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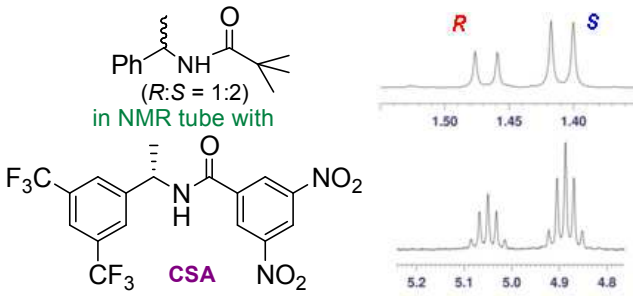
Modified Kagan's Amide: Synthesis and Applications as Chiral Solvating Agent for Hydrogen-Bonding Based Chiral Discrimination in NMR

Nilesh Jain, Ravi B. Patel and Ashutosh V. Bedekar*



A modified Kagan's amide, *N*-((*S*)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl)-3,5-dinitrobenzamide has been designed, synthesized and screened as Chiral Solvating Agent for discrimination of optically active substrates.

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Modified Kagan's Amide: Synthesis and Applications as Chiral Solvating Agent for Hydrogen-Bonding Based Chiral Discrimination in NMR

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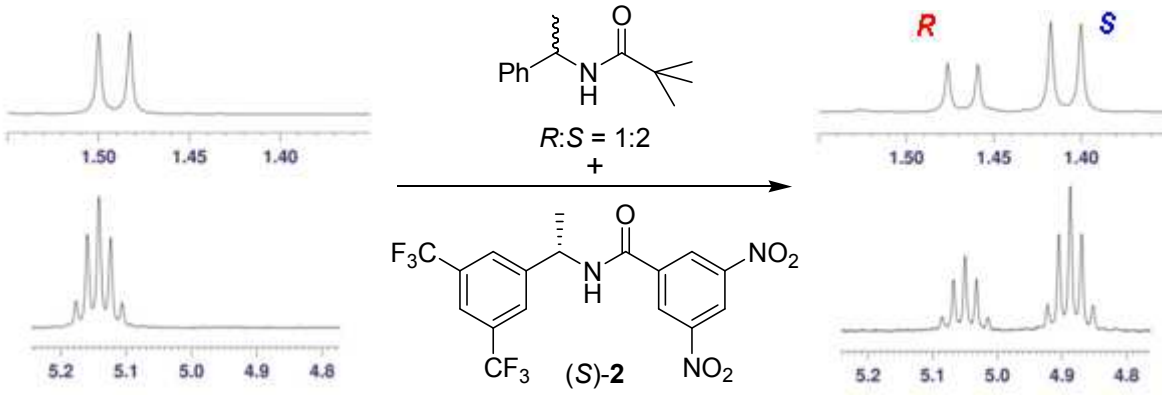
Abstract:

A modified Kagan's amide, *N*-((*S*)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl)-3,5-dinitrobenzamide [(*S*)-**2**] has been designed, synthesized and screened as Chiral Solvating Agent (CSA) for discrimination of optically active substrates. The proposed mode of the action of recognition of chiral isomers of analytes by CSA is based on hydrogen-bonding. The ^{1}H NMR signals of the two isomers of chiral amides, sulfoxides, α-substituted acids, α-hydroxy ketone, epoxy ketone and *N*-protected amino acids with (*S*)-**2** were well resolved for practical applications of determination of optical purity. The CSA was also screened for detection of separation of signals in ^{19}F NMR.



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Introduction:

Advent of chemistry of chiral molecules in recent years has been triggered by discoveries of their special properties in many fields. The specific properties of chiral molecules are often linked with the particular optical isomer and drastically differ on its purity. In some cases different chiral isomers have been found to posses completely divergent properties. Hence, establishing the enantiomeric purity and absolute configuration of chiral compounds is a critical factor in the study and applications of optically active molecules. The optical character of the chemical sample can be analyzed by different techniques ranging from chromatography,[1] mass spectrometry,[2] IR, UV and fluorescence spectroscopy,[3] circular dichroism and electrophoresis[4] etc. These techniques need a certain type of structural requirement or depend on the presence of certain functional group in the analyte or need different accessories of the analytical machine, such as special chiral columns for the chromatographic techniques. Recently some biochemical methods are also developed to determine enantiomeric excess of the chiral products.[5]

The technique of Nuclear Magnetic Resonance (NMR) spectroscopy, with its highly advance and sensitive mode of analysis, also offers an alternative methods of quick and accurate determination of optical purity of chiral molecules.[6] However, the standard NMR analysis of chiral molecules in achiral environment cannot differentiate the signals of the two enantiomers. Few isolated attempts to use chiral solvents in NMR analysis have met with limited success.[7] For the detectable NMR discrimination the enantiomers need to be converted to diastereomers, either permanently by covalent bond formation or temporarily by non-covalent, supramolecular interactions. One such classical technique involves *in situ* preparation of diastereomeric lanthanide chelate complexes.[8] This can also be done by the use of chiral derivatizing agents (CDA)[9] for formation of diastereomeric compounds, either prior to the analysis or for the *in situ* in NMR tube

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analysis.[10] Similarly the diastereomer formation for NMR analysis may also be done by *in situ* complex formation with chiral solvating agent (CSA) during the measurement of the spectra.[11] Although examination of ^{1}H NMR is more widely investigated, the researchers have also focused on targeting the analysis of other NMR active nuclei to determine optical purity using this protocol.[12-16] These techniques involves non-covalent interactions between the test sample and the chirally pure molecule of CSA. These are primarily hydrogen-bonding, π-π stacking, CH-π interactions, van der Waals interactions etc. The efficiency of a given CSA to recognize two isomers of chiral analyte depends on combination of these forces and hence they are often selective and case sensitive in their action. The specific nature of the action of each CSA for different substrates necessitates the need to have a library to scan for new analytes for the NMR analysis.

Chiral amide of 3,5-dinitro benzoic acid **1a** reported by Kagan is one of the oldest and well studied CSA for efficiently discriminating several types of molecules by NMR analysis.[17] This is a simple molecule with basic functional units present to enable hydrogen-bonding and π-π interactions with substrates for tight complex formations in NMR conditions. These type of compounds were first developed by Pirkle for the Whelk-O type materials for separation of chiral compounds on HPLC colums.[18] Over the years few more derivatives of Kagan's amide have been explored with good success in molecular recognition of chiral compounds (Chart 1).[19] The range of chiral analytes successfully screened with these CSAs include amides,[19c] sulfoxides,[17b,17d] multifunctional *tert*-alcohols,[19d] and phosphine oxides.[17c]

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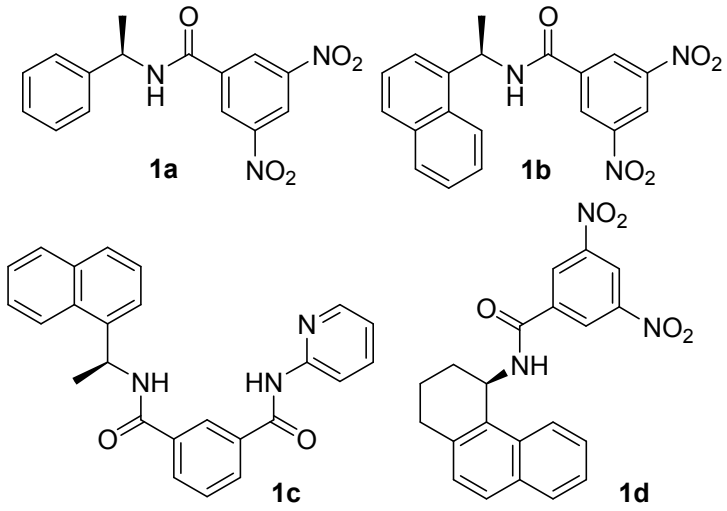

Chart 1. Kagan's amide **1a** and its analogues

Generally accepted mode of interaction between the two molecules involve Hydrogen-bonding between the CSA and the analyte, N-H·····O=X (X = C or S of analyte), and the π-π interaction between the aromatic units.[19d] It is also proposed that the analyte fits between the cleft type conformation created by perpendicularly arranged dinitro benzoyl and the naphthalene rings in case of **1b**,[19c] similar type of explanations are offered for the other derivatives **1c** and **1d**.[20] The proposed interactions were also corroborated by up-field and down-field shifts of appropriate examples in the ^{1}H NMR experiments.

