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General Asymmetric Hydrogenation of 2-Alkyl- and 2-Aryl-Substituted Quinoxaline Derivatives Catalyzed by Iridium-Difluorphos: Unusual Halide Effect and Synthetic Application

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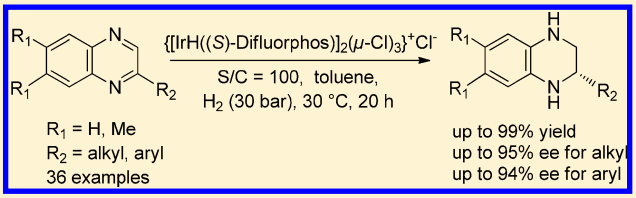
Supporting Information

ABSTRACT: A general asymmetric hydrogenation of a wide range of 2-alkyl- and 2-aryl-substituted quinoxaline derivatives catalyzed by an iridium−difluorphos complex has been developed. Under mild reaction conditions, the corresponding biologically relevant 2-substituted-1,2,3,4-tetrahydroquinoxaline units were obtained in high yields and good to excellent enantioselectivities up to 95%. With a catalyst ratio of S/C = 1000 and on a gram scale, the catalytic activity of the Ir−difluorphos complex was maintained showing its potential value. Finally, we demonstrated the application of our process in the synthesis of compound (*S*)-**9**, which is an inhibitor of cholesteryl ester transfer protein (CETP).



INTRODUCTION

Asymmetric hydrogenation of prochiral unsaturated compounds using inexpensive, clean molecular hydrogen and small amounts of a chiral catalyst is considered as one of the most efficient and atom economical ways to produce a wide range of enantioenriched compounds on large scale without forming any waste.[1] Asymmetric hydrogenation of ketones, imines and olefins, has been intensively studied and usually provided high levels of selectivity, whereas asymmetric hydrogenation of heteroaromatic compounds has been much less explored until very recently, because of the high stability of heteroarenes and deactivation and/or poisoning of the catalysts by the presence of heteroatoms. Despite these challenges, significant progress in the development of transition-metal-catalyzed asymmetric hydrogenation of heteroaromatic compounds[2] such as quinolines,[3] indoles,[4] pyrroles,[5] furanes,[6] pyridines,[7] and pyrazines[8] has been made in the past decade. In sharp contrast, asymmetric hydrogenation of quinoxaline derivatives[9] has been rarely explored, despite the fact that tetrahydroquinoxaline cores are subunits of many biologically active compounds (Figure 1).[10] In 1987, Murata et al.[9a] described the first example of asymmetric hydrogenation of 2-methylquinoxaline **1a** using an hydridorhodium catalyst containing the (+)-DIOP ligand, resulting in the formation of 2-methyltetrahydroquinoxaline **2a** in 72% yield but with only 3% of ee. A great improvement for the same substrate was reported by Bianchini et al.[9b] in 1998, using an orthometalated iridium dihydride complex, providing the hydrogenated product **2a** in good enantioselectivity, up to 90%, but with a modest conversion of 54%. Three years later, the same group reported the synthesis of new iridium and rhodium complexes bearing (*R*,*R*)-BPP-BzP as a ligand, which allowed the formation of **2a** in excellent yields up to 93% but with considerably lower ee values of 23 and 11%, respectively.[9c] In 2003, Henschke et al.[9d] showed that a wide range of ruthenium complexes of the type [$RuCl_2$(diamine)(diphosphine)] can be efficiently used to hydrogenate **1a**. For example, complete conversion and 73% ee were obtained when the electron-rich (*S*)-Xyl-HexaPHEMP ligand was used in combination with the chiral (*S*,*S*)-DACH diamine. Similar results were subsequently described in 2006 by Chan et al.[9e] using the [Ir(μ-Cl)(cod)]$_2$/PQ-Phos/I_2 catalyst system (99% conv, 80% ee). As can be seen from the above examples, the substrate scope for the asymmetric hydrogenation of quinoxaline derivatives described so far in the literature was restricted to 2-methylquinoxaline **1a**. During the course of our study, Xu, Fan, and Chan[9f] reported in 2009 the first general asymmetric hydrogenation of a wide range of 2-alkyl-substituted quinoxaline derivatives, with good to excellent enantioselectivities ranging from 85 to 98%, using the [Ir(μ-Cl)(cod)]$_2$/H_8−Binapo/I_2 catalyst generated in situ. Simultaneously, de Vries, Minnaard, and Feringa[9g] described comparable results in terms of both reactivity and selectivity using a combination of [Ir(μ-Cl)(cod)]$_2$ and their monodentate phosphoramidite PipPhos ligand in the presence of piperidine hydrochloride as additive (75 to 96% ee).

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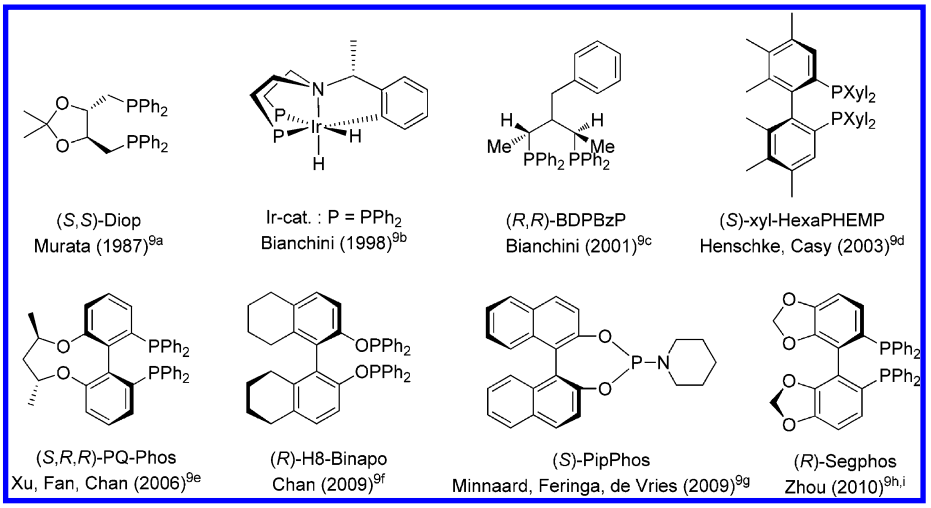


Figure 1. Previous ligands used for the asymmetric hydrogenation of quinoxalines.

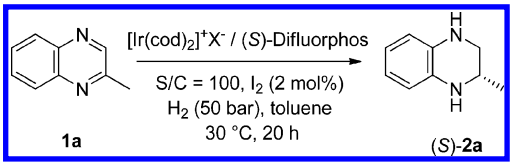
Although the above catalytic systems showed high selectivity for asymmetric hydrogenation of 2-alkyl-substituted quinoxalines, they turned out to be less efficient for the reduction of 2-aryl-substituted quinoxaline derivatives. Indeed, 84% ee was obtained for the hydrogenation of 2-phenylquinoxaline and 2-*o*′-MeO-phenylquinoxaline substrates using $[Ir(\mu\text{-Cl})(cod)]_2$/$H_8$−Binapo/$I_2$,[9f] whereas an enantiomeric excess of 86% was achieved with $[Ir(\mu\text{-Cl})(cod)]_2$/PipPhos/piperidine·HCl.[9g] Using $[Ir(\mu\text{-Cl})(cod)]_2$/SegPhos as catalyst in the presence of Brønsted acid, a moderate ee of 65% was obtained for the hydrogenation of 2-phenylquinoxaline by Zhou et al.[9h,i] In 2011, Zhou and Fan disclosed an efficient metal/Brønsted acid relay catalysis for asymmetric reduction of 2-aryl quinoxalines through convergent disproportionation of dihydroquinoxalines with good to excellent enantioselectivities ranging from 83 to 96%.[9k] Fan and co-workers[9l] also reported a highly efficient asymmetric transfer hydrogenation of 2-alkyl- and 2-aryl-substituted quinoxalines by using a cationic Ru(η^6-cymene)-(monosulfonylated diamine)(BarF) system under 80 atm of H_2 pressure (94 to 99% ee). In addition to metal-catalyzed asymmetric hydrogenation, a highly enantioselective organocatalyzed transfer hydrogenation of 2-aryl quinoxalines using Hantzsh esters as a hydride source has also been developed by Rueping et al. (80 to 98% ee).[9j]

In previous communications,[11,12] we demonstrated that Difluorphos was an efficient ligand for the iridium-catalyzed asymmetric hydrogenation of 2-substituted quinoxaline[11] and quinoline[12] derivatives. In the present study, we wish to report the full details of both our investigations in designing an optimized Ir/ligand catalyst for the enantioselective hydrogenation of a full set of 2-alkyl- and 2-aryl-substituted quinoxalines and a straightforward synthesis of an inhibitor of cholesteryl ester transfer protein (CETP) developed by Pfizer for the treatment of diverse diseases including atherosclerosis and obesity.[10a]

RESULTS AND DISCUSSION

On the basis of the good results previously obtained with Difluorphos for the asymmetric hydrogenation of heteroaromatic compounds,[11,12] we started our investigation by searching for the best catalyst system using Difluorphos as chiral auxiliary to perform asymmetric hydrogenation of 2-methylquinoxaline **1a** as a model substrate. We focused on optimizing a few parameters such as metal precursor, additive, solvent, H_2 pressure, reaction temperature, catalyst loading, and substrates. At first, we examined the effect of the counterion.[13] Several cationic iridium precursors bearing weakly coordinating counterions such as BF_4^-, NO_3^-, OTf^-, PF_6^-, SbF_6^-, and $BarF^-$ were prepared and tested in the hydrogenation of 2-methylquinoxaline **1a** (Table 1). The reaction was carried out in toluene, at 50 bar of hydrogen pressure and 30 °C, using 1 mol % of catalyst, prepared in situ from $[Ir(cod)_2]^+X^-$ with (*S*)-Difluorphos ligand in the presence of 2 mol % of I_2 as additive.

Table 1. Iridium Precursor Effect[a]



entry	iridium precursor	conv (%)[b]	ee (%)[c]
1	$[Ir(\mu\text{-Cl})(cod)]_2$	>99	89
2	$[Ir(cod)_2]^+BF_4^-$	63	40
3	$[Ir(cod)_2]^+NO_3^-$	71	40
4	$[Ir(cod)_2]^+OTf^-$	>99	50
5	$[Ir(cod)_2]^+PF_6^-$	>99	73
6	$[Ir(cod)_2]^+SbF_6^-$	>99	76
7	$[Ir(cod)_2]^+BarF^-$	>99	86

[a]Reaction conditions: **1a** (1.0 mmol). [b]Conversion was determined by ^1H NMR of the crude product. [c]Enantiomeric excess (ee) was determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC) on a Chiralcel AD-H column.

