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Editor's choice paper

Synthesis of enantiomerically pure aryl, hetero aryl and alkyl sulfinimides catalyzed by recyclable tungstophosphoric acid

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ABSTRACT

A simple and efficient procedure was developed for the preparation of a variety of aryl, hetero aryl and alkyl N-sulfinylimines (**2b-2u**) with excellent yields (85–94%) using tungstophosphoric acid as catalyst. Also, this new synthetic protocol features high conversion, shorter reaction time, a straight forward and simple work up procedure. Catalyst was recycled for 10 times without much loss in activity and also scaled up in gram level with high yield. Hence, it is highly applicable for the industrial scale up process.

1. Introduction

Enantiomerically pure aldsulfinimides are important building blocks for the synthesis of a number of biologically active molecules [1,2], chiral amines [3–7], aziridines [8–10] and α- and β-aminophosphonic acids [11,12]. Though there are reports on the synthesis of aldimines [13–16], most of them have their own disadvantages such as use of stoichiometric, expensive reagents, harsh conditions, less yield and longer reaction time. Furthermore, titanium tetraethoxide mediated imine formation is the choice of most of the reactions reported so far. But the drawback of this particular reagent is the removal of titanium salt during the work up and also stoichiometric quantity used [13]. Yet, other reagents are also used for the aldimine formation such as metal based reagents or catalysts [14,15]. Recently, an effective method was developed by Reeves et al., wherein they use tris (2, 2, 2-trifluoroethyl) borate as reagent [16] for both aldimines and ketimines. But, it requires the use of very expensive and stoichiometric amount of reagent.

Chemical and pharmaceutical industries are forced to reduce the overall manufacturing cost in addition to environmentally benign synthetic procedure due to global competitiveness and stringent regulations enforced by the Environmental Protection Agencies (EPA's). Heteropoly acids (HPAs) are solid acids which are employed as homogenous and heterogeneous catalyst [17]. Interestingly, HPAs in solution are found to be stronger than the mineral acids such as H_2SO_4, HCl, HNO_3, etc., [18]. Furthermore, HPAs have significant properties like less toxic, suitable to handle in any quantity, environmentally benign character, cost effectiveness and commercial availability [19]. Among the many available acids, keggin's HPAs are more stable and readily employable (tungstophosphoric acid (TPA), phosphomolybdic acid (PMA), silicotungstic acid (STA)) [20,21].

Furthermore, a clean, high yielding, recyclable, optically pure and scalable method would offer many advantages such as operational simplicity and less wastage generation. Usage of recyclable catalyst is more favored in industries due to its economic viability, easy separation and less wastage generation. Hence, we herein wish to report a simple and efficient process for the preparation of aryl, hetero aryl and aliphatic aldimines in the presence of tungstophosphoric acid as catalyst. To the best of our knowledge, the use of the TPA as catalyst for synthesis of aldsulfinyl imines has not been reported so far.

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2468-8231/

Table 1
Effect of amounts of TPA and other catalysts on the synthesis of (*S*)-**2a** by the reaction of benzaldehyde (**1a**), with (*S*)-*t*-butylsulfinamide ((*S*)-**3**).

Entries	Catalyst	Substrate/Amine /Cat. (Equiv.)	Time (h)	Temp (°C)	Isolated yield (%)[c]
1	SPEEK/TPA (A)[a]	1:1.2:40[b]	24	rt	90
2	SPEEK/TSA (B)[a]	1:1.2:40[b]	24	rt	87
3	$H_4SiW_{12}O_{40}nH_2O$ (C)	1:1.2:0.2	20	rt	80
4	$H_3PW_{12}O_{40}$ (D)	1:1.2:0.2	12	rt	93
5	$H_3PW_{12}O_{40}$ (D)	1:1.2:0.1	1	60	93
6	$H_3PW_{12}O_{40}$ (D)	1:1.2:0.01	2	60	92
7	Zeolite ZSM-5 (E)	1:1:20[b]	2	60	60
8	Amberlite® IR120 hydrogen form (F)	1:1:20[b]	2	60	75
9	Montmorillonite (G)	1:1:20[b]	2	60	70
10	Aluminium silicate (H)	1:1:20[b]	2	60	48

[a] SPEEK – Sulfonylated poly (ether ether ketone).
[b] 40 and 20 represent the wt% with the starting material.
[c] The products were purified by column chromatography on silica gel (230–400 mesh, EtOAc – petroleum ether, 9:1).

