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Enantioselective Synthesis of Chiral Sulfones by Rh-Catalyzed Asymmetric Addition of Boronic Acids to α,β-Unsaturated 2-Pyridyl Sulfones

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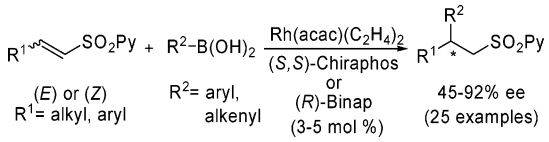

A general and efficient method for the rhodium-catalyzed enantioselective catalytic conjugate addition of organoboronic acids to α,β-unsaturated sulfones is described. The success of the process relies on the use of α,β-unsaturated 2-pyridyl sulfones as key metal-coordinating substrates; typical sulfones such as vinyl phenyl sulfones are inert under the reaction conditions. Among a variety of chiral ligands, Chiraphos provided the best asymmetric induction. This rhodium [Rh(acac)(C_2H_4)$_2$]/Chiraphos catalyst system has a broad scope, being applicable to the addition of both aryl and alkenyl boronic acids to *cis* and *trans* α,β-unsaturated 2-pyridyl sulfones. In most cases, especially in the addition of aryl boronic acids, the reactions take place cleanly and with high enantioselectivity, affording chiral β-substituted 2-pyridyl sulfones in good yields and enantioselectivities (70−92% ee). The sense and magnitude of this enantioselectivity have been studied by DFT theoretical calculations of the aryl−rhodium insertion step. These calculations strongly support the formation of a five-membered pyridyl−rhodium chelated species as the most stable complex after the insertion into the C═C bond. These highly enantioenriched chiral sulfones are very appealing building blocks in enantioselective synthesis. For instance, the straightforward elimination of the 2-pyridylsulfonyl group by either Julia−Kociensky olefination or alkylation/desulfonylation sequences provides a variety of functionalized chiral compounds, such as allylic substituted alkenes or β-substituted ketones and esters.

Introduction

Since the first report described by Miyaura et al. in 1997,[1a] the Rh(I)-catalyzed asymmetric conjugate addition of boronic acids to electron-deficient olefins has gained increasing importance, becoming one of the most useful and versatile tools for the introduction of both aryl and alkenyl fragments at the β-position of such substrates in a highly enantioselective fashion.[1] The current state of the art includes the extension of the methodology to a wide variety of Michael acceptors, such as α,β-unsaturated ketones,[2] esters,[3] amides and imides,[4] nitroalkenes,[5] phosphonates,[6] and aldehydes.[7] However, despite the well-known importance of sulfones in organic synthesis,[8] the rhodium-catalyzed conjugate addition of boronic acids to α,β-unsaturated sulfones had not been previously described. In

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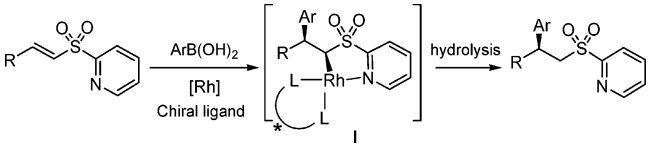
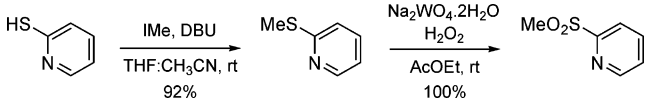
fact, to the best of our knowledge, the only precedent on the use of α,β-unsaturated sulfones and carbon nucleophiles in enantioselective Rh-catalyzed addition reactions was reported by Hayashi et al. in 2003, which described that the reaction with aryltitanium species provided a *cine*-substitution alkene product instead of the 1,4-addition product.[9]

Removable metal-coordinating groups have been often used in metal-catalyzed transformations to accelerate or even enable reactions that would otherwise be extremely sluggish, the coordination of such ancillary groups with late transition metals rendering these processes pseudo intramolecular.[10] For example, heterocyclic nitrogen coordinating groups such as 2-pyridyl, 2-pyridyldimethylsilyl, or 2,6-pyrimidylsulfenyl have been widely employed in highly efficient C−C bond-forming reactions catalyzed by transition metals, mainly Pd, Ru, Rh, and Cu.[11] As part of an ongoing research program dealing with potentially metal-coordinating α,β-unsaturated sulfones in transition-metal-catalyzed processes, our research group has reported that the *o*-(dimethylamino)phenyl sulfonyl group allowed intermolecular Heck reactions on α,β-unsaturated sulfones,[12] and the 2-pyridyl sulfonyl group played a key role in the development of the Cu-catalyzed asymmetric reduction of β,β-disubstituted vinyl sulfones.[13]

SCHEME 1



SCHEME 2



In a previous communication we reported that this kind of chelation-controlled strategy can also be applied to the enantioselective 1,4-addition of boronic acids to α,β-unsaturated sulfones, especially utilizing a 2-pyridyl sulfone as the key auxiliary coordinating group.[14] Herein, we report a full account of the scope of this Rh-catalyzed asymmetric conjugate addition of boronic acids to β-substituted α,β-unsaturated sulfones with regard to the substitution at the boronic acid and vinyl sulfone, *cis*/*trans* stereochemistry of the vinyl sulfone, nature of the chiral ligand, and synthetic applications of the resulting enantioenriched β-chiral 2-pyridyl sulfones. A DFT theoretical study to rationalize the origin of the enantioselectivity of the process, presumably through the participation of the chelated Rh−N species I (Scheme 1), is also presented.

Results and Discussion

1. Preparation of the Model Aryl and Heteroaryl 1-Propenyl Sulfones. It is surprising that, despite the well-established utility of the sulfonyl group, the vast majority of the reactions reported to date with α,β-unsaturated sulfones refer exclusively to the use of the traditional phenyl or *p*-tolyl sulfones. Thus, as a starting point in our agenda, we set out to develop an efficient synthetic route to heteroaryl vinyl sulfones. As a first approach, we studied the addition of a heteroaryl methyl sulfone to an aldehyde and further dehydration. For that purpose, we chose methyl 2-pyridyl sulfone as starting material, which was prepared by methylation of the commercially available 2-mercaptopyridine and further oxidation at sulfur[15] (Scheme 2). However, deprotonation of methyl 2-pyridyl sulfone with *n*-BuLi (THF, −78 °C) and in situ treatment with acetaldehyde led to a complex reaction mixture, most likely due to competitive self-condensation reactions of the aldehyde.

In light of these results, we turned to the Horner−Wadsworth−Emmons olefination as a plausible approach to the synthesis of this type of functionalized alkenes. As a first alternative to prepare the required phosphonate, we tried the direct phosphorylation of the lithium anion of methyl 2-pyridyl sulfone (prepared by treatment with *n*-BuLi, THF, −78 °C) with diethyl chlorophosphate. Unfortunately, a complex mixture was observed by ^{1}H NMR. Then, a two-step sequence was studied:

(3) (a) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047. (b) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951. (c) Shintani, R.; Ueyama, K.; Yamada, I.; Hayashi, T. *Org. Lett.* **2004**, *6*, 3425. (d) Paquin, J.-F.; Stephenson, C. R. J.; Defieber, C.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 3821. (e) Chen, G.; Tokunaga, N.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2285. (f) See also ref 2h.

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(9) Yoshida, K.; Hayashi, T. *J. Am. Chem. Soc.* **2003**, *125*, 2872.

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(13) Llamas, T.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3329.

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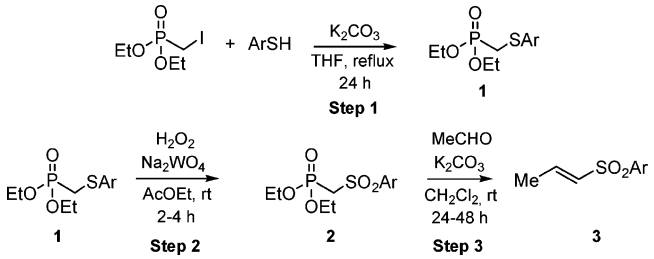
(15) Blacklock, T. J.; Sohar, P.; Butcher, J. W.; Lamanec, T.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 1672.

SCHEME 3



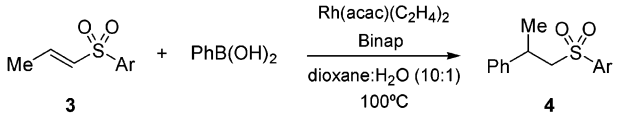
ArSH	Step 1, (%)	Step 2, (%)	Step 3, (%)
1-Phenyl-1H-tetraazole-SH	62	98	64
Benzothiazole-SH	59	96	71
2,6-Pyrimidine-SH	73	99	29
2,5-Imidazole-SH	71	96	68
2-Pyridine-SH	75	98	85

a S_N2 reaction of the commercially available diethyl iodomethylphosphonate with an aromatic thiol[16] and further oxidation of the thioether to the sulfone. As outlined in Scheme 3, in the presence of K_2CO_3 as base (THF, reflux) the reaction of diethyl iodomethylphosphonate with a set of five heteroaromatic thiols took place in good yields (59−75%). The oxidation of the so formed thioethers (**1**) to the corresponding sulfones (**2**) was effected by adding 3 equiv of hydrogen peroxide in the presence of catalytic amounts of Na_2WO_4 in ethyl acetate.[15] In all cases, the oxidation took place cleanly, without any competitive formation of *N*-oxides, providing the required phosphonates in excellent yields (96−99%). With these sulfonyl phosphonates in hand, we studied the Horner−Wadsworth−Emmons olefination with acetaldehyde. After trying a number of reaction conditions, testing different solvents and bases, we found as optimal conditions the use of inexpensive K_2CO_3 as base and CH_2Cl_2 as solvent, at room temperature. Under these conditions, the olefination process gave rise to the desired 1-propenyl heteroaryl sulfones **3** in good yields (64−85%, except for the pyrimidylsulfonyl derivative **3e**) and with complete (*E*) stereoselectivity.

2. Rh-Catalyzed Addition of $PhB(OH)_2$ to Aryl and Heteroaryl 1-Propenyl Sulfones: Effect of the Substitution at the Sulfone. Having prepared a variety of 1-propenyl sulfones, ranging from the simple non-coordinating phenyl sulfone (**3a**) to the substrate bearing an *o*-*N*,*N*-dimethylaminophenyl moiety (**3b**) or the previously mentioned heteroaromatic sulfones[17] (**3c**−**g**), we studied the Rh-catalyzed reactions of all of these substrates with $PhB(OH)_2$ under the conditions originally described by Miyaura and Hayashi for the addition to enones[2a] [$Rh(acac)(C_2H_4)_2$ as catalyst, racemic Binap as ligand, in dioxane/H_2O at 100 °C] (Table 1).