Result ad Discussion:

Based on these proposed models (**A** in Figure 1) we suggest to introduce a modification in Kagan's amide where the chiral amine portion will possess an aromatic ring with two strongly electron withdrawing groups. With this modification the hydrogen attached to the nitrogen of the amide group of CSA will be more electron deficient due to the inductive effect and may form stronger hydrogen bonding with the carbonyl of the test sample (**B** in Figure 1). We propose to

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introduce two trifluoromethyl groups at the *meta* positions of aromatic ring at the amine portion of the amide unit keeping the chiral centre unchanged. Our proposed model compound **2** has been known in the literature[18c] and has been employed as a support in chiral phase HPLC analysis. We present the synthesis and evaluation of **2** as CSA for determining chiral purity of suitable range of substrates by ^{1}H NMR analysis.

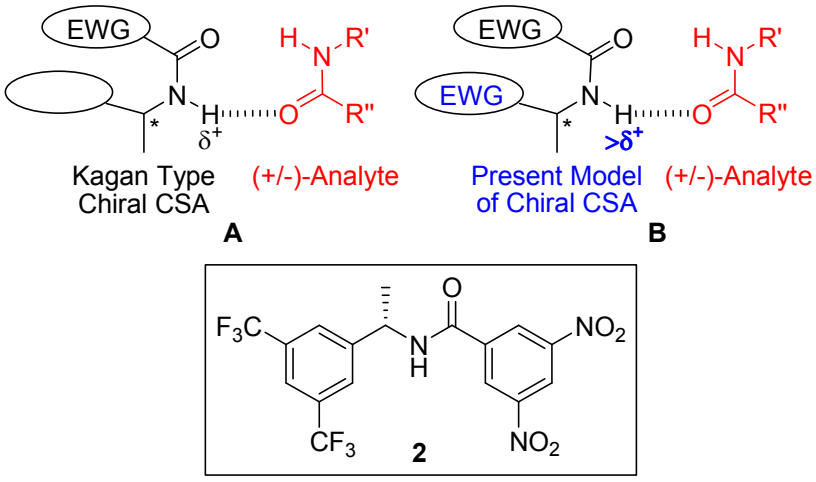

Figure 1. Proposed modification in Kagan type CSA

The synthesis of chiral **2** was based on condensation of the optically pure 1-(3,5-bis(trifluoromethyl)phenyl)ethanamine with 3,5-dinitrobenzoyl chloride under suitable conditions. Separation of isomers of optically pure alcohols using bio-catalytic selective methods is a well established protocol. Several studies have been conducted for elegant separation of alcohols based on kinetic resolution methods, where one of the enantiomers undergoes esterification while the other remains unaffected.[21] As a part of our ongoing project we have separated isomers of chiral roof shape alcohols[22] using enzyme mediated resolution process. Some of these alcohols have been converted to roof shape chiral amines and screened as CSAs for determination of optical purity of α-substituted acids.[22b] In the present synthesis we have accessed optically pure 1-(3,5-bis(trifluoromethyl)phenyl)ethanol **3** from its racemic sample via enzyme mediated

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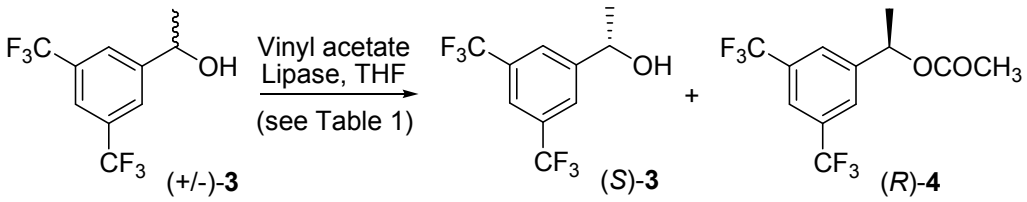
transesterification process and the alcohol was converted to its amine by usual steps. The enzyme mediated process to resolve (+/-)-**3** was conducted with vinyl acetate as the acyl source in presence of immobilized lipase (Scheme 1). The optically pure **3**, which is an intermediate of aprepitant, a potent and orally active antagonist of human neurokinin receptor, has also been accessed by similar process.[23] The improved and standardized parameters of the enantiomer separation study have been summarized in Table 1.



Scheme 1. Enzymatic resolution of (+/-)-**3**

Table 1: Select conditions for resolution of (+/-)-**3**

No	Conditions			% ee of **4**[a] (% Yield)	% ee of **3**[b] (% Yield)	C	E
	Acyl donor	Solvent	Time (h)				
1	IPA	THF	72	>99 (38)	86 (37)	46	>200
2	VA	THF	72	>99 (40)	89 (45)	47	>200
3	EA	THF	72	--[c]	--	--	--
4	--	EA	72	94 (16)	32 (75)	25	44
5	BA	THF	72	--[d]	--	--	--
6	IPA	THF	84	>99 (40)	92 (35)	48	>200
7	VA	THF	84	>99 (43)	>99 (41)	50	>200

All the reactions were run at r.t.; [a]Determined by HPLC by converting to alcohol **3**; [b]Determined by HPLC; [c]Trace reaction, not isolated; [d]No reaction. IPA= iso-propenyl acetate, VA = vinyl acetate, EA = ethyl acetate, BA = butyl acetate. All experiments were run with Novozyme-435.

However, the kinetic resolution of chiral alcohols cannot furnish either compound in more than 50% chemical yield in optically pure form. To overcome this difficulty a strategy of combination of enzymatic resolution and Mitsunobu reaction[24] has been developed by few groups.[25] The Mitsunobu reaction involves direct substitution of alcohols with new nucleophiles in presence of triphenyl phosphine and diethyl azodicarboxylate (DEAD) with complete inversion of configuration. In the above reaction (Scheme 1) the "*R*" isomer of the alcohol **3** was selectively

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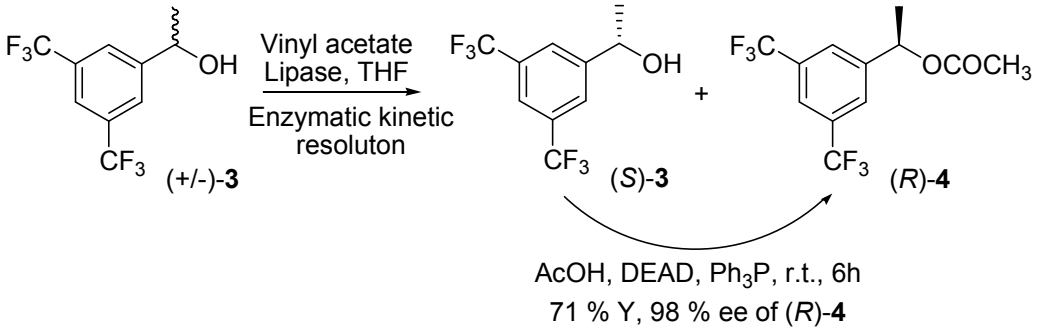
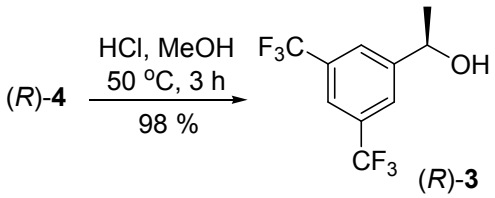
converted to its acetate (*R*)-**4** with excellent selectivity and moderate yield. The unaffected alcohol (*S*)-**3** was also left in high optical purity. In the present effort the same reaction was conducted in presence of acetic acid under Mitsunobu conditions, where the acetate ion acts as new nucleophile and the unreacted alcohol (*S*)-**3** was converted selectively to (*R*)-**4** with complete inversion in overall good chemical yield (Scheme 2).



