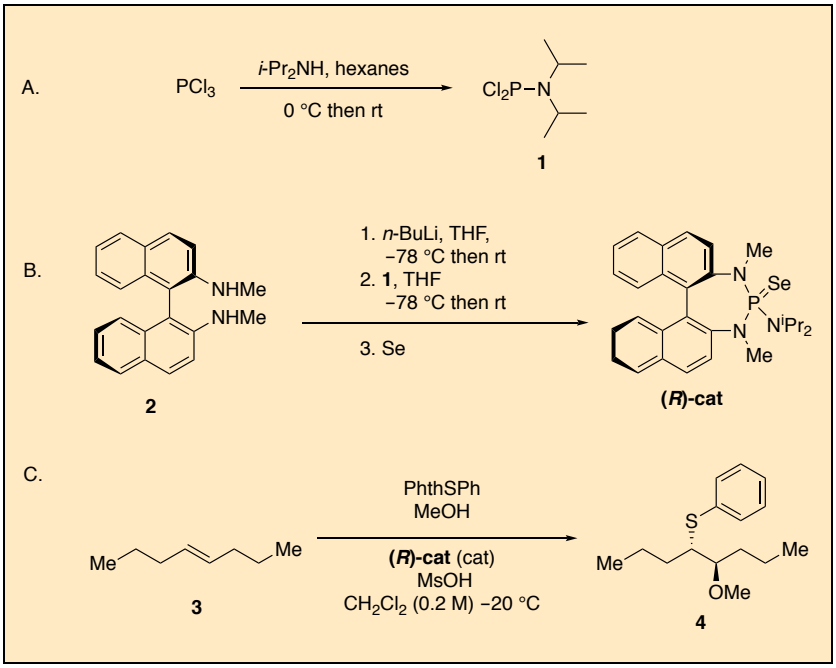
Organic Syntheses

Preparation of a Diisopropylselenophosphoramide Catalyst and its Use in Enantioselective Sulfenoetherification

Scott E. Denmark,* Pavel Ryabchuk, Hyung Min Chi, and Anastassia Matviitsuk[1]

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801, United States

Checked by Michael Rombola and Sarah E. Reisman



Procedure (Note 1)

A. *Dichloro(diisopropylamino)phosphine (**1**)* A flame-dried, 250-mL, two-necked, round-bottomed flask (24/40 joints) (Note 2) containing a 16 x 37 mm

DOI: 10.15227/orgsyn.096.0400 Published on the Web 10/2/2019

Teflon-coated, ellipsoid-shaped magnetic stirring bar is fitted with a nitrogen inlet adaptor on the central neck and a rubber septa on the side neck, and a thermocouple probe is inserted through the septa. The flask is evacuated and back-filled with nitrogen three times. Phosphorus trichloride (2.0 mL, 22.9 mmol) is added via syringe through a rubber septum, followed by the addition of hexanes (50 mL) via syringe (Note 3) (Figure 1). The resulting solution is cooled to +2 °C (internal temperature) with an ice-bath, and diisopropylamine (6.0 mL, 42.8 mmol, 1.87 equiv) (Note 4) is added dropwise via syringe over 10 min, whereupon the solution immediately turns into a white suspension. The flask is removed from the bath and the mixture is stirred for 1 h at 23 °C (Figure 2).

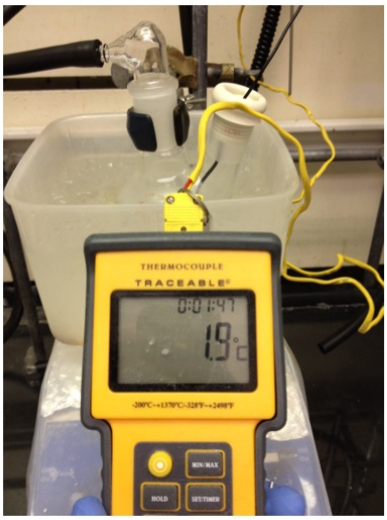


Figure 1. Reaction set-up

Figure 2. Reaction appearance

The gas inlet adaptor is replaced with an oven-dried Schlenk filter (160 mm long, Ø - 40 mm, medium porosity) and the white suspension is filtered to a flame-dried, 500-mL round-bottomed-flask under high vacuum (0.1 mmHg) (Note 5) (Figure 3). The resulting white cake is washed with hexanes (30 mL x 3) to give a turbid solution, and the filtrate is concentrated by rotary evaporation (23 °C, 10 mmHg). The crude material is transferred to a 50-mL, round-bottomed flask with 20 mL of hexanes, concentrated by rotary evaporation (23 °C, 10 mmHg) to afford 3.22 g (69%) of crude product as a cloudy oil. This oil is further purified by short-path distillation

(bp = 49–50 °C, 0.7 mmHg) (Note 6) to yield 2.75 g (59%) of dichloro(diisopropylamino)phosphine **1** as a colorless solid which melts upon gentle warming (Notes 7 and 8).

