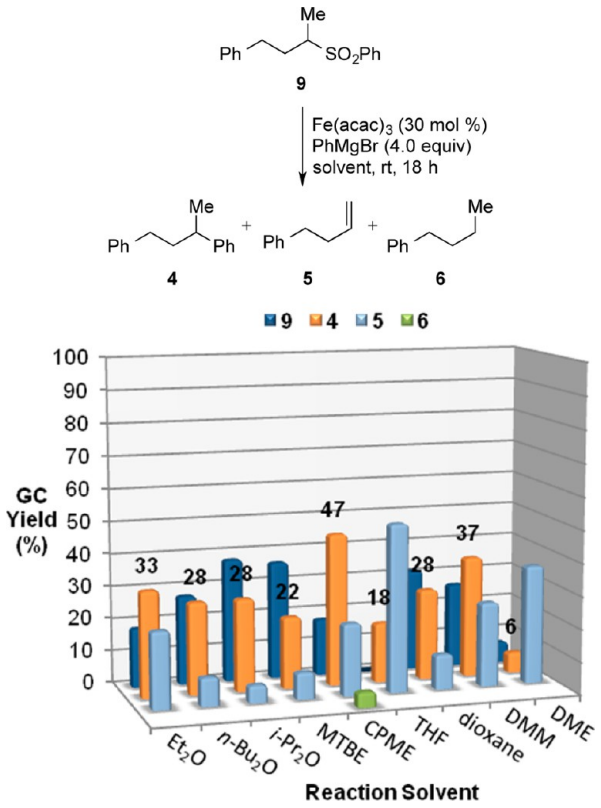


Figure 6. Evaluation of reaction solvent. All yields were measured against tetradecane (0.5 equiv) as an internal standard. MTBE, methyl *tert*-butyl ether; CPME, cyclopentyl methyl ether; DMM, dimethoxymethane; and DME, 1,2-dimethoxyethane.

formation of alkene **5**. However, the reaction began to recover at 5.0 equiv of TMEDA, and at 10 equiv of TMEDA, the yield of product **4** increased dramatically to 84% (GC). Satisfyingly, the yield of undesired alkene **5** was also reduced to only 2%

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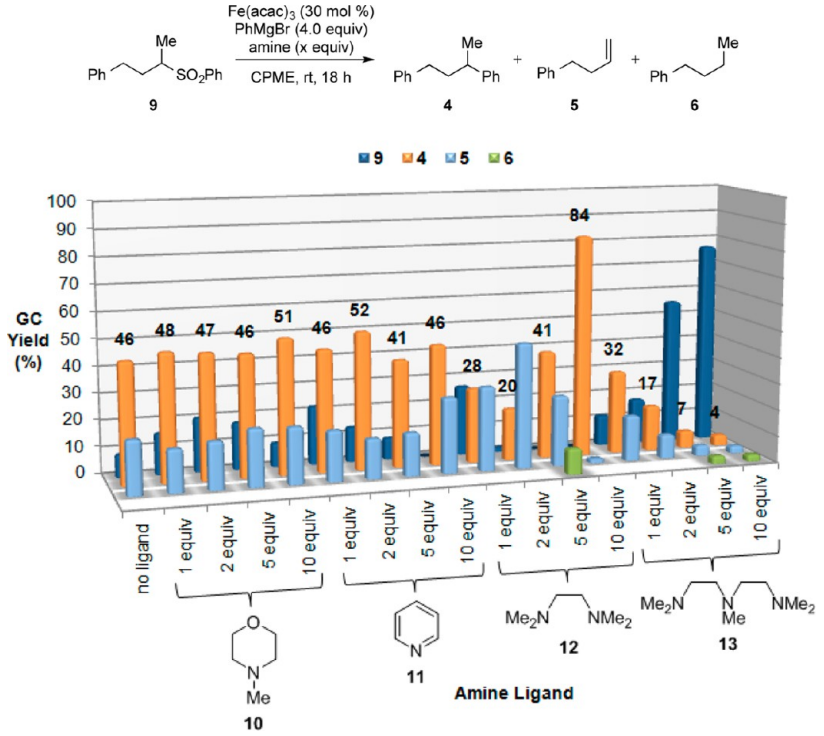

Figure 7. Evaluation of amine additives. All yields were measured against tetradecane (0.5 equiv) as an internal standard.

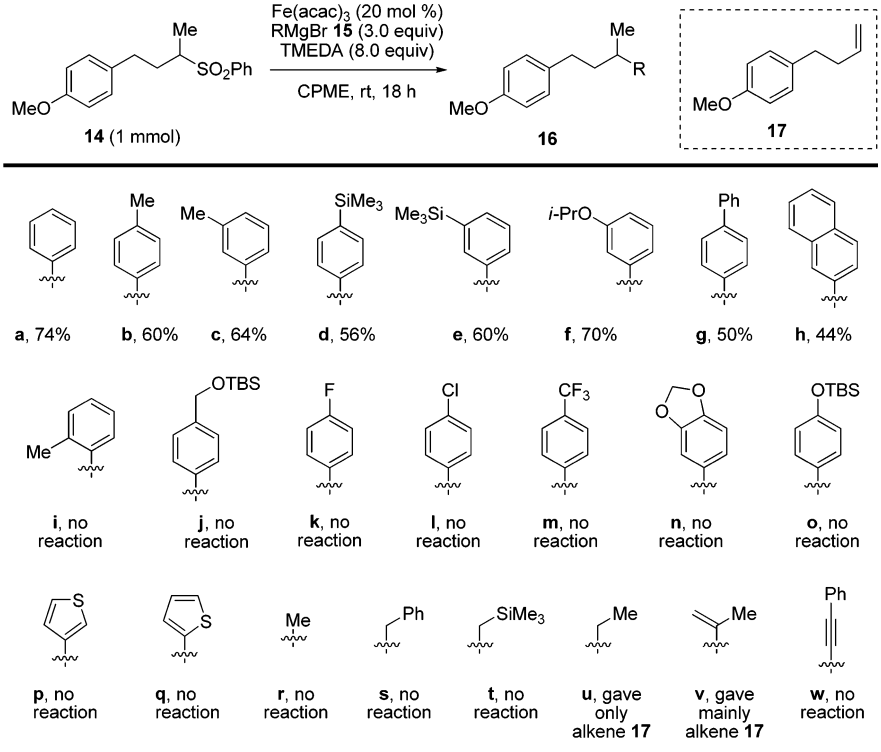

Figure 8. Scope of the organomagnesium nucleophile.

(GC). In contrast to TMEDA, the use of tridentate amine PMDETA **13** led to complete suppression of the reaction.

2.2.5. Reaction Scope. 2.2.5.1. Nucleophile. Following some final optimization experiments to lower the amounts of $Fe(acac)_3$, PhMgBr, and TMEDA (to 20 mol %, 3.0 equiv, and 8.0 equiv, respectively) (see the Supporting Information), the scope of the cross-coupling with respect to the Grignard nucleophile **15** was next established using sulfone **14** (1.00 mmol) as a representative substrate (Figure 8). In all cases, the Grignard reagent was employed in Et_2O solution. Other than PhMgBr (**15a**, 74% yield of **16a**), the reaction was also tolerant of electron-neutral aryl Grignard reagents bearing 4- or 3-substitution, including methyl groups (**15b,c**, 60−64% yield) or trimethylsilyl groups (**15d,e**, 56−60% yield). Notably, the

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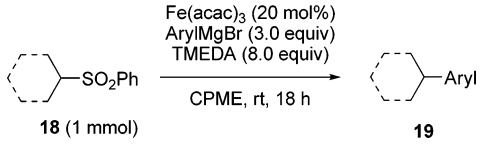
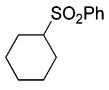
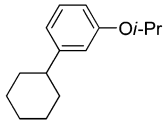
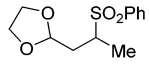
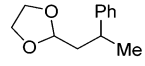
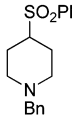
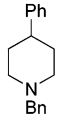
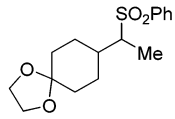
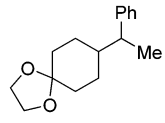
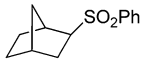
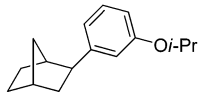
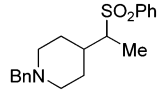
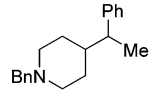
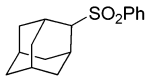
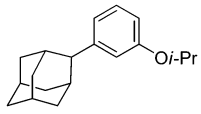
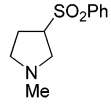
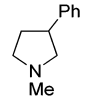
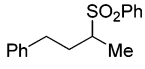
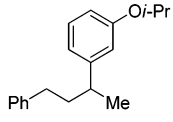
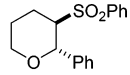
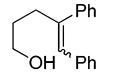
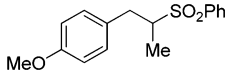
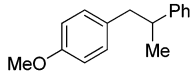
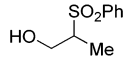
Table 4. Evaluation of Scope of the Sulfone Substrate



18 (1 mmol) **19**

entry	sulfone	product	entry	sulfone	product
1	 **18a**	 **19a**, 67%	7	 **18g**	 **19g**, 51%
2	 **18b**	 **19b**, 59%	8	 **18h**	 **19h**, 69%
3	 **18c**, >99:1 dr	 **19c**, 62%, 98:2 dr	9	 **18i**	 **19i**, 43%[b]
4	 **18d**	 **19d**, 66%	10	 **18j**	 **19j**, 25%
5	 **9**	 **19e**, 53%[a]	11	 **18k**, >99:1 dr	 **20**, not isolated[c]
6	 **18f**	 **19f**, 63%	12	 **18l**	no reaction[d]

[a]Contaminated with ~5% of 3-isopropoxybiphenyl. [b]Sacrificial purification was required to obtain analytically pure material. [c]Gave a mixture of products containing a ~4:1 ratio of starting material **18k** to 4,5-diphenylpent-4-en-1-ol **20** (configuration undetermined). [d]Returned starting material **18l** (note that an additional equivalent of PhMgBr was employed to deprotonate the hydroxyl group in **18l**).

trimethylsilyl moieties in products such as **16d,e** are highly versatile handles for various *ipso* functionalizations, including oxidation,[61] halogenation,[62] borylation,[63] sulfonylation,[64] nitration,[64a] acylation,[64b] or even the recently developed gold-catalyzed alkylation[65] or arylation[66] protocols. A 3-isopropoxyphenylmagnesium bromide nucleophile (**15f**)[67] also participated, affording the corresponding product **16f** in 70% yield; the isopropyl group can be readily removed to reveal the phenol from such products if desired.[68] Both 4-biphenyl (**15g**) and 2-naphthyl (**15h**) Grignard reagents also proved to be competent nucleophiles in the cross-coupling.[69] The reaction did, however, prove highly sensitive to steric effects, as both the 2-methyl (**15i**) and 4-(*tert*-butyldimethylsilyloxy)methyl (**15j**) substituted phenylmagnesium bromides returned unreacted starting material **14**. Moreover, Grignard reagents bearing electron-withdrawing (**15k−m**) or strongly electron-donating (**15n−o**)[70] 4-substituents failed to react. The origin of these steric and electronic effects is not clear at the present time, especially because several of the unreactive Grignard reagents (**15i** and **15k−m**) have been used successfully in similar iron-catalyzed couplings of alkyl halides.[8a−c,m,t,u,aa] Although alkyl (**15r−u**), alkenyl (**15v**), and alkynyl (**15w**) Grignard reagents were also briefly investigated, these gave either no reaction (**15r−t** and **15w**) or led to predominant or even exclusive formation of the *β*-hydride elimination product **17** (**15u** and **15v**).

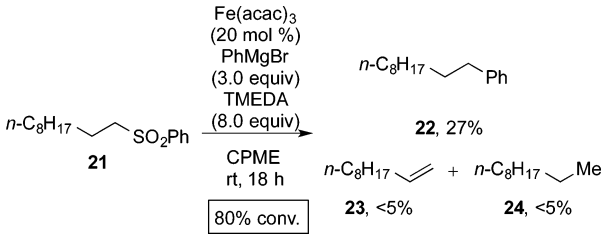
2.2.5.2. Sulfone Substrate. The scope of the reaction with respect to the secondary alkyl phenyl sulfone coupling partner **18** was next assessed (Table 4). Although the functional group compatibility is inherently restricted because of the use of Grignard reagents at ambient temperature, tertiary amino groups (**18b** and **18i**) and acetals (**18g** and **18h**) were well-tolerated. As evidenced by the cross-coupling of substrates **18c−d** and **18h−i**, branching at the adjacent carbon(s) does

dx.doi.org/10.1021/jo402246h | J. Org. Chem. 2013, 78, 12593−12628

not impede the reaction. Notably, with norbornyl substrate **18c**, the reaction proceeded with excellent diastereoselectivity (98:2 *exo/endo*). Homobenzylic sulfone **18f** was cross-coupled uneventfully despite the anticipated potential for β-hydride elimination to generate a conjugated alkene. Unfortunately, β-heteroatoms on the sulfone substrate were poorly tolerated (**18j–l**), although pyrrolidine **18j** did afford a low yield (25%) of desired product **9j**. In the case of tetrahydropyran substrate **18k**, the reaction returned a ~4:1 mixture of starting material **18k** to 4,5-diphenylpent-4-en-1-ol **20** (configuration undetermined).

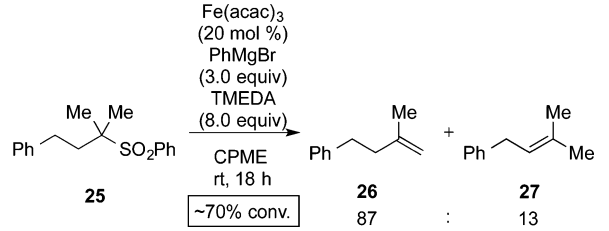
To examine whether primary sulfones are viable substrates for the cross-coupling reaction, **21** was subjected to the optimized reaction conditions with PhMgBr as the nucleophile. However, the reaction did not prove synthetically useful and led to incomplete (80%) conversion of **21** to give product **22** in only 27% yield (GC) along with trace amounts (<5%) of alkene **23** and alkane **24**, accounting for <45% of the mass balance (Scheme 6). The remainder of the mass comprised a complex mixture of unidentified products that were insufficiently volatile to detect under the GC conditions employed.

Scheme 6



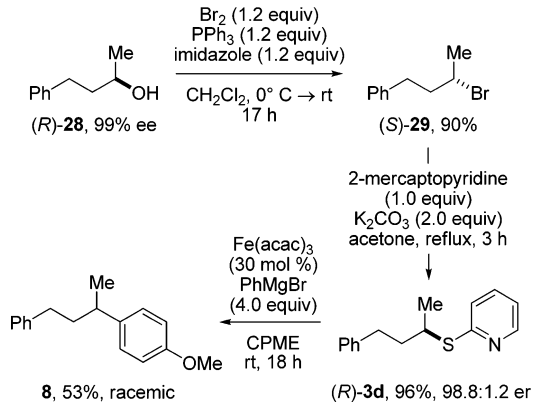
Similarly, to determine whether tertiary sulfones are competent electrophiles, **25** was subjected to the optimized reaction conditions, again with PhMgBr as the nucleophile. Under these conditions, ~70% conversion of **25** occurred to give a 87:13 mixture of alkenes **26** and **27**, respectively, and no peaks consistent with the desired cross-coupled product were observed by ^{1}H NMR spectroscopy (Scheme 7).

Scheme 7



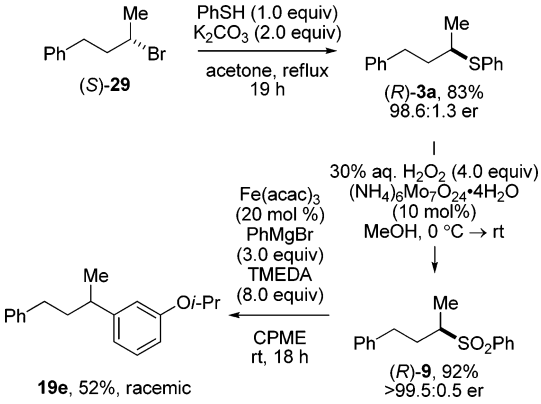
2.3. Mechanistic Investigations. *2.3.1. Stereochemical Course of the Cross-Coupling of Alkyl 2-Pyridyl Thio Ether **3d**.* To ascertain the stereochemical course of the cross-coupling reaction of alkyl 2-pyridyl thio ether **3d**, an enantioenriched sample of (*R*)-**3d** (98.8:1.2 er) was prepared in a two-step bromination-displacement sequence from commercially available (*R*)-4-phenylbutan-2-ol **28**. Following subjection to the optimized reaction conditions with 4-methoxyphenylmagnesium bromide as the nucleophile, product **8** was isolated in 53% yield and found to be racemic (Scheme 8).

Scheme 8



2.3.2. Stereochemical Course of the Cross-Coupling of Secondary Alkyl Phenyl Sulfones. The stereochemical course of the cross-coupling of secondary alkyl phenyl sulfones was next assessed. An enantiopure sample of sulfone (*R*)-**9** (>99.5:0.5 er) was first prepared from bromide (*S*)-**29** via a thiolate displacement-oxidation sequence. Cross-coupling of sulfone (*R*)-**9** with 3-isopropoxyphenylmagnesium bromide under the optimized conditions then gave **19e** in 52% isolated yield as a racemic mixture (Scheme 9).

Scheme 9



3. DISCUSSION

3.1. Cross-Coupling of Alkyl Aryl Thio Ethers. *3.1.1. Effect of the S-Aryl Group.* The nature of the S-aryl group of alkyl aryl thio ether substrates **3** proved critical in enabling oxidative addition of the low-valent iron species to the C(sp^3)–S bond. The original hypothesis supposed that electron-deficient S-aryl groups may facilitate the oxidative addition step by polarizing the C(sp^3)–S bond; however, thio ethers **3b**, **3c**, and **3e** bearing simple fluorinated phenyl groups on sulfur showed little reactivity under the optimized conditions (≤10% conversion of **3** to give **4** in yields of 6–10% by GC). Unexpectedly, substrate **3d** bearing a 2-pyridylthio group underwent efficient cross-coupling under the same conditions (63% yield of **4** by GC). This result suggests the possibility of an oxidative addition of the C(sp^3)–S bond to the iron center that may be assisted by coordination of the 2-pyridyl group of **3d** to the metal, rendering the process pseudointramolecular. Notably, the 2-pyridyl group has been employed in a similar role for the oxidative addition of

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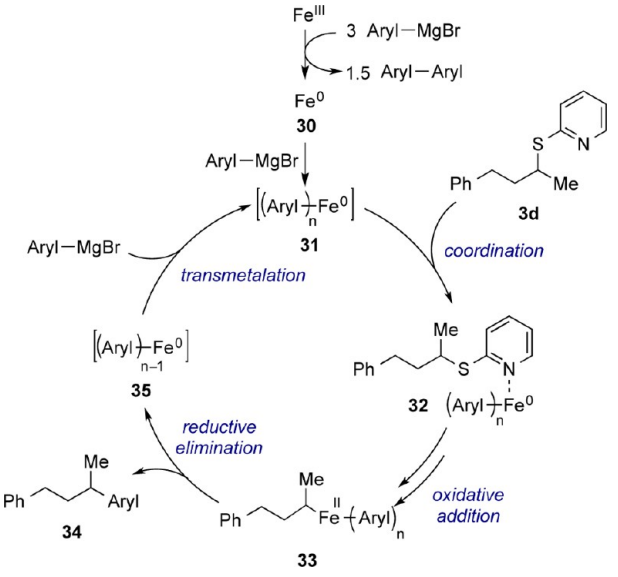
unactivated C(sp^3)−O bonds of alkyl 2-pyridyl ethers to ruthenium[71] or iridium[72] complexes. In addition, a 2-pyrimidyl group on sulfur was beneficial in the iron-catalyzed cross-coupling of alkenyl thio ethers with aryl Grignard reagents.[73] Interestingly, thio ethers **3g** and **3i**−**k** bearing proximal pyridyl-type nitrogen atoms on the S-aryl moiety also showed significant competence in the cross-coupling with PhMgBr (48−59% yield of **4** by GC). Even the electron-rich thio ethers **3l** and **3m** bearing proximal dimethylamino groups proved relatively efficient as electrophiles (30−37% yield of **4** by GC), at least when compared to thio ethers **3b**, **3c**, and **3e** bearing simple fluorinated phenyl groups (6−10% yield of **4** by GC). Notably, 3-pyridyl thio ether **3f**, in which the pyridyl nitrogen atom is less well disposed to steer the iron center toward the C(sp^3)−S bond, displayed significantly lower reactivity than its 2-pyridyl counterpart **3d** (26% of **4** for **3f** versus 63% for **3d**). Taken together, these results lend credence to the notion that the "directing effect" of a proximal nitrogen atom on the S-aryl group is indeed key to reaction efficiency.

3.1.2. Speculation on the Mechanism. Any mechanistic proposal for iron-catalyzed cross-coupling reactions of Grignard reagents must be tempered with the caveat that the oxidation states of the low-valent catalytic species are obscure in many cases and are likely to be dependent on the precise reaction conditions as well as the presence of ligands or other additives.[7] On the basis of extensive studies of characterized, low-valent organoiron species, Fürstner has proposed that an Fe(0)/Fe(II^-) catalytic manifold is likely operative in low-temperature cross-coupling reactions employing alkyl Grignard reagents bearing β-hydrogens.[8m,74] However, in the case of aryl Grignard reagents, there is no conclusive evidence that oxidation states as low as Fe(II^-) are kinetically accessible from Fe(II) or Fe(III) precatalysts under the conditions generally employed in preparative cross-coupling reactions. An Fe(I)/Fe(III) catalytic cycle, originally proposed by Kochi on the basis of byproduct analysis and EPR measurements,[75] has been suggested to be the most plausible pathway (at least under the specific reaction conditions) in the cross-coupling of alkyl halides[76] and aryl halides[77] with alkyl Grignard reagents and benzyl halides with arylzinc reagents.[78] An Fe(II)/Fe(III) catalytic cycle for the cross-coupling of aryl Grignard reagents with alkyl halides in the presence of TMEDA has also found experimental support in studies of isolated organoiron species.[54] This catalytic manifold has similarly been invoked in related couplings of arylborates[8r] and alkynyl Grignard reagents[8v] on the basis that nucleophile homocoupling products were not observed when using Fe(II) precatalysts.[8r,v] Although soluble Fe(0) species have seldom been postulated to be the active agents in iron-catalyzed couplings of aryl Grignard reagents with alkyl halides,[8k,79] Bedford and co-workers have clearly demonstrated that Fe(0) nanoparticles are produced from the reduction of $FeCl_3$-dpph or $FeCl_3$−PEG (PEG = poly(ethylene glycol)) with 4-tolylmagnesium bromide and that they are catalytically active in the cross-coupling of alkyl halides.[8g] However, the possibility that the nanoparticles served merely as a reservoir for catalytically active, soluble Fe(0) species could not be ruled out. Similarly, Krafft and Holton have shown that the addition of 3.0 equiv of MeMgBr to $FeCl_3$ in Et_2O leads initially to a finely divided black powder (speculated to be $Me_2Fe(II)L_n$), which, over the course of 1 h at room temperature, undergoes decomposition to Fe(0) (as characterized by elemental analysis and titration with potassium chromate).[80] Similarly, solutions of Fe(III) salts, including $FeCl_3$ and Fe(acac)$_3$, in THF solution at room temperature are reduced to Fe(0) nanoparticles upon treatment with various Grignard reagents (3.0 equiv), including EtMgBr and PhMgBr.[81]

On the basis of these observations and the fact that reaction mixtures in this study rapidly turn black on addition of the aryl Grignard reagent, it is proposed that the Fe(acac)$_3$ precatalyst in the cross-coupling of thio ether **3d** is initially reduced by the aryl Grignard reagent to Fe(0) nanoparticles (Scheme 10).[82] The Fe(0) species **30**, whether part of a nanocluster or a soluble, mononuclear Fe(0) complex, may then react further with the arylmagnesium reagent to give a catalytically active Fe(0)(aryl)$_n$ ferrate species **31**. Notably, a homoleptic Fe(0) ferrate species [$Ph_4Fe(0)$][$Li(OEt_2)$]$_4$, prepared from the reaction of $FeCl_3$ with excess PhLi in Et_2O at low temperature, has been isolated and characterized by X-ray crystallography and shown to be active in the reduction of N_2, possibly by precomplexation of the π-acceptor N_2 molecule to the iron center.[83] Following the generation of the catalytically active Fe(0)(aryl)$_n$ ferrate species **31**, coordination of the thio ether substrate **3d** through the pyridyl nitrogen atom may give adduct **32**. Oxidative addition of the C(sp^3)−S bond to the iron center (vide infra) could then generate Fe(II) species **33**, which would suffer reductive elimination to afford the product **34** and furnish an Fe(0)(aryl)$_{n-1}$ species **35**. Finally, arylation of **35** by the aryl Grignard reagent would regenerate the active catalyst species **31**.

Scheme 10



The catalytic cycle in Scheme 10 does not address the elementary steps in the crucial oxidative addition, and there are several scenarios by which this may proceed (Scheme 11). One possibility, depicted in route a, is that a directed C(sp^3)−H bond activation may occur from adduct **32** to furnish a cyclometalated species **36**. Following α-elimination of the thiolato group to produce an iron carbene **37**, a 1,2-hydride shift could give the alkyliron intermediate **33**, which is primed for reductive elimination to the product **34**. An analogous pathway is probably operative in the (formal) oxidative addition of the unactivated C(sp^3)−O bonds of alkyl 2-pyridyl ethers to ruthenium[71] or iridium[72] and finds its origin in studies on the activation of the C(sp^3)−O bond of anisole with iridium pincer complexes.[84] An alternative scenario is an inner-sphere electron

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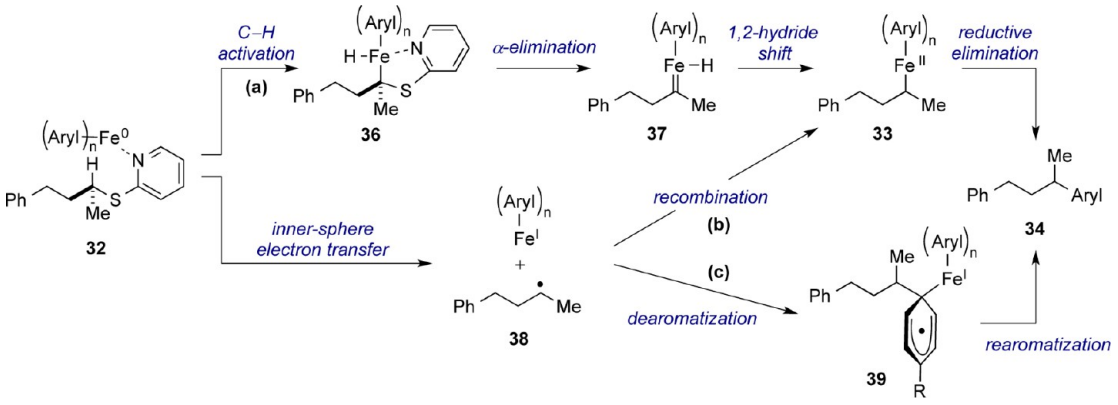
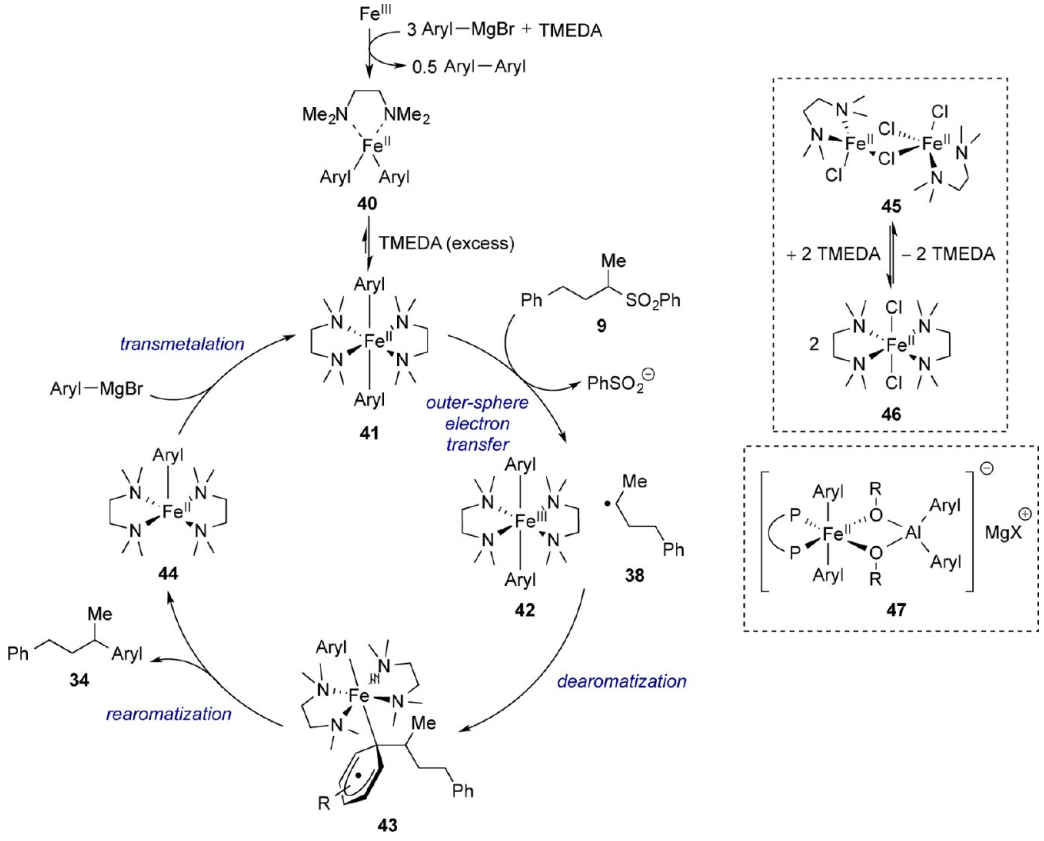
Scheme 11



Scheme 12



transfer from the iron center to (presumably) the π^* orbital of the pyridine ring within adduct **32**, initiating C(sp^3)–S bond cleavage to give a transient alkyl radical **38**, which undergoes recombination with the iron center (route b), affording the same alkyliron intermediate **33** as route a. Alternatively, the alkyl radical **38** could potentially attack the arene ring attached to iron to generate cyclohexadienyl radical **39** followed by rearomatization by loss of the metal fragment (route c).[8r,x,aa] There is a general consensus, on the basis of stereochemical studies and radical clock experiments, that the oxidative addition of alkyl halides with low-valent iron species follows a radical-based oxidative addition pathway. However, our finding that the cross-coupling of enantiopure (*R*)-**3d** proceeds with complete racemization does not allow distinction between any of the aforementioned pathways, although it does argue against a concerted oxidative addition step, which should be highly enantiospecific.[85]

A final point to make concerns catalyst deactivation, and this is likely the origin of the rather high loading of $Fe(acac)_3$ (30 mol %) as well as the large excess of Grignard reagent (4.0 equiv) required in the cross-coupling of **3d**. Oligomerization of low-valent iron has been proposed as a possible deactivation pathway in iron-catalyzed cross-coupling,[75c] and it has been suggested that more reactive electrophiles (i.e., faster oxidative addition) or appropriate stabilizing ligands/additives can serve to minimize the unproductive aggregation of the low-valent iron species.[77] In the present case, it may be that the relatively unreactive nature of thio ether **3d** (with respect to alkyl halides) and the lack of a stabilizing ligand/additive may serve to enable catalyst deactivation.