The results listed in Table 1 clearly indicated that the stereochemical outcome of the reaction is strongly dependent on the nature of the cationic iridium precursor. When $[Ir(cod)_2]^+BF_4^-$ or $[Ir(cod)_2]^+NO_3^-$ were used, both conversions and enantioselectivities decreased significantly compared to the results obtained with the neutral $[Ir(\mu\text{-Cl})(cod)]_2$ complex (Table 1, compare entries 1 vs 2, 3). The $[Ir(cod)_2]^+OTf^-$ precursor gave full conversion but with only a moderate enantioselectivity of 50% (Table 1, entry 4). A better catalytic activity was achieved when $[Ir(cod)_2]^+PF_6^-$, $[Ir(cod)_2]^+SbF_6^-$, and $[Ir(cod)_2]^+BarF^-$ were used, providing the 2-methyl tetrahydroquinoxaline **2a** in 73, 76, and 86% ee respectively, with complete conversion (Table 1, entries 5−7). Finally, from this iridium catalyst

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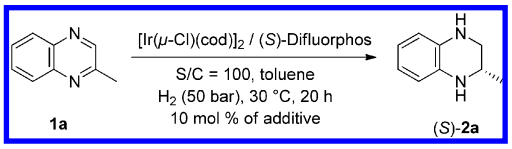
screening, $[Ir(\mu\text{-}Cl)(cod)]_2$ emerged as the most suitable metal precursor in terms of both reactivity and selectivity (Table 1, entry 1).

It is well-known that additives could play a crucial role in improving the reactivity and selectivity of many asymmetric reactions.[14] We and others have recently reported that acids can be used as additives to improve the stereochemical outcome in ruthenium-catalyzed asymmetric hydrogenation of α-ketoesters[15] and β-ketoesters.[16] Accordingly, we decided to evaluate the effect of such additives for the asymmetric hydrogenation of **1a** under the above reaction conditions. As demonstrated in Table 2, good to excellent conversions were obtained, but the

Table 2. Effect of Acids as Additives[a]



entry	additive[b]	conv (%)[c]	ee (%)[d]
1[e]	I_2	>99	89
2	PPTS	7	19
3	HI	>99	74
4	HCl	>99	81
5	HBr	>99	84
6	TsOH	>99	85
7	CH_3CO_2H	>99	86
8	H_2SO_4	90	89
9	HBF_4	>99	89
10	Piperidine·HCl	>99	90

[a]Reaction conditions: **1a** (1.0 mmol). [b]10 mol % of additive. [c]Conversion was determined by ^1H NMR of the crude product. [d]Enantiomeric excess (ee) was determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC) on a Chiralcel AD-H column. [e]2 mol % of iodine were used.

selectivity of the reaction was greatly influenced by the nature of the acids. Very low reactivity and enantiomeric excess were obtained with PPTS, while the use of aqueous HX (X = Br, Cl, I), TsOH, or CH_3COOH slightly decreased the ee values of the hydrogenated product **2a** (Table 2, compare entries 1 vs 2−7). When the reaction was performed in the presence of H_2SO_4 or HBF_4, no difference was observed regarding the selectivity compared to the result obtained with iodine (Table 2, entries 8, 9 vs 1). Finally, piperidine·HCl salt was found to be an efficient additive, since it afforded the best result in terms of enantioselectivity, providing the desired 2-methyl-tetrahydroquinoxaline **2a** in 90% ee, with complete conversion (Table 2, entry 10).

These results were in agreement with those previously reported by de Vries, Minnaard, and Feringa[9g] considering the asymmetric hydrogenation of quinoline and quinoxaline derivatives using the $[Ir(\mu\text{-}Cl)(cod)]_2$/PipPhos/piperidine·HCl catalytic system. We therefore performed a screening of a range of chiral ligands (Figure 2) and a comparative study between piperidine·HCl and I_2 as additives (Table 3). The reactions were conducted in dichloromethane at 60 °C under 25 bar of hydrogen pressure and with either 10 mol % of piperidine·HCl salt or 2 mol % of I_2 using 1 mol % of catalyst, prepared in situ by mixing $[Ir(\mu\text{-}Cl)(cod)]_2$ and the corresponding **L1**−**L11** ligands (Figure 2). Excellent conversions were obtained with an enantioselectivity depending on the nature of the considered ligand. This screening demonstrated that spiromonodentate

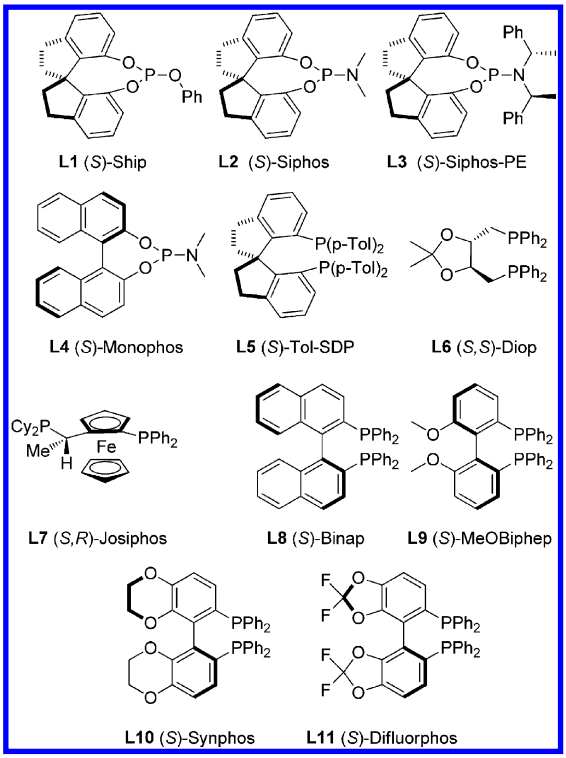
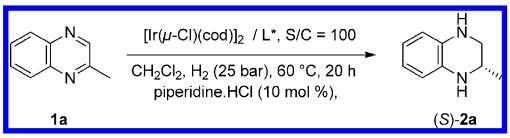


Figure 2. Ligands **L1**−**L11** used in this study.

Table 3. Screening of Ligands[a]



entry	ligand[b]	ee (%)[c]	ee (%)[d] with I_2
1	**L1** (*S*)-Ship	62	14
2	**L2** (*S*)-Siphos	76	12
3	**L3** (*S*)-Siphos-PE	33	12
4	**L4** (*R*)-Monophos	82	18
5	**L5** (*S*)-tol-SDP	33	13
6	**L6** (*S,S*)-Diop	49	38
7	**L7** (*S,R*)-Josiphos	82	48
8	**L8** (*S*)-Binap	77	58
9	**L9** (*S*)-MeO-Biphep	81	67
10	**L10** (*S*)-Synphos	84	74
11	**L11** (*S*)-Difluorphos	90	89

[a]Reaction conditions: **1a** (1.0 mmol). [b]Conversion was determined by ^1H NMR of the crude product. All conversions were complete except for **L3** (35%). [c]Enantiomeric excess (ee) was determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC) on a Chiralcel AD-H column. Absolute configuration was determined to be *S* by comparison of the specific rotation with reported data. [d]With 2 mol % of iodine as additive instead of piperidine HCl.

phosphorus ligands **L1**−**L3**[17] led to moderate enantioselectivities (Table 3, entries 1−3, 33−76%). When the reaction was carried out with Monophos **L4**,[18] an increased enantioselectivity up to 82% ee was observed (Table 3, entry 4). With the exception of (*S*)-tol-SDP **L5**,[17] which provided 33% ee, better results were obtained with bidentate phosphorus ligands compared to monodentate phosphorus ligands (Table 3, entries 5−11). (*S,S*)-Diop **L6**[19] and (*S,R*)-Josiphos **L7**[20] afforded the reduced product **2** with respectively 49 and 82% ee (Table 3, entries 6−7).

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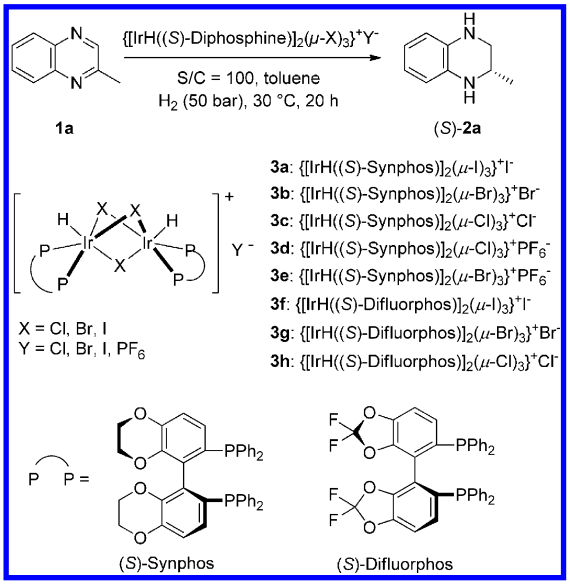
The data of Table 3 clearly show that among all the tested bidendate ligands, atropisomeric diphosphines were found to be the more effective. The (*S*)-Binap **L8**[21] and (*S*)-MeO-Biphep **L9**[22] diphosphines gave 77 and 81% ee, respectively, while (*S*)-Synphos **L10**[23] and (*S*)-Difluorphos **L11**,[24] developed in our group, resulted in an enhancement of the enantioselectivity up to 90% with the electron deficient Difluorphos ligand (Table 3, entries 8−11), so this ligand was selected for further studies. For this comparative study, a dramatic improvement of enantioselectivity was observed when using piperidine·HCl instead of iodine (Table 3). One exception was the result obtained with Difluorphos ligand **L11**, for which no significant difference was observed in terms of both reactivity and enantioselectivity (Table 3, entry 11).

Recently, we have reported a new class of cationic dinuclear triply halogen-bridged iridium complexes {[Ir(H)((*S*)-diphosphine)]$_2$(μ-X)$_3$}X (Table 4, **3a**−**3h**), which proved to be highly efficient catalysts for asymmetric hydrogenation of quinoline derivatives.[12] On the basis of our previous work,[11] we therefore decided to evaluate the catalytic potential of these complexes in the hydrogenation of **1a**. Several catalysts bearing (*S*)-Synphos[23] (**3a**−**3e**) and (*S*)-Difluorphos[24] (**3f**−**3h**) ligands were prepared by reacting the free ligands with [IrCl(coe)$_2$]$_2$ in toluene at room temperature in the presence of an excess of aqueous HX (X = Cl, Br, I).[25] Complexes **3d** and **3e** were obtained by anion metathesis reaction between $NaPF_6$ and the corresponding chloride and bromide complexes **3c** and **3b**, respectively. Initial experiments were performed under the standard set of reaction conditions (30 °C, 50 bar of H_2, S/C = 100, toluene) and the results are depicted in Table 4. In almost all cases, complete conversions were obtained, but the selectivity of the reaction was greatly influenced by the nature of the catalyst.