2. Experimental section

Unless otherwise stated, all reactions were performed in flame-dried glassware under an atmosphere of N_2. All chemicals and reagents such as aldehydes, (*S*)-*t*-$BuSONH_2$, (*RS*)-*t*-$BuSONH_2$, phosphotungstic acid, tungstosilisic acid, zeolite ZSM-5 (SiO_2:Al_2O_3 = 50:1), amberlite® IR120 hydrogen form, montmorillonite K10 and aluminium silicate ($3Al_2O_3 \cdot 2SiO_2$) were purchased from Aldrich and Alfa Aesar suppliers and used without further purification. Flash column chromatography was performed with silica gel (230–400 mesh size). Thin layer chromatography (TLC) was performed on precoated silica gel plates (Merck 60, F254, 0.25 mm); detection was accomplished using a UV254 light and staining with phosphomolybdic acid staining solution; NMR data was recorded on a Bruker 500 MHz spectrometer, operating at 500 MHz for ^1H acquisitions in the indicated deuterated solvent. Chemical shifts (δ) are reported in parts per million (ppm) and relative to TMS at 0 ppm. The data is reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz). HPLC analysis was performed on a Shimadzu prominence UFLC binary gradient HPLC system. Conversion was determined by the HPLC using analytical C_{18} column. The enantiomeric purities (% e.e.) of **2b** and **2l** were determined by chiral HPLC analysis in comparison with racemates. The column used was Chiralpak® AD-H LC column 250 × 4.6 mm. The mobile phase was hexane – isopropanol at a flow rate of 0.4 mL min^{-1} and the absorbance was monitored using a UV detector at 254 nm.

2.1. Synthesis of sulfonated poly (ether ether ketone) (*SPEEK*)

The sulfonation of poly (ether ether ketone) (PEEK) was performed according to the reported literature [25,26]. The powdered form of PEEK was first dried in a vacuum oven at 100 °C for 24 h. A volume of 100 mL of conc. sulfuric acid was taken in a round bottom flask and heated up to 40 °C in a water bath fitted in a magnetic stirrer. A quantity of 2.0 g of dried PEEK was slowly transferred to the acid for the period of 1 h. The reaction mass was constantly stirred and maintained at 50 °C for 5 h. The obtained viscous solution was slowly transferred to the beaker containing large excess of ice-water. The resultant pink colored solid was filtered and washed thoroughly with de-ionized water until the neutral pH reached. The resulted sulfonated PEEK was dried at 100 °C for 12 h in a vacuum oven.

2.2. Preparation of SPEEK – Heteropoly acids (HPA) composite membranes

The acid form of 5 wt% SPEEK polymer was dissolved in N, N-dimethylacetamide with constant stirring using a magnetic stirrer. After the whole dissolution of SPEEK, 20 wt% heteropoly acids (silicotungstic acid and phosphotungstic acid) was added, stirred well and heated up to 60 °C for 6 h. After that the viscous polymer solution was cast onto a flat glass plate using a thin glass rod and was kept in a closed chamber for 24 h. The cast membranes were dried at 60 °C for 6 h, 90 °C for 8 h and 140 °C for 3 h. The resultant dried films were soaked in de-ionized water overnight to release the membranes from the glass plates. Then the composite membranes were carefully washed with de-ionized water and dried in a vacuum oven at 100 °C for 12 h. The infra-red absorption bands of W-O-W and W = O vibrations for HPA were obtained at 895 cm^{-1} and 980 cm^{-1} respectively. These characteristic absorptions confirm the successful incorporation of the tungstic acid in to the SPEEK polymer.

2.3. Synthesis of (E)-N-benzylidene-2-methylpropane-2-sulfinamide (2b) using SPEEK/heteropoly acids (HPA or STA) or STA or TPA

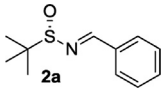
To a stirred solution of benzaldehyde **1** (2 mmol) in toluene (5 mL) was added 2-methyl-2-propanesulfinamide (**3**; 2.4 mmol) under inert conditions. Catalysts A or B (40 wt%) and catalysts C or D (as mentioned in Table 1) was added and the reaction mixture was heated to 60 °C for 2–4 h. Progress of the reaction was monitored by TLC. After the reaction was complete, the reaction mixture was allowed to room temperature. Crude reaction mixture was filtered and then washed with toluene. The solvent was evaporated under reduced pressure to obtain a crude mass, which was purified by flash chromatography on silica gel using hexanes-EtOAc as eluent to afford pure compound **2a.**

2.4. Recyclability test on PTA for the synthesis of (E)-N-benzylidene-2-methylpropane-2-sulfinamide (2b)

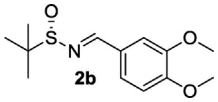
To a stirred solution of benzaldehyde **1a** (2 mmol) in toluene (5 mL) was added 2-methyl-2-propanesulfinamide (**3**; 2.4 mmol) under inert conditions in a 10 mL screw capped vial. TPA (1 mol%) was added and the reaction mixture was heated to 60 °C for 2–6 h. Progress of the reaction was monitored by TLC. The reaction mixture was allowed to room temperature and then filtered through a sintered crucible and washed with toluene (2 × 2 mL). The solvent was evaporated under reduced pressure to obtain a crude compound, which was purified by flash chromatography on silica gel using hexanes–EtOAc as eluent to obtain compound **2a.** Recovered catalyst was reused by following the same procedure. The reaction was repeated using recovered catalyst for 10 subsequent cycles. Yields ranged from 90 to 92%.