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3.2. Cross-Coupling of Alkyl Phenyl Sulfones.

3.2.1. Speculation on the Mechanism. A plausible catalytic cycle for the $Fe(acac)_3$-catalyzed cross-coupling of sulfone **9** with an aryl Grignard reagent in the presence of excess TMEDA is depicted in Scheme 12. On the basis of studies by Nakamura and co-workers,[54] it is possible that reduction of the $Fe(acac)_3$ precatalyst with an aryl Grignard reagent in the presence of TMEDA gives (TMEDA)Fe(II)$aryl_2$ **40** as the initial low-valent iron species. Similarly, Sen and co-workers have observed (TMEDA)Fe(II)Bn_2 as an intermediate during coupling reactions of benzyl halides mediated by [CpFe(0)(COD)][Li(TMEDA)].[86] It should be noted that many other examples of bidentate ligands, often nitrogen-based, are known to stabilize Fe(II)$alkyl_2$ species against reductive elimination to Fe(0).[87,88] In the present case, the requirement for such a large excess (8.0 equiv) of TMEDA in the cross-coupling of sulfone **9** as well as notable reactivity differences with certain aryl Grignard reagents suggests that the catalytic cycle deviates from that put forward by Nakamura for the coupling of alkyl halides. It is thus proposed that (TMEDA)Fe(II)$aryl_2$ **40** undergoes reversible association with a second molecule of TMEDA to generate a more electron-rich species, *trans*-$(TMEDA)_2$Fe(II)-$aryl_2$ **41**. Similar dicomplexes of Fe(II) with TMEDA are known: *trans*-$[FeCl_2(TMEDA)_2]$ has been characterized by X-ray crystallography and shown to be unstable with respect to the binuclear complex $[\{FeCl(TMEDA)\}_2(\mu\text{-}Cl)_2]$ **45** except in the presence of an excess of TMEDA.[89] Similarly, *cis*-(2,2′-bipy)$_2$Fe(II)Et_2 has been isolated and characterized by X-ray crystallography.[87b,90]

Coordinatively saturated complex **41** could then engage sulfone **9** by an outer-sphere electron transfer (presumably to the π^* orbital of the SO_2Ph moiety) to generate a transient radical anion that collapses to alkyl radical **38** and a phenylsulfinate anion; this radical could then attack the arene ligand on iron in an *ipso*-substitution reaction[8r,x,aa] to afford a cyclohexadienyl radical **43**, which would then expel the iron fragment **44** and furnish the product **34**. A very similar catalytic cycle has been proposed by Nakamura and co-workers in their iron-catalyzed cross-coupling of halohydrins with aryl aluminum reagents: specifically, the ferrate intermediate **47** was suggested to be the active species that transfers an electron to the halide,[8x] and this intermediate is directly analogous to **41** in this catalytic cycle. This mechanistic proposal is consistent with the fact that enantiopure (*R*)-**9** undergoes cross-coupling with 3-isopropoxyphenylmagnesium bromide to give **19e** as a racemic mixture.

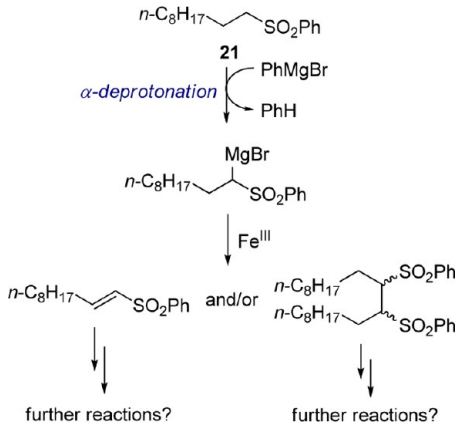
The requirement for such a large excess (8.0 equiv) of TMEDA in the cross-coupling reaction is intriguing. Although TMEDA is a crucial additive in some previously reported iron-catalyzed cross-couplings of alkyl halides with Grignard reagents,[8a,e,f,i,k,o,w,54] its role in the reaction is not always clear. The large excess required in this case is likely a consequence of interaction with PhMgBr as well as the iron species, and PhMgBr with TMEDA in THF-d_8 has been shown to afford a mixture of PhMgBr(TMEDA), Ph_2Mg(TMEDA), and $MgBr_2(TMEDA)_n(THF)_{2-n}$ (n = 1 or 2).[54] According to the current mechanistic hypothesis, the catalytically active intermediate **41** can be generated only in the presence of excess (i.e., free) TMEDA, and, for this to be possible, the PhMgBr (and Ph_2Mg and $MgBr_2$) must first be saturated with TMEDA.

3.2.2. Scope of the Nucleophile. Although the cross-coupling reaction was successfully performed with a variety of electron-neutral 3- and 4-substituted aryl Grignard reagents, **15a**–**h**, the use of sterically encumbered nucleophiles **15i** and **15j** or those bearing electron-withdrawing (**15k**–**m**) or strongly electron-donating (**15n**–**o**) 4-substituents led to no reaction. The catalytic cycle proposed in Scheme 12 does not allow a rationalization of these particular results. However, it is clear that an intermediate like **41** derived from nonaromatic Grignard reagents could not react productively with alkyl radical **38**, which may be the reason that alkyl (**15r**–**t**), alkenyl (**15v**), and alkynyl (**15w**) nucleophiles do not react. In the case of alkyl Grignard reagents bearing β-hydrogens, reduction of the iron to oxidation states as low as Fe(II$^-$) becomes possible,[8m,74] and this may be why EtMgBr (**15u**) leads to complete consumption of the sulfone **14**, albeit to give the β-hydride elimination product **17**.

3.2.3. Scope of the Sulfone Substrate. Although the cross-coupling reaction proved applicable to a variety of unactivated, secondary alkyl phenyl sulfones (Table 4, entries 1–10), the reaction was largely unsuccessful with substrates bearing β-heteroatom substituents (Table 4, entries 10–13). Only in the case of pyrrolidine sulfone **18j** could any cross-coupling product be isolated (25% of **19j**). For tetrahydropyran sulfone **18k**, the major product, which was not isolated in pure form, was 4,5-diphenylpent-4-en-1-ol **20** of unassigned configuration. This compound presumably arises from an $E1_{cB}$ elimination process followed by cross-coupling of the resultant vinyl sulfone with PhMgBr.[32]

With respect to the poor cross-coupling efficiency and low mass balance in the reaction of primary sulfones such as **21**, it is likely that α-deprotonation of the primary sulfone (which is both kinetically and thermodynamically more acidic than a similar secondary sulfone) by the PhMgBr is occurring[60] followed by oxidation of the resultant carbanion by Fe(III) to give a variety of possible products, including vinyl sulfones or dimeric products such as vicinal disulfones or symmetrical alkenes[91] (Scheme 13). These initial sulfone byproducts could then undergo further reaction (e.g., cross-coupling) under the reaction conditions, accounting for the complex mixture. This undesired α-deprotonation process may also account for the incomplete mass balance (88%) observed in the cross-coupling of secondary sulfone **9** under the optimized conditions (see data in the Supporting Information), implying that this side reaction is operative, albeit to a much lesser extent, in the coupling of secondary alkyl sulfones.

Scheme 13



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4. CONCLUSIONS AND OUTLOOK

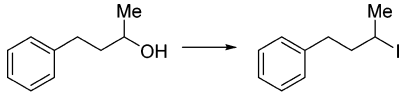
This study chronicles the first attempts to explore systematically the potential of unactivated aliphatic sulfur compounds as electrophiles in transition-metal-catalyzed cross-coupling. The first phase of the investigation focused on discerning the structural and electronic features of the alkyl sulfur substrate that enable the difficult oxidative addition to the C(sp^3)−S bond in an iron-catalyzed cross-coupling of unactivated alkyl aryl thio ethers **3** with aryl Grignard reagents. Through extensive optimization efforts, a critical role of a nitrogen "directing group" on the S-aryl moiety of thio ethers **3** was uncovered, which served to facilitate the crucial oxidative addition step. Thus, employing 2-pyridyl thio ether **3d** as the electrophile, PhMgBr as the nucleophile, and $Fe(acac)_3$ as the catalyst, the first example of the cross-coupling of an unactivated alkyl aryl thio ether was achieved. In addition, alkyl phenyl sulfones were found to be effective electrophiles in the $Fe(acac)_3$-catalyzed cross-coupling with aryl Grignard reagents. A thorough assessment of the various reaction parameters revealed a dramatic enhancement in reaction efficiency with an excess of TMEDA (8.0 equiv). The optimized reaction protocol was used to evaluate the scope of the method with respect to both the Grignard nucleophile and sulfone electrophile.

Although the motivation behind this work was principally the development of a new cross-coupling process, it was essential to draw upon existing mechanistic studies of the iron-catalyzed cross-coupling of alkyl halides to present plausible (albeit speculative) reaction mechanisms and catalytic cycles for the new reactions. In light of the myriad challenges accompanying the study of processes mediated by low-valent iron species, a deeper understanding of the mechanistic underpinnings of the reactions described herein would necessarily be the focus of an independent investigation, and future efforts are currently directed toward this goal.

5. EXPERIMENTAL SECTION

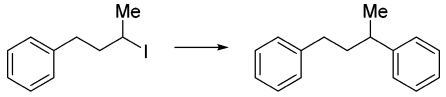
5.1. General Procedures. *General Procedure 1 for Cross-Coupling of Secondary Alkyl Phenyl Sulfones.* An oven-dried, 25 mL, one-necked, round-bottomed flask was charged with the requisite sulfone (1.00 mmol, 1.0 equiv) and $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %) in a glovebox and was then sealed with a rubber septum and removed from the box. Outside of the glovebox, a 25 mL Schlenk flask equipped with a stirrer bar, rubber septum, and argon inlet was evacuated, flame-dried, left to cool under vacuum, and flushed three times with argon. TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv) was added via syringe to the Schlenk flask, and stirring was commenced. The round-bottomed flask containing the sulfone and $Fe(acac)_3$ was charged with CPME (4.0 mL) and then sonicated until homogeneous. The clear red solution was then transferred via cannula to the Schlenk flask holding the TMEDA, and the residual material was rinsed across with further portions of CPME (6.0 mL). The requisite aryl Grignard reagent (solution in Et_2O, 3.00 mmol, 3.0 equiv) was then added by syringe over ca. 30 s. During addition, the color of the solution changed from red to pale-yellow to brown but remained clear throughout, and no visible deposits were formed on the edges of the flask. After stirring for 18 h at rt, 1 M HCl(aq) (10 mL) was added in one portion, and the mixture was filtered through a pad of Celite (5 g) in a 40 mm Ø, porosity 3, sintered funnel under house vacuum. EtOAc (2 × 5 mL) was used to rinse any residual material though the Celite pad. The filtrate was transferred to a separatory funnel, and the layers were separated. The organic layer was washed with 1 M HCl(aq) (2 × 10 mL), and the combined aqueous layers were extracted with EtOAc (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg).

5.2. Preparation of Authentic Samples.



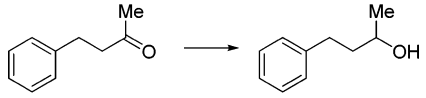
28 **48**

*Preparation of (rac)-(3-Iodobutyl)benzeze (**48**).* A 25 mL, one-necked, round-bottomed flask equipped with a stirrer bar, rubber septum, and argon inlet was charged with **28** (98%, 613 mg, 627 μL, 4.00 mmol), triphenylphosphine (1.59 g, 6.00 mmol), imidazole (413 mg, 6.00 mmol) and CH_2Cl_2 (8.0 mL), and stirring was commenced. The resultant mixture was then cooled in an ice/water bath, and iodine (1.52 g, 6.00 mmol) was added in one portion. The mixture was allowed to warm to rt over 2 h, and pentane (25 mL) was added. The mixture was then rinsed through a pad of neutral alumina (5 g) using minimal pentane and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a colorless oil (1.05 g). Purification via short-path distillation under reduced pressure (0.5 mmHg) gave **48** as a clear, colorless oil (773 mg, 74%). The ^{1}H NMR spectroscopic data and boiling point matched that for alternative preparations.[92] Data for **48**: bp 104−105 °C (0.5 mmHg).



48 **4**

*Preparation of (rac)-1,1′-(1-Methyl-1,3-propanediyl)bisbenzene (**4**).* This preparation is based on a previously reported method for the iron-catalyzed cross-coupling of aryl Grignard reagents with alkyl halides.[8f] In a glovebox, $FeCl_3$ (16.2 mg, 10 mol %) was added to a flame-dried, 20 mL scintillation vial, which was then sealed with a rubber septum and removed from the box. CH_2Cl_2 (2.0 mL) and TMEDA (11.6 mg, 15.0 μL, 0.10 mmol) were added sequentially via syringe to give a rust-colored suspension of black $FeCl_3$, and the solvent was removed in vacuo (50 °C, ca. 5 mmHg) to give a rust-colored solid residue. Et_2O (3.0 mL) was then added to give a suspension of the latter solid. **48** (260 mg, 178 μL, 1.00 mmol) was added via syringe followed by dropwise addition of PhMgBr (2.70 M in Et_2O, 742 μL, 2.00 mmol). A significant exotherm occurred, and some of the Et_2O evaporated. The reaction mixture was transferred via syringe to a flame-dried, 10 mL, round-bottomed flask equipped with a stirrer bar and reflux condenser, and the residual mixture was rinsed across with an additional portion of Et_2O (0.5 mL). The mixture was then heated at reflux for 30 min and then quenched by addition of H_2O (5 mL). The mixture was rinsed through a pad of Celite (5 g) using minimal EtOAc, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 5 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a yellow oil (223 mg). Purification via flash column chromatography (30 g of SiO_2, 30 mm Ø, hexane, ca. 5 mL fractions) gave **4** as a clear, colorless oil (121 mg, 57%). The ^{1}H NMR spectroscopic data matched that for alternative preparations.[8aa] Data for **4**: GC: t_R 3.82 min.



28

*Preparation of (rac)-4-Phenyl-2-butanol (**28**).* A 1 L, one-necked, round-bottomed flask equipped with a stirrer bar and rubber septum was charged with 4-phenylbutan-2-one (25.0 g, 165 mmol, 1.0 equiv) and MeOH (400 mL), and stirring was commenced. The mixture was cooled to 4 °C in an ice/water bath, and then sodium borohydride (6.88 g, 182 mmol, 1.1 equiv) was added portionwise (the internal temperature did not exceed 17 °C). The resultant turbid, colorless mixture was stirred in the ice/water bath for 20 min and then allowed to warm to rt over 65 h. The mixture was then concentrated in vacuo (50 °C, ca. 5 mmHg) and partitioned between EtOAc (200 mL) and

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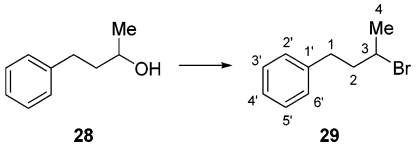
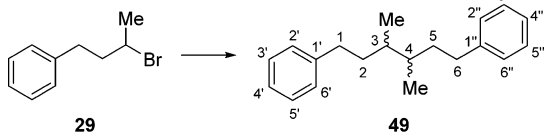
H_2O (200 mL). The layers were separated, the aqueous layer was extracted with EtOAc (2 × 100 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a cloudy, colorless oil (25.3 g). Purification via short-path distillation under reduced pressure (0.5 mmHg) gave **28** as a clear, colorless oil (24.3 g, 98%). The ^{1}H NMR spectroscopic data and boiling point matched that for alternative preparations.[93] Data for **28**: bp 77−78 °C (0.5 mmHg) [lit.[94] 75 °C (0.3 mmHg)].



28 **29**

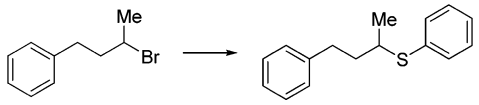
*Preparation of (rac)-(3-Bromobutyl)benzene (**29**).* Bromine (11.6 g, 3.70 mL, 72.0 mmol, 1.2 equiv) was added dropwise from a 5 mL measuring cylinder by Pasteur pipet to a stirred suspension of triphenylphosphine (19.08 g, 72.0 mmol, 1.2 equiv) in CH_2Cl_2 (200 mL) in a 1 L, single-necked, round-bottomed flask equipped with a stirrer bar and cooled in an ice/water bath (open to air). The flask was then sealed with a rubber septum and purged with argon via an inlet needle. After stirring the resultant pale-yellow suspension for 15 min, a solution of **28** (9.01 g, 60.0 mmol, 1.0 equiv) and imidazole (4.95 g, 72.0 mmol, 1.2 equiv) in CH_2Cl_2 (100 mL) was added via cannula over ca. 5 min. The cooling bath was removed, and the reaction mixture was allowed to warm to rt over 27 h. The mixture was then filtered through a 40 mm Ø, porosity 3, sintered funnel under house vacuum and carefully concentrated in vacuo to leave a yellow oil residue (i.e., avoiding precipitating the phosphorus-containing residues at this point). A stirrer bar was added to the residue, a wide-neck plastic funnel was added to the neck of the flask, and rapid stirring was commenced. Pentane (300 mL) was quickly added in one portion to precipitate the phosphorus-containing residues as a fine white solid. The mixture was filtered through a 40 mm Ø, porosity 3, sintered funnel under house vacuum and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a clear, colorless oil (14.26 g). Purification via short-path distillation under reduced pressure (0.5 mmHg) gave **29** as a clear, colorless oil (11.58 g, 91%). The ^{1}H NMR spectroscopic data and boiling point matched that for alternative preparations.[95] Data for **29**: bp 59−60 °C (0.5 mmHg) [lit.[94] 60−65 °C (0.2 mmHg)].



29 **49**

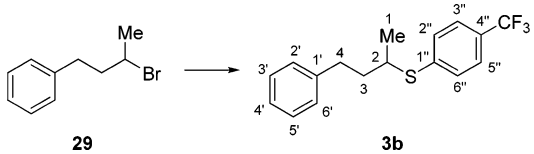
*Preparation of (l)- and (u)-1,1′-(3,4-Dimethyl-1,6-hexanediyl)-bisbenzene (**49**).* This preparation is based on a previously reported method for the iron-catalyzed homocoupling of alkyl bromides.[96] A flame-dried, 50 mL, one-necked, round-bottomed flask equipped with a stirrer bar, rubber septum, and argon inlet was charged with magnesium turnings (389 mg, 16.0 mmol, 2.0 equiv), $Fe(acac)_3$ (Strem, 99%, 57.1 mg, 0.16 mmol, 2 mol %), and THF (24.0 mL). **29** (1.70 g, 1.38 mL, 8.00 mmol, 1.0 equiv) was then added via syringe, and the resultant mixture was stirred at rt. After ca. 15 min, the solution changed color from red to black. After stirring for 1 h 40 min, the mixture was filtered through a pad of Florisil (5 g) in a 40 mm Ø, porosity 3, sintered funnel using minimal EtOAc and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a yellow oil (973 mg). Purification via flash column chromatography (50 g SiO_2, 30 mm Ø, hexane, ca. 5 mL fractions) gave a ∼1:1 mixture of (*l*)- and (*u*)-**49** as a clear, pale-yellow oil (177 mg, 17%). Data for (*l*)- and (*u*)-**49**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.31−7.24 (for both diastereoisomers: m, 4H each), 7.22−7.14 (for both diastereoisomers: m, 6H each), 2.71−2.41 (for both diastereoisomers: m, 4H each), 1.71−1.33 (for both diastereoisomers: m, 6H), 0.92 (for one diastereoisomer: d, J = 6.3 Hz, 6H), 0.86 (for one diastereoisomer: d, J = 6.2 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) 143.4, 143.4, 128.7, 128.7, 128.6, 128.6, 125.9, 125.9, 37.4, 37.2, 36.6, 35.3, 34.4, 34.3, 16.7, 14.7. MS: (EI$^+$, 70 eV) 266.2 (M^+, 8), 91.1 ($C_7H_7^+$, 100), 65.1 (16). HRMS (EI$^+$, double focusing sector field) calcd for $C_{20}H_{26}$, 266.2035; found, 266.2031. TLC R_f 0.38 (hexane) [$KMnO_4$]. GC: first diastereoisomer, t_R 5.14 min (47%); second diastereoisomer, t_R 5.16 min (53%).

5.3. Preparation of Thio Ether Substrates.



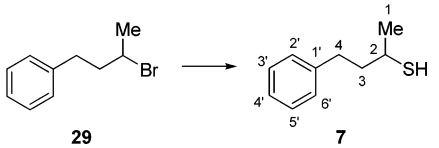
29 **3a**

*Preparation of (rac)-(4-Phenylbutan-2-ylthio)benzene (**3a**).* A 500 mL, one-necked, round-bottomed flask equipped with a stirrer bar, water-jacketed reflux condenser, and argon inlet was charged with **29** (6.39 g, 30.0 mmol, 1.0 equiv), thiophenol (3.41 g, 3.18 mL, 30.0 mmol, 1.0 equiv), potassium carbonate (8.29 g, 60.0 mmol, 2.0 equiv), and acetone (150 mL), and stirring was commenced. The resultant mixture was heated at reflux for 24 h and was then allowed to cool to rt. The mixture was filtered through a 40 mm Ø, porosity 3, sintered funnel under house vacuum and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a pale-yellow oil (7.69 g). Purification via short-path distillation under reduced pressure (0.5 mmHg) gave **3a** as a clear, colorless oil (7.07 g, 97%). The ^{1}H NMR spectroscopic data and boiling point matched that for alternative preparations.[97] Data for **3a**: bp 136−137 °C (0.5 mmHg) [lit. 124−126 °C (0.1 mmHg)]. GC: t_R 4.66 min.



29 **3b**

*Preparation of (rac)-4-Trifluoromethyl(4-phenylbutan-2-ylthio)-benzene (**3b**).* A 25 mL, one-necked, round-bottomed flask equipped with a stirrer bar, water-jacketed reflux condenser, and argon inlet was charged with **29** (213 mg, 1.00 mmol, 1.0 equiv), (4-trifluoromethyl)-thiophenol (184 mg, 141 μL, 1.00 mmol, 1.0 equiv), potassium carbonate (276 g, 2.00 mmol, 2.0 equiv), and acetone (5.0 mL), and stirring was commenced. The resultant mixture was heated at reflux for 16 h and was then allowed to cool to rt. The mixture was filtered through a 40 mm Ø, porosity 3, sintered funnel under house vacuum and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a yellow-orange oil (323 mg). Purification via flash column chromatography (20 g SiO_2, 20 mm Ø, 95:5, hexane/toluene, ca. 5 mL fractions) gave **3b** as a clear, colorless oil (292 mg, 94%). Data for **3b**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.49 (d, J = 8.1, 2H), 7.37−7.27 (m, 4H), 7.24−7.15 (m, 3H), 3.36−3.28 (m, 1H), 2.87−2.73 (m, 2H), 2.03−1.82 (m, 2H), 1.38 (dd, J = 6.7, 1.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 141.5, 141.5, 129.9, 128.7, 128.7, 128.2 (q, J = 32.7 Hz), 126.3, 125.8 (q, J = 3.8 Hz), 124.4 (q, J = 272 Hz), 41.6, 38.4, 33.3, 21.2. IR (neat) 3085 (w), 3064 (w), 3027 (w), 2963 (m), 2926 (m), 2860 (w), 1607 (s), 1496 (m), 1454 (m), 1401 (m), 1377 (w), 1326 (s), 1165 (s), 1124 (s), 1095 (s), 1063 (s), 1030 (w), 1013 (m), 948 (w), 914 (w), 826 (m), 779 (w), 747 (m), 699 (m), 593 (w). MS (EI$^+$, 70 eV) 310.1 (M^+, 17), 132.1 (36), 117.1 (27), 91.1 ($C_7H_7^+$, 100), 65.1 (18). HRMS (EI$^+$, double focusing sector field) calcd for $C_{17}H_{17}F_3S$, 310.1003; found, 310.1007. TLC R_f 0.36 (99:1, hexane/EtOAc) [$KMnO_4$]. GC t_R 4.50 min.



29 **7**

*Preparation of (rac)-4-Phenylbutane-2-thiol (**7**).* A 200 mL, one-necked, round-bottomed flask equipped with a stirrer bar, water-jacketed reflux condenser, and argon inlet was charged with **29** (2.56 g, 12.0 mmol, 1.0 equiv), potassium thioacetate (4.20 g, 36.0 mmol, 3.0 equiv), and DMF (30 mL), and stirring was commenced. The resultant mixture was heated at 100 °C for 17 h and was then allowed to cool to rt. Four molar NaOH(aq) (9.0 mL, 36.0 mmol, 3.0 equiv)

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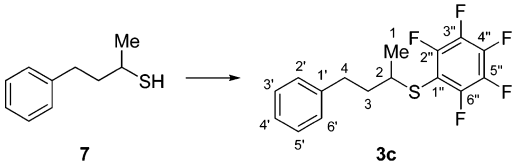
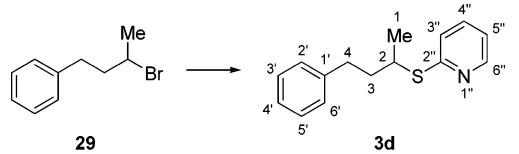
was added, stirring was continued for a further 32 h, and then the mixture was cooled in an ice/water bath and 3 M H_2SO_4(aq) was added to pH 2. The mixture was then partitioned between EtOAc (75 mL) and H_2O (300 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 75 mL), and the combined organic extracts were washed with brine (4 × 50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a dark brown oil (2.90 g). Purification via flash column chromatography (30 g SiO_2, 30 mm Ø, 98:2, hexane/EtOAc, ca. 5 mL fractions) gave **7** as a clear, yellow oil (1.23 g, 62%). Data for **7**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.35−7.29 (m, 2H), 7.26−7.20 (m, 3H), 2.99−2.90 (m, 1H), 2.86−2.70 (m, 2H), 1.99−1.80 (m, 2H), 1.54 (d, J = 6.5 Hz, 1 H, S*H*), 1.41 (d, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 141.8, 128.7, 128.7, 126.2, 42.8, 35.3, 33.9, 26.1. IR (neat) 3084 (m), 3061 (m), 3026 (m), 2956 (m), 2922 (m), 2860 (m), 1603 (m), 1496 (m), 1453 (m), 1376 (m), 1030 (m), 747 (m), 699 (s). MS (EI$^+$, 70 eV) 166.1 (M^+, 19), 132.1 (33), 117.1 (72), 105.1 (11), 91.1 ($C_7H_7^+$, 100), 77.0 (17), 65.1 (32), 63.1 (12), 61.1 (16), 51.0 (19). HRMS (EI$^+$, double focusing sector field) calcd for $C_{10}H_{14}S$, 166.0816; found, 166.0815. TLC R_f 0.38 (99:1, hexane/EtOAc) [$KMnO_4$]. GC t_R 2.58 min.