Not unexpectedly,[9] the simple phenyl sulfone **3a** proved to be unreactive under the reaction conditions. Unfortunately, no evolution was observed from the sulfones **3b, 3c**, or **3d**, bearing 2-(dimethylamino)phenyl (**3b**), tetrazoyl (**3c**), and benzothiazo-2-yl (**3d**) groups (entries 2−4), and an incomplete conversion occurred in the case of the 2,6-pyrimidyl sulfone **3e** (entry 5).[18] However, a very smooth and clean reaction took place when **3f** (imidazoyl group) or **3g** (pyridyl group) was used as substrate, leading to the desired β-phenylsubstituted sulfone as the sole detected product. Among both substrates, the 2-pyridyl sulfone **3g** proved to be more efficient than the imidazoyl homologue **3f**, affording the addition product in 12 h in 98% isolated yield (as opposed to 74% yield).

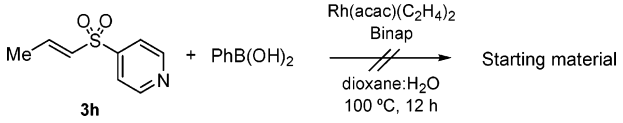
TABLE 1. Rh-Catalyzed Addition of $PhB(OH)_2$ to (*E*)-1-Propenyl Aryl Sulfones



Entry [a]	3	Ar	Conv. (%)[b]	4, yld. (%)[c]
1	**3a**		<2	-
2	**3b**		<2	-
3	**3c**		<2	-
4	**3d**		<2	-
5	**3e**		65	**4e**, 44
6	**3f**		>98	**4f**, 74
7	**3g**		>98	**4g**, 98

[a] Reaction conditions: $PhB(OH)_2$ (500 mol %), [Rh] (3 mol %), Binap (3 mol %), dioxane/H_2O (10:1), 100 °C, 12 h. [b] Estimated by ^1H NMR analysis of the crude reaction mixtures. [c] In pure isolated product after chromatography.

SCHEME 4



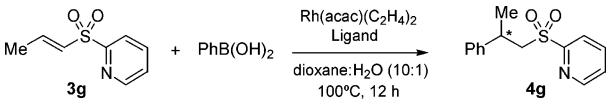
At this point we decided to clarify if the high reactivity observed with the sulfone **3g** was due to merely the electron-withdrawing effect of the pyridyl group or if, as first envisaged, it would be the result of the participation of Rh−N five-membered chelated species (such as **I** in Scheme 1). With that purpose in mind, and following the reaction sequence optimized for the synthesis of α,β-unsaturated heteroaryl sulfones, we prepared the pyridyl sulfone **3h**, a structural isomer of **3g** that presents the nitrogen atom in position 4 at the pyridine unit. As such, the electronic properties of both isomers should be very similar, but in the case of **3h** the nitrogen atom in position 4 makes the formation of chelated Rh−N species unfeasible. Interestingly, unlike the high reactivity observed for **3g**, no reaction took place when **3h** was treated with $PhB(OH)_2$ under the standard Rh-catalyzed reaction conditions, **3h** being fully recovered after 12 h (Scheme 4). This result substantiates our hypothesis that the high reactive profile of **3g** could be due to chelation Rh−N effects rather than mere electronic factors.

(16) Erian, A.; Kwonno, A.; Fuchigami, T. *J. Org. Chem.* **1995**, *60*, 7654.

(17) See supporting information for details on the preparation of substrates **3**.

(18) Although we previously found that sulfone **3e** does not react with phenylboronic acid,[14a] we have recently observed that this substrate is slightly reactive when a very fresh sample of $Rh(acac)(C_2H_4)_2$ is used as catalyst.

TABLE 2. Ligand Screening for Rh-catalyzed Enantioselective Addition of $PhB(OH)_2$ to Model Sulfone 3g



entry[a]	ligand	conv (%)[b]	yield (%)[c]	ee (%)[d]
1	(*R*)-Binap	>98	97	73 (*R*)
2	(*R*)-Tol-Binap	>98	92	60 (*R*)
3	(*S*,*S*)-Chiraphos	>98	97	81 (*S*)
4	(*R*)-Norphos	10		
5	(*R*)-Phanephos	<10		
6	Josiphos 1	73	68	41 (*R*)
7	Josiphos 2	<10		
8	Taniaphos	<10		
9	Mandyphos	<10		
10[e]	Fesulphos 1	87	78	76 (*S*)
11[e]	Fesulphos 2	70	66	81 (*S*)
12	Phosphoramidite	39	31	73 (*S*)

[a] Reaction conditions: $PhB(OH)_2$ (500 mol %), [Rh] (3 mol %), ligand (3 mol %), dioxane/H_2O (10:1), 100 °C, 12 h. [b] Estimated by ^1H NMR analysis of the crude reaction mixtures. [c] In pure isolated product after chromatography. [d] Determined by chiral HPLC (Chiralpak AD). [e] 6 mol % of ligand and Rh catalyst were used.

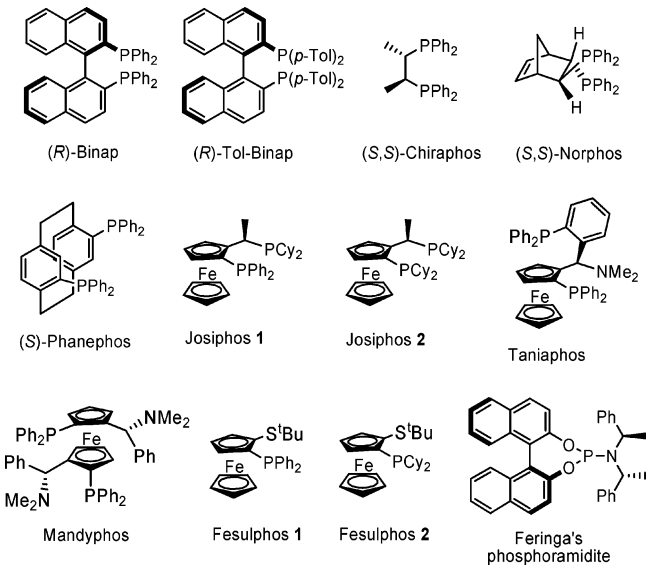
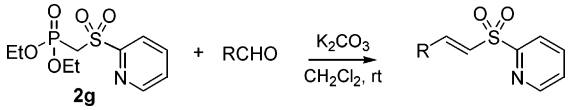


FIGURE 1. Chiral ligands tested.

3. Rh-Catalyzed Asymmetric Addition of $PhB(OH)_2$ to 1-Propenyl 2-Pyridyl Sulfone: Effect of the Chiral Ligand. With the 2-pyridyl sulfone **3g** as optimal substrate, we next studied the enantioselectivity of the process in the presence of a variety of structurally different chiral ligands (Table 2, Figure 1).

To establish appropriate reactivity comparisons, all the reactions were conducted for 12 h. Complete conversions were only observed when certain P,P-bisphosphines were employed, namely, Binap, Tol-Binap, and Chiraphos (entries 1−3, respectively). On the other hand, other bidentate ligands with P,P coordination (entries 4, 5, and 7), or P,N coordination (entries 8 and 9) almost completely inhibited the process. An intermediate situation was observed in the cases of Josiphos **1** (entry 6), Fesulphos **1** and **2** (entries 10 and 11), and the monodentate Feringa's phosphoramidite (entry 12). In all of these cases, incomplete conversions were obtained after 12 h. Regarding the enantioselectivity of the process, despite Binap having been successfully used in many reported Rh-catalyzed additions, in our case it was found that (*S*,*S*)-Chiraphos afforded a better result (81% ee, entry 3) than (*R*)-Binap (73% ee, entry 1) or (*R*)-Tol-Binap (60% ee, entry 2). Also worth noting are the high levels of enantioselectivity obtained with the P,S-Fesulphos ligands, recently developed in our group,[19] albeit their reactivity was significantly lower than that exhibited by (*S*,*S*)-Chiraphos. The absolute configuration of the addition product **4g** was unequivocally determined by chemical correlation with a known chiral compound, as will be discussed later (compound **20** in Table 7).

TABLE 3. Horner−Wadsworth−Emmons Olefination of 2g with Various Aldehydes



entry[a]	R	*E*/*Z* ratio[b]	**3**, yield (%)[c]
1	Me	>98/<2	**3g**, 85
2	*n*-pent	>98/<2	**3i**, 72
3	*i*-Pr	>98/<2	**3j**, 76
4	β-naphth	>98/<2	**3k**, 78

[a] Reaction conditions: RCHO (1.5 equiv), K_2CO_3 (1.5 equiv), CH_2Cl_2, rt, 24−48 h. [b] Estimated by ^1H NMR analysis of the crude reaction mixtures. [c] In pure isolated product.

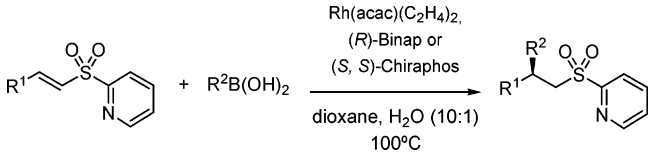
4. Scope of the Catalytic Asymmetric Addition of Aryl and Alkenyl Boronic Acids to α,β-Unsaturated 2-Pyridyl Sulfones. (a) Synthesis of (*E*) and (*Z*) α,β-Unsaturated 2-Pyridyl Sulfones. To address the effect of the substitution at the vinyl sulfone, a series of substrates with sterically different substitution at the β position were prepared. Thus, in addition to the model substrate **3g**, substrates **3i**, **3j**, and **3k** (bearing *n*-pentyl, isopropyl, and β-naphthyl groups, respectively) were readily obtained in good yields (72−78%) and complete (*E*) stereoselectivity by Horner−Wadsworth−Emmons olefination of 2-pyridylsulfonyl phosphonate **2g** and the corresponding aldehyde (Table 3).

The (*Z*)-propenyl 2-pyridyl sulfone (**3l**) was prepared to study the effect of the configuration at the C=C bond. This compound was easily synthesized taking advantage of the fact that the Horner−Wadsworth−Emmons reaction of the sulfenyl phosphonate **1g** is (*Z*)-stereoselective, instead of highly (*E*)-stereoselective as in the case of the sulfonyl phosphonate **2g**. Thus, the reaction of **1g** with acetaldehyde employing KHMDS as base (DME, −78 °C) provided the (*Z*) isomer as the major product (*Z*:*E* = 70:30). After chromatographic separation and sulfur oxidation ($Na_2WO_4{\cdot}2H_2O/H_2O_2$) the sulfone **3l** was obtained in 45% overall yield (Scheme 5).

Finally, in addition to all the previous acyclic vinyl 2-pyridyl sulfones, we also prepared the cyclic vinyl sulfone **3m.** This compound was readily prepared in two steps by the known Pummerer rearrangement of cyclohexyl 2-pyridyl sulfoxide,[20] followed by tungsten/H_2O_2 oxidation of the resulting sulfide (Scheme 6).

