Inverse-Electron-Demand Diels–Alder Reactions of *N*-(Heteroarylsulfonyl)-1-aza-1,3-dienes Catalyzed by Chiral Lewis Acids

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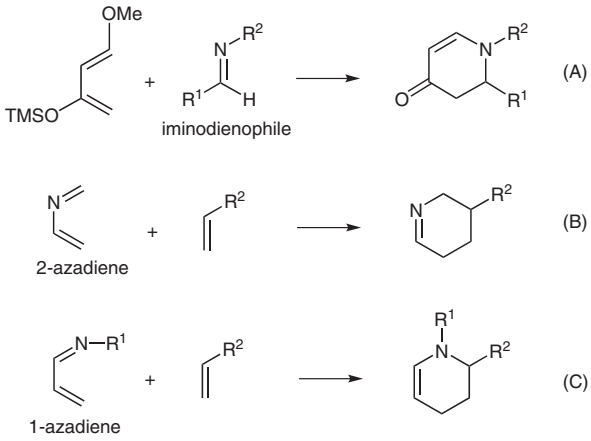
Received 4 November 2008

Abstract: The feasibility of using chiral Lewis acids as catalysts to promote the inverse-electron-demand Diels–Alder reactions of 1-azadienes with vinyl ethers has been demonstrated. Two catalyst systems were identified for this reaction, both relying on the presence of a coordinating 2-pyridylsulfonyl or 8-quinolylsulfonyl group at the imine nitrogen of the 1-azadiene. The combination of a 8-quinolylsulfonyl moiety and nickel(II)/DBFOX-Ph proved to be highly efficient, allowing the synthesis of substituted piperidine derivatives in good yields, excellent *endo* selectivity, and enantioselectivities typically in the range of 77 to 92% ee.

Key words: Diels–Alder reactions, *N*-sulfonyl-1-azadienes, vinyl ethers, chiral Lewis acids, imines, asymmetric catalysis

The catalytic asymmetric aza-Diels–Alder reaction (ADAR) of imines, in which the imine component acts either as azadienophile (strategy A, Scheme 1) or as azadiene (strategies B and C), is a convergent strategy for the preparation of highly valuable optically active piperidine derivatives.[1] Remarkable progress has been achieved in the ADAR of electron-rich dienes with imines, resulting in the development of some very efficient chiral Lewis acid catalyst systems[2] based on zirconium,[3] silver,[4] copper,[5] zinc,[6] scandium,[7] and niobium,[8] as well as organocatalytic versions.[9] In sharp contrast, very few precedents have been disclosed on the participation of azadienes in catalytic asymmetric ADAR. Ghosez and co-worker[10] first described the copper(II) triflate/BOX-catalyzed ADAR of electron-rich 2-azadienes with *N*-alkenoyloxazolidinones. The inverse-electron-demand ADAR of benzylideneaniline as 2-azadiene with vinyl ethers in the presence of chiral titanium[11] and aluminum[12] catalysts has also been reported. The use of 1-azadienes is also a very appealing strategy in the ADAR (strategy C, Scheme 1),[13] even though it is well known that 1-azadienes are much less reactive than 2-azadienes. In this field, Boger et al. have found that *N*-phenylsulfonyl α,β-unsaturated imines participate as dienes in inverse-electron-demand ADAR with vinyl ethers under harsh thermal conditions (high pressure or high temperature), albeit with high *endo* selectivity.[14] The smoother reaction conditions required when the 1,3-azabutadiene system is activated with an electron-withdrawing ester group at C-4 paved the way for the development of the first asymmetric variant of this reaction,



Scheme 1 Intermolecular aza-Diels–Alder approaches to piperidine derivatives

in which vinyl ethers bearing chiral auxiliaries are used.[15,16]

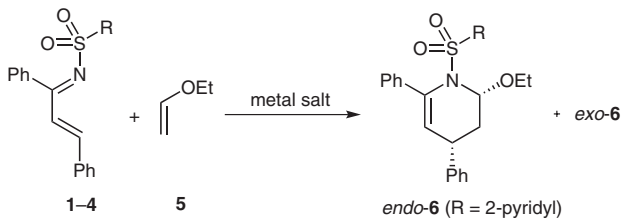
In 2006, Bode and co-workers[17] reported the first catalytic asymmetric inverse-electron-demand ADAR between 1-azadienes (*N*-sulfonyl α,β-unsaturated imines) and β-activated enals using chiral *N*-heterocyclic carbenes. The nucleophilic catalyst reacts with the enal leading to a chiral enolate that acts as reactive dienophile. More recently, the group of Chen has reported an inverse-electron-demand ADAR of *N*-tosyl-1-azadienes and enolizable aldehydes catalyzed by a chiral secondary amine.[18] In this case, the chiral enamine generated in situ reacts as dienophile leading to an aminal that is subsequently hydrolyzed by the water present in the reaction medium, thus enabling release of the catalyst and catalytic turnover.

With these precedents, the development of a chiral Lewis acid catalyst capable of promoting the ADAR of 1-azadienes with electron-rich olefins would significantly expand the scope of this process, providing a valuable alternative route to optically active functionalized piperidine derivatives. This task, however, represents a big challenge, as it has to provide solutions to the low reactivity associated with 1-azadienes and the high propensity of both azadiene and electron-rich dienophile to decompose in the presence of Lewis acids. In fact, to the best of our knowledge, no chiral Lewis acid has been reported to promote ADAR of 1-azadienes.[19]

The use of *N*-sulfonylimines bearing potentially coordinating heteroaryl groups at sulfur has been demonstrated

SYNTHESIS 2009, No. 1, pp 0113–0126
Advanced online publication: 12.12.2008
DOI: 10.1055/s-0028-1083276; Art ID: C05908SS

Table 1 Substrate and Catalyst Optimization[a]



Entry	R (imine)	Metal salt	Time (h)	Ratio *endo*/*exo*[b]	Yield[c,d] (%)
1	4-Tol (**1**)	$Cu(OTf)_2$	120	–	n.r.
2	2-thienyl (**2**)	$Cu(OTf)_2$	120	–	n.r.
3	NMe_2 (**3**)	$Cu(OTf)_2$	120	–	n.r.
4	2-Py (**4**)	$Cu(OTf)_2$	72	85:15	67
5	2-Py (**4**)	AgOTf	72	87:13	32
6	2-Py (**4**)	$Ti(O\textit{i}\text{-}Pr)_4$	72	83:17	41
7	2-Py (**4**)	$Zn(OTf)_2$	72	80:20	50
8	2-Py (**4**)	$Mg(ClO_4)_2 \cdot 6H_2O$	120	–	n.r.
9	2-Py (**4**)	$Ni(ClO_4)_2 \cdot 6H_2O$	36	80:20	80
10[e]	2-Py (**4**)	$Ni(ClO_4)_2 \cdot 6H_2O$	48	84:16	73

[a] Reagents and conditions: imine (1 equiv), **5** (20 equiv), metal salt (10 mol%), CH_2Cl_2, r.t.
[b] Determined by ^1H NMR from the crude reaction mixture.
[c] Yield of *endo*-product after chromatography.
[d] n.r. = no reaction.
[e] Ether **5** (5 equiv) was used.

by others[20] and us[21] to result in unique levels of reactivity and/or selectivity not feasible with the traditional *N*-phenylsulfonyl or *N*-tosyl groups. Herein we describe the successful application of this strategy to bring about ADAR of 1-azadienes with alkenyl ethers catalyzed by chiral Lewis acids.[22]

On the basis of the good results obtained in copper-catalyzed addition reactions to (heteroarylsulfonyl)imines,[21] we initially evaluated the influence of the sulfonyl protecting group in the copper(II) triflate catalyzed (10 mol%) reaction of a set of ketimines **1**–**4** of chalcone[23,24] with ethyl vinyl ether (**5**; 20 equiv)[25] in dichloromethane[26] at room temperature (Table 1, entries 1–4). The tosyl-, (2-thienylsulfonyl)-, and (*N*,*N*-dimethylsulfamoyl)imine derivatives **1**–**3** (Table 1, entries 1–3, respectively) were recovered unaltered after five days at room temperature. In contrast, the *N*-(2-pyridylsulfonyl)imine **4** led to an 85:15 mixture of cycloadducts *endo*-**6** and *exo*-**6** after three days, the major product *endo*-**6** being isolated in 67% yield (Table 1, entry 4).

After the superiority of the 2-pyridylsulfonyl group had been identified, other metal salts (10 mol%) were explored in the model reaction between **4** and **5** (Table 1, entries 5–9). With the exception of magnesium(II) perchlorate hexahydrate (Table 1, entry 8), all metal sources catalyzed the reaction with similar good *endo* selectivity (*endo*/*exo* = 80:20 to 87:13). Silver(I) triflate, titanium(IV) isopropoxide, and zinc(II) triflate were less effective than copper(II) triflate, all providing *endo*-**6** in yields ≤50% (Table 1, entries 5–7). However, nickel(II) perchlorate hexahydrate was superior to copper(II) triflate, providing *endo*-**6** in good yield (80%) after 36 hours (Table 1, entry 9). The higher reactivity of this Lewis acid allowed for a reduction in the amount of dipolarophile **5** used, from 20 to 5 equivalents (Table 1, entry 10).

The asymmetric variant of this procedure was next investigated by use of copper(II) triflate or nickel(II) perchlorate hexahydrate with a variety of P,P- and N,N-coordinating chiral ligands (Table 2). The copper(II)-catalyzed ADAR of imine **4** with **5** required 20 equivalents of dienophile, while 5 equivalents of **5** were sufficient when using the more reactive nickel(II) catalyst. The following conclusions are drawn from this study:

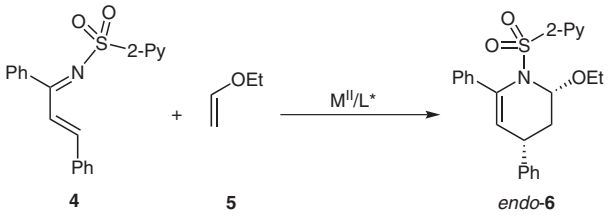
– While the reactivity of the copper(II)-catalyzed reaction is not greatly influenced by the chiral ligand, the reaction yields generally improved when nickel(II)–ligand catalysts were used.

– In both copper(II)- and nickel(II)-catalyzed reactions, the presence of the chiral ligand resulted in excellent *endo* selectivity (*endo*/*exo* typically 98:2).

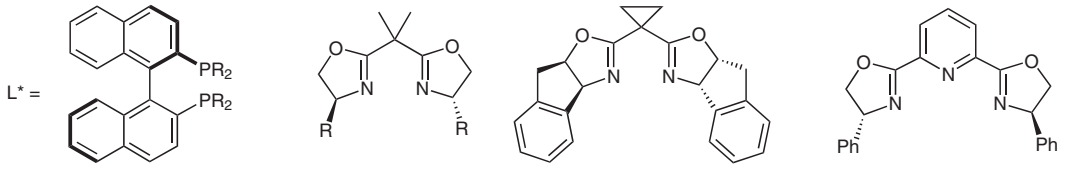
– The enantiocontrol is low with most of the ligands examined, with only the combinations copper(II) triflate/BOX-**V** (65% ee, Table 2, entry 5) and nickel(II) perchlorate hexahydrate/BOX-**IV** (54% ee, entry 4) providing enantioselectivities higher than 50% ee. BOX ligands gave the best results, although the amount of asymmetric induction was strongly influenced by the nature of the substitution at the bis-oxazoline core (entries 3–6).