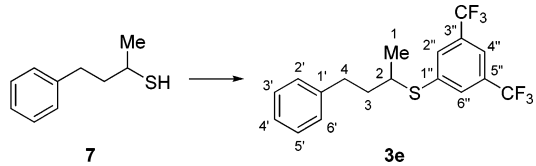
7 **3c**

*Preparation of (rac)-2,3,4,5,6-Pentafluoro(4-phenylbutan-2-ylthio)benzene (**3c**).* A 25 mL, one-necked, round-bottomed flask equipped with a stirrer bar, rubber septum, and argon inlet was charged with **7** (748 mg, 4.50 mmol, 1.0 equiv), hexafluorobenzene (846 mg, 523 μL, 4.50 mmol, 1.0 equiv), potassium carbonate (746 mg, 5.40 mmol, 1.2 equiv), and DMF (11.3 mL), and stirring was commenced. The resultant mixture was stirred at rt for 4.5 h, sat. NH_4Cl(aq) (100 mL) was added, and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (4 × 50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a yellow oil (1.76 g). Purification via flash column chromatography (50 g SiO_2, 30 mm Ø, 98:2, hexane/EtOAc, ca. 5 mL fractions) gave **3c** as a yellow oil that solidified on standing (931 mg, 62%). To obtain an analytical sample, a 433 mg portion of the above material was dissolved in hexane (3.0 mL) in a 20 mL scintillation vial, and the vial sealed with a screw top cap and left in the freezer at −20 °C overnight to give white, needle-like crystals. The crystals were collected via filtration through filter paper in a Hirsch funnel under house vacuum and were then crushed with a glass rod and dried in vacuo (0.05 mmHg) to give a white, crystalline solid (297 mg, 69% mass return). Data for **7**: mp 64−65 °C (hexane). ^{1}H NMR (500 MHz, $CDCl_3$) 7.33−7.27 (m, 2H), 7.24−7.17 (m, 3H), 3.44−3.35 (m, 1H), 2.87−2.76 (m, 2H), 1.97−1.81 (m, 2H), 1.32 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 148.7−146.4 (m[98]) 141.4, 128.7, 128.6, 126.3, 114.3 (m), 44.0, 39.0, 33.2, 21.7. IR ($CHCl_3$ mull) 3086 (w), 3063 (w), 3027 (m), 2962 (m), 2925 (m), 2861 (w), 1603 (w), 1496 (m), 1458 (s), 1377 (m), 1245 (m), 1030 (m), 955 (s), 813 (m), 747 (m), 698 (m). MS (EI$^+$, 70 eV) 332.1 (M^+, 7), 199.0 (15), 117.1 (10), 91.1 ($C_7H_7^+$, 100), 65.1 (15). HRMS (EI$^+$, double focusing sector field) calcd for $C_{16}H_{13}SF_5$, 332.0658; found, 332.0662. TLC R_f 0.20 (99:1, hexane/EtOAc) [$KMnO_4$].



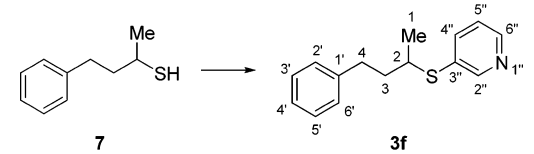
29 **3d**

*Preparation of (rac)-2-(4-Phenylbutan-2-ylthio)pyridine (**3d**).* A 500 mL, one-necked, round-bottomed flask equipped with a stirrer bar, water-jacketed reflux condenser, and argon inlet was charged with **29** (8.52 g, 40.0 mmol, 1.0 equiv), 2-mercaptopyridine (4.54 g, 40.0 mmol, 1.0 equiv), potassium carbonate (11.06 g, 80.0 mmol, 2.0 equiv), and acetone (200 mL), and stirring was commenced. The resultant mixture was heated at reflux for 4 h and was then allowed to cool to rt. The mixture was filtered through a 40 mm Ø, porosity 3, sintered funnel under house vacuum and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a yellow oil (9.97 g). Purification via short-path distillation under reduced pressure (1.2 mmHg) gave **3d** as a clear, yellow oil (9.19 g, 94%). To obtain an analytical sample, a 1.75 g portion of the above material was purified on an automated flash column chromatography platform [40 g SiO_2 cartridge, hexane (1 CV) then 100:0 → 70:30, hexane/CH_2Cl_2 (10 CV) then 70:30, hexane/CH_2Cl_2 (10 CV), 40 mL min^{-1} flow rate, 8 mL fractions] to give **3d** as a clear, colorless oil (1.67 g, 95% mass return). Data for **3d**: bp 127−130 °C (1.2 mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 8.45−8.42 (m, 1H), 7.46 (td, J = 7.7, 1.9 Hz, 1H), 7.32−7.27 (m, 2H), 7.24−7.14 (m, 4H), 6.97 (ddd, J = 7.3, 4.9, 1.0 Hz, 1H), 4.04−3.94 (m, 1H), 2.88−2.75 (m, 2H), 2.12−1.91 (m, 2H), 1.48 (d, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 159.6, 149.7, 142.2, 136.1, 128.7, 128.6, 126.1, 123.1, 119.6, 39.7, 38.8, 33.6, 21.7. IR (neat) 3084 (w), 3063 (w), 3043 (w), 3026 (w), 2994 (w), 2957 (m), 2922 (m), 2858 (w), 1602 (w), 1578 (s), 1556 (m), 1495 (m), 1453 (s), 1413 (s), 1373 (w), 1353 (w), 1280 (w), 1242 (w), 1178 (w), 1147 (w), 1125 (s), 1089 (w), 1043 (w), 1030 (w), 984 (w), 958 (w), 912 (w), 757 (s), 724 (m), 699 (s), 619 (w). MS (EI$^+$, 70 eV) 243.1 (M^+, 16), 182.1 (67), 152.1 (49), 117.1 (28), 111.0 (53), 106.1 (18), 91.1 ($C_7H_7^+$, 100), 78.0 (37), 77.0 (11), 67.1 (23), 65.1 (29), 51.0 (24). HRMS (EI$^+$, double focusing sector field) calcd for $C_{15}H_{17}SN$, 243.1082; found, 243.1077. TLC R_f 0.34 (90:10, hexane/EtOAc) [$KMnO_4$]. GC t_R 4.75 min.



7 **3e**

*Preparation of (rac)-3,5-Bis(trifluoromethyl)(4-phenylbutan-2-ylthio)benzene (**3e**).* This preparation is based on a previously reported method for the palladium-catalyzed cross-coupling of alkyl thiols with aryl halides.[99] 1-Bromo-3,5-bis(trifluoromethyl)benzene (299 mg, 176 μL, 1.00 mmol, 1.0 equiv), *i*-Pr_2NEt (142 mg, 192 μL, 1.10 mmol, 1.1 equiv), and **7** (166 mg, 170 μL, 1.00 mmol, 1.0 equiv) were added sequentially to a stirred solution of $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol, 1 mol %) and dppf (11.1 mg, 0.02 mmol, 2 mol %) in toluene (1.0 mL) in an oven-dried, one-piece, 5 mL, round-bottomed flask/water-jacketed reflux condenser equipped with a stirrer bar, rubber septum, and argon inlet. The resultant orange solution was heated to reflux for 3 h and was then allowed to cool to rt. Brine (5 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a brown oil (410 mg). Purification via flash column chromatography (10 g SiO_2, 20 mm Ø, 98:2, hexane/EtOAc, ca. 5 mL fractions) gave **3e** as a clear, pale-yellow oil (353 mg, 93%). Data for **3e**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.73−7.65 (m, 3H), 7.34−7.27 (m, 2H), 7.25−7.14 (m, 3H), 3.37−3.29 (m, 1H), 2.88−2.75 (m, 2H), 2.03−1.85 (m, 2H), 1.39 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 141.1, 140.0, 132.3 (q, J = 32.9 Hz), 128.8, 128.6, 126.4, 123.3 (q, J = 273 Hz), 42.5, 38.2, 33.3, 21.1. IR (neat) 3087 (m), 3065 (m), 3028 (m), 2967 (m), 2927 (m), 2862 (m), 1602 (m), 1497 (m), 1455 (m), 1378 (m), 1352 (s), 1277 (s), 1182 (s), 1135 (s), 1030 (w), 881 (m), 843 (m), 825 (m), 747 (m), 713 (m), 699 (m), 681 (m). MS (EI$^+$, 70 eV) 378.1 (M^+, 49), 132.1 (38), 117.1 (31), 91.1 ($C_7H_7^+$, 100). HRMS (EI$^+$, TOF) calcd for $C_{18}H_{16}SF_6$, 378.0877; found, 378.0873. TLC R_f 0.49 (99:1, hexane/EtOAc) [$KMnO_4$].



7 **3f**

*Preparation of (rac)-3-(4-Phenylbutan-2-ylthio)pyridine (**3f**).* This preparation is based on a previously reported method for the

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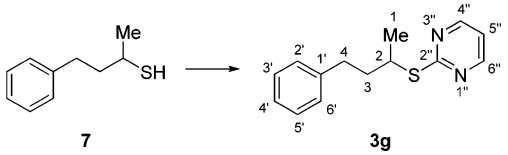
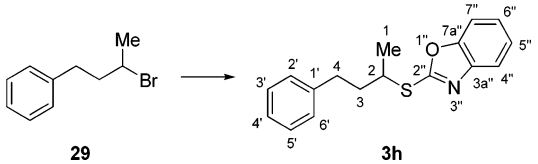
palladium-catalyzed cross-coupling of alkyl thiols with aryl halides.[99] 3-Bromopyridine (160 mg, 99 μL, 1.00 mmol, 1.0 equiv), *i*-Pr_2NEt (142 mg, 192 μL, 1.10 mmol, 1.1 equiv), and **7** (166 mg, 170 μL, 1.00 mmol, 1.0 equiv) were added sequentially to a stirred solution of $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol, 1 mol %) and dppf (11.1 mg, 0.02 mmol, 2 mol %) in toluene (1.0 mL) in an oven-dried, one-piece, 5 mL, round-bottomed flask/water-jacketed reflux condenser equipped with a stirrer bar, rubber septum, and argon inlet. The resultant orange solution was heated to reflux for 3 h and was then allowed to cool to rt. Brine (5 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a brown oil (0.28 g). Purification via flash column chromatography (10 g SiO_2, 20 mm Ø, 80:20, hexane/EtOAc, ca. 5 mL fractions followed by 20 g SiO_2, 20 mm Ø, 90:10, hexane/EtOAc, ca. 5 mL fractions) gave **3f** as a clear, orange-yellow oil (227 mg, 93%). Data for **3f**: ^{1}H NMR (500 MHz, $CDCl_3$) 8.73 (br s, 1H), 8.58 (br s, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.36−7.15 (m, 6H), 3.24−3.15 (m, 1H), 2.88−2.75 (m, 2H), 1.99−1.80 (m, 2H), 1.34 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 152.9, 148.0, 141.5, 140.0, 132.7, 128.7, 128.6, 126.3, 124.2, 43.1, 38.4, 33.3, 21.5. IR (neat) 3060 (m), 3026 (m), 2960 (m), 2922 (m), 2858 (m), 1602 (m), 1559 (m), 1495 (m), 1457 (m), 1402 (m), 1375 (m), 1317 (m), 1109 (m), 1018 (m), 799 (m), 749 (m), 700 (m). MS (EI$^+$, 70 eV) 243.1 (M^+, 46), 132.1 (35), 117.1 (31), 91.1 ($C_7H_7^+$, 100). HRMS (EI$^+$, TOF) calcd for $C_{15}H_{17}NS$, 243.1082; found, 243.1081. TLC R_f 0.31 (80:20, hexane/EtOAc) [$KMnO_4$]. GC t_R 4.92 min.



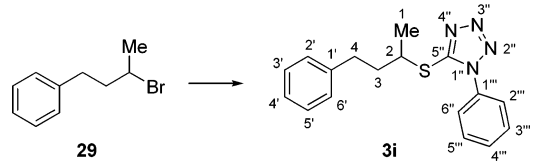
7 **3g**

*Preparation of (rac)-2-(4-Phenylbutan-2-ylthio)pyrimidine (**3g**).* This preparation is based on a previously reported method for the palladium-catalyzed cross-coupling of alkyl thiols with aryl halides.[99] *i*-Pr_2NEt (142 mg, 192 μL, 1.10 mmol, 1.1 equiv) and **7** (166 mg, 170 μL, 1.00 mmol, 1.0 equiv) were added sequentially to a stirred solution of 3-bromopyrimidine (164 mg, 99 μL, 1.00 mmol, 1.0 equiv), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol, 1 mol %), and dppf (11.1 mg, 0.02 mmol, 2 mol %) in toluene (1.0 mL) in an oven-dried, one-piece, 5 mL, round-bottomed flask/water-jacketed reflux condenser equipped with a stirrer bar, rubber septum, and argon inlet. The resultant orange solution was heated to reflux for 3 h and was then allowed to cool to rt. Brine (5 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a brown oil (0.44 g). Purification via flash column chromatography (20 g SiO_2, 20 mm Ø, 90:10, hexane/EtOAc, ca. 5 mL fractions) gave **3g** as a clear, orange oil (193 mg, 79%). Data for **3g**: ^{1}H NMR (500 MHz, $CDCl_3$) 8.50 (d, *J* = 4.8 Hz, 2H), 7.33−7.25 (m, 2H), 7.25−7.16 (m, 3H), 6.94 (t, *J* = 4.8 Hz, 1H), 3.98−3.89 (m, 1H), 2.89−2.77 (m, 2H), 2.14−1.94 (m, 2H), 1.50 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 173.0, 157.4, 142.0, 128.7, 128.6, 126.1, 116.5, 40.4, 38.4, 33.6, 21.5. IR (neat) 3060 (m), 3026 (m), 2959 (m), 2923 (m), 2858 (m), 1602 (m), 1565 (s), 1546 (s), 1495 (m), 1454 (m), 1381 (s), 1254 (m), 1191 (s), 1030 (m), 980 (m), 798 (m), 773 (s), 748 (s), 699 (s), 628 (m). MS (EI$^+$, 70 eV) 244.1 (M^+, 22), 183.1 (100), 153.0 (21), 140.0 (12), 132.1 (14), 117.1 (43), 113.0 (29), 107.1 (12), 91.1 ($C_7H_7^+$, 61). HRMS (EI$^+$, TOF) calcd for $C_{14}H_{16}N_2S$, 244.1034; found, 244.1036. TLC R_f 0.45 (80:20, hexane/EtOAc) [$KMnO_4$].



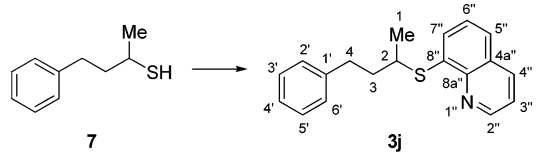
29 **3h**

*Preparation of (rac)-2-(4-Phenylbutan-2-ylthio)benzo[d]oxazole (**3h**).* A 50 mL, one-necked, round-bottomed flask equipped with a stirrer bar, water-jacketed reflux condenser, and argon inlet was charged with **29** (852 mg, 4.00 mmol, 1.0 equiv), 2-mercaptobenzoxazole (637 mg, 4.00 mmol, 1.0 equiv), potassium carbonate (111 mg, 8.00 mmol, 2.0 equiv), and acetone (20.0 mL), and stirring was commenced. The resultant mixture was heated at reflux for 3 h and was then allowed to cool to rt. The mixture was filtered through a 40 mm Ø, porosity 3, sintered funnel under house vacuum and concentrated in vacuo (50 °C, ca. 5 mmHg) to give an orange solid (1.15 g). Purification via flash column chromatography (30 g SiO_2, 30 mm Ø, 97:3, hexane/EtOAc, ca. 10 mL fractions) gave **3h** as a clear, colorless oil (696 mg, 70%). To obtain an analytical sample, a 677 mg portion of the above material was purified on an automated flash column chromatography platform [40 g SiO_2 cartridge, hexane (1 CV) then 100:0 → 70:30, hexane/CH_2Cl_2 (10 CV) then 70:30, hexane/CH_2Cl_2 (10 CV), 40 mL min^{-1} flow rate, 8 mL fractions] to give **3h** as a clear, colorless oil (643 mg, 95% mass return). Data for **3h**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.64 (d, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.35−7.20 (m, 7H), 4.03−3.94 (m, 1H), 2.93−2.80 (m, 2H), 2.23−2.03 (m, 2H), 1.62 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 164.7, 151.9, 142.3, 141.4, 128.7, 128.7, 126.3, 124.5, 124.1, 118.7, 110.1, 43.2, 38.6, 33.5, 22.1. IR (neat) 3084 (w), 3062 (w), 3026 (m), 2964 (w), 2925 (m), 2859 (w), 1602 (w), 1497 (s), 1472 (m), 1453 (s), 1376 (w), 1354 (w), 1339 (w), 1282 (w), 1238 (s), 1213 (s), 1180 (w), 1129 (s), 1094 (s), 1030 (w), 1002 (w), 924 (w), 807 (m), 743 (s), 699 (s), 623 (w). MS (EI$^+$, 70 eV) 283.1 (M^+, 24), 264.0 (23), 222.1 (68), 219.0 (55), 151.0 (40), 131.0 (31), 122.0 (37), 117.1 (17), 91.1 ($C_7H_7^+$, 100), 69.0 (38), 65.0 (10). HRMS (EI$^+$, TOF) calcd for $C_{17}H_{17}NOS$, 283.1031; found, 283.1031. TLC R_f 0.32 (95:5, hexane/EtOAc) [$KMnO_4$]. GC t_R 6.12 min.



29 **3i**

*Preparation of (rac)-1-Phenyl-5-(4-phenylbutan-2-ylthio)-1H-tetrazole (**3i**).* A 50 mL, one-necked, round-bottomed flask equipped with a stirrer bar, water-jacketed reflux condenser, and argon inlet was charged with **29** (852 mg, 4.00 mmol, 1.0 equiv), 1-phenyl-1*H*-tetrazole-5-thiol (727 mg, 4.00 mmol, 1.0 equiv), potassium carbonate (111 mg, 8.00 mmol, 2.0 equiv), and acetone (20.0 mL), and stirring was commenced. The resultant mixture was heated at reflux for 27 h and was then allowed to cool to rt. The mixture was filtered through a 40 mm Ø, porosity 3, sintered funnel under house vacuum and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a cloudy, white oil (1.44 g). Purification via flash column chromatography (30 g SiO_2, 30 mm Ø, 90:10, hexane/EtOAc, ca. 5 mL fractions) gave **3i** as a clear, colorless oil (1.14 g, 92%). Data for **3i**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.62−7.53 (m, 5H), 7.33−7.27 (m, 2H), 7.24−7.18 (m, 3H), 4.14−4.05 (m, 1H), 2.87−2.75 (m, 2H), 2.23−2.01 (m, 2H), 1.59 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 154.1, 141.1, 134.0, 130.4, 130.0, 128.8, 128.6, 126.4, 124.3, 44.6, 38.5, 33.4, 21.7. IR (neat) 3061 (m), 3026 (m), 2965 (m), 2926 (m), 2859 (m), 1597 (s), 1498 (s), 1454 (s), 1386 (s), 1316 (m), 1277 (m), 1238 (s), 1177 (m), 1159 (m), 1088 (s), 1074 (s), 1056 (m), 1030 (m), 1014 (s), 979 (m), 914 (m), 761 (s), 698 (s). MS (EI$^+$, 70 eV) 310.1 (M^+, 25), 249.1 (100), 132.1 (59), 117.1 (80), 91.1 ($C_7H_7^+$, 98), 77.0 (26), 65.0 (23). HRMS (EI$^+$, TOF) calcd for $C_{17}H_{18}N_4S$, 310.1252; found, 310.1252. TLC R_f 0.28 (90:10, hexane/EtOAc) [$KMnO_4$].



7 **3j**

*Preparation of (rac)-8-(4-Phenylbutan-2-ylthio)quinoline. (**3j**).* This preparation is based on a previously reported method for the palladium-catalyzed cross-coupling of alkyl thiols with aryl halides.[99] *i*-Pr_2NEt (142 mg, 192 μL, 1.10 mmol, 1.1 equiv) and **7** (166 mg, 170 μL, 1.00 mmol, 1.0 equiv) were added sequentially to a stirred solution

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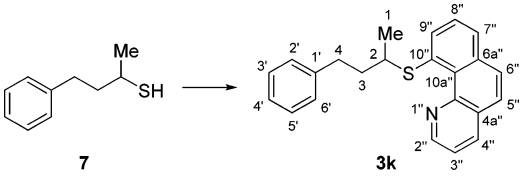
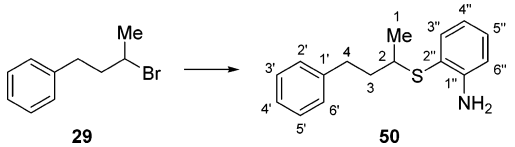
of 8-(trifluoromethanesulfonyloxy)quinoline[100] (277 mg, 1.00 mmol, 1.0 equiv), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol, 1 mol %), and dppf (11.1 mg, 0.02 mmol, 2 mol %) in toluene (1.0 mL) in an oven-dried, one-piece, 5 mL, round-bottomed flask/water-jacketed reflux condenser equipped with a stirrer bar, rubber septum, and argon inlet. The resultant orange solution was heated to reflux for 3 h and was then allowed to cool to rt. Brine (5 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a brown syrup (450 mg). Purification via flash column chromatography (15 g SiO_2, 20 mm Ø, 88:12, hexane/EtOAc, ca. 5 mL fractions) gave **3j** as a clear, yellow-green syrup (268 mg, 91%). To obtain an analytical sample, a 188 mg portion of the above material was purified on an automated flash column chromatography platform [24 g SiO_2 cartridge, hexane (1 CV) then 100:0 → 80:20, hexane/CH_2Cl_2 (18 CV), 35 mL min^{-1} flow rate, 8 mL fractions] to give **3j** as a clear, pale-yellow syrup (117 mg, 62% mass return) in addition to a portion of **3j** slightly contaminated with a yellow-colored impurity (52.7 mg). Data for **3j**: ^{1}H NMR (500 MHz, $CDCl_3$) 8.98 (dd, J = 4.2, 1.7 Hz, 1H), 8.14 (dd, J = 8.3, 1.7 Hz, 1H), 7.59 (dd, J = 7.7, 1.6 Hz, 1H), 7.47−7.38 (m, 3H), 7.34−7.28 (m, 2H), 7.26−7.21 (m, 3H), 3.64−3.55 (m, 1H), 2.98−2.84 (m, 2H), 2.22−2.11 (m, 1H), 2.07−1.96 (m, 1H), 1.52 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 149.5, 146.3, 141.9, 137.9, 136.7, 128.8, 128.7, 128.6, 126.7, 126.2, 125.9, 124.5, 121.8, 38.8, 38.5, 33.5, 21.0. IR (neat) 3081 (w), 3059 (m), 3024 (m), 2959 (m), 2923 (s), 2859 (m), 1603 (m), 1593 (m), 1556 (m), 1490 (s), 1455 (s), 1419 (w), 1374 (m), 1359 (m), 1301 (m), 1214 (m), 1178 (w), 1129 (w), 1068 (w), 1029 (w), 984 (s), 914 (w), 820 (s), 789 (s), 749 (s), 700 (s), 657 (s), 571 (w). MS (EI$^+$, 70 eV) 293.1 (M^+, 14), 260.1 (18), 232.1 (33), 202.1 (100), 189.1 (50), 161.0 (46), 156.1 (14), 129.1 (16), 116.1 (18), 91.1 ($C_7H_7^+$, 29). HRMS (EI$^+$, TOF) calcd for $C_{19}H_{19}NS$, 293.1238; found, 293.1237. TLC R_f 0.18 (90:10, hexane/EtOAc) [$KMnO_4$].



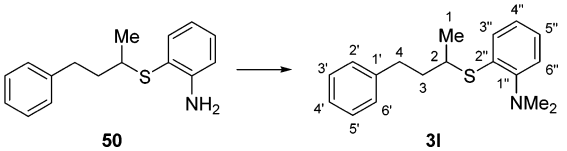
7 **3k**

*Preparation of (rac)-10-(4-Phenylbutan-2-ylthio)benzo[h]-quinoline (**3k**).* This preparation is based on a previously reported method for the palladium-catalyzed cross-coupling of alkyl thiols with aryl halides.[99] *i*-Pr_2NEt (142 mg, 192 μL, 1.10 mmol, 1.1 equiv) and **7** (166 mg, 170 μL, 1.00 mmol, 1.0 equiv) were added sequentially to a stirred solution of 10-bromobenzo[*h*]quinoline[101] (258 mg, 1.00 mmol, 1.0 equiv), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol, 1 mol %), and dppf (11.1 mg, 0.02 mmol, 2 mol %) in toluene (1.0 mL) in an oven-dried, one-piece, 5 mL, round-bottomed flask/water-jacketed reflux condenser equipped with a stirrer bar, rubber septum, and argon inlet. The resultant orange solution was heated to reflux for 3 h and was then allowed to cool to rt. Brine (5 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a brown syrup (0.40 g). Purification via flash column chromatography (10 g SiO_2, 20 mm Ø, 90:10, hexane/EtOAc, ca. 5 mL fractions followed by 20 g SiO_2, 20 mm Ø, 95:5, hexane/EtOAc, ca. 5 mL fractions) gave **3k** as a cloudy, colorless syrup (283 mg, 82%). To obtain an analytical sample, a 207 mg portion of the above material was purified via flash column chromatography (20 g SiO_2, 20 mm Ø, 60:40, hexane/toluene, ca. 5 mL fractions) to give **3k** as a cloudy, colorless syrup (173 mg, 83% mass return). Data for **3k**: ^{1}H NMR (500 MHz, $CDCl_3$) 9.15 (dd, J = 4.4, 1.8 Hz, 1H), 8.18 (dd, J = 8.0, 1.8 Hz, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.57−7.50 (m, 2H), 7.45 (d, J = 7.8 Hz, 1H), 7.37−7.32 (m, 2H), 7.30−7.23 (m, 3H), 3.56−3.47 (m, 1H), 3.02−2.85 (m, 2H), 2.34−2.24 (m, 1H), 2.05−1.95 (m, 1H), 1.58 (d, J = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 147.8, 146.6, 142.0, 138.8, 135.7, 135.3, 128.9, 128.9, 128.7, 128.7, 127.5, 127.4, 126.2, 125.8, 124.3, 124.2, 121.0, 39.3, 38.0, 33.8, 20.3. IR (neat) 3084 (w), 3060 (w), 3042 (w), 3023 (w), 2957 (m), 2922 (m), 2860 (w), 1621 (w), 1601 (w), 1583 (m), 1556 (s), 1494 (m), 1454 (m), 1438 (m), 1412 (m), 1394 (m), 1374 (w), 1327 (w), 1289 (w), 1190 (w), 1151 (w), 1140 (w), 1105 (w), 1052 (w), 1052 (w), 1030 (w), 1013 (w), 928 (m), 910 (w), 886 (w), 833 (s), 821 (m), 757 (m), 719 (s), 699 (m), 647 (m). MS (EI$^+$, 70 eV) 343.1 (M^+, 8), 252.1 (14), 210.0 ($C_{13}H_8NS^+$, 100), 166.1 (12). HRMS (EI$^+$, TOF) calcd for $C_{23}H_{21}NS$, 343.1395; found, 343.1397. TLC R_f 0.19 (95:5, hexane/EtOAc) [$KMnO_4$].



29 **50**

*Preparation of (rac)-2-(4-Phenylbutan-2-ylthio)aniline (**50**).* A 50 mL, one-necked, round-bottomed flask equipped with a stirrer bar, water-jacketed reflux condenser, and argon inlet was charged with **29** (852 mg, 4.00 mmol, 1.0 equiv), 2-aminothiophenol (506 mg, 0.43 mL, 4.00 mmol, 1.0 equiv), potassium carbonate (111 mg, 8.00 mmol, 2.0 equiv), and acetone (20.0 mL), and stirring was commenced. The resultant mixture was heated at reflux for 3 h and was then allowed to cool to rt. The mixture was filtered through a pad of Celite (5 g) in a 40 mm Ø, porosity 3, sintered funnel under house vacuum using minimal EtOAc and then concentrated in vacuo (50 °C, ca. 5 mmHg) to give an orange oil (1.20 g). Purification via flash column chromatography (25 g SiO_2, 20 mm Ø, 90:10, hexane/EtOAc, ca. 9 mL fractions) gave **50** as a clear, yellow-orange oil (882 mg, 86%). Data for **50**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.39−7.34 (m, 1H), 7.32−7.25 (m, 2H), 7.23−7.17 (m, 4H), 7.16−7.11 (m, 2H), 4.36 (br s, 2H), 3.13−3.03 (m, 1H), 2.87−2.72 (m, 2H), 2.01−1.77 (m, 2H), 1.27 (d, J = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 149.3, 142.0, 137.5, 130.2, 128.7, 128.7, 126.1, 118.5, 117.1, 115.1, 43.3, 38.6, 33.5, 21.6. IR (neat) 3465 (m), 3365 (m), 3061 (m), 3024 (m), 2921 (m), 2858 (m), 1604 (s), 1495 (m), 1477 (s), 1446 (s), 1373 (m), 1307 (s), 1250 (m), 1157 (m), 1140 (m), 1028 (m), 748 (s), 699 (s). MS (EI$^+$, 70 eV) 257.1 (M^+, 97), 125.0 (100), 91.1 ($C_7H_7^+$, 91), 80.1 (17), 65.0 (12). HRMS (EI$^+$, TOF) calcd for $C_{16}H_{19}NS$, 257.1238; found, 257.1238. TLC R_f 0.37 (90:10, hexane/EtOAc) [$KMnO_4$].