(19) (a) Priego, J.; García Mancheño, O.; Cabrera, S.; Gómez Arrayás, R.; Llamas, T.; Carretero, J. C. *J. Org. Chem.* **2003**, *68*, 3679. (b) Cabrera, S.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3944. (c) García Mancheño, O.; Gómez Arrayás, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 456. (d) Cabrera, S.; Gómez Arrayás, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (e) Cabrera, S.; Gómez Arrayás, R.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 17938. (f) Cabrera, S.; García Mancheño, O.; Gómez Arrayás, R.; Alonso, I.; Mauleón, P.; Carretero, Juan C. *Pure Appl. Chem.* **2006**, *78*, 257.

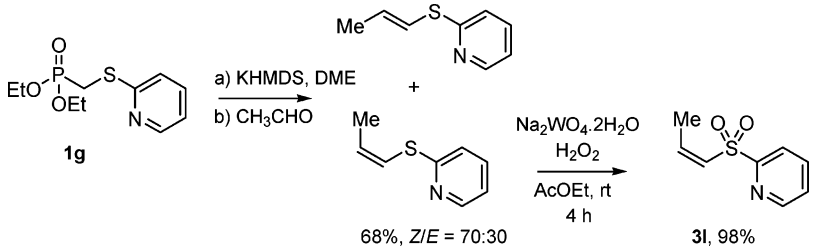
TABLE 4. Rh-Catalyzed Enantioselective Conjugate Addition of Aryl Boronic Acids to (*E*)-2-Pyridyl α,β-Unsaturated Sulfones



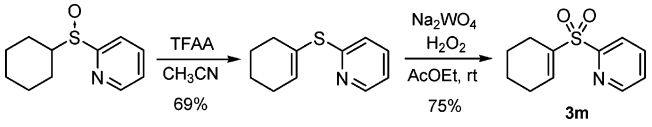
entry[a]	sulfone	R^1	R^2	ligand	product	yield (%)[b]	ee (%)[c]
1[d]	**3g**	Me	Ph	B	**4g**	97	73 (*R*)
2[d]	**3g**	Me	Ph	C	**4g**	98	81 (*S*)
3[d]	**3g**	Me	*p*-FC_6H_4	B	**5**	98	76 (*R*)
4[d]	**3g**	Me	*p*-FC_6H_4	C	**5**	98	84 (*S*)
5	**3g**	Me	*p*-$MeOC_6H_4$	B	**6**	97	54 (*R*)
6	**3g**	Me	*p*-$MeOC_6H_4$	C	**6**	89	77 (*S*)
7	**3i**	*n*-pent	Ph	B	**7**	98	74 (*R*)
8	**3i**	*n*-pent	Ph	C	**7**	98	84 (*S*)
9	**3i**	*n*-pent	*p*-FC_6H_4	C	**8**	94	87 (*S*)
10	**3i**	*n*-pent	*p*-$MeOC_6H_4$	C	**9**	92	81 (*S*)
11[e]	**3j**	*i*-Pr	Ph	B	**10**	62 (89)[f]	76 (*R*)
12[e]	**3j**	*i*-Pr	Ph	C	**10**	93	78 (*S*)
13[e]	**3j**	*i*-Pr	*p*-FC_6H_4	C	**11**	93	85 (*S*)
14[e]	**3j**	*i*-Pr	*p*-$MeOC_6H_4$	C	**12**	74 (94)[f]	76 (*S*)
15[e]	**3k**	β-naphth	Ph	B	**13**	76 (95)[f]	76 (*S*)
16[e]	**3k**	β-naphth	Ph	C	**13**	96	87 (*R*)
17[e]	**3k**	β-naphth	*p*-FC_6H_4	C	**14**	97	92 (*R*)
18[e]	**3k**	β-naphth	*p*-$MeOC_6H_4$	C	**15**	84 (94)[f]	85 (*R*)

[a] Reaction conditions: $R^2B(OH)_2$ (5 equiv), $Rh(acac)(C_2H_4)_2$ (3 mol %), L* (3 mol %), dioxane/H_2O (10:1), 24 h. B: (*R*)-Binap, C: (*S*,*S*)-Chiraphos. [b] In pure isolated product. [c] Determined by chiral HPLC (Chiralpak AD or Chiralcel OD). [d] Reaction time 12 h. [e] 5 mol % of ligand and Rh catalyst were used. [f] In converted product.

SCHEME 5



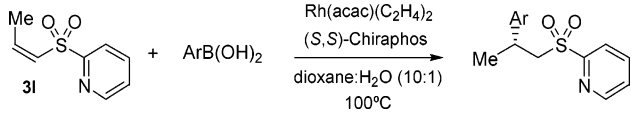
SCHEME 6



(b) Catalytic Asymmetric Addition of Aryl Boronic Acids to α,β-Unsaturated 2-Pyridyl Sulfones. In Tables 4 and 5 are shown the results of the Rh-catalyzed addition of three electronically different aryl boronic acids [$PhB(OH)_2$, *p*-$MeOC_6H_4B(OH)_2$, and *p*-$FC_6H_4B(OH)_2$] to the four (*E*) vinyl sulfones **3g**−**k** (Table 4) and the (*Z*) substrate **3l** (Table 5). For comparison purposes and because Chiraphos is not a very common chiral ligand in Rh-catalyzed conjugate additions (unlike Binap), we decided at this point to study more systematically the asymmetric performance of Binap versus Chiraphos.

Certain important conclusions can be extracted from these results: (a) Yields above 90% in pure isolated product and moderate to high asymmetric inductions, ranging 69−92% ee, were obtained regardless of the substitution at the vinyl sulfone and the boronic acid. Only in the reaction of the bulkier substrates **3j** and **3k** with *p*-$MeOC_6H_4B(OH)_2$ were the yields slightly lower as a result of incomplete conversions (entries 11, 14, 15, and 18). Addition of methyl boronic acid over **3i** was also attempted; however, no reaction at all was observed under the optimized conditions. (b) (*S*,*S*)-Chiraphos (ligand C in Table 4) proved to be more efficient than (*R*)-Binap (ligand B in Table 4) in all of the tested reactions (enantioselectivities from 2 to 23 points higher with Chiraphos than with (*R*)-Binap). This effect is particularly remarkable in the case of the addition of *p*-methoxyphenyl boronic acid to the sulfone **3g** (entries 5 and 6, 54% and 77% ee, respectively). Additionally, in the case of the more bulky substrates the chemical yields obtained using

TABLE 5. Rh-Catalyzed Enantioselective Addition of Aryl Boronic Acids to (*Z*)-α,β-Unsaturated 2-Pyridyl Sulfone 3l



entry[a]	Ar	prod, yield (%)[b]	ee (%)[c]
1	Ph	**4g**, 97	70 (*R*)
2	*p*FC_6H_4	**5**, 94	74 (*R*)
3	*p*$MeOC_6H_4$	**6**, 92	69 (*R*)

[a] Reaction conditions: $ArB(OH)_2$ (500 mol %), [Rh] (3 mol %), (*S*,*S*)-Chiraphos (3 mol %), dioxane/H_2O (10:1), 100 °C, 12 h. [b] In pure isolated product. [c] Determined by chiral HPLC (Chiralpak AD).

(20) Shimazaki, M.; Hikita, M.; Hosoda, T.; Ohta, A. *Heterocycles* **1991**, *32*, 937.

SCHEME 7

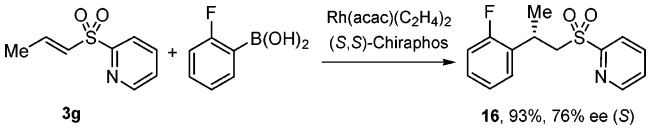
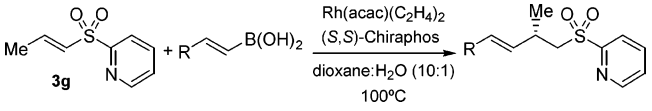


TABLE 6. Rh/Chiraphos-Catalyzed Enantioselective Addition of Alkenylboronic Acids to 3g



entry[a]	R	prod, yield (%)[b]	ee (%)[c]
1	Me	**17**, 91	43 (*S*)
2	Ph	**18**, 94	45 (*S*)
3	CH_2Ph	**19**, 93	92 (*S*)

[a] Reaction conditions: $RCH{=}CHB(OH)_2$ (500 mol %), [Rh] (3 mol %), (*S*,*S*)-Chiraphos (3 mol %), dioxane/H_2O (10:1), 100 °C, 24 h. [b] In pure isolated product. [c] Determined by chiral HPLC (Chiralpak AD).

Binap were significantly lower than those obtained with Chiraphos (entries 11 and 15 vs 12 and 16). (c) As expected for a process involving the participation of Rh−N chelated species in the addition step, the reaction of the (*E*/*Z*) diastereomeric olefins **3g** (entries 2, 4, and 6, Table 4) and **3l** (Table 5) employing (*S*,*S*)-Chiraphos as chiral ligand led to opposite enantiomers (*β-re* face addition in the case of **3g** and *β-si* face addition for **3l**), albeit the enantioselectivity provided by the (*Z*) isomer **3l** was somewhat lower than that of the (*E*) isomer **3g** (69−74% ee vs 77−84% ee).

We also explored the behavior of an *ortho*-substituted arylboronic acid, a substitution pattern that has scarcely been studied in Rh-catalyzed conjugate additions (Scheme 7). Thus, under the standard conditions, the reaction of 2-fluorophenyl boronic acid with sulfone **3g** provided the addition product **16** in 93% yield and 76% ee.

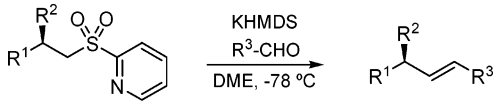
(c) Addition of Alkenyl Boronic Acids. As a complementary study devoted to broadening the scope of the reaction, we also explored the behavior of some commercially available alkenyl boronic acids as nucleophilic partners in the reaction with the model substrate **3g** (Table 6).

Again, excellent yields were obtained in the three cases (91−94%). However, regarding the enantioselectivity of the process, the results were not as consistent. Thus, whereas *trans*-propenyl or *trans*-styryl boronic acids afforded modest enantioselectivities (43% and 45% ee, entries 1 and 2), the reaction of 3-phenyl-1-propenyl boronic acid was much more enantioselective, affording **19** in 92% ee (entry 3).

Finally, the reactivity of 1-cyclohexenyl 2-pyridyl sulfone (**3m**) was studied. Unfortunately, no reaction was observed after treatment with phenyl and *trans*-styryl boronic acids, using either Binap or Chiraphos (3−10 mol %), for 24 h at 100 °C, showing that the substitution at α-position has a deep detrimental effect in the reactivity of the vinyl 2-pyridyl sulfone.

5. Synthetic Applications: Removal of the 2-Pyridyl Sulfonyl Group by Julia−Kocienski Olefination and Reductive Elimination. Because of the versatility of the sulfonyl group in organic synthesis, the enantioenriched sulfones obtained in the addition of boronic acids to vinyl sulfones are very appealing intermediates in the formation of C−C and C═C bonds. In this context the 2-pyridylsulfonyl group plays a dual role: not only is it essential for achieving the Rh-catalyzed addition, but its elimination by direct Julia−Kocienski reaction[21] provides a practical alternative for the introduction of a C═C bond.