We next examined the scope of the ADAR with regard to both the azadiene and the vinyl ether in the presence of this catalyst system. Table 3 (entries 1–6) summarizes the evaluation of a series of *N*-(2-pyridylsulfonyl)imines **7**–**12**[23] derived from substituted chalcones in the reaction with **5** (R = Et) under the optimized conditions. In general, very similar diastereoselectivities and enantioselectivities were obtained, regardless of the electronic or the steric nature of the aryl groups Ar^1 and Ar^2. Excellent *endo* selectivity (*endo*/*exo* = 98:2 in all cases) and asymmetric inductions in the range of 59–65% ee were obtained (Table 3, entries 1–4 and 6), except for substrate **11** (Ar^1 = 4-$O_2NC_6H_4$, 30% ee; entry 5). With regard to reactivity, the presence of electron-withdrawing groups on Ar^1 (Table 3, entries 4 and 6) or Ar^2 (entry 2) led to a significant increase in the cycloaddition yield (typically from 55–60% to 71–93%). Much more limited was the structural versatility in the dienophile counterpart. For example, the reaction of the model imine **4** with the bulky *tert*-butyl vinyl ether under identical reaction conditions gave adduct **19** in low yield (20%), low *endo* selectivity (80:20), and low enantioselectivity (25% ee; Table 3, entry 7). The same reaction with a cyclic vinyl ether such as dihydrofuran was completely unsuccessful owing to the rapid de-

Table 2 Enantioselective ADAR of Imine **4** with Ethyl Vinyl Ether[a]

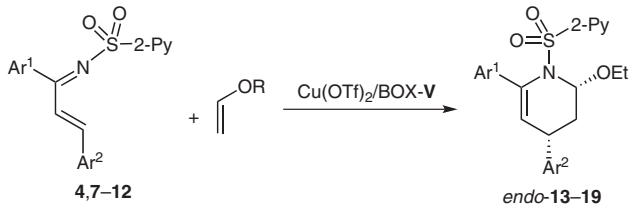


Entry	L*	Time (h)		Ratio *endo*/*exo*[b]		Yield[c] (%)		ee[b] (%)	
		Cu^{II}	Ni^{II}	Cu^{II}	Ni^{II}	Cu^{II}	Ni^{II}	Cu^{II}	Ni^{II}
1	**I**	72	48	98:2	98:2	60	89	26	0
2	**II**	72	48	98:2	98:2	52	85	21	0
3	BOX-**III**	72	48	98:2	98:2	57	73	43	0
4	BOX-**IV**	72	48	98:2	98:2	50	84	20	54
5	BOX-**V**	72	24	98:2	98:2	62	91	65	20
6	BOX-**VI**	72	48	98:2	98:2	61	74	15	35
7	PyBOX-**VII**	72	48	97:3	98:2	49	68	7	0



[a] Reagents and conditions: Cu^{II}: **4** (1 equiv), **5** (20 equiv), $Cu(OTf)_2$ (10 mol%), L* (11 mol%), CH_2Cl_2, r.t.; Ni^{II}: **4** (1 equiv), **5** (5 equiv), $Ni(ClO_4)_2 \cdot 6H_2O$ (10 mol%), L* (11 mol%), CH_2Cl_2, r.t.
[b] Determined by chiral HPLC.
[c] Yield of *endo*-product after chromatography.

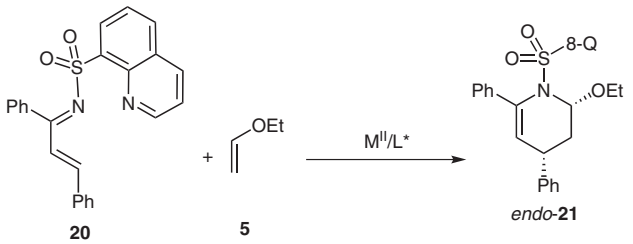
Table 3 Scope of the ADAR Catalyzed by Copper(II) Triflate/BOX-**V**[a]



Entry	Ar^1	Ar^2	Imine	R (vinyl ether)	Product	Yield[b] (%)	ee[c] (%)
1	Ph	Naph	**7**	Et (**5**)	**13**[d]	55	59
2	Ph	4-FC_6H_4	**8**	Et (**5**)	**14**[d]	71	60
3	Naph	Ph	**9**	Et (**5**)	**15**[d]	59	60
4	4-ClC_6H_4	Ph	**10**	Et (**5**)	**16**[d]	80	62
5	4-$O_2NC_6H_4$	Ph	**11**	Et (**5**)	**17**[d]	93	30
6	4-$F_3CC_6H_4$	Ph	**12**	Et (**5**)	**18**[d]	87	65
7[b]	Ph	Ph	**4**	*t*-Bu	**19**[e]	20	25

[a] Reagents and conditions: imine (1 equiv), vinyl ether (20 equiv), $Cu(OTf)_2$ (10 mol%), BOX-**V** (11 mol%), CH_2Cl_2, r.t., 3 d.
[b] Isolated yield after chromatography.
[c] Determined by chiral HPLC.
[d] For **13**–**18**: *endo*/*exo* = 98:2.
[e] For **19**: *endo*/*exo* = 80:20.

Table 4 ADAR of (8-Quinolylsulfonyl)imine **20** with Vinyl Ether **5** Catalyzed by Different Lewis Acids[a]



Entry	Metal salt	L*	Time (d)	Ratio *endo*/*exo*	Yield[b] (%)	ee[c] (%)
1[d]	$Cu(OTf)_2$	–	5	–	–	–
2[d]	$Zn(ClO_4)_2{\cdot}6H_2O$	–	5	–	–	–
3[d]	$Mg(ClO_4)_2{\cdot}6H_2O$	–	5	–	–	–
4[e]	$Ni(ClO_4)_2{\cdot}6H_2O$	–	3	70:30	62	–
5[e]	$Ni(ClO_4)_2{\cdot}6H_2O$	**I**	3	80:20	83	<5
6[e]	$Ni(ClO_4)_2{\cdot}6H_2O$	**II**	3	80:20	81	<5
7[e]	$Ni(ClO_4)_2{\cdot}6H_2O$	BOX-**III**	3	90:10	53	<5
8[e]	$Ni(ClO_4)_2{\cdot}6H_2O$	BOX-**IV**	3	87:13	42	<5
9[e]	$Ni(ClO_4)_2{\cdot}6H_2O$	BOX-**V**	3	–	<10	–
10[e]	$Ni(ClO_4)_2{\cdot}6H_2O$	BOX-**VI**	3	87:13	52	<5
11[e]	$Ni(ClO_4)_2{\cdot}6H_2O$	PyBOX-**VII**	3	88:12	55	<5

[a] Reagents and conditions: **20** (1 equiv), **5** (5 or 20 equiv)[d,e], M^{II} (10 mol%), L* (11 mol%), CH_2Cl_2, r.t.
[b] Isolated yield after chromatography.
[c] Determined by chiral HPLC.
[d] Ether **5** (20 equiv) was used.
[e] Ether **5** (5 equiv) was used.

composition of the dienophile in the presence of the Lewis acid catalyst.

To summarize these initial studies: the catalyst system composed of copper(II) triflate/BOX-**V** proved to be efficient in promoting the asymmetric ADAR of *N*-(2-pyridylsulfonyl)-1-azadienes with ethyl vinyl ether, which represents an important advance with regard to previously described protocols based on thermal reaction conditions.[13–16] However, this procedure still has important limitations: (a) necessity to use a large excess of dienophile (20 equiv), (b) limited versatility in dienophile substitution, and (c) insufficient enantiocontrol (typically 59–65% ee). With the aim of improving the levels of reactivity, versatility, and enantioselectivity, we revisited our original *N*-sulfonyl substitution study with the expectation of finding a more efficient directing group. In particular, we decided to replace the 2-pyridyl group by an 8-quinolyl (8-Q) unit, with the sp^2 nitrogen one position further with respect to the sulfonyl group.

The *N*-(8-quinolylsulfonyl)imine **20** of chalcone (Table 4) was readily prepared by direct condensation between 8-quinolylsulfonamide and chalcone under the conditions typically used for the preparation of other *N*-sulfonyl-1-azadienes.[23] First we examined the ADAR of **20** with **5** in the presence of several Lewis acids (10 mol%) under the optimized reaction conditions (CH_2Cl_2, r.t.) (Table 4, entries 1–4). We were surprised to find no reaction under copper(II) triflate catalysis even after five days (entry 1), and identical results were obtained with zinc(II) and magnesium(II) perchlorates (entries 2 and 3, respectively). In contrast, the reaction of **20** with **5** (5 equiv) catalyzed by nickel(II) perchlorate hexahydrate (entry 4) led to the cycloadduct *endo*-**21** in good yield (62%) and moderate diastereocontrol (*endo*/*exo* = 70:30).

Encouraged by the results obtained with the nickel(II) Lewis acid/8-quinolylsulfonyl group combination, ligands **I**–**VII** (see Table 2) were tested in the ADAR of **20** with **5** (5 equiv) under nickel(II) catalysis (10 mol%). The results are collected in Table 4, entries 5–11. As expected, the *endo* selectivity improved to acceptable levels (80:20 to 90:10) in all cases. Unfortunately, and to our surprise, all tested ligands provided almost racemic products (<5% ee). In terms of reactivity, only the diphosphine ligands Binap (**I**) and Tol-Binap (**II**) led to complete conversions, providing *endo*-**21** in yields above 80% (Table 4, entries 5 and 6). The BOX-**V** ligand, which was the best ligand in the case of the copper(II) triflate/2-pyridylsulfonyl combination, proved to be unproductive under nickel(II) catalysis (<10% yield, entry 9). Modest

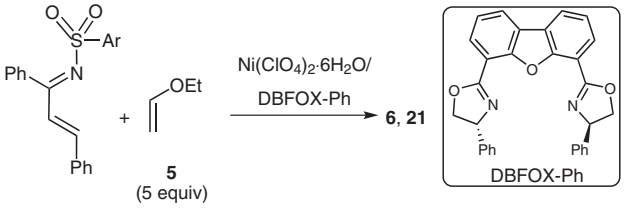
reactivity was observed with the rest of the BOX and Py-BOX ligands (42–55% yield, entries 7, 8, 10, and 11).

In an attempt to generate a deeper chiral environment around the nickel(II) aqua complex, the *trans*-chelating DBFOX-Ph ligand[27] was tested (Table 5). The chiral nickel catalyst was preformed in situ by stirring of equimolar amounts of nickel(II) perchlorate hexahydrate and DBFOX-Ph in dichloromethane[28] at room temperature for at least four to five hours, since lower catalyst-aging times result in a significant loss of enantioselectivity. Fortunately, this ligand proved to be highly efficient in the ADAR of imine **20** with **5** (Table 5, entry 2), leading to the cycloaddition product **21** in good yield (73%), excellent *endo* selectivity (>30:1) and high enantiocontrol (88% ee). In contrast, this catalyst system was much less efficient for the (2-pyridylsulfonyl)imine **4** (entry 1) in terms of asymmetric induction (42% ee). The presence of water seems to be crucial for achieving high enantiocontrol,[29] as the reaction of **20** with **5** in the presence of activated 4-Å molecular sieves led to *endo*-**21** in good yield and diastereoselectivity, but in racemic form (entry 3).

The structural scope and limitations of the nickel(II)/DBFOX-Ph/8-quinolylsulfonyl catalyst system was investigated by screening a set of alkenyl ethers in the reaction with imine **20** (Table 6, entries 1–5). This procedure proved to be efficient with monosubstituted vinyl ethers with primary or secondary alkyl substituents at oxygen (88–91% ee, entries 1–2). Even the bulky *tert*-butyl vinyl ether led to the corresponding adduct **24** with acceptable diastereoselectivity (*endo*/*exo* = 80:20) and enantioselectivity (68% ee), although with poor yield (35%, entry 3). The asymmetric induction was found to be much more sensitive to the substitution at the double bond of the alkene. Thus, a 50:50 mixture of (*E*)- and (*Z*)-prop-1-enyl ether (5 equiv) led exclusively to product **25**, resulting from the ADAR of the kinetically more reactive dipolarophile of *E*-configuration (entry 4). However, despite the good reactivity (68% yield) and high *endo* selectivity (98:2), *endo*-**25** was isolated with only 4% ee. Similarly, dihydrofuran showed a particularly high reactivity, affording the corresponding cycloadduct **26** in excellent yield (93%) and *endo* selectivity (98:2) after 24 hours of reaction, albeit also with low enantioselectivity (20% ee, entry 5). The high reactivity displayed by this dienophile allowed the temperature to be reduced to 0 °C, which resulted in an increased asymmetric induction (58% ee), while maintaining a high yield (91%, entry 5). Electron-rich styrene derivatives such as *p*-methoxystyrene proved also to be suitable, providing an acceptable chemical yield (58%) and high *endo* selectivity (98:2), although with very low enantiocontrol (5% ee, entry 6).