Table 4. Asymmetric Hydrogenation of 1a Using {[Ir(H)((*S*)-diphosphine)]$_2$(μ-X)$_3$}Y Catalysts[a]



entry	catalyst	conv (%)[b]	ee (%)[c]
1	{[IrH((*S*)-Synphos)]$_2$(μ-I)$_3$}$^+$I$^-$	>99	72
2	{[IrH((*S*)-Synphos)]$_2$(μ-Br)$_3$}$^+$Br$^-$	>99	75
3	{[IrH((*S*)-Synphos)]$_2$(μ-Cl)$_3$}$^+$Cl$^-$	>99	75
4	{[IrH((*S*)-Synphos)]$_2$(μ-Cl)$_3$}$^+$PF$_6^-$	>99	48
5	{[IrH((*S*)-Synphos)]$_2$(μ-Br)$_3$}$^+$PF$_6^-$	93	64
6	{[IrH((*S*)-Difluorphos)]$_2$(μ-I)$_3$}$^+$I$^-$	>99	69
7	{[IrH((*S*)-Difluorphos)]$_2$(μ-Br)$_3$}$^+$Br$^-$	>99	87
8	{[IrH((*S*)-Difluorphos)]$_2$(μ-Cl)$_3$}$^+$Cl$^-$	>99	92

[a]Reaction conditions: **1a** (1.0 mmol). [b]Conversion was determined by ^{1}H NMR of the crude product. [c]Enantiomeric excess (ee) was determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC) on a Chiralcel AD-H column.

When the reaction was carried out with {[IrH((*S*)-Synphos)]$_2$-(μ-I)$_3$}$^+$I$^-$ catalyst **3a**, the desired hydrogenated product **2a** was obtained in 72% ee (Table 4, entry 1). The use of catalysts {[IrH((*S*)-Synphos)]$_2$(μ-Br)$_3$}$^+$Br$^-$ **3b** and {[IrH((*S*)-Synphos)]$_2$-(μ-Cl)$_3$}$^+$Cl$^-$ **3c** did not improve the selectivity of the reaction, since it resulted in the formation of **2a** in 75% ee (Table 4, entries 2−3). In contrast, a marked decrease in enantioselectivity was observed when the reaction was conducted in the presence of catalysts {[IrH((*S*)-Synphos)]$_2$(μ-Cl)$_3$}$^+$PF$_6^-$ **3d** and {[IrH((*S*)-Synphos)]$_2$(μ-Br)$_3$}$^+$PF$_6^-$ **3e** bearing the weakly coordinating PF_6^- counterion instead of chloride or bromide. This result indicated that the counterion associated with the catalyst had a significant impact on the enantioselectivity (Table 4, entries 4, 5). When the (*S*)-Synphos ligand was replaced by (*S*)-Difluorphos, comparable results in terms of both conversion and enantioselectivity were obtained for the triply iodide-bridged catalyst {[IrH((*S*)-Difluorphos)]$_2$(μ-I)$_3$}$^+$I$^-$ **3f**. Finally, we were pleased to find that the use of {[IrH((*S*)-Difluorphos)]$_2$(μ-Br)$_3$}$^+$Br$^-$ catalyst **3g** greatly improved the selectivity of the reaction, giving (*S*)-**2a** in 87% ee (Table 4, entry 7). An even higher enantioselectivity was obtained with {[IrH((*S*)-Difluorphos)]$_2$(μ-Cl)$_3$}$^+$Cl$^-$ catalyst **3h** bearing chloride ligand, providing the 2-methyl-tetrahydroquinoxaline (*S*)-**2a** with an ee up to 92% (Table 4, entry 8). It should be noted that this unprecedented halide dependence was once again in good agreement with our earlier observations on the asymmetric hydrogenation of 2-aryl- and 2-alkyl-substituted quinolinium salts for which chloro- and bromo-iridium catalysts gave better catalytic performance than the corresponding iodo-iridium catalyst.[12]

With the optimal catalyst **3h** in hand, we then decided to study other parameters that might improve the enantioselectivity of the reaction. To this end, the effects of solvent, temperature, and hydrogen pressure were examined using 1 mol % of catalyst {[(IrH((*S*)-Difluorphos)]$_2$(μ-Cl)$_3$}$^+$Cl$^-$ **3h**. As illustrated in Table 5, complete conversions were obtained for all tested solvents, but the selectivity of the reaction was found to be strongly solvent-dependent (Table 5, entries 1−7). The use of MeOH resulted in the formation of the hydrogenated product **2a** in a low 19% ee with the opposite (*R*) configuration, whereas running the reaction in *i*-PrOH provided (*S*)-**2a** in a moderate ee of 53% (Table 5, entries 1 and 2). The reaction proceeded well in dichloromethane, tetrahydrofuran, dioxane, diethylether with enantioselectivities ranging from 85 to 90% ee (Table 5, entries 3−6), but from this solvent screening, toluene proved to be the solvent of choice, providing the desired 2-methyl-tetrahydroquinoxaline **2a** in 92% ee (Table 5, entry 7). The data in Table 5 also illustrated that variation of the temperature and the hydrogen pressure had only little effect on the catalytic activity in terms of both conversion and selectivity (Table 5, entries 8−13). A temperature increase led to a decrease in selectivity, giving **2a** with 90% ee, whereas an excellent ee, up to 93%, was obtained when the reaction was carried out at 10 °C, but with a lower conversion of 86% (Table 5, compare entries 8 vs 9 and 10). A change in the hydrogen pressure from 10 to 70 bar had little impact on the stereochemical outcome of the reaction, since an excellent catalytic

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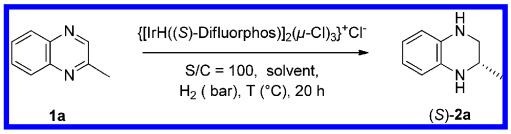
Table 5. Optimization of the Reaction Conditions[a]



entry	solvent	H_2 (bar)	T (°C)	conv (%)[b]	ee (%)[c]
1	MeOH	50	30	>99	19 (*R*)
2	*i*-PrOH	50	30	>99	53 (*S*)
3	CH_2Cl_2	50	30	>99	88 (*S*)
4	THF	50	30	>99	85 (*S*)
5	dioxane	50	30	>99	85 (*S*)
6	Et_2O	50	30	>99	90 (*S*)
7	toluene	50	30	>99	92 (*S*)
8	toluene	50	10	86	93 (*S*)
9	toluene	50	50	>99	90 (*S*)
10	toluene	50	70	>99	90 (*S*)
11	toluene	70	30	>99	92 (*S*)
12	toluene	30	30	>99	94 (*S*)
13	toluene	10	30	95	94 (*S*)
14[d]	toluene	50	50	>99	94 (*S*)
15[e]	toluene	50	50	>99	94 (*S*)

[a]Reaction conditions: **1a** (1.0 mmol). [b]Conversion was determined by ^{1}H NMR of the crude product. [c]Enantiomeric excess was determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC) on a Chiralcel AD-H column. [d]Reactions run with S/C = 500 for 36 h. [e]Reactions run with S/C = 1000 for 36 h.

activity was still maintained, with enantiomeric excesses ranging from 92 to 94% (Table 5, entries 11−13). Interestingly, the catalyst loading could be reduced from 1 to 0.2 or 0.1% without erosion of the enantioselectivity, although the reaction was required to be conducted at 50 °C and 50 bar of H_2 for 36 h to reach completion (Table 5, entries 14, 15).

Through these screenings, the best reaction conditions for asymmetric hydrogenation of **1a** were therefore set as the following: 1 mol % of $\{[(IrH((S)\text{-Difluorphos})]_2(\mu\text{-Cl})_3\}^+Cl^-$ **3h** as catalyst, toluene as solvent, under 30 bar of H_2 at 30 °C.

Under these optimized conditions, we then investigated the scope of the reaction. To this end, several 2-alkyl-substituted quinoxalines were prepared according to known procedures[26] and subsequently hydrogenated. As outlined in Table 6, all 2-alkyl-quinoxaline derivatives **1a−p** were quantitatively converted to their corresponding tetrahydroquinoxaline derivatives **2a−p** in excellent chemical yields and good to excellent enantioselectivities (Table 6, entries 1−16, 94−99% yield and 82−95% ee). The length of the alkyl chain had a significant effect on the ee values (Table 6, entries 1−6). When the methyl group at the 2-position was replaced by an ethyl group as in **1b**, a slight increase in enantioselectivity up to 95% was observed, while substrate **1d** bearing an isopropyl substituent gave similar results to those obtained with the 2-methylquinoxaline **1a** (Table 6, entries 1, 2, and 4). The *n*-butyl- and phenethyl-substituted derivatives **1c** and **1f** resulted in an enantiomeric excess of 91% (Table 6, entries 3 and 6), whereas the bulky *t*-butyl group **1e** led to a drastic drop in selectivity (Table 6, entry 5, 82% ee). In the case of 2-styryl-substituted quinoxalines **1g−m**, the reaction proceeded well, and the position and the nature of the substituent on the phenyl ring of the styryl moiety seem to have no significant effect on the stereochemical outcome of the reaction. However, as already observed by Fan et al.,[9l] both the double bond and the quinoxaline ring were simultaneously reduced, giving 2-phenethyl-tetrahydroquinoxaline derivatives in high enantiomeric excesses and excellent yields (Table 6, entries 7−13, 94−98% yield and 86−92% ee). Comparable results in terms of both chemical yield and enantioselectivity were obtained with 2-alkyl-substituted quinoxalines bearing a methyl substituent at the 6- and 7-positions of the aromatic ring, regardless of the size of the alkyl chain (Table 6, entries 14−16, 97−98% yield and 90−91% ee).

The absolute configuration of the 2-phenethyl-1,2,3,4-tetrahydroquinoxaline **2g** was determined to be *S* on the basis of a single-crystal X-ray structure analysis[27] of the corresponding 4-*N*-tosyl-2-phenethyl-1,2,3,4-tetrahydroquinoxaline **6** (Figure 3). The configurations of the other products were then assigned by analogy and by comparison with literature data.

