Ruthenium Catalyzed Asymmetric Reduction of Isoxazolium Salts: Access to Optically Active Δ^4-Isoxazolines

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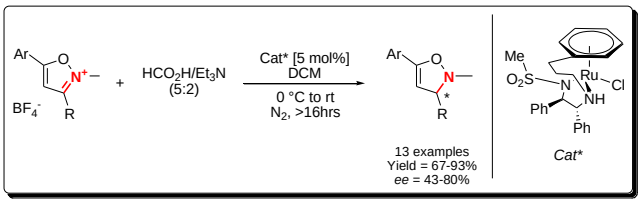


Abstract: A tethered MsDPEN-ruthenium catalyst reduces a series of isoxazolium salts, affording optically-active Δ^4-isoxazolines in moderate to good yields and enantioenrichment. The redundancy for heating or high pressures allowed for chemoselective reduction with no subsequent heterocyclic ring opening. Results obtained reinforce our understanding of the workings of these Noyori-class catalysts.

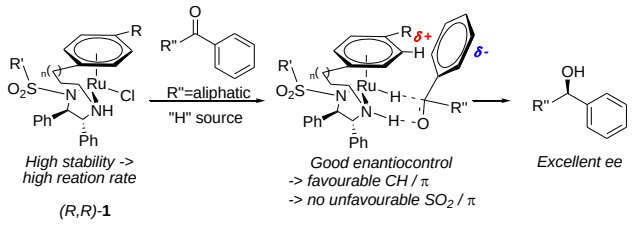
Keywords: ruthenium; asymmetric catalysis; isoxazolines; mild conditions; transfer hydrogenation

Nitrogen containing heterocycles are one of the most prevalent structural motifs in biologically active compounds. Isoxazolines, in particular are valuable synthons *en route* to prized compounds such as alkaloids,[1] steroids[2] and amino acids[3]/sugars.[4] Moreover, they exhibit a wide-spectrum of biological activities, rendering them among others, effective acaricidal,[5] anti-cancer[6] and anti-microbial agents.[7]

A routine approach in the preparation of isoxazolines involves the [3+2]-dipolar cycloaddition between nitrones and alkenes/alkynes.[8] Recently, the gold(I) catalyzed intramolecular cyclization of propargylic N-hydroxylamines has been reported.[9] Retrosynthetic analysis reveal a possible approach for the synthesis of enantioenriched Δ^4-isoxazolines will be the chemo- and stereoselective reduction of the C=N bond in isoxazoles. However, inherent challenges especially for the reduction of heteroarenes bearing adjacent heteroatoms include: a) difficulty in the dearomatization of isoxazoles,

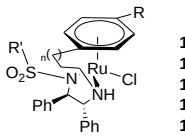
comparably more arduous than oxazoles and furans,[10] b) strong binding of the heteroatoms to metal-based catalyst(s) potentially reducing catalytic efficiency,[11] c) lability of the nitrogen-oxygen bond which is prone to ring opening even under relatively mild reducing conditions,[12] as well as d) achieving satisfactory enantiocontrol. Accordingly, the asymmetric reduction of isoxazoles under mild conditions with appreciable enantioselectivity is of considerable challenge in organic synthesis. To the best of our knowledge, the sole example of said work has very recently been reported by the group of Kawano.[13]

Our group having improved on the antecedent Noyori's catalyst,[14] fashioned an additional tether which links the arene ring with the sulfonyl-protected 1,2-diphenylethylene-1,2-diamine ligand. This 3-point attachment to the ruthenium metal centre enhances the stability of the organometallic (**1**), engendering enhancements in reaction rates.[15] Simultaneous operation of two interactions may influence enantiocontrol: (a) an attractive CH/π (electronic) interaction between the arene ring of the catalyst and the π cloud of the substrate, and (b) a repulsive SO_2 lone pair/ π repulsion between the oxygen atoms of the SO_2 moiety of the catalyst and the π cloud of the substrate, typically a ketone containing an electron rich aromatic group (Scheme 1). These synergistic effects cumulate to give a highly robust and effective catalytic system, allowing for advancements on the asymmetric reduction of a handful of substrate classes,[16] including the challenging enantioselective reduction of *α,α'*-heteroatomic ketones under mild conditions.[17] Seeking to broaden the scope of these tethered catalysts, we envisioned the enantioselective reduction of prochiral isoxazoles or their derivatives thereof. Herein, we divulge the asymmetric reduction of 5-arylisoxazolium salts, affording a series of optically active Δ^4-isoxazolines in moderate to good yields and enantioselectivities.



Scheme 1. Mechanistic insights of asymmetric reduction employing **1** as the catalyst for ATH of aromatic ketones.

We began the study by attempting the direct reduction of 3-methyl-5-phenylisozaxole in the presence of **1a** (Figure 1) as well as a Pd(II) co-catalyst, in the hope that the latter would aid in activation of the C=N bond for reduction. Asymmetric transfer hydrogenation (ATH) conditions were selected for they are considerably milder than pressure hydrogenation which customarily require heating, hence reducing the prospect of thermal induced heterocyclic ring opening[18] upon C=N reduction if any. However, the desired activation by the co-catalyst, in conjunction with a high possibility of protonation at the heterocyclic nitrogen (reaction was conducted in a weakly acidic medium) was inadequate, resulting in a lack of product formation. Determined to overcome the obstacle, a methyl group was introduced onto the nitrogen in hopes of achieving our objectives.



(R,R)-**1**

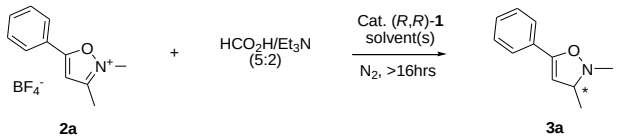
1a: n=1, R=H, R'=4-MeC_6H_4
1b: n=2, R=H, R'=4-MeC_6H_4
1c: n=1, R=H, R'=Me
1d: n=1, R=H, R'=2,4,6-$^{i}PrC_6H_2$
1e: n=1, R=OMe, R'=4-MeC_6H_4

Figure 1. Variation of functional groups in **1**.