To evaluate the scope of this cycloaddition protocol with regard to the 1-azadiene counterpart, a representative set of *N*-sulfonyl α,β-unsaturated ketimines was surveyed in the reaction with *n*-propyl vinyl ether under the optimal experimental conditions. As shown in Table 7, good yields (52–75%) and high levels of *endo* selectivity and enantioselectivity (80–92% ee) were achieved in most cases. Aryl substituents of varied electronic and steric nature at the β-position of the azadiene (R^2) are well tolerated (entries 1–4), although electron-rich groups led to a slight decrease of enantioselectivity (entries 3 and 4). Even substrate **32**, with a *tert*-butyl group as R^2 proved to be suitable (entry 5, 84% ee). In contrast, a more limited

Table 5 ADAR Catalyzed by Nickel(II) Perchlorate Hexahydrate/DBFOX-Ph[a]



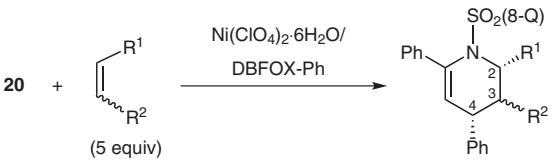
4, Ar = 2-Py
20, Ar = 8-Q

endo-**6**, Ar = 2-Py
endo-**21**, Ar = 8-Q

Entry	Ar	Additive	Ratio *endo*/*exo*[b]	Yield[c] (%)	ee[b] (%)
1	2-Py	–	98:2	80	42
2	8-Q	–	97:3	73	88
3	8-Q	4-Å MS	90:10	68	0

[a] Reagents and conditions: **4** or **20** (1 equiv), **5** (5 equiv), $Ni(ClO_4)_2·6H_2O$/DBFOX-Ph (10 mol%), CH_2Cl_2, r.t., 3 d.
[b] Determined by chiral HPLC.
[c] Isolated yield after chromatography.

Table 6 Scope of the Dienophile in the ADAR with Imine **20** Catalyzed by Nickel(II)/DBFOX-Ph[a]

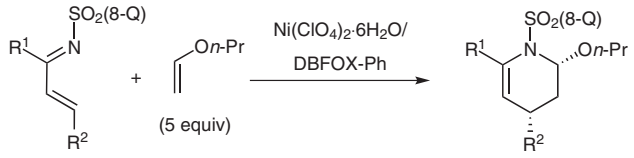


22–27

Entry	R^1	R^2	Product	Ratio *endo*/*exo*[b]	Yield (%)[c]	ee (%)[b]
1	O*n*-Pr	H	**22**	98:2	69	91
2	OCy	H	**23**	98:2	70	88
3	O*t*-Bu	H	**24**	80:20	35	68
4	OEt[d]	Me[d]	**25**[e]	98:2	67	4
5[f]	OCH_2CH_2		**26**	98:2 (98:2)[g]	93 (91)[g]	20 (58)[g]
6	PMP	H	**27**	98:2	58	5

[a] Reagents and conditions: **20** (1 equiv), alkene (5 equiv), $Ni(ClO_4)_2·6H_2O$ (10 mol%), DBFOX-Ph (11 mol%), CH_2Cl_2, r.t., 3 d.
[b] Determined by chiral HPLC.
[c] Isolated yield after chromatography.
[d] A 50:50 mixture of *E*- and *Z*-alkenes.
[e] Product with 2*R*,3*S*,4*R* configuration was exclusively formed.
[f] Reaction at r.t. for 24 h or at 0 °C for 3 d.
[g] Values in parentheses were obtained at 0 °C.

Table 7 Scope of the Azadiene in the ADAR with a Vinyl Ether Catalyzed by Nickel(II)/DBFOX-Ph[a]



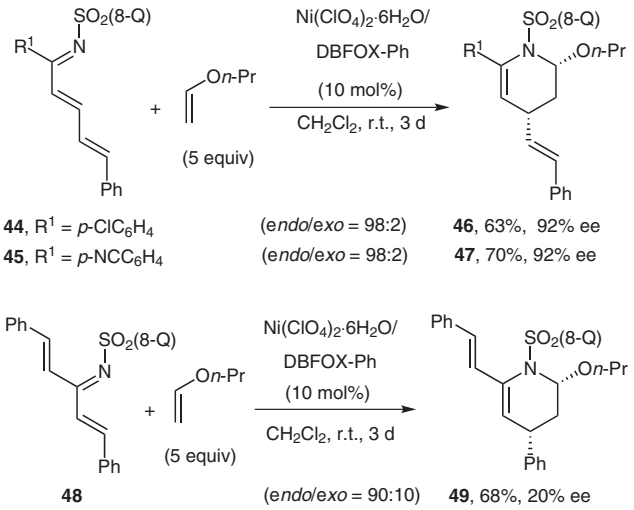
28–35 **36–43**

Entry	R^1	R^2	Imine	Product	Ratio *endo*/*exo*[b]	Yield[c] (%)	ee[b] (%)
1	Ph	4-FC_6H_4	**28**	**36**	98:2	75	92
2	Ph	Naph	**29**	**37**	97:3	69	90
3	Ph	PMP	**30**	**38**	98:2	65	80
4	Ph	2-furyl	**31**	**39**	97:3	52	77
5	Ph	*t*-Bu	**32**	**40**	98:2	61	84
6	4-ClC_6H_4	Ph	**33**	**41**	97:3	73	90
7	4-$F_3CC_6H_4$	Ph	**34**	**42**	97:3	69	91
8	Naph	Ph	**35**	**43**	98:2	67	6

[a] Reagents and conditions: imine (1 equiv), alkene (5 equiv), $Ni(ClO_4)_2·6H_2O$/DBFOX-Ph (10 mol%), CH_2Cl_2, r.t., 3 d.
[b] Determined by chiral HPLC.
[c] Isolated yields after flash chromatography.

versatility was found with respect to the substitution at the imine carbon (R^1). *para*-Substituted aryl groups led to excellent results (90–91% ee, entries 6 and 7), whereas a dramatic drop in enantioselectivity resulted with more sterically demanding aryl groups such as 2-naphthyl (6% ee, entry 8).

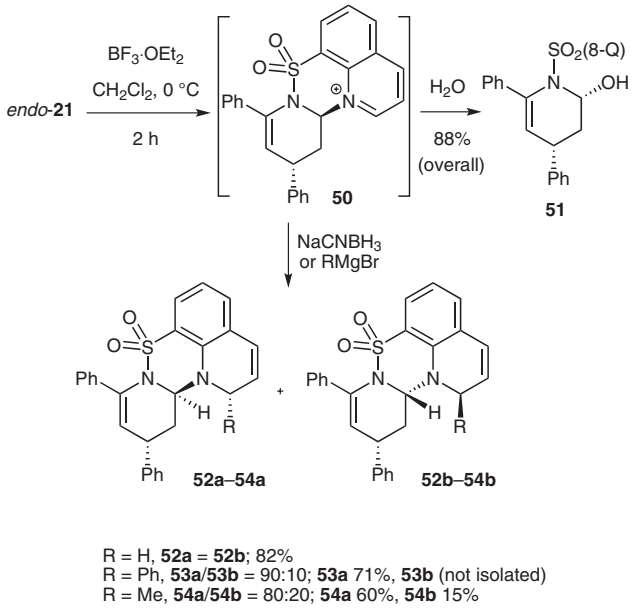
The cycloaddition of imines **44** and **45** with an additional double bond (part of a styryl substituent) conjugated with the azadiene system (Scheme 2) deserves particular attention. In both cases studied, complete chemoselectivity in favor of the hetero-Diels–Alder cycloaddition was observed, the corresponding 4-alkenyl-substituted tetrahydropyridine products **46** and **47** being isolated in good yield and excellent diastereo- and enantioselectivities (92% ee in both cases). Less satisfactory results were obtained with the *N*-(8-quinolylsulfonyl)imine of dibenzylidene acetone (**48**), whose ADAR with *n*-propyl vinyl ether provided tetrahydropyridine **49** in good yield (68%) and *endo* selectivity (90:10), but poor enantioselectivity (20% ee, Scheme 2). This result highlights again the much higher sensitivity of this reaction to the substitution at the imine carbon of the azadiene than that at the β-position.



Scheme 2 Nickel(II)/DBFOX-Ph-catalyzed ADAR of conjugated azatrienes

Regarding the potential synthetic interest in the obtained cycloadducts, we tried first to effect the nucleophilic displacement of the alkoxy group at C-2 with carbon nucleophiles such as allyltrimethylsilane in the presence of a Lewis acid, which is known to occur with inversion of the configuration.[15] However, treatment of cycloadduct *endo*-**21** with boron trifluoride–diethyl ether (1.5 equiv) in dichloromethane led quantitatively to the quinolinium salt **50** after two hours at 0 °C (TLC monitoring), likely formed by intramolecular trapping of the resulting intermediate iminium ion by the quinoline moiety (Scheme 3). Subsequent aqueous treatment of **50** produced the 2-hydroxy derivative **51** with complete stereoselectivity in 88% yield.

Alternatively, trapping of intermediate **50** with stronger nucleophiles such as hydride or Grignard reagents resulted in selective attack at the 2-position of the bicyclic quinoline ring system, affording tetracyclic compounds **52**–**54** in good yields (Scheme 3). Product **52** (R = H) was isolated as the only diastereomer in 82% yield in the reaction of **50** with sodium cyanoborohydride (Scheme 3). The use of phenylmagnesium bromide as nucleophile led to a 90:10



Scheme 3 Stereoselective transformations of the cycloadducts

diastereomeric mixture of **53a** and **53b**, the major product **53a** being obtained in 71% isolated yield. An 80:20 mixture of **54a** and **54b** (60% and 15% yield, respectively) was produced with the less hindered Grignard reagent methylmagnesium bromide. Products **52**–**54** are medically attractive, because they can be considered as chiral nonracemic [1,2,4]benzothiadiazine-5,5-dioxide derivatives,[30] which have proven to be potential drugs for memory and learning disorders, as well as neurodegenerative diseases.[31]

It is well known that the Diels–Alder reaction of *N*-tosyl-1-aza-1,3-dienes takes place with very high *endo* selectivity.[15] This relative stereochemistry in the 2-pyridylsulfonyl- and 8-quinolylsulfonyl cycloadducts was confirmed by comparison of their NMR data with those reported for the corresponding tosyl derivatives, and further confirmed by X-ray diffraction analysis of a single-crystal sample of (±)-*endo*-**18**[32] (Figure 1).

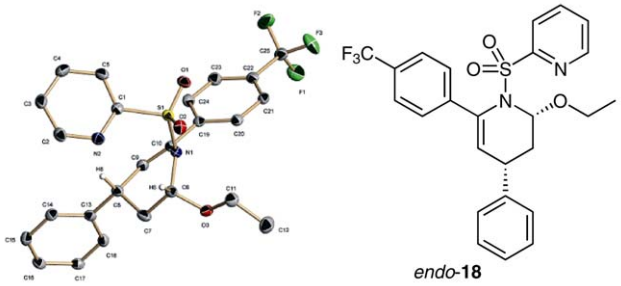
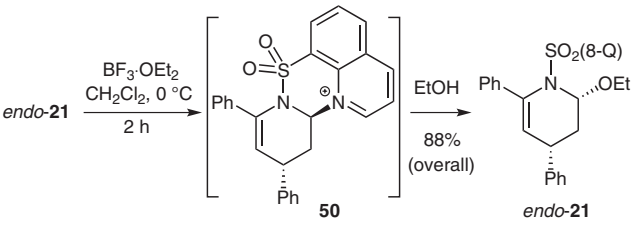


Figure 1 X-ray crystal structure of cycloadduct *endo*-**18**

To verify the overall retention of stereochemistry in the transformation of *endo*-**21** into **51** (Scheme 3), we designed the experiment shown in Scheme 4. Adduct *endo*-**21** (R_f = 0.68, *n*-hexane–EtOAc, 1:1) was treated with boron trifluoride–diethyl ether complex (1.2 equiv), confirming by TLC its complete transformation into **50** after two hours (R_f = 0, *n*-hexane–EtOAc, 1:1). When it was quenched with ethanol, the instantaneous re-formation of *endo*-**21** resulted.