TABLE 7. Julia−Kocienski Olefination of Chiral 2-Pyridyl Sulfones Having a *β*-Tertiary Stereocenter



entry[a]	R^1	R^2	R^3	*E*/*Z* ratio[b]	prod, yield[c] (%)
1	Me	Ph	Ph	>99/<1	**20**, 93
2	Me	Ph	*p*-FC_6H_4	90/10	**21**, 81
3	Me	Ph	PhC_2H_2	87/13	**22**, 89[d]
4	Me	Ph	*i*-Pr	65/35	**23**, 48
5	Me	*p*-FC_6H_4	Ph	>99/<1	**24**, 92
6	*n*-pent	Ph	Ph	>99/<1	**25**, 91

[a] Reaction conditions: KHMDS (1.5 equiv), DME, −78 °C, 2 h. [b] Estimated by ^1H NMR analysis of the crude reaction mixtures. [c] In pure (*E*) olefin after flash chromatography. [d] As a mixture of (*E*/*Z*) isomers (87:13).

As shown in Table 7, the treatment of the 2-pyridyl sulfones having a tertiary stereocenter at *β*-position with KHMDS (DME at −78 °C), followed by the addition of the aldehyde, either aromatic (entries 1, 2, 5, and 6), α,*β*-unsaturated (entry 3), or aliphatic (entry 4), afforded the corresponding alkene in excellent yields (81−93%), usually with very high or complete (*E*) stereoselectivity (except entry 4). In addition, we confirmed that, as expected, this olefination reaction takes place without erosion of the optical purity of the product. For instance, starting from an enantioenriched sample of substrate **4g** (81% ee), the known alkene (*R*)-**20**[22] was obtained with the same enantiomeric excess (HPLC, Chiralcel OD), allowing also for the unequivocal assignment of the absolute configuration of the stereogenic center created in the Rh-catalyzed conjugate addition step.

From a synthetic point of view, this reaction sequence (conjugate addition to an α,*β*-unsaturated 2-pyridyl sulfone and Julia−Kocienski olefination) constitutes a complementary alternative to the enantioselective metal-catalyzed allylic substitution of allylic acetates and related compounds.[23] Interestingly, unlike processes involving *π*-allyl intermediates, this two-step procedure avoids any regiochemical uncertainty in the formation of the C═C bond, allowing the unequivocal substitution at positions 1 and 3 at the alkene. This point is clearly illustrated in Table 7 by the synthesis of both 1,3-diaryl regioisomers **21** and **24** (entries 2 and 5, respectively).

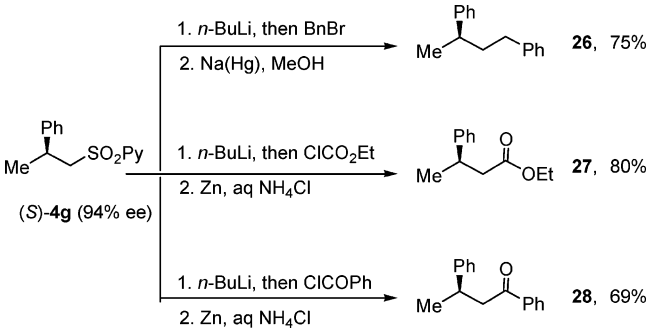
Finally, to further highlight the chemical versatility of these *β*-substituted enantioenriched sulfones in the preparation of differently functionalized chiral compounds,[13] the conversion of (*S*)-**4g** (of 94% ee) into the benzylated compound (*R*)-**26**, the known *β*-substituted ester (*R*)-**27**,[24] and the known *β*-substituted ketone (*R*)-**28**,[25] is shown in Scheme 8. All these straightforward transformations are based on the generation of the highly nucleophilic α-sulfonyl carbanion, formation of the

(21) For a review on the Julia−Kocienski olefination, see: (a) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563. For some recent references, see: (b) Charette, A. B.; Berthelette, C.; St-Martin, D. *Tetrahedron Lett.* **2001**, *42*, 5149. Corrigendum: Charette, A. B.; Berthelette, C.; St-Martin, D. *Tetrahedron Lett.* **2001**, *42*, 6619. (c) Alonso, D. A.; Nájera, C.; Varea, M. *Tetrahedron Lett.* **2004**, *45*, 573.

(22) Knochel, P.; Schwink, L. *Chem.−Eur. J.* **1998**, *4*, 950.

(23) Recent reviews: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M.; Carawheg, M. L. *Chem. Rev.* **2003**, *103*, 2921. (c) Graening, T.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2580.

SCHEME 8. Further Functional Group Transformations



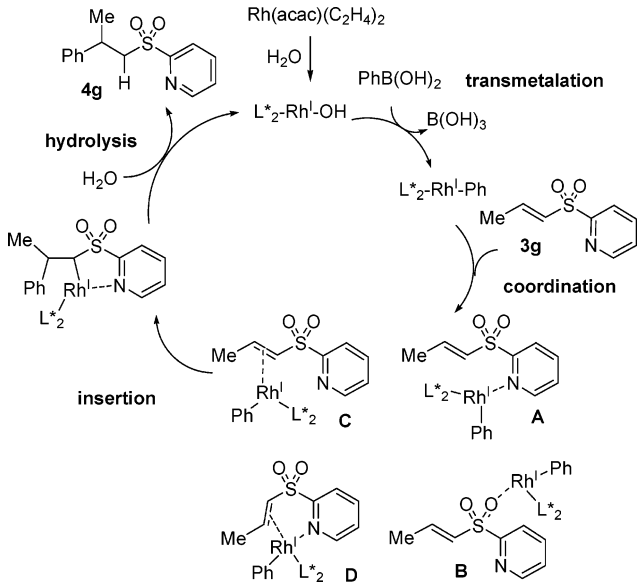
C−C bond by reaction with an appropriate carbon electrophile and final desulfonylation.[26] Thus, α-deprotonation of (*S*)-**4g** with *n*-BuLi and reaction with benzyl bromide, ethyl chloroformate, or benzoyl chloride afforded the corresponding functionalized α-substituted sulfones as mixtures of epimers at the α-position. Subsequent desulfonylation with Na(Hg) or Zn led to the final chiral compounds (*R*) **26**−**28** in good overall yields (69−80%).

6. Mechanistic Hypothesis and DFT Theoretical Studies. The mechanism of the rhodium-catalyzed conjugate addition of aryl boronic acids to enones has been deeply studied by Hayashi.[27] It has been proposed that the catalytic cycle involves the following steps: (a) initial transmetallation of an aryl group from boron to rhodium, (b) coordination with the C═C bond, (c) insertion of the alkene into the aryl−rhodium bond to generate an oxa-π-allyl rhodium intermediate, and (d) hydrolysis of this rhodium enolate to give the β-aryl addition product and regeneration of the hydroxorhodium catalyst. According to this well accepted catalytic cycle, we postulate a similar transmetalation/coordination/insertion/hydrolysis sequence for the conjugate addition to vinyl pyridyl sulfones, which would presumably involve the formation of a five-membered pyridyl−rhodium chelate in the insertion step (Scheme 9).

To shed some light on the origin of the enantioselectivity in the addition to vinyl pyridyl sulfones and the role of the nitrogen atom at the pyridine ring, the stereochemically key coordination and insertion steps were theoretically studied at DFT (B3LYP)[28] level by using the Gaussian03 program.[29] The standard 6-31G(d)[30] basis set was used for all of the atoms except Rh, for which LANL2DZ[31] was employed. Harmonic frequencies were calculated at the same level of theory to characterize the stationary points and to determine the zero-point energies (ZPE). Sulfone **3g** was used as model substrate, whereas ligand (*S*,*S*)-Chiraphos was simplified, changing phenyl by methyl groups (modL*).

The molecular structures and relative energies of the possible phenyl−rhodium complexes formed by coordination of **3g** through pyridyl nitrogen (**A**), sulfonyl oxygen (**B**), or olefin (**C**) are shown in Figure 2.[32] The rhodium complexes coordinated to nitrogen and especially to oxygen were much less stable than those coordinated with the olefin (**C1**). This result could be ascribed to the fact that in these complexes the rhodium atom

SCHEME 9. Mechanistic Proposal (L_2*= (*S*,*S*)-Chiraphos)



does not show any electrophilic character; indeed it is negatively charged (−0.11 to −0.12 au). Probably because of this reason the pentacoordinated electron-rich rhodium complex **D** could not be found. Regarding the alkene coordinated complexes, the most stable, **C1*re*** and **C1*si***, showed the C═C bond in a perpendicular arrangement with regard to the coordination plane of the metal [Ph−Rh−(C═C) dihedral angle being 112.2° and −110.5°, respectively]. However, in the conformers **C2*re*** and **C2*si*** the alkene moiety is in a quasi coplanar arrangement [Ph−Rh−(C═C) dihedral angle being −26.3° and 28.6°, respectively], and so these complexes were considered as starting points of the insertion step. The stability of these coordinated complexes, especially the π-complexes **C**, seems to be directly related to an important stabilizing electrostatic interaction between the closest sulfonyl oxygen and phosphorus atom (located at an interatomic distances of 3.33−3.74 Å), the corresponding natural charges being −0.98 to −0.99 and 1.07 to 1.08 au, respectively.[33]

The insertion steps through the β-*re* face, to afford the major enantiomer (*S*)-**4g,** and through the β-*si* face, to afford the minor

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(29) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision B.05; Gaussian, Inc.: Pittsburgh PA, 2003.

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(32) Slight differences in energy were observed depending upon the conformation of the pyridyl ring that always locates the nitrogen atom in *anti* arrangement with respect to one of the sulfonyl oxygens, probably in order to minimize dipole interactions.