Scheme 2. Combination of lipase mediated resolution and Mitsunobu reaction

Thus a practical process was developed to access optically pure (*R*)-**4**, which was converted to chiral alcohol (*R*)-**3** under the acidic hydrolysis conditions (Scheme 3).



Scheme 3. Synthesis of (*R*)-**3**

Optically pure alcohol (*R*)-**3** was then converted to corresponding amine (*S*)-**6** (Scheme 4). This operation involved inversion of configuration by its reaction with phthalimide, Ph_3P and DEAD in dry tetrahydrofuran, furnishing the corresponding protected amine (*S*)-**5**, which was subsequently deprotected with hydrazine.[26] The amine (*S*)-**6**[27] was not isolated but converted

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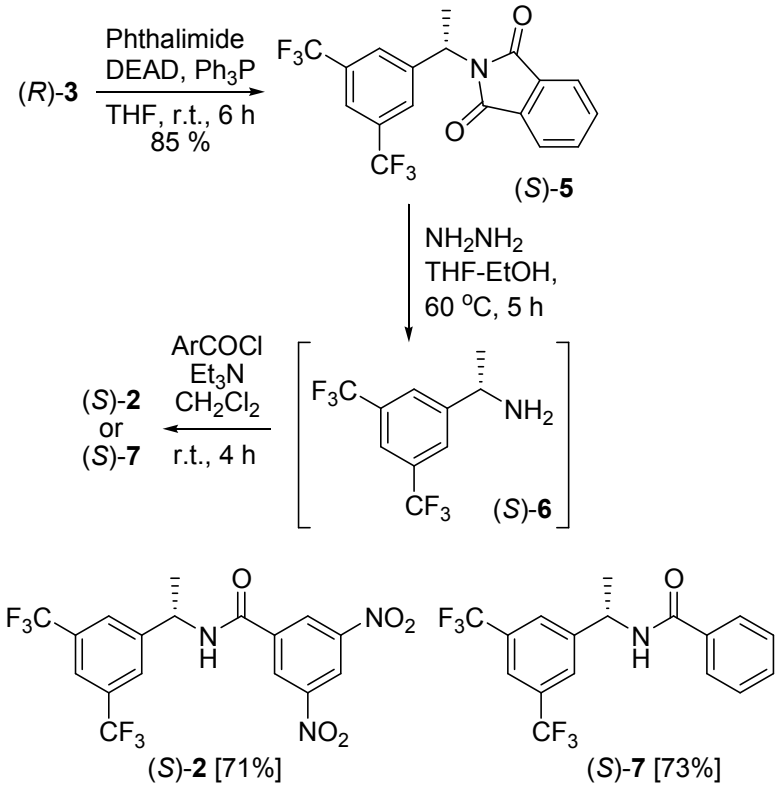
directly to the desired amide (*S*)-**2** by treatment with 3,5-dinitrobenzoyl chloride. Similarly (*S*)-**6** was also converted to (*S*)-**7** by treatment with benzoyl chloride.

The single crystal analysis of **1b** indicated a cleft-like arrangement caused by having the 3,5-dinitrobenzoyl group placed orthogonal to the naphthalene plane.[19c] The selective recognition of the two isomers of chiral amide analyte was attributed to this arrangement and was proposed to be responsible for the supramolecular interactions. We could also grow a single crystal of (*S*)-**2** and its X-ray diffraction analysis was performed (Figure 2).[28] We observed that the angle between the planes passing through the two aromatic rings bisecting each other at an angle of 119.6° making the arrangement of the aromatic rings quite open compared to **1b** (where the same angle was noted to be 99.9°) The intramolecular hydrogen bonding N-H·····O=C was detected with the bond distance of 2.104 Å.



Scheme 4. Synthesis of (*S*)-**2** and (*S*)-**7**

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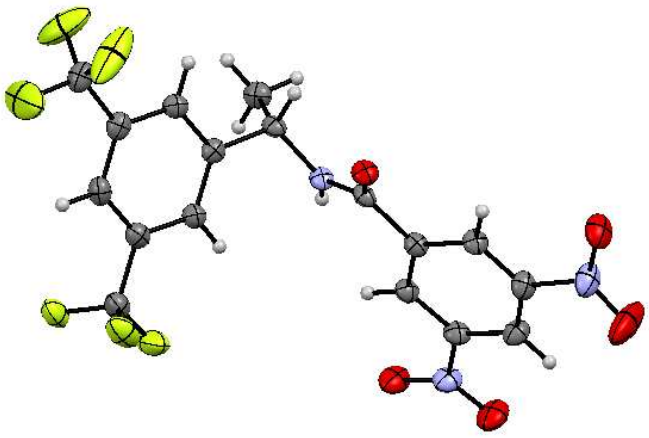

Figure 2. ORTEP diagram of (*S*)-**2**

Having prepared two derivatives of modified CSAs, (*S*)-**2** and (*S*)-**7**, we next screened them to test their ability to discriminate the signals of chiral amide analytes. We made three types of the chiral amides Ph*CH(CH_3)NHCOR (**8a** - **8m**) in the unequal ratio of its enantiomers and tested them with CSAs (Table 2). The first set of amides was made with aromatic acid moieties being phenyl, naphthyl and anthryl (**8a** - **8c**). The second set where the phenyl was substituted with electron donating or withdrawing groups (**8d** – **8i**). The third set of amides was made where the alkyl acids were condensed with α-methyl benzyl amine (**8j** – **8m**). The recognition study was conducted in $CDCl_3$ (400 MHz; 10 mM concentration; ratio of 1:1) targeting two protons $C^{\alpha}H$ of Ph*C*H*(CH_3)NHCOR and methyl protons attached to the chiral center of Ph*CH(C*H*$_3$)NHCOR. As can be seen there is not much difference in case of benzene and naphthalene derivatives (**8a** and **8b**) while the latter signals were much resolved in case of anthracene derivative (**8c**). When the aromatic ring is attached with electron withdrawing group the degree of induced chemical shift (Δδ) and nonequivalences (ΔΔδ) for both sets of protons was observed to be marginally on the lower side (**8d**, **8f** and **8p**) while with electron donating group attached showed considerably enhance shifts in both the parameters (**8g** and **8i**). In case of alkyl derivatives a pattern was observed where both the parameters were seen to increase with increase in the size of R group (**8j** and **8m**). Higher values

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were seen in case of pivaloyl (**8l**) and adamantly (**8m-8o**) supporting this trend (Table 3). The adamantly amide prepared from naphthyl ethyl amide (**8n**) showed remarkable separation of signals with high nonequivalences of 0.502. The pattern observed for the second set of amide analytes was consistent with the proposed hydrogen bonding model (Figure 1), where the electron donating groups on the amide (ArCO) would make the oxygen of carbonyl more electron rich and hence should favor the interaction by becoming better hydrogen bond acceptor. The opposite phenomena may account for the lower values in case of electron withdrawing substituents.