To broaden the scope of this reaction, we challenged the hydrogenation of 2-aryl-substituted-quinoxalines **4a−4t**.[28] The results are presented in Table 7. In contrast to 2-alkyl-quinoxaline derivatives, the reaction conducted in toluene under 30 bar of H_2 at 30 °C using catalyst **3h** gave complete conversion but a disappointingly low enantiomeric excess of 60%. A rapid screening of solvents revealed that dioxane gave the best results, providing the desired 2-phenyl-tetrahydroquinoxaline **5a** in 89% ee (Table 7, entries 1−4). Using these new reaction conditions, all substrates were hydrogenated in high chemical yields and with moderate to excellent asymmetric inductions (Table 7, entries 4−23, 89−99% yield and 60−94% ee). The electron-withdrawing or electron-donating substituents on the phenyl ring influenced the selectivity of the reaction. A slight improvement in enantioselectivity was observed with arylquinoxaline derivatives **4b**, **4d**, and **4f** bearing methyl or methoxy groups at the *ortho* or *para* positions compared to the 2-phenylquinoxaline **4a**, resulting in the formation of the hydrogenated products **5b**, **5d**, and **5f** in 90−91% ee (Table 7, entries 5, 7 and 9). The same substituents at the *meta* position (**4c** and **4e**) showed lower enantiomeric excesses (Table 7, entries 6 and 8, 86% and 87% ee). A similar trend was observed for 2-aryl-substituted quinoxalines containing electron-withdrawing groups irrespective of the nature of the substituents. Indeed, hydrogenation of compounds **4h**, **4i**, and **4j** with *p*-NO_2, *p*-F, and *p*-Cl groups gave good to excellent enantioselectivities ranging from 89 to 94% (Table 7, entries 11−13), whereas the bromide derivative **4l** provided **5l** with 86% ee (Table 7, entry 15). The same reaction conducted with *m*-NO_2 and *m*-Br quinoxaline derivatives **4g** and **4k** gave slightly lower selectivities, 85 and 88% ee, respectively (Table 7, entries 10 and 14). The results depicted in Table 7 also illustrated that the asymmetric hydrogenation of 2-aryl substituted quinoxalines bearing a methyl substituent at the 6- and 7-positions of the aromatic ring proceeded well but led to a significant decrease in the catalytic activity (Table 7, compare entries 4, 7, 9, 13, and 15 vs 16, 18, 20, 22, and 23). Furthermore, the reaction appears to be sensitive to the electronic nature of the substituent attached to the 2-substituted aromatic ring. Indeed, substrates bearing electron-donating groups were reduced in lower enantioselectivities (Table 7, entries 17−20, 60−66% ee) than those with electron-withdrawing substituents (Table 7, entries 21−23, 72−79% ee).

Finally, in the context of the importance of tetrahydroquinoxaline derivatives as biologically relevant molecules,[10] we demonstrated the application of our process in the synthesis of compound (*S*)-**9**, which is an inhibitor of cholesteryl ester transfer protein (CETP), developed by Pfizer for the treatment of diverse diseases including atherosclerosis and obesity.[10a] Thus, the hydrogenation of 6,7-dimethyl-2-ethylquinoxaline **1o** was carried out on a gram scale using the optimized reaction conditions to give (*S*)-**2o** in a quantitative chemical yield with 91% ee.

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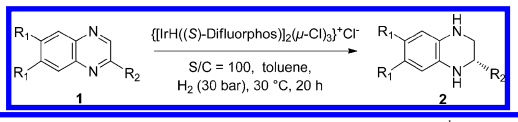
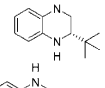
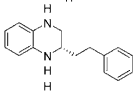
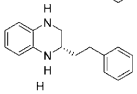
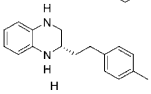
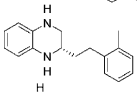
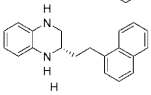
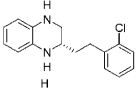
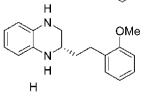
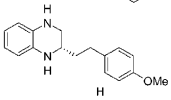
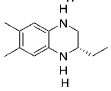
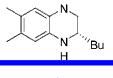
Table 6. Asymmetric Hydrogenation of 2-Alkyl-quinoxalines[a]



entry		product	yield (%)[b,c]	ee (%)[d]
1	**2a**		99	94
2	**2b**		99	95
3	**2c**		98	91
4	**2d**		98	94
5	**2e**		98	82
6	**2f**		97	91
7[e]	**2g**		98	92
8[e]	**2h**		97	91
9[e]	**2i**		96	88
10[e]	**2j**		94	86
11[e]	**2k**		97	90
12[e]	**2l**		96	87
13[e]	**2m**		97	91
14	**2n**		98	90
15	**2o**		98	91
16	**2p**		97	91

[a]Reaction conditions: **1** (1.0 mmol). [b]Yield after flash column chromatography on silica gel. [c]In each case, complete conversion was achieved. [d]Enantiomeric excess was determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC) on Chiralcel AD-H and OD-H columns for **2a**−**p** (see the Supporting Information). Absolute configuration was determined to be *S* by comparison of the specific rotation with reported data. [e]The C═C bond was also hydrogenated.

Subsequent chemoselective *N*-Boc protection afforded compound **7**, which was then treated with ethylchloroformate to give **8**. A final Boc deprotection using neat TFA led to the formation of the target molecule (*S*)-**9** with 90% ee and 57% overall yield (Scheme 1).

CONCLUSION

In conclusion, we have developed a convenient and efficient protocol for the preparation of relevant chiral 2-substituted tetrahydroquinoxalines by asymmetric hydrogenation of their corresponding quinoxaline derivatives, using a cationic dinuclear iridium(III) chloride complex bearing Difluorphos as a ligand. A notable feature of this catalyst system is the superiority of the chloro-iridium catalyst over the corresponding iodo-iridium catalyst, which is opposite to the halide effect usually observed. Moreover, the efficiency of our catalyst system was demonstrated through the broad substrate scope of the reaction. Indeed, a large variety of 2-alkyl- and 2-aryl-substituted quinoxalines were hydrogenated in high chemical yields and with excellent enantioselectivities up to 95% ee. Finally, to illustrate the

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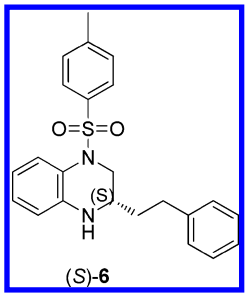

Figure 3. Structure of *N*-tosyl tetrahydroquinoxaline derivative **6**.

applicability of the present method, we synthesized compound (*S*)-**9**, an inhibitor of cholesteryl ester transfer protein (CETP), developed by Pfizer for the treatment of diverse diseases such as atherosclerosis and obesity.[10a]

EXPERIMENTAL SECTION

General Information. All reactions were run under an atmosphere of argon. Reaction vessels were flame-dried under a vacuum and cooled under a stream of argon. Toluene and dichloromethane (DCM) were distilled on calcium hydride prior to use. THF, dioxane, and diethylether (Et_2O) were distilled on sodium/benzophenone prior to use. Isopropanol and methanol were distilled on sodium prior to use. All the solvents were degassed prior to use. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using a 300 MHz apparatus. Chemical shifts are reported in delta (δ) units, part per million (ppm) downfield from tetramethylsilane (TMS) relative to the singlet at 7.26 ppm for deuterochloroform. Coupling constants are reported in Hertz (Hz). The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a 75 MHz apparatus. Chemical shifts are reported in delta (δ) units, part per million (ppm) relative to the center line of the triplet at 77.0 ppm for deuterochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling. Analytical thin layer chromatography (TLC) was carried out using commercial silica-gel plates, and spots were detected with UV light and revealed with $KMnO_4$ or Kagi–Mosher solutions (add 15 mL of AcOH and 3.5 mL of *p*-anisaldehyde to 350 mL of ice cold EtOH, and cautiously add 50 mL of concentrated H_2SO_4 dropwise over 60 min). Enantiomeric excesses were determined by HPLC using Chiralcel columns (OD-H or IB) and eluting with hexane/isopropanol mixture as indicated or chiral stationary phase–supercritical fluid chromatography (CSP–SFC) using Chiralcel columns (AD-H or IA) and eluting with a $scCO_2$/isopropanol mixture as indicated. Optical rotations were measured on a polarimeter at 589 nm (sodium lamp). High resolution mass spectroscopic (HRMS) analysis were measured on LTQ-Orbitrap (Thermo Fisher Scientific) at Pierre et Marie Curie University.

General Procedure for the Ir-Catalyzed Asymmetric Hydrogenation of 2-Substituted Quinoxalines. A glass tube was charged with 2-substituted quinoxaline (1 mmol) and iridium dinuclear complex (5 μmol, 0.50 mol %). The tube was placed in a stainless steel autoclave, which was subjected to three vacuum/argon cycles. Anhydrous and degassed solvent (7 mL) was then added under argon. The hydrogenation was performed at 30 °C under an atmosphere of hydrogen (30 bar) for 20 h. After the careful release of the hydrogen gas, the resulting mixture was filtrated through a short pad of silica gel and concentrated under reduced pressure. The conversion was determined by ^{1}H NMR analysis of the crude product, and the enantiomeric excess was determined by chiral SFC/HPLC analysis of the filtrate using a Chiralcel OD-H, AD-H, IA or IB column.

(*S*)-2-Methyl-1,2,3,4-tetrahydroquinoxaline (2a). (Known compound[9g]), orange solid, 0.147 g, 0.99 mmol, 99% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61–6.58 (m, 2H), 6.54–6.48 (m, 2H), 3.55–3.49 (m, 1H), 3.34–3.30 (dd, J = 10.5, 3.0 Hz, 1H), 3.07–3.01 (dd, J = 10.5, 8.1 Hz, 1H), 1.19 (d, J = 6.30 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.5, 133.1, 118.6, 114.4, 114.3, 48.2, 45.6, 19.8; CSP-SFC (Chiralcel AD-H, $scCO_2$/MeOH 85:15, 5 mL/min, P = 100 bar, λ = 215 nm) t_1 = 3.08 min (minor), t_2 = 4.21 min (major, ee = 94%); $[\alpha]^{24}_D$ = −34.6 (c 1.0, CH_2Cl_2; lit.[9g] −34.4, c 0.065, CH_2Cl_2, 93% ee (*S*)); mp = 80 °C.

(*S*)-2-Ethyl-1,2,3,4-tetrahydroquinoxaline (2b). (Known compound[9g]), yellow oil, 0.160 g, 0.99 mmol, 99% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62–6.59 (m, 2H), 6.53–6.50 (m, 2H), 3.64 (br, 2H), 3.40 −3.36 (dd, J = 10.5, 3.0 Hz, 1H), 3.33–3.25 (m, 1H), 3.10–3.04 (dd, J = 10.5, 7.8 Hz, 1H), 1.58–1.49 (m, 2H), 1.02 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.4, 133.3, 118.6, 118.4, 114.3, 114.3, 51.6, 46.2, 27.0, 10.0; CSP-SFC (Chiralcel AD-H, $scCO_2$/MeOH 85:15, 5 mL/min, P = 100 bar, λ = 215 nm) t_1 = 3.41 min (minor), t_2 = 4.08 min (major, ee = 95%); $[\alpha]^{24}_D$ = −37.6 (c 1.0, CH_2Cl_2; lit.[9g] −30.1, c 0.105, CH_2Cl_2, 89% ee (*S*)).