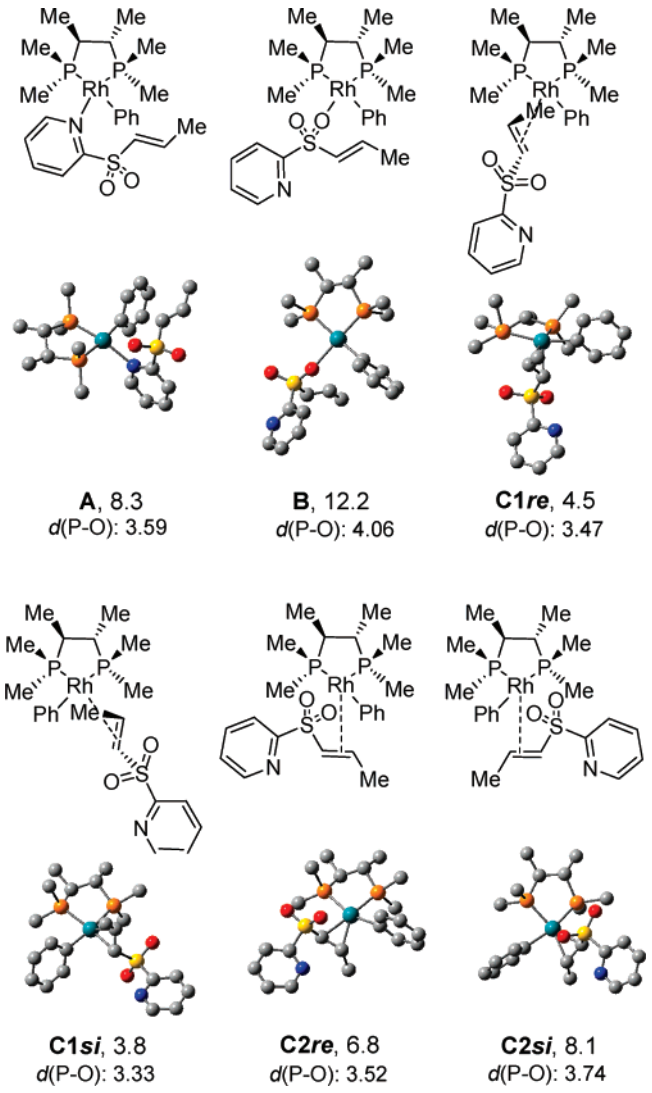

FIGURE 2. Relative energies (kcal mol^{-1}) evaluated with respect to RhPh(H_2O)(modL*)+**3g**-H_2O. ZPE correction included. The closest P−O distances (Å) are also indicated. Hydrogen atoms have been omitted for clarity.

enantiomer (*R*)-**4g,** were studied from **C2*re*** and **C2*si*** respectively. The corresponding energy profiles are shown in Figures 3 and 4. In the formation of the new C−C bond through **TS*re*** and **TS*si*** the initial C═C/Ph distance in **C2*re*** and **C2*si*** is strongly shortened [*d*(C═C)/Ph from 2.65 Å in **C2*re*** to 2.07 Å in **TS*re*** and from 2.78 Å in **C2*si*** to 2.07 Å in **TS*si***]. However the distance variation of the C−Rh bond being broken is quite small [*d*(Rh−Ph) is only lengthened from 2.11 Å in **C2*re*** to 2.20 Å in **TS*re*** and from 2.12 Å in **C2*si*** to 2.19 Å in **TS*si***]. This is in agreement with the fact that the first intermediate found after the formation of the new C−C bond was **E1** in which the free coordination site of the Rh atom was occupied by a C−C bond of the aromatic ring. This moiety is displaced by the nitrogen atom of the pyridyl unit to give the much more stable N-complexes **F1** and **F2**, the later having an additional stabilizing interaction by π-stacking between phenyl and pyridyl groups (distance between centroids 3.97 and 4.04 Å for **F2*re*** and **F2*si***, respectively).

(33) Natural bond orbital method of Weinhold: Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

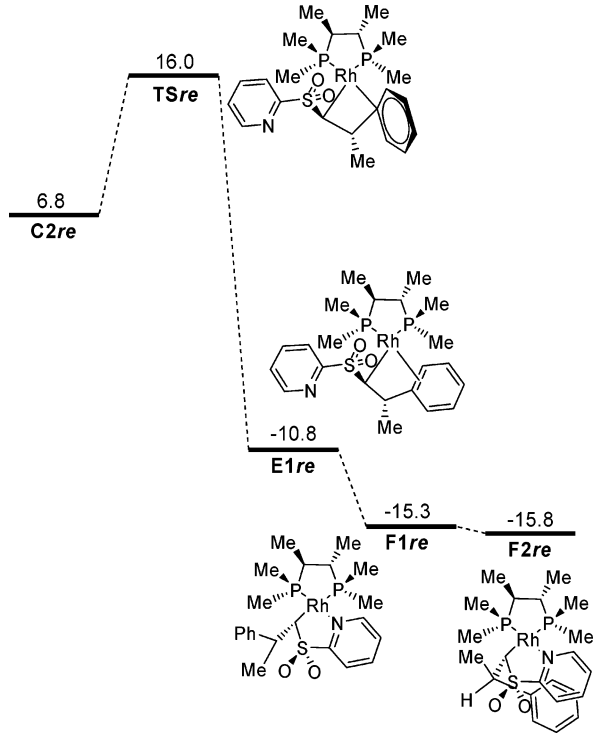

FIGURE 3. Energy profile for the insertion step through the β-*re* face to give the major enantiomer (*S*)-**4g**. Relative energies (kcal mol^{-1}) evaluated with respect to RhPh(H_2O)(modL*)+**3g**-H_2O. ZPE correction included.

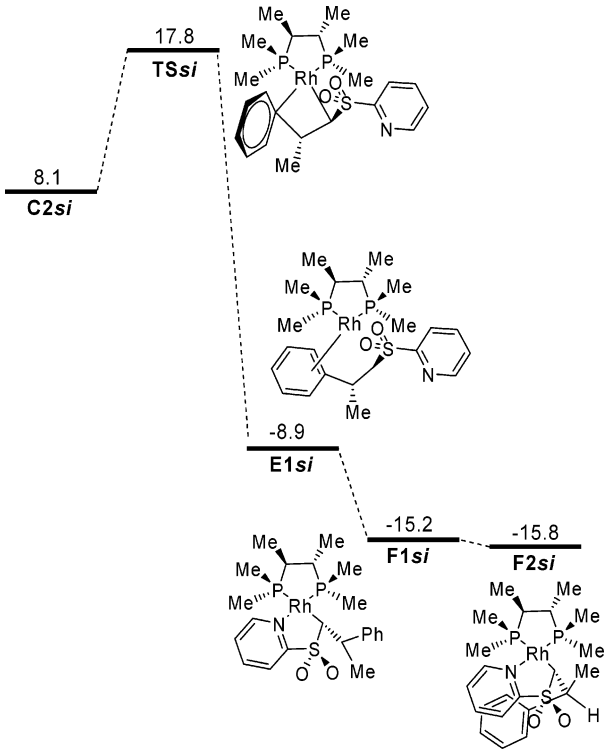

FIGURE 4. Energy profile for the insertion step through the β-*si* face to give the minor enantiomer (*R*)-**4g**. Relative energies (kcal mol^{-1}) evaluated with respect to RhPh(H_2O)(modL*)+**3g**-H_2O. ZPE correction included.

The activation energy is similar for *re*-face and *si*-face approximations (9.2 and 9.7 kcal mol^{-1}, respectively), and the

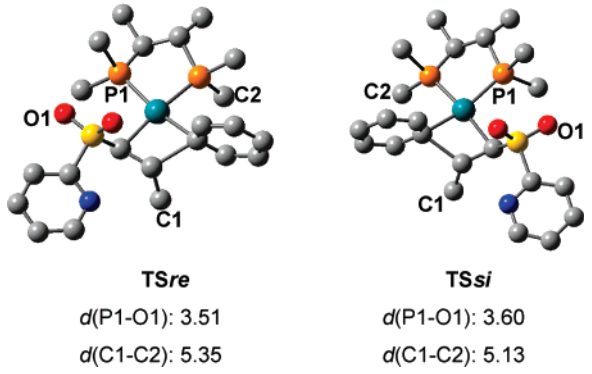

FIGURE 5. Molecular structures of transition states **TS*re*** and **TS*si***. Distances (Å) between selected atoms are also indicated. Hydrogen atoms have been omitted for clarity.

difference in energy content between **TS*re*** and **TS*si*** is 1.8 kcal mol^{-1}. This value predicts that products of this model reaction, at 100 °C, will be formed in about 84% ee, indeed close to the experimental value obtained (81% ee) employing Chiraphos as chiral ligand. The difference in energy between both **TSs** may be due to the attractive electrostatic interaction between P and O atoms indicated before (shorter for **TS*re*** than **TS*si***; see P1−O1 distance in Figure 5), as well as a somewhat greater steric interaction between the Me group present in **3g** and the Me group bonded to the anti P atom in **TS*si*** than in **TS*re*** (shorter C1−C2 distance for **TS*si*** than **TS*re***). This steric interaction would become more important as a function of the size of the group bonded to the vinyl sulfone, which might explain the slight enhancement of the enantioselectivity observed with the increasing steric bulk of the β-substituent.

Conclusions

In summary, we have developed a general procedure for the Rh-catalyzed asymmetric conjugate addition of boronic acids to vinyl sulfones. The success of this strategy heavily relies on two factors: (a) the use of vinyl 2-pyridyl sulfones as key Michael acceptors and (b) the use of Chiraphos as chiral ligand. Under these conditions the addition of aryl and alkenyl boronic acids to β-substituted vinyl sulfones shows a broad scope, providing the sulfonylated conjugate addition products with a chiral tertiary stereocenter in very good yields and moderate to high enantioselectivities (up to 92% ee). The sense and magnitude of this high enantioselectivity has been explained by DFT theoretical calculations. The difference in energy for the key transition states of the Rh−Ph insertion step, through both *re* and *si* olefin faces of the vinyl sulfone, seems to be determined by a combination of steric interactions and a strong electrostatic interaction between the closest sulfonyl oxygen in the substrate and one of the phosphorus atoms in the ligand. A five-membered pyridyl−rhodium chelated species is formed as the most stable complex after insertion into the C=C bond.

Taking advantage of the versatile reactivity inherent to the 2-pyridyl sulfonyl group, the enantioenriched addition products are very interesting building blocks in the straightforward enantioselective synthesis of other chiral functionalized compounds, such as allylic derivatives (by Julia−Kocienski olefination) or β-substituted esters and ketones (by an acylation/desulfonylation sequence).

Experimental Section

Typical Procedure for the Rh-Catalyzed Enantioselective Addition of Boronic Acids to α,β-Unsaturated Pyridyl Sulfones: Synthesis of (*S*)-2-Phenyl-1-((2-pyridyl)sulfonyl)propane (4g). A 1 mL portion of anhydrous 1,4-dioxane and 0.1 mL of water were sequentially added to a mixture of [Rh(acac)(C_2H_4)$_2$ (3.9 mg, 0.015 mmol), (*S*,*S*)-chiraphos (6.4 mg, 0.015 mmol), $PhB(OH)_2$ (303 mg, 2.5 mmol), and the α,β-unsaturated sulfone **3g** (91.5 mg, 0.500 mmol), previously placed under argon or nitrogen in a Schlenk tube. The pale yellow solution was stirred at 100 °C for 12 h, after which time the resulting orange mixture was cooled to room temperature, diluted with CH_2Cl_2 (ca. 3 mL) and filtered through a short pad of silica gel (eluent CH_2Cl_2). After concentration of the filtrate, the residue was purified by flash chromatography (AcOEt/hexanes, 2:3) to give **4g** as a white solid (128 mg, 0.49 mmol, 98% yield). Mp: 90−92 °C. ^{1}H NMR (300 MHz): 8.73−8.69 (m, 1H), 7.84−7.74 (m, 2H), 7.41 (ddd, J = 1.2, 4.2 and 7.5 Hz, 1H), 7.18−7.03 (m, 5H), 3.89 (dd, J = 6.5 and 14.2 Hz, 1H), 3.58−3.42 (m, 2H), 1.41 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz): 157.5, 150.0, 143.3, 137.8, 128.5, 127.0, 126.7, 122.0, 58.7, 35.0, 22.1. HRMS (FAB+, *m/z*): calcd for $C_{14}H_{16}NO_2S$ [M+H]$^+$, 262.0901; found, 262.0903. $[\alpha]_D$ = +9.6 (*c* 0.5, $CHCl_3$). HPLC: 81% ee [Daicel Chiralpak AD column, hexane/isopropanol 90:10, 0.6 mL min^{-1}, λ = 254 nm; t_R/min = 25.7 (*R*) and 29.1 (*S*)].