2.5. Synthesis of enantiomerically pure N-*(*tert*-Butylsulfinyl) imines (2a to 2u) using PTA; General procedure*

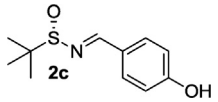
To a dry 10 mL conical vial were added aldehyde, **1a** to **1 u** (2.0 mmol, 1.0equiv), (*S*)-*tert*-butanesulfinamide (291 mg, 2.4 mmol, 1.2 equiv) and toluene (5.0 mL) under nitrogen atmosphere. To this solution was added TPA (1 mol%) and the solution was stirred at 60 °C for 2–4 h. Reaction progress was monitored by TLC and HPLC. After completion of the reaction, the reaction mixture was allowed to room temperature and then catalyst was filtered through filter paper and washed with toluene (2 × 2 mL). The solvent was evaporated under reduced pressure to obtain a crude compound, which was purified by flash chromatography on silica gel using eluant hexanes–EtOAc to obtain enantiomerically pure aldsulfinimides, **2a** to **2u.**



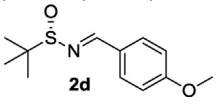
1. (*S*)-(*E*)-N-benzylidene-2-methylpropane-2-sulfinamide (2a): Yield: 92%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 8.50 (s, 1H), 7.77 (m, 2H), 7.38 (m, 2H), 1.17(s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 161.82, 132.02, 131.43, 128.36, 127.92, 56.76, 21.58.



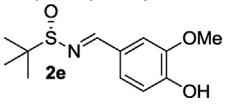
2. (*S*)-(*E*)-N-(3,4-dimethoxybenzylidene)-2-methylpropane-2-sulfinamide (**2b**): Yield: 91%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 8.49 (s, 1H), 7.45 (S, 1H), 7.38 (d, *J* = 8.0 Hz, 1H, ArH), 6.95 (d, *J* = 8.50 Hz, 1H), 3.95 (s, 6H), 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 162.0, 152.9, 149.4, 127.4, 125.0, 110.7, 109.9, 57.5, 56.0, 55.9, 22.5



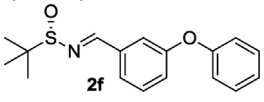
3. (*S*)-(*E*)-*N*-(4-hydroxybenzylidene)-2-methylpropane-2-sulfinamide (2c): Yield: 86%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 10.37(bs, 1H); 8.41 (s, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 1.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) = 162.24, 162.16, 132.00, 125.86, 116.40, 57.33, 22.48.



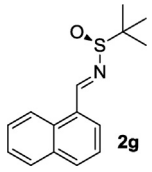
4. *(S)-(E)-N*-(4-Methoxybenzylidene)-2-methylpropane-2-sulfinamide (**2d**): Yield: 93%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 8.42 (s, 1H), 7.72- 7.70 (d, *J* = 8 Hz, 2H), 6.88-6.87 (d, *J* = 8 Hz, 2H). 3.78 (s, 3H), 1.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 163.1, 161.8, 131.3, 127.3, 114.4, 57.6, 55.5, 22.6.



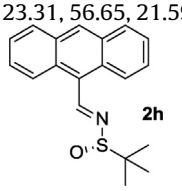
5. (*S*)-(*E*)-*N*-(4-hydroxy-3-methoxybenzylidene)-2-methylpropane-2-sulfinamide (2e): Yield: 92%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 8.47 (s, 1H), 7.42 (s, 1H), 7.36 (d, *J* = 7.0 Hz, 1H), 7.00 (d, *J* = 8 Hz, 1H), 6.41(bs, 1H), 3.96(s, 3H) 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm)162.16, 150.00, 147.06, 127.10, 125.46, 114.66, 109.83, 57.65, 56.06, 22.60



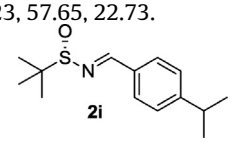
6. (*S*)-(*E*)-2-methyl-*N*-(3-phenoxybenzylidene)propane-2-sulfinamide (2f): Yield: 91%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 8.53 (m, 1H), 7.57 (d, *J* = 8 Hz, 1H), 7.50 (t, *J* = 2.5 Hz, 1H, 1H), 7.42 (t, *J* = 8 Hz, 1H), 7.31 (t, *J* = 8 Hz, 1H), 7.15 (m, 2H), 7.05 (d, *J* = 8 Hz, 2H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 157.46, 153.31, 151.75, 131.08, 125.56, 125.22, 119.53, 119.18, 117.72, 114.52, 113.96, 53.17, 17.90.