50 **3l**

*Preparation of (rac)-N,N-Dimethyl-2-(4-phenylbutan-2-ylthio)-aniline (**3l**).* A 25 mL, one-necked, round-bottomed flask equipped with a stirrer bar, rubber septum, and argon inlet was charged with **50** (257 mg, 1.00 mmol, 1.0 equiv), glacial acetic acid (0.29 mL, 5.00 mmol, 5.0 equiv), formaldehyde (37% in H_2O, 0.30 mL, 4.00 mmol, 4.0 equiv), and CH_2Cl_2 (4.0 mL), and stirring was commenced. After 5 min, sodium triacetoxyborohydride (1.12 g, 5.00 mmol, 5.0 equiv) was added portionwise, and the resultant mixture was stirred at rt for 3.5 h. CH_2Cl_2 (6 mL) and sat. $NaHCO_3$(aq) (10 mL) were then added, and the layers were separated. The organic layer was washed with sat. $NaHCO_3$(aq) (2 × 10 mL), and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a yellow oil (0.32 g). Purification via flash column chromatography (10 g SiO_2, 20 mm Ø, 97:3, hexane/EtOAc, ca. 5 mL fractions) gave **3l** as a clear, pale-yellow oil (233 mg, 82%). Data for **3l**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.32−7.25 (m, 2H), 7.23−7.10 (m, 5H), 7.09−7.04 (m, 1H), 6.99−6.93 (m, 1H), 3.44−3.35 (m, 1H), 2.88−2.73 (m, 2H) overlapping 2.77 (s, 6H), 2.06−1.96 (m, 1H), 1.92−1.82 (m, 1H), 1.37 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 153.0, 142.0, 131.5, 129.5, 128.8, 128.6, 126.3, 126.1, 123.6, 119.6, 44.6, 39.7, 38.5, 33.5, 21.1. IR (neat) 3084 (m), 3058 (m), 3025 (m), 2938 (m), 2857 (m), 2825 (m), 2778 (m), 1602 (m), 1581 (m), 1495 (m), 1477 (m), 1453 (m), 1373 (m), 1316 (m), 1266 (m), 1188 (m), 1157 (m), 1123 (m), 1094 (m), 1062 (m), 1044 (m), 944 (m), 758 (m), 731 (m), 699 (m), 675

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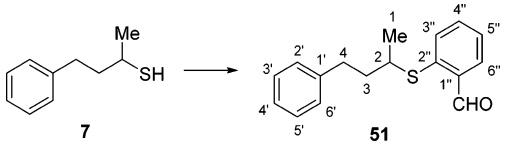
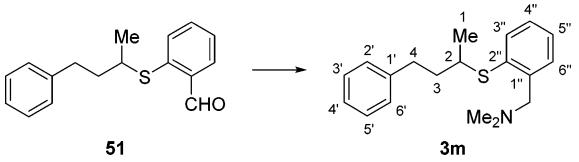
(m). MS (EI$^+$, 70 eV) 285.2 (M$^+$, 75), 252.2 (32), 240.1 (15), 224.1 (14), 194.1 (36), 179.1 (20), 164.1 (93), 153.1 (100), 136.0 (55), 122.0 (17), 109.0 (20), 91.1 ($C_7H_7^+$, 74), 77.0 (13), 65.0 (16). HRMS (EI$^+$, TOF) calcd for $C_{18}H_{23}NS$, 285.1551; found, 285.1549. TLC R_f 0.49 (95:5, hexane/EtOAc) [$KMnO_4$].



7 51

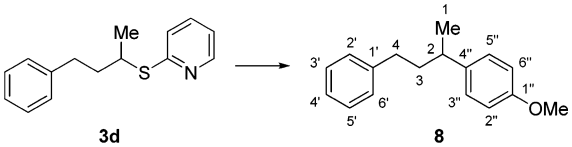
*Preparation of (rac)-2-(4-Phenylbutan-2-ylthio)benzaldehyde (**51**).* This preparation is based on a previously reported method for the palladium-catalyzed cross-coupling of alkyl thiols with aryl halides.[99] 2-Bromobenzaldehyde (83.1 mg, 52 μL, 0.44 mmol, 1.0 equiv) and *i*-Pr$_2$NEt (62.6 mg, 84 μL, 0.48 mmol, 1.1 equiv) were added sequentially to a stirred solution of **7** (73.2 mg, 0.44 mmol, 1.0 equiv), $Pd_2(dba)_3$ (4.0 mg, 4 μmol, 1 mol %), and dppf (4.9 mg, 9 μmol, 2 mol %) in toluene (0.5 mL) in an oven-dried, one-piece, 5 mL, round-bottomed flask/water-jacketed reflux condenser equipped with a stirrer bar, rubber septum, and argon inlet. The resultant orange solution was heated to reflux for 3 h and was then allowed to cool to rt. Brine (5 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a brown oil (134 mg). Purification via flash column chromatography on an automated flash column chromatography platform [24 g SiO_2 cartridge, 100:0 → 92:8, hexane/EtOAc (10 CV), 35 mL min^{-1} flow rate, 8 mL fractions] gave **51** as a clear, pale-yellow oil (111 mg, 93%). Data for **51**: ^{1}H NMR (500 MHz, $CDCl_3$) 10.56 (s, 1H), 7.89 (dd, J = 7.7, 1.6, 1H), 7.48 (ddd, J = 8.0, 7.2, 1.6, 1H), 7.40 (dd, J = 8.0, 1.1, 1H), 7.37−7.33 (m, 1H), 7.33−7.28 (m, 2H), 7.24−7.17 (m, 3H), 3.33−3.23 (m, 1H), 2.89−2.75 (m, 2H), 2.07−1.97 (m, 1H), 1.95−1.86 (m, 1H), 1.37 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 192.1, 141.4, 140.5, 136.1, 134.1, 132.4, 130.6, 128.7, 128.7, 129.5, 126.3, 43.1, 38.4, 33.4, 21.1. IR (neat) 3084 (w), 3061 (w), 3025 (m), 2960 (m), 2924 (m), 2857 (m), 2735 (w), 1690 (s), 1602 (w), 1586 (m), 1557 (w), 1495 (m), 1456 (m), 1397 (w), 1376 (m), 1287 (w), 1260 (m), 1194 (m), 1127 (w), 1113 (w), 1060 (w), 1030 (w), 843 (w), 824 (m), 750 (m), 699 (m), 634 (w). MS (EI$^+$, 70 eV) 270.1 (M$^+$, 20), 252.1 (40), 210.1 (11), 148.0 (15), 137.0 (59), 109.0 (53), 91.1 ($C_7H_7^+$, 100), 65.0 (20). HRMS (EI$^+$, TOF) calcd for $C_{17}H_{18}OS$, 270.1078; found, 270.1072. TLC R_f 0.26 (95:5, hexane/EtOAc) [$KMnO_4$].



51 3m

*Preparation of (rac)-N,N-Dimethyl-1-[2-(4-phenylbutan-2-ylthio)phenyl]methanamine (**3m**).* A 25 mL, one-necked, round-bottomed flask equipped with a stirrer bar, rubber septum, and argon inlet was charged with **51** (216 mg, 0.80 mmol, 1.0 equiv), glacial acetic acid (ca. 2 drops), dimethylamine (2.0 M in THF, 640 μL, 1.28 mmol, 1.6 equiv), and 1,2-dichloroethane (2.7 mL), and stirring was commenced. Sodium triacetoxyborohydride (268 mg, 1.20 mmol, 1.3 equiv) was added portionwise, and the resultant mixture was stirred at rt for 24 h. CH_2Cl_2 (6 mL) and sat. $NaHCO_3$(aq) (10 mL) were then added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a yellow oil (0.33 g). Purification via flash column chromatography (10 g SiO_2, 20 mm Ø, 95:5, hexane/EtOAc to EtOAc, ca. 5 mL fractions) gave impure **3m** as a clear, yellow oil (141 mg), and a second flash column chromatography (10 g SiO_2, 20 mm Ø, 94:5:1 CH_2Cl_2/MeOH/Et_3N, ca. 5 mL fractions) failed to increase the purity. However, a third flash column chromatography (10 g SiO_2, 20 mm Ø, 99:1, CH_2Cl_2/Et_3N, ca. 5 mL fractions) gave **3m** as a clear, yellow oil (120 mg, 50%). Data for **3m**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.40−7.36 (m, 1H), 7.33−7.25 (m, 3H), 7.22−7.15 (m, 5H), 3.57 (s, 2H), 3.31−3.22 (m, 1H), 2.87−2.73 (m, 2H), 2.27 (s, 6H), 2.04−1.94 (m, 1H), 1.90−1.81 (m, 1H), 1.33 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 141.9, 140.2, 136.0, 131.4, 130.2, 128.7, 128.6, 127.5, 126.4, 126.1, 62.1, 45.6, 42.5, 38.6, 33.4, 21.2. IR (neat) 3083 (m), 3059 (m), 3025 (m), 2969 (m), 2939 (m), 2923 (m), 2853 (m), 2814 (m), 2768 (m), 1693 (m), 1681 (m), 1603 (m), 1588 (m), 1495 (m), 1463 (m), 1454 (m), 1373 (m), 1359 (m), 1251 (m), 1173 (m), 1148 (m), 1096 (m), 1064 (m), 1029 (m), 846 (m), 747 (m), 698 (m). MS (EI$^+$, 70 eV) 299.2 (M$^+$, 30), 284.1 (11), 238.2 (19), 208.1 (36), 166.1 ($C_9H_{12}NS^+$, 100), 152.1 (15), 132.1 (13), 123.0 (16), 91.1 ($C_7H_7^+$, 53). HRMS (EI$^+$, TOF) calcd for $C_{19}H_{25}NS$, 299.1708; found, 299.1699. TLC R_f 0.16 (97:2.7:0.3, CH_2Cl_2/MeOH/aq. NH_3) [$KMnO_4$].

5.4. Cross-Coupling of Thio Ether 3d.



3d 8

*Preparation of (rac)-1-Methoxy-4-(4-phenylbutan-2-yl)benzene (**8**).* An oven-dried, 20 mL scintillation vial was charged with **3d** (243 mg, 1.00 mmol, 1.0 equiv) and Fe(acac)$_3$ (106 mg, 0.30 mmol, 30 mol %) in a glovebox, and the vial was sealed with a rubber septum and removed from the box. Outside of the glovebox, a 25 mL Schlenk flask equipped with a stirrer bar, rubber septum, and argon inlet was evacuated, flame-dried, left to cool under vacuum, and flushed three times with argon. The vial containing **3d** and Fe(acac)$_3$ was charged with CPME (4.0 mL) and then sonicated until homogeneous. The clear red solution was then transferred via cannula to the Schlenk flask, and the residual material was rinsed across with further portions of CPME (6.0 mL). 4-Methoxyphenylmagnesium bromide (2.17 M in Et_2O, 1.84 mL, 4.00 mmol, 4.0 equiv) was then added by syringe over ca. 2 min. During addition, the color of the solution changed from red to black, and small clusters of black solid could be seen forming during addition. Black deposits were also visible at the top of the solution. After stirring for 18 h at rt, 1 M HCl(aq) (10 mL) was added in one portion, and the mixture was filtered through a pad of Celite (5 g) in a 40 mm Ø, porosity 3, sintered funnel under house vacuum. EtOAc (2 × 5 mL) was used to rinse any residual material though the Celite pad. The filtrate was transferred to a separatory funnel, and the layers were separated. The organic layer was washed with 1 M HCl(aq) (2 × 10 mL), and the combined aqueous layers were extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a pale-green residue comprising mainly a white solid (1.40 g). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 85:15, hexane/toluene, ca. 5 mL fractions) gave a cloudy, colorless oil (173 mg). Further purification via flash column chromatography (C18 reversed-phase silica gel, 20 × 160 mm, MeOH, ca. 2.5 mL fractions, loaded with minimal MeCN for solubility reasons) gave a clear, pale-yellow oil (149 mg). Several further purifications via flash column chromatography (C18 reversed-phase silica gel, 20 × 160 mm, 98:2 MeOH/H_2O, ca. 2.5 mL fractions, loaded with minimal MeCN for solubility reasons) gave **8** as a clear, colorless oil (133 mg, 55%). Data for **8**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.31−7.23 (m, 2H), 7.21−7.10 (m, 5H), 6.91−6.84 (2 H, m), 3.81 (s, 3H), 2.75−2.62 (m, 1H), 2.58−2.44 (m, 2H), 1.96−1.82 (m, 2H), 1.26 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 158.1, 142.9, 139.6, 128.7, 128.5, 128.2, 125.9, 114.0, 55.5, 40.5, 38.9, 34.2, 23.0. IR (neat) 3083 (w), 3061 (w), 3026 (w), 2999 (w), 2955 (w), 2927 (w), 2867 (w), 2856 (w), 2834 (w), 1610 (m), 1583 (w), 1511 (s), 1496 (m), 1454 (m), 1374 (w), 1300 (m), 1246 (s), 1177 (m), 1034 (m), 829 (m), 808 (w), 747 (m), 699 (m). MS (EI$^+$, 70 eV) 240.2 (M$^+$, 43), 135.1 ($C_9H_{11}O^+$, 100), 105.1 (14), 91.1 ($C_7H_7^+$, 39), 77.0 (11). TLC R_f 0.30 (80:20, hexane/toluene) [$KMnO_4$]. Anal. Calcd for $C_{17}H_{20}O$ (240.34): C, 84.96; H, 8.39%. Found: C, 84.81; H, 8.26%.

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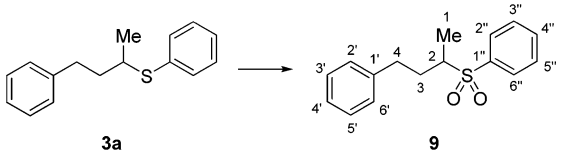
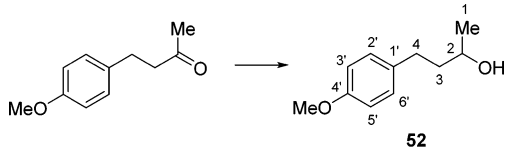
5.5. Preparation of Alkyl Phenyl Sulfone Substrates.



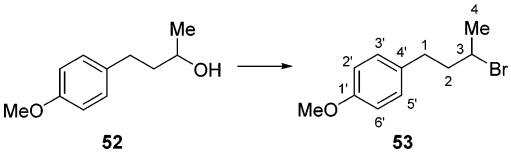
3a 9

*Preparation of (rac)-[(4-Phenylbutan-2-yl)sulfonyl]benzene (**9**).* A 250 mL, one-necked, round-bottomed flask equipped with a stirrer bar and rubber septum was charged with **3a** (6.06 g, 25.0 mmol, 1.0 equiv), ammonium molybdate tetrahydrate (3.09 g, 2.50 mmol, 10 mol %), and MeOH (63 mL), and stirring was commenced. The mixture was cooled to 0 °C in an ice/water bath, and then hydrogen peroxide (30% in H_2O, 11.3 g, 10.2 mL, 100 mmol, 4.0 equiv) was added dropwise via a syringe pump over 1 h (the internal temperature did not exceed 8 °C). The resultant turbid, pale-yellow mixture was stirred in the ice/water bath for 30 min and then allowed to warm to rt over 1 h, during which time the yellow color intensified. The mixture was then cooled to 1 °C in an ice/water bath and sat. Na_2SO_3(aq) (30 mL) was added dropwise via a syringe pump over 30 min (the internal temperature did not exceed 15 °C). Starch-iodide paper was used to confirm that no oxidant remained. EtOAc (100 mL) and H_2O (100 mL) were then added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a cloudy, colorless syrup (6.88 g). Purification via flash column chromatography on an automated flash column chromatography platform [120 g SiO_2 cartridge, hexane (1 CV) then 100:0 → 60:40, hexane/EtOAc (9 CV), 85 mL min^{-1} flow rate, 24 mL fractions] gave **9** as a clear, colorless syrup (6.20 g, 90%). The ^{1}H NMR spectroscopic data matched that for alternative preparations.[102]



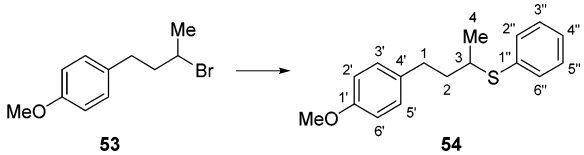
52

*Preparation of (rac)-4-(4-Methoxyphenyl)-2-butanol (**52**).* A 500 mL, one-necked, round-bottomed flask equipped with a stirrer bar and rubber septum was charged with 4-(4-methoxyphenyl)-2-butanone (10.0 g, 55.0 mmol, 1.0 equiv) and MeOH (140 mL), and stirring was commenced. The mixture was cooled to 0 °C in an ice/water bath, and sodium borohydride (2.29 g, 60.5 mmol, 1.1 equiv) was added portionwise over ca. 25 min (the internal temperature did not exceed 8 °C). The resultant turbid, colorless mixture was stirred in the ice/water bath for 25 min and then allowed to warm to rt over 15 min. The mixture was then concentrated in vacuo (50 °C, ca. 5 mmHg) and partitioned between EtOAc (50 mL) and H_2O (100 mL). The layers were separated, the aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a cloudy, colorless oil (10.8 g). Purification via short-path distillation under reduced pressure (0.01 mmHg) gave **52** as a clear, colorless oil (9.70 g, 98%). The ^{1}H NMR spectroscopic data matched that for alternative preparations.[103] Data for **52**: bp 114−116 °C (0.01 mmHg).



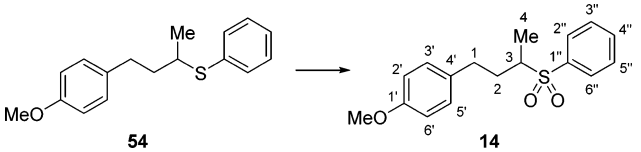
52 53

*Preparation of (rac)-4-(3-Bromobutyl)-1-methoxybenzene (**53**).* Bromine (10.2 g, 3.3 mL, 63.6 mmol, 1.2 equiv) was added in one-portion from a 5 mL measuring cylinder to a stirred suspension of triphenylphosphine (16.85 g, 63.6 mmol, 1.2 equiv) in CH_2Cl_2 (175 mL) in a 1 L, single-necked, round-bottomed flask equipped with a stirrer bar and cooled in an ice/water bath (open to air). The flask was then sealed with a rubber septum and purged with argon via an inlet needle. After stirring the resultant pale-yellow suspension for 15 min, a solution of **52** (9.55 g, 53.0 mmol, 1.0 equiv) and imidazole (4.37 g, 63.6 mmol, 1.2 equiv) in CH_2Cl_2 (90 mL) was added via cannula over ca. 10 min. The cooling bath was removed, and the reaction mixture was allowed to warm to rt over 17 h. The mixture was then filtered through a 40 mm Ø, porosity 3, sintered funnel under house vacuum and carefully concentrated in vacuo to leave a yellow oil residue (i.e., avoiding precipitating the phosphorus-containing residues at this point). A stirrer bar was added to the residue, a wide-neck plastic funnel was added to the neck of the flask, and rapid stirring was commenced. Pentane (265 mL) was quickly added in one portion to precipitate the phosphorus-containing residues as a fine white solid. The mixture was filtered through a 40 mm Ø, porosity 3, sintered funnel under house vacuum and was then concentrated in vacuo (50 °C, ca. 5 mmHg) to give a clear, colorless oil (15.24 g). Purification via short-path distillation under reduced pressure (0.01 mmHg) gave **53** as a clear, colorless oil (11.10 g, 86%). The ^{1}H NMR spectroscopic data matched that for an alternative preparation of the (*R*)-enantiomer.[104] Data for **53**: bp 98−100 °C (0.01 mmHg).



53 54

*Preparation of (rac)-1-Methoxy-4-[3-(phenylthio)butyl]benzene (**54**).* A 500 mL, one-necked, round-bottomed flask equipped with a stirrer bar, water-jacketed reflux condenser, and argon inlet was charged with **53** (7.29 g, 30.0 mmol, 1.0 equiv), thiophenol (3.41 g, 3.18 mL, 30.0 mmol, 1.0 equiv), potassium carbonate (8.29 g, 60.0 mmol, 2.0 equiv), and acetone (150 mL), and stirring was commenced. The resultant mixture was heated at reflux for 38 h and was then allowed to cool to rt. The mixture was filtered through a pad of Celite (5 g) in a 40 mm Ø, porosity 3, sintered funnel under house vacuum using minimal EtOAc and then concentrated in vacuo (50 °C, ca. 5 mmHg) to give a clear, pale-yellow oil (8.68 g). Purification via short-path distillation under reduced pressure (bp 157−158 °C, 0.01 mmHg) gave a clear, colorless oil (7.53 g). Further purification via flash column chromatography (200 g SiO_2, 70 mm Ø, hexane then 60:40, hexane/toluene, ca. 24 mL fractions) gave **54** as a clear, colorless oil (7.06 g, 86%). To obtain an analytical sample, a 157 mg portion of the above material was purified via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) to give a clear, colorless oil (154 mg, 98% mass return). Data for **54**: bp 150 °C ABT (10^{-5} mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 7.41−7.36 (m, 2H), 7.32−7.27 (m, 2H), 7.26−7.22 (m, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 3.81 (s, 3H), 3.26−3.17 (m, 1H), 2.82−2.70 (m, 2H), 1.98−1.88 (m, 1H), 1.87−1.76 (m, 1H), 1.34 (dd, *J* = 6.7, 0.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 158.1, 135.4, 133.9, 132.2, 129.6, 129.0, 126.9, 114.0, 55.5, 42.7, 38.7, 32.5, 21.5. IR (neat) 3071 (m), 3057 (m), 3030 (m), 3000 (m), 2955 (s), 2926 (s), 2858 (m), 2833 (m), 1879 (m), 1611 (s), 1583 (s), 1511 (s), 1479 (s), 1438 (s), 1374 (m), 1300 (s), 1246 (s), 1177 (s), 1113 (m), 1091 (m), 1068 (m), 1037 (s), 895 (m), 823 (s), 744 (s), 692 (s). MS (EI$^+$, 70 eV) 272.0 (M^+, 35), 162.1 (69), 147.0 (31), 121.0 ($C_8H_9O^+$, 100), 109.0 (10), 83.9 (11), 77.0 (13). TLC R_f 0.24 (60:40, hexane/toluene) [$KMnO_4$]. Anal. Calcd for: $C_{17}H_{20}OS$ (272.41): C, 74.96; H, 7.40%. Found: C, 75.03; H, 7.49%.



54 14

*Preparation of (rac)-1-Methoxy-4-[3-(phenylsulfonyl)butyl]-benzene (**14**).* A 250 mL, one-necked, round-bottomed flask equipped with a stirrer bar and rubber septum was charged with **54** (6.81 g, 25.0 mmol, 1.0 equiv), ammonium molybdate tetrahydrate (3.09 g, 2.50 mmol, 10 mol %), and MeOH (63 mL), and stirring was commenced. The mixture was cooled to 0 °C in an ice/water bath, and hydrogen

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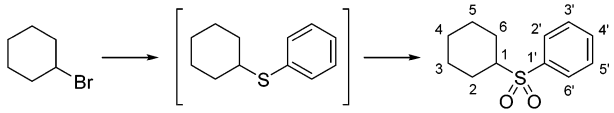
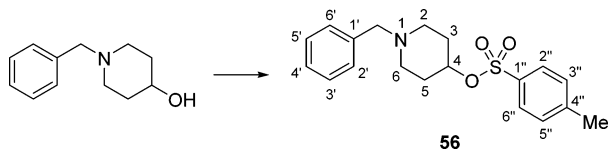
peroxide (30% in H_2O, 11.3 g, 10.2 mL, 100 mmol, 4.0 equiv) was added dropwise via a syringe pump over 1.5 h (the internal temperature did not exceed 4 °C). The resultant turbid, pale-yellow mixture was stirred in the ice/water bath for 30 min and then allowed to warm to rt over 1 h, during which time the yellow color intensified. The mixture was then cooled to 1 °C in an ice/water bath and sat. Na_2SO_3(aq) (35 mL) was added dropwise via a syringe pump over 1 h (the internal temperature did not exceed 12 °C). Starch-iodide paper was used to confirm that no oxidant remained. EtOAc (120 mL) and H_2O (120 mL) were then added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a cloudy, colorless syrup (7.62 g). Purification via flash column chromatography (200 g SiO_2, 70 mm Ø, 80:20, hexane/EtOAc then 70:30, hexane/EtOAc, ca. 24 mL fractions) gave **14** as a clear, colorless oil (7.58 g, 100%). Data for **14**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.83 (d, J = 9.1 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.56−7.50 (m, 2H), 7.01 (d, J = 8.5, 2H), 6.80 (d, J = 8.5 Hz, 2H), 3.76 (s, 3H), 3.06−2.97 (m, 1H), 2.79−2.70 (m, 1H), 2.56−2.47 (m, 1H), 2.31−2.22 (m, 1H), 1.73−1.62 (m, 1H), 1.29 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 158.3, 137.4, 133.9, 132.3, 129.5, 129.3, 129.2, 114.2, 59.3, 55.5, 31.8, 31.1, 13.5. IR (neat) 3062 (w), 3030 (w), 2953 (m), 2935 (m), 2865 (w), 2835 (w), 1611 (m), 1583 (m), 1513 (s), 1461 (m), 1446 (s), 1420 (w), 1380 (w), 1303 (s), 1246 (s), 1178 (s), 1145 (s), 1085 (s), 1034 (s), 999 (w), 929 (w), 902 (w), 821 (m), 764 (m), 729 (s), 693 (s), 660 (w), 637 (w), 620 (w), 593 (s), 566 (m). MS (ESI) 327.1 ([M+Na]$^+$, 100), 322.1 ([M+NH$_4$]$^+$, 32), 305.1 ([M+H]$^+$, 98), 163.1 (22), 143.0 (17), 121.1 ($C_8H_9O^+$, 25). HRMS (ESI, TOF) calcd for $C_{17}H_{21}O_3S$, 305.1211; found, 305.1214. TLC R_f 0.48 (70:30, hexane/EtOAc) [$KMnO_4$].



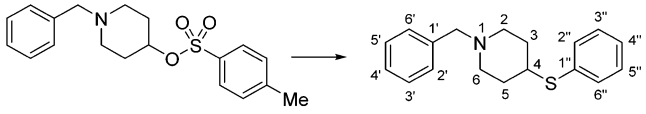
55 **18a**

*Preparation of (Phenylsulfonyl)cyclohexane (**18a**).* A 500 mL, one-necked, round-bottomed flask equipped with a stirrer bar, water-jacketed reflux condenser, and argon inlet was charged with cyclohexyl bromide (8.24 g, 50.0 mmol, 1.0 equiv), thiophenol (5.68 g, 5.29 mL, 50.0 mmol, 1.0 equiv), potassium carbonate (13.82 g, 100.0 mmol, 2.0 equiv), and acetone (250 mL), and stirring was commenced. The resultant mixture was heated at reflux for 24 h and was then allowed to cool to rt. The mixture was filtered through a pad of SiO_2 (5 g) in a 40 mm Ø, porosity 3, sintered funnel under house vacuum using minimal EtOAc and then concentrated in vacuo (50 °C, ca. 5 mmHg) to give a clear, yellow oil (6.02 g). Purification via short-path distillation under reduced pressure (bp 98−100 °C, 0.5 mmHg) gave **55** contaminated with thiophenol (∼5%) as a clear, colorless oil (3.33 g). Further purification via flash column chromatography [200 g basic alumina (Brockmann grade 1), 50 mm Ø, hexane, ca. 10 mL fractions] gave **55** that was still contaminated with thiophenol (∼5%) as a clear, colorless oil (3.23 g). The ^{1}H NMR spectroscopic data for **55** matched that for an alternative preparation.[105] A 25 mL, one-necked, round-bottomed flask equipped with a stirrer bar and rubber septum was then charged with **55** (577 mg, approximately 3.00 mmol, 1.0 equiv), ammonium molybdate tetrahydrate (371 mg, 0.30 mmol, 10 mol %), and MeOH (8.5 mL), and stirring was commenced. The mixture was cooled in an ice/water bath, and hydrogen peroxide (30% in H_2O, 1.36 g, 1.23 mL, 12.0 mmol, 4.0 equiv) was added dropwise via syringe over ca. 10 min. The resultant turbid, pale-yellow mixture was stirred in the ice/water bath for 40 min and then allowed to warm to rt over 1 h, during which time the yellow color intensified. The mixture was then cooled in an ice/water bath and sat. Na_2SO_3(aq) (3.5 mL) was added dropwise via syringe over ca. 5 min. Starch-iodide paper was used to confirm that no oxidant remained. EtOAc (10 mL) and H_2O (10 mL) were then added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a cloudy, colorless syrup (651 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 75:25, hexane/EtOAc, ca. 5 mL fractions) gave **18a** as a clear, colorless syrup that solidified on standing to a white, crystalline solid (611 mg, approximately 91%). The ^{1}H NMR spectroscopic data and melting point matched that for an alternative preparation.[106]



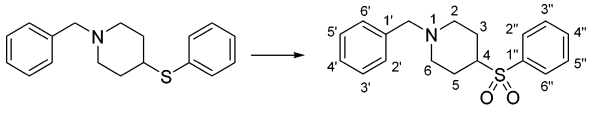
56

*Preparation of N-Benzylpiperidin-4-yl 4-Toluenesulfonate (**56**).* A 200 mL, one-necked, round-bottomed flask equipped with a stirrer bar, rubber septum, and argon inlet was charged with *N*-benzyl-4-hydroxypiperidine (5.00 g, 26.1 mmol, 1.0 equiv), Et_3N (7.94 g, 10.9 mL, 78.4 mmol, 3.0 equiv), and CH_2Cl_2 (65 mL), and stirring was commenced. The mixture was cooled to 0 °C in an ice/water bath, and 4-toluenesulfonyl chloride (5.98 g, 31.4 mmol, 1.2 equiv) was added portionwise over ca. 10 min (the internal temperature did not exceed 1 °C). The resultant mixture was stirred in the ice/water bath for 30 min and then allowed to warm to rt over 21 h. Sat. $NaHCO_3$(aq) (100 mL) was then added, and the layers were separated. The organic layer was washed with sat. $NaHCO_3$(aq) (2 × 50 mL), and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were then dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give an orange syrup (10.55 g). Purification via flash column chromatography on an automated flash column chromatography platform [120 g SiO_2 cartridge, 100:0 → 40:60, hexane/EtOAc (1 CV) then *i*-PrOH, 85 mL min^{-1} flow rate, 24 mL fractions] gave impure **56** as a clear, orange syrup that solidified on standing to a yellow, crystalline solid (5.28 g) in addition to mixed fractions, returned starting material and other unidentified products. Attempted purification of a 100 mg portion of the impure product via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) led to decomposition to a black tar (ca. 150 °C ABT). The remainder of the impure **56** was purified via recrystallization from 90:10, hexane/toluene (10 mL) in a 20 mL scintillation vial. The crystals were collected via filtration through filter paper in a Hirsch funnel under house vacuum, washed with a minimal amount of cold (−78 °C) hexane, crushed with a glass rod, and dried in vacuo (0.05 mmHg) to give a cream-colored, crystalline solid (2.92 g). This material was subsequently combined with a second crop (997 mg) and third crop (535 mg) (both of comparable purity to the first crop according to ^{1}H NMR spectroscopic analysis) to give **56** as a cream-colored, crystalline solid (4.45 g, 50%). To obtain an analytical sample, a 1.03 g portion of the above material was dissolved in EtOH (4.0 mL) in a 20 mL scintillation vial, and the vial was sealed with a screw top cap and left in the freezer at −20 °C overnight. The resultant crystals were collected via filtration through filter paper in a Hirsch funnel under house vacuum, washed with cold (0 °C) EtOH (2.0 mL), and crushed with a glass rod and dried in vacuo (0.05 mmHg) to give **56** as a white, crystalline solid (301 mg, 29% mass return). Data for **56**: mp 66−67 °C (EtOH). ^{1}H NMR (500 MHz, $CDCl_3$) 7.78 (d, J = 8.3 Hz, 2H), 7.35−7.20 (m, 7H), 4.58−4.47 (br m, 1H), 3.46 (s, 2H), 2.69−2.55 (br m, 2H), 2.43 (s, 3H), 2.31−2.11 (br m, 2H), 1.87−1.71 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) 144.8, 138.3, 134.8, 130.0, 129.2, 128.5, 127.8, 127.4, 79.2, 63.0, 50.3, 31.8, 21.9. IR ($CHCl_3$ mull) 3086 (w), 3063 (w), 3029 (w), 2952 (w), 2811 (w), 2773 (w), 1598 (w), 1494 (w), 1454 (m), 1398 (w), 1357 (s), 1306 (w), 1291 (w), 1267 (w), 1253 (w), 1211 (w), 1188 (m), 1176 (s), 1141 (w), 1132 (w), 1120 (w), 1097 (m), 1072 (w), 1037 (w), 1028 (w), 1019 (w), 998 (m), 945 (m), 910 (m), 870 (m), 845 (m), 814 (m), 796 (w), 741 (m), 699 (m), 680 (m), 670 (m), 617 (w), 573 (m), 555 (m). MS (ESI) 346.1 ([M+H]$^+$, 100), 192.0 (26). TLC R_f 0.50 (50:50, hexane/EtOAc) [$KMnO_4$]. Anal. Calcd for $C_{19}H_{23}NO_3S$ (345.46): C, 66.06; H, 6.71; N, 4.05%. Found: C, 65.80; H, 6.70; N, 4.15%.