(*S*)-2-(4-Fluorophenyl)-1-((2-pyridyl)sulfonyl)propane (5). White solid. Mp: 96−98 °C. ^{1}H NMR (300 MHz): 8.62 (dt, J = 1.2 and 4.7 Hz, 1H), 7.83−7.76 (m, 2H), 7.46−7.42 (m, 1H), 7.07−7.00 (m, 2H), 6.85−6.77 (m, 2H), 3.98 (dd, J = 6.9 and 13.7 Hz, 1H), 3.56−3.41 (m, 2H), 1.39 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, full list of peaks including C−F coupling): 163.1, 157.6, 150.0, 138.9, 137.9, 128.6, 128.5, 127.0, 122.0, 115.4, 115.1, 58.7, 34.4, 22.3. HRMS (FAB+, *m/z*): calcd for $C_{14}H_{15}NO_2SF$ [M + H]$^+$, 280.0807; found, 280.0808. $[\alpha]_D$ = +10.4 (*c* 0.51, $CHCl_3$). HPLC: 84% ee [Daicel Chiralpak AD column, hexane/isopropanol 90:10, 0.6 mL min^{-1}, λ = 254 nm; t_R/min = 35.5 (*R*) and 40.1 (*S*)].

(*S*)-2-(4-Methoxyphenyl)-1-((2-pyridyl)sulfonyl)propane (6). ^{1}H NMR (300 MHz): 8.63 (dt, J = 1.2 and 4.4 Hz, 1H), 7.83−7.74 (m, 2H), 7.44 (ddd, J = 2.0, 4.4 and 6.4 Hz, 1H), 7.00−6.95 (m, 2H), 6.63−6.68 (m, 2H), 3.85 (dd, J = 6.9 and 14.1 Hz, 1H), 3.72 (s, 3H), 3.55−3.35 (m, 2H), 1.38 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz): 158.2, 157.6, 149.9, 137.8, 135.4, 128.0, 126.8, 122.0, 113.8, 59.0, 55.2, 34.2, 22.2. HRMS (FAB+, *m/z*): calcd for $C_{15}H_{18}NO_3S$ [M + H]$^+$, 292.1007; found, 292.1010. $[\alpha]_D$ = −29.2 (*c* 0.59, $CHCl_3$). HPLC: 77% ee [Daicel Chiralpak AD column, hexane/isopropanol 90:10, 0.6 mL min^{-1}, λ = 254 nm; t_R/min = 43.4 (*R*) and 51.2 (*S*)].

(*S*)-2-Phenyl-1-((2-pyridyl)sulfonyl)heptane (7). White solid. Mp: 85−87 °C. ^{1}H NMR (300 MHz): 8.56 (dt, J = 1.2 and 4.4 Hz, 1H), 7.71−7.64 (m, 2H), 7.34 (q, J = 4.4 Hz, 1H), 7.09−6.94 (m, 5H), 3.94 (dd, J = 6.9 and 15.0 Hz, 1H), 3.55 (dd, J = 5.3 and 15.0 Hz, 1H), 3.26−3.20 (m, 1H), 1.85−1.71 (m, 1H), 1.68−1.52 (m, 1H), 1.27−0.96 (m, 6H), 0.84−0.73 (m, 3H). ^{13}C NMR (75 MHz): 157.4, 149.8, 141.3, 137.6, 128.2, 127.7, 126.7, 126.6, 122.0, 57.7, 40.6, 36.3, 31.3, 26.5, 22.3, 13.9. HRMS (FAB+, *m/z*): calcd for $C_{18}H_{24}NO_2S$ [M + H]$^+$, 318.1527; found, 318.1520. $[\alpha]_D$ = −29.4 (*c* 0.51, $CHCl_3$). HPLC: 84% ee [Daicel Chiralcel OD column, hexane/isopropanol 90:10, 0.6 mL min^{-1}, λ = 254 nm; t_R/min = 26.7 (*R*) and 36.3 (*S*)].

(*S*)-2-(4-Fluorophenyl)-1-((2-pyridyl)sulfonyl)heptane (8). White solid. Mp: 65−67 °C. ^{1}H NMR (300 MHz): 8.56 (dt, J = 1.2 and 4.9 Hz, 1H), 7.75−7.63 (m, 2H), 7.40−7.35 (m, 1H), 6.96−6.89 (m, 2H), 6.77−6.69 (m, 2H), 3.92 (dd, J = 9.3 and 15.0 Hz, 1H), 3.52 (dd, J = 4.9 and 15.0 Hz, 1H), 3.26−3.20 (m, 1H), 1.82−1.67 (m, 1H), 1.64−1.48 (m, 1H), 1.25−0.96 (m, 6H), 0.84−0.72 (m, 3H). ^{13}C NMR (75 MHz, full list of peaks including C−F coupling): 163.0, 159.7, 157.4, 149.8, 137.6, 137.0, 136.9, 129.3, 129.2, 126.7, 121.9, 115.1, 114.8, 57.7, 40.0, 36.4, 31.3, 26.4, 22.3, 13.8. HRMS (FAB+, *m/z*): calcd for $C_{18}H_{23}NO_2SF$ [M + H]$^+$, 336.1433; found, 336.1434. $[\alpha]_D$ = −30.5 (*c* 1, $CHCl_3$). HPLC: 87% ee [Daicel Chiralcel OD column, hexane/isopropanol 90:10, 0.6 mL min^{-1}, λ = 254 nm; t_R/min = 18.1 (*R*) and 28.1 (*S*)].

(*S*)-2-(4-Methoxyphenyl)-1-((2-pyridyl)sulfonyl)heptane (9). ^{1}H NMR (300 MHz): 8.58 (dt, J = 1.2 and 4.9 Hz, 1H), 7.73−7.65 (m, 2H), 7.39−7.33 (m, 1H), 6.91−6.86 (m, 2H), 6.61−6.56 (m, 2H), 3.92 (dd, J = 8.9 and 14.6 Hz, 1H), 3.72 (s, 3H), 3.53 (dd, J = 5.3 and 14.6 Hz, 1H), 3.24−3.18 (m, 1H), 1.82−1.67 (m, 1H), 1.64−1.48 (m, 1H), 1.25−0.96 (m, 6H), 0.84−0.72 (m, 3H). ^{13}C NMR (75 MHz): 158.1, 157.6, 149.8, 137.5, 133.3, 128.7, 126.6, 122.1, 113.6, 58.1, 55.1, 39.9, 36.4, 31.4, 26.5, 22.3, 13.9. HRMS (FAB+, *m/z*): calcd for $C_{19}H_{26}NO_3S$ [M + H]$^+$, 348.1633; found, 348.1643. $[\alpha]_D$ = +30.5 (*c* 0.38, $CHCl_3$). HPLC: 81% ee [Daicel Chiralcel OD column, hexane/isopropanol 90:10, 0.5 mL min^{-1}, λ = 254 nm; t_R/min = 32.1 (*R*) and 42.3 (*S*)].

(*S*)-3-Methyl-2-phenyl-1-((2-pyridyl)sulfonyl)butane (10). White solid. Mp: 87−89 °C. ^{1}H NMR (300 MHz): 8.53 (dt, J = 1.2 and 4.4 Hz, 1H), 7.62−7.50 (m, 2H), 7.32−7.27 (m, 1H), 7.00−6.85 (m, 5H), 4.08 (dd, J = 10.9 and 15.0 Hz, 1H), 3.65 (dd, J = 3.6 and 15.0 Hz, 1H), 3.05−2.98 (m, 1H), 1.92−1.87 (m, 1H), 0.96 (d, J = 6.9 Hz, 3H), 0.71 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz): 157.2, 149.7, 139.5, 137.4, 128.6, 127.8, 126.5, 126.4, 122.1, 55.5, 47.4, 33.4, 20.5, 19.7. HRMS (FAB+, *m/z*): calcd for $C_{16}H_{20}NO_2S$ [M + H]$^+$, 290.1214; found, 290.1213. $[\alpha]_D$ = +22.2 (*c* 0.51, $CHCl_3$). HPLC: 78% ee [Daicel Chiralpak AD column, hexane/isopropanol 90:10, 0.6 mL min^{-1}, λ = 254 nm; t_R/min = 33.6 (*R*) and 46.5 (*S*)].

(*S*)-2-(4-Fluorophenyl)-3-methyl-1-((2-pyridyl)sulfonyl)butane (11). ^{1}H NMR (300 MHz): 8.55 (ddd, J = 0.8, 1.6 and 4.9 Hz, 1H), 7.65 (dt, J = 1.6 and 7.7 Hz, 1H), 7.53 (dt, J = 1.2 and 8.1 Hz, 1H), 7.35 (ddd, J = 1.2, 4.9 and 7.7 Hz, 1H), 6.89−6.80 (m, 2H), 6.71−6.61 (m, 2H), 4.05 (dd, J = 11.3 and 15.0 Hz, 1H), 3.69 (dd, J = 3.6 and 15.0 Hz, 1H), 3.05−2.98 (m, 1H), 1.90−1.82 (m, 1H), 0.95 (d, J = 6.9 Hz, 3H), 0.69 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, full list of peaks including C−F coupling): 163.0, 159.7, 157.3, 149.8, 137.5, 135.3, 130.2, 130.1, 126.6, 122.1, 114.7, 114.5, 55.6, 46.7, 33.4, 20.6, 19.7. HRMS (FAB+, *m/z*): calcd for $C_{16}H_{19}NO_2SF$ [M + H]$^+$, 308.1120; found, 308.1111. $[\alpha]_D$ = +29.3 (*c* 0.67, $CHCl_3$). HPLC: 85% ee [Daicel Chiralcel OD column, hexane/isopropanol 90:10, 0.5 mL min^{-1}, λ = 254 nm; t_R/min = 23.8 (*R*) and 41.3 (*S*)].