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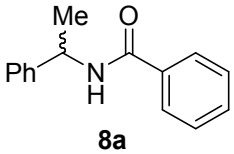
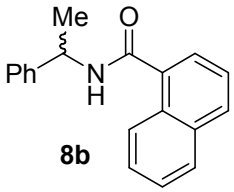
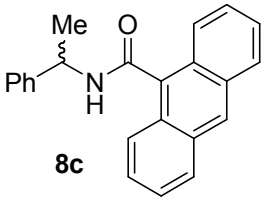
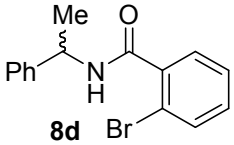
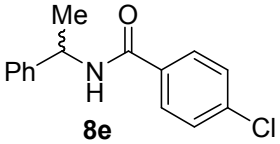
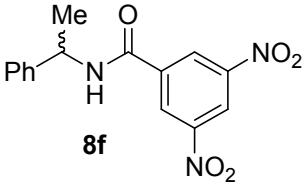
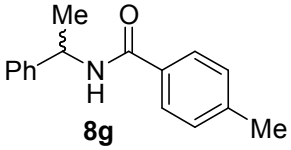
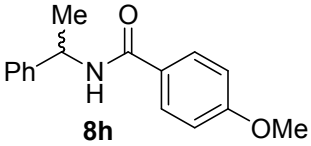
Table 2: ^{1}H NMR induced chemical shift (Δδ) and nonequivalences (ΔΔδ) of amides **8a** – **8m** in presence of CSA (*S*)-**2** and in some cases (*S*)-**7** [in ratio 1:1].

No	Amide **8**	ArC*H*MeNHCOR		ArCH*Me*NHCOR	
		Δδ	ΔΔδ	Δδ	ΔΔδ
1	 **8a**	-0.086	0.060	-0.018	0.025
2	 **8b**	-0.084	0.063	-0.018	0.022
3	 **8c**	--[a]	--[a]	-0.049	0.045
4	 **8d**	-0.077	0.043	-0.025	0.015
5	 **8e**	-0.072	0.044	-0.012	0.017
6	 **8f**	-0.046	--[a]	-0.014	0.018
7	 **8g**	-0.090	0.059	-0.021	0.024
8	 **8h**	-0.091	0.059	-0.019	0.025

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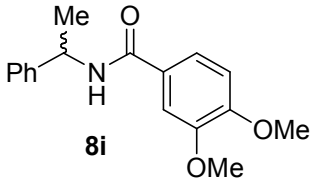
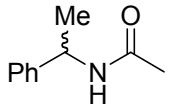
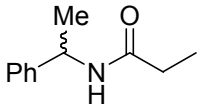
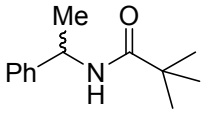
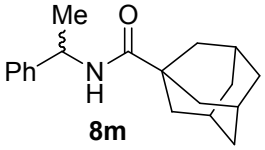
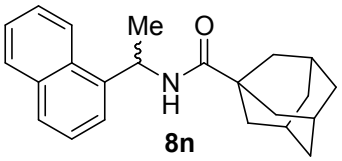
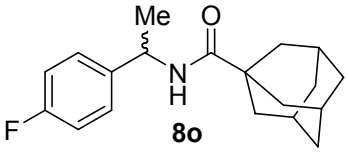
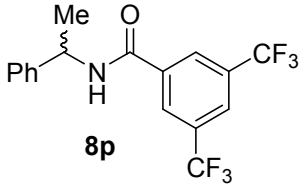
9	 **8i**	-0.067	0.076	-0.016	0.030
10	 **8j**	-0.110 (-0.004)[b]	0.081 (--[a,b])	-0.028 (-0.004)[b]	0.034 (--[a,b])
11	 **8k**	-0.154	0.108	-0.046	0.047
12	 **8l**	-0.158 (-0.007)[b]	0.156 (--[a,b])	-0.047 (-0.004[b])	0.057 (--[a,b])
13	 **8m**	-0.174	0.163	-0.018	0.059
14	 **8n**	-0.39	0.502	-0.212	0.241
15	 **8o**	-0.061	0.157	-0.036	0.053
16	 **8p**	-0.015	--[c]	-0.014	0.021

[a]Not resolved. [b]With (*S*)-**7**. [c]Complex pattern. All NMR recorded at 400 MHz in $CDCl_3$ at 10 mM (1:1).

The hypothesis of designing the present modification in the Kagan's reagent **1a** hinges on making the aromatic ring of CSA (ArNHCO-) more electron deficient by attaching two strongly electron withdrawing groups in (*S*)-**2** (B of Figure 1). By making the ring electron deficient and the subsequent inductive effect (-*I*) we expect the hydrogen of N-H acquire more +δ character and hence becoming a better hydrogen bond donor. This hypothesis was then tested by comparing the

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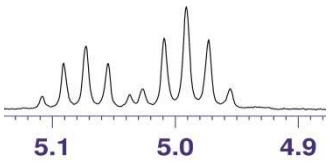
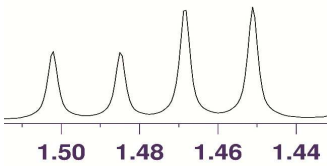
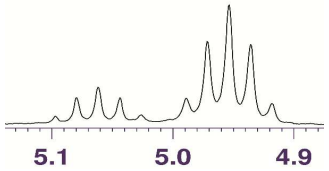
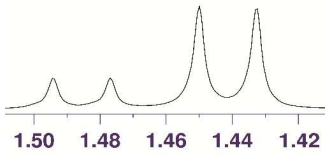
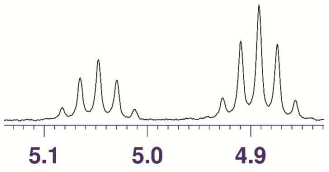
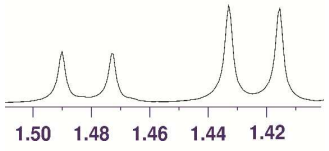
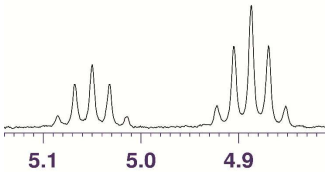
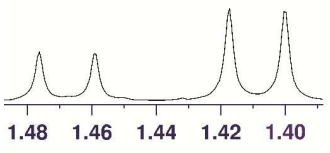
CSA activity of Kagan's reagent **1a**, the known data for **1b**,[19c] and our present study for (*S*)-**2** for the pivaloyl (**8l**) analyte derivative (Table 4). Another analogue was prepared without nitro groups (*S*)-**7** and also scanned for the comparison. The present modified Kagan's reagent (*S*)-**2** showed marginally better values of the nonequivalences (ΔΔδ) for the amide **8l** for both the targeted hydrogens in the ^{1}H NMR analysis supporting the concept. The other derivative (*S*)-**7** failed to effect the discrimination in both the protons of **8l** indicating the need of strongly electron withdrawing groups on the ArC=O of CSA to make the carbonyl oxygen sufficiently electron deficient (+δ) for effective hydrogen bond formation. The role of hydrogen bond in the mechanism of the action of recognition of isomers for chiral solvation has been well established.[29]

Table 3. Select portion of ^{1}H NMR with (*S*)-**2** as CSA

No.	Amide	ArC*H*MeNHCOR	ArCH*Me*NHCOR
1	**8j**		
2	**8k**		
3	**8l**		
4	**8m**		

All NMR recorded at 400 MHz in $CDCl_3$ at 10 mM (1:1).
Ratio of *S*:*R* for **8j**, **8l**, **8m** 1(*R*):2(*S*) & for **8k** 1(*R*):3(*S*)

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Table 4: Comparison of CSA activity of **1a**, **1b**, (*S*)-**2** and (*S*)-**7** for amide **8l**.

No	CSA	ArC*H*MeNHCOR	ArCH*Me*NHCOR
		ΔΔδ	ΔΔδ
1	**1a**	0.061	0.023
2	**1b**	0.141	0.049
3	(*S*)-**2**	0.156	0.057
4	(*S*)-**7**	--[a]	--[a]

[a]Not resolved.