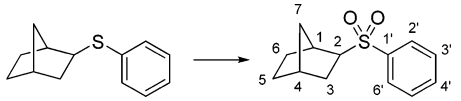
56 57

*Preparation of N-Benzyl-4-(phenylthio)piperidine (**57**).* A 25 mL, one-necked, round-bottomed flask equipped with a stirrer bar, air condenser, and argon inlet was charged with **56** (1.04 g, 3.00 mmol, 1.0 equiv), thiophenol (511 mg, 476 μL, 4.50 mmol, 1.5 equiv), and DMF (8.0 mL), and stirring was commenced. Sodium hydride (60% in mineral oil, 240 mg, 6.00 mmol, 2.0 equiv) was added portionwise, and the resultant mixture was heated at 70 °C for 16 h and then allowed to cool to rt. The mixture was then partitioned between EtOAc (10 mL) and H_2O (40 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were washed with H_2O (5 × 40 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a clear, yellow oil (927 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 85:15, hexane/EtOAc, ca. 5 mL fractions) gave impure **57** as a clear, orange oil that solidified on standing to an orange, crystalline solid (635 mg). Further purification was performed via recrystallization from hexane (4.0 mL) in a 20 mL scintillation vial. The crystals were collected via filtration through filter paper in a Hirsch funnel under house vacuum, washed with cold (−78 °C) hexane (2.0 mL), crushed with a glass rod, and dried in vacuo (0.05 mmHg) to give a cream-colored, crystalline solid (557 mg). Further purification was performed via recrystallization from MeOH (4.0 mL) in a 20 mL scintillation vial. The crystals were collected via filtration through filter paper in a Hirsch funnel under house vacuum, washed with cold (−78 °C) MeOH (2.0 mL), crushed with a glass rod, and dried in vacuo (0.05 mmHg) to give a white, crystalline solid (471 mg). This material was subsequently combined with a second crop (63.4 mg) (of comparable purity to the first crop according to ^{1}H NMR spectroscopic analysis) to give **57** as a white, crystalline solid (534 mg, 63%). Data for **57**: mp 83−84 °C (MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) 7.46−7.41 (m, 2H), 7.36−7.23 (m, 8H), 3.52 (s, 2H), 3.17−3.04 (br m, 1H), 2.94−2.79 (m, 2H), 2.18−2.03 (m, 2H), 2.02−1.92 (m, 2H), 1.78−1.64 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) 138.6, 134.8, 132.5, 129.4, 129.1, 128.4, 127.3, 127.1, 63.4, 53.3, 44.8, 32.8. IR ($CHCl_3$ mull) 3058 (w), 2955 (m), 2920 (m), 2850 (w), 2787 (m), 2750 (m), 2717 (w), 2691 (w), 2671 (w), 1585 (m), 1493 (m), 1480 (s), 1450 (m), 1435 (m), 1388 (w), 1354 (m), 1339 (m), 1302 (m), 1271 (w), 1258 (w), 1222 (w), 1211 (w), 1198 (w), 1185 (w), 1166 (w), 1140 (m), 1130 (m), 1091 (m), 1069 (w), 1026 (m), 996 (m), 973 (w), 902 (w), 890 (w), 802 (m), 769 (w), 731 (s), 698 (s), 689 (m). MS (EI$^+$, 70 eV) 283.1 (M^+, 28), 174.1 (74), 91.1 ($C_7H_7^+$, 100). TLC R_f 0.28 (80:20, hexane/EtOAc) [$KMnO_4$]. Anal. Calcd for $C_{18}H_{21}NS$ (283.43): C, 76.28; H, 7.47; N, 4.94%. Found: C, 75.98; H, 7.59; N, 5.01%.



57 18b

*Preparation of N-Benzyl-4-(phenylsulfonyl)piperidine (**18b**).* A 50 mL, one-necked, round-bottomed flask equipped with a stirrer bar and rubber septum was charged with **57** (562 mg, 1.98 mmol, 1.0 equiv), MeOH (8.0 mL), and THF (6.0 mL), and stirring was commenced. The mixture was cooled in an ice/water bath, and a solution of oxone [49.5% $KHSO_5$, 1.83 g, 5.95 mmol (of $KHSO_5$), 3.0 equiv (of $KHSO_5$)] was added dropwise via Pasteur pipet over ca. 5 min. The resultant turbid, white mixture was then allowed to warm to rt over 19 h. H_2O (10 mL) was added, the mixture was filtered through a 40 mm Ø, porosity 3, sintered funnel under house vacuum, and the solid residue rinsed with EtOAc (2 × 10 mL). The filtrate was transferred to a 250 mL separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic extracts were washed sequentially with sat. $NaHCO_3$(aq) (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a clear, yellow syrup (495 mg). Two molar NaOH(aq) (10 mL) was added to the combined aqueous layers, which were then extracted with EtOAc (3 × 10 mL) and dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a clear, colorless syrup (186 mg). The two portions of organic material were combined to give a clear, yellow syrup (682 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 60:40, hexane/EtOAc, ca. 5 mL fractions) gave a clear, colorless syrup (559 mg). Further purification was performed via recrystallization from MeOH (4.0 mL) in a 20 mL scintillation vial. Following brief cooling in an ice/water bath, the crystals were collected via filtration through filter paper in a Hirsch funnel under house vacuum, washed with cold (−78 °C) MeOH (2.0 mL), crushed with a glass rod, and dried in vacuo (0.05 mmHg) to give **18b** as a white, crystalline solid (345 mg, 55%). Data for **18b**: mp 87−88 °C (MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) 7.89−7.84 (m, 2H), 7.68−7.63 (m, 1H), 7.59−7.52 (m, 2H), 7.32−7.20 (m, 5H), 3.46 (s, 2H), 3.00−2.94 (m, 2H), 2.90 (tt, J = 12.3, 3.7 Hz, 1H), 2.01−1.88 (m, 4H), 1.78−1.67 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) 138.1, 137.1, 133.9, 129.4, 129.3, 129.2, 128.5, 127.4, 62.9, 62.2, 52.4, 25.7. IR ($CHCl_3$ mull) 3062 (w), 3026 (m), 2953 (m), 2806 (m), 2762 (m), 1585 (w), 1494 (m), 1467 (w), 1447 (s), 1394 (w), 1366 (m), 1342 (m), 1304 (s), 1273 (s), 1233 (m), 1145 (s), 1086 (s), 1028 (m), 994 (m), 932 (w), 909 (w), 877 (w), 813 (m), 752 (s), 721 (s), 690 (s), 667 (m), 646 (w), 617 (s), 602 (s), 565 (s). MS (EI$^+$, 70 eV) 315.1 (M^+, 9), 174.1 (58), 120.1 (16), 110.0 (11), 91.1 ($C_7H_7^+$, 100), 82.1 (22), 77.1 (26), 65.1 (13), 51.0 (20). HRMS (EI$^+$, double focusing sector field) calcd for $C_{18}H_{21}NO_2S$, 315.1293; found, 315.1288. TLC R_f 0.16 (60:40, hexane/EtOAc) [$KMnO_4$].



18c

*Preparation of (1*l*,2*l*,4*u*)-2-(Phenylthio)bicyclo[2.2.1]heptane (**18c**).* A 50 mL, one-necked, round-bottomed flask equipped with a stirrer bar and rubber septum was charged with (1*l*,2*l*,4*u*)-2-(phenylthio)bicyclo[2.2.1]heptane[107] (462 mg, 2.26 mmol, 1.0 equiv), ammonium molybdate tetrahydrate (280 mg, 0.23 mmol, 10 mol %), and MeOH (6.5 mL), and stirring was commenced. The mixture was cooled in an ice/water bath, and hydrogen peroxide (30% in H_2O, 1.03 g, 0.92 mL, 9.05 mmol, 4.0 equiv) was added dropwise via syringe over ca. 15 min. The resultant turbid, pale-yellow mixture was stirred in the ice/water bath for 40 min and then allowed to warm to rt over 1 h, during which time the yellow color intensified. The mixture was then cooled in an ice/water bath, and sat. Na_2SO_3(aq) (3.3 mL) was added dropwise via syringe over ca. 6 min. Starch-iodide paper was used to confirm that no oxidant remained. EtOAc (10 mL) and H_2O (10 mL) were then added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a cloudy, colorless syrup (568 mg). Purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave a clear, colorless syrup that solidified on standing to a white, crystalline solid (521 mg). Further purification was performed via recrystallization from MeOH (4.0 mL) in a 20 mL scintillation vial, which was sealed with a screw top cap and left in the freezer at −20 °C for ca. 30 min. The resultant crystals were collected via filtration through filter paper in a Hirsch funnel under house vacuum, washed with cold (−78 °C) MeOH (1.0 mL), crushed with a glass rod, and dried in vacuo (0.05 mmHg) to give a white, crystalline solid (311 mg). This material was subsequently combined with a second crop (120 mg) (of comparable purity to the first crop according to ^{1}H NMR spectroscopic analysis) to give **18c** as a white, crystalline solid (431 mg, 81%, >99:1 dr). Data for **18c**: mp 81−82 °C (MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) 7.90−7.84 (m, 2H), 7.64−7.59 (m, 1H), 7.57−7.50 (m, 2H), 2.98 (dd, J = 8.5, 6.2 Hz, 1H), 2.67−2.63 (br m, 1H), 2.39−2.34 (br m, 1H), 2.05−1.97 (m, 1H), 1.83−1.76 (m, 1H), 1.61−1.45 (m, 3H), 1.20−1.09 (m, 3H). ^{13}C

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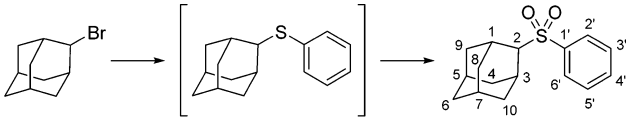
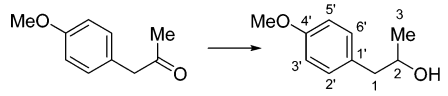
NMR (125 MHz, $CDCl_3$) 139.3, 133.6, 129.4, 128.6, 66.9, 39.0, 36.3, 36.3, 32.8, 30.0, 28.3. IR ($CHCl_3$ mull) 3062 (w), 2962 (m), 2872 (m), 1585 (w), 1478 (w), 1446 (m), 1325 (m), 1303 (s), 1272 (m), 1243 (w), 1205 (w), 1146 (s), 1086 (s), 1071 (w), 1047 (w), 1024 (w), 998 (w), 957 (w), 922 (w), 905 (w), 878 (w), 843 (w), 788 (w), 758 (m), 721 (s), 694 (s), 670 (w), 611 (s), 559 (s). MS (CI) 237.0 ($[M+H]^+$, 31), 171.0 (26), 143.0 (80), 95.0 ($C_7H_{11}^+$, 100). TLC R_f 0.35 (80:20, hexane/EtOAc) [$KMnO_4$]. Anal. Calcd for $C_{13}H_{16}O_2S$ (236.33): C, 66.07; H, 6.82%. Found: C, 65.79; H, 6.86%.



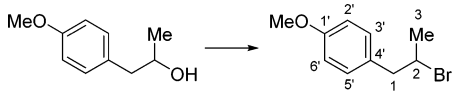
58 18d

*Preparation of 2-(Phenylsulfonyl)tricyclo[3.3.1.1^{3,7}]decane (**18d**).* A 25 mL Schlenk flask equipped with a stirrer bar, rubber septum, and argon inlet was evacuated, flame-dried, left to cool to rt, and flushed with argon three times. Magnesium turnings (233 mg, 9.60 mmol, 1.2 equiv) were quickly added against a backflow of argon followed by iodine (several crystals) and THF (1.0 mL), and stirring was commenced. Meanwhile, an oven-dried, 20 mL scintillation vial was charged with 2-bromoadamantane (1.76 g, 8.00 mmol, 1.0 equiv), and the vial was then sealed with an inverted rubber septum and purged with argon. THF (1.0 mL) was then added via syringe, and a small portion of the resultant solution was transferred via cannula to the Schlenk flask containing the magnesium and iodine to initiate the reaction. Once the reaction mixture had decolorized (several minutes), THF (8.0 mL) was added to the vial containing the 2-bromoadamantane, and the resultant solution was added dropwise via cannula to the Schlenk flask over ca. 15 min. A water-jacketed reflux condenser was added, and the reaction mixture was heated at reflux for 1 h and then allowed to cool to rt. The mixture was cooled in an ice/water bath, and a solution of diphenyl disulfide (1.68 g, 7.60 mmol, 0.95 equiv) in THF (5.0 mL) was added dropwise via cannula over ca. 5 min, and the reaction was allowed to warm to rt over 24 h with stirring. One molar HCl(aq) (10 mL) was added followed by EtOAc (30 mL) and H_2O (30 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a suspension of white solid in a clear, yellow oil (1.97 g). Purification via flash column chromatography [100 g basic alumina (Brockmann grade 1), 30 mm Ø, hexane, ca. 10 mL fractions] gave a ∼1:1 mixture of **58** and diphenyl disulfide as a clear, yellow oil (680 mg) in addition to fractions containing a mixture of **58**, diphenyl disulfide, and thiophenol. The latter fractions were concentrated in vacuo (50 °C, ca. 5 mmHg) and purified via flash column chromatography [100 g basic alumina (Brockmann grade 1), 30 mm Ø, hexane, ca. 10 mL fractions] to give a ∼1:1 mixture of **58** and diphenyl disulfide as a clear, yellow oil (193 mg). Attempted purification of the combined material (873 mg) via preparative, radial, centrifugally accelerated, thin-layer chromatography on a Harrison Chromatotron (4 mm SiO_2 plate, hexane, ca. 5 mL fractions) proved unsuccessful in removing the diphenyl disulfide contaminant. Thus, the ∼1:1 mixture of **58** and diphenyl disulfide (873 mg) was carried forward in the next step. The ^{1}H NMR spectroscopic data for the **58** present in the mixture matched that for a pure sample prepared via an alternative procedure.[108] A 100 mL, one-necked, round-bottomed flask equipped with a stirrer bar and rubber septum was then charged with the ∼1:1 mixture of **58** and diphenyl disulfide (873 mg), ammonium molybdate tetrahydrate (989 mg, 0.80 mmol), and MeOH (25.0 mL), and stirring was commenced. The mixture was cooled to 0 °C in an ice/water bath, and hydrogen peroxide (30% in H_2O, 3.63 g, 3.27 mL, 32.0 mmol) was added dropwise via a syringe pump over 1 h (the internal temperature did not exceed 1 °C). The resultant turbid, pale-yellow mixture was stirred in the ice/water bath for 30 min and then allowed to warm to rt over 2 h, during which time the yellow color intensified. The mixture was then cooled to 0 °C in an ice/water bath, and sat. Na_2SO_3(aq) (20 mL) was added dropwise via a syringe pump over 1 h (the internal temperature did not exceed 9 °C). Starch-iodide paper was used to confirm that no oxidant remained. The mixture was filtered through a 40 mm Ø, porosity 3, sintered funnel under house vacuum, and EtOAc (40 mL) and H_2O (40 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give almost pure **18d** as a white solid (571 mg). The material was purified via recrystallization from MeOH (5.0 mL) in a 20 mL scintillation vial, which was sealed with a screw top cap and left at rt overnight. The resultant crystals were collected via filtration through filter paper in a Hirsch funnel under house vacuum and washed with cold (0 °C) MeOH (2.0 mL) to give a white, crystalline solid (493 mg). A second recrystallization of this material under the same conditions using MeOH (4.0 mL) gave crystals that were crushed with a glass rod and dried in vacuo (0.05 mmHg) to give **18d** as a white, crystalline solid (448 mg, 21% based on diphenyl disulfide as the limiting reagent from the first step). Data for **18d**: mp 135−136 °C (MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) 7.90−7.85 (m, 2H), 7.65−7.59 (m, 1H), 7.57−7.51 (m, 2H), 3.15−3.10 (br m, 1H), 2.63−2.53 (m, 2H), 2.39−2.32 (br m, 2H), 1.98−1.81 (m, 4H), 1.76−1.69 (br m, 2H), 1.64−1.53 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) 139.1, 133.6, 129.3, 128.6, 69.4, 39.2, 37.4, 31.5, 28.2, 27.7, 27.0. IR ($CHCl_3$ mull) 2918 (s), 2853 (m), 1583 (w), 1472 (m), 1451 (m), 1409 (w), 1357 (w), 1342 (w), 1321 (m), 1300 (s), 1288 (s), 1240 (m), 1221 (m), 1180 (w), 1166 (w), 1148 (s), 1114 (m), 1101 (m), 1086 (m), 1076 (m), 1036 (w), 1022 (w), 998 (w), 981 (w), 967 (w), 939 (w), 903 (w), 828 (m), 784 (w), 766 (m), 756 (m), 722 (m), 695 (m), 666 (m), 623 (w). MS (CI) 277.3 ($[M+H]^+$, 27), 135.2 ($C_{10}H_{15}^+$, 100). TLC R_f 0.43 (80:20, hexane/EtOAc) [$KMnO_4$]. Anal. Calcd for $C_{16}H_{20}O_2S$ (276.39): C, 69.53; H, 7.29%. Found: C, 69.28; H, 7.37%.



59

*Preparation of (rac)-1-(4-Methoxyphenyl)-2-propanol (**59**).* A 50 mL, one-necked, round-bottomed flask equipped with a stirrer bar and rubber septum was charged with 4-methoxyphenylacetophenone (575 mg, 3.50 mmol, 1.0 equiv) and MeOH (8.8 mL), and stirring was commenced. The mixture was cooled to 0 °C in an ice/water bath, and sodium borohydride (146 mg, 3.85 mmol, 1.1 equiv) was added portion wise over ca. 5 min. The resultant turbid, colorless mixture was stirred in the ice/water bath for 10 min and then allowed to warm to rt over 30 min. The mixture was then concentrated in vacuo (50 °C, ca. 5 mmHg) and partitioned between EtOAc (10 mL) and H_2O (20 mL). The layers were separated, the aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a cloudy, colorless oil (624 mg). Purification via bulb-to-bulb distillation under reduced pressure (0.05 mmHg) gave **59** as a clear, colorless oil (568 mg, 98%). The ^{1}H NMR spectroscopic data matched that for alternative preparations.[109] Data for **59**: bp 140 °C ABT (0.05 mmHg).



59 60

*Preparation of (rac)-4-(2-Bromopropyl)-1-methoxybenzene (**60**).* Bromine (578 mg, 186 μL, 3.60 mmol, 1.2 equiv) was added via syringe to a stirred suspension of triphenylphosphine (954 mg, 3.60 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) in a 50 mL, single-necked, round-bottomed flask equipped with a stirrer bar and cooled in an ice/water bath (open to air). The flask was then sealed with a rubber septum and purged with argon via an inlet needle. After stirring the resultant pale-yellow suspension for 15 min, a solution of **59** (499 mg, 3.00 mmol, 1.0 equiv) and imidazole (248 mg, 3.60 mmol, 1.2 equiv) in CH_2Cl_2 (5 mL) was added via cannula over ca. 10 min. The cooling

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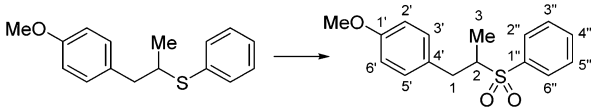
bath was removed, and the reaction mixture was allowed to warm to rt over 4 h 20 min. The mixture was then filtered through a 40 mm Ø, porosity 3, sintered funnel under house vacuum and carefully concentrated in vacuo to leave a yellow oil residue (i.e., avoiding precipitating the phosphorus-containing residues at this point). A stirrer bar was added to the residue, a wide-neck plastic funnel was added to the neck of the flask, and rapid stirring was commenced. Pentane (15 mL) was quickly added in one portion to precipitate the phosphorus-containing residues as a fine white solid. The mixture was filtered through a 40 mm Ø, porosity 3, sintered funnel under house vacuum and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a clear, colorless oil (536 mg). Purification via bulb-to-bulb distillation under reduced pressure (160 °C ABT, 0.05 mmHg) gave **60** contaminated with (*E*)-1-(4-methoxyphenyl)prop-1-ene[110] (~5%) as a clear, colorless oil (469 mg). Data for **60**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.13 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.31−4.23 (m, 1H), 3.81 (s, 3H), 3.18 (dd, *J* = 14.1, 6.9 Hz, 1H), 3.02 (dd, *J* = 14.1, 7.2 Hz, 1H), 1.69 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 158.7, 130.9, 130.5, 114.0, 55.5, 51.4, 46.9, 25.8. MS (EI$^+$, 70 eV) 230.0 ([^{81}Br]M$^+$, 8), 228.0 ([^{79}Br]M$^+$, 8), 149.1 ($C_{10}H_{13}O^+$, 13), 121.1 ($C_8H_9O^+$, 100). HRMS (EI$^+$, double focusing sector field) calcd for $C_{10}H_{13}O^{79}Br$, 228.0150; found, 228.0147.

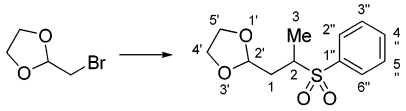
60 **61**

*Preparation of (rac)-1-Methoxy-4-[2-(phenylthio)propyl]benzene (**61**).* A 25 mL, one-necked, round-bottomed flask equipped with a stirrer bar, water-jacketed reflux condenser, and argon inlet was charged with **60** (462 mg, approximately 2.00 mmol, 1.0 equiv), thiophenol (227 mg, 212 μL, 1.00 mmol, 1.0 equiv), potassium carbonate (553 mg, 4.00 mmol, 2.0 equiv), and acetone (10.0 mL), and stirring was commenced. The resultant mixture was heated at reflux for 14 h and was then allowed to cool to rt. The mixture was filtered through a 40 mm Ø, porosity 3, sintered funnel under house vacuum and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a colorless oil containing a 84:16 ratio of product/starting material. Resubjection of this material to the above reaction conditions for a further 15 h gave a clear, yellow oil (761 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, hexane then 70:30, hexane/toluene, ca. 5 mL fractions) gave a clear, colorless oil (443 mg). Further purification via bulb-to-bulb distillation under reduced pressure (0.03 mmHg) gave **61** as a clear, colorless oil (421 mg, approximately 80%). Data for **61**: bp 175 °C ABT (0.03 mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 7.47−7.42 (m, 2H), 7.36−7.30 (m, 2H), 7.28−7.23 (m, 1H), 7.14−7.09 (m, 2H), 6.88−6.83 (m, 2H), 3.81 (s, 3H), 3.49−3.40 (m, 1H), 3.04−2.95 (m, 1H), 2.68−2.59 (m, 1H), 1.25 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 158.1, 135.5, 132.2, 131.5, 130.4, 129.1, 127.0, 114.0, 55.5, 44.9, 42.5, 20.4. IR (neat) 3072 (w), 3057 (w), 3031 (w), 3001 (w), 2958 (w), 2925 (w), 2864 (w), 2834 (w), 1612 (w), 1583 (w), 1513 (m), 1480 (w), 1472 (w), 1463 (w), 1454 (w), 1439 (w), 1373 (w), 1301 (w), 1249 (m), 1177 (w), 1113 (w), 1091 (w), 1036 (w), 814 (w), 745 (w), 692 (w). MS (EI$^+$, 70 eV) 258.1 (M$^+$, 31), 149.1 ($C_{10}H_{13}O^+$, 30), 137.0 ($C_8H_9S^+$, 100), 121.1 ($C_8H_9O^+$, 74), 109.0 (15), 91.0 (12), 77.1 (14). TLC R_f 0.39 (60:40, hexane/toluene) [$KMnO_4$]. Anal. Calcd for $C_{16}H_{18}OS$ (258.38): C, 74.38; H, 7.02%. Found: C, 74.56; H, 6.94%.



61 **18f**

*Preparation of (rac)-1-Methoxy-4-[2-(phenylsulfonyl)propyl]-benzene (**18f**).* A 25 mL, one-necked, round-bottomed flask equipped with a stirrer bar and rubber septum was charged with **61** (394 mg, 1.52 mmol, 1.0 equiv), ammonium molybdate tetrahydrate (188 mg, 0.15 mmol, 10 mol %), and MeOH (4.5 mL), and stirring was commenced. The mixture was cooled in an ice/water bath, and hydrogen peroxide (30% in H_2O, 691 mg, 622 μL, 6.09 mmol, 4.0 equiv) was added dropwise via syringe over ca. 14 min. The resultant turbid, pale-yellow mixture was stirred in the ice/water bath for 35 min and then allowed to warm to rt over 1 h, during which time the yellow color intensified. The mixture was then cooled in an ice/water bath, and sat. Na_2SO_3(aq) (2.3 mL) was added dropwise via syringe over ca. 7 min. Starch-iodide paper was used to confirm that no oxidant remained. EtOAc (10 mL) and H_2O (10 mL) were then added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a cloudy, colorless syrup (477 mg). Purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave **18f** as a clear, colorless syrup (438 mg, 99%). Data for **18f**: bp 200 °C ABT (10^{-5} mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 7.94−7.90 (m, 2H), 7.68−7.63 (m, 1H), 7.60−7.54 (m, 2H), 6.99 (d, *J* = 8.7, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 3.75 (s, 3H), 3.35 (dd, *J* = 13.5, 3.1 Hz, 1H), 3.26−3.16 (m, 1H), 2.47 (dd, *J* = 13.5, 11.5 Hz, 1H), 1.13 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 158.7, 137.4, 134.0, 134.0, 130.3, 129.4, 129.0, 114.3, 62.0, 55.5, 34.7, 12.9. IR ($CHCl_3$ mull) 3063 (w), 3031 (w), 2994 (w), 2935 (m), 2875 (w), 2836 (w), 1611 (s), 1584 (m), 1513 (s), 1446 (s), 1421 (w), 1377 (w), 1303 (s), 1249 (s), 1202 (w), 1179 (s), 1145 (s), 1116 (m), 1086 (s), 1070 (m), 1033 (s), 999 (w), 911 (w), 865 (w), 847 (m), 817 (s), 776 (m), 759 (m), 731 (s), 692 (s), 594 (s), 579 (m), 556 (s). MS (ESI) 345.1 (60), 313.0 ([M+Na]$^+$, 100), 149.1 ($C_{10}H_{13}O^+$, 40). TLC R_f 0.17 (80:20, hexane/EtOAc) [$KMnO_4$]. Anal. Calcd for: $C_{16}H_{18}O_3S$ (290.38): C, 66.18; H, 6.25%. Found: C, 66.43; H, 6.39%.