(*S*)-2-Butyl-1,2,3,4-tetrahydroquinoxaline (2c). (Known compound[9g]), yellow solid, 0.186 g, 0.98 mmol, 98% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61–6.57 (m, 2H), 6.54–6.50 (m, 2H), 3.59 (br, 2H), 3.39–3.32 (m, 2H), 3.10–3.03 (m, 1H), 1.50–1.35 (m, 6H), 0.92–0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.5, 133.4, 118.6, 118.5, 114.40, 114.3, 50.2, 46.6, 34.0, 27.8, 22.8, 14.0; CSP-SFC (Chiralcel OD-H, $scCO_2$/MeOH 85:15, 5 mL/min, P = 100 bar, λ = 215 nm) t_1 = 2.84 min (minor), t_2 = 4.04 min (major, ee = 91%); $[\alpha]^{24}_D$ = −35.4 (c 1.0, CH_2Cl_2; lit.[9g] −30.4, c 0.150, CH_2Cl_2, 93% ee (*S*)); mp = 51 °C.

(*S*)-2-Isopropyl-1,2,3,4-tetrahydroquinoxaline (2d). (Known compound[11]), brown solid, 0.172 g, 0.98 mmol, 98% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65–6.60 (m, 2H), 6.57–6.52 (m, 2H), 3.68 (br, 2H), 3.39–3.36 (m, 1H), 3.21–3.11 (m, 2H), 1.83–1.71 (m, 1H), 1.08 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.7, 133.3, 118.5, 118.2, 114.1, 55.8, 43.8, 30.9, 18.6, 18.4; CSP-SFC (Chiralcel OD-H, $scCO_2$/MeOH 85:15, 5 mL/min, P = 100 bar, λ = 215 nm) t_1 = 2.33 min (minor), t_2 = 2.83 min (major, ee = 94%); HRMS (ESI) m/z calcd for $C_{11}H_{17}N_2$ (MH^+) 177.1392, found 177.1388; $[\alpha]^{24}_D$ = −36.2 (c 1.0, CH_2Cl_2); mp = 54 °C.

(*S*)-2-*t*-Butyl-1,2,3,4-tetrahydroquinoxaline (2e). (Known compound[9g]), brown solid, 0.186 g, 0.98 mmol, 98% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63–6.56 (m, 2H), 6.54–6.49 (m, 2H), 3.53 (br, 2H), 3.40–3.32 (m, 1H), 3.19–3.11 (m, 2H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5, 133.2, 118.8, 118.1, 114.3, 114.2, 58.9, 42.4, 33.54, 26.0; CSP-SFC (Chiralcel OD-H, $scCO_2$/MeOH 85:15, 5 mL/min, P = 100 bar, λ = 215 nm) t_1 = 1.89 min (minor), t_2 = 2.20 min (major, ee = 82%); $[\alpha]^{24}_D$ = −5.6 (c 1.0, CH_2Cl_2; lit.[9g] −18.9, c 0.090, CH_2Cl_2, 85% ee (*S*)); mp = 73 °C.

(*S*)-2-Phenethyl-1,2,3,4-tetrahydroquinoxaline (2f). (Known compound[9f]), brown solid, 0.230 g, 0.97 mmol, 97% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5H), 6.68–6.65 (m, 2H), 6.55–6.51 (m, 2H), 3.60 (br, 2H), 3.42–3.35 (m, 2H), 3.14–3.08 (dd, J = 9.9, 8.1 Hz, 1H), 2.78 (t, J = 7.5 Hz, 2H), 1.86 (quartet. J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 133.2, 133.1, 128.3, 128.2, 125.8, 118.5, 118.4, 114.3, 114.2, 49.6, 46.1, 35.6, 31.9; CSP-SFC (Chiralcel OD-H, $scCO_2$/MeOH 80:20, 5 mL/min, P = 100 bar, λ = 215 nm) t_1 = 5.86 min (minor), t_2 = 9.58 min (major, ee = 91%); $[\alpha]^{24}_D$ = −46.3 (c 1.0, CH_2Cl_2; lit.[9f] −30.5, c 0.98, $CHCl_3$, 75% ee (*S*)); mp = 64 °C.

(*S*)-2-(2-*p*-Tolyl-ethyl)-1,2,3,4-tetrahydroquinoxaline (2h). (Known compound[9f]), yellow solid, 0.244 g, 0.97 mmol, 97% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–6.95 (m, 4H), 6.55–6.35 (m, 4H), 3.60–3.32 (brs, 2H), 3.30–3.20 (m, 2H), 3.05–2.90 (m, 1H), 2.70–2.55 (m, 2H), 2.23 (s, 3H), 1.70 (quartet, J = 7.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 134.5, 132.3, 128.2, 127.2, 117.7, 117.6, 113.5, 113.4, 48.8, 45.4, 34.9, 30.6, 20.0; CSP-SFC (Chiralcel OD-H, $scCO_2$/MeOH 80:20, 5 mL/min, P = 100 bar, λ = 215 nm) t_1 = 5.64 min (minor), t_2 = 9.91 min (major, ee = 91%); mp = 55 °C.

(*S*)-2-(2-*o*-Tolyl-ethyl)-1,2,3,4-tetrahydroquinoxaline (2i). Orange solid, 0.241 g, 0.96 mmol, 96% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.10 (m, 4H), 6.65–6.55 (m, 2H), 6.54–6.46 (m, 2H), 3.50–3.40 (m, 2H), 3.20–3.13 (m, 1H), 2.80–2.70 (m, 2H), 2.33 (s, 3H), 1.85–1.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.9, 135.9, 133.4, 130.5, 128.9, 126.4, 126.3, 118.9, 118.8, 114.7, 114.6, 50.3, 46.6, 34.7, 29.6, 19.5; CSP-SFC (Chiralcel IB, $scCO_2$/

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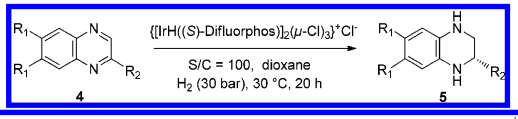
Table 7. Asymmetric Hydrogenation of 2-Aryl-Substituted Quinoxalines[a]



entry	product	solvent	yield (%)[b]	ee (%)[c]
1	**5a**	toluene	94	60
2[d]	**5a**	CH_2Cl_2	70	68
3	**5a**	THF	91	80
4	**5a**	dioxane	98	89
5	**5b**	dioxane	97	91
6	**5c**	dioxane	98	86
7	**5d**	dioxane	99	91
8	**5e**	dioxane	97	87
9	**5f**	dioxane	97	90
10	**5g**	dioxane	97	85
11	**5h**	dioxane	96	91
12	**5i**	dioxane	97	89
13	**5j**	dioxane	98	94
14	**5k**	dioxane	98	88
15	**5l**	dioxane	97	86
16	**5m**	dioxane	95	67
17	**5n**	dioxane	96	60
18	**5o**	dioxane	97	60
19	**5p**	dioxane	96	67
20	**5q**	dioxane	89	66
21	**5r**	dioxane	95	72
22	**5s**	dioxane	89	79
23	**5t**	dioxane	89	77

[a]Reaction conditions: **4** (1.0 mmol). In each case, complete conversion was achieved. [b]Yield after flash column chromatography on silica gel. [c]Enantiomeric excess was determined by HPLC or SFC on a Chiralcel OD-H column for **5a–t** (see the Supporting Information). Absolute configuration was determined to be *S* by comparison of the specific rotation with reported data. [d]77% conversion was obtained.

MeOH 80:20, 4 mL/min, P = 150 bar, λ = 215 nm) t_1 = 4.19 min (minor), t_2 = 6.02 min (major, ee = 88%); HRMS (ESI) m/z calcd for $C_{17}H_{21}N_2$ (MH^+) 253.1699, found 253.1697; $[\alpha]^{24}_D$ = −26.0 (c 1.23, $CHCl_3$); mp = 54 °C.

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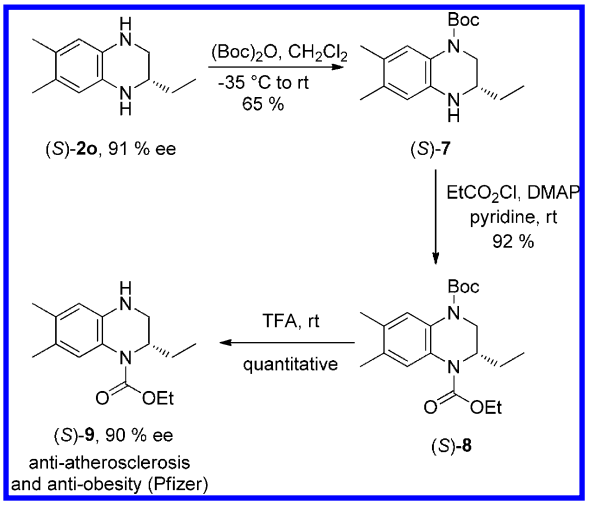
Scheme 1. Asymmetric Synthesis of Pfizer's CETP Inhibitor (*S*)-9



(*S*)-2-(2-Naphthalen-1-yl-ethyl)-1,2,3,4-tetrahydroquinoxaline (2j). Orange solid, 0.270 g, 0.94 mmol, 94% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 7.43 Hz, 1H), 7.92−7.85 (m, 1H), 7.72 (d, J = 7.45 Hz, 1H), 7.60−7.50 (m, 2H), 7.45−7.35 (m, 2H), 6.65−6.50 (m, 4H), 3.60−3.45 (m, 2H), 3.25−3.15 (m, 3H), 2.05−1.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.7, 134.1, 133.3, 131.8, 129.0, 127.1, 126.1, 125.7, 123.7, 119.1, 118.9, 114.8, 114.7, 50.3, 46.6, 35.2, 29.4; CSP-SFC (Chiralcel IA, $scCO_2$/MeOH 80:20, 4 mL/min, P = 150 bar, λ = 215 nm) t_1 = 11.26 min (minor), t_2 = 11.81 min (major, ee = 86%); HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2$ (MH^+) 289.1699, found 289.1702; $[\alpha]^{24}_D$ = −22.3 (c 1.10, $CHCl_3$); mp = 70 °C.