Further evidence of effect of polarity of solvent was studied with conducting ^{1}H NMR experiments in different solvents (Table 5). Very poor resolution was observed in polar solvents such as acetone-d_6 and also with mixture of DMSO-d_6/$CDCl_3$ which is capable of forming hydrogen bond, while better separation was found in less polar benzene-d_6.[111] However, due to the high cost of benzene-d_6 we have focused on the use of more commonly available chloroform-*d* for further study.

Table 5: Effect of solvent on the CSA activity of (*S*)-**2** for amide **8l**.

No	Solvent	ArC*H*MeNHCOR	ArCH*Me*NHCOR
		ΔΔδ	ΔΔδ
1	$CDCl_3$	0.156	0.057
2	C_6D_6	0.201	0.070
3	CD_3COCD_3	--[a]	--[a]
4	$CDCl_3$ + DMSO-d_6 (9:1)	--[a]	--[a]

[a]Not resolved.

The two sets of signals in ^{1}H NMR of pivaloyl derivative **8l** and (*S*)-**2** in equimolar ratio were well resolved (Figure 3). In which both the signals C$^{\alpha}$*H* and the methyl signals of "*S*" isomer experienced up-field shift, more than the other isomer.

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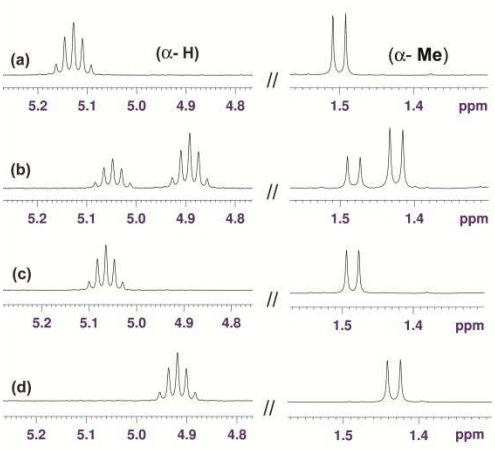

Figure 3. Selected region of ^{1}H NMR of **8l** in $CDCl_3$ (1:1 ratio, 10 mM): (a) blank **8l**; (b) non racemic sample of **8l** ratio of *S*:*R* [2:1] in presence of (*S*)-**2**; (c) *R*-isomer of **8l** with *S*-**2**; (d) *S*-isomer of **8l** with (*S*)-**2**.

This separation was further studied to establish the linear relationship between the observed and actual values of ee for establishing practical utility of the CSA (Figure 4). The observed ee values were found to be within 0.5 % of actual values, which confirms the accuracy and consistency of the analysis.

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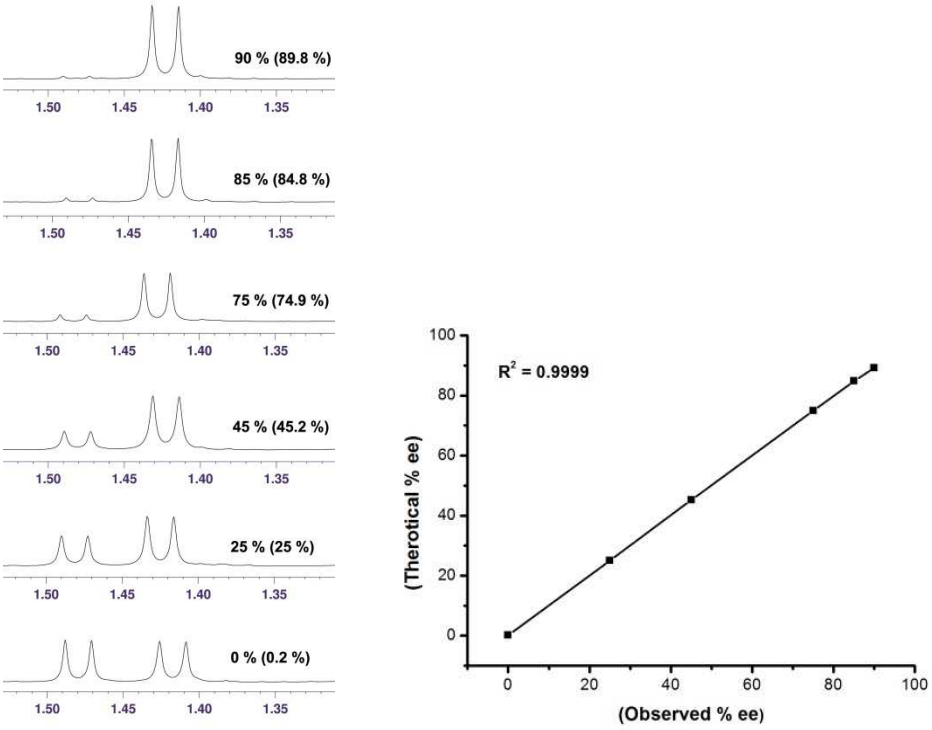

Figure 4. Selected region of ^{1}H NMR spectra of scalemic mixture of **8l** in presence of (*S*)-**2** (Left) and its correlation between theoretical and observed % ee values (Right).

The scope of the present CSA was further explored with chiral sulfoxides to determine their efficacy in recognition of the isomers. Since sulfoxides are also effective acceptors of hydrogen bonding we believe the mode of action of molecular recognition of the present CSA will be on the similar lines. Few derivatives of CSA are available to determine the enantiomer ratio by ^{1}H NMR analysis.[11g,17b,17d,30] To test the efficiency we screened a sample of unsymmetrical sulfoxides **9** with (*S*)-**2** in $CDCl_3$ under the established conditions (Figure 5). A distinct shift of the signals of alkyl protons was observed with base line separation of the two sets of signals corresponding to the two enantiomers, but the values were on the lower side compared to the amide analytes **8**. This could be attributed to the possibility of two point hydrogen bonding in **8** rather than one point attachment in sulfoxides **9**. For comparison, our molecules showed similar values ($\Delta\Delta\delta$ = 0.008 ppm or 3.2 Hz) compared to the **1b** for separation of signals for **9a**.[17b]

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We further investigated application of (*S*)-**2** to check separation of signals in case of racemic benzoin **10a** and keto epoxide**10b** a product of Darzen condensation, where the carbonyl is expected to be less polarized compared to other substrates and hence may have weaker hydrogen bonding. There are very few reports on the methods to discriminate these substrates for analytical purpose.[31] Since our CSA has worked well in differentiating the isomers based on hydrogen bonding we scanned (*S*)-**2** with racemic **10a** and **10b** under similar conditions and observed small shift in the signals of the C$^{\alpha}$*H* in ^{1}H NMR (Figure 5 and 6).

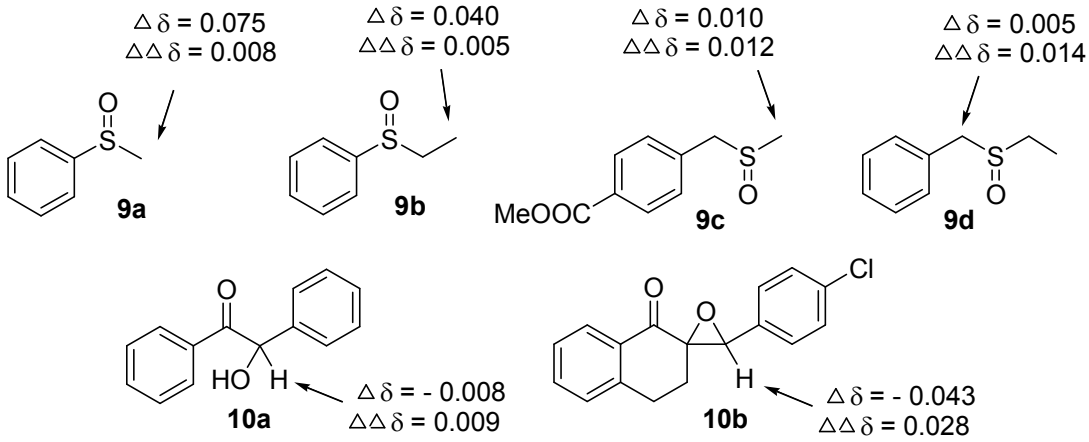

Figure 5. Discrimination of sulfoxides **9** and benzoin **10** with (*S*)-**2**.