Employing 2,3-dimethyl-5-phenylisoxazolium tetrafluoroborate (**2a**) as the prototypical substrate, the ATH reaction was re-examined. The desired reaction worked favourably in acetone, affording the product in moderate yield and enantioselectivity. Equally important is that the C=N bond is exclusively reduced and that no heterocyclic ring opening product ensued. Encouraged by these outcomes, reaction conditions were optimized and the results presented in Table 1.

Owing to solubility considerations, the reaction was initially conducted in acetone which the salt was fairly soluble in (Table 1, entry 1). However, employment of a mixed system of chloroform and acetone (10% v/v) afforded improved yields, albeit poor solubility of the reactant at the onset of the reaction (Table 1, entry 2). A handful of catalysts (**1**) as shown in Figure 1 were studied (Table 1, entries 2-6), with (*R*,*R*)-**1b** and **1c** producing the best enantiomeric excess at 73%. The latter however gave a slight superior yield at 51% and as such was selected as the catalyst of choice for further investigation. An increase in catalyst loading from 3 to 5 mol% led to a modest improvement in *ee* (Table 1, entry 7), while substituting chloroform with dichloromethane (DCM) or ethyl acetate in the mixed system culminated in significant advancement in yields (Table 1, entry 8 and 9). As we

Table 1. Optimization of conditions for the (*R*,*R*)-**1** catalyzed asymmetric transfer reduction of 2,3-dimethyl-5-phenylisoxazolium tetrafluoroborate **2a**.[a]



2a **3a**

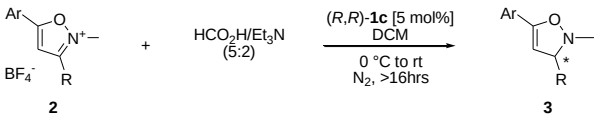
Entry	Cat. / Loading	Solvent	Yield[b]	*ee*[c]
1	**1a** / 3%	acetone	63	69
2	**1a** / 3%	$CHCl_3$/acetone (10%)	72	72
3	**1b** / 3%	$CHCl_3$/acetone (10%)	42	73
4	**1c** / 3%	$CHCl_3$/acetone (10%)	51	73
5	**1d** / 3%	$CHCl_3$/acetone (10%)	42	32
6	**1e** / 3%	$CHCl_3$/acetone (10%)	88	64
7	**1c** / 5%	$CHCl_3$/acetone (10%)	50	75
8	**1c** / 5%	DCM/acetone (10%)	85	77
9	**1c** / 5%	EtOAc/acetone (10%)	75	70
10	**1c** / 5%	THF	87	70
11	**1c** / 5%	DCM	91	78
12	**1c** / 5%	$CHCl_3$	85	78
13	**1c** / 5%	neat	0	-
14[d]	**1c** / 5%	DCM	90	78

[a] Reaction conditions: ca. 0.15 mmol **2a**, [**2a**] = 0.25M [v/v (HCO_2H/Et_3N : solvent) = 1:7], reaction time = >16 hrs, temperature = 15 ^{o}C to rt ; [b] Isolated yield; [c] Enantiomeric excess as determined by chiral HPLC; [d] Temperature = 0 ^{o}C to rt.

postulated that the presence of acetone could negatively impact effective extraction of product during work-up[19] hence reducing isolated yields, the investigation subsequently switched to the employment of pure solvent systems (Table 1, entries 10-13) with DCM affording the best outcomes at 91% yield and 78% *ee*. Omission of solvents, neat in triethylamine and formic acid solution gave no products (Table 1, entry 13). A lowering in temperature upon commencement of the reaction from 15 to 0 ^{o}C aimed to improve enantioselectivity. Surprisingly, it produced identical results within tolerable experimental limits as with the higher temperature (Table 1, entries 11 & 14); the lower temperature was selected due to the ease of starting at 0 ^{o}C. With the optimal conditions established, a series of representative arylisoxazolium salts **2** were screened and the outcomes displayed in Table 2. The

majority of the substrates bearing various substituents on the phenyl ring afforded a relatively consistent degree of enantioenrichment (Table 2, entries 1-9), with the electron-withdrawing analog **2i** producing a modest reduction in *ee* at 72% (Table 2, entry 9). Unlike the well-understood transition state (TS) control that operates for ketone reduction, where 1) CH/π interaction favours the TS leading to the major enantiomer (Scheme 1), and 2) repulsive interaction destabilises the TS leading to the minor enantiomer;[20] enantiocontrol during C=N bond reduction is less well understood. Nevertheless, our group[21] and others[22] have proposed that the major TS leading to imine reduction adopt an "open" TS (whilst retaining the stabilising CH/π interaction) as opposed to the cyclic (closed) TS involved in ketone reduction. Translating this proposition to the current system means that the observed stereocontrol could be attributed to the lesser or weaker extent of CH/π interaction within the transition state between the catalyst (**1c**) and **2i**, for the electronically deficient arene ring in **1c**

Table 2. Substrate scope for the (*R*,*R*)-**1c** catalyzed asymmetric transfer hydrogenation of arylisoxazolium salts **2**.[a]



Entry	Product	Ar	R	Yield[b]	*ee*[c]
1	**3a**	Ph	Me	90	78
2	**3b**	1-Nap	Me	93	76
3	**3c**	2-Nap	Me	88	79
4	**3d**	4-MeC_6H_4	Me	83	80
5	**3e**	4-MeOC_6H_4	Me	87	77
6	**3f**	3-MeOC_6H_4	Me	78	80
7	**3g**		Me	80	78
8	**3h**	2-MeOC_6H_4	Me	85	75
9	**3i**	4-ClC_6H_4	Me	89	72
10	**3j**	2-furyl	Me	68	62
11	**3k**	2-thiophene	Me	67	73
12	**3l**	3-thiophene	Me	70	81
13	**3m**	Ph	Ph	73	43

[a] Reaction conditions: ca. 0.15 mmol **2**, [**2**] = 0.25M [v/v (HCO_2H/Et_3N : DCM) = 1:7], reaction time = >16 hrs, temperature = 0 ^{o} C to rt; [b] Isolated yield; [c] Enantiomeric excess as determined by chiral HPLC.

favours an electron-rich ring over a poorer analog in **2** (Figure 2).