18g

*Preparation of (rac)-2-[2-(Phenylsulfonyl)propyl]-1,3-dioxolane (**18g**).* A 25 mL Schlenk flask equipped with a stirrer bar, rubber septum, and argon inlet was evacuated, flame-dried, left to cool to rt, and flushed with argon three times. Ethyl phenyl sulfone (511 mg, 3.00 mmol, 1.0 equiv) was quickly added against a backflow of argon followed by THF (6.0 mL), and stirring was commenced. The resultant solution was cooled in a dry ice/acetone bath, and BuLi (2.38 M in hexanes, 1.26 mL, 3.00 mmol, 1.0 equiv) was added dropwise via syringe, causing a color change from colorless to yellow. After 15 min, 2-bromomethyl-1,3-dioxolane (517 mg, 317 μL, 3.00 mmol, 1.0 equiv) was added in one portion via syringe, and the resultant mixture was allowed to warm to rt over 20 h. One molar HCl(aq) (3 mL) and EtOAc (12 mL) were then added sequentially, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 6 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a brown oil (792 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 70:30, hexane/EtOAc, ca. 5 mL fractions then 20 g SiO_2, 20 mm Ø, 70:30, hexane/EtOAc, ca. 5 mL fractions) gave a clear, pale-yellow oil (472 mg). Further purification via preparative, radial, centrifugally accelerated, thin-layer chromatography on a Harrison Chromatotron (4 mm SiO_2 plate, 65:35, hexane/EtOAc, ca. 5 mL fractions) gave a clear, colorless oil (407 mg). Further purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave **18g** as a clear, colorless oil (390 mg, 51%). Data for **18g**: bp 175 °C ABT (10^{-5} mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 7.88−7.83 (m, 2H), 7.66−7.60 (m, 1H), 7.57−7.51 (m, 2H), 4.96−4.91 (m, 1H), 3.95−3.75 (m, 4H), 3.34−3.23 (m, 1H), 2.32−2.23 (m, 1H), 1.78−1.65 (m, 1H), 1.32 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 137.0, 134.0, 129.4, 129.3, 102.2, 56.6, 33.7, 14.2. IR (neat) 3064 (w), 2981 (m), 2938 (m), 2888 (s), 2254 (w), 1728 (w), 1585 (w), 1478 (m), 1447 (s), 1407 (m), 1362 (w), 1303 (s), 1247 (m), 1214 (m), 1140 (s), 1084 (s), 1025 (s), 999 (m), 961 (s), 916 (m), 853 (w), 826 (m), 769 (s), 735 (s), 692 (s), 635 (m), 595 (s), 578 (s). MS (CI) 256.9 ([M+H]$^+$, 10), 115.0 ($C_6H_{11}O_2^+$, 100). HRMS (Cl$^+$, double focusing sector field)

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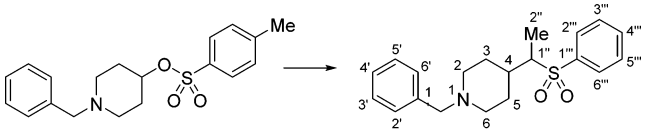
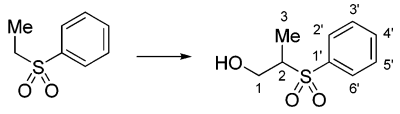
calcd for $C_{12}H_{17}O_4S$, 257.0848; found, 257.0852. TLC R_f 0.35 (60:40, hexane/EtOAc) [$KMnO_4$].



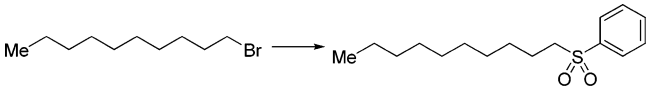
56 18i

*Preparation of (rac)-N-Benzyl-4-[1-(phenylsulfonyl)ethyl]-piperidine (**18i**).* A 100 mL Schlenk flask equipped with a stirrer bar, rubber septum, and argon inlet was evacuated and flame-dried, then left to cool to rt and flushed with argon three times. Ethyl phenyl sulfone (1.02 g, 6.00 mmol, 1.5 equiv) was quickly added against a backflow of argon followed by THF (18.0 mL), and stirring was commenced. The resultant solution was cooled in an ice/water bath, and BuLi (2.38 M in hexanes, 2.52 mL, 6.00 mmol, 1.5 equiv) was added dropwise via syringe, causing a color change from colorless to yellow. After 30 min, a solution of **56** (1.38 g, 4.00 mmol, 1.0 equiv) in THF (6.0 mL) was added dropwise via cannula over ca. 5 min, causing a color change from yellow to orange. The resultant mixture was allowed to warm to rt over 26 h, H_2O (30 mL) and EtOAc (30 mL) were then added sequentially, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a yellow oil (1.85 g). Purification via flash column chromatography (100 g SiO_2, 55 mm Ø, 90:10 → 70:30 → 50:50 → 0:100, hexane/EtOAc, ca. 24 mL fractions) gave a cream-colored solid (768 mg). Further purification of this material was performed via recrystallization from 60:40, hexane/CH_2Cl_2 (ca. 6 mL) in a 20 mL scintillation vial. The crystals were collected via filtration through filter paper in a Hirsch funnel under house vacuum, crushed with a glass rod, and dried in vacuo (0.05 mmHg) to give a white, crystalline solid (679 mg). Further purification of this material was performed via recrystallization from MeOH (5.0 mL) in a 20 mL scintillation vial. The crystals were collected via filtration through filter paper in a Hirsch funnel under house vacuum, washed with cold (0 °C) MeOH (2.0 mL), crushed with a glass rod, and dried in vacuo (0.05 mmHg) to give **18i** as a white, crystalline solid (561 mg, 41%). Data for **18i**: mp 123−124 °C (MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) 7.89−7.85 (m, 2H), 7.66−7.61 (m, 1H), 7.58−7.52 (m, 2H), 7.33−7.27 (m, 4H), 7.27−7.21 (m, 1H), 3.53−3.41 (m, 2H), 2.99−2.86 (m, 3H), 2.26−2.16 (m, 1H), 2.03−1.92 (m, 2H), 1.92−1.84 (m, 1H), 1.61−1.43 (m, 3H), 1.21 (d, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 138.7, 138.5, 133.8, 129.4, 129.4, 128.8, 128.4, 127.2, 64.2, 63.5, 54.0, 53.7, 34.8, 31.4, 27.0, 9.8. IR ($CHCl_3$ mull) 3061 (w), 3027 (w), 2940 (m), 2803 (m), 2758 (w), 2723 (w), 1584 (w), 1494 (w), 1446 (m), 1394 (w), 1381 (w), 1367 (w), 1343 (w), 1304 (s), 1214 (w), 1149 (s), 1086 (m), 1071 (w), 1043 (m), 1027 (w), 1011 (w), 999 (w), 985 (w), 911 (w), 831 (w), 786 (w), 764 (m), 734 (s), 698 (m), 646 (w), 592 (s). MS (EI$^+$, 70 eV) 343.2 (M^+, 10), 202.2 ($C_{14}H_{20}N^+$, 24), 161.1 (31), 110.0 (12), 105.0 (19), 91.1 ($C_7H_7^+$, 100), 77.1 (26), 51.0 (15). TLC R_f 0.29 (EtOAc) [$KMnO_4$]. Anal. Calcd for $C_{20}H_{25}NO_2S$ (343.48): C, 69.93; H, 7.34; N, 4.08%. Found: C, 70.11; H, 7.37;N, 4.17%.



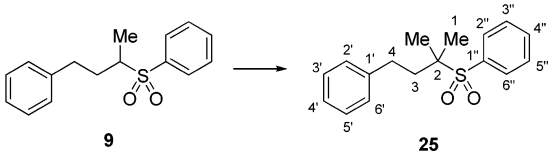
18l

*Preparation of 2-(Phenylsulfonyl)-1-propanol (**18l**).* A 50 mL Schlenk flask equipped with a stirrer bar, rubber septum, and argon inlet was evacuated, flame-dried, left to cool to rt, and flushed with argon three times. Ethyl phenyl sulfone (1.02 mg, 6.00 mmol, 1.0 equiv) was quickly added against a backflow of argon followed by THF (12 mL), and stirring was commenced. The resultant solution was cooled in a dry ice/acetone bath, and BuLi (2.38 M in hexanes, 2.52 mL, 6.00 mmol, 1.0 equiv) was added dropwise via syringe, causing a color change from colorless to yellow. After 15 min, paraformaldehyde (901 mg, 317 μL, 30.0 mmol, 5.0 equiv) was added in one portion against a backflow of argon, and the resultant mixture was allowed to warm to rt over 13 h. One molar HCl(aq) (6 mL) and EtOAc (24 mL) were then added sequentially, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 12 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a dark pink oil (1.17 g). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 70:30, hexane/EtOAc, ca. 5 mL fractions then 20 g SiO_2, 20 mm Ø, 50:50, hexane/EtOAc, ca. 5 mL fractions) gave a clear, colorless oil (329 mg). Further purification via preparative, radial, centrifugally accelerated, thin-layer chromatography on a Harrison Chromatotron (4 mm SiO_2 plate, 50:50, hexane/EtOAc, ca. 5 mL fractions) gave a clear, colorless oil (300 mg). Further purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave **18l** as a clear, colorless oil (274 mg, 23%). Data for **18l**: bp 175 °C ABT (10^{-5} mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 7.89−7.84 (m, 2H), 7.69−7.64 (m, 1H), 7.60−7.54 (m, 2H), 3.92 (dd, J = 12.5, 6.8 Hz, 1H), 3.78 (dd, J = 12.5, 4.0 Hz, 1H), 3.31−3.22 (m, 1H), 2.95 (br s, 1H), 1.23 (d, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 137.1, 134.3, 129.5, 129.0, 61.8, 61.8, 11.5. IR (neat) 3499 (br, O*H*), 3064 (w), 2983 (w), 2940 (m), 2882 (w), 1584 (w), 1303 (s), 1220 (m), 1143 (s), 1084 (s), 1045 (s), 999 (m), 982 (m), 929 (w), 865 (m), 765 (m), 733 (s), 690 (s), 665 (m), 646 (m), 596 (s). MS (EI$^+$, 70 eV) 200.0 (M^+, 2), 170 (10), 142.0 (38), 125 (16), 94.0 (17), 78.1 (100), 59.0 (100). HRMS (EI$^+$, double focusing sector field) calcd for $C_9H_{12}O_3S$, 200.0507; found, 200.0509. TLC R_f 0.30 (50:50, hexane/EtOAc) [$KMnO_4$].



21

*Preparation of 1-(Phenylsulfonyl)decane (**21**).* A 50 mL, one-necked, round-bottomed flask equipped with a stirrer bar and rubber septum was charged with 1-bromodecane (790 mg, 741 μL, 3.50 mmol, 1.0 equiv), benzenesulfinic acid sodium salt (689 mg, 4.20 mmol, 1.2 equiv), and DMF (12.0 mL), and stirring was commenced. The resultant mixture was stirred at rt for 14 h, H_2O (60 mL) and EtOAc (20 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic extracts were washed with H_2O (5 × 40 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a clear, colorless oil (948 mg). Purification via flash column chromatography (20 g SiO_2, 20 mm Ø, 90:10 hexane/EtOAc, ca. 5 mL fractions) gave **21** as a clear, colorless oil (507 mg, 51%). The ^{1}H NMR spectroscopic data matched that for alternative preparations.[111]



9 25

*Preparation of (rac)-[(2-Methyl-4-phenylbutan-2-yl)sulfonyl]-benzene (**25**).* A 100 mL Schlenk flask equipped with a stirrer bar, rubber septum, and argon inlet was evacuated, flame-dried, left to cool to rt, and flushed with argon three times. A solution of **9** (960 mg, 3.50 mmol, 1.0 equiv) in THF (10.0 mL) was added via cannula followed by additional THF (23.0 mL), and stirring was commenced. The resultant solution was cooled to −78 °C in a dry ice/acetone bath, and BuLi (2.57 M in hexanes, 1.36 mL, 3.50 mmol, 1.0 equiv) was added dropwise via syringe, causing a color change from colorless to yellow. After 1 h, iodomethane (745 mg, 327 μL, 5.20 mmol, 1.5 equiv) was added dropwise via syringe over ca. 1 min, causing a color change from yellow to colorless after a further ca. 1 min. The resultant mixture was allowed to warm to rt over 20 h. Sat. NH_4Cl(aq) (10 mL) and H_2O (10 mL) were then added sequentially, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were washed with a 2:1 mixture of brine and sat. $Na_2S_2O_3$(aq) (30 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a clear, yellow

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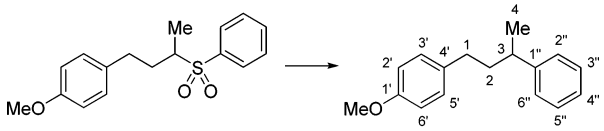
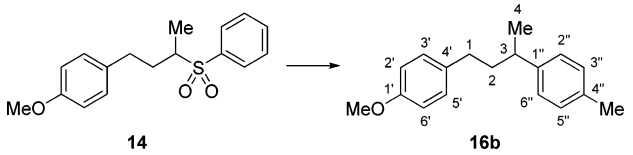
oil that solidified on standing to a white crystalline solid (1.09 g). Purification was performed via recrystallization from MeOH (3.0 mL) in a 20 mL scintillation vial. The crystals were collected via filtration through filter paper in a Hirsch funnel under house vacuum, washed with cold (−78 °C) MeOH (2.0 mL), crushed with a glass rod, and dried in vacuo (0.05 mmHg) to give **25** as a white, crystalline solid (853 mg, 85%). The ^{1}H NMR spectroscopic data and melting point matched that for alternative preparations.[112]

5.6. Cross-Coupling of Alkyl Phenyl Sulfones. *5.6.1. Scope of Nucleophile.*



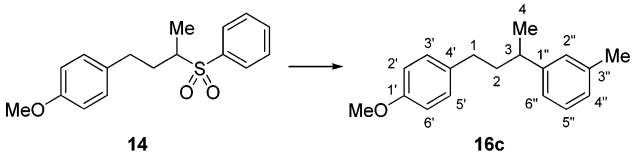
14 **16a**

*Preparation of (rac)-1-Methoxy-4-(3-phenylbutyl)benzene (**16a**).* Following general procedure 1, **14** (304 mg, 1.00 mmol, 1.0 equiv), PhMgBr (3.12 M in Et_2O, 962 μL, 3.00 mmol, 3.0 equiv), $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %), TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv), and CPME (10.0 mL) were reacted to give an orange oil (386 mg). Purification via preparative, radial, centrifugally accelerated, thin-layer chromatography on a Harrison Chromatotron (4 mm SiO_2 plate, 80:20, hexane/toluene, ca. 5 mL fractions) gave a clear, colorless oil (187 mg). Further purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave **16a** as a clear, colorless oil (177 mg, 74%). The ^{1}H NMR spectroscopic data matched that for alternative preparations.[113] Data for **16a**: bp 100 °C ABT (10^{-5} mmHg).



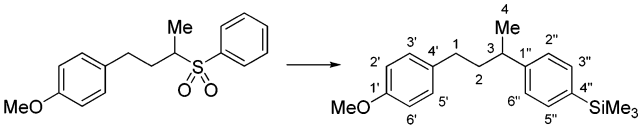
14 **16b**

*Preparation of (rac)-1-Methoxy-4-[3-(4-tolyl)butyl]benzene (**16b**).* Following general procedure 1, **14** (304 mg, 1.00 mmol, 1.0 equiv), 4-tolylmagnesium bromide (1.14 M in Et_2O, 2.63 mL, 3.00 mmol, 3.0 equiv), $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %), TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv), and CPME (10.0 mL) were reacted to give a suspension of solid in an orange oil (1.08 g). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 100:0 → 75:25, hexane/toluene, ca. 5 mL fractions) gave a clear, colorless oil (161 mg). Further purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave **16b** as a clear, colorless oil (152 mg, 60%). Data for **16b**: bp 100 °C ABT (10^{-5} mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 7.17−7.09 (m, 4H), 7.07 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 3.80 (s, 3H), 2.75−2.65 (m, 1H), 2.53−2.42 (m, 2H), 2.36 (s, 3H), 1.95−1.81 (m, 2H), 1.27 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 157.8, 144.6, 135.6, 134.9, 129.5, 129.3, 127.2, 113.9, 55.5, 40.5, 39.2, 33.2, 22.9, 21.3. IR (neat) 3094 (w), 3004 (m), 2955 (s), 2925 (s), 2857 (m), 2834 (m), 1612 (m), 1583 (m), 1512 (s), 1455 (m), 1374 (m), 1299 (m), 1245 (s), 1176 (m), 1116 (m), 1038 (s), 817 (s), 750 (w), 722 (m), 702 (w). MS (EI$^+$, 70 eV) 254.1 (M$^+$, 71), 135.0 (44), 121.0 ($C_8H_9O^+$, 100), 105.0 (27), 91.0 (27), 77.0 (18). TLC R_f 0.28 (70:30, hexane/EtOAc) [$KMnO_4$]. Anal. Calcd for $C_{18}H_{22}O$ (254.37): C, 84.99; H, 8.72%. Found: C, 84.81; H, 8.89%.



14 **16c**

*Preparation of (rac)-1-Methoxy-4-[3-(3-tolyl)butyl]benzene (**16c**).* Following general procedure 1, **14** (304 mg, 1.00 mmol, 1.0 equiv), 3-tolylmagnesium bromide (2.21 M in Et_2O, 1.36 mL, 3.00 mmol, 3.0 equiv), $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %), TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv), and CPME (10.0 mL) were reacted to give an orange oil (600 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 100:0 → 90:10, hexane/toluene, ca. 5 mL fractions) gave a clear, yellow oil (170 mg). Further purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave **16c** as a clear, colorless oil (163 mg, 64%). Data for **16c**: bp 100 °C ABT (10^{-5} mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 7.27−7.72 (m, 1H), 7.12−7.03 (m, 5H), 6.85 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H), 2.76−2.67 (m, 1H), 2.57−2.44 (m, 2H), 2.39 (s, 3H), 1.99−1.84 (m, 2H), 1.30 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 157.9, 147.6, 138.1, 134.9, 129.5, 128.5, 128.1, 126.9, 124.3, 113.9, 55.5, 40.5, 39.6, 33.3, 22.8, 21.8. IR (neat) 3100 (m), 3027 (m), 3006 (m), 2956 (s), 2926 (s), 2857 (m), 2834 (m), 1609 (s), 1584 (m), 1511 (s), 1489 (m), 1456 (s), 1374 (m), 1299 (m), 1245 (s), 1176 (s), 1113 (m), 1038 (s), 880 (m), 828 (s), 785 (s), 750 (m), 704 (s). MS (EI$^+$, 70 eV) 254.1 (M$^+$, 78), 135.0 (34), 121.0 ($C_8H_9O^+$, 100), 105.0 (35), 91.0 (23), 77.0 (14). TLC R_f 0.25 (70:30, hexane/toluene) [$KMnO_4$]. Anal. Calcd for $C_{18}H_{22}O$ (254.37): C, 84.99; H, 8.72%. Found: C, 84.73; H, 8.85%.



14 **16d**

*Preparation of (rac)-1-Methoxy-4-[3-(4-trimethylsilylphenyl)-butyl]benzene (**16d**).* An oven-dried, 25 mL, one-necked, round-bottomed flask was charged with **14** (304 mg, 1.00 mmol, 1.0 equiv) and $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %) in a glovebox and was then sealed with a rubber septum and removed from the box. Outside of the glovebox, a 25 mL Schlenk flask equipped with a stirrer bar, rubber septum, and argon inlet was evacuated, flame-dried, left to cool under vacuum, and flushed three times with argon. TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv) was added via syringe to the Schlenk flask, and stirring was commenced. The round-bottomed flask containing **14** and $Fe(acac)_3$ was charged with CPME (4.0 mL) and then sonicated until the mixture was homogeneous. The clear red solution was then transferred via cannula to the Schlenk flask holding the TMEDA, and the residual material was rinsed across with further portions of CPME (6.0 mL). 4-(Trimethylsilyl)phenylmagnesium bromide (1.52 M in Et_2O, 1.97 mL, 3.00 mmol, 3.0 equiv) was then added by syringe over ca. 30 s. During addition, the color of the solution changed from red to pale-yellow to brown but remained clear throughout, and no visible deposits were formed on the edges of the flask. After stirring for 18 h at rt, H_2O (10 mL) was added in one portion, and the mixture was filtered through a pad of Celite (5 g) in a 40 mm Ø, porosity 3, sintered funnel under house vacuum. H_2O (2 × 10 mL) and EtOAc (3 × 10 mL) were used to rinse any residual material though the Celite pad. The filtrate was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a brown oil (822 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 70:30, hexane/toluene, ca. 5 mL fractions) gave a clear, colorless oil (235 mg). Further purification via flash column chromatography (C18 reversed-phase silica gel, 20 × 160 mm, MeOH, ca. 5 mL fractions, loaded with minimal MeCN for solubility reasons) gave a clear, colorless oil (185 mg). Further purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave **16d** as a clear, colorless oil (174 mg, 56%). Data for **16d**: bp 130 °C ABT (10^{-5} mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 7.53 (d, J = 7.7 Hz, 2H), 7.26 (d, J = 7.7 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 3.83 (s, 3H), 2.81−2.72 (m, 1H), 2.59−2.48 (m, 2H), 2.03−1.87 (m, 2H), 1.33 (d, J = 7.0 Hz, 3H), 0.33 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) 157.9, 147.3, 137.8, 134.9, 133.8, 129.5, 126.8, 114.0, 55.5, 40.4, 39.6, 33.3, 22.6, −0.7. IR (neat) 3065 (w), 3030 (w), 3008 (w), 2955 (m), 2930 (m), 2870 (w), 2855 (w), 2833 (w), 1611 (w), 1600 (w), 1584 (w), 1512 (m), 1455 (w), 1398 (w), 1299 (w), 1246 (m), 1176 (w), 1116 (w), 1039 (w), 838 (m), 819 (m), 755 (w), 725 (w), 693 (w), 640 (w), 562 (w). MS (EI$^+$, 70 eV) 312.2 (M$^+$, 36), 297.2 (21), 267.1 (11), 177.1 (13), 161.1

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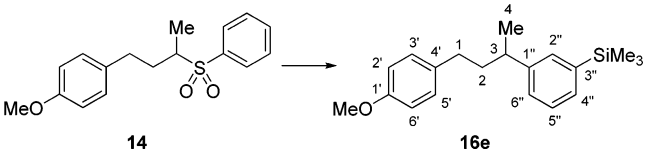
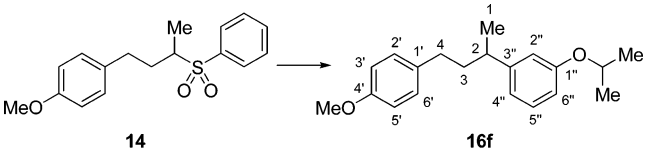
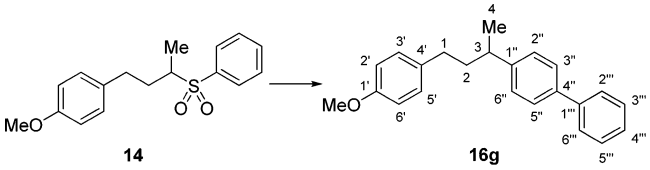
(65), 135.1 (26), 121.1 ($C_8H_9O^+$, 100), 119.0 (12), 91.1 (22), 77.1 (21), 73.1 (59), 59.1 (14). HRMS (EI^+, double focusing sector field) calcd for $C_{20}H_{28}OSi$, 312.1910; found, 312.1904. TLC R_f 0.33 (70:30, hexane/toluene) [$KMnO_4$].



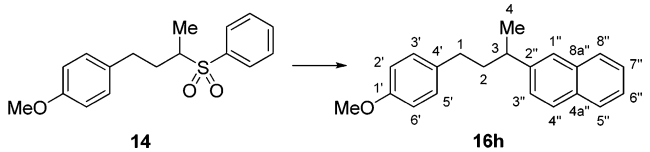
*Preparation of (rac)-1-Methoxy-4-[3-(3-trimethylsilylphenyl)-butyl]benzene (**16e**).* An oven-dried, 25 mL, one-necked, round-bottomed flask was charged with **14** (304 mg, 1.00 mmol, 1.0 equiv) and $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %) in a glovebox and was then sealed with a rubber septum and removed from the box. Outside of the glovebox, a 25 mL Schlenk flask equipped with a stirrer bar, rubber septum, and argon inlet was evacuated, flame-dried, left to cool under vacuum, and flushed three times with argon. TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv) was added via syringe to the Schlenk flask, and stirring was commenced. The round-bottomed flask containing **14** and $Fe(acac)_3$ was charged with CPME (4.0 mL) and was then sonicated until homogeneous. The clear red solution was then transferred via cannula to the Schlenk flask holding the TMEDA, and the residual material was rinsed across with further portions of CPME (6.0 mL). 3-(Trimethylsilyl)phenylmagnesium bromide (2.10 M in Et_2O, 1.43 mL, 3.00 mmol, 3.0 equiv) was then added by syringe over ca. 30 s. During addition, the color of the solution changed from red to pale-yellow to brown but remained clear throughout, and no visible deposits were formed on the edges of the flask. After stirring for 18 h at rt, H_2O (10 mL) was added in one portion, and the mixture was filtered through a pad of Celite (5 g) in a 40 mm Ø, porosity 3, sintered funnel house vacuum. H_2O (2 × 10 mL) and EtOAc (3 × 10 mL) were used to rinse any residual material though the Celite pad. The filtrate was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a brown oil (786 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 70:30, hexane/toluene, ca. 5 mL fractions) gave a clear, colorless oil (220 mg). Further purification via flash column chromatography (C18 reversed-phase silica gel, 20 × 160 mm, MeOH, ca. 5 mL fractions, loaded with minimal MeCN for solubility reasons) gave a clear, colorless oil (202 mg). Further purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave **16e** as a clear, colorless oil (186 mg, 60%). Data for **16e**: bp 130 °C ABT (10^{-5} mmHg). ^1H NMR (500 MHz, $CDCl_3$) 7.43 (dt, J = 7.2, 1.2 Hz, 1H), 7.39 (br s, 1H), 7.37 (dd, J = 7.6, 7.2 Hz, 1H), 7.26 (dt, J = 7.6, 1.5 Hz, 1H), 7.13−7.09 (m, 2H), 6.90−6.86 (m, 2H), 3.84 (s, 3H), 2.81−2.73 (m, 1H), 2.56−2.51 (m, 2H), 2.03−1.89 (m, 2H), 1.34 (d, J = 7.0 Hz, 3H), 0.34 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) 157.9, 146.7, 140.6, 134.9, 132.6, 131.3, 129.5, 128.1, 127.6, 114.0, 55.5, 40.5, 39.7, 33.3, 22.8, −0.7. IR (neat) 3028 (w), 2995 (w), 2955 (m), 2932 (m), 2870 (w), 2855 (w), 2833 (w), 1611 (w), 1583 (w), 1511 (m), 1458 (w), 1406 (w), 1373 (w), 1299 (w), 1246 (m), 1176 (w), 1121 (w), 1039 (w), 861 (m), 837 (m), 794 (w), 752 (m), 706 (w), 621 (w), 560 (w). MS (EI^+, 70 eV) 312.2 (M^+, 34), 297.2 (14), 161.1 (53), 135.1 (20), 121.0 ($C_8H_9O^+$, 100), 119.0 (13), 91.1 (20), 77.0 (17), 73.1 (78), 59.1 (11). TLC R_f 0.40 (70:30, hexane/toluene) [$KMnO_4$]. Anal. Calcd for $C_{20}H_{28}OSi$ (312.52): C, 76.86; H, 9.03%. Found: C, 77.13; H, 9.07%.



*Preparation of 1-Isopropoxy-3-[4-(4-methoxyphenyl)butan-2-yl]-benzene (**16f**).* Following general procedure 1, **14** (304 mg, 1.00 mmol, 1.0 equiv), 3-isopropoxyphenylmagnesium bromide (1.55 M in Et_2O, 1.94 mL, 3.00 mmol, 3.0 equiv), $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %), TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv), and CPME (10.0 mL) were reacted to give an orange oil (842 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 100:0 → 80:20 → 50:50, hexane/toluene, ca. 5 mL fractions) gave **16f** as a clear, pale-orange oil (123 mg) in addition to a mixture of **16f** and 3,3′-diisopropoxybiphenyl as a clear, colorless oil (138 mg). The mixed fractions were further purified via flash column chromatography (20 g SiO_2, 20 mm Ø, 50:50, hexane/toluene, ca. 2.5 mL fractions then 20 g SiO_2, 20 mm Ø, 60:40, hexane/toluene, ca. 2.5 mL fractions) to give **16f** as a clear, colorless oil (97 mg). The combined portions of **16f** (220 mg) were further purified via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) to give **16f** as a clear, colorless oil (209 mg, 70%). Data for **16f**: bp 135 °C ABT (10^{-5} mmHg). ^1H NMR (500 MHz, $CDCl_3$) 7.24−7.18 (m, 1H), 7.09−7.03 (m, 2H), 6.84−6.80 (m, 2H), 6.80−6.71 (m, 3H), 4.56 (hept, J = 6.1 Hz, 1H), 3.79 (s, 3H), 2.72−2.63 (m, 1H), 2.53−2.42 (m, 2H), 1.95−1.79 (m, 2H), 1.36 (d, J = 6.1 Hz, 6H), 1.26 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 158.2, 157.9, 149.4, 134.9, 129.5, 129.5, 119.7, 115.3, 113.9, 113.0, 69.9, 55.5, 40.4, 39.7, 33.2, 22.7, 22.4. IR (neat) 3031 (m), 2974 (s), 2931 (s), 2870 (m), 2834 (m), 1609 (s), 1582 (s), 1512 (s), 1484 (s), 1453 (s), 1383 (m), 1372 (m), 1246 (s), 1177 (s), 1156 (m), 1137 (m), 1117 (s), 1038 (s), 999 (m), 973 (m), 873 (m), 822 (m), 777 (m), 701 (s). MS (ESI) 321.2 ([M+Na]$^+$, 22), 316.2 ([M+NH$_4$]$^+$, 6), 299.2 ([M+H]$^+$, 100), 257.2 ([M−C$_3$H$_6$+H]$^+$, 96). TLC R_f 0.09 (70:30, hexane/toluene) [$KMnO_4$]. Anal. Calcd for $C_{20}H_{26}O_2$ (298.42): C, 80.50; H, 8.78%. Found: C, 80.48; H, 8.88%.