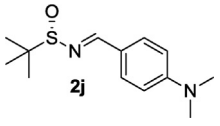
7. (*S*)-(*E*)-2-methyl-*N*-(naphthalen-1-ylmethylene)propane-2-sulfinamide (**2 g**): Yield: 94%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 9.05 (s, 1H), 8.93 (d, *J* = 8.5 Hz, 1H), 7.93 (m, 2H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.53-7.45(4H, m), 1.22 (9H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 161.46, 132.84, 132.27, 130.97, 130.17, 128.31, 127.80, 127.00, 125.45, 124.18, 123.31, 56.65, 21.59.



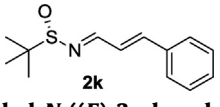
8.(*S*)-(*E*)-*N*-(anthracen-9-ylmethylene)-2-methylpropane-2-sulfinamide (2 h): Yield: 90%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 9.79 (s, 1H), 8.76 (d, *J* = 8.0 Hz, 2H), 8.43 (s, 1H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.49–7.47 (m, 2H), 7.41–7.40 (m, 2H), 1.27 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 61.88, 132.62, 131.20, 129.23, 128.3, 128.00, 125.55, 124.23, 57.65, 22.73.



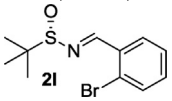
9. (*S*)-(*E*)-*N*-(4-isopropylbenzylidene)-2-methylpropane-2-sulfinamide (2i): Yield: 90%, ^{1}H— NMR ($CDCl_3$, 500 MHz) (δ, ppm) 8.48 (s, 1H), 7.71-7.69 (d, *J* = 8 Hz, 2H), 7.26-7.24 (d, *J* = 8 Hz, 2H), 2.88 (m, 1H), 1.20 −1.17 (m, 15H). ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 157.78, 149.24, 127.28, 124.83, 122.34, 52.94, 29.59, 18.98, 17.87.



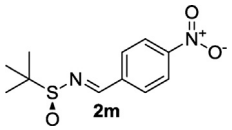
10. (*S*)-(*E*)-*N*-(4-(dimethylamino)benzylidene)-2-methylpropane-2-sulfinamide (**2j**): Yield: 89%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 8.31 (s, 1H), 7.60-8.58 (d, *J* = 8 Hz, 2H), 6.56-6.54 (d, *J* = 8 Hz, 2H), 2.89(s, 6H), 1.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 161.56, 153.01, 131.16, 122.27, 111.33, 57.23, 40.00, 22.49.



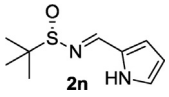
11. (*S*)-(*E*)-2-methyl-*N*-((*E*)-3-phenylallylidene)propane-2-sulfinamide (2k): Yield: 89%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 8.28 (d, *J* = 9.0 Hz, 1H), 7.43-7.40 (dd, *J* = 1.5; 8 Hz, 2H), 7.28-7.26 (m, 3H), 7.12 (d, *J* = 16.0 Hz, 2H), 7.00 (dd, *J* = 9.0, 15.5 Hz, 1H), 1.15 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 163.77, 146.38, 135.00, 130.24, 128.96, 127.90, 125.50, 57.53, 22.49.



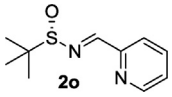
12. (*S*)-(*E*)-*N*-(2-bromobenzylidene)-2-methylpropane-2-sulfinamide (2l): Yield: 92%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 8.90 (s, 1H), 7.97 (dd, *J* = 1.5; 7.5 Hz, 1H), 7.57 (dd, *J* = 1.0; 7.5 Hz, 1H), 7.31 (m, 2H), 1.20 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 162.17, 133.65, 133.36, 132.85, 129.64, 127.73, 126.41, 58.03, 22.72.



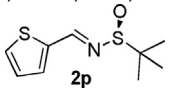
13. (*S*)-(*E*)-2-methyl-*N*-(4-nitrobenzylidene)propane-2-sulfinamide (2m): Yield: 93%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 8.60 (s, 1H), 8.27-8.25 (d, *J* = 8.5 Hz, 2H), 6.56-6.54 (d, *J* = 8.5 Hz, 2H), 1.22 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 160.7, 149.8, 138.9, 130.0, 124.2, 58.5, 22.7.