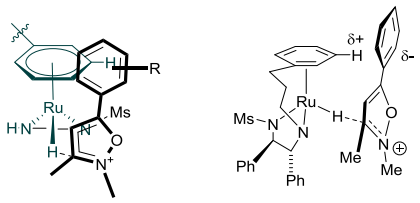


Figure 2. Postulated stereochemical perspective of the electronic interaction between (*R*,*R*)-**1c** and isoxazolium salts **2**.

Substrates possessing a heterocyclic ring generally produced poorer yields but comparable enantioselectivities compared to phenyl substituted derivatives (Table 2, entries 10-12). Isoxazolium **2m** bearing a 3-phenyl group in place of the typical methyl is a noteworthy example for it expectedly afforded a pronounced reduction in enantioenrichment (Table 2, entry 13). By virtue of the 2 phenyl rings present in **2m**, the newly added 3-phenyl ring now competes with the 5-positioned moiety for electronic interaction with the catalyst, bringing about a greater probability of nucleophilic hydride attack on both faces of the prochiral iminium carbon centre (Figure 3). A lowered degree of optical enrichment ensued, but more importantly, it supports and validates the mechanistic model whereby the aforementioned edge-face electronic interaction between the substrate and the catalyst is pivotal in imparting enantiocontrol.

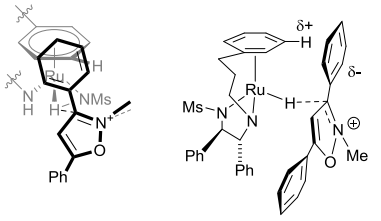


Figure 3. Competitive binding by 3-substituted phenyl to (*R*,*R*)-**1c**, bringing about poor optical enrichment of the corresponding product.

In conclusion, the employment of a tethered Noyori-type catalyst for the mild asymmetric reduction of arylisoxazolium tetrafluoroborate salts is reported. No undesired heterocyclic ring

opening was observed subsequent to iminium reduction. The employment of a 3,5-diphenyl substrate which expectedly produced a poorer outcome validates the established mechanism for the reduction of various substrates, reinforcing our understanding of the aforementioned class of ruthenium catalysts.

Experimental Section

General Experimental. Analytical grade solvents were used directly without further purification as purchased from commercial sources: dichloromethane (DCM), acetone and tetrahydrofuran from Merck; chloroform, ethyl acetate and petroleum spirit from Fischer Scientific. Chiral tethered ruthenium catalysts (*R,R*)-**1** supplied by Johnson Matthey, benzoylacetone and dibenzoylmethane from Sigma-Aldrich and trimethyl oxonium tetrafluoroborate (95%) from Acros Organics were used directly without further purification. Flash chromatography on silica was conducted on Sigma Aldrich silica gel (technical grade, pore size 60Å, 230-400 mesh, 40-63 µm particle size). Room temperature is defined to be approximately 21 ^{o}C.

NMR spectra were recorded on Bruker Avance 300 or Bruker Avance III HDF 500 spectrometers. ^{1}H NMR spectra chemical shifts were reported in δ ppm relative to chloroform-d (δ = 7.26 ppm) or acetone-d^{6} (δ = 2.05 ppm). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by nH while coupling constants were reported as *J* value in Hertz (Hz). ^{13}C NMR spectra chemical shifts were recorded relative to solvent resonance ($CDCl_3$: δ = 77.26 ppm or $(CD_3)_2CO$ δ = 29.84 or 206.26 ppm). Optical rotations of optically active amines were measured in the specified solution using a 2 dm cell with an Optical Activity Ltd. AA-1000 polarimeter. Chiral HPLC was performed on a Hewlett Packard 1050 HPLC machine incorporating a Diacel CHIRAPAK® IC, AD-H or CHIRALCEL® OJ, OD-H column.

General Procedure A for the Syntheses of Isoxazolium Salts with Dimethylsulphate. Procedure was adapted and modified from *J. Heterocyclic Chem.* **2003**, *40*, 1097. A mixture of the isoxazole (1 eq.) and dimethylsulphate (1.1 eq.) was refluxed in anhydrous toluene for 48-72 hours. Toluene was removed via rotary evaporation and a solution of sodium tetrafluoroborate (4 eq.) was

added to the reaction flask before cooling in an ice-bath. Crystals/solids formed were obtained by filtration and subsequently dried under high vacuum to afford isoxazolium salts (**2**).

General Procedure B for the Syntheses of Isoxazolium Salts with Trimethyloxonium Tetrafluoroborate. Procedure was adapted and modified from *Angew. Chem. Int. Ed*. **2008**, *47*, 7446. To a nitrogen filled 2-neck RBF was charged with the isoxazole (1 eq.) and anhydrous DCM before cooling with an ice bath. Trimethyloxonium tetraflurorborate (0.98 eq.) was subsequently added and the mixture allowed to stir overnight from 0 ^{o}C to room temperature (ice bath allowed to melt). Several drops of methanol were added to quench the reaction before subjecting the reaction flask to rotary evaporation. The residue was triturated with diethyl ether, filtered and washed twice with diethyl ether to afford **2**.

General Procedure C for the (*R*,*R*)-1 catalyzed asymmetric transfer hydrogenation (ATH) of 2. To a nitrogen flushed Schlenk tube was charged with isoxazolium tetrafluoroborate salt **2** (ca. 0.15 mmol) and catalyst (*R*,*R*)-**1** (3-5 mol%). Analytical grade solvent(s) were added to the mixture and cooled (0 or 15 ^{o}C) with stirring before addition of a 5:2 formic acid/triethylamine (TEAF) solution (v/v solvent(s) : TEAF = 7:1, [**2**] = 0.25M). The mixture was stirred overnight (> 16 hrs, 0/15 ^{o}C to rt) before quenching the unreacted formic acid with excess saturated sodium hydrogen carbonate (ca. 2 mL). The biphasic mixture was extracted 4 times with ethyl acetate and twice with DCM. Combined organic layers were concentrated then purified by flash chromatography on silica gel (eluent: petroleum spirit/ethyl acetate) to afford optically enriched Δ^4-isoxazolines (**3**).