Scheme 4 Ethanolysis of quinolinium intermediate **50**

The relative stereochemistry of tetracyclic compounds **52**–**54** (see Scheme 3) was determined by NMR spectroscopy (HMBC, COSY, and NOESY) of diastereomers **54a** and **54b**.[33] This stereochemistry is in concordance with the approach of the nucleophile from the less hindered convex face of the molecule. The absolute configuration of compound **54b** was unambiguously established by X-ray diffraction analysis of a single crystal from enantiopure **54b**, obtained by recrystallization of a 91% ee sample (Figure 2).[34]

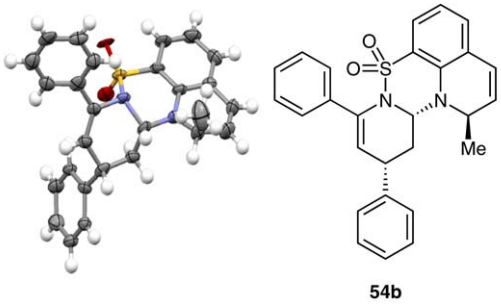
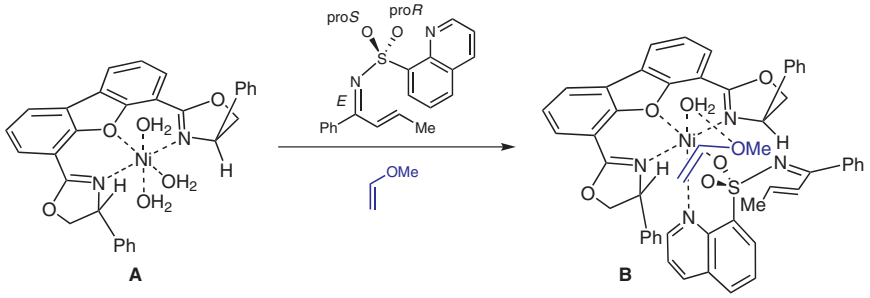


Figure 2 X-ray crystal structure of compound **54b**

To shed some light on the origin of the enantioselectivity in the Ni/DBFOX-Ph-catalyzed ADAR of *N*-(8-quinolinesulfonyl)-1-aza-1,3-dienes with vinyl ethers, the theoretical structures of different catalyst–imine complexes, based on the previously reported X-ray crystal structure of the DBFOX-Ph–Ni$(ClO_4)_2 \cdot 3H_2O$ complex **A**,[27a] were studied (Scheme 5). The 1-aza-1,3-diene in which R^1 = Ph and R^2 = Me (see Table 7) and methyl vinyl ether were used as model substrates. Several complexes were first analyzed by using a semi-empirical PM3(tm) procedure, as implemented in HyperChem 6.02,[35] varying the coordinated prochiral sulfonyl oxygen, the imine configuration, the O–S–N–C dihedral angle and the mode of coordination of the quinolinesulfonyl moiety (that can locate the N atom either in the plane of the chiral ligand, designated as equatorial, or in a perpendicular arrangement, designated as axial). This preliminary study showed that complexes with the quinoline moiety in an axial arrangement are much more stable, probably due to a π-stacking interaction with the closest Ph group. These complexes



Scheme 5 Stereochemical model for the cycloaddition

were re-optimized at the DFT (B3LYP)[36] level by using the Gaussian03 program.[37] The standard 6-31G(d)[38] basis set was used for S, O, and N atoms, 3-21G[39] for C and H, and the LANL2DZ[40] was employed for the Ni atom. Harmonic frequencies were calculated at the same level of theory to characterize the stationary points and to determine the zero-point energies (ZPE).

Because the H_2O ligand in the starting nickel salt $Ni(ClO_4)_2{\cdot}6H_2O$ has a key role in the reaction outcome (addition of molecular sieves led to racemic mixtures) and that electron-rich olefins different from vinyl ethers, such as styrenes, afforded the product in almost racemic form, we envisaged the possibility of the participation of both azadiene and olefin in the reactive complex, the latter being stabilized by a hydrogen bond with water. Thus the complex model **B** shown in Scheme 5, with the *proS* oxygen coordinated to Ni and *E*-configuration at the imine, could account for the fact that the main product of the reaction comes from the *endo* approach of the olefin to the *re* face of the imine. The equivalent *proR*-oxygen-coordinated complex that would afford the other enantiomer was shown to be only 0.2 kcal·mol^{-1} less stable. However, the slightly longer distances between the carbons to be bonded (4.62 and 5.62 Å, vs 4.57 and 5.36 Å in *proS* complex **B**), and between the centroids of the aromatic rings showing the π-stacking interaction (4.38 Å vs 3.99 Å in *proS* complex **B**) observed in *proR* complex, could result in a higher energy difference in the transition state, favoring the reaction from complex **B**.

In conclusion, we have demonstrated that the presence of an appropriate heteroarylsulfonyl group at the imine nitrogen confers unique reactivity to the 1-aza-1,3-diene system, allowing the development of a hetero-Diels–Alder reaction with alkenyl ethers that is catalyzed by a chiral Lewis acid. The performance of the combination of the 8-quinolylsulfonyl moiety at the substrate and nickel(II)/DBFOX-Ph as catalyst was very good, leading to functionalized piperidine derivatives in good yields, excellent *endo* selectivity, and enantioselectivities typically in the range of 80–91% ee. A tentative model based on theoretical DFT calculations is provided to explain the origin of this high reactivity and selectivity.

All the reactions were carried out in anhydrous solvents and under argon atmosphere. Melting points were taken in open-end capillary tubes. NMR spectra were recorded at 300 MHz (^{1}H) or 75 MHz (^{13}C) at room temperature in $CDCl_3$ [calibrated at δ = 7.26 (^{1}H), and δ = 77.0 (^{13}C)]. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter. Mass spectra were recorded on a VG AutoSpec mass spectrometer. HPLC experiments were conducted using Daicel Chiralpak columns (AD, OD or AS). Flash column chromatography was performed on silica gel (Merck-60, 230–400 mesh). *N*-Heteroarylsulfonyl α,β-unsaturated imines were prepared according to procedures previously described.[23]

Copper(II)-Catalyzed Asymmetric Inverse-Electron-Demand ADAR; General Procedure

A soln of $Cu(OTf)_2$ (7.2 mg, 0.02 mmol) and BOX-**V** (7.0 mg, 0.021 mmol) in CH_2Cl_2 (1.0 mL) was stirred for 30 min before a soln of the *N*-(2-pyridylsulfonyl) ketimine (0.2 mmol) in CH_2Cl_2 (1.0 mL) and the vinyl ether (20 equiv) were successively added. The reaction mixture was stirred at r.t. until consumption of the starting imine, before it was quenched with sat. aq NH_4Cl and extracted several times with CH_2Cl_2. The combined organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (deactivated silica gel, CH_2Cl_2).

Nickel(II)-Catalyzed Asymmetric Inverse-Electron-Demand ADAR; General Procedure

A soln of $Ni(ClO_4)_2$ 6 H_2O (7.2 mg, 0.02 mmol) and (*R*,*R*)-DBFOX-Ph (9.2 mg, 0.022 mmol) in CH_2Cl_2 (1 mL) was stirred at r.t. for 4 h before a soln of *N*-(8-quinolylsulfonyl) ketimine (0.2 mmol) in CH_2Cl_2 (1.0 mL) and the vinyl ether (5 equiv) were successively added. Isolation of the product was performed as in the previous case.

2-Ethoxy-4,6-diphenyl-1-[(2-pyridyl)sulfonyl]-1,2,3,4-tetrahydropyridine (*endo*-6)

Yield: 60%; white solid; mp 69–71 °C; $[\alpha]_D^{20}$ –43 (*c* 0.65, $CHCl_3$); 65% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 15.7 (minor), t_R = 23.1 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.80 (ddd, *J* = 4.6, 1.6, 0.8 Hz, 1 H), 7.80 (m, 1 H), 7.65 (m, 1 H), 7.53 (ddd, *J* = 7.5, 4.6, 1.1 Hz, 1 H), 7.34–7.05 (m, 10 H), 5.98 (dd, *J* = 6.1, 4.2 Hz, 1 H), 5.96 (d, *J* = 3.4 Hz, 1 H), 4.19 (dq, *J* = 9.5, 7.0 Hz, 1 H), 3.83 (dq, *J* = 9.5, 7.0 Hz, 1 H), 2.87 (td, *J* = 7.3, 3.4 Hz, 1 H), 2.62 (ddd, *J* = 14.0, 7.1, 5.9 Hz, 1 H), 2.07 (ddd, *J* = 14.0, 7.8, 4.2 Hz, 1 H), 1.27 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.3, 150.0, 144.0, 138.6, 137.6, 136.6, 128.4, 127.9, 127.7, 127.5, 126.9, 126.6, 126.5, 123.6, 85.4, 63.9, 40.2, 37.6, 14.9.

MS–FAB: *m*/*z* (%) = 375.0 (100) [M$^+$ – OEt].

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{25}N_2O_3S$: 421.15076; found: 421.15104.

(2*R*,4*S*)-2-Ethoxy-6-phenyl-4-(2-naphthyl)-1-[(2-pyridyl)sulfonyl]-1,2,3,4-tetrahydropyridine (13)
Yield: 55%; white solid; mp 60–62 °C; $[\alpha]_D^{20}$ –33 (*c* 0.50, $CHCl_3$); 59% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 19.7 (minor), t_R = 33.2 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (ddd, *J* = 4.6, 1.6, 0.8 Hz, 1 H), 7.86–7.63 (m, 5 H), 7.58–7.52 (m, 2 H), 7.46–7.40 (m, 2 H), 7.38–7.21 (m, 6 H), 6.01 (d, *J* = 3.2 Hz, 1 H), 5.99 (dd, *J* = 5.6, 3.8 Hz, 1 H), 4.20 (dq, *J* = 9.7, 7.3 Hz, 1 H), 3.81 (dq, *J* = 9.7, 7.3 Hz, 1 H), 3.13 (td, *J* = 7.1, 3.2 Hz, 1 H), 2.69 (ddd, *J* = 13.7, 7.7, 5.9 Hz, 1 H), 2.27 (ddd, *J* = 13.9, 6.9, 3.8 Hz, 1 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 149.9, 138.6, 137.6, 133.3, 132.2, 128.0, 127.9, 127.6, 127.5, 127.0, 126.8, 126.7, 126.5, 126.4, 125.9, 125.5, 85.3, 64.0, 39.7, 37.6, 15.0.

MS–FAB: *m*/*z* (%) = 425.1 (100) [M^+ – OEt].

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{27}N_2O_3S$: 471.1742; found: 471.1740.

(2*R*,4*S*)-2-Ethoxy-4-(4-fluorophenyl)-6-phenyl)-1-[(2-pyridyl)sulfonyl]-1,2,3,4-tetrahydropyridine (14)
Yield: 71%; white solid; mp 116–118 °C; $[\alpha]_D^{20}$ –40 (*c* 0.80, $CHCl_3$); 60% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 21.2 (minor), t_R = 29.6 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.77 (ddd, *J* = 4.6, 1.6, 0.8 Hz, 1 H), 7.78 (m, 1 H), 7.59 (m, 1 H), 7.51 (ddd, *J* = 7.7, 4.6, 1.2 Hz, 1 H), 7.30–7.19 (m, 7 H), 7.09 (d, *J* = 8.3 Hz, 2 H), 5.93 (dd, *J* = 5.2, 3.4 Hz, 1 H), 5.80 (d, *J* = 3.2 Hz, 1 H), 4.12 (dq, *J* = 9.5, 7.1 Hz, 1 H), 3.79 (dq, *J* = 9.5, 7.1 Hz, 1 H), 3.05 (td, *J* = 7.4, 3.4 Hz, 1 H), 2.58 (ddd, *J* = 14.0, 8.1, 5.3 Hz, 1 H), 2.07 (ddd, *J* = 14.0, 5.9, 3.4 Hz, 1 H), 1.26 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 149.9, 143.0, 138.6, 137.6, 136.6, 132.2, 129.5, 128.4, 128.0, 127.9, 126.9, 126.8, 125.5, 123.4, 84.9, 64.0, 39.0, 36.8, 14.9.

MS–FAB: *m*/*z* (%) = 394.1 (100) [M^+ – OEt].

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{24}N_2O_3SF$: 439.1413; found: 439.1410.