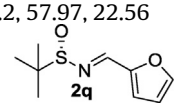
14. (*S*)-(*E*)-*N*-((1*H*-pyrrol-2-yl)methylene)-2-methylpropane-2-sulfinamide (2n): Yield: 92%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 9.72 (bs, 1H), 8.41 (s, 1H), 7.04 (s, 1H), 6.77 (s, 1H), 6.32(d, J = Hz, 1H) 1.22 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 152.00, 129.34, 124.87, 118.40, 111.04, 57.50, 22.43.



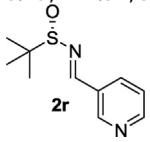
15. (*S*)-(*E*)-2-methyl-*N*-(pyridin-2-ylmethylene)propane-2-sulfinamide (2o): Yield: 93%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 8.75 (m, 1H), 8.71 (s, 1H), 8.01 (d; *J* = 7.8, 1H), 7.82 (m, 1H), 7.40 (m, 1H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 163.7, 152.5, 150.2, 136.8, 125.9, 123.1, 58.5, 22.7



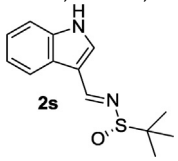
16. (*S*)(*E*)-2-methyl-*N*-(thiophen-2-ylmethylene) propane-2-sulfinamide (2p): Yield: 92%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 8.68 (s, 1H), 7.59 (d, *J* = 5.0 Hz, 1H), 7.53 (dd, *J* = 3.6, 0.9 Hz, 1H), 7.12-7.16 (m, 1H), 1.25 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 155.5, 140.5, 133.8, 132.3, 128.2, 57.97, 22.56



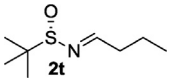
17. (*S*)-(*E*)-*N*-(furan-2-ylmethylene)-2-methylpropane-2-sulfinamide (2q): Yield: 91%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 8.31 (s, 1H), 7.57 (s, 1H), 6.95 (d, *J* = 3.5 Hz, 1H), 6.50(dd, *J* = 1.5; 3.5 Hz, 1H), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 150.76, 149.83, 146.84, 118.73, 112.54, 57.80, 22.45.



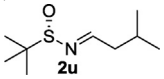
18. (*S*)-(*E*)-2-methyl-*N*-(pyridin-3-ylmethylene)propane-2-sulfinamide (2r): Yield: 92%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 8.97(s, 1H), 8.67(d, *J* = 5 Hz, 1H), 8.58(s, 1H), 8.12(d, *J* = 8 Hz, 1H), 7.37(m, 1H), 1.21(s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 160.43, 152.86, 150.94, 135.78, 129.70, 123.98, 58.16, 22.63.



19. (*S*)-(*E*)-*N*-((1H-indol-3-yl)methylene)-2-methylpropane-2-sulfinamide (2s): Yield: 92%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 9.56 (bs, 1H), 8.78(s, 1H), 8.31 (dd, *J* = 2.5,7 Hz, 1H), 7.64(d, *J* = 3 Hz, 1H), 7.47 (dd, *J* = 1.5; 6.5 Hz, 2H), 7.33–7.27 (m, 2H), 1.31 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 156.37, 137.09, 132.70, 124.87, 124.04, 122.35, 122.18, 115.20, 111.74, 57.13, 22.50.



20. (*S*)-(*E*)-*N*-butylidene-2-methylpropane-2-sulfinamide (2t): Yield: 85%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 7.99 (m, 1H), 2.43 (m, 2H), 1.60 (m, 2H), 1.12 (s, 9H), 0.92 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 168.54, 55.41, 37.02, 21.31, 17.91, 12.79.



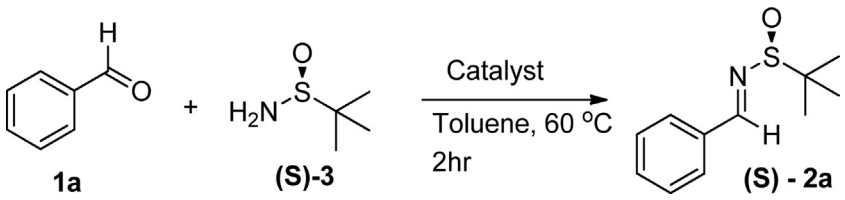
21. (*S*)-(*E*)-2-methyl-*N*-(3-methylbutylidene)propane-2-sulfinamide (2u): Yield: 87%, ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, ppm) 8.05 (m, 1H), 2.41 (m, 2H), 2.08 (m, 1H), 1.20 (s, 9H), 1.01 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) (δ, ppm) 169.42, 56.52, 44.94, 26.15, 22.62, 22.54, 22.36.