2,3-dimethyl-5-phenylisoxazolium tetrafluoroborate 2a. Prepared in accordance to General Procedure A as colourless crystals (1.33g, 66%). ^{1}H ($(CD_3)_2CO$, 500 MHz): 2.84 (s, 3H), 4.51 (s, 3H), 7.67-7.70 (m, 3H), 7.74-7.77 (m, 1H), 8.05 (d, 2H, *J* = 8Hz); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 12.4 (1C), 39.0 (1C), 106.2 (1C), 124.2 (1C), 128.0 (2C), 130.7 (2C), 134.6 (1C), 162.3 (1C), 170.9 (1C); Melting range = 148-150 ^{o}C; HRMS (ESI-TOF) calcd. for $C_{11}H_{12}NO$ $[M\text{-}BF_4^-]^+$: 174.0913, found 174.0916.

2,3-dimethyl-5-(1-napthyl)isoxazolium tetrafluoroborate 2b. Prepared in accordance to General Procedure B as off-white solids (1.03g, 80%). ^{1}H ($(CD_3)_2CO$, 500 MHz): 2.94 (s, 3H), 4.61 (s, 3H), 7.71- 7.77 (m, 4H), 8.12-8.15 (m, 2H), 8.32 (d, 2H, *J* = 8Hz), 8.38 (d, 2H, *J* = 9Hz); ^{13}C (jmod)

($(CD_3)_2CO$, 126 MHz): 12.5 (1C), 39.2 (1C), 110.1 (1C), 121.4 (1C), 121.4 (1C), 124.9 (1C), 126.3 (1C), 128.2 (1C), 129.7 (1C), 130.1 (1C), 130.6 (1C), 131.1 (1C), 135.0 (1C), 161.9 (1C), 171.2 (1C); Melting range = 139-141 °C; HRMS (ESI-TOF) calcd. for $C_{15}H_{14}NO$ $[M\text{-}BF_4^-]^+$: 224.1070, found 224.1074.

2,3-dimethyl-5-(2-napthyl)isoxazolium tetrafluoroborate 2c. Prepared in accordance to General Procedure B as off-white solids (0.27g, 63%). ^1H ($(CD_3)_2CO$, 500 MHz): 2.89 (s, 3H), 4.56 (s, 3H), 7.69- 7.78 (m, 3H), 8.02-8.19 (m, 4H), 8.72 (s, 1H); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 12.4 (1C), 39.1 (1C), 106.4 (1C), 121.4 (1C), 123.2 (1C), 128.8 (1C), 129.0 (1C), 129.5 (1C), 130.2 (1C), 130.3 (1C), 130.7 (1C), 133.7 (1C), 136.3 (1C), 162.3 (1C), 171.1 (1C); Melting range = 169-170 °C; HRMS (ESI-TOF) calcd. for $C_{15}H_{14}NO$ $[M\text{-}BF_4^-]^+$: 224.1070, found 224.1068.

2,3-dimethyl-5-(4-methylphenyl)isoxazolium tetrafluoroborate 2d. Prepared in accordance to General Procedure A as white solids (0.23g, 24%). ^1H ($(CD_3)_2CO$, 500 MHz): 2.50 (s, 3H), 2.84 (s, 3H), 4.50 (s, 3H), 7.50 (d, 2H, *J* = 8Hz), 7.61 (s, 1H), 7.94 (d, 2H, *J* = 8Hz); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 12.3 (1C), 21.7 (1C), 38.9 (1C), 105.5 (1C), 121.5 (1C), 128.0 (2C), 131.3 (2C), 145.9 (1C), 162.1 (1C), 171.2 (1C); Melting range = 136-139 °C; HRMS (ESI-TOF) calcd. for $C_{12}H_{14}NO$ $[M\text{-}BF_4^-]^+$: 188.1070, found 188.1067.

2,3-dimethyl-5-(4-methoxyphenyl)isoxazolium tetrafluoroborate 2e. Prepared in accordance to General Procedure B as white solids (0.26g, 65%). ^1H ($(CD_3)_2CO$, 500 MHz): 2.82 (s, 3H), 3.95 (s, 3H), 4.48 (s, 3H), 7.21 (d, 2H, *J* = 9Hz), 7.51 (s, 1H), 8.01 (d, 2H, *J* = 9Hz); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 12.3 (1C), 38.8 (1C), 56.3 (1C), 104.4 (1C), 116.2 (2C), 116.4 (1C), 130.2 (2C), 161.9 (1C), 165.1 (1C), 171.2 (1C); Melting range = 166-167 °C; HRMS (ESI-TOF) calcd. for $C_{12}H_{14}NO_2$ $[M\text{-}BF_4^-]^+$: 204.1019, found 204.1018.

2,3-dimethyl-5-(3-methoxyphenyl)isoxazolium tetrafluoroborate 2f. Prepared in accordance to General Procedure B as white solids, (0.34g, 73%). ^1H ($(CD_3)_2CO$, 500 MHz): 2.86 (s, 3H), 3.92 (s, 3H), 4.52 (s, 3H), 7.30-7.32 (m, 1H), 7.58-7.63 (m, 3H), 7.70 (s, 1H); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 12.4 (1C), 39.0 (1C), 56.2 (1C), 106.4 (1C), 112.9 (1C), 120.2 (1C), 120.6 (1C), 125.3 (1C), 132.0 (1C), 161.4 (1C), 162.3 (1C), 170.8 (1C); Melting range = 170-171 °C; HRMS (ESI-TOF) calcd. for $C_{12}H_{14}NO_2$ $[M\text{-}BF_4^-]^+$: 204.1019, found 204.1021.