(2*R*,4*S*)-2-Ethoxy-4-phenyl-6-(2-naphthyl)-1-[(2-pyridyl)sulfonyl]-1,2,3,4-tetrahydropyridine (15)
Yield: 59%; white solid; mp 59–60 °C; $[\alpha]_D^{20}$ –33 (*c* 0.58, $CHCl_3$); 60% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 29.5 (minor), t_R = 41.0 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.81 (ddd, *J* = 4.6, 1.6, 0.8 Hz, 1 H), 7.83–7.65 (m, 1 H), 7.61 (m, 1 H), 7.53–7.40 (m, 4 H), 7.30–7.11 (m, 6 H), 6.09 (d, *J* = 3.4 Hz, 1 H), 6.02 (dd, *J* = 5.8, 4.2 Hz, 1 H), 4.24 (dq, *J* = 9.7, 7.3 Hz, 1 H), 3.85 (dq, *J* = 9.7, 7.3 Hz, 1 H), 2.95 (td, *J* = 7.7, 3.8 Hz, 1 H), 2.68 (ddd, *J* = 13.5, 7.3, 6.1 Hz, 1 H), 2.10 (ddd, *J* = 13.9, 7.7, 4.0 Hz, 1 H), 1.31 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 149.9, 144.0, 137.5, 136.5, 136.0, 132.9, 128.4, 128.2, 128.1, 127.9, 127.6, 127.5, 126.8, 126.5, 125.9, 125.4, 124.7, 123.5, 85.5, 64.0, 40.2, 37.7, 14.9.

MS–FAB: *m*/*z* (%) = 425.1 (100) [M^+ – OEt].

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{27}N_2O_3S$: 471.1742; found: 471.1739.

(2*R*,4*S*)-6-(4-Chlorophenyl)-2-ethoxy-4-phenyl-1-[(2-pyridyl)sulfonyl]-1,2,3,4-tetrahydropyridine (16)
Yield: 80%; white solid; mp 150–151 °C; $[\alpha]_D^{20}$ –38 (*c* 0.56, $CHCl_3$); 62% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 20.3 (minor), t_R = 28.6 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.79 (ddd, *J* = 4.6, 1.6, 0.8 Hz, 1 H), 7.84 (m, 1 H), 7.69 (m, 1 H), 7.55 (ddd, *J* = 7.7, 4.6, 1.1 Hz, 1 H), 7.30–7.18 (m, 7 H), 7.11–7.06 (m, 2 H), 5.94 (dd, *J* = 5.9, 4.0 Hz, 1 H), 5.93 (d, *J* = 3.4 Hz, 1 H), 4.13 (dq, *J* = 9.7, 7.3 Hz, 1 H), 3.79 (dq, *J* = 9.7, 7.3 Hz, 1 H), 2.84 (td, *J* = 7.4, 3.4 Hz, 1 H), 2.60 (ddd, *J* = 14.0, 7.3, 6.1 Hz, 1 H), 2.05 (ddd, *J* = 14.0, 7.7, 4.0 Hz, 1 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.3, 150.1, 143.9, 137.7, 137.2, 135.6, 133.8, 128.4, 128.2, 128.0, 127.9, 127.0, 126.6, 123.5, 85.5, 64.0, 40.1, 37.7, 14.9.

MS–FAB: *m*/*z* (%) = 409.0 (100) [M^+ – OEt].

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{24}N_2O_3SCl$: 455.1196; found: 455.1193.

(2*R*,4*S*)-2-Ethoxy-4-phenyl-6-(4-nitrophenyl)-1-[(2-pyridyl)sulfonyl]-1,2,3,4-tetrahydropyridine (17)
Yield: 93%; white solid; mp 140–142 °C; $[\alpha]_D^{20}$ –12 (*c* 0.46, $CHCl_3$); 30% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 12.3 (minor), t_R = 20.5 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.83 (ddd, *J* = 4.2, 1.6, 0.7 Hz, 1 H), 8.18 (d, *J* = 8.9 Hz, 2 H), 7.91 (td, *J* = 7.4, 1.6 Hz, 1 H), 7.77 (dt, *J* = 7.9, 0.7 Hz, 1 H), 7.60 (ddd, *J* = 7.7, 4.6, 1.0 Hz, 1 H), 7.54 (d, *J* = 8.9 Hz, 2 H), 7.30–7.18 (m, 3 H), 7.11–7.06 (m, 2 H), 6.14 (d, *J* = 3.4 Hz, 1 H), 5.90 (dd, *J* = 4.2, 6.1 Hz, 1 H), 4.11 (dq, *J* = 9.7, 7.3 Hz, 1 H), 3.81 (dq, *J* = 9.7, 7.3 Hz, 1 H), 2.84 (td, *J* = 7.5, 3.4 Hz, 1 H), 2.56 (ddd, *J* = 14.0, 7.3, 6.1 Hz, 1 H), 2.05 (ddd, *J* = 14.0, 7.7, 4.0 Hz, 1 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.9, 150.3, 147.2, 145.4, 143.2, 137.9, 134.9, 131.1, 128.5, 127.8, 127.0, 126.7, 123.4, 123.3, 85.4, 64.2, 39.5, 37.7, 14.9.

(2*R*,4*S*)-2-Ethoxy-4-phenyl-6-(4-trifluoromethylphenyl)-[(2-pyridyl)sulfonyl]-1,2,3,4-tetrahydropyridine (18)
Yield: 87%; white solid; mp 122–123 °C; $[\alpha]_D^{20}$ –40 (*c* 0.52, $CHCl_3$); 65% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 16.9 (minor), t_R = 27.4 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (ddd, *J* = 4.3, 1.6, 0.7 Hz, 1 H), 8.18 (d, *J* = 8.9 Hz, 2 H), 7.91 (td, *J* = 7.4, 1.6 Hz, 1 H), 7.77 (dt, *J* = 7.8, 0.8 Hz, 1 H), 7.70 (d, *J* = 7.7, Hz, 1 H), 7.60–7.41 (m, 5 H), 7.31–7.13 (m, 3 H), 7.12–7.06 (m, 2 H), 6.06 (d, *J* = 3.4 Hz, 1 H), 5.94 (dd, *J* = 5.7, 4.0 Hz, 1 H), 4.15 (dq, *J* = 9.7, 7.3 Hz, 1 H), 3.80 (dq, *J* = 9.7, 7.3 Hz, 1 H), 2.87 (td, *J* = 7.5, 3.6 Hz, 1 H), 2.60 (ddd, *J* = 14.0, 7.3, 6.1 Hz, 1 H), 2.05 (ddd, *J* = 14.0, 7.7, 4.0 Hz, 1 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2, 150.2, 143.7, 142.4, 137.8, 135.2, 130.1, 129.6, 128.5, 127.9, 127.1, 126.8, 126.7, 125.1, 125.0, 123.4, 85.4, 64.2, 39.9, 37.7, 14.9.

(2*R*,4*S*)-2-*tert*-Butoxy-4,6-diphenyl-1-[(2-pyridyl)sulfonyl]-1,2,3,4-tetrahydropyridine (19)
Yield: 20%; white solid; mp 31–32 °C; $[\alpha]_D^{20}$ –6 (*c* 0.5, $CHCl_3$); 25% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 14.7 (minor), t_R = 23.1 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.68 (ddd, *J* = 4.1, 1.7, 0.8 Hz, 1 H), 7.92 (dt, *J* = 7.8, 1.8 Hz, 1 H), 7.69 (d, *J* = 7.9 Hz, 1 H), 7.41 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1 H), 7.30 (m, 2 H), 7.20–7.10 (m, 8 H), 6.02 (dd, *J* = 4.1, 2.6 Hz, 1 H), 5.71 (d, *J* = 3.2 Hz, 1 H), 3.05 (dt, *J* = 9.2, 3.2 Hz, 1 H), 2.45 (ddd, *J* = 13.9, 9.3, 4.3 Hz, 1 H), 1.83 (dt, *J* = 13.9, 2.6 Hz, 1 H), 1.26 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.7, 149.8, 145.4, 139.1, 137.5, 136.1, 128.6, 128.0, 127.9, 127.8, 127.2, 126.9, 126.7, 126.1, 125.3, 123.8, 79.3, 76.0, 39.0, 37.2, 28.5.

(2*R*,4*S*)-2-Ethoxy-4,6-diphenyl-1-[(8-quinolyl)sulfonyl]-1,2,3,4-tetrahydropyridine (21)

Yield: 73%; white solid; mp 65–67 °C; $[\alpha]_D^{20}$ –22 (*c* 0.4, $CHCl_3$); 88% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 32.3 (minor), t_R = 37.3 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.20 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.32 (dd, *J* = 8.3, 1.7 Hz, 1 H), 8.11 (dd, *J* = 7.4, 1.4 Hz, 1 H), 8.06 (dd, *J* = 8.2, 1.3 Hz, 1 H), 7.63 (dd, *J* = 8.3, 4.2 Hz, 1 H), 7.47 (m, 1 H), 7.31–7.12 (m, 9 H), 6.89 (dd, *J* = 7.9, 1.7 Hz, 1 H), 6.55 (dd, *J* = 5.7, 4.3 Hz, 1 H), 5.87 (d, *J* = 3.3 Hz, 1 H), 4.22 (dq, *J* = 9.6, 7.1 Hz, 1 H), 3.91 (dq, *J* = 9.6, 7.1 Hz, 1 H), 2.73–2.55 (m, 2 H), 2.08 (ddd, *J* = 13.2, 7.4, 3.4 Hz, 1 H), 1.27 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.1, 144.3, 144.0, 139.0, 137.4, 136.7, 133.9, 133.8, 128.9, 128.2, 127.9, 127.7, 126.9, 126.8, 126.3, 125.4, 122.2, 85.1, 63.7, 41.3, 37.8, 15.2.

MS–FAB: *m*/*z* (%) = 425.1 (85) [M^+ – OEt].

HRMS–FAB: *m*/*z* [M^+] calcd for $C_{28}H_{28}O_3N_2S$: 471.1742; found: 471.1758.

(2*R*,4*S*)-4,6-Diphenyl-2-propoxy-1-[(8-quinolyl)sulfonyl]-1,2,3,4-tetrahydropyridine (22)

Yield: 69%; white solid; mp 53–55 °C; $[\alpha]_D^{20}$ –35 (*c* 0.4, $CHCl_3$); 91% ee; HPLC (AD) 0.8 mL/min; *n*-hexane–*i*-PrOH, 97:3): t_R = 40.0 (minor), t_R = 44.8 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.09 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.22 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.98 (dd, *J* = 7.4, 1.3 Hz, 1 H), 7.94 (dd, *J* = 8.2, 1.3 Hz, 1 H), 7.53 (dd, *J* = 8.3, 4.2 Hz, 1 H), 7.37 (m, 1 H), 7.21–7.02 (m, 9 H), 6.83 (dd, *J* = 7.9, 1.7 Hz, 1 H), 6.39 (dd, *J* = 5.6, 3.8 Hz, 1 H), 5.74 (d, *J* = 3.4 Hz, 1 H), 4.02 (dq, *J* = 9.5, 6.7 Hz, 1 H), 3.69 (dq, *J* = 9.5, 6.7 Hz, 1 H), 2.65 (td, *J* = 7.3, 3.4 Hz, 1 H), 2.48 (ddd, *J* = 15.0, 7.2, 1.4 Hz, 1 H), 1.98 (ddd, *J* = 13.9, 7.2, 3.8 Hz, 1 H), 1.56 (m, 2 H), 0.86 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.1, 144.6, 144.0, 139.0, 137.4, 137.3, 136.6, 133.9, 133.7, 128.9, 128.2, 127.9, 127.7, 127.6, 126.9, 126.4, 126.2, 125.4, 122.2, 85.2, 70.1, 40.8, 37.7, 22.9, 10.9.

MS–FAB: *m*/*z* (%) = 425.1 (75) [M^+ – OPr].

HRMS–FAB: *m*/*z* [M^+] calcd for $C_{26}H_{21}O_2N_2S$: 425.1318; found: 425.1312.

Anal. Calcd for $C_{29}H_{28}O_3N_2S$: C 71.87, H 5.82, N 5.78, S 6.62; found: C 71.57, H 6.13, N 5.53, S 6.24.