3. Results and discussion

Chiral aldsulfinimides are important building blocks for medicinal chemistry research [22,23]. We aimed to investigate for an effective catalyst on the synthesis of chiral aldsulfinimides from aldehydes and (*S*)-2-methyl-2-propanesulfinamide (**3**). Reported methods on direct condensation of sulfinamide with aldehydes using either molecular sieves or sodium sulfate were not effective to obtain the aldsulfinimides in high yields. Also, use of magnesium sulfate coupled with pyridium *p*-toluenesulfonate for the imine formation has resulted in quantitative yield but process may not be feasible for large scale production under stringent dry conditions [24]. Hence, we envisaged to make use of polymer supported heteropoly acid (HPA) as catalyst for the formation of aldsulfinimides by treating the benzaldehyde (**1**) as a model substrate. Employing the polymer supported HPA's would help the easy separation of catalyst from the reaction mixture and its subsequent reuse. Therefore, the preparation of the polymer supported HPA's (entries **1** and **2**; Table 1) was carried out based on the parallel procedure reported in the literature [25,26]. The synthesized polymer supported catalysts (**A** and **B,** Table 1) were employed for the proposed reaction (Scheme 1). Reaction was carried out in toluene using 40 wt% catalysts at rt for 24 h. Reaction proceeded smoothly and gave isolated yields of 87% and 90% for polymer supported STA and TPA respectively. Catalyst employed was recovered without any loss and reused for another two cycles. However, its activity was found to be diminishing after two cycles.

This result has encouraged us to use the HPA's without any support or modification. To our delight, the reaction proceeded to almost complete conversion using tungstophosphoric acid (TPA) (20 mol%) at rt after 12 h, whereas silicotungstic acid (STA) (20 mol%) gave only 85% conversion (entries **3** and **4**, Table 1). After the reaction, TPA was found to be in heterogeneous state at rt in the reaction medium. Furthermore, TPA was taken for subsequent optimization since high yield was obtained.

With the focus on catalyst loading, 10 and 1 mol% of catalyst was employed under similar reaction conditions at rt. Both the reactions were found to be slow. To overcome this drawback, temperature of the reaction was increased to 60 °C and the reaction was completed in 2 h. 10 and 1 mol% did not show any drastic change in the yield obtained. Reaction mixture was allowed to rt and catalyst was recovered by simple filtration. Concentration of crude filtrate was found to be containing the benzaldsulfinimide (**2b**) as the only product, without significant amounts of either **1a** or **3**. Yields ranged from 92 to 93% (entries **5** and **6**, Table 1). Also, time course of the reaction was studied for the formation of **2b** catalyzed by TPA as shown in Fig. 1. Furthermore, reaction was carried out using other solid catalysts such as zeolite ZSM-5 (E), amberlite® IR120 hydrogen form (F), montmorillonite K10 (G) and silica-alumina (H) for the synthesis of sulfinamide under opti-



Scheme 1. Synthesis of (*E*)-*N*-benzylidene-2-methylpropane-2-sulfinamide **(2a).**

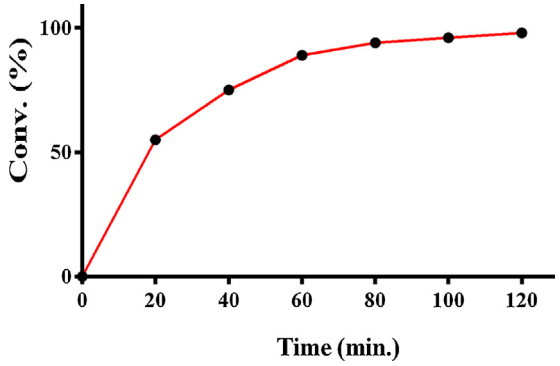


Fig. 1. Time course for the formation of benzaldsulfinamide catalyzed by TPA. Reaction conditions: TPA (1 mol%), benzaldehyde (2.0 mmol), 2-methyl-2-propanesulfinamide (2.4 mmol), Toluene (5 mL), 60 °C, under N_2 atm.

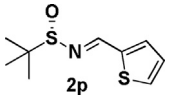
mized conditions. All of them led to the desired product with yields ranging from 48 to 75%. The results obtained, as shown in Table 1 (entries 7, 8, 9 and 10), have clearly prompted us to proceed with TPA as the choice of catalyst in order to further study the scope of the reaction. Earlier, Sanaboina et al., had reported the synthesis of *N*-(*tert*-butylsulfinyl)imines catalyzed by Amberlist-15 under microwave conditions [27]. However, reaction requires 20 mol% of the catalyst and THF as solvent.