2,3-dimethyl-5-(3,4-methylenedioxyphenyl)isoxazolium tetrafluoroborate 2g. Prepared in accordance to General Procedure B as off-white solids (0.50g, 66%). ^{1}H ($(CD_3)_2CO$, 500 MHz): 2.83 (s, 3H), 4.48 (s, 3H), 6.22 (s, 2H), 7.14 (d, 1H, *J* = 8Hz), 7.50-7.52 (m, 2H), 7.65 (dd, 1H, *J* = 3,8Hz); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 12.3 (1C), 38.8 (1C), 103.8 (1C), 104.8 (1C), 107.3 (1C), 110.3 (1C), 117.8 (1C), 124.3 (1C), 150.0 (1C), 153.6 (1C), 162.0 (1C), 170.9 (1C); Melting range = 162-164 ^{o}C; HRMS (ESI-TOF) calcd. for $C_{12}H_{12}NO_3$ $[M\text{-}BF_4^-]^+$: 218.0812, found 218.0819.

2,3-dimethyl-5-(2-methoxyphenyl)isoxazolium tetrafluoroborate 2h. Prepared in accordance to General Procedure B as white solids (0.30g, 74%). ^{1}H ($(CD_3)_2CO$, 500 MHz): 2.85 (s, 3H), 4.10 (s, 3H), 4.50 (s, 3H), 7.22 (t, 1H, *J* = 8Hz), 7.37 (d, 1H, *J* = 9Hz), 7.62 (s, 1H), 7.71-7.75 (m, 1H), 7.96 (dd, 1H, *J* = 1,8Hz); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 12.3 (1C), 38.8 (1C), 56.7 (1C), 106.1 (1C), 112.7 (1C), 113.6 (1C), 122.2 (1C), 129.0 (1C), 136.4 (1C), 159.5 (1C), 161.8 (1C), 167.8 (1C); Melting range = 218-219 ^{o}C; HRMS (ESI-TOF) calcd. for $C_{12}H_{14}NO_2$ $[M\text{-}BF_4^-]^+$: 204.1019, found 204.1019.

2,3-dimethyl-5-(4-chlorophenyl)isoxazolium tetrafluoroborate 2i. Prepared in accordance to General Procedure A as white solids (0.82g, 66%). ^{1}H ($(CD_3)_2CO$, 500 MHz): 2.88 (s, 3H), 4.54 (s, 3H), 7.72 (s, 1H), 7.74 (d, 2H, *J* = 9Hz), 8.09 (d, 2H, *J* = 9Hz); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 12.5 (1C), 39.1 (1C), 106.7 (1C), 123.0 (1C), 129.8 (2C), 131.0 (2C), 140.4 (1C), 162.4 (1C), 169.9 (1C); Melting range = 163-164 ^{o}C; HRMS (ESI-TOF) calcd. for $C_{12}H_{11}NOCl$ $[M\text{-}BF_4^-]^+$: 208.0524 and 210.0494, found 208.0523 and 210.0491.

2,3-dimethyl-5-(2-furyl)isoxazolium tetrafluoroborate 2j. Prepared in accordance General Procedure A as pale brown crystals (0.75g, 35%). ^{1}H ($(CD_3)_2CO$, 500 MHz): 2.83 (s, 3H), 4.46 (s, 3H), 6.88-6.89 (m, 1H), 7.42 (s, 1H), 7.60 (d, 1H, *J* = 4Hz), 8.09 (s, 1H); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 12.4 (1C), 39.0 (1C), 104.6 (1C), 114.5 (1C), 118.8 (1C), 140.0 (1C), 149.9 (1C), 161.5 (1C), 162.1 (1C); Melting range = 144-146 ^{o}C; HRMS (ESI-TOF) calcd. for $C_9H_{10}NO_2$ $[M\text{-}BF_4^-]^+$: 164.0706, found 164.0709.

2,3-dimethyl-5-(2-thiophene)isoxazolium tetrafluoroborate 2k. Prepared in accordance to General Procedure B as off-white solids (0.49g, 82%). ^{1}H ($(CD_3)_2CO$, 500 MHz): 2.83 (s, 3H), 4.48 (s, 3H), 7.41 (t, 1H, *J* = 4Hz), 7.51 (s, 1H), 8.07 (d, 1H, *J* = 4Hz), 8.13 (d, 1H, *J* = 5Hz); ^{13}C (jmod)

($(CD_3)_2CO$, 126 MHz): 12.3 (1C), 38.9 (1C), 105.0 (1C), 125.1 (1C), 130.5 (1C), 134.0 (1C), 135.5 (1C), 162.2 (1C), 166.3 (1C); Melting range = 171-174 ^oC; HRMS (ESI-TOF) calcd. for $C_9H_{10}NOS$ $[M\text{-}BF_4^-]^+$: 180.0478, found 180.0480.

2,3-dimethyl-5-(3-thiophene)isoxazolium tetrafluoroborate 2l. Prepared in accordance to General Procedure B as pale brown solids (0.35g, 80%). ^1H ($(CD_3)_2CO$, 500 MHz): 2.83 (s, 3H), 4.47 (s, 3H), 7.51 (s, 1H), 7.72 (d, 1H, *J* = 3Hz), 7.85-7.86 (m, 1H), 8.55-8.55 (m, 1H); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 12.3 (1C), 38.8 (1C), 105.6 (1C), 125.5 (1C), 126.3 (1C), 130.4 (1C), 132.1 (1C), 162.1 (1C), 167.0 (1C); Melting range = 84-87 ^oC; HRMS (ESI-TOF) calcd. for $C_9H_{10}NOS$ $[M\text{-}BF_4^-]^+$: 180.0478, found 180.0479.

2-dimethyl-3,5-diphenylsoxazolium tetrafluoroborate 2m. Prepared in accordance to General Procedure B as white solids (0.22g, 37%). ^1H ($(CD_3)_2CO$, 500 MHz): 4.70 (s, 3H), 7.72-7.86 (m, 6H), 8.06 (d, 2H, *J* = 8Hz), 8.12 (s, 1H), 8.17 (d, 2H, *J* = 7Hz); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 41.0 (1C), 105.6 (1C), 123.8 (1C), 124.3 (1C), 128.3 (2C), 103.5 (2C), 130.8 (2C), 130.8 (2C), 134.6 (1C), 135.0 (1C), 161.5 (1C), 171.7 (1C); Melting range = 224-225 ^oC; HRMS (ESI-TOF) calcd. for $C_{16}H_{14}NO$ $[M\text{-}BF_4^-]^+$: 236.1070, found 236.1073.