(2*R*,4*S*)-2-Cyclohexyloxy-4,6-diphenyl-1-[(8-quinolyl)sulfonyl]-1,2,3,4-tetrahydropyridine (23)

Yield: 70%; yellow solid; mp 78–80 °C; $[\alpha]_D^{20}$ –33 (*c* 0.15, $CHCl_3$); 88% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 17.6 (minor), t_R = 20.5 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.10 (dd, *J* = 4.2, 1.8 Hz, 1 H), 8.22 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.95 (m, 2 H), 7.52 (dd, *J* = 8.3, 4.1 Hz, 1 H), 7.36 (t, *J* = 7.8 Hz, 1 H), 7.20–7.03 (m, 8 H), 6.89 (m, 2 H), 6.46 (dd, *J* = 5.4, 3.6 Hz, 1 H), 5.75 (d, *J* = 3.4 Hz, 1 H), 4.11 (m, 1 H), 2.75 (m, 1 H), 2.46 (m, 1 H), 2.00 (m, 1 H), 1.85–1.55 (m, 4 H), 1.25–1.15 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.1, 144.9, 144.0, 139.1, 137.5, 137.0, 136.6, 133.8, 133.7, 128.8, 128.1, 128.0, 127.6, 127.5, 126.8, 126.3, 126.0, 125.3, 122.0, 81.6, 73.1, 40.7, 37.6, 33.2, 31.6, 29.1, 25.9, 22.6.

(2*R*,4*S*)-2-*tert*-Butoxy-4,6-diphenyl-1-[(8-quinolyl)sulfonyl]-1,2,3,4-tetrahydropyridine (24)

Yield: 35%; white solid; mp 66–68 °C; $[\alpha]_D^{20}$ –13 (*c* 0.4, $CHCl_3$); 68% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 98:2): t_R = 54.7 (minor), t_R = 78.1 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.07 (dd, *J* = 4.1, 1.7 Hz, 1 H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1 H), 8.01 (dd, *J* = 7.4, 1.3 Hz, 1 H), 7.92 (dd, *J* = 8.3, 1.3 Hz, 1 H), 7.49 (dd, *J* = 8.3, 4.3 Hz, 1 H), 7.36 (t, *J* = 7.7 Hz, 1 H), 7.26 (m, 2 H), 7.15–6.93 (m, 8 H), 6.37 (dd, *J* = 4.5, 3.0 Hz, 1 H), 5.65 (d, *J* = 3.4 Hz, 1 H), 2.76 (m, 1 H), 2.34 (ddd, *J* = 13.4, 8.5, 4.5 Hz, 1 H), 1.83 (ddd, *J* = 13.8, 4.3, 3.2 Hz, 1 H), 1.31 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.1, 145.4, 139.6, 139.4, 136.4, 134.2, 133.7, 128.3, 127.9, 127.6, 127.5, 127.1, 125.9, 125.4, 124.6, 122.0, 78.8, 75.7, 40.8, 37.4, 28.7.

MS–FAB: *m*/*z* (%) = 425.1 (100) [M^+ – O*t*-Bu].

HRMS–FAB: *m*/*z* [M^+] calcd for $C_{26}H_{21}O_2N_2S$: 425.1318; found: 425.1306.

(2*R*,3*S*,4*R*)-2-Ethoxy-4,6-diphenyl-3-methyl-1-[(8-quinolyl)sulfonyl]-1,2,3,4-tetrahydropyridine (25)

Yield: 67%; white solid; mp 139–140 °C; 4% ee; HPLC (AD) (0.8 mL/min; *n*-hexane–*i*-PrOH, 97:3): t_R = 40.0 (minor), t_R = 44.8 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.16 (dd, *J* = 4.1, 1.6 Hz, 1 H), 8.26 (dd, *J* = 8.2, 1.6 Hz, 1 H), 7.98 (dd, *J* = 7.3, 1.2 Hz, 1 H), 7.84 (dd, *J* = 8.2, 1.3 Hz, 1 H), 7.59 (dd, *J* = 8.3, 4.2 Hz, 1 H), 7.41–7.02 (m, 11 H), 5.96 (d, *J* = 2.6 Hz, 1 H), 5.63 (d, *J* = 3.2 Hz, 1 H), 4.10 (dq, *J* = 9.5, 6.7 Hz, 1 H), 3.83 (dq, *J* = 9.5, 6.7 Hz, 1 H), 3.49 (dd, *J* = 8.9, 3.2 Hz, 1 H), 2.55 (m, 1 H), 1.21 (t, *J* = 7.0 Hz, 3 H), 0.86 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.0, 143.9, 141.3, 139.1, 137.8, 136.4, 135.7, 133.6, 133.4, 131.4, 128.7, 127.5, 127.4, 127.3, 127.2, 126.1, 125.3, 123.1, 122.1, 87.5, 64.3, 43.3, 37.6, 15.2, 15.1.

2,3,3a,4,7,7a-Hexahydro-4,6-diphenyl-7-[(8-quinolyl)sulfonyl]furo[2,3-*b*]pyridine (26)

Yield: 83%; white solid; mp 65–67 °C; $[\alpha]_D^{20}$ –15 (*c* 0.26, $CHCl_3$); 58% ee; HPLC (AD) (1.0 mL/min; *n*-hexane–*i*-PrOH, 70:30): t_R = 26.9 (major), t_R = 38.8 (minor).

^{1}H NMR (300 MHz, $CDCL_3$): δ = 9.25 (dd, *J* = 4.2, 1.8 Hz, 1 H), 8.31 (dd, *J* = 8.3, 1.7 Hz, 1 H), 8.06 (dd, *J* = 7.5, 1.4 Hz, 1 H), 8.03 (dd, *J* = 8.1, 1.4 Hz, 1 H), 7.65 (dd, *J* = 8.3, 4.1 Hz, 1 H), 7.44 (t, *J* = 7.8 Hz, 1 H), 7.31–7.15 (m, 9 H), 6.95 (m, 2 H), 6.09 (dd, *J* = 3.9, 0.8 Hz, 1 H), 3.96 (m, 1 H), 3.63 (m, 1 H), 3.22 (m, 2 H), 1.89 (m, 1 H), 1.55 (m, 1 H).

^{13}C NMR (75 MHz, $CDCL_3$): δ = 151.1, 143.8, 141.0, 138.0, 137.6, 136.5, 133.6, 133.3, 128.9, 128.6, 128.0, 127.7, 127.6, 126.7, 126.6, 125.3, 125.2, 122.2, 90.3, 67.3, 52.4, 41.2, 26.8.

MS–FAB: *m*/*z* (%) = 469.0 (7) [M^+ + H].

HRMS–FAB: *m*/*z* [M^+] calcd for $C_{28}H_{25}O_3N_2S$: 469.1585; found: 469.1581.

(2*S*,4*S*)-4,6-Diphenyl-2-(4-methoxyphenyl)-1-[(8-quinolyl)sulfonyl]-1,2,3,4-tetrahydropyridine (27)

Yield: 58%; yellow solid; mp 78–80 °C; 5% ee; HPLC (OD) (1.0 mL/min; *n*-hexane–*i*-PrOH, 95:5): t_R = 54.7 (minor), t_R = 67.2 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.91 (dd, *J* = 4.1, 1.7 Hz, 1 H), 8.19 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.91 (ddd, *J* = 15.7, 8.2, 1.4 Hz, 2 H), 7.46 (dd, *J* = 8.4, 4.2 Hz, 1 H), 7.40–7.29 (m, 3 H), 7.15–6.95 (m, 7 H), 6.74–6.68 (m, 4 H), 6.44 (t, *J* = 7.4, Hz, 1 H), 5.69 (d, *J* = 3.5 Hz, 1 H), 3.71 (s, 3 H), 3.02 (m, 1 H), 2.65 (m, 1 H), 2.25 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.1, 144.9, 144.0, 139.1, 137.5, 137.0, 136.6, 133.8, 133.7, 128.8, 128.1, 128.0, 127.6, 127.5, 126.8, 126.3, 126.0, 125.3, 122.0, 81.6, 73.1, 40.7, 37.6, 33.2, 31.6, 29.1, 25.9, 22.6.

(2*R*,4*S*)-4-(4-Fluorophenyl)-6-phenyl-2-propoxy-1-[(8-quinolyl)sulfonyl]-1,2,3,4-tetrahydropyridine (36)
Yield: 75%; white solid; mp 62–64 °C; $[\alpha]_D^{20}$ –81 (*c* 0.4, $CHCl_3$); 92% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 31.9 (minor), t_R = 42.7 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.10 (dd, *J* = 4.2, 1.8 Hz, 1 H), 8.20 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.93 (m, 2 H), 7.52 (dd, *J* = 8.3, 4.1 Hz, 1 H), 7.42 (t, *J* = 7.8 Hz, 1 H), 7.16–7.01 (m, 5 H), 6.89 (m, 2 H), 6.78 (m, 2 H), 6.30 (dd, *J* = 5.1, 3.3 Hz, 1 H), 5.65 (d, *J* = 3.3 Hz, 1 H), 3.94 (dq, *J* = 9.4, 6.6 Hz, 1 H), 3.67 (dq, *J* = 9.4, 6.6 Hz, 1 H), 2.85 (td, *J* = 7.3, 3.4 Hz, 1 H), 2.46 (ddd, *J* = 13.6, 7.2, 5.6 Hz, 1 H), 2.02 (ddd, *J* = 13.9, 5.5, 3.4 Hz, 1 H), 1.52 (m, 2 H), 0.82 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.0, 144.0, 140.7, 138.9, 137.5, 137.2, 136.6, 133.8, 133.7, 133.5, 129.6, 129.5, 128.8, 127.7, 127.6, 127.0, 125.4, 124.8, 122.2, 114.9, 114.7, 84.7, 70.2, 39.7, 36.7, 22.9, 10.8.

MS–FAB: *m*/*z* (%) = 443.0 (78) [M^+ – OPr].

HRMS–FAB: *m*/*z* [M^+] calcd for $C_{29}H_{28}O_3N_2FS$: 503.18043; found: 503.18046.

(2*R*,4*S*)-4-(2-Naphthyl)-6-phenyl-2-propoxy-1-[(8-quinolyl)sulfonyl]-1,2,3,4-tetrahydropyridine (37)
Yield: 69%; white solid; mp 68–70 °C; $[\alpha]_D^{20}$ –97 (*c* 0.4, $CHCl_3$); 90% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 33.7 (minor), t_R = 42.1 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.20 (dd, *J* = 4.2, 1.8 Hz, 1 H), 8.32 (dd, *J* = 8.4, 1.7 Hz, 1 H), 8.06 (m, 2 H), 7.83 7.61 (m, 4 H), 7.51–7.33 (m, 4 H), 7.26–7.10 (m, 6 H), 6.46 (dd, *J* = 5.5, 3.8 Hz, 1 H), 5.92 (d, *J* = 3.3 Hz, 1 H), 4.10 (dq, *J* = 9.5, 6.6 Hz, 1 H), 3.79 (dq, *J* = 9.5, 6.6 Hz, 1 H), 3.04 (td, *J* = 7.3, 3.4 Hz, 1 H), 2.65 (ddd, *J* = 13.6, 7.5, 5.7 Hz, 1 H), 2.22 (ddd, *J* = 13.7, 7.1, 3.7 Hz, 1 H), 1.65 (m, 2 H), 0.94 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.1, 144.0, 142.2, 139.1, 137.5, 137.3, 136.6, 133.8, 133.7, 133.3, 132.1, 128.8, 127.8, 127.7, 127.6, 127.5, 127.0, 126.6, 126.3, 125.9, 125.5, 125.4, 122.2, 85.0, 70.2, 40.1, 37.7, 22.9, 10.9.

MS–FAB: *m*/*z* (%) = 475.1 (78) [M^+ – OPr].

HRMS–FAB: *m*/*z* [M^+] calcd for $C_{33}H_{31}O_3N_2S$: 535.20554; found: 535.20674.

Anal. Calcd for $C_{33}H_{31}O_3N_2S$: C, 74.13; H, 5.66; N, 5.24; S, 6.00. Found: C, 73.89; H, 5.94; N, 4.87; S, 5.69.