Figure 3. Filtration process, with the cold bath removed for clarity of the photo

B. *(R)-4-(Diisopropylamino)-3,5-dimethyl-4,5-dihydro-3H-dinaphtho[2,1-d:1′,2′-f][1,3,2]diazaphosphepine-4-selenide) (**R-cat**).* An oven-dried, 100-mL Schlenk flask, fitted with a rubber septum through which is inserted a thermocouple probe, is charged with a 1.7 cm, Teflon-coated, magnetic oval stir bar. The flask is evacuated under vacuum and back-filled with nitrogen three times. Under increased nitrogen flow the flask is charged with (*R*)-*N*,*N*′-dimethyl-1,1′-binaphthyl-2,2′-diamine **2** (1.56 g, 5.0 mmol) followed by the addition of anhydrous THF (33 mL) via syringe and then is placed in a dry ice/*i*-PrOH bath (Notes 9 and 10). After stirring the solution for 30 min at −74 °C (internal temperature), a solution of *n*-BuLi in hexanes (4.29 mL, 2.33 M, 10.0 mmol, 2.0 equiv) is added dropwise over 10 min via syringe whereupon the solution turned deep-orange (Note 11). The flask is then removed from the cooling bath and the solution is stirred for 20 min such that the internal temperature reaches 8 °C and the orange color intensifies. Then

the flask is immersed back into the dry ice/*i*-PrOH bath and the solution is stirred for another 30 min. When the solution reaches an internal temperature of −74 °C, a solution of dichloro(diisopropylamino)phosphine **1** (0.91 mL, 5.0 mmol, 1.0 equiv) in THF (8 mL) is added dropwise via syringe over 10 min (Note 12). The flask is then removed from the cooling bath and the solution is stirred for 45 min as the internal temperature reaches +18 °C and the solution turns from bright orange to yellow. The rubber septum is removed and under increased nitrogen flow selenium powder (1.18 g, 15.0 mmol, 3.0 equiv) is then added in one portion with a spatula whereupon the color turns brown-black immediately. The mixture is stirred at room temperature for 1 h (Note 13) and the resulting heterogeneous mixture is vacuum-filtered through a pad of Celite (25 g) in a sintered glass funnel (35 mm Ø, porosity 3) into a 250-mL, round-bottomed flask (Figure 4). The reaction flask and Celite are washed with EtOAc (5 × 50 mL) and the filtrate is combined before being concentrated by rotary evaporation (25 °C, ca. 20 mmHg) to afford a yellow foam (Figure 5).

Figure 4. Filtration through Celite

Figure 5. Crude as a yellow foam

The crude product is purified by flash chromatography on silica gel to afford ***(R)-cat*** (2.08 g, 80%) as a pale yellow solid (Note 14 and 15) (Figure 6).

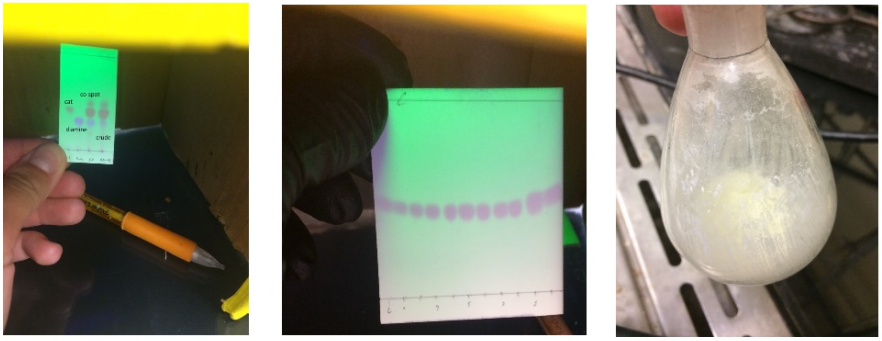


Figure 6. Left: TLC of the crude reaction mixture. Middle: fractions 60-69 of the flash chromatography. Right: isolated product.

For further purification, the product is placed in a 100 mL round-bottomed flask equipped with a condenser, a 1.3 cm Teflon-coated magnetic stirbar, and 20 mL pentane. The mixture is refluxed for 2 min. The mixture is then cooled to room temperature, and the solids are filtered using a sintered glass funnel and a small amount of pentane (10 mL), leaving the purified product on the filter as a white solid. The solid is transferred into a 50-mL round-bottomed flask with dichloromethane (8 mL) and concentrated by rotary evaporation (25 °C, ca. 20 mmHg). The solid is then placed under vacuum for 18 h (0.1 mmHg, 70 °C) to give the (*R*)-cat (1.69 g, 65%) as a white powder (Note 16) (Figure 7).