*Preparation of (rac)-1-Methoxy-4-[3-(4-biphenyl)butyl]benzene (**16g**).* Following general procedure 1, **14** (304 mg, 1.00 mmol, 1.0 equiv), 4-biphenylmagnesium bromide (1.42 M in Et_2O, 2.11 mL, 3.00 mmol, 3.0 equiv), $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %), TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv), and CPME (10.0 mL) were reacted to give a dark orange oil (914 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 80:20, hexane/toluene, ca. 5 mL fractions) gave a clear, pale-yellow oil (204 mg). Further purification via flash column chromatography (C18 reversed-phase silica gel, 20 × 160 mm, MeOH, ca. 5 mL fractions, loaded with minimal MeCN for solubility reasons) gave a clear, colorless oil (174 mg). Further purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave **16g** as a clear, colorless oil (159 mg, 50%). Data for **16g**: bp 180 °C ABT (10^{-5} mmHg). ^1H NMR (500 MHz, $CDCl_3$) 7.68−7.63 (m, 2H), 7.62−7.58 (m, 2H), 7.51−7.46 (m, 2H), 7.41−7.35 (m, 1H), 7.35−7.30 (m, 2H), 7.14−7.09 (m, 2H), 6.90−6.84 (m, 2H), 3.83 (s, 3H), 2.86−2.76 (m, 1H), 2.61−2.49 (m, 2H), 2.05−1.89 (m, 2H), 1.36 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 157.9, 146.8, 141.4, 139.1, 134.8, 129.5, 129.0, 127.8, 127.4, 127.3, 114.0, 55.5, 40.5, 39.3, 33.3, 22.8. IR (neat) 3056 (m), 3028 (m), 3000 (m), 2956 (m), 2929 (m), 2869 (m), 2855 (m), 2834 (m), 1611 (m), 1583 (m), 1512 (s), 1486 (m), 1454 (m), 1408 (w), 1374 (w), 1346 (w), 1299 (m), 1244 (s), 1177 (m), 1118 (w), 1075 (w), 1037 (m), 1008 (m), 837 (m), 765 (m), 733 (m), 697 (m), 573 (w), 559 (w). MS (EI^+, 70 eV) 316.2 (M^+, 63), 181.1 (88), 178.1 (25), 165.1 (39), 152.1 (24), 135.1 (36), 121.0 ($C_8H_9O^+$, 100), 115.1 (12), 103.1 (11), 91.0 (31), 77.0 (37), 65.1 (13), 51.0 (10). TLC R_f 0.22 (70:30, hexane/toluene) [$KMnO_4$]. Anal. Calcd for: $C_{23}H_{24}O$ (316.44): C, 87.30; H, 7.64%. Found: C, 87.54; H, 7.70%.



*Preparation of (rac)-1-Methoxy-4-[3-(2-naphthyl)butyl]benzene (**16h**).* Following general procedure 1, **14** (304 mg, 1.00 mmol, 1.0 equiv), 2-naphthylmagnesium bromide (1.61 M in Et_2O, 1.86 mL, 3.00

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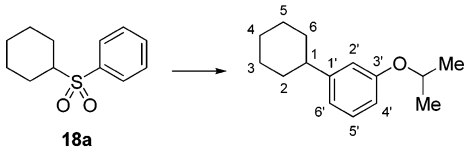
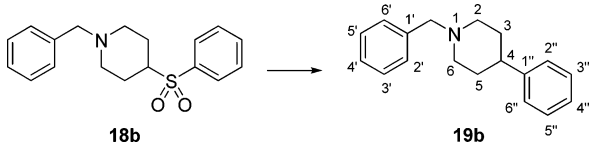
mmol, 3.0 equiv), $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %), TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv), and CPME (10.0 mL) were reacted to give a sticky, orange solid (1.3 g). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 100:0 → 80:20, hexane/toluene, ca. 5 mL fractions then 40 g SiO_2, 30 mm Ø, 100:0 → 80:20 hexane/toluene, ca. 5 mL fractions then 20 g SiO_2, 20 mm Ø, 80:20, hexane/toluene, ca. 2.5 mL fractions) gave a clear, colorless oil (142 mg). Further purification via flash column chromatography (C18 reversed-phase silica gel, 20 × 160 mm, MeOH, ca. 5 mL fractions, loaded with minimal MeCN for solubility reasons) gave a clear, colorless oil (140 mg). Further purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave **16h** as a clear, colorless oil (128 mg, 44%). Data for **16h**: bp 180 °C ABT (10^{-5} mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 7.89−7.83 (m, 3H), 7.68 (s, 1H), 7.54−7.45 (m, 2H), 7.44−7.40 (m, 1H), 7.12−7.08 (m, 2H), 6.88−6.84 (m, 2H), 3.82 (s, 3H), 2.98−2.89 (m, 1H), 2.60−2.47 (m, 2H), 2.11−1.95 (m, 2H), 1.40 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 157.9, 145.0, 134.8, 133.9, 132.5, 129.5, 128.3, 127.9, 127.8, 126.1, 126.0, 125.6, 125.4, 114.0, 55.5, 40.3, 39.8, 33.3, 22.8. IR (neat) 3052 (m), 3027 (w), 3006 (m), 2956 (m), 2930 (m), 2867 (m), 2855 (m), 2833 (m), 1632 (w), 1611 (m), 1583 (w), 1511 (s), 1455 (m), 1440 (m), 1378 (m), 1320 (w), 1299 (m), 1244 (s), 1177 (m), 1127 (w), 1111 (w), 1037 (m), 950 (w), 890 (w), 855 (m), 819 (m), 747 (m), 702 (w), 660 (w), 621 (w), 564 (w). MS (EI$^+$, 70 eV) 290.2 (M^+, 27), 156.1 (100), 141.1 (39), 135.1 (12), 128.1 (27), 121.0 ($C_8H_9O^+$, 61), 91.1 (22), 77.0 (26), 65.1 (10). TLC R_f 0.24 (70:30, hexane/toluene) [$KMnO_4$]. Anal. Calcd for $C_{21}H_{22}O$ (290.40): C, 86.85; H, 7.64%. Found: C, 87.08; H, 7.88%.

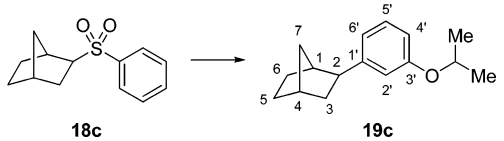
5.6.2. Scope of Sulfone Substrate.



*Preparation of 1-Cyclohexyl-3-isopropoxybenzene (**19a**).* Following general procedure 1, **18a** (224 mg, 1.00 mmol, 1.0 equiv), 3-isopropoxyphenylmagnesium bromide (2.24 M in Et_2O, 1.34 mL, 3.00 mmol, 3.0 equiv), $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %), TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv), and CPME (10.0 mL) were reacted to give a yellow oil (712 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 95:5, hexane/toluene, ca. 5 mL fractions) gave a clear, colorless oil (213 mg). Further purification via flash column chromatography (C18 reversed-phase silica gel, 20 × 160 mm, MeOH, ca. 2.5 mL fractions, loaded with minimal MeCN for solubility reasons) gave a clear, colorless oil (152 mg). Further purification via bulb-to-bulb distillation under reduced pressure (0.03 mmHg) gave **19a** as a clear, colorless oil (145 mg, 67%). Data for **19a**: bp 75 °C ABT (0.03 mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 7.19 (app t, J = 7.8 Hz, 1H), 6.80−6.74 (m, 2H), 6.73−6.68 (m, 1H), 4.60−4.50 (hept, J = 6.1 Hz, 1H), 2.53−2.39 (m, 1H), 1.93−1.70 (m, 5H), 1.49−1.17 (m, 5H) overlapping 1.34 (d, J = 6.1 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) 158.1, 150.1, 129.4, 119.4, 115.0, 112.9, 69.8, 44.9, 34.7, 27.2, 26.5, 22.4. IR (neat) 3029 (m), 2975 (s), 2925 (s), 2851 (s), 1600 (s), 1580 (s), 1489 (s), 1447 (s), 1382 (m), 1371 (m), 1350 (m), 1316 (m), 1287 (s), 1255 (s), 1225 (m), 1181 (m), 1156 (s), 1118 (s), 1017 (m), 999 (m), 977 (s), 919 (m), 872 (m), 829 (m), 774 (m), 751 (m), 698 (s). MS (EI$^+$, 70 eV) 218.2 (M^+, 83), 176.1 ([M−C_3H_6]$^+$, 100), 161.1 (19), 147.1 (16), 133.1 (56), 120.1 (76), 108.1 (79), 91.1 (26), 77.0 (17). TLC R_f 0.34 (90:10, hexane/toluene) [$KMnO_4$]. Anal. Calcd for $C_{15}H_{22}O$ (218.33): C, 82.52; H, 10.16%. Found: C, 82.64; H, 10.28%.



*Preparation of N-Benzyl-4-phenylpiperidine (**19b**).* An oven-dried, 20 mL scintillation vial was charged with **18b** (315 mg, 1.00 mmol, 1.0 equiv) and $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %) in a glovebox and was then sealed with a rubber septum and removed from the box. Outside of the glovebox, a 25 mL Schlenk flask equipped with a stirrer bar, rubber septum, and argon inlet was evacuated, flame-dried, left to cool under vacuum, and flushed three times with argon. TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv) was added via syringe to the Schlenk flask, and stirring was commenced. The vial containing **18b** and $Fe(acac)_3$ was charged with CPME (4.0 mL) and then sonicated until homogeneous. The clear red solution was then transferred via cannula to the Schlenk flask holding the TMEDA, and the residual material was rinsed across with further portions of CPME (6.0 mL). PhMgBr (2.76 M in Et_2O, 1.09 mL, 3.00 mmol, 3.0 equiv) was then added by syringe over ca. 20 s. During addition, the color of the solution changed from red to pale-yellow to brown but remained clear throughout, and no visible deposits were formed on the edges of the flask. After stirring for 18 h at rt, 1 M HCl(aq) (10 mL) was added in one portion, and the mixture was filtered through a pad of Celite (5 g) in a 40 mm Ø, porosity 3, sintered funnel under house vacuum. EtOAc (2 × 5 mL) was used to rinse any residual material though the Celite pad. The filtrate was brought to pH 9 by addition of 5% NaOH(aq) and transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a dark red oil (397 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 98:1.8:0.2 CH_2Cl_2/MeOH/NH_3(aq), ca. 5 mL fractions) gave an 87:13 mixture of **19b**/**18b** as a clear, orange oil (254 mg). Further purification via flash column chromatography [C18 reversed-phase silica gel, 20 × 160 mm, MeOH, ca. 5 mL fractions then C18 reversed-phase silica gel, 20 × 160 mm, MeOH, ca. 2.5 mL fractions (loaded with minimal MeCN in both cases for solubility reasons)] gave **19b** as a clear, pale-yellow oil (165 mg). Further purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave **19b** as a clear, colorless oil (149 mg, 59%). Data for **19b**: bp 130 °C ABT (10^{-5} mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 7.40−7.17 (m, 10H), 3.58 (s, 2H), 3.03 (d, J = 11.3 Hz, 2H), 2.50 (tt, J = 8.1, 8.0 Hz, 1H), 2.19−2.02 (m, 2H), 1.91−1.73 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) 146.8, 138.7, 129.6, 128.7, 128.5, 127.3, 127.2, 126.4, 63.8, 54.6, 43.0, 33.8. IR (neat) 3083 (m), 3060 (m), 3026 (m), 3002 (m), 2933 (s), 2874 (m), 2848 (m), 2798 (s), 2755 (s), 2719 (m), 2693 (m), 2677 (m), 1601 (m), 1493 (s), 1465 (m), 1452 (s), 1392 (m), 1365 (m), 1341 (m), 1313 (m), 1263 (m), 1197 (m), 1145 (m), 1125 (m), 1068 (m), 1028 (m), 991 (m), 970 (m), 907 (m), 824 (m), 785 (m), 756 (m), 737 (s), 698 (s), 647 (m). MS (EI$^+$, 70 eV) 251.2 (M^+, 100), 174.1 (20), 160.1 (30), 91.1 ($C_7H_7^+$, 65). TLC R_f 0.19 (98:1.8:0.2 CH_2Cl_2:MeOH:aq. NH_3) [$KMnO_4$]. Anal. Calcd for $C_{18}H_{21}N$ (251.37): C, 86.01; H, 8.42; N, 5.57%. Found: C, 85.93; H, 8.50; N, 5.73%.



*Preparation of (1*l*,2*l*,4*u*)-2-(3-Isopropoxyphenyl)bicyclo[2.2.1]-heptane (**19c**).* Following general procedure 1, **18c** (>99:1 dr, 236 mg, 1.00 mmol, 1.0 equiv), 3-isopropoxyphenylmagnesium bromide (2.24 M in Et_2O, 1.34 mL, 3.00 mmol, 3.0 equiv), $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %), TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv), and CPME (10.0 mL) were reacted to give a yellow oil (800 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 95:5, hexane/toluene, ca. 5 mL fractions) gave a clear, colorless oil (240 mg). Further purification via flash column chromatography (C18 reversed-phase silica gel, 20 × 160 mm, MeOH, ca. 2.5 mL fractions, loaded with minimal MeCN for solubility reasons) gave a clear, colorless oil (152 mg). Further purification via bulb-to-bulb distillation under reduced pressure (0.03 mmHg) gave **19c** as a clear, colorless oil (143 mg, 62%, 98:2 dr). Data for **19c**: bp 110 °C ABT (0.03 mmHg).

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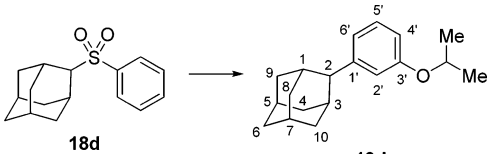
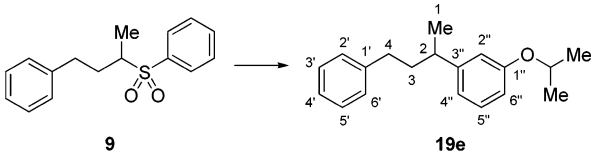
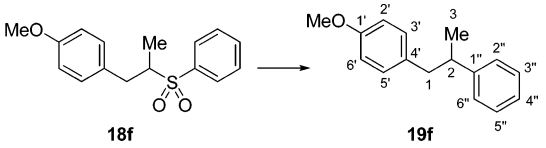
^{1}H NMR (500 MHz, $CDCl_3$) 7.22−7.15 (for both diastereoisomers: m, 1H each), 6.82−6.66 (for both diastereoisomers: m, 3H each), 4.60−4.49 (for both diastereoisomers: m, 1H each), 3.22−3.16 (for minor diastereoisomer: m, 1H), 2.70 (for major diastereoisomer: dd, J = 9.1, 5.6 Hz, 1H), 1.99−1.91 (for minor diastereoisomer: m, 1H), 1.79−1.72 (for major diastereoisomer: m, 1H), 1.69−1.12 (for both diastereoisomers: m, 13H each). ^{13}C NMR (125 MHz, $CDCl_3$) For major diastereoisomer: 158.1, 149.6, 129.3, 119.6, 115.4, 112.4, 69.8, 47.6, 43.1, 39.4, 37.0, 36.4, 30.9, 29.2, 22.4. For minor diastereoisomer (1 peak obscured in aliphatic region): 157.9, 145.7, 129.0, 120.8, 116.5, 112.6, 69.9, 46.3, 42.8, 40.8, 37.8, 34.5, 30.4, 23.3. IR (neat) 3026 (w), 2951 (s), 2870 (s), 1606 (s), 1580 (s), 1487 (s), 1454 (m), 1383 (m), 1371 (m), 1334 (m), 1310 (m), 1250 (m), 1181 (m), 1157 (m), 1136 (m), 1118 (s), 1000 (m), 991 (m), 953 (m), 874 (m), 839 (w), 818 (w), 776 (m), 721 (m), 697 (m). MS (EI$^+$, 70 eV) 230.2 (M^+, 43), 188.1 ([M−C_3H_6]$^+$, 52), 120.1 (44), 108.1 (100), 91.1 ($C_7H_7^+$, 12). TLC R_f 0.33 (90:10, hexane/toluene) [$KMnO_4$]. Anal. Calcd for $C_{16}H_{22}O$ (230.35): C, 83.43; H, 9.63%. Found: C, 83.53; H, 9.65%.



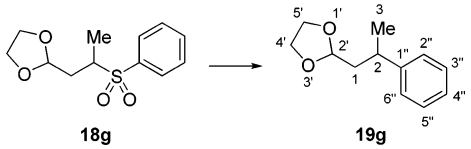
*Preparation of 2-(3-Isopropoxyphenyl)tricyclo[3.3.1.1^{3,7}]decane (**19d**).* Following general procedure 1, **18d** (276 mg, 1.00 mmol, 1.0 equiv), 3-isopropoxyphenylmagnesium bromide (2.24 M in Et_2O, 1.34 mL, 3.00 mmol, 3.0 equiv), $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %), TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv), and CPME (10.0 mL) were reacted to give a yellow oil (827 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 95:5, hexane/toluene, ca. 5 mL fractions) gave a clear, pale-yellow oil (225 mg). Further purification via flash column chromatography (C18 reversed-phase silica gel, 20 × 160 mm, MeOH, ca. 2.5 mL fractions, loaded with minimal ~1:1 MeCN/CH_2Cl_2 for solubility reasons) gave a clear, colorless oil (203 mg). Further purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave **19d** as a clear, colorless oil (179 mg, 66%). Data for **19d**: bp 150 °C ABT (10^{-5} mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 7.25−7.20 (m, 1H), 6.96−6.89 (m, 2H), 6.74−6.69 (m, 1H), 4.55 (hept, J = 6.1 Hz, 1H), 2.99−2.95 (br s, 1H), 2.48−2.42 (br s, 2H), 2.04−1.83 (m, 7H), 1.82−1.74 (m, 3H), 1.59−1.52 (m, 2H), 1.34 (d, J = 6.1 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) 158.2, 149.5, 129.2, 119.4, 115.5, 112.2, 69.9, 47.1, 39.4, 38.1, 32.3, 31.4, 28.3, 28.1, 22.4. IR (neat) 3077 (w), 3026 (w), 2974 (s), 2904 (s), 2848 (s), 1604 (s), 1578 (s), 1487 (s), 1467 (m), 1450 (s), 1382 (m), 1371 (m), 1354 (m), 1331 (m), 1289 (m), 1258 (s), 1180 (m), 1157 (m), 1136 (m), 1118 (s), 1069 (w), 1001 (m), 980 (m), 965 (m), 948 (m), 918 (w), 874 (m), 783 (m), 768 (m), 756 (m), 695 (m). MS (EI$^+$, 70 eV) 270.2 (M^+, 37), 228.2 ([M−C_3H_6]$^+$, 100), 107.1 (11). TLC R_f 0.28 (90:10, hexane/toluene) [$KMnO_4$]. Anal. Calcd for $C_{19}H_{26}O$ (270.41): C, 84.39; H, 9.69%. Found: C, 84.53; H, 9.67%.



*Preparation of (rac)-1-Isopropoxy-3-(4-phenylbutan-2-yl)-benzene (**19e**).* Following general procedure 1, **9** (274 mg, 1.00 mmol, 1.0 equiv), 3-isopropoxyphenylmagnesium bromide (2.24 M in Et_2O, 1.34 mL, 3.00 mmol, 3.0 equiv), $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %), TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv), and CPME (10.0 mL) were reacted to give a yellow oil (812 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 90:10, hexane/toluene, ca. 5 mL fractions) gave a clear, colorless oil (147 mg). Further purification via flash column chromatography (C18 reversed-phase silica gel, 20 × 160 mm, MeOH, ca. 2.5 mL fractions, loaded with minimal MeCN for solubility reasons) gave a clear, colorless oil (140 mg). Further purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave **19e** as a clear, colorless oil (142 mg, 53%) that was contaminated with ~5% of a compound tentatively assigned as 3-isopropoxybiphenyl. Data for **19e**: bp 125 °C ABT (10^{-5} mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 7.30−7.11 (m, 6H), 6.82−6.71 (m, 3H), 4.56 (hept, J = 6.1 Hz, 1H), 2.74−2.64 (m, 1H), 2.60−2.47 (m, 2H), 1.99−1.83 (m, 2H), 1.36 (d, J = 6.1 Hz, 6H), 1.27 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 158.3, 149.3, 142.9, 129.6, 128.7, 128.5, 125.9, 119.7, 115.4, 113.2, 69.9, 40.2, 39.9, 34.3, 22.7, 22.4. IR (neat) 3084 (w), 3062 (w), 3026 (m), 2975 (m), 2927 (m), 2870 (w), 1601 (m), 1582 (m), 1485 (m), 1454 (m), 1383 (m), 1372 (m), 1348 (w), 1334 (w), 1312 (w), 1286 (m), 1253 (m), 1180 (m), 1157 (m), 1137 (m), 1118 (m), 1030 (w), 999 (w), 973 (m), 874 (w), 777 (w), 748 (m), 699 (s). MS (EI$^+$, 70 eV) 268.2 (M^+, 53), 170.1 (21), 164.1 (46), 122.1 (100), 107.0 (22), 91.1 ($C_7H_7^+$, 35), 77.0 (14). HRMS (ESI, TOF) calcd for $C_{19}H_{24}O$, 268.1827; found, 268.1828. TLC R_f 0.19 (90:10, hexane/toluene) [$KMnO_4$].



*Preparation of (rac)-1-Methoxy-4-(2-phenylpropyl)benzene (**19f**).* Following general procedure 1, **18f** (290 mg, 1.00 mmol, 1.0 equiv), PhMgBr (2.76 M in Et_2O, 1.09 mL, 3.00 mmol, 3.0 equiv), $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %), TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv), and CPME (10.0 mL) were reacted to give an orange oil (455 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 75:25, hexane/toluene, ca. 5 mL fractions) gave a clear, colorless oil (152 mg). Further purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave **19f** as a clear, colorless oil (142 mg, 63%). Data for **19f**: bp 100 °C ABT (10^{-5} mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 7.31−7.25 (m, 2H), 7.21−7.15 (m, 3H), 7.01−6.97 (m, 2H), 6.80−6.76 (2 H, m), 3.78 (s, 3H), 3.00−2.91 (m, 1H), 2.88 (dd, J = 13.4, 6.4 Hz, 1H), 2.71 (dd, J = 13.4, 8.2 Hz, 1H), 1.23 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 158.0, 147.3, 133.2, 130.3, 128.5, 127.3, 126.2, 113.8, 55.4, 44.4, 42.3, 21.4. IR (neat) 3060 (m), 3026 (m), 2999 (m), 2958 (m), 2927 (m), 2833 (m), 1610 (m), 1583 (m), 1509 (s), 1493 (m), 1452 (m), 1374 (m), 1300 (m), 1246 (s), 1177 (m), 1111 (m), 1037 (m), 1013 (m), 817 (m), 783 (m), 761 (m), 699 (s). MS (EI$^+$, 70 eV) 226.1 (M^+, 46), 121.1 ($C_8H_9O^+$, 100), 105.1 (23), 77.0 (24). TLC R_f 0.42 (70:30, hexane/toluene) [$KMnO_4$]. Anal. Calcd for $C_{16}H_{18}O$ (226.31): C, 84.91; H, 8.02%. Found: C, 84.68; H, 8.14%.



*Preparation of (rac)-2-(2-Phenylpropyl)-1,3-dioxolane (**19g**).* An oven-dried, 25 mL, one-necked, round-bottomed flask was charged with **18g** (256 mg, 1.00 mmol, 1.0 equiv) and $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %) in a glovebox and was then sealed with a rubber septum and removed from the box. Outside of the glovebox, a 25 mL Schlenk flask equipped with a stirrer bar, rubber septum, and argon inlet was evacuated, flame-dried, left to cool under vacuum, and flushed three times with argon. TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv) was added via syringe to the Schlenk flask, and stirring was commenced. The round-bottomed flask containing **18g** and $Fe(acac)_3$ was charged with CPME (4.0 mL) and then sonicated until homogeneous. The clear red solution was then transferred via cannula to the Schlenk flask holding the TMEDA, and the residual material was rinsed across with further portions of CPME (6.0 mL). PhMgBr (2.78 M in Et_2O, 1.08 mL, 3.00 mmol, 3.0 equiv) was then added by syringe over ca. 20 s. During addition, the color of the solution changed from red to pale-yellow to brown but remained clear throughout, and no visible deposits were formed on the edges of the flask. After stirring for 18 h at rt, H_2O (10 mL) was added in one

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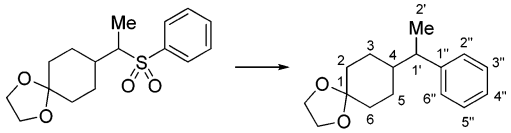
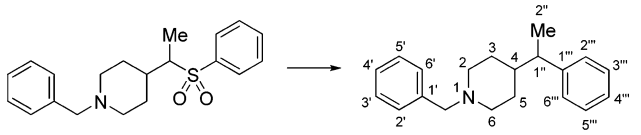
portion, and the mixture was filtered through a pad of Celite (5 g) in a 40 mm Ø, porosity 3, sintered funnel under house vacuum. H_2O (2 × 10 mL) and EtOAc (3 × 10 mL) were used to rinse any residual material though the Celite pad. The filtrate was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a red oil (408 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 95:5, hexane/EtOAc, ca. 5 mL fractions) gave a clear, yellow oil (108 mg). Further purification via preparative, radial, centrifugally accelerated, thin-layer chromatography on a Harrison Chromatotron (4 mm SiO_2 plate, 25:75, hexane/CH_2Cl_2, ca. 5 mL fractions) gave a clear, yellow oil (102 mg). Further purification via bulb-to-bulb distillation under reduced pressure (0.03 mmHg) gave **19g** as a clear, colorless oil (98.9 mg, 51%). The ^{1}H NMR spectroscopic data matched that for an alternative preparation of (*R*)-**19g**.[114] Data for **19g**: bp 75 °C ABT (0.03 mmHg).



18h **19h**

*Preparation of (rac)-4-(1-Phenylethyl)cyclo-1-hexanone Ethylene Ketal (**19h**).* An oven-dried, 25 mL, one-necked, round-bottomed flask was charged with **18h** (310 mg, 1.00 mmol, 1.0 equiv) and $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %) in a glovebox and was then sealed with a rubber septum and removed from the box. Outside of the glovebox, a 25 mL Schlenk flask equipped with a stirrer bar, rubber septum, and argon inlet was evacuated, flame-dried, left to cool under vacuum, and flushed three times with argon. TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv) was added via syringe to the Schlenk flask, and stirring was commenced. The round-bottomed flask containing **18h** and $Fe(acac)_3$ was charged with CPME (4.0 mL) and then sonicated until homogeneous. The clear red solution was then transferred via cannula to the Schlenk flask holding the TMEDA, and the residual material was rinsed across with further portions of CPME (6.0 mL). PhMgBr (2.78 M in Et_2O, 1.08 mL, 3.00 mmol, 3.0 equiv) was then added by syringe over ca. 30 s. During addition, the color of the solution changed from red to pale-yellow to brown but remained clear throughout, and no visible deposits were formed on the edges of the flask. After stirring for 18 h at rt, H_2O (10 mL) was added in one portion, and the mixture was filtered through a pad of Celite (5 g) in a 40 mm Ø, porosity 3, sintered funnel under house vacuum. H_2O (2 × 10 mL) and EtOAc (3 × 10 mL) were used to rinse any residual material though the Celite pad. The filtrate was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a red oil (426 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 95:5, hexane/EtOAc, ca. 5 mL fractions) gave a clear, pale-yellow oil (214 mg). Further purification via preparative, radial, centrifugally accelerated, thin-layer chromatography on a Harrison Chromatotron (4 mm SiO_2 plate, 25:75, hexane/CH_2Cl_2, ca. 5 mL fractions) gave a clear, pale-yellow oil (185 mg). Further purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave **19h** as a clear, colorless oil (169 mg, 69%). Data for **19h**: bp 110 °C ABT (10^{-5} mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 7.32−7.27 (m, 2H), 7.22−7.14 (m, 3H), 3.98−3.89 (m, 4H), 2.54−2.45 (m, 1H), 1.96−1.89 (m, 1H), 1.83−1.76 (m, 1H), 1.71−1.63 (m, 1H), 1.54 (td, *J* = 13.2, 4.2 Hz, 1H), 1.50−1.38 (m, 3H), 1.37−1.30 (m, 1H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.24−1.13 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) 147.2, 128.4, 127.7, 126.1, 109.2, 64.4, 64.4, 45.4, 43.1, 34.8, 34.8, 29.0, 27.8, 19.4. IR (neat) 3082 (w), 3060 (w), 3025 (m), 2943 (s), 2876 (s), 1603 (w), 1582 (w), 1493 (s), 1449 (s), 1375 (s), 1359 (m), 1337 (m), 1285 (m), 1256 (w), 1224 (m), 1199 (m), 1175 (m), 1153 (s), 1095 (s), 1035 (s), 1003 (w), 996 (m), 932 (s), 904 (s), 816 (w), 761 (s), 702 (s), 663 (w), 575 (w). MS (EI$^+$, 70 eV) 246.1 (M^+, 18), 105.1 (11), 99.0 (100), 86.0 (12). HRMS (EI$^+$, double focusing sector field) calcd for $C_{16}H_{22}O_2$, 246.1620; found, 246.1623. TLC R_f 0.36 (90:10, hexane/EtOAc) [$KMnO_4$].