(2*R*,4*S*)-4-(4-Methoxyphenyl)-6-phenyl-2-propoxy-1-[(8-quinolyl)sulfonyl]-1,2,3,4-tetrahydropyridine (38)
Yield: 65%; white solid; mp 72–74 °C; $[\alpha]_D^{20}$ –27 (*c* 0.4, $CHCl_3$); 80% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 50.12. (minor), t_R = 55.5 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.09 (dd, *J* = 4.2, 1.8 Hz, 1 H), 8.21 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.96 (m, 2 H), 7.52 (dd, *J* = 8.3, 4.1 Hz, 1 H), 7.36 (t, *J* = 7.9 Hz, 1 H), 7.20–7.03 (m, 5 H), 6.75 (d, *J* = 8.7 Hz, 2 H), 6.62 (d, *J* = 8.7 Hz, 2 H), 6.36 (dd, *J* = 5.6, 3.8 Hz, 1 H), 5.65 (d, *J* = 3.3 Hz, 1 H), 3.99 (dq, *J* = 9.5, 6.7 Hz, 1 H), 3.69 (dq, *J* = 9.5, 6.7 Hz, 1 H), 3.64 (s, 3 H), 2.61 (td, *J* = 7.3, 3.4 Hz, 1 H), 2.46 (ddd, *J* = 13.5, 7.1, 5.6 Hz, 1 H), 1.95 (ddd, *J* = 13.7, 5.5, 3.4 Hz, 1 H), 1.54 (m, 2 H), 0.86 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.7, 148.7, 141.7, 136.7, 135.1, 134.7, 134.4, 131.6, 131.3, 126.5, 125.3, 124.6, 124.4, 123.0, 119.8, 111.2, 82.8, 67.8, 52.9, 38.5, 34.5, 20.6, 8.5.

Anal. Calcd for $C_{30}H_{30}N_2O_4S$: C, 70.01; H, 5.88; N, 5.44; S, 6.23. Found: C, 69.86; H, 6.01; N, 5.22; S, 5.89.

(2*R*,4*S*)-4-(2-Furyl)-6-phenyl-2-propoxy-1-[(8-quinolyl)sulfonyl]-1,2,3,4-tetrahydropyridine (39)
Yield: 52%; white solid; mp 56–58 °C; $[\alpha]_D^{20}$ –17 (*c* 0.4, $CHCl_3$); 77% ee; HPLC (AS) (1.0 mL/min; *n*-hexane–*i*-PrOH, 94:6): t_R = 71.12. (minor), t_R = 74.5 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.06 (dd, *J* = 4.2, 1.8 Hz, 1 H), 8.17 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.90 (m, 2 H), 7.50 (dd, *J* = 8.3, 4.1 Hz, 1 H), 7.31 (t, *J* = 7.9 Hz, 1 H), 7.14–7.01 (m, 6 H), 6.30 (dd, *J* = 4.7, 3.5 Hz, 1 H), 6.11 (dd, *J* = 3.1, 1.9 Hz, 1 H), 5.81 (d, *J* = 2.5, 1 H), 5.67 (d, *J* = 3.4 Hz, 1 H), 3.89 (dq, *J* = 9.4, 6.6 Hz, 1 H), 3.65 (dq, *J* = 9.4, 6.6 Hz, 1 H), 3.04 (td, *J* = 8.0, 5.2 Hz, 1 H), 2.42 (ddd, *J* = 13.9, 7.8, 5.6 Hz, 1 H), 1.95 (ddd, *J* = 13.9, 5.3, 3.4 Hz, 1 H), 1.50 (m, 2 H), 0.79 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2, 151.0, 143.8, 140.6, 138.9, 137.4, 137.1, 136.5, 133.7, 128.8, 127.7, 127.5, 127.3, 127.2, 125.3, 122.1, 121.1, 110.1, 104.8, 84.4, 69.9, 35.8, 30.9, 22.9, 10.8.

MS–FAB: *m*/*z* (%) = 416.1 (100) [M^+ – OPr].

HRMS–FAB: *m*/*z* [M^+] calcd for $C_{27}H_{27}N_2O_4S$: 475.1613; found: 475.1610.

(2*R*,4*S*)-4-*tert*-Butyl-6-phenyl-2-propoxy-1-[(8-quinolyl)sulfonyl]-1,2,3,4-tetrahydropyridine (40)
Yield: 61%; white solid; mp 65–67 °C; $[\alpha]_D^{20}$ 82 (*c* 0.5, $CHCl_3$); 84% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 11.6 (major), t_R = 15.9 (minor).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.09 (dd, *J* = 4.2, 1.8 Hz, 1 H), 8.16 (m, 2 H), 7.95 (d, *J* = 8.1 Hz, 1 H), 7.49 (m, 2 H), 7.38–7.15 (m, 5 H), 7.00 (m, 1 H), 6.57 (dd, *J* = 7.7, 5.8 Hz, 1 H), 5.78 (d, *J* = 4.0 Hz, 1 H), 4.12 (dq, *J* = 9.4, 6.6 Hz, 1 H), 3.79 (dq, *J* = 9.4, 6.6 Hz, 1 H), 2.25 (m, 1 H), 1.67 (m, 1 H), 1.22 (m, 1 H), 0.98 (t, *J* = 7.3 Hz, 3 H), 0.82 (m, 2 H), 0.26 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.1, 144.2, 139.3, 138.3, 137.0, 136.6, 134.2, 133.5, 129.2, 128.9, 127.8, 127.7, 127.3, 126.1, 125.2, 121.9, 87.5, 69.9, 42.1, 36.9, 30.3, 26.8, 22.9, 10.9.

(2*R*,4*S*)-6-(4-Chlorophenyl)-4-phenyl-2-propoxy-[(8-quinolyl)sulfonyl]-1,2,3,4-tetrahydropyridine (41)
Yield: 73%; white solid; mp 58–60 °C; $[\alpha]_D^{20}$ –35 (*c* 0.4, $CHCl_3$); 90% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 30.8 (major), t_R = 37.0 (minor).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.10 (dd, *J* = 4.2, 1.8 Hz, 1 H), 8.24 (dd, *J* = 8.3, 1.7 Hz, 1 H), 8.02 (m, 2 H), 7.53 (dd, *J* = 8.4, 4.2 Hz, 1 H), 7.42 (m, 1 H), 7.28–7.0 (m, 7 H), 6.83 (m, 2 H), 6.34 (dd, *J* = 5.6, 3.8 Hz, 1 H), 5.74 (d, *J* = 3.4 Hz, 1 H), 3.96 (dq, *J* = 9.5, 6.7 Hz, 1 H), 3.67 (dq, *J* = 9.5, 6.7 Hz, 1 H), 2.63 (td, *J* = 7.3, 3.4 Hz, 1 H), 2.44 (ddd, *J* = 13.6, 7.2, 5.6 Hz, 1 H), 1.99 (ddd, *J* = 13.5, 7.2, 3.8 Hz, 1 H), 1.56 (m, 2 H), 0.86 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.1, 144.2, 143.9, 137.6, 137.3, 136.7, 136.3, 133.9, 133.8, 133.5, 128.8, 128.2, 128.1, 127.9, 127.8, 126.9, 126.4, 125.4, 122.2, 85.2, 70.1, 40.7, 37.6, 22.9, 10.9.

MS–FAB: *m*/*z* (%) = 459.1 (100) [M^+ – OPr].

HRMS–FAB: *m*/*z* [M^+] calcd for $C_{29}H_{28}O_3N_2ClS$: 519.1503; found: 519.1547.

Anal. Calcd for $C_{29}H_{27}O_3N_2ClS$: C, 67.10; H, 5.29; N, 5.40; S, 6.18. Found: C, 67.48; H, 5.53; N, 5.03; S, 5.84.

(2*R*,4*S*)-4-Phenyl-2-propoxy-1-[(8-quinolyl)sulfonyl]-6-[4-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydropyridine (42)
Yield: 69%; white solid; mp 68–70 °C; $[\alpha]_D^{20}$ –43 (*c* 0.4, $CHCl_3$); 91% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 37.8 (major), t_R = 40.4 (minor).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.09 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.23 (dd, *J* = 8.3, 1.6 Hz, 1 H), 7.99 (m, 2 H), 7.55 (dd, *J* = 8.3, 4.1

Hz, 1 H), 7.44–7.28 (m, 6 H), 7.14–7.02 (m, 3 H), 6.83 (m, 2 H), 6.32 (dd, *J* = 5.5, 3.6 Hz, 1 H), 5.83 (d, *J* = 3.4 Hz, 1 H), 3.98 (dq, *J* = 9.5, 6.7 Hz, 1 H), 3.69 (dq, *J* = 9.5, 6.7 Hz, 1 H), 2.69 (td, *J* = 7.2, 3.4 Hz, 1 H), 2.41 (ddd, *J* = 13.6, 7.6, 5.6 Hz, 1 H), 1.99 (ddd, *J* = 13.8, 6.9, 3.7 Hz, 1 H), 1.55 (m, 2 H), 0.86 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.1, 144.1, 144.0, 142.7, 137.2, 136.7, 136.3, 133.9, 133.8, 129.3, 128.9, 128.3, 128.1, 127.9, 127.0, 126.4, 125.4, 124.7, 124.6, 122.3, 85.1, 70.3, 40.3, 37.7, 22.9, 10.8.

MS–FAB: *m*/*z* (%) = 494.1 (100) [M^+ – OPr].

HRMS–FAB: *m*/*z* [M^+] calcd for $C_{30}H_{28}F_3N_2O_3S$: 553.1694; found: 553.1691.

(2*R*,4*S*)-6-(2-Naphthyl)-4-phenyl-2-propoxy-1-[(8-quinolyl)sulfonyl]-1,2,3,4-tetrahydropyridine (43)

Yield: 67%, white solid; mp 78–80 °C; 6% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 45.8 (major), t_R = 60.2 (minor).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.13 (dd, *J* = 4.2, 1.8 Hz, 1 H), 8.21 (dd, *J* = 8.4, 1.7 Hz, 1 H), 7.89 (m, 2 H), 7.69 (m, 1 H), 7.60–7.41 (m, 4 H), 7.40–7.28 (m, 3 H), 7.26–7.03 (m, 4 H), 6.88 (m, 2 H), 6.45 (dd, *J* = 5.5, 3.8 Hz, 1 H), 5.90 (d, *J* = 3.3 Hz, 1 H), 4.09 (dq, *J* = 9.5, 6.6 Hz, 1 H), 3.75 (dq, *J* = 9.5, 6.6 Hz, 1 H), 2.77 (td, *J* = 7.3, 3.4 Hz, 1 H), 2.57 (ddd, *J* = 13.6, 7.5, 5.7 Hz, 1 H), 2.06 (ddd, *J* = 13.7, 7.1, 3.7 Hz, 1 H), 1.59 (m, 2 H), 0.88 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.1, 144.5, 137.4, 137.2, 136.6, 136.4, 133.9, 133.6, 133.0, 132.8, 128.8, 128.2, 128.0, 127.9, 127.5, 127.1, 127.0, 126.3, 125.8, 125.6, 125.3, 125.2, 124.6, 122.1, 85.2, 70.2, 40.8, 37.8, 23.0, 10.9.

(2*R*,4*S*)-6-(4-Chlorophenyl)-2-propoxy-4-styryl-1-[(8-quinolyl)sulfonyl]-1,2,3,4-tetrahydropyridine (46)

Yield: 63%; white solid; mp 65–67 °C; $[\alpha]_D^{20}$ –140 (*c* 0.2, $CHCl_3$); 92% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 28.7 (major), t_R = 38.1 (minor).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.06 (dd, *J* = 4.2, 1.8 Hz, 1 H), 8.19 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.95 (dd, *J* = 8.1, 1.3 Hz, 1 H), 7.86 (dd, *J* = 7.5, 1.4 Hz, 1 H), 7.51 (dd, *J* = 8.3, 4.1 Hz, 1 H), 7.35 (t, *J* = 7.9 Hz, 1 H), 7.20–7.15 (m, 4 H), 7.00–6.95 (m, 4 H), 6.16 (m, 3 H), 5.36 (d, *J* = 3.6 Hz, 1 H), 3.87 (dq, *J* = 9.4, 6.6 Hz, 1 H), 3.70 (dq, *J* = 9.4, 6.6 Hz, 1 H), 2.66 (m, 1 H), 2.13 (ddd, *J* = 14.0, 7.7, 3.8 Hz, 1 H), 1.96 (dt, = 14.0 and 2.7 Hz, 1 H), 1.55 (m, 3 H), 0.87 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.1, 143.9, 137.9, 137.4, 136.5, 135.0, 133.8, 133.6, 133.4, 133.3, 129.2, 128.8, 128.6, 128.5, 128.4, 128.0, 127.4, 126.0, 125.3, 122.4, 122.2, 84.3, 70.1, 35.6, 35.1, 23.1, 10.9.