The scope of the reaction was subsequently explored with respect to various aromatic aldehydes, hetero aromatic aldehydes and aliphatic aldehydes (Scheme 2, Table 2, substrates **1b-1m, 1n –1s and 1t- 1u**, respectively). Very good to excellent yields were obtained for both electron withdrawing and electron donating (**1b-1m**) aryl aldehydes. Progress of the reaction was analyzed by TLC and HPLC except aliphatic aldehydes wherein NMR was used. Maximum conversion was achieved in 2–4 h for all the substrates (**1b**-**1u**, Table 2).

In order to study the electronic effects of the substituents, we employed the aryl aldehydes with electron donating substituents for the synthesis of aldsulfinimides (**2b-2k**, Table 2). All of them resulted in high yields. Reaction with unreactive electron rich aldehyde, 4-methoxy benzaldehyde gave **2d** in excellent yield (93%). Furthermore, the substrate with larger substituent at *m*-position (**1f**) was found to be desirable and afforded in 91% yield. Nevertheless, it is significant to note that, our results are very much comparable with the work reported in the literature using stoichiometric quantity of reagents such as $Ti(OEt)_4$ and $B(OCH_2CF_3)_3$ [14,16,28]. Imine formation for the substrates with electron withdrawing substituents (**1l** to **1m**) proceeded smoothly and resulted in high yields (90–92%). From the above experiments, it was evident that, the method was tolerant to various functional groups such as electron-rich as well as electron-deficient on aromatic rings under the optimized conditions (Table 2).

Heterocyclic aldehydes such as pyridine, pyrrole, indole, furan and thiophene, (**1n-1s**) were also converted into their corresponding imines in high yields ranging from 90 to 93% (Table 2). It was observed that, pyridine-3-carboxaldehyde does not give the expected product in the presence of $CuSO_4$ since it is ineffective as

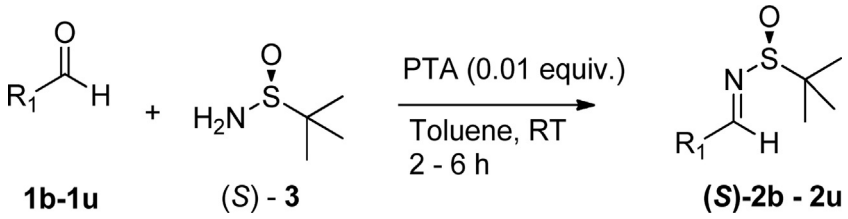
Table 2
TPA catalyzed synthesis of enantiomerically pure various substituted aryl, hetero aryl and aliphatic aldsulfinimides ((*S*) – **2b-2u**).

Substrates[a]	R_1	Time (h)	Yield (%)[b]
1b	3,4-$(MeO)_2$Ph—	2	91
1c	*4*-OH Ph-	3	86
1d	4-OMePh-	2	93
1e		2	92
1f	*m*-Pho- C6H4-	4	91
1g		3	94
1h		3	90
1i	p-^{i}PrPh	2	90
1j		2	89
1k		3	89
1l	*2*-Br Ph		92
1m	4-NO_2Ph	3	93
1n		3	92
1o		3	93
1p		3	92
1q		3	91
1r		4	92
1s		2	92
1t		3	85
1u		3	87

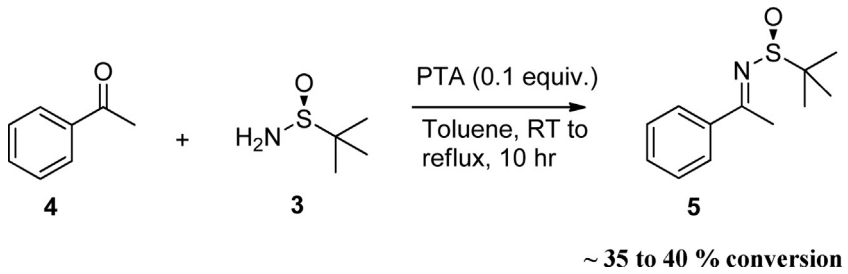
[a] Substrates 1b-u and (S)-3 were used in 1:1.2 ratio unless otherwise mentioned.
[b] Yield refers to isolated material. Products were characterized by ^1H and ^{13}C NMR analyses.

noted by Liu and co-workers [14]. In contrast, our reaction required only 2.0 equiv. of **3** to afford the desired product **2 s** in 92% yield. Interestingly, even the less active aldehyde, furfural (**1q**) was also effectively converted to their corresponding imine product (**2q**) in quantitative yield.