18i **19i**

*Preparation of (rac)-N-Benzyl-4-(1-phenylethyl)piperidine (**19i**).* An oven-dried, 20 mL scintillation vial was charged with **18i** (343 mg, 1.00 mmol, 1.0 equiv) and $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %) in a glovebox and was then sealed with a rubber septum and removed from the box. Outside of the glovebox, a 25 mL Schlenk flask equipped with a stirrer bar, rubber septum, and argon inlet was evacuated, flame-dried, left to cool under vacuum, and flushed three times with argon. TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv) was added via syringe to the Schlenk flask, and stirring was commenced. The vial containing **18i** and $Fe(acac)_3$ was charged with CPME (4.0 mL) and then sonicated until homogeneous. The clear red solution was then transferred via cannula to the Schlenk flask holding the TMEDA, and the residual material was rinsed across with further portions of CPME (6.0 mL). PhMgBr (2.76 M in Et_2O, 1.09 mL, 3.00 mmol, 3.0 equiv) was then added by syringe over ca. 20 s. During addition, the color of the solution changed from red to pale-yellow to brown but remained clear throughout, and no visible deposits were formed on the edges of the flask. After stirring for 18 h at rt, 1 M HCl(aq) (10 mL) was added in one portion, and the mixture was filtered through a pad of Celite (5 g) in a 40 mm Ø, porosity 3, sintered funnel under house vacuum. EtOAc (2 × 5 mL) was used to rinse any residual material though the Celite pad. The filtrate was brought to pH 9 by addition of 5% NaOH(aq) and transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a dark red oil (393 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 98:1.8:0.2 CH_2Cl_2/MeOH/NH_3(aq), ca. 5 mL fractions) gave a clear, orange oil (287 mg). Further purification via flash column chromatography (C18 reversed-phase silica gel, 20 × 160 mm, *i*-PrOH, ca. 2.5 mL fractions, loaded with minimal MeCN for solubility reasons) gave **19i** contaminated with traces of terminal and internal alkene byproducts as a clear, yellow oil (256 mg). A dihydroxylation protocol was next performed to convert the alkene impurities to more readily separable diols. The residue was dissolved in acetone (2.0 mL) in a 20 mL scintillation vial, and *N*-methylmorpholine *N*-oxide (164 mg, 1.20 mmol) and osmium tetraoxide (4% in H_2O, 0.13 mL, 0.02 mmol) were added sequentially. The resultant dark yellow-orange, biphasic mixture was sealed with a screw cap and stirred at rt (under air) for 45 h. Sat. Na_2SO_3(aq) (0.5 mL) was then added, and the resultant mixture was stirred vigorously at rt for 30 min. H_2O (10 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered through a pad of Celite (4 g) in a 40 mm Ø, porosity 3, sintered funnel under house vacuum, and then concentrated in vacuo (50 °C, ca. 5 mmHg) to give a black oil (271 mg). Purification via flash column chromatography (C18 reversed-phase silica gel, 20 × 160 mm, *i*-PrOH, ca. 2.5 mL fractions, loaded with minimal MeCN for solubility reasons) gave an orange-brown oil (158 mg). Further purification via flash column chromatography (20 g SiO_2, 20 mm Ø, 98:1.8:0.2 CH_2Cl_2/MeOH/NH_3(aq), ca. 5 mL fractions) gave a clear, yellow oil (130 mg). Further purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave **19i** as a clear, colorless oil (121 mg, 43%). Data for **19i**: bp 160 °C ABT (10^{-5} mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 7.32−7.21 (m, 7H), 7.19−7.10 (m, 3H), 3.52−3.43 (br s, 2H), 2.94 (d, *J* = 11.5 Hz, 1H), 2.81 (d, *J* = 11.5 Hz, 1H), 2.49−2.40 (m, 1H), 1.99−1.74 (m, 3H), 1.43−1.09 (m, 4H) overlapping 1.24 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 146.8, 138.7, 129.5, 128.4, 128.3, 127.8, 127.1, 126.1, 63.7, 54.3, 54.2, 45.8, 42.7, 31.1, 30.4, 19.2. IR (neat) 3082 (m), 3060 (m), 3026 (s), 3000 (m), 2937 (s), 2906 (s), 2875 (s), 2849 (s), 2799 (s), 2753 (s),

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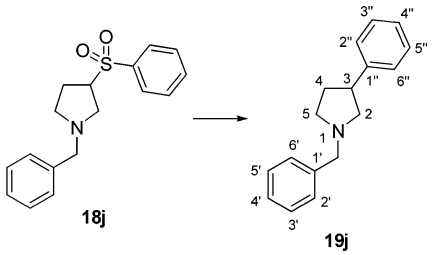
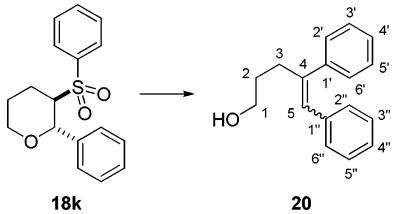
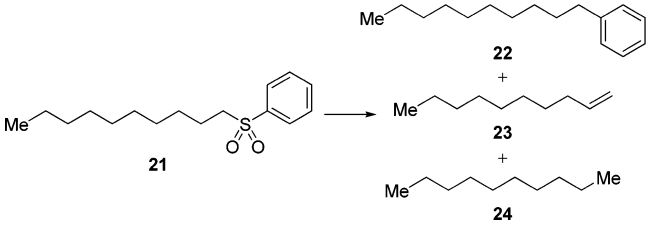
2723 (m), 2692 (m), 2677 (m), 1601 (m), 1493 (s), 1452 (s), 1366 (s), 1342 (m), 1313 (m), 1298 (m), 1274 (m), 1262 (m), 1148 (s), 1120 (m), 1074 (m), 1049 (m), 1028 (m), 1012 (m), 996 (m), 984 (m), 970 (m), 907 (m), 845 (m), 793 (m), 761 (s), 737 (s), 699 (s). MS (EI$^+$, 70 eV) 279.2 (M$^+$, 65), 202.2 (14), 188.1 (14), 174.1 (21), 172.1 (14), 159.1 (20), 146.1 (12), 120.1 (20), 105.1 (21), 91.1 ($C_7H_7^+$, 100), 77.0 (10). TLC R_f 0.14 (98:1.8:0.2 CH_2Cl_2:MeOH:aq. NH_3) [$KMnO_4$]. Anal. Calcd for $C_{20}H_{25}N$ (279.42): C, 85.97; H, 9.02; N, 5.01%. Found: C, 85.93; H, 8.96; N, 5.17%.



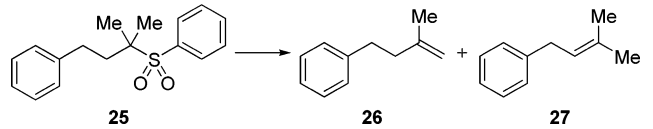
*Preparation of (rac)-N-Benzyl-3-phenylpyrrolidine (**19j**).* An oven-dried, 25 mL, one-necked, round-bottomed flask was charged with **18j** (225 mg, 1.00 mmol, 1.0 equiv) and $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %) in a glovebox and was then sealed with a rubber septum and removed from the box. Outside of the glovebox, a 25 mL Schlenk flask equipped with a stirrer bar, rubber septum, and argon inlet was evacuated, flame-dried, left to cool under vacuum, and flushed three times with argon. TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv) was added via syringe to the Schlenk flask, and stirring was commenced. The flask containing **18j** and $Fe(acac)_3$ was charged with CPME (4.0 mL) and then sonicated until homogeneous. The clear red solution was then transferred via cannula to the Schlenk flask holding the TMEDA, and the residual material was rinsed across with further portions of CPME (6.0 mL). PhMgBr (2.78 M in Et_2O, 1.08 mL, 3.00 mmol, 3.0 equiv) was then added by syringe over ca. 20 s. During addition, the color of the solution changed from red to pale-yellow to brown but remained clear throughout, and no visible deposits were formed on the edges of the flask. After stirring for 18 h at rt, 1 M HCl(aq) (10 mL) was added in one portion, and the mixture was filtered through a pad of Celite (5 g) in a 40 mm Ø, porosity 3, sintered funnel under house vacuum. EtOAc (2 × 5 mL) was used to rinse any residual material though the Celite pad. The filtrate was brought to pH 9 by addition of 2 M NaOH(aq) and transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a red oil (305 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 92:7.2:0.8 CH_2Cl_2/MeOH/NH_3(aq), ca. 5 mL fractions) gave a clear, orange oil (53.9 mg). Further purification via bulb-to-bulb distillation under reduced pressure (0.03 mmHg) gave **19j** as a clear, colorless oil (40.0 mg, 25%). The ^{1}H NMR spectroscopic data matched that for alternative preparations.[115] Data for **19j**: bp 75 °C ABT (0.03 mmHg).



*Reaction of (u)-2-Phenyl-3-(phenylsulfonyl)tetrahydropyran (**18k**).* Following general procedure 1, **18k** (>99:1 dr, 302 mg, 1.00 mmol, 1.0 equiv), PhMgBr (2.76 M in Et_2O, 1.09 mL, 3.00 mmol, 3.0 equiv), $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %), TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv), and CPME (10.0 mL) were reacted to give a ~4:1 mixture of **18k**/**20** as an orange oil (484 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, 75:25, hexane/EtOAc, ca. 5 mL fractions) gave an impure sample of **20** as a pale-yellow oil (3.7 mg) and an impure sample of **18k** as a white solid/yellow oil (181 mg). Data for **20**: ^{1}H NMR (500 MHz, $CDCl_3$) (selected peaks) 6.75 (s, 1H), 3.60 (t, J = 6.4 Hz, 2H), 2.84−2.78 (m, 2H), 1.72−1.65 (m, 2H). MS (EI$^+$, 70 eV) 238.1 (M$^+$, 76), 205.1 (35), 194.1 (82), 178.1 (58), 165.1 (34), 152.1 (16), 147.1 (100), 105.0 (45). HRMS (EI$^+$, TOF) calcd for $C_{17}H_{18}O$, 238.1358; found, 238.1359. TLC R_f 0.32 (70:30 hexane/EtOAc) [$KMnO_4$].

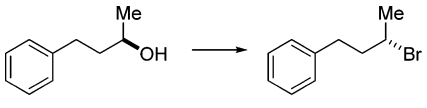


*Reaction of 1-(Phenylsulfonyl)decane (**21**).* A 12 × 75 mm test tube equipped with a stirrer bar was oven-dried, transferred to a glovebox, charged with **21** (28.2 mg, 0.10 mmol, 1.0 equiv) and $Fe(acac)_3$ (7.1 mg, 0.02 mmol, 20 mol %), and sealed with a rubber septum and electrical tape before being removed from the glovebox. Outside the glovebox, the test tube was charged with TMEDA (93.0 mg, 120 μL, 0.80 mmol, 8.0 equiv), tetradecane (9.9 mg, 13 μL, 0.05 mmol, 0.5 equiv), and CPME (1.0 mL) via syringe, and stirring was commenced. PhMgBr (3.06 M solution in Et_2O, 98 μL, 0.30 mmol, 3.0 equiv) was added via syringe, causing a color change from red to pale-yellow to brown/black. After 18 h, the reaction was quenched by addition of MeOH (0.3 mL) via syringe. A 50 μL aliquot of the organic layer was then transferred via syringe to a fresh GC vial and diluted with EtOAc (1 mL) for analysis. According to GC analysis, the reaction had proceeded to 80% conversion to give **22** (27%), **23** (≤5%), and **24** (≤5%). No other products were detected under the conditions of the run.



*Reaction of (rac)-[(2-Methyl-4-phenylbutan-2-yl)sulfonyl]-benzene (**25**).* Following general procedure 1, **25** (288 mg, 1.00 mmol, 1.0 equiv), PhMgBr (2.60 M in Et_2O, 1.15 mL, 3.00 mmol, 3.0 equiv), $Fe(acac)_3$ (70.6 mg, 0.20 mmol, 20 mol %), TMEDA (930 mg, 1.20 mL, 8.00 mmol, 8.0 equiv), and CPME (10.0 mL) were reacted to give a 87:13 mixture of **26**/**27** in addition to unreacted **25** (~30%) as an orange oil (456 mg). Purification via flash column chromatography (40 g SiO_2, 30 mm Ø, hexane, ca. 5 mL fractions) gave an 80:20 mixture of **26**/**27** contaminated with hexane and biphenyl as a pale-yellow oil (40.4 mg, ~28%). The ^{1}H NMR spectroscopic data for the **26**[116] and **27**[117] present in the mixture matched that for alternative preparations.

5.7. Preparation and Cross-Coupling of Enantiopure Substrates.



*Preparation of (S)-(3-Bromobutyl)benzene (**29**).* Bromine (1.26 g, 0.40 mL, 7.83 mmol, 1.2 equiv) was added dropwise via syringe to a stirred suspension of triphenylphosphine (2.07 g, 7.83 mmol, 1.2 equiv) in CH_2Cl_2 (23 mL) in a 1 L, single-necked, round-bottomed flask equipped with a stirrer bar and cooled in an ice/water bath (open to air). The flask was then sealed with a rubber septum and purged with argon via an inlet needle. After stirring the resultant pale-yellow suspension for 15 min, a solution of (*R*)-**28** (99% ee, 1.00 g, 6.52 mmol, 1.0 equiv) and imidazole (538 mg, 7.83 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) was added via cannula over ca. 5 min. The cooling bath was removed, and the reaction mixture was allowed to warm to rt over 17 h. The mixture was then filtered through a 40 mm Ø, porosity

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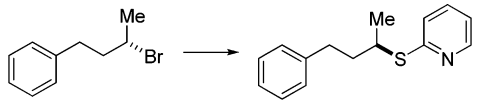
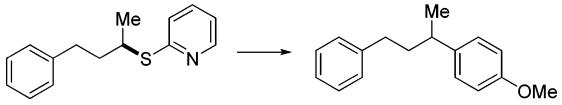
3, sintered funnel under house vacuum and carefully concentrated in vacuo to leave a yellow oil residue (i.e., avoiding precipitating the phosphorus-containing residues at this point). A stirrer bar was added to the residue, a wide-neck plastic funnel was added to the neck of the flask, and rapid stirring was commenced. Pentane (33 mL) was quickly added in one portion to precipitate the phosphorus-containing residues as a fine white solid. The mixture was rinsed through a pad of SiO_2 (7 g) in a 40 mm Ø, porosity 3, sintered funnel under house vacuum using pentane (3 × 15 mL), and the filtrate was concentrated in vacuo (50 °C, ca. 5 mmHg) to give a clear, colorless oil (1.31 g). Purification via bulb-to-bulb distillation under reduced pressure (0.05 mmHg) gave (*S*)-**29** as a clear, colorless oil (1.25 g, 90%).[118] The spectral data matched that for (*rac*)-**29**. Data for (*S*)-**29**: bp 90 °C ABT (0.05 mmHg). $[\alpha]_D^{25}$ +77.4 (*c* 0.87, $CHCl_3$).



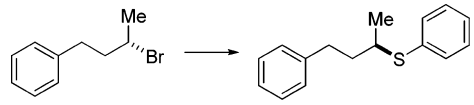
(*S*)-**29** (*R*)-**3d**

*Preparation of (R)-2-(4-Phenylbutan-2-ylthio)pyridine (**3d**).* A 15 mL, one-necked, round-bottomed flask equipped with a stirrer bar, water-jacketed reflux condenser, and argon inlet was charged with (*S*)-**29** (213 mg, 1.00 mmol, 1.0 equiv), 2-mercaptopyridine (113 mg, 1.00 mmol, 1.0 equiv), potassium carbonate (276 mg, 2.00 mmol, 2.0 equiv), and acetone (5.0 mL), and stirring was commenced. The resultant mixture was heated at reflux for 1 h and was then allowed to cool to rt. The mixture was filtered through a 40 mm Ø, porosity 3, sintered funnel under house vacuum and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a yellow oil (305 mg). Purification via flash column chromatography (10 g SiO_2, 20 mm Ø, 95:5, hexane/EtOAc, ca. 3 mL fractions) gave (*R*)-**3d** as a clear, colorless oil (235 mg, 96%, 98.8:1.2 er). The ^{1}H NMR spectroscopic data matched that for (*rac*)-**3d**. Data for (*R*)-**3d**: $[\alpha]_D^{25}$ +38.4 (*c* 1.16, $CHCl_3$). SFC (*R*)-**3d**, t_R 5.7 min (98.8%); (*S*)-**3d**, t_R 6.5 min (1.2%) (Chiralpak AD, 5% MeOH in CO_2, 2.0 mL min^{-1}, 220 nm, 40 °C).



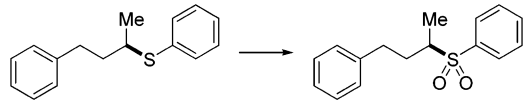
(*R*)-**3d** **8**

*Reaction of (R)-2-(4-Phenylbutan-2-ylthio)pyridine (**3d**).* A 4.0 mL screw-top vial containing (*R*)-**3d** (98.8:1.2 er, 72.9 mg, 0.30 mmol, 1.0 equiv) was taken into a glovebox, charged with $Fe(acac)_3$ (31.7 mg, 0.09 mmol, 20 mol %), sealed with a rubber septum, and removed from the box. Outside of the glovebox, a 10 mL Schlenk flask equipped with a stirrer bar, rubber septum, and argon inlet was evacuated, flame-dried, left to cool under vacuum, and flushed three times with argon. The vial containing (*R*)-**3d** and $Fe(acac)_3$ was charged with CPME (1.0 mL) and then sonicated until homogeneous. The clear red solution was then transferred via cannula to the Schlenk flask, and the residual material was rinsed across with further portions of CPME (2.0 mL). 4-Methoxyphenylmagnesium bromide (2.17 M in Et_2O, 552 μL, 1.20 mmol, 4.0 equiv) was then added by syringe over ca. 1 min. During addition, the color of the solution changed from red to opaque black, and small clusters of black solid could be seen forming during addition. Black deposits were also visible at the top of the solution. After stirring for 18 h at rt, 1 M HCl(aq) (3 mL) was added in one portion, and the mixture was filtered through a pad of Celite (5 g) in a 40 mm Ø, porosity 3, sintered funnel under house vacuum. EtOAc (2 × 5 mL) was used to rinse any residual material though the Celite pad. The filtrate was transferred to a separatory funnel, and the layers were separated. The organic layer was washed with 1 M HCl(aq) (2 × 3 mL), and the combined aqueous layers were extracted with EtOAc (2 × 5 mL). The combined organic extracts were then dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a pale-orange residue comprising mainly a white solid (236 mg). Purification via flash column chromatography (20 g SiO_2, 20 mm Ø, 80:20, hexane/toluene, ca. 5 mL fractions) gave a colorless oil (54.2 mg). Further purification via flash column chromatography (C18 reversed-phase silica gel, 20 × 160 mm, 98:2 MeOH/H_2O, ca. 2 mL fractions, loaded with minimal MeCN for solubility reasons) gave **8** as a clear, colorless oil (38.0 mg, 53%, 50.5:49.5 er). The ^{1}H NMR spectroscopic data matched that for **8** prepared from (*rac*)-**3d**. Data for **8**: SFC first enantiomer, t_R 11.7 min (49.5%); second enantiomer, t_R 12.8 min (50.5%) (Chiralcel OB, 5% MeOH in CO_2, 1.0 mL min^{-1}, 220 nm, 40 °C).



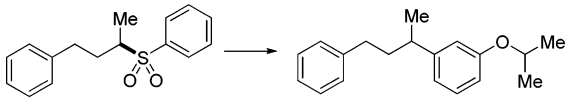
(*S*)-**29** (*R*)-**3a**

*Preparation of (R)-(4-Phenylbutan-2-ylthio)benzene (**3a**).* A 15 mL, one-necked, round-bottomed flask equipped with a stirrer bar, water-jacketed reflux condenser, and argon inlet was charged with (*S*)-**29** (213 mg, 1.00 mmol, 1.0 equiv), thiophenol (114 mg, 106 μL, 1.00 mmol, 1.0 equiv), potassium carbonate (276 mg, 2.00 mmol, 2.0 equiv), and acetone (5.0 mL), and stirring was commenced. The resultant mixture was heated at reflux for 19 h and was then allowed to cool to rt. The mixture was filtered through a 40 mm Ø, porosity 3, sintered funnel under house vacuum and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a colorless oil (246 mg). Purification via preparative, radial, centrifugally accelerated, thin-layer chromatography on a Harrison Chromatotron (1 mm SiO_2 plate, 90:10, hexane/toluene, ca. 5 mL fractions) gave (*R*)-**3a** as a clear, colorless oil (202 mg, 83%, 98.6:1.3 er). The ^{1}H NMR spectroscopic data matched that for (*rac*)-**3a**. Data for (*R*)-**3a**: $[\alpha]_D^{25}$ −2.1 (*c* 10.5, $CHCl_3$). SFC (*R*)-**3a**, t_R 6.5 min (98.6%); (*S*)-**3a**, t_R 7.4 min (1.3%) (Chiralpak AD, 1.5% MeOH in CO_2, 2.0 mL min^{-1}, 220 nm, 40 °C).



(*R*)-**3a** (*R*)-**9**

*Preparation of (R)-[(4-Phenylbutan-2-yl)sulfonyl]benzene (**9**).* A 10 mL, one-necked, round-bottomed flask equipped with a stirrer bar and rubber septum was charged with (*R*)-**3a** (195 mg, 0.81 mmol, 1.0 equiv), ammonium molybdate tetrahydrate (99.6 mg, 0.08 mmol, 10 mol %), and MeOH (2.5 mL), and stirring was commenced. The mixture was cooled in an ice/water bath, and hydrogen peroxide (30% in H_2O, 366 mg, 329 μL, 3.22 mmol, 4.0 equiv) was added dropwise via syringe over ca. 2 min. The resultant turbid, pale-yellow mixture was stirred in the ice/water bath for 40 min and then allowed to warm to rt over 1 h, during which time the yellow color intensified. The mixture was then cooled in an ice/water bath, and sat. Na_2SO_3(aq) (1.5 mL) was added dropwise via syringe over ca. 2 min. Starch-iodide paper was used to confirm that no oxidant remained. EtOAc (10 mL) and H_2O (10 mL) were then added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (50 °C, ca. 5 mmHg) to give a cloudy, colorless syrup (0.2 g). Purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave (*R*)-**9** as a clear, colorless syrup (204 mg, 92%, >99.5:0.5 er). The ^{1}H NMR spectroscopic data matched that for (*rac*)-**9**. Data for (*R*)-**9**: bp 170 °C ABT (10^{-5} mmHg). $[\alpha]_D^{25}$ +8.7 (*c* 1.86, $CHCl_3$). SFC (*R*)-**9**, t_R 10.2 min (>99.5%); (*S*)-**9**, t_R 13.1 min (<0.5%) (Chiralcel OB, 7.5% MeOH in CO_2, 2.0 mL min^{-1}, 220 nm, 40 °C).



(*R*)-**9** **19e**

*Reaction of (R)-[(4-Phenylbutan-2-yl)sulfonyl]benzene (**9**).* Following general procedure 1, (*R*)-**9** (>99.5:0.5 er, 173 mg, 0.63 mmol, 1.0 equiv), 3-isopropoxyphenylmagnesium bromide (2.24 M in Et_2O, 842 μL, 1.89 mmol, 3.0 equiv), $Fe(acac)_3$ (44.4 mg, 0.13 mmol, 20 mol %), TMEDA (585 mg, 755 μL, 5.03 mmol, 8.0 equiv), and CPME

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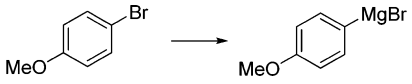
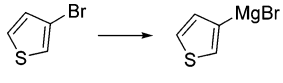
(6.3 mL) were reacted to give a yellow oil (562 mg). Purification via flash column chromatography (30 g SiO_2, 30 mm Ø, 90:10, hexane/toluene, ca. 5 mL fractions) gave a clear, colorless oil (105 mg). Further purification via flash column chromatography (C18 reversed-phase silica gel, 20 × 160 mm, MeOH, ca. 2.5 mL fractions, loaded with minimal MeCN for solubility reasons) gave a clear, colorless oil (91.7 mg). Further purification via bulb-to-bulb distillation under reduced pressure (10^{-5} mmHg) gave **19e** as a clear, colorless oil (92.4 mg, 55%, 50.7:49.3 er) that was contaminated with ∼5% of a compound tentatively assigned as 3-isopropoxybiphenyl. The ^{1}H NMR spectroscopic data and boiling point matched that for **19e** prepared from (*rac*)-**9**. Data for **19e**: bp 125 °C ABT (10^{-5} mmHg). SFC first enantiomer, t_R 7.5 min (49.3%); second enantiomer, t_R 7.9 min (50.7%) (Chiralcel OD, 5% MeOH in CO_2, 2.0 mL min^{-1}, 220 nm, 40 °C).

5.8. Preparation of Grignard Reagents. Grignard reagents **15a**−**h**, **i**, **k**−**m**, and **q** were prepared from the corresponding aryl bromides and magnesium turnings in Et_2O (Representative Procedure 1 below). Grignard reagents **15j**, **n**−**p**, and **v** could not be prepared directly using magnesium turnings in Et_2O and were instead prepared from the corresponding aryl/alkenyl bromides by lithium−bromine exchange with *t*-BuLi followed by transmetalation with $MgBr_2$ (Representative Procedure 2 below). Phenylacetylenylmagnesium bromide **15w** was prepared by deprotonation of phenylacetylene with EtMgBr in Et_2O. Grignard reagents **15r**−**u** were commercially available as solutions in Et_2O from Aldrich and were used as received. Titration of the Grignard reagents was carried out using the protocol reported by Watson and Eastham.[119] THF was typically added as a cosolvent in these titrations to ensure homogeneity and, in some cases, to give a stronger color to the solution than Et_2O alone.



Representative Procedure 1: Preparation of 4-Methoxyphenylmagnesium Bromide. An oven-dried, 50 mL, three-necked, round-bottomed flask equipped with a stirrer bar, an oven-dried water-jacketed reflux condenser, two rubber septa, and an argon inlet (at the top of the condenser) was assembled under a flow of argon and charged sequentially with magnesium turnings (729 mg, 30.0 mmol, 1.2 equiv), Et_2O (2.0 mL), and a few crystals of iodine, and stirring was commenced. A small portion of neat 4-bromoanisole (from 4.72 g, 3.16 mL, 25.0 mmol, 1.0 equiv) was then added via cannula from an oven-dried, 25 mL, single-necked, round-bottomed flask under argon. Once the reaction had initiated (signified by decoloration and bubbling), Et_2O (8.0 mL) was added to the 25 mL flask containing the 4-bromoanisole, and the resultant solution was added dropwise via cannula over ca. 20 min to the reaction. The mixture was then heated at reflux for 1 h, stirring was then ceased, and the mixture was allowed to cool to rt. The brown supernatant solution (∼9 mL) was then transferred via cannula to a 50 mL plastic centrifuge tube capped with an inverted rubber septum under argon. The solution was then centrifuged at 3220 rcf for 10 min. The clear, dark yellow-brown supernatant solution was then transferred via cannula to an oven-dried, 25 mL Schlenk flask under argon. On the basis of the titration protocol reported by Watson and Eastham,[119] a 350 μL aliquot of the solution of 4-methoxyphenylmagnesium bromide was added to a stirred solution of 1,10-phenanthroline (ca. 1 to 2 mg) in 2:1 Et_2O/THF (3.0 mL) in an oven-dried, 25 mL, three-necked, round-bottomed flask under argon. The resultant deep burgandy solution was titrated against *s*-BuOH (1.00 M solution in xylenes), with the end point indicated by a sudden color change from deep burgandy to clear yellow. The solution of 4-methoxyphenylmagnesium bromide was 2.17 M.



15p

*Representative Procedure 2: Preparation of 3-Thienylmagnesium Bromide (**15p**).* A 100 mL Schlenk flask (marked at 8 mL volume) was equipped with a stirrer bar and water-jacketed reflux condenser, oven-dried, assembled under a flow of argon (via an inlet at the top of the condenser), and a septum was placed on the remaining neck of the Schlenk along with an exit needle. Magnesium turnings (217 mg, 8.91 mmol, 1.1 equiv) were then added against a backflow of argon, and the apparatus was allowed to cool to rt, at which point the exit needle was removed and the argon flow was reduced. The flask was charged sequentially with benzene (2.2 mL) and Et_2O (6.7 mL), and 1,2-dibromoethane (1.61 g, 743 μL, 8.51 mmol, 1.05 equiv) was added dropwise to the flask via syringe over ca. 20 min (with cooling in an ice/water bath as necessary to prevent thermal runaway). Once addition was complete, the ca. 1 M solution was stirred for a further 30 min and then left to stand at rt (the solution was clear and colorless aside from residual magnesium). Meanwhile, a 100 mL, single-necked, round-bottomed flask equipped with a stirrer bar and rubber septum was flame-dried while being purged with argon via an inlet and exit needle. Once the flask had cooled to rt, it was charged with a solution of 3-bromothiophene (1.32 g, 759 μL, 8.10 mmol, 1.0 equiv) in Et_2O (16.0 mL) and then cooled to in a dry ice/acetone bath with stirring. *t*-BuLi (1.62 ± 0.03 M in pentanes, 10.0 mL, 16.2 mmol, 2.0 equiv) was transferred to a flame-dried, 10 mL volumetric flask under argon via syringe and then added dropwise via cannula to the solution of 3-bromothiophene over ca. 10 min. Once added, the mixture was stirred in the dry ice/acetone bath for a further 30 min. The clear, colorless solution of 3-thienyllithium was then removed from the cooling bath and added dropwise via cannula to the previously prepared solution of $MgBr_2$ in Et_2O/benzene at rt. The resultant homogeneous solution was stirred in a hot water bath under a strong argon flow to reduce the solvent volume to ca. 8 mL (as marked on the Schlenk flask). On doing so, the lithium salts precipitated as a fine white solid and the supernatant, pale-yellow solution, was transferred via syringe to an oven-dried, 25 mL Schlenk flask under argon. On the basis of the titration protocol reported by Watson and Eastham,[119] a 500 μL aliquot of the solution of **15p** was added to a stirred solution of 1,10-phenanthroline (ca. 1−2 mg) in 1:1 CPME/THF (6.0 mL) in an oven-dried, 25 mL, three-necked, round-bottomed flask under argon. The resultant red-orange solution was titrated against *s*-BuOH (1.00 M solution in xylenes), with the end point indicated by a sudden color change from red-orange to clear yellow. The solution of **15p** was 0.95 M.

■ ASSOCIATED CONTENT

Supporting Information

Optimization studies, calibration tables, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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