(2*R*,4*S*)-6-(4-Cyanophenyl)-2-propoxy-4-styryl-1-[(8-quinolyl)sulfonyl]-1,2,3,4-tetrahydropyridine (47)

Yield: 70%; yellow solid; mp 85–86 °C; $[\alpha]_D^{20}$ –102 (*c* 0.4, $CHCl_3$); 92% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 45.9 (minor), t_R = 53.5 (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.06 (dd, *J* = 4.2, 1.8 Hz, 1 H), 8.21 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.96 (m, 2 H), 7.52 (dd, *J* = 8.3, 4.1 Hz, 1 H), 7.40 (t, *J* = 7.8 Hz, 1 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 7.15 (m, 5 H), 6.16 (m, 2 H), 6.05 (m, 1 H), 5.51 (d, *J* = 3.6 Hz, 1 H), 3.86 (dq, *J* = 9.4, 6.6 Hz, 1 H), 3.68 (dq, *J* = 9.4, 6.6 Hz, 1 H), 2.62 (m, 1 H), 1.92 (m, 1 H), 1.55 (m, 3 H), 0.87 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.2, 144.4, 143.9, 137.2, 136.6, 134.9, 134.2, 133.3, 133.0, 131.5, 129.6, 128.9, 128.5, 127.7, 127.2, 126.0, 125.4, 124.7, 122.4, 119.0, 110.9, 84.3, 70.2, 35.7, 34.7, 23.0, 10.9.

(2*R*,4*S*)-4-Phenyl-2-propoxy-4-styryl-1-[(8-quinolyl)sulfonyl]-1,2,3,4-tetrahydropyridine (49)

Yield: 68%; yellow solid; mp 80–81 °C; $[\alpha]_D^{20}$ –13 (*c* 0.4, $CHCl_3$); 20% ee; HPLC (AD) (0.7 mL/min; *n*-hexane–*i*-PrOH, 90:10): t_R = 24.2 (major), t_R = 43.4 (minor).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.05 (dd, *J* = 4.2, 1.8 Hz, 1 H), 8.35 (dd, *J* = 8.3, 1.7 Hz, 1 H), 8.02 (d, *J* = 8.3 Hz, 1 H), 7.93 (d, *J* = 8.4 Hz, 1 H), 7.52 (dd, *J* = 8.3, 4.1 Hz, 1 H), 7.40 (t, *J* = 7.8 Hz, 1 H), 7.21–7.00 (m, 7 H), 6.90 (m, 3 H), 6.36 (d, *J* = 16.0 Hz, 1 H), 6.25 (dd, *J* = 5.0, 4.3 Hz, 1 H), 5.70 (d, *J* = 3.5 Hz, 1 H), 3.78 (dq, *J* = 9.4, 6.6 Hz, 1 H), 3.50 (dq, *J* = 9.4, 6.6 Hz, 1 H), 2.70 (m, 1 H), 2.52 (m, 1 H), 2.03 (ddd, *J* = 13.7, 6.0, 3.3 Hz, 1 H), 1.49 (m, 3 H), 0.82 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.2, 144.7, 143.9, 137.4, 136.9, 136.7, 135.3, 134.3, 133.9, 129.4, 128.9, 128.5, 128.2, 127.9, 127.6, 127.4, 126.6, 125.5, 123.2, 122.2, 85.0, 69.7, 39.4, 42.1, 26.0, 10.8.

(2*R*,4*S*)-2-Hydroxy-4,6-diphenyl-1-[(8-quinolyl)sulfonyl]-1,2,3,4-tetrahydropyridine (51)

To a soln of **21** (91% ee, 99 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ (0.026 mL, 0.21 mmol). The mixture was stirred at 0 °C for 2 h before it was quenched with sat. aq NH_4Cl (10 mL). The mixture was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (deactivated silica gel, *n*-hexane–EtOAc, 3:1); this afforded **51**.

Yield: 82 mg (88%); white solid; mp 67–69 °C; $[\alpha]_D^{20}$ +17 (*c* 0.4, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.00 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.22 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.84 (dd, *J* = 7.4, 1.3 Hz, 1 H), 7.54 (dd, *J* = 8.2, 1.3 Hz, 1 H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1 H), 7.21–7.02 (m, 6 H), 6.91–6.62 (m, 5 H), 5.65 (s, 1 H), 5.05 (dd, *J* = 2.7, 1.3 Hz, 1 H), 3.83 (ddd, *J* = 9.5, 6.7, 2.8 Hz, 1 H), 2.51 (dddd, *J* = 14.0, 6.7, 3.0, 1.4 Hz, 1 H), 2.08 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.1, 144.7, 144.3, 139.0, 137.5, 137.3, 135.9, 133.9, 133.2, 128.9, 128.2, 128.0, 127.7, 127.6, 126.9, 126.4, 126.2, 125.4, 122.2, 85.2, 71.4, 45.2, 33.4.

Tetracyclic Compounds 52–54; General Procedure

To a soln of **21** (91% ee, 99 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ (0.026 mL, 0.21 mmol). The mixture was stirred at 0 °C for 2 h before it was cooled to –78 °C and treated with the nucleophile (1.2 equiv). The mixture was stirred for 30 min at –78 °C, and then quenched with sat. aq. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (deactivated silica gel, *n*-hexane–EtOAc, 3:1).

Compound 52

Yield: 82%; white solid; mp 76–78 °C; $[\alpha]_D^{20}$ –203 (*c* 0.4, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15–6.94 (m, 12 H), 6.78 (dd, *J* = 7.4, 1.4 Hz, 1 H), 6.44 (t, *J* = 7.5 Hz, 1 H), 6.18 (m, 1 H), 5.59 (ddd, *J* = 7.9, 4.9, 2.9 Hz, 1 H), 5.21 (dd, *J* = 2.7, 0.8 Hz, 1 H), 5.16 (dd, *J* = 6.8, 2.5 Hz, 1 H), 4.01 (ddd, *J* = 15.4, 4.9, 1.2 Hz, 1 H), 3.82 (ddd, *J* = 15.3, 2.6, 0.8 Hz, 1 H), 3.60 (m, 1 H), 2.73 (dtd, *J* = 13.9, 6.1, 1.0 Hz, 1 H), 1.91 (ddd, *J* = 14.2, 8.4. and 2.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.0, 140.8, 138.0, 136.9, 130.8, 128.8, 127.9, 127.7, 127.6, 127.5, 127.4, 127.0, 125.8, 123.7, 123.4, 122.6, 121.0, 119.5, 117.4, 72.9, 45.6, 36.4, 31.6.

MS–FAB: *m*/*z* (%) = 427.1 (100) [M^+ + H].

HRMS–FAB: *m/z* [M$^+$] calcd for $C_{26}H_{23}N_2O_2S$: 427.1403; found: 427.1435.

Compound 53a

Yield: 71%, white solid; mp 83–85 °C; $[\alpha]_D^{20}$ –323 (*c* 0.34, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.18 (m, 16 H), 6.94 (dd, *J* = 7.4, 1.5 Hz, 1 H), 6.63 (t, *J* = 7.6 Hz, 1 H), 6.22 (dd, *J* = 10.0, 1.5 Hz, 1 H), 5.77 (d, *J* = 3.8 Hz, 1 H), 5.65 (dd, *J* = 9.8, 4.9 Hz, 1 H), 5.25 (dd, *J* = 5.1, 1.1 Hz, 1 H), 4.20 (m, 1 H), 3.66 (ddd, *J* = 10.5, 5.0, 2.2 Hz, 1 H), 2.80 (dtd, *J* = 14.2, 5.2, 1.2 Hz, 1 H), 2.04 (ddd, *J* = 14.2, 10.6. and 2.2 Hz, 1 H), 1.15 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.8, 139.8, 138.1, 137.4, 130.8, 128.8, 128.3, 128.0, 127.8, 127.5, 127.0, 124.1, 123.8, 122.0, 118.5, 117.2, 70.8, 49.2, 36.1, 32.4, 17.7.

Compound 54a

Yield: 60%; white solid; mp 79–81 °C; $[\alpha]_D^{20}$ –354 (*c* 0.3, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.12 (m, 11 H), 7.01 (dd, *J* = 7.4, 1.4 Hz, 1 H), 6.61 (t, *J* = 7.6 Hz, 1 H), 6.36 (d, *J* = 9.6 Hz, 1 H), 5.82 (dd, *J* = 9.6, 5.9 Hz, 1 H), 5.75 (dd, *J* = 5.1, 2.2 Hz, 1 H), 5.12 (dd, *J* = 1.9, 1.5 Hz, 1 H), 4.20 (m, 1 H), 3.66 (ddd, *J* = 10.5, 5.0, 2.2 Hz, 1 H), 2.80 (dtd, *J* = 14.2, 5.2, 1.2 Hz, 1 H), 2.04 (ddd, *J* = 14.2, 10.6. and 2.2 Hz, 1 H), 1.15 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.8, 139.8, 138.1, 137.4, 130.8, 128.8, 128.3, 128.0, 127.8, 127.5, 127.0, 124.1, 123.8, 122.0, 118.5, 117.2, 70.8, 49.2, 36.1, 32.4, 17.7.

Anal. Calcd for $C_{27}H_{24}N_2O_2S$: C, 73.61; H, 5.49; N, 6.36; S, 7.28. Found: C, 73.28; H, 5.68; N, 6.04; S, 7.89.

Compound 54b

Yield: 15%; white solid; mp 83–85 °C; $[\alpha]_D^{20}$ –134 (*c* 0.4, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.15 (m, 11 H), 6.94 (dd, *J* = 7.2, 1.4 Hz, 1 H), 6.64 (dd, *J* = 7.8, 7.3 Hz, 1 H), 6.23 (d, *J* = 9.8 Hz, 1 H), 5.81 (d, *J* = 3.6 Hz, 1 H), 5.62 (dd, *J* = 9.7, 5.4 Hz, 1 H), 5.18 (dd, *J* = 11.2, 3.1 Hz, 1 H), 4.09 (m, 1 H), 3.76 (ddd, *J* = 10.4, 7.0, 3.6 Hz, 1 H), 2.74 (m, 1 H), 2.30 (ddd, *J* = 13.4, 7.1, 3.3 Hz, 1 H), 1.30 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.0, 140.2, 138.3, 136.9, 131.8, 128.8, 127.8, 127.7, 127.6, 127.2, 127.4, 127.0, 125.8, 123.7, 123.4, 122.6, 121.0, 119.5, 117.4, 72.9, 36.4, 31.4, 18.3.

Acknowledgment

The 'Ministerio de Ciencia e Innovación' (MICINN, BQU2003-0508), and 'Consejería de Educación de la Comunidad Autónoma de Madrid' (CAM) and the UAM (Project CCG07-UAM/PPQ-1799) are gratefully acknowledged for financial support. J.E. thanks the MICINN for a Predoctoral Fellowship. A generous allocation of computer time at the 'Centro de Computación Científico-UAM' is also acknowledged.

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(24) In agreement with literature data, only decomposition products were obtained in the reactions of *N*-tosyl-, *N*-(2-thienylsulfonyl)-, and *N*-(2-pyridylsulfonyl)imines of benzaldehyde with **5** in the presence of 10 mol% of $Cu(OTf)_2$ after 48 hours at room temperature.

(25) Amounts of dienophile lower than 20 equivalents led to incomplete conversions.

(26) Similar enantioselectivities were obtained in other solvents, such as toluene (61% ee), 1,2-dichloroethane (62% ee), tetrahydrofuran (58% ee), or 1,4-dioxane (60% ee).

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(32) Unit cell parameters: a = 9.4345 (2), b = 11.1796 (3), c = 21.8461 (6); space group $P2_12_12_1$. CCDC 641861 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(33) Critical NOE contacts for **54a** and **54b** are shown in Figure 3 below.

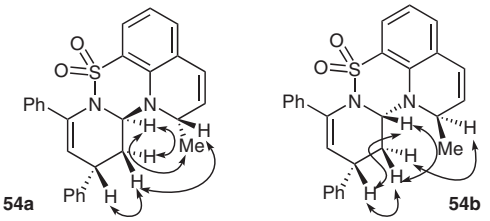

Figure 3

(34) The supplementary crystallographic data for **54b** can be found in the Supporting Information of ref. 22.

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