(+)-2,3-dimethyl-5-phenyl-2,3-dihydroisoxazole 3a. Prepared in accordance to General Procedure C as a yellow oil, (Eluent: pet. ether / ethyl acetate (v/v) = 5/1, 22.0 mg, 90% yield, 78% *ee*). ^1H ($CDCl_3$, 500 MHz): 1.28 (d, 3H, *J* = 7Hz), 2.83 (s, 3H), 3.86 (br. s, 1H), 5.23 (d, 1H, *J* = 3Hz), 7.31-7.36 (m, 3H), 7.54 (d, 2H, *J* = 7Hz); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 22.1 (1C), 46.9 (1C), 69.0 (1C), 97.2 (1C), 125.8 (2C), 128.6 (2C), 129.0 (1C), 129.4 (1C), 152.0 (1C); HRMS (ESI-TOF) calcd. for $C_{11}H_{13}NONa$ $[M+Na]^+$: 198.0889, found 198.0884; HPLC (Diacel OD-H column, Hexane:IPA = 96:4, detection wavelength: λ = 254 nm, flow rate = 1 mL/min): t_1 = 5.94 min, t_2 = 7.22 min; $[\alpha]_D^{25}$ = +58.80^o (c = 0.99, $CHCl_3$).

(+)-2,3-dimethyl-5-(1-napthyl)-2,3-dihydroisoxazole 3b. Prepared in accordance to General Procedure C as a colourless oil (Eluent: pet. ether / ethyl acetate (v/v) = 5/1, 30.5 mg, 93% yield, 76% *ee*). ^1H ($CDCl_3$, 500 MHz): 1.40 (d, 3H, *J* = 7Hz), 2.95 (s, 3H), 3.98 (br. s, 1H), 5.20 (d, 1H, *J* = 3Hz), 7.44-7.55 (m, 4H), 7.67 (d, 1H, *J* = 7Hz), 7.85 (d, 2H, *J* = 8Hz), 8.38 (d, 1H, *J* = 9Hz); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 22.4 (1C), 46.9 (1C), 69.2 (1C), 101.8 (1C), 125.3 (1C), 125.7 (1C), 126.2

(1C), 126.7 (1C), 127.1 (1C), 127.2 (1C), 128.6 (1C), 129.8 (1C), 131.3 (1C), 133.9 (1C), 151.7 (1C); HRMS (ESI-TOF) calcd. for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1226, found 226.1228; HPLC (Diacel OD-H column, Hexane:IPA = 98:2, detection wavelength: λ = 254 nm, flow rate = 1 mL/min): t_1 = 15.98 min, t_2 = 21.04 min; $[\alpha]_D^{26}$ = +19.55° (c = 0.99, $CHCl_3$).

(+)-2,3-dimethyl-5-(2-napthyl)-2,3-dihydroisoxazole 3c Prepared in accordance to General Procedure C as a pale yellow oil (Eluent: pet. ether / ethyl acetate (v/v) = 5/1, 29.1 mg, 88% yield, 79% *ee*): ^1H ($CDCl_3$, 500 MHz): 1.32 (d, 3H, *J* = 7Hz), 2.88 (s, 3H), 3.92 (br. s, 1H), 5.37 (d, 1H, *J* = 3Hz), 7.47-7.49 (m, 2H), 7.60-7.62 (m, 1H), 7.79-7.86 (m, 3H), 8.01 (s, 1H); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 22.1 (1C), 46.9 (1C), 69.1 (1C), 98.1 (1C), 123.7 (1C), 124.8 (1C), 126.6 (1C), 126.7 (1C), 126.7 (1C), 127.9 (1C), 128.2 (1C), 128.6 (1C), 133.3 (1C), 133.6 (1C), 152.0 (1C); HRMS (ESI-TOF) calcd. for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1226, found 226.1224; HPLC (Diacel OD-H column, Hexane:IPA = 98:2, detection wavelength: λ = 254 nm, flow rate = 1 mL/min): t_1 = 14.72 min, t_2 = 18.56 min; $[\alpha]_D^{25}$ = +58.77° (c = 1.02, $CHCl_3$).

(+)-2,3-dimethyl-5-(4-methylphenyl)-2,3-dihydroisoxazole 3d. Prepared in accordance to General Procedure C as a colourless oil (Eluent: pet. ether / ethyl acetate (v/v) = 5/1, 23.7 mg, 83% yield, 80% *ee*). ^1H ($CDCl_3$, 300 MHz): 1.27 (d, 3H, *J* = 6Hz), 2.35 (s, 3H), 2.82 (s, 3H), 3.85 (br. s, 1H), 5.17 (d, 1H, *J* = 2Hz), 7.15 (d, 2H, *J* = 8Hz), 7.43 (d, 2H, *J* = 8Hz); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 21.6 (1C), 22.2 (1C), 46.8 (1C), 68.9 (1C), 96.3 (1C), 125.7 (2C), 126.6 (1C), 129.2 (2C), 139.0 (1C), 152.0 (1C); HRMS (ESI-TOF) calcd. for $C_{12}H_{15}NONa$ $[M+Na]^+$: 212.1046, found 212.1049; HPLC (Diacel IC column, Hexane:IPA = 97:3, detection wavelength: λ = 254 nm, flow rate = 1 mL/min): t_1 = 8.34 min, t_2 = 9.34 min; $[\alpha]_D^{25}$ = +53.77° (c = 1.01, $CHCl_3$).