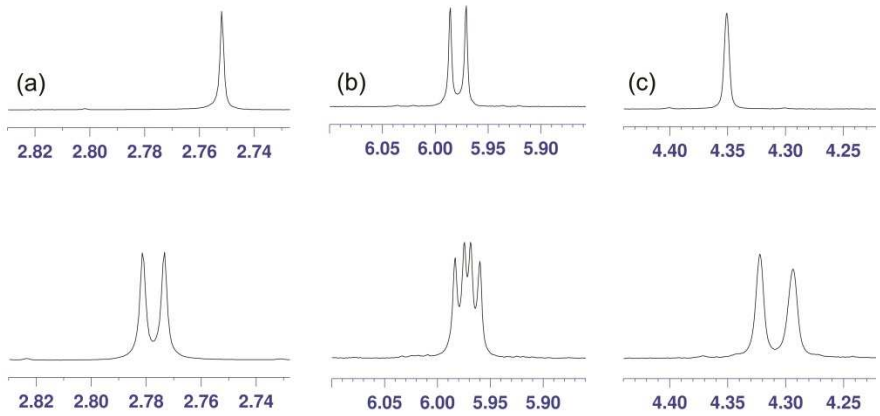

Figure 6. Discrimination of sulfoxides **9a** (a), benzoin **10a** (b) and keto epoxide **10b** with (*S*)-**2**. The top represents the select signal of the ^{1}H NMR spectra without CSA and the bottom with CSA (1:1, $CDCl_3$, 10 mM).

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The use of chiral solvating agents (CSA) for determining optical purity by ^{1}H NMR analysis is emerging as a useful tool and hence we need to scan different types of analytes to prove its wider applicability. Hence we further scanned the present CSA (*S*)-**2** for α-substituted acids as they form an important class of chiral compounds. Usually the CSAs used for analyzing chiral acids are basic in nature and the mode of interactions are based on the formation of diastereometric complex or salt with the substrates.[32] The nature of (*S*)-**2** is neutral and hence our initial experiment of mixing only mandelic acid **11a** and (*S*)-**2** in $CDCl_3$ and recording ^{1}H NMR did not result in any separation of signals, although a small degree of up field shift was recorded (Δδ = - 0.19 ppm). The use of external base to help abstraction of acid proton of such analytes, making the hydrogen bonding possible between the carboxylate with hydrogen bond donor bis-thiourea type CSA is reported.[29f] For similar phenomena in the present study we initially used DMAP along with (*S*)-**2** to determine if the C$^{\alpha}$*H* of mandelic acid can be distinguished in ^{1}H NMR. Indeed, the C$^{\alpha}$*H* proton was observed to shift much up field and two distinct singlets were seen for the two isomers (Table 6). Further improved resolution was observed when the base was replaced with DABCO, with equivimolar quantity and even better separation with excess CSA. Number of derivatives of α-hydroxy aryl acetic acids, **11b** to **11e**, were scanned to establish generality of the analysis. An example of α-chloro phenyl acetic **11f** was also scanned with good separation. All these molecules showed a clear base line separation of the C$^{\alpha}$*H* signals for practical and accurate determination of optical purity.

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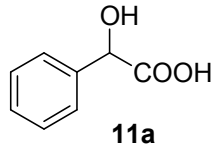
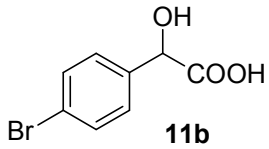
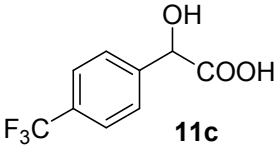
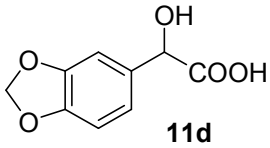
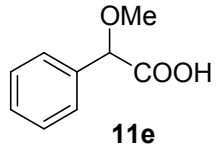
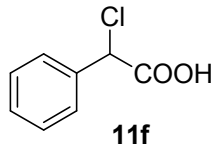
Table 6. Study of CSA activity of (*S*)-**2** for α-hydroxy/alkoxy acids.

No	α-hydroxy/alkoxy acid	CSA (eq.)	Base (1 eq.)	ArC*H*(OH)COOH Δδ	ΔΔδ
1	 **11a**	1.0	DMAP	-0.278	0.022
2	**11a**	1.0	DABCO	-0.384	0.040
3	**11a**	2.0	DABCO	-0.425	0.047
4	 **11b**	2.0	DABCO	-0.430	0.056
5	 **11c**	2.0	DABCO	-0.402	0.030
6	 **11d**	2.0	DABCO	-0.441	0.048
7	 **11e**	2.0	DABCO	-0.250	0.066
8	 **11f**	2.0	DABCO	-0.130	0.053

All NMR recorded at 400 MHz in $CDCl_3$ at 10 mM (2:1), with indicated amount of DMAP / DABCO.

Natural and unnatural amino acids in optically pure form are important intermediates in the synthesis and study of bioactive molecules. We further extended the scope of our reagent (*S*)-**2** to scan for differently *N*-protected phenyl glycine as a test case. The effectiveness is general for some commonly used derivatives of this amino acid (Table 7).

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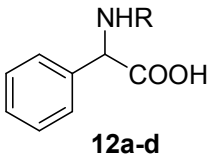
Table 7. Study of CSA activity for the derivatives of *N*-protected phenyl glycine **12**.



12a-d

No	R	ArC*H*(NHR)COOH	
		Δδ	ΔΔδ
1	$COCH_3$ (**12a**)	-0.565 [-0.003][a]	0.038 [0.071][a]
2	COPh (**12a**)	-0.526	0.030
3	Boc (**12a**)	-0.284[b] [Cα-H_1] -0.409[b] [Cα-H_2]	0.071[b] [Cα-H_1] 0.101[b] [Cα-H_2]
4	Ts (**12a**)	-0.490	0.065

[a]For $COCH_3$; [b]For the two rotamers.

The importance of chiral drugs in medicinal chemistry is now a well established phenomenon. In the present work we have scanned our CSA (*S*)-**2** for some chiral drugs and drug intermediates. Non steroidal anti-inflammatory agents such as ibuprofen **13a**, ketoprofen **13b** and flurbiprofen **13e** are some of the important chiral drugs.[34a] These α-alkyl aryl acetic acids showed significant baseline splitting of signal of $C^{\alpha}H$ in ^{1}H NMR analysis (Figure 7). The separation of signals in ^{19}F NMR were also observed in case of **13e** (Figure 8). There is always an advantage if two nuclei can be analyzed in a chiral molecule to confirm its optical purity. Some of the optically active drugs posses sulfoxide chiral center and the activity is believed to be associated with the chirality. One of these class of drugs is used as proton pump inhibitor to treat gastroesophageal reflux disease, peptic ulcers, erosive asophagitis and Zollinger-Ellison syndrome.[34b,c] Omeprazole **13c** is one such active drug commercially available. We scanned (*S*)-**2** to detect discrimination of

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the signals in ^{1}H NMR of **13c**. However, the expected split for the α-protons of SOCH_2- was not observed but the aromatic methyl signals got separated with small chemical shift nonequivalences (0.008 ppm). Another chiral molecule 2-hydroxy-3-methoxy-3,3-diphenyl propionic acid **13d**, which is an intermediate for few pharmaceutical entities[34d] was also tested. Although C$^{\alpha}H$ was not resolved completely the signals of C$^{\beta}$OCH_3 showed good separation in ^{1}H NMR. We extend the study with the analysis of **13f**, an intermediate of Nebivolol, a beta blocker agent.[34e] In this candidate we could observe very good separation of signals of C$^{\alpha}H$ in ^{1}H NMR along with separation of ^{19}F NMR analysis (Figure 8).