(*S*)-2-(4-Methoxyphenyl)-3-methyl-1-((2-pyridyl)sulfonyl)butane (12). ^{1}H NMR (300 MHz): 8.56 (ddd, J = 0.8, 1.6 and 4.9 Hz, 1H), 7.61 (dt, J = 1.6 and 7.7 Hz, 1H), 7.51 (d, J = 7.7 Hz, 1H), 7.31 (ddd, J = 1.2, 4.9 and 7.7 Hz, 1H), 6.81−6.76 (m, 2H), 6.53−6.48 (m, 2H), 4.06 (dd, J = 10.9 and 15.0 Hz, 1H), 3.70 (s, 3H), 3.63 (dd, J = 3.6 and 15.0 Hz, 1H), 3.00−2.94 (m, 1H), 1.90−1.82 (m, 1H), 0.95 (d, J = 6.9 Hz, 3H), 0.71 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz): 158.0, 157.4, 149.7, 137.4, 131.4, 129.7, 126.4, 122.2, 113.2, 55.9, 55.1, 46.6, 33.4, 20.6, 19.7. HRMS (FAB+, *m/z*): calcd for $C_{17}H_{22}NO_3S$ [M + H]$^+$, 320.1320; found, 320.1306. $[\alpha]_D$ = +31.6 (*c* 0.49, $CHCl_3$). HPLC: 76% ee [Daicel Chiralcel OD column, hexane/isopropanol 90:10, 0.6 mL min^{-1}, λ = 254 nm; t_R/min = 33.4 (*R*) and 46.4 (*S*)].

(*R*)-2-(2-Naphthyl)-2-phenyl-1-((2-pyridyl)sulfonyl)ethane (13). White solid. Mp: 127−129 °C. ^{1}H NMR (300 MHz): 8.47 (ddd, J = 0.8, 1.6 and 5.0 Hz, 1H), 7.71−7.65 (m, 2H), 7.59−7.53 (m, 2H), 7.49 (dt, J = 1.2 and 8.1 Hz, 1H), 7.46−7.37 (m, 2H), 7.33 (dt, J = 1.6 and 8.1 Hz, 1H), 7.24−7.05 (m, 7H), 4.83 (t, J = 7.3 Hz, 1H), 4.45 (dd, J = 8.1 and 15.0 Hz, 1H), 4.26 (dd, J = 6.9 and 15.0 Hz, 1H). ^{13}C NMR (75 MHz): 156.9, 149.7, 140.9, 138.1, 137.1, 133.0, 132.1, 128.6, 128.3, 127.7, 127.6, 127.3, 126.9, 126.5, 126.4, 126.1, 126.0, 125.9, 122.1, 56.7, 46.2. HRMS (FAB+, *m/z*): calcd for $C_{23}H_{20}NO_2S$ [M + H]$^+$, 374.1214; found, 374.1201. $[\alpha]_D$ = −23.6 (*c* 0.5, $CHCl_3$). HPLC: 87% ee [Daicel Chiralpak AD column, hexane/isopropanol 90:10, 0.6 mL min^{-1}, λ = 254 nm; t_R/min = 63.3 (*R*) and 70.4 (*S*)].

(*R*)-2-(4-Fluorophenyl)-2-(2-naphthyl)-1-((2-pyridyl)sulfonyl)-ethane (14). White solid. Mp: 123−125 °C. ^{1}H NMR (300 MHz): 8.49 (ddd, J = 0.8, 1.6 and 4.5 Hz, 1H), 7.74−7.65 (m, 2H), 7.63−7.50 (m, 3H), 7.48−7.37 (m, 3H), 7.22−7.11 (m, 4H), 6.89−6.79 (m, 2H), 4.83 (t, J = 7.3 Hz, 1H), 4.38 (dd, J = 7.7 and 15.0 Hz, 1H), 4.28 (dd, J = 7.3 and 15.0 Hz, 1H). ^{13}C NMR (75 MHz, full list of peaks including C−F coupling): 163.2, 159.9, 157.0, 149.7, 138.1, 137.2, 136.7, 133.0, 132.2, 129.5, 129.4, 128.5, 127.7, 127.4, 126.5, 126.3, 126.2, 126.0, 125.8, 122.1, 115.5, 115.2, 56.7, 45.4. HRMS (FAB+, *m/z*): calcd for $C_{23}H_{19}NO_2SF$ [M + H]$^+$, 392.1120; found, 392.1113. $[\alpha]_D$ = −35.9 (*c* 0.51, $CHCl_3$). HPLC: 92% ee [Daicel Chiralpak AD column, hexane/isopropanol 90:10, 0.6 mL min^{-1}, λ = 254 nm; t_R/min = 63.7 (*R*) and 81.8 (*S*)].

(*R*)-2-(4-Methoxyphenyl)-2-(2-naphtyl)-1-((2-pyridyl)sulfonyl)-ethane (15). ^{1}H NMR (300 MHz): 8.43 (ddd, J = 0.8, 1.6 and 5.0 Hz, 1H), 7.71−7.64 (m, 2H), 7.59−7.53 (m, 2H), 7.54−7.45 (m, 1H), 7.46−7.32 (m, 3H), 7.21−7.08 (m, 4H), 6.71−6.66 (m, 2H), 4.78 (t, J = 7.3 Hz, 1H), 4.39 (dd, J = 7.7 and 14.5 Hz, 1H), 4.24 (dd, J = 6.9 and 14.5 Hz, 1H), 3.71 (s, 3H). ^{13}C NMR (75 MHz): 158.4, 157.1, 149.7, 138.5, 137.1, 133.1, 132.2, 128.8, 128.3, 127.7, 127.4, 126.3, 126.2, 126.1, 126.0, 125.9, 122.2, 114.0, 56.9, 55.2, 45.4. HRMS (FAB+, *m/z*): calcd for $C_{24}H_{22}NO_3S$ [M + H]$^+$, 404.1320; found, 404.1312. $[\alpha]_D$ = −21.1 (*c* 0.75, $CHCl_3$). HPLC: 85% ee [Daicel Chiralpak AD column, hexane/isopropanol 90:10, 0.7 mL min^{-1}, λ = 254 nm; t_R/min = 86.6 (*R*) and 110.2 (*S*)].

(*S*)-2-(2-Fluorophenyl)-1-((2-pyridyl)sulfonyl)propane (16). ^{1}H NMR (300 MHz): 8.62 (dt, J = 1.2 and 4.7 Hz, 1H), 7.88−7.75 (m, 2H), 7.46−7.40 (m, 1H), 7.13−7.00 (m, 2H), 6.99−6.88 (m, 1H), 6.85−6.76 (m, 1H), 4.04−3.89 (m, 1H), 3.70−3.53 (m, 2H), 1.42 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, full list of peaks including C−F coupling): 162.0, 158.7, 157.2, 150.0, 137.8, 129.9, 129.8, 129.0, 128.9, 128.5, 128.4, 124.1, 124.0, 122.0, 115.7, 115.4, 57.1, 30.0, 20.7. HRMS (FAB+, *m/z*): calcd for $C_{14}H_{15}NO_2SF$ [M + H]$^+$, 280.0807; found, 280.0794. $[\alpha]_D$ = −1.6 (*c* 0.61, $CHCl_3$). HPLC: 76% ee [Daicel Chiralpak AD column, hexane/isopropanol 90:10, 0.6 mL min^{-1}, λ = 254 nm; t_R/min = 25.5 (*R*) and 27.7 (*S*)].

(2*E*,4*S*)-3-Methyl-5-[(2-pyridyl)sulfonyl]-2-pentene (17). Colorless oil. ^{1}H NMR (300 MHz): 8.74 (d, J = 5.2 Hz, 1H), 8.05 (dt, J = 1.3 and 7.9 Hz, 1H), 7.79 (dt, J = 1.8 and 7.7 Hz, 1H), 7.52 (ddd, J = 1.2, 4.4 and 7.4 Hz, 1H), 5.38 (m, 1H), 5.11 (m, 1H), 3.55 (dd, J = 7.2 and 14.2 Hz, 1H), 3.24 (dd, J = 6.4 and 14.4 Hz, 1H), 2.81 (m, 1H), 1.46 (d, J = 6.9 Hz, 3H), 1.12 (d, J = 6.7 Hz, 3H). HRMS (FAB+, *m/z*): calcd for $C_{11}H_{16}NO_2S$ [M + H]$^+$, 226.0901; found, 226.0905. $[\alpha]_D$ = −30.1 (*c* 0.84, $CHCl_3$). HPLC: 45% ee [Daicel Chiralpak AD Column, hexane/isopropanol 80:20, 0.5 mL min^{-1}, λ = 254 nm; t_R/min = 17.4 (*R*) and 18.9 (*S*)].

(1*E*,3*S*)-3-Methyl-1-phenyl-4-((2-pyridyl)sulfonyl)-1-butene (18). ^{1}H NMR (300 MHz): 8.77−8.70 (m, 1H), 8.09−8.00 (m, 1H), 7.79 (dt, J = 1.6 and 7.7 Hz, 1H), 7.42 (ddd, J = 1.2, 4.9 and 6.7 Hz, 1H), 7.36−7.06 (m, 5H), 6.33 (d, J = 15.8 Hz, 1H), 5.82 (dd, J = 8.1 and 15.8 Hz, 1H), 3.77 (dd, J = 7.7 and 14.6 Hz, 1H), 3.41 (dd, J = 6.1 and 14.6 Hz, 1H), 3.14−3.06 (m, 1H), 1.29 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz): 157.9, 150.0, 138.0, 136.6, 131.7, 130.2, 128.3, 127.4, 127.0, 126.1, 122.1, 57.4, 32.7, 20.6. HRMS (FAB+, *m/z*): calcd for $C_{16}H_{18}NO_2S$ [M + H]$^+$, 288.1058; found, 288.1056. $[\alpha]_D$ = −40.7 (*c* 0.73, $CHCl_3$). HPLC: 45% ee [Daicel Chiralpak AD column, hexane/isopropanol 90:10, 0.6 mL min^{-1}, λ = 254 nm; t_R/min = 28.0 (*R*) and 33.0 (*S*)].

(2*E*,4*S*)-1-Phenyl-4-methyl-5-[(2-pyridyl)sulfonyl]-2-pentene (19). Colorless oil. ^{1}H NMR (300 MHz): 8.72 (m, 1H), 8.04 (m, 1H), 7.89 (dt, J = 1.6 and 7.6 Hz, 1H), 7.51 (ddd, J = 1.1, 4.4 and 7.5 Hz, 1H), 7.32−7.08 (m, 5H), 5.56 (m, 1H), 5.31 (m, 1H), 3.56 (dd, J = 6.6 and 14.1 Hz, 1H), 3.31 (dd, J = 6.6 and 14.1 Hz, 1H), 3.19 (d, J = 6.6 Hz, 2H), 2.85 (m, 1H), 1.17 (d, J = 6.7 Hz,

3H). HRMS (FAB+, *m/z*): calcd for $C_{17}H_{20}NO_2S$ [M + H]$^+$, 302.4122; found, 302.4126. $[\alpha]_D = -41.5$ (*c* 0.91, $CHCl_3$). HPLC: 92% ee [Daicel Chiralpak AD Column, hexane/isopropanol 80:20, 0.5 mL min^{-1}, $\lambda = 254$ nm; t_R/min = 19.9 (*R*) and 21.5 (*S*)].