(+)-2,3-dimethyl-5-(4-methoxyphenyl)-2,3-dihydroisoxazole 3e. Prepared in accordance to General Procedure C as a colourless oil (Eluent: pet. ether / ethyl acetate (v/v) = 5/1, 26.0 mg, 87% yield, 77% *ee*). ^1H ($CDCl_3$, 500 MHz): 1.26 (d, 3H, *J* = 6Hz), 2.81 (s, 3H), 3.82 (s, 3H), 3.84 (br. s, 1H), 5.09 (d, 1H, *J* = 2Hz), 6.87 (d, 2H, *J* = 9Hz), 7.47 (d, 2H, *J* = 9Hz); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 22.2 (1C), 46.8 (1C), 55.6 (1C), 69.0 (1C), 95.3 (1C), 114.0 (2C), 122.1 (1C), 127.2 (2C), 151.8 (1C), 160.2 (1C); HRMS (ESI-TOF) calcd. for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1176, found 206.1178;

HPLC (Diacel AD-H column, Hexane:IPA = 97:3, detection wavelength: λ = 254 nm, flow rate = 1 mL/min): t_1 = 9.05 min, t_2 = 10.41 min; $[\alpha]_D^{22}$ = +19.95° (c = 1.01, $CHCl_3$).

(+)-2,3-dimethyl-5-(3-methoxyphenyl)-2,3-dihydroisoxazole 3f. Prepared in accordance to General Procedure C as a colourless oil (Eluent: pet. ether / ethyl acetate (v/v) = 10/1, 23.2 mg, 78% yield, 80% *ee*). ^{1}H ($CDCl_3$, 300 MHz): 1.31 (d, 3H, *J* = 6Hz), 2.86 (s, 3H), 3.85 (s, 3H), 3.89 (br. s, 1H), 5.27 (d, 1H, *J* = 2Hz), 6.88-6.91 (m, 1H), 7.10 (s, 1H), 7.16-7.18 (m, 1H), 7.29-7.31 (m, 1H); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 22.1 (1C), 46.9 (1C), 55.5 (1C), 69.0 (1C), 97.6 (1C), 110.9 (1C), 115.0 (1C), 118.4 (1C), 129.6 (1C), 130.7 (1C), 151.9 (1C), 159.8 (1C); HRMS (ESI-TOF) calcd. for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1176, found 206.1176; HPLC (Diacel IC column, Hexane:IPA = 97:3, detection wavelength: λ = 254 nm, flow rate = 1 mL/min): t_1 = 11.98 min, t_2 = 14.25 min; $[\alpha]_D^{23}$ = +39.93° (c = 0.99, $CHCl_3$).

(+)-2,3-dimethyl-5-(3,4-methylenedioxyphenyl)-2,3-dihydroisoxazole 3g. Prepared in accordance to General Procedure C as a colourless oil (Eluent: pet. ether / ethyl acetate (v/v) = 10/1, 26.5 mg, 80% yield, 78% *ee*). ^{1}H ($CDCl_3$, 500 MHz): 1.26 (d, 3H, *J* = 6Hz), 2.81 (s, 3H), 3.83 (br. s, 1H), 5.08 (d, 1H, *J* = 3Hz), 5.97 (s, 2H), 6.78 (d, 1H, *J* = 8Hz), 7.00 (d, 1H, *J* = 1Hz), 7.06 (dd, 1H, *J* = 2,8Hz); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 22.2 (1C), 46.8 (1C), 69.0 (1C), 96.0 (1C), 101.4 (1C), 106.4 (1C), 108.4 (1C), 119.9 (1C), 123.5 (1C), 147.8 (1C), 148.3 (1C), 151.7 (1C); HRMS (ESI-TOF) calcd. for $C_{12}H_{14}NO_3$ $[M+H]^+$: 220.0968, found 220.0964; HPLC (Diacel OD-H column, Hexane:IPA = 98:2, detection wavelength: λ = 254 nm, flow rate = 1 mL/min): t_1 = 17.47 min, t_2 = 21.52 min; $[\alpha]_D^{21}$ = +59.24° (c = 1.01, $CHCl_3$).

(+)-2,3-dimethyl-5-(2-methoxyphenyl)-2,3-dihydroisoxazole 3h. Prepared in accordance to General Procedure C as a colourless oil (Eluent: pet. ether / ethyl acetate (v/v) = 5/1, 26.1 mg, 85% yield, 75% *ee*). ^{1}H ($CDCl_3$, 300 MHz): 1.27 (d, 3H, *J* = 6Hz), 2.79 (s, 3H), 3.89 (br. s, 1H), 3.92 (s, 3H), 5.65 (d, 1H, *J* = 2Hz), 6.91-6.99 (m, 2H), 7.26-7.31 (m, 1H), 7.58-7.61 (m, 1H); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 22.1 (1C), 46.7 (1C), 55.6 (1C), 69.4 (1C), 102.3 (1C), 110.7 (1C), 118.1 (1C), 120.6 (1C), 127.7 (1C), 129.6 (1C), 147.2 (1C), 157.1 (1C); HRMS (ESI-TOF) calcd. for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1176, found 206.1171; HPLC (Diacel AD-H column, Hexane:IPA = 97:3, detection

wavelength: λ = 254 nm, flow rate = 1 mL/min): t_1 = 9.33 min, t_2 = 10.64 min; $[\alpha]_D^{23}$ = +59.75° (c = 1.00, $CHCl_3$).

(+)-2,3-dimethyl-5-(4-chlorophenyl)-2,3-dihydroisoxazole 3i. Prepared in accordance to General Procedure C as a colourless oil (Eluent: pet. ether / ethyl acetate (v/v) = 10/1, 28.0 mg, 89% yield, 72% *ee*). ^{1}H ($CDCl_3$, 500 MHz): 1.27 (d, 3H, *J* = 4Hz), 2.81 (s, 3H), 3.86 (br. s, 1H), 5.22 (d, 1H, *J* = 3Hz), 7.31 (d, 2H, *J* = 9Hz), 7.45 (d, 2H, *J* = 9Hz); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 22.0 (1C), 46.8 (1C), 69.0 (1C), 97.8 (1C), 127.1 (2C), 127.8 (1C), 128.8 (2C), 134.7 (1C), 151.1 (1C); HRMS (ESI-TOF) calcd. for $C_{11}H_{13}NOCl$ $[M+H]^+$: 210.0680 & 212.0651, found 210.0678 & 212.0650; HPLC (Diacel OJ column, Hexane:IPA = 98:2, detection wavelength: λ = 254 nm, flow rate = 1 mL/min): t_1 = 13.66 min, t_2 = 18.55 min; $[\alpha]_D^{22}$ = +39.28° (c = 1.01, $CHCl_3$).