(*S*)-2-[2-(2-Chloro-phenyl)-ethyl]-1,2,3,4-tetrahydroquinoxaline (2k). Yellow solid, 0.265 g, 0.97 mmol, 97% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (dd, J = 3 Hz, 9 Hz, 1H), 7.25−7.15 (m, 3H), 6.65−6.50 (m, 4H), 3.54 (brs, 2H), 3.45−3.40 (m, 2H), 3.15 (dd, J = 6 Hz, 9 Hz, 1H), 2.90−2.85 (m, 2H), 1.90−1.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.2, 133.9, 133.4, 133.3, 130.4, 129.7, 127.7, 127.1, 119.0, 118.9, 114.8, 114.7, 49.9, 46.4, 34.3, 29.8; CSP-SFC (Chiralcel IA, $scCO_2$/MeOH 80:20, 4 mL/min, P = 150 bar, λ = 215 nm) t_1 = 6.07 min (minor), t_2 = 6.52 min (major, ee = 90%); HRMS (ESI) m/z calcd for $C_{16}H_{18}N_2Cl$ (MH^+) 273.1153, found 273.1156; $[\alpha]^{24}_D$ = +46.9 (c 1.45, $CHCl_3$); mp = 62 °C.

(*S*)-2-[2-(2-Methoxy-phenyl)-ethyl]-1,2,3,4-tetrahydroquinoxaline (2l). Red oil, 0.257 g, 0.96 mmol, 96% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25−7.10 (m, 2H), 6.95−6.85 (m, 2H), 6.60−6.45 (m, 4H), 3.85 (s, 3H), 3.45−3.30 (m, 2H), 3.20−3.10 (m, 1H), 2.85−2.70 (m, 2H), 1.85−1.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.3, 133.2, 129.9, 129.8, 127.3, 120.6, 118.8, 118.6, 114.5, 110.3, 55.3, 49.4, 46.7, 34.3, 25.9; CSP-SFC (Chiralcel IA, $scCO_2$/*i*-PrOH 80:20, 4 mL/min, P = 150 bar, λ = 215 nm) t_1 = 5.92 min (major, ee = 87%), t_2 = 6.83 min (minor); HRMS (ESI) m/z calcd for $C_{17}H_{21}ON_2$ (MH^+) 269.1648, found 269.1649; $[\alpha]^{24}_D$ = +77.4 (c 1.15, $CHCl_3$).

(*S*)-2-[2-(4-Methoxy-phenyl)-ethyl]-1,2,3,4-tetrahydroquinoxaline (2m). Red solid, 0.260 g, 0.97 mmol, 97% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 9 Hz, 2H), 6.84 (d, J = 9 Hz, 2H), 6.65−6.57 (m, 2H), 6.55−6.45 (m, 2H), 3.80 (s, 3H), 3.45−3.33 (m, 2H), 3.18−3.05 (m, 1H), 2.75−2.65 (m, 2H), 1.85−1.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.1, 133.6, 133.4, 129.4, 118.8, 114.7, 114.6, 114.1, 55.4, 49.9, 46.6, 36.1, 31.3; CSP-SFC (Chiralcel OD-H, $scCO_2$/MeOH 80:20, 4 mL/min, P = 150 bar, λ = 215 nm) t_1 = 5.88 min (major, ee = 91%), t_2 = 8.74 min (minor); HRMS (ESI) m/z calcd for $C_{17}H_{21}ON_2$ (MH^+) 269.1648, found 269.1649; $[\alpha]^{24}_D$ = +37.7 (c 1.06, $CHCl_3$); mp = 88 °C.

(*S*)-2,6,7-Trimethyl-1,2,3,4-tetrahydroquinoxaline (2n). (Known compound[9g]), brown solid, 0.172 g, 0.98 mmol, 98% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (s, 1H), 6.33 (s, 1H), 3.50−3.43 (m, 2H), 3.31−3.26 (dd, J = 3.0, 10.8 Hz, 1H), 3.03−2.96 (dd, J = 10.8, 8.1 Hz, 1H), 2.10 (s, 6H), 1.18 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.3, 130.9, 126.4, 126.3, 116.3, 48.5, 46.0, 19.8, 18.8; CSP-SFC (Chiralcel OD-H, $scCO_2$/MeOH 80:20, 5 mL/min, P = 100 bar, λ = 215 nm) t_1 = 2.26 min (minor), t_2 = 3.47 min (major, ee = 90%); $[\alpha]^{24}_D$ = −29.7 (c 1.0, CH_2Cl_2; lit.[9g] −26.5, c = 0.150, CH_2Cl_2, 87% ee (*S*)); mp = 74 °C.

(*S*)-2-Ethyl-6,7-dimethyl-1,2,3,4-tetrahydroquinoxaline (2o). (Known compound[9g]), brown solid, 0.186 g, 0.98 mmol, 98% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (s, 1H), 6.31 (s, 1H), 3.47 (br, 2H), 3.33−3.28 (dd, J = 10.8, 3.0 Hz, 1H), 3.24−3.17 (m, 1H), 3.02−2.96 (dd, J = 10.8, 8.1 Hz, 1H), 2.10 (s, 6H), 1.53−1.42 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.2, 131.1, 126.2, 126.0, 116.1, 51.8, 46.4, 26.9, 18.7, 9.9; CSP-SFC (Chiralcel OD-H, $scCO_2$/MeOH 80:20, 5 mL/min, P = 100 bar, λ = 215 nm) t_1 = 2.28 min (minor), t_2 = 3.81 min (major, ee = 91%); $[\alpha]^{24}_D$ = −36.2 (c 1.0, CH_2Cl_2; lit.[9g] −35.5, c 0.150, CH_2Cl_2, 91% ee (*S*)); mp = 74 °C.

(*S*)-2-Butyl-6,7-dimethyl-1,2,3,4-tetrahydroquinoxaline (2p). (Known compound[11]), yellow solid, 0.211 g, 0.97 mmol, 97% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (s, 1H), 6.40 (s, 1H), 3.62 (br, 2H), 3.40−3.37 (m, 2H), 3.12−3.05 (dd, J = 10.8, 8.4 Hz, 1H), 2.23 (s, 6H), 1.56−1.48 (m, 6H), 1.06 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.1, 131.0, 125.9, 125.7, 116.02, 50.2, 46.7, 33.7, 27.6, 22.67, 18.8, 13.8; CSP-SFC (Chiralcel OD-H, $scCO_2$/MeOH 80:20, 5 mL/min, P = 100 bar, λ = 215 nm) t_1 = 2.64 min (minor), t_2 = 5.29 min (major, ee = 91%) HRMS (ESI) m/z calcd for $C_{14}H_{23}N_2$ (MH^+) 219.1861, found 219.1856; $[\alpha]^{24}_D$ = −38.4 (c 1.0, CH_2Cl_2); mp = 54 °C.

(*S*)-2-Phenyl-1,2,3,4-tetrahydroquinoxaline (5a). (Known compound[9g]), yellow solid, 0.206 g, 0.98 mmol, 98% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7. 42−7.33 (m, 5H), 6.67−6.58 (m, 4H), 4.48 (d, J = 5.6 Hz, 1H), 3.82 (br s, 2H), 3.47 (dd, J = 10.4, 2.0 Hz, 1H), 3.34 (t, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 134.1, 132.7, 128.7, 127.8, 126.9, 118.8, 118.7, 114.7, 114.4, 54.7, 49.1; HPLC (Chiralcel OD-H, hexane/*i*PrOH 90:10, 1 mL/min, λ = 254 nm) t_1 = 21.5 min (minor), t_2 = 32.8 min (major, ee = 89%); HRMS (EI) m/z calcd for $C_{14}H_{14}N_2$ (M^+) 210.1157, found 210.1180; $[\alpha]^{24}_D$ = −23.8 (c 0.17, $CHCl_3$; lit.[9g] −10.5, c 0.10, CH_2Cl_2, 85% ee (*S*)); mp = 109 °C.

(*S*)-2-*o*-Tolyl-1,2,3,4-tetrahydroquinoxaline (5b). (Known compound[11]), pale yellow oil, 0.217 g, 0.97 mmol, 97% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.0 Hz, 1H), 7.13−7.04 (m, 3H), 6.52−6.41 (m, 4H), 4.56 (dd, J = 8.0, 2.8 Hz, 1H), 3.66 (br, 2H), 3.29 (dd, J = 10.8, 2.8 Hz, 1H), 3.11 (dd, J = 10.8, 8.0 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 135.0, 134.3, 132.7, 130.2, 130.0, 127.2, 126.4, 118.6, 118.5, 114.5, 114.3, 50.5, 47.6, 19.0; HPLC (Chiralcel OD-H, hexane/*i*PrOH 95:5, 1 mL/min, λ = 254 nm) t_1 = 34.8 min (minor), t_2 = 39.3 min (major, ee = 91%); HRMS (EI) m/z calcd for $C_{15}H_{16}N_2$ (M^+) 224.1313, found 224.1302; $[\alpha]^{24}_D$ = −18.2 (c 0.26, $CHCl_3$).

(*S*)-2-*m*-Tolyl-1,2,3,4-tetrahydroquinoxaline (5c). (Known compound[11]), pale yellow oil, 0.220 g, 0.98 mmol, 98% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07−7.22 (m, 4H), 6.59−6.56 (m, 2H), 6.50−6.47 (m, 2H), 4.39−4.32 (m, 1H), 3.79 (s, 2H), 3.34 (d, J = 8.8 Hz, 1H), 3.23 (t, J = 9.2 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 138.6, 134.6, 133.2, 129.0, 128.9, 128.1, 124.5, 119.2, 119.1, 115.1, 114.8, 55.1, 49.6, 21.8; HPLC (Chiralcel OD-H, hexane/*i*PrOH 90:10, 1 mL/min, λ = 254 nm) t_1 = 15.9 min (minor), t_2 = 22.4 min (major, ee = 86%); HRMS (EI) m/z calcd for $C_{15}H_{16}N_2$ (M^+) 224.1313, found 224.1287; $[\alpha]^{24}_D$ = −3.6 (c 1.27, $CHCl_3$).

(*S*)-2-*p*-Tolyl-1,2,3,4-tetrahydroquinoxaline (5d). (Known compound[11]), yellow oil, 0.222 g, 0.99 mmol, 99% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 7.6 Hz, 1H), 6.58−6.55 (m, 2H), 6.49−6.46 (m, 2H), 4.33 (d, J = 6.0 Hz, 1H), 3.83 (s, 2H), 3.33 (d, J = 9.2 Hz, 1H), 3.21 (t, J = 5.2 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 137.1, 134.0, 132.6, 129.0, 128.3, 128.2, 126.7, 118.5, 118.3, 114.4, 114.1, 54.2, 49.0, 20.8; HPLC (Chiralcel OD-H, hexane/*i*PrOH 90:10, 1 mL/min, λ = 254 nm) t_1 = 16.8 min (minor), t_2 = 24.4 min (major, ee = 91%); HRMS (EI) m/z calcd for $C_{15}H_{16}N_2$ (M^+) 224.1313, found 224.1333; $[\alpha]^{24}_D$ = −4.2 (c 0.95, $CHCl_3$).