Typical Procedure for the Julia−Kocienski Olefination: Synthesis of (1*E*,3*R*)-1,3-Diphenyl-1-butene (*R*)-20. To a stirred solution of the starting chiral nonracemic 2-pyridyl sulfone **4g** (46 mg, 0.176 mmol, 81% ee) dissolved in anhydrous DME (4.6 mL, 0.033 M) under argon and cooled at −78 °C was added via syringe (530 μL, 0.264 mmol) a solution of potassium hexamethyldisilazide (0.5 M in toluene). The yellow-orange solution was stirred for 3 min, then benzaldehyde (27 μL, 0.264 mmol) was added, and the mixture was stirred at −78 °C for 2 h. The pale yellow solution was quenched with saturated NH_4Cl at the same temperature, the mixture was diluted with CH_2Cl_2 (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, the solvent was removed in vacuo, and the resulting pale yellow oil was purified by column chromatography (hexanes) to give (*R*)-**20** (34 mg, 0.163 mmol, 93% yield). ^{1}H NMR (300 MHz): 7.51−7.30 (m, 10H), 6.61−6.49 (m, 2H), 3.83−3.74 (m, 1H), 1.62 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (75 MHz): 145.6, 137.6, 135.2, 128.6, 128.4, 127.3, 127.0, 126.2, 126.1, 42.5, 21.2. HRMS (EI+, *m/z*): calcd for $C_{16}H_{16}$ [M]$^+$, 208.1252; found, 208.1243. $[\alpha]_D = +32.0$ (*c* 0.4, $CHCl_3$). HPLC: 81% ee (this ee was identical to that of the starting sulfone (*S*)-**4g**). The absolute (*R*) configuration was determined by comparison of the optical rotation and chiral HPLC data with the literature values[22] [$[\alpha]_D^{lit}$ (*S*)-**20** = −39.3 (*c* 2.51, $CHCl_3$), 93% ee. Daicel Chiralcel OD column, hexane/isopropanol 99.5:0.5, 0.2 mL min^{-1}, $\lambda = 215$ nm; t_R/min = 29.6 (*S*) and 31.8 (*R*)].

(*E*)-1-(4-Fluorophenyl)-3-phenyl-1-butene (21). Colorless oil. ^{1}H NMR (300 MHz): 7.36−7.20 (m, 7H), 7.01−6.96 (m, 2H), 6.42−6.27 (m, 2H), 3.69−3.59 (m, 1H), 1.45 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (75 MHz): 163.7, 160.4, 145.5, 135.0, 133.7, 128.5, 127.6, 127.5, 127.4, 127.3, 126.3, 115.5, 115.2, 42.5, 21.2. HRMS (EI+, *m/z*): calcd for $C_{16}H_{15}F$ [M]$^+$, 226.1157; found, 226.1147.

(1*E*,3*E*)-1,5-Diphenyl-1,3-hexadiene (22). Obtained as a mixture of isomers [87:13, (*E*,*E*):(*E*,*Z*)]. (*E*,*E*) isomer: ^{1}H NMR (300 MHz): 7.47−7.29 (m, 10H), 6.78 (dd, $J = 10.1$ and 15.4 Hz), 6.49 (d, $J = 15.4$ Hz), 6.19 (dd, 10.1 and 15.0 Hz, 1H), 6.01 (dd, $J = 6.9$ and 15.0 Hz, 1H), 3.64−3.55 (m, 1H), 1.49−1.39 (d, $J = 6.9$ Hz, 3H). (*E*,*Z*) isomer (representative signals): ^{1}H NMR (300 MHz): 6.58 (d, $J = 15.8$ Hz, 1H), 6.17 (t, $J = 10.5$ Hz, 1H), 5.64 (t, $J = 10.5$ Hz, 1H), 4.08 (m, 1H).

(*E*)-5-Methyl-2-phenyl-3-hexene (23). Colorless oil. ^{1}H NMR (300 MHz): 7.30−7.00 (m, 5H), 5.54 (ddd, $J = 1.2$, 6.5 and 15.4 Hz, 1H), 5.41 (ddd, $J = 0.8$, 6.5 and 15.4 Hz, 1H), 3.46−3.37 (m, 1H), 2.30−2.22 (m, 1H), 1.33 (d, $J = 6.9$ Hz, 3H), 0.98 (d, $J = 6.5$ Hz, 3H), 0.97 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (75 MHz): 146.7, 136.4, 131.9, 128.3, 127.2, 125.9, 42.1, 31.0, 29.7, 22.6, 21.6.

(*E*)-3-(4-Fluorophenyl)-1-phenyl-1-butene (24). Colorless oil. ^{1}H NMR (300 MHz): 7.45−7.21 (m, 7H), 7.09−7.02 (m, 2H), 6.49−6.35 (m, 2H), 3.69 (dq, $J = 6.9$ and 14.2 Hz, 1H), (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (75 MHz): 163.0, 159.8, 141.2, 137.4, 135.0, 128.8, 128.7, 128.6, 128.5, 127.1, 126.1, 115.3, 115.0, 41.8, 21.3. HRMS (EI+, *m/z*): calcd for $C_{16}H_{15}F$ [M]$^+$, 226.1157; found, 226.1150.

(*E*)-1,3-Diphenyl-1-octene (25). Colorless oil. ^{1}H NMR (300 MHz): 7.44−7.20 (m, 10H), 6.49−6.35 (m, 2H), 3.46 (q, $J = 7.3$ Hz, 1H), 1.92−1.78 (m, 2H), 1.47−1.24 (m, 6H), 1.01−0.84 (m, 3H). ^{13}C NMR (75 MHz): 144.7, 137.6, 134.5, 129.2, 128.4, 127.6, 127.0, 126.1, 49.2, 35.8, 31.8, 27.3, 22.5, 14.1. HRMS (EI+, *m/z*): calcd for $C_{20}H_{24}F$ [M]$^+$, 264.1878; found, 264.1869.

(*R*)-1,3-Diphenylbutane (26). To a solution of sulfone **3a** (50 mg, 0.19 mmol, 94% ee) in THF (5 mL), cooled to −78 °C, was added a 2.5 M solution of *n*-BuLi in hexane (84 mL, 0.21 mmol). The resulting orange solution was stirred for 30 min at −78 °C before benzyl bromide (25 μL, 0.21 mmol) was added. The mixture was stirred at −78 °C for 2 h, and then aqueous saturated NH_4Cl (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in MeOH (5 mL) and treated with 5% Na(Hg) (230 mg) and Na_2HPO_4 (93 mg, 0.6 mmol). The resulting suspension was stirred for 5 h at room temperature before it was poured into CH_2Cl_2 (10 mL), filtered, and washed with water (2 × 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 100:1), to afford **26** as a colorless oil; yield: 30 mg (75%). $[\alpha]^{20}_D = +9.2$ (c 0.7, $CHCl_3$), 94% ee. ^{1}H NMR (300 MHz): δ 7.45−7.35 (m, 5H), 7.20−7.09 (m, 5H), 2.59 (sextuplet, $J = 7.1$ Hz, 1H), 2.48 (t, $J = 7.9$ Hz, 2H), 2.08−1.65 (m, 2H), 1.22 (d, $J = 7.1$ Hz, 3H). ^{13}C NMR (75 MHz): δ 139.7, 139.4. 128.7, 128.4, 128.3, 128.1 126.1, 125.8, 42.5, 41.4, 33.1, 21.2. HRMS (FAB+): calcd for $C_{16}H_{19}$, 211.1409; found, 211.1420.

Ethyl (*R*)-3-Phenylbutyrate (27).[24] To a solution of sulfone **3a** (50 mg, 0.19 mmol, 94% ee) in THF (5 mL), cooled to −78 °C, was added a 2.5 M solution of *n*-BuLi in hexane (84 μL, 0.21 mmol). The resulting orange solution was stirred at −78 °C for 30 min before ethyl chloroformate (21 μL, 0.21 mmol) was added. The mixture was stirred at −78 °C for 2 h, and then saturated aqueous NH_4Cl (10 mL) was added. The organic phase was separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in THF (2 mL) and added to a suspension of activated Zn (350 mg) in THF (4 mL) and aqueous saturated NH_4Cl (4 mL). The mixture was stirred for 12 h at room temperature before it was filtered through Celite and washed with CH_2Cl_2 (2 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 4:1) to afford **27** as a colorless oil; yield 29.4 mg (80%). $[\alpha]^{20}_D = -17.9$ (*c* 0.8, $CHCl_3$), 94% ee; $[\alpha]_D^{lit}$ (for the (*S*)-isomer of 90% ee) = +19.0 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz): δ 7.32−7.27 (m, 2H), 7.22−7.17 (m, 3H), 4.07 (q, $J = 7.1$ Hz, 2H), 3.28 (sextet, $J = 7.6$ Hz, 1H), 2.61 (dd, $J = 7.0$, 15.0 Hz, 1H), 2.53 (dd, $J = 8.0$, 15.0 Hz, 1H), 1.31 (d, $J = 7.1$ Hz, 3H), 1.18 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75 MHz): δ 172.3, 145.7, 128.4, 126.7, 126.3, 60.2, 42.9, 36.5, 21.7, 14.1.

(*R*)-1,3-Diphenylbutan-1-one (28).[25] To a solution of sulfone **3a** (50 mg, 0.19 mmol, 94% ee) in THF (5 mL), cooled to −78 °C, was added a 2.5 M solution of *n*-BuLi in hexane (84 μL, 0.21 mmol). The resulting orange solution was stirred for 30 min at −78 °C before benzoyl chloride (24 μL, 0.21 mmol) was added. The resulting solution was stirred at −78 °C for 2 h, and then aqueous saturated NH_4Cl (10 mL) was added. The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in THF (2 mL) and added to a suspension of Zn activated (350 mg) in THF (4 mL) and aqueous saturated NH_4Cl (4 mL). The mixture was stirred for 12 h at room temperature before it was filtered through Celite and washed with CH_2Cl_2 (2 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 3:1), to afford **28** as a white solid; yield 29.2 mg (69%). Mp = 51−52 °C. $[\alpha]^{20}_D = -16.2$ (c 0.7, $CHCl_3$), 94% ee; $[\alpha]_D^{lit}$ (for a sample of 82% ee) = −13.5 (*c* 1.0, CCl_4). ^{1}H NMR (300 MHz): δ 7.93 (dd, $J = 0.9$, 8.0 Hz, 2H), 7.57−7.52 (m, 1H), 7.44 (dt, $J = 1.8$, 8.2 Hz, 2H), 7.33−7.27 (m, 4H), 7.22−7.17 (m, 1H), 3.51 (sextet, $J = 7.2$ Hz, 1H), 3.31 (dd, $J = 5.8$, 16.5 Hz, 1H), 3.16 (dd, $J = 8.1$, 16.2 Hz, 1H), 1.34 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (75 MHz): δ 199.0, 146.5, 132.9, 128.5, 128.2, 128.0, 126.8, 126.2, 47.0, 35.5,

21.8. HPLC: Daicel Chiralcel OD, *i*-PrOH/hexane 2:98, 1 mL min^{-1}, t_R/min = 17.6 (*S*) and 19.9 (*R*), 210 nm.

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Supporting Information Available: Experimental procedures for the preparation of the starting vinyl sulfones and characterization data. Copies of ^1H NMR and ^{13}C NMR of the new compounds. Cartesian coordinates for all optimized structures and their absolute energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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