Also, we were very much interested in employing the enolizable aliphatic aldehydes **1 t** and **1 u** containing alkyl chains such as isobutyl (**1t**) and *n*-propyl (**1u**). The previous reports on aliphatic aldehydes have shown the decrease [14] or equal [16] in yield when compared to our yields. Gratifyingly, reaction of aliphatic aldehydes using TPA resulted in good yields ranged from 85 to 87% (Table 2). Another important observation is that, all the preparation of aldimines **2b-2u**, was pure enough and can be taken for next stage since the catalyst was simply filtered it off.



Scheme 2. Synthesis of various aldsulfinamides (**2b-2u**).



Scheme 3. Synthesis of (*S*)-(*E*)-2-methyl-*N*-(1-phenylethylidene)propane-2-sulfinamide (**5**) using TPA.

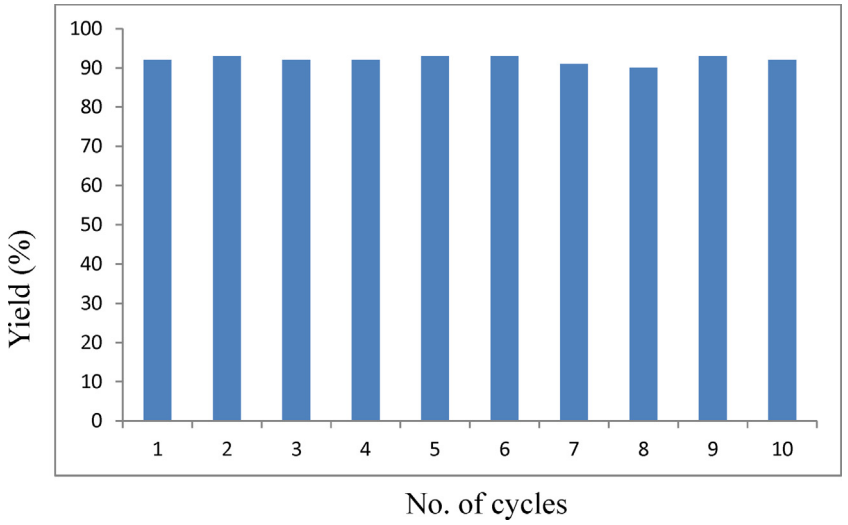


Fig. 2. Recyclability of TPA for the synthesis of (*E*)-N-benzylidene-2-methylpropane-2-sulfinamide (**2a**) at 60 °C (t = 2–6 h).

Also, we have extended the reaction to check the recyclability of the catalyst under the same reaction conditions. Recyclability was tested in 2 mmol scale for 10 cycles. The conversion was found to be same even after 10th cycle as shown in Fig. 2. Catalytic activity almost remained as same as that of the 1st cycle. Yield of the reaction at the 10th cycle was 91%. Besides the recyclability, study was also carried out for the scale up viability. Reaction was performed in 1 g scale by treating the benzaldehyde (**1a**; 1 g, 9.4 mmol) with 2-methyl-2-propanesulfinamide (**3**; 1.36 g, 11.28 mmol) under the optimized conditions. Reaction gave rise to the desired product (**2a**) in quantitative yield (1.82 g, 93%). Recyclability coupled with scalability, the process can be employed for the preparation of aldsulfinimides on commercial scale.

Enantiomeric purity of selective products (**2a** and **2l**) was analyzed by chiral HPLC. Gratifyingly, enantiomeric excess (e.e.) of the products formed were found to be as same as that of the e.e., of starting material (**3a**) (supplementary data). There was no racemization during the reaction. Hence, this method shows that, it is suitable for the synthesis of enantiomerically pure aldsulfinimides. Also, it is imperative to note that the first asymmetric synthesis of aldsulfinimides was reported by Liu and co-workers [14].

To study the scope of the methodology, reaction was also extended to the ketone moieties. As a result, acetophenone (**4**) was treated with methyl-2-propanesulfinamide (**3**) under the standard conditions (Scheme 3). Though the reaction gave the desired product, ketosulfinimide (**5**) in lower conversion (~35 to 40%), but it did not generate any side product. Even increasing the temperature to reflux as well as extending the reaction time to 24 h did not show any improvement in the conversion of product.

4. Conclusion

A simple, efficient, scalable and environmentally benign procedure was developed for the synthesis of enantiomerically pure aldsulfinimides (**2a-2u**) using tungstophosphoric acid as catalyst. The efficiency of the catalyst on recyclability and scalability was effectively demonstrated. Also, the method was very effective for the synthesis of aryl, heteroaryl and aliphatic aldsulfinamides in good yields and shorter reaction times with simple work up procedure. Developed method can be easily employed on commercial scale in industries.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.mcat.2017.06.035.

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