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(*S*)-2-(3-Methoxyphenyl)-1,2,3,4-tetrahydroquinoxaline (5e). (Known compound[11]), red oil, 0.233 g, 0.97 mmol, 97% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, J = 8.0 Hz, 1H), 6.93−6.90 (m, 2H), 6.80 (ddd, J = 8.4, 2.4, 0.8 Hz, 1H), 6.59−6.56 (m, 2H), 6.51−6.48 (m, 2H), 4.35 (d, J = 5.6 Hz, 1H), 3.80 (br, 2H), 3.74 (s, 3H), 3.36 (d, J = 9.2 Hz, 1H), 3.23 (t, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 143.5, 133.9, 132.6, 129.3, 119.1, 118.6, 118.5, 114.5, 114.2, 113.0, 112.3, 55.0, 54.4, 48.9; HPLC (Chiralcel OD-H, hexane/*i*PrOH 90:10, 1 mL/min, λ = 254 nm) t_1 = 30.4 min (minor), t_2 = 51.2 min (major, ee = 87%); HRMS (EI) m/z calcd for $C_{15}H_{16}N_2O$ (M^+) 240.1263, found 240.1239; $[\alpha]^{24}_D$ = −2.8 (c 1.22, $CHCl_3$).

(*S*)-2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroquinoxaline (5f). (Known compound[11]), orange oil, 0.233 g, 0.97 mmol, 97% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.8 Hz, 2H), 6.86−6.83 (m, 2H), 6.58−6.55 (m, 2H), 6.51−6.47 (m, 2H), 4.32 (d, J = 6.0 Hz, 1H), 3.80 (br, 2H), 3.75 (s, 3H), 3.32 (dd, J = 9.2, 2.0 Hz, 1H), 3.20 (t, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 134.1, 133.9, 132.6, 127.9, 118.5, 118.6, 114.4, 114.2, 113.8, 55.0, 53.9, 49.1; HPLC (Chiralcel OD-H, hexane/*i*PrOH 90:10, 1 mL/min, λ = 254 nm) t_1 = 20.0 min (minor), t_2 = 34.4 min (major, ee = 90%); HRMS (EI) m/z calcd for $C_{15}H_{16}N_2O$ (M^+) 240.1263, found 240.1234; $[\alpha]^{24}_D$ = −5.3 (c = 0.81, $CHCl_3$).

(*S*)-2-(3-Nitrophenyl)-1,2,3,4-tetrahydroquinoxaline (5g). Yellow oil, 0.247 g, 0.97 mmol, 97% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (t, J = 2.0 Hz, 1H), 8.14 (t, J = 1.2 Hz, 1H), 8.12 (dd, J = 0.8, 2.4 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 4.60 (dd, J = 7.6, 2.8 Hz, 1H), 4.04−3.98 (m, 2H), 3.49 (dd, J = 7.2, 3.2 Hz, 1H), 3.30 (dd, J = 7.6, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 144.3, 133.2, 132.3, 129.6, 122.8, 122.0, 119.5, 119.3, 115.1, 114.8, 54.1, 48.6, 25.3; HPLC (Chiralcel OD-H, hexane/*i*PrOH 70:30, 1 mL/min, λ = 254 nm) t_1 = 41.0 min (minor), t_2 = 64.1 min (major, ee = 85%); HRMS (EI) m/z calcd for $C_{14}H_{13}N_3O_2$ (M^+) 255.1008, found 255.1001; $[\alpha]^{24}_D$ = −7.1 (c 0.75, $CHCl_3$).

(*S*)-2-(4-Nitrophenyl)-1,2,3,4-tetrahydroquinoxaline (5h). (Known compound[11]), pale yellow oil, 0.245 g, 0.96 mmol, 96% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (td, J = 8.8, 2.0 Hz, 2H), 7.55 (td, J = 9.2, 2.0 Hz, 2H), 6.68−6.64 (m, 2H), 6.62−6.56 (m, 2H), 4.62 (dd, J = 7.2, 3.2 Hz, 1H), 3.79 (br, 2H), 3.50 (dd, J = 11.2, 4.0 Hz, 1H), 3.30 (dd, J = 11.2, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 133.2, 132.7, 128.0, 127.8, 123.8, 119.3, 119.3, 118.6, 115.1, 115.0, 114.7, 54.3, 48.5; HPLC (Chiralcel OD-H, hexane/*i*PrOH 70:30, 1 mL/min, λ = 254 nm) t_1 = 29.4 min (minor), t_2 = 55.6 min (major, ee = 91%); HRMS (EI) m/z calcd for $C_{14}H_{13}N_3O_2$ (M^+) 255.1008, found 255.1000; $[\alpha]^{24}_D$ = −3.5 (c 0.77, $CHCl_3$).

(*S*)-2-(4-Chlorophenyl)-1,2,3,4-tetrahydroquinoxaline (5j). (Known compound[11]), yellow oil, 0.239 g, 0.98 mmol, 98% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.40−7.37 (m, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 6.61−6.57 (m, 2H), 6.52−6.48 (m, 2H), 4.33 (d, J = 5.2 Hz, 1H), 3.82 (br, 2H), 3.34 (dd, J = 10.8, 2.4 Hz, 1H), 3.18 (t, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 133.6, 132.5, 130.7, 130.0, 129.9, 125.5, 122.5, 118.8, 118.7, 114.6, 114.3, 54.0, 48.7; HPLC (Chiralcel OD-H, hexane/*i*PrOH 70:30, 1 mL/min, λ = 254 nm) t_1 = 13.4 min (minor), t_2 = 22.4 min (major, ee = 94%); HRMS (EI) m/z calcd for $C_{14}H_{13}ClN_2$ (M^+) 244.0767, found 244.0778; $[\alpha]^{24}_D$ = −12.1 (c 0.44, $CHCl_3$).

(*S*)-2-(3-Bromophenyl)-1,2,3,4-tetrahydroquinoxaline (5k). (Known compound[11]), orange oil, 0.282 g, 0.98 mmol, 98% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.38 (ddd, J = 7.6, 1.6, 1.2 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 6.60−6.57 (m, 2H), 6.52−6.48 (m, 2H), 4.33 (dd, J = 7.6, 2.4 Hz, 1H), 3.82 (br, 2H), 3.34 (dd, J = 8.4, 2.6 Hz, 1H), 3.18 (t, J = 9.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 133.6, 132.5, 130.6, 130.0, 129.9, 125.5, 122.5, 118.8, 118.7, 114.5, 114.3, 54.0, 48.7; HPLC (Chiralcel OD-H, hexane/*i*PrOH 70:30, 1 mL/min, λ = 254 nm) t_1 = 12.1 min (minor), t_2 = 23.0 min (major, ee = 88%); HRMS (EI) m/z calcd for $C_{14}H_{13}BrN_2$ (M^+) 288.0262, found 288.0247; $[\alpha]^{24}_D$ = −8.1 (c 0.8, $CHCl_3$).

(*S*)-2-(4-Bromophenyl)-1,2,3,4-tetrahydroquinoxaline (5l). Pale yellow oil, 0.279 g, 0.97 mmol, 97% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 7.6 Hz, 2H), 7.23 (dd, J = 8.4, 2.0 Hz, 2H), 6.63−6.61 (m, 2H), 6.55−6.53 (m, 2H), 4.40 (br, 1H), 3.83 (br, 2H), 3.40 (d, J = 5.4 Hz, 1H), 3.24 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 133.6, 132.6, 131.6, 128.6, 121.5, 118.9, 114.6, 114.4, 54.0, 53.4, 48.8; HPLC (Chiralcel OD-H, hexane/*i*PrOH 80:20, 1 mL/min, λ = 254 nm) t_1 = 17.9 min (minor), t_2 = 38.4 min (major, ee = 86%); HRMS (EI) m/z calcd for $C_{14}H_{13}BrN_2$ (M^+) 288.0262, found 288.0229; $[\alpha]^{24}_D$ = −8.6 (c 0.41, $CHCl_3$).

(*S*)-6,7-Dimethyl-2-phenyl-1,2,3,4-tetrahydroquinoxaline (5m). Yellow solid, 0.226 g, 0.95 mmol, 95% yield: ^{1}H NMR (300 MHz, $CDCl_3$,) δ 7.50−7.27 (m, 5H), 6.41 (s, 2H), 4.45 (brs, 1H), 3.70 (brs, 2H), 3.50−3.20 (m, 2H), 2.13 (brs, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.2, 130.5, 128.7, 127.9, 127.1, 126.6, 116.9, 116.3, 55.2, 49.6, 19.1; CSP-SFC (Chiralcel IA, $scCO_2$/MeOH 80:20, 4 mL/min, P = 150 bar, λ = 215 nm) t_1 = 7.26 min (major, ee = 67%), t_2 = 8.92 min (minor); HRMS (ESI) m/z calcd for $C_{16}H_{19}N_2$ (MH^+) 239.1542, found 239.1535; $[\alpha]^{24}_D$ = −64.1 (c 0.515, $CHCl_3$); mp = 102 °C.

(*S*)-6,7-Dimethyl-2-naphthalen-1-yl-1,2,3,4-tetrahydroquinoxaline (5n). Yellow oil, 0.276 g, 0.96 mmol, 96% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90−7.80 (m, 4H), 7.55−7.45 (m, 3H), 6.46 (s, 2H), 4.65 (brs, 1H), 3.90 (brs, 2H), 3.60−3.30 (m, 2H), 2.15 (brs, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.6, 133.5, 133.2, 128.5, 128.0, 127.8, 126.7, 126.3, 126.0, 125.8, 125.3, 116.9, 116.4, 55.3, 49.6, 19.1; HPLC (Chiralcel IB, hexane/*i*PrOH 90:10, 1 mL/min, λ = 215 nm) t_1 = 21.9 min (major, ee = 60%), t_2 = 32.9 min (minor); HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2$ (MH^+) 289.1699, found 289.1697; $[\alpha]^{24}_D$ = −63.2 (c 1.14, $CHCl_3$).