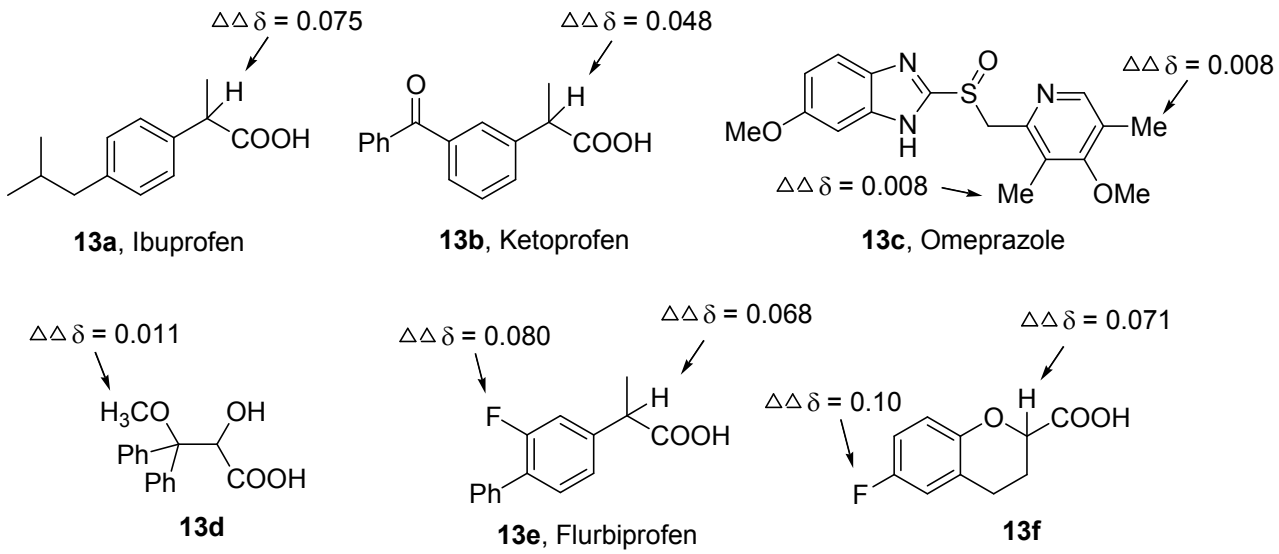

Figure 7. Application of CSA (*S*)-**2** for some drugs and drug intermediates.

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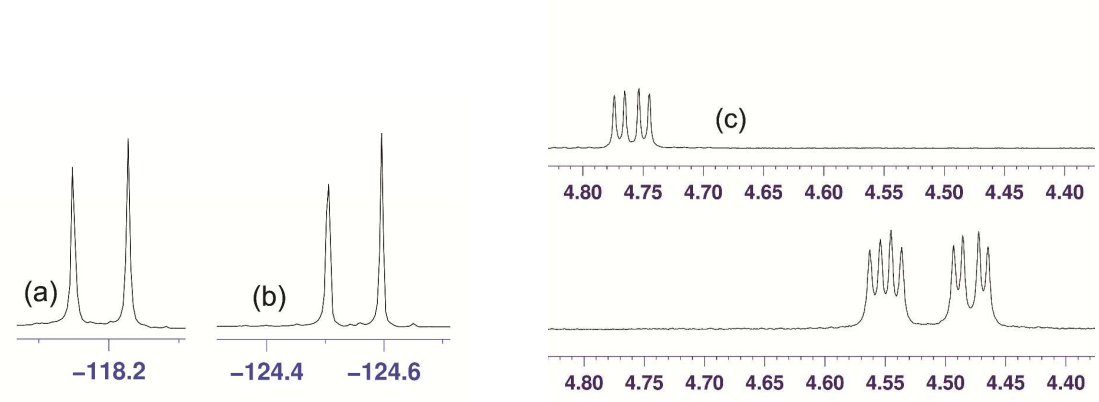

Figure 8. ^{19}F NMR spectrum of **13e** (a) and **13f** (b); C$^{\alpha}$*H* of **13f** in ^{1}H NMR, top without CSA and bottom with (*S*)-**2** (2.0 eq.) and DABCO (1.0 eq) in $CDCl_3$ (10 mmol) (c).

Hence in this work we have developed a modified derivative of Kagan's reagent capable of distinguishing the protons of the enantiomers by simple ^{1}H NMR experiments. We have demonstrated the improved ability of (*S*)-**2** to accurately detect protons of a wide variety of compounds of amides, sulfoxides, benzoin, α-substituted aryl acetic acids, keto epoxides with good separations. The modified CSA has been scanned for few chiral drugs and drug intermediates with good separations. Few examples of the separation of signals in ^{19}F NMR can widen the scope of analysis for fluorine containing chiral compounds.

Experimental Section:

General procedure for the enzymatic resolution.

Synthesis of compound (*S*)-3 and (*R*)-4.

A solution of racemic alcohol (±)-**3** (1.0 g, 3.87 mmol) in dry THF (10 mL) lipase (Novozyme-435) (0.3 g, 30% w/w) and vinyl acetate (0.36 mL, 3.87 mmol) were added and reaction mixture was stirred at room temperature. The reaction was followed by TLC. The material was filtered and the filtrate was concentrated in vacuum. Separation was carried out by column chromatography over

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silica gel using petroleum ether and ethyl acetate as the eluent. The acetate (*R*)-**4** was isolated with ethyl acetate in petroleum ether (2%) and the alcohol with ethyl acetate in petroleum ether (5%).

1-[3,5-bis(trifluoromethyl)phenyl] ethanol: (*S*)-**3**

m.p. = 86-87 ºC (lit.[23c] 88 ºC). $[\alpha]_D$ = -24.8(c = 1.0 $CHCl_3$) (lit.[33] $[\alpha]_D$ = -24.1 (c = 1.0 $CHCl_3$)) HPLC condition for alcohol (*S*)-**3** Chiralpak OD-H column: 5% IpA-Hexane, UV= 254nm, Flow= 0.5 mL/min R_t – 9.5 min (1st Peak) - [*S*-isomer] and R_t – 10.5 min (2nd peak)-[*R*-isomer].

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (d, *J* = 6.4 Hz, 3H), 2.24 (s, 1H), 5.01-5.10 (q, *J* = 6.4 Hz, 1H), 7.78 (s, 1H), 7.84 (s, 2H).

^{19}F NMR (376 MHz, $CDCl_3$): -62.88.

^{13}C NMR (100 MHz, $CDCl_3$): 25.5, 69.3, 121.3 (sep, J_{C-F} = 4.4Hz), 123.3 (q, J_{C-F} = 271.0 Hz), 125.6, 131.9 (q, J_{C-F} = 33.0 Hz), 148.2.

Mass (EI): 258(10), 242(100), 243(96), 240(20), 195(74), 194(87), 69(50).

IR (KBr): υ 3257-3159, 2980, 1625, 1467, 1280, 1024, 924, 896, 842, 705, 683 $cm.^{-1}$

Synthesis of 1-[3,5-bis(trifluoromethyl)phenyl]ethylacetate:(*R*)-4.

Procedure for Enzymatic reaction followed by Mitsunobu reaction:

After enzymatic resolution catalyst was filtered off. To the filtrate AcOH (0.11 mL, 1.93 mmol) and triphenyl phosphine (0.51 g, 1.93 mmol) were added under nitrogen atmosphere followed by the slow addtion of solution of DEAD (0.38 mL, 2.42 mmol) in dry THF (1 mL) at 0 ^oC. The reaction mixture was stirred (6 h). The solvent was removed under reduced pressure and the crude product was purified by silica-gel column chromatography with ethyl acetate and petroleum ether (2%).