(+)-2,3-dimethyl-5-(2-furyl)-2,3-dihydroisoxazole 3j. Prepared in accordance to General Procedure C as a pale yellow oil (Eluent: pet. ether / ethyl acetate (v/v) = 10/1, 17.1 mg, 68% yield, 62% *ee*). ^{1}H ($CDCl_3$, 500 MHz): 1.26 (d, 3H, *J* = 6Hz), 2.80 (s, 3H), 3.84 (br. s, 1H), 5.20 (d, 1H, *J* = 3Hz), 6.41 (dd, 1H, *J* = 2,3Hz), 6.48 (d, 1H, *J* = 4Hz), 7.41 (s, 1H); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 21.9 (1C), 46.8 (1C), 68.8 (1C), 97.4 (1C), 108.6 (1C), 111.4 (1C), 143.2 (1C), 144.3 (1C), 144.8 (1C); HRMS (ESI-TOF) calcd. for $C_9H_{12}NO_2$ $[M+H]^+$: 166.0863, found 166.0860; HPLC (Diacel OJ column, Hexane:IPA = 99:1, detection wavelength: λ = 254 nm, flow rate = 1 mL/min): t_1 = 10.60 min, t_2 = 18.00 min; $[\alpha]_D^{23}$ = +45.74° (c = 1.02, $CHCl_3$).

(+)-2,3-dimethyl-5-(2-thiophene)-2,3-dihydroisoxazole 3k. Prepared in accordance to General Procedure C as a yellow oil (Eluent: pet. ether / ethyl acetate (v/v) = 10/1, 18.3 mg, 67% yield, 73% *ee*). ^{1}H ($CDCl_3$, 500 MHz): 1.27 (d, 3H, *J* = 7Hz), 2.82 (s, 3H), 3.84 (br. s, 1H), 5.13 (d, 1H, *J* = 3Hz), 7.00 (dd, 1H, *J* = 4,5Hz), 7.21 (d, 1H, *J* = 4Hz), 7.27 (d, 1H, *J* = 5Hz); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 22.0 (1C), 46.8 (1C), 69.1 (1C), 97.3 (1C), 125.8 (1C), 126.1 (1C), 127.6 (1C), 131.6 (1C), 147.2 (1C); HRMS (ESI-TOF) calcd. for $C_9H_{11}NOSNa$ $[M+Na]^+$: 204.0454, found 204.0451; HPLC (Diacel OD-H column, Hexane:IPA = 98:2, detection wavelength: λ = 254 nm, flow rate = 1 mL/min): t_1 = 9.34 min, t_2 = 12.24 min; $[\alpha]_D^{20}$ = +67.69° (c = 1.00, $CHCl_3$).

(+)-2,3-dimethyl-5-(3-thiophene)-2,3-dihydroisoxazole 3l. Prepared in accordance to General Procedure C as a pale yellow oil (Eluent: pet. ether / ethyl acetate (v/v) = 10/1, 18.7 mg, 70% yield,

81% *ee*). ^{1}H ($CDCl_3$, 500 MHz): 1.26 (d, 3H, *J* = 7Hz), 2.81 (s, 3H), 3.83 (br. s, 1H), 5.08 (d, 1H, *J* = 3Hz), 7.18 (d, 1H, *J* = 5Hz), 7.28-7.29 (m, 1H), 7.41 (d, 1H, *J* = 3Hz); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 22.1 (1C), 46.9 (1C), 68.8 (1C), 97.0 (1C), 122.6 (1C), 125.8 (1C), 126.2 (1C), 130.7 (1C), 148.4 (1C); HRMS (ESI-TOF) calcd. for $C_9H_{11}NOSNa$ $[M+Na]^+$: 204.0454, found 204.0450; HPLC (Diacel OD-H column, Hexane:IPA = 98:2, detection wavelength: λ = 254 nm, flow rate = 1 mL/min): t_1 = 11.42min, t_2 = 15.82 min; $[\alpha]_D^{23}$ = +51.90° (c = 1.01, $CHCl_3$).

(+)-2-dimethyl-3,5-diphenyl-2,3-dihydroisoxazole 3m. Prepared in accordance to General Procedure C as a pale yellow oil (Eluent: pet. ether / ethyl acetate (v/v) = 15/1, 26.4 mg, 73% yield, 43% *ee*). ^{1}H ($CDCl_3$, 500 MHz): 2.99 (s, 3H), 4.85 (br. s, 1H), 5.38 (d, 1H, *J* = 5Hz), 7.28-7.61 (m, 10H), 7.41 (d, 1H, *J* = 3Hz); ^{13}C (jmod) ($(CD_3)_2CO$, 126 MHz): 47.5 (1C), 77.3 (1C), 96.0 (1C), 126.0 (2C), 127.3 (1C), 128.0 (1C), 128.6 (2C), 128.9 (2C), 129.0 (1C), 129.3 (2C), 142.3 (1C), 152.7 (1C); HRMS (ESI-TOF) calcd. for $C_{16}H_{15}NONa$ $[M+Na]^+$: 260.1046, found 260.1040; HPLC (Diacel AD-H column, Hexane:IPA = 96:4, detection wavelength: λ = 254 nm, flow rate = 1 mL/min): t_1 = 7.36min, t_2 = 8.88 min; $[\alpha]_D^{25}$ = +56.52° (c = 1.01, $CHCl_3$).

Associated Content

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HPLC chromatograms of racemic and enantioenriched samples and copies of ^{1}H and ^{13}C NMR spectra.

R.J. Chew conceived the project, conducted the experiments and prepared the manuscript; M. Wills supervised the study and proofread the manuscript.

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