(*S*)-2-(4-Methoxy-phenyl)-6,7-dimethyl-1,2,3,4-tetrahydroquinoxaline (5o). Yellow solid, 0.260 g, 0.97 mmol, 97% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 8.73 Hz, 2H), 6.90 (d, J = 8.71 Hz, 2H), 6.41 (d, J = 9.65 Hz, 2H), 4.40 (brs, 1H), 3.81 (s, 3H), 3.50−3.20 (m, 4H), 2.12 (brs, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.4, 134.3, 132.3, 130.4, 128.2, 126.6, 116.8, 116.3, 114.1, 55.4, 54.6, 49.7, 19.1; CSP-SFC (Chiralcel IA, $scCO_2$/MeOH 80:20, 4 mL/min, P = 150 bar, λ = 215 nm) t_1 = 9.65 min (major, ee = 60%), t_2 = 14.88 min (minor); HRMS (ESI) m/z calcd for $C_{17}H_{21}ON_2$ (MH^+) 269.1648, found 269.1647; $[\alpha]^{24}_D$ = −50.7 (c 1.045, $CHCl_3$); mp = 87 °C.

(*S*)-2-(3-Methoxy-phenyl)-6,7-dimethyl-1,2,3,4-tetrahydroquinoxaline (5p). Orange solid, 0.257 g, 0.96 mmol, 96% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.20 (m, 2H), 6.99−6.95 (m, 2H), 6.90−6.82 (m, 1H), 6.41 (s, 2H), 4.45 (brs, 1H), 3.81 (s, 3H), 3.50−3.20 (m, 2H), 2.18 (brs, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.0, 143.9, 132.1, 130.5, 129.7, 127.1, 126.7, 119.4, 116.9, 116.3, 113.3, 112.5, 55.4, 55.2, 49.7, 19.1; CSP-SFC (Chiralcel IA, $scCO_2$/MeOH 80:20, 4 mL/min, P = 150 bar, λ = 215 nm) t_1 = 9.39 min (major, ee = 67%), t_2 = 10.63 min (minor); HRMS (ESI) m/z calcd for $C_{17}H_{21}ON_2$ (MH^+) 269.1648, found 269.1647; $[\alpha]^{24}_D$ = −64.4 (c 0.900, $CHCl_3$); mp = 60 °C.

(*S*)-6,7-Dimethyl-2-*p*-tolyl-1,2,3,4-tetrahydroquinoxaline (5q). Yellow solid, 0.224 g, 0.89 mmol, 89% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8 Hz, 2H), 7.17 (d, J = 7.96 Hz, 2H), 6.41 (d, J = 6.78 Hz, 2H), 4.42 (brs, 1H), 3.80 (brs, 2H), 3.45−3.20 (m, 2H), 2.35 (s, 3H), 2.12 (brs, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.2, 137.6, 132.3, 130.5, 129.4, 127.0, 126.5, 116.8, 116.2, 54.9, 49.7, 21.3, 19.0; CSP-SFC (Chiralcel IA, $scCO_2$/MeOH 80:20, 4 mL/min, P = 150 bar, λ = 215 nm) t_1 = 7.91 min (major, ee = 66%), t_2 = 10.89 min (minor); HRMS (ESI) m/z calcd for $C_{17}H_{21}N_2$ (MH^+) 253.1699, found 253.1695; $[\alpha]^{24}_D$ = −55.2 (c 0.905, $CHCl_3$); mp = 122 °C.

(*S*)-2-(3-Bromo-phenyl)-6,7-dimethyl-1,2,3,4-tetrahydroquinoxaline (5r). Pale yellow oil, 0.300 g, 0.95 mmol, 95% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.43 (d, J = 9 Hz, 1H), 7.30−7.20 (m, 2H), 6.41 (s, 2H), 4.41 (brs, 1H), 3.60−3.20 (m, 4H), 2.13 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.7, 131.7, 130.9, 130.4, 130.3, 130.2 127.2, 126.9, 125.8, 122.8, 116.9, 116.4, 54.7, 49.4, 19.1; HPLC (Chiralcel IB, hexane/*i*PrOH 90:10, 1 mL/min, λ = 215 nm) t_1 = 16.95 min (major, ee = 72%), t_2 = 26.77 min (minor); HRMS (ESI) m/z calcd for $C_{16}H_{18}N_2Br$ (MH^+) 317.0647, found 317.0643; $[\alpha]^{24}_D$ = −72.5 (c 0.400, $CHCl_3$).

(*S*)-2-(4-Chloro-phenyl)-6,7-dimethyl-1,2,3,4-tetrahydroquinoxaline (5s). Orange solid, 0.242 g, 0.89 mmol, 89% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 4H), 6.41 (s, 2H), 4.43 (brs, 1H), 3.70−2.80 (m, 4H), 2.13 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.8,

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133.6, 130.3, 128.9, 128.5, 127.3, 126.9, 116.9, 116.3, 54.6, 49.4, 19.1; CSP-SFC (Chiralcel IA, $scCO_2$/MeOH 80:20, 4 mL/min, P = 150 bar, λ = 215 nm) t_1 = 10.22 min (major, ee = 79%), t_2 = 13.11 min (minor); HRMS (ESI) m/z calcd for $C_{16}H_{18}N_2Cl$ (MH^+) 273.1153, found 273.1153; $[\alpha]^{24}_D$ = −81.9 (c 0.885, $CHCl_3$); mp = 115 °C.

(*S*)-2-(4-Bromo-phenyl)-6,7-dimethyl-1,2,3,4-tetrahydroquinoxaline (5t). Orange solid, 0.281 g, 0.89 mmol, 89% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, J = 8.43 Hz, 2H), 7.25 (d, J = 8.28 Hz, 2H), 6.41 (d, J = 6 Hz, 2H), 4.41 (brs, 1H), 3.39 (m, 1H), 3.23 (m, 1H), 2.13 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.4, 131.8, 130.4, 128.8, 127.2, 126.9, 121.7, 116.9, 116.3, 54.6, 49.4, 19.1; CSP-SFC (Chiralcel IA, $scCO_2$/MeOH 80:20, 4 mL/min, P = 150 bar, λ = 215 nm) t_1 = 13.37 min (major, ee = 77%), t_2 = 19.05 min (minor); HRMS (ESI) m/z calcd for $C_{16}H_{18}N_2Br$ (MH^+) 317.0647, found 317.0643; $[\alpha]^{24}_D$ = −62.3 (c 0.915; $CHCl_3$); mp = 108 °C.

(*S*)-3-Phenethyl-1-tosyl-1,2,3,4-tetrahydroquinoxaline (6). (Known compound[11]), white solid, 0.307 g, 0.784 mmol, 80% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.65 (dd, J = 8.4, 1.5 Hz, 1H), 7.37−7.24 (m, 5H), 7.15 (d, J = 7.8 Hz, 2H), 7.09 (d, J = 7.8 Hz, 2H), 6.99−6.93 (m, 1H), 6.71−6.65 (m, 1H), 6.45−6.41 (dd, J = 8.1, 1.2 Hz, 2H), 4.35−4.30 (dd, J = 13.8, 3.6 Hz, 1H), 3.03−2.95 (dd, J = 13.8, 10.2 Hz, 1H), 2.79−2.55 (m, 3H), 2.35 (s, 3H), 1.68 (q, J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 140.5, 137.5, 136.3, 129.5, 128.6, 128.2, 127.1, 126.3, 126.2, 125.5, 121.9, 117.3, 114.6, 48.8, 47.0, 35.2, 31.4 21.5; HRMS (ESI) m/z calcd for $C_{23}H_{24}N_2O_2SNa$ (MNa^+) 415.1456, found 415.1451; $[\alpha]^{24}_D$ = −45.1 (c 1.0, CH_2Cl_2); mp = 66 °C.

(*S*)-*t*-Butyl-3-ethyl-6,7-dimethyl-3,4-dihydroquinoxaline-*N*1-carboxylate (7). (Known compound[10a]), pale yellow oil, 0.992 g, 3.42 mmol, 65% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (br, 1H), 6.38 (s, 1H), 3.99−3.97 (m, 1H),3.78 (s, 1H), 3.25−3.22 (m, 2H), 2.15 (s, 3H), 2.14 (s, 3H), 1.53 (s, 9H), 1.52−1.43 (m, 2H), 1.01 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 134.3, 132.1, 124.6, 123.7, 121.7, 115.3, 80.0, 52.5, 45.4, 27.9, 26.5, 18.9, 18.6, 9.6; HRMS (ESI) m/z calcd for $C_{17}H_{26}N_2O_2Na$ (MNa^+) 313.1892, found 313.1888; $[\alpha]^{24}_D$ = −22.4 (c 1.0, CH_2Cl_2).

(*S*)-*N*4-*t*-Butyl-*N*1-ethyl-2-ethyl-6,7-dimethyl-2,3-dihydroquinoxaline-1,4-dicarboxylate (8). (Known compound[10a]), yellow solid, 1.14 g, 3.15 mmol, 92% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (br, 1H), 7.43 (s, 1H), 4.53−4.45 (m, 1H), 4.30−4.17 (m, 2H), 3.83−3.78 (dd, J = 12.9, 3.6 Hz, 1H), 3.74−3.68 (dd, J = 12.9, 5.1 Hz, 1H), 2.21 (s, 3H), 2.20 (s, 3H), 1.52 (s 9H), 1.49−1.32 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 153.0, 131.8, 131.2, 128.6, 125.8, 125.0, 123.5, 80.8, 61.6, 53.8, 48.0, 28.0, 24.0, 19.3, 19.2, 14.3, 10.0; HRMS (ESI) m/z calcd for $C_{20}H_{30}N_2O_4Na$ 385.2103, found 385.2098; $[\alpha]^{24}_D$ = −20.3 (c 1.0, CH_2Cl_2); mp = 83 °C.

(*S*)-Ethyl-2-ethyl-6,7-dimethyl-3,4-dihydroquinoxaline-1-carboxylate (9). (Known compound[10a]), yellow oil, 0.825 g, 3.15 mmol, 100% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (br, 1H), 6.36 (s, 1H), 4.49−4.46 (m, 1H), 4.32−4.16 (m, 2H), 3.78 (br, 1H), 3.40−3.35 (dd, J = 11.7, 3.6 Hz, 1H), 3.27−3.23 (dd, J = 11.7, 1.8 Hz, 1H), 2.16 (s, 3H), 2.14 (s, 3H), 1.54−1.38 (m, 2H), 1.32 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 133.9, 132.9, 126.0, 124.8, 119.5, 115.5, 61.6, 50.6, 44.4, 23.1, 19.3, 19.0, 14.5, 10.5; CSP-SFC (Chiralcel OD-H, $scCO_2$/MeOH 85:15, 5 mL/min, P = 100 bar, λ = 215 nm) t_1 = 1.57 min (major, ee = 90%), t_2 = 2.11 min (minor); HRMS (ESI) m/z calcd for $C_{15}H_{23}N_2O_2$ (MH^+) 263.1760, found 263.1757; $[\alpha]^{24}_D$ = −18.5 (c 1.0, CH_2Cl_2).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, copies of ^{1}H, ^{13}C NMR, SFC/HPLC spectra, and the crystal information file (CIF) for compound (*S*)-**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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