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White solid 0.82 g (70.7% Yield) m.p. = 59-60^{o}C $[\alpha]_D$ = +55.2 (c = 1.0 methanol) lit.[23c] $[\alpha]_D$ = +57 (c = 1.0 methanol) for (*R*)-isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (d, *J* = 6.8 Hz, 3H), 2.24 (s, 3H), 5.94-5.99 (q, *J* = 6.8 Hz, 1H), 7.81 (s, 1H), 7.83 (s, 2H).

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.90.

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 22.3, 70.9, 121.9 (sep, J_{C-F} = 4.4 Hz), 123.2, (q, J_{C-F} = 271 Hz), 126.2, 131.4 (q, J_{C-F} = 33 Hz), 144.3, 170.1.

Mass (EI): 299(18), 281(10), 258(100), 257(89), 239(91), 238(56), 200(47), 150(21), 71(18).

IR (KBr): υ 3007, 2941.61, 1732, 1456, 1285, 1173, 1021, 898, 706, 684 cm.$^{-1}$

General procedure for hydrolysis of (*R*)-4.

To a solution of (*R*)-**4** (0.82 g, 3.18 mmol) in methanol (15 mL), HCl (0.5 mL, 4.76 mmol, 36 %) was added. The reaction mixture was refluxed (3 h). After completion of reaction, as indicated by TLC, MeOH was evaporated under reduce pressure. The residue was taken in ethyl acetate, and washed with water. The organic layer was dried with sodium sulphate and concentrated to afford (*R*)-**3** in 0.80 g (98%).

Synthesis of 1-[3,5-bis(trifluoromethyl)phenyl]ethylphthalimide (*S*)-5.

A solution of (*R*)-**3** alcohol (1.0 g, 3.86 mmol) in dry THF (10 mL) kept in ice bath at 0^{o}C under nitrogen atmosphere. To this solution PPh_3 (1.01 g, 3.86 mmol) and pthalimide (0.57 g, 3.86 mmol) were added. A solution of diethylazodicarboxylate (DEAD) (0.77 mL, 4.24 mmol) in THF (3 mL) was added drop wise, and the reaction was stirred for 6 h. The reaction was followed by TLC. The product was purified by column chromatography over silica gel (10% Ethyl acetate- Petroleum ether) affording white solid. Yield 1.2 g (80 %) m.p = 124-126 ^{0} C $[\alpha]_D$ = -59.8 (c= 0.5 $CHCl_3$)

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^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (d, J = 7.2 Hz, 3H), 5.79-5.86 (q, J = 7.2Hz, 1H), 6.16 (d, J = 7.2Hz, 1H), 7.28.-7.23 (m, 2H), 7.40-7.36 (m, 1H), 7.47-7.51 (m, 2H), 7.74-7.78 (m, 2H), 8.04 (s, 2H).

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.76.

^{13}C NMR (100 MHz, $CDCl_3$): δ 17.4, 48.7, 121.9 (sep, J_{C-F} = 4.4 Hz), 123.2 (q, J_{C-F} = 271 Hz), 127.9 131.6, 131.7, 132.3 (q, J_{C-F} = 33 Hz), 134.3, 142.6, 167.8.

Mass (EI): 387(89), 386(53), 372(100), 371(84), 368(89), 343(42), 239(25), 159(45).

IR (KBr): υ 2999, 2923, 1780, 1705, 1467, 1284, 1126, 1060, 895, 712, 528 cm.$^{-1}$

HRMS (TOF-MS) m/z calculated for $C_{18}H_{11}F_6NO_2$ $[M+H]^+$ 388.0772, found 388.0773.

General Procedure for synthesis of amide ligand:

Synthesis of N-(1-(3,5-bis(triflouromethyl)phenyl)ethyl)-3,5-dinitrobenzamide (*S*)-2.

Phthalimide (*S*)-**5** (0.50 g, 1.29 mmol) was dissolved in a mixture of THF (40 mL) and ethanol (10 mL) hydrazine hydrate (0.63 mL, 12.9 mmol, 99%) was added drop wise. The reaction mixture was stirred at 60^{o}C (5 h). The white suspension formed after this time was filtered washed with THF (2X20mL) and then organic solvent was evaporated under reduced pressure. To this water was added and extracted with dichloromethane (2X50 mL). The organic layer was concentrated in vacuum to furnish viscous liquid. Viscous liquid was dissolved in dry chloroform (5 mL) in which triethyl amine (0.18 mL, 1.28 mmol) was added. The reaction mixture was allowed to cool at 0^{o}C. A solution of 3,5-dinitrobenzoyol chloride (0.30 g, 1.28 mmol) in chloroform was added slowly over a period of half an hour. The reaction mixture was stirred for another 4h at room temperature. The solvent was evaporated and residue was washed with sodium bicarbonate and extracted with dichloromethane (2X75 mL). The organic layer were dried over sodium sulphate and concentrated in reduce pressure. The crude product was purified by column chromatography over silica gel (30%

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ethyl acetate- petroleum ether). white solid, Yield 0.415g (71%) m.p.=196^{o} C. White Solid, Yield m.p = 196-97 ^{o}C $[\alpha]_D$ = 37.2 (c= 0.5 $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75 (d, *J* = 7.2 Hz, 3H), 5.43-5.50 (m, 1H), 6.90 (d, *J* = 6.8 Hz, 1H), 7.85(s, 1H), 7.87 (s, 2H), 9.00 (d, *J* = 2.0 Hz, 2H), 9.20-9.211 (t, *J* = 2.0 Hz, 1H).

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.78.

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 49.8, 121.5, 121.9 ((sep J_{C-F} = 4.4 Hz), 127.3. 125.8 (q, J_{C-F} = 271 Hz), 126.6, 132.3 (q, J_{C-F} = 33Hz), 136.9, 144.8, 148.7, 162.1.

Mass (EI): δ 451(29), 450(11), 240(44), 195(100).

IR (KBr): υ 3343, 3088, 1647, 1544, 1348, 1278, 897, 731 cm.$^{-1}$

HRMS (TOF-MS) m/z calculated for $C_{17}H_{11}F_6N_3O_5$ $[M-H]^-$ 450.0530, found 450.0527.

Synthesis of (*S*)-N-(1-(3,5-bis(triflouromethyl)phenyl)ethyl)benzamide (*S*)-7.

The amide was (*S*)-**7** was prepared similarly in 73 % yield starting from (*S*)-**5** as described above. White Solid, Yield = 73 % m.p = 156 ^{o}C $[\alpha]_D$ = 22.4 (c= 1, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (d, *J* = 7.2 Hz, 3H), 5.38-5.45 (m, 1H), 6.44 (d, *J* = 6.8 Hz), 7.46-7.58 (m, 3H), 7.79-7.78 (m, 3H), 7.84 (s, 2H).

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.77.

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 48.9, 121.4 (sep J_{C-F} = 4.4 Hz), 123.3 (q, J_{C-F} = 271Hz), 126.4, 126.9,128.7, 131.9,132.4 (q, J_{C-F} = 33Hz), 133.7, 146.2, 166.9.

Mass (EI): δ 361(100), 360(58), 240(19), 105(90), 104(71).

IR (KBr): υ 3340, 3087, 1639, 1530, 1382, 1124, 920, 895, 845, 703 cm.$^{-1}$

HRMS (ESI+) m/z calculated for $C_{17}H_{13}F_6NO$ $[M+Na]^+$ 384.0799, found 384.0794.

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28. Crystallographic data for the structures of compound (*S*)-**2** have been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 1042105). Copies of the data can be obtained from http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CD21EZ, UK (fax: +44-1223-336-033; e-mail: eposit@ccdc.cam.ac.uk

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