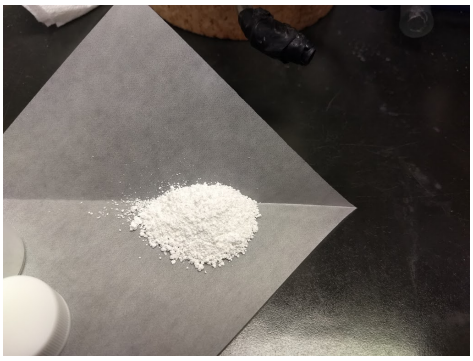


Figure 7. (*R*)-cat upon trituration

C. *[(1S,2R)-2-Methoxy-1-propylpentyl]thiobenzene (***4***)*. An oven-dried, 100-mL Schlenk flask, fitted with a rubber septum, is charged with a 2.1 cm

Teflon-coated magnetic oval stir bar, phenylthiophthalimide (2.553 g, 10.0 mmol, 1.0 equiv), (*R*)-*cat* (260 mg, 0.5 mmol, 0.05 equiv), *trans*-4-octene **3** (1.122 g, 1.57 mL, 10.0 mmol), and methanol (641 mg, 810 μL, 20.0 mmol, 2.0 equiv). The flask is flushed with nitrogen via a nitrogen line and charged with anhydrous dichloromethane (50 mL) with a 50-mL syringe (Note 17) (Figure 8).

Figure 8. Reaction set-up

The stirred homogeneous solution is cooled to –20 °C using a cryocool unit (Note 18). After 10 min, the internal temperature is stabilized to –20 °C and MsOH (650 μL, 10.0 mmol, 1.0 equiv) is added dropwise to the cooled solution via syringe over 1 h (Note 19). The resulting yellow solution is stirred at –20 °C for 48 h (Note 20) (Figure 9).

The reaction is quenched by the addition of sat. aq. $NaHCO_3$ solution (50 mL) with stirring. The resulting biphasic mixture is transferred to a 250-mL separatory funnel and the reaction flask is rinsed with additional dichloromethane (20 mL). After vigorous extraction, the organic layer is separated and the remaining aqueous layer is further extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts are dried over Na_2SO_4 (10 g), filtered through a 30-mL, coarse porosity sintered glass funnel, and then are concentrated on a rotary evaporator (23 °C, 10 mmHg) to afford yellow solid (4.06 g). The crude product is purified by flash chromatography on silica gel to afford **4** (1.66 g, 66%) as a pale-yellow oil (Notes 21 and 22).

Figure 9. Reaction temperature control

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with Phosphorus trichloride, hexanes, diisopropylamine, (*R*)-*N*,*N*′-dimethyl-1,1′-binaphthyl-2,2′-diamine, tetrahydrofuran, dry ice, isopropyl alcohol, *n*-butyllithium, selenium powder, Celite, ethyl acetate, silica gel, pentane,

dichloromethane, phenylthiophthalimide, *trans*-4-octene, methanesulfonic acid, sodium bicarbonate, sodium sulfate, 1,3,5-trimethoxybenzene, acetone, and $CDCl_3$.

2. The use of 24/40 joints was critical to prevent solidifying of the methanesulfonic acid in the syringe. The use of smaller joints (14/20) resulted in significantly slower filtration of the amine salts.
3. Phosphorus trichloride (ReagentPlus, 99%) was purchased from Sigma-Aldrich Co. and was freshly distilled from CaH_2. Hexanes (Fisher, HPLC grade) was dried by percolation through two columns packed with neutral alumina under a positive pressure of argon.
4. Diisopropylamine (Alfa Aesar, 99+%) was freshly distilled from CaH_2.
5. To facilitate the transfer of the white precipitate to the porous filter, the original flask is washed with hexanes (3 x 30 mL), which is added via syringe through the rubber septum. A magnet is used to fix the stirbar to the bottom of the flask to prevent clogging. The filtrate is cooled in a dry ice/acetone bath during filtration.
6. Room temperature water was only intermittently run through the condenser during distillation to prevent clogging.
7. Characterization data for product **1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (d, J = 6.9 Hz, 12H), 3.92 (tt, J = 13.2, 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.5 (d, J = 8.9 Hz), 48.3 (d, J = 13.9 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ: 169.5 (s); mp = 26–27 °C (upon standing); bp = 49–50 °C (0.7 mmHg). The purity of **1** was determined to be 97% as measured by Quantitative - NMR analysis using biphenyl as an internal standard.
8. A second reaction on identical scale provided 2.84 g (62%) of the compound **1** with identical purity.
9. THF (Fisher, HPLC grade) was dried by percolation through two columns packed with neutral alumina under a positive pressure of argon.
10. (*R*)-*N*,*N*′-Dimethyl-1,1′-binaphthyl-2,2′-diamine **2** can be synthesized following a previously published procedure (*Org. Synth.* **2019**, *96*, 382–399).
11. The internal temperature was monitored using digital thermometer, the temperature probe was placed through the rubber septum. The temperature was monitored during the addition and did not exceed −69 °C.
12. The temperature was monitored during the addition and did not exceed −65 °C.

13. Selenium (≥99.5%, powder, − 100 mesh) was purchased from Sigma-Aldrich Co. and used as received.
14. **(*R*)-Cat** was purified by flash column chromatography (silica gel, 90 g, diameter: 45 mm, height: 140 mm, ca. 25 mL fractions, column packed using hexanes, sample loaded as a suspension on Celite (5.0 g), eluent: hexanes, 0.2 L followed by 0.5 L of 99:1 hexanes/EtOAc, then 0.5 L of 98:2 hexanes/EtOAc, then 0.5 L of 97:3 hexanes/EtOAc, then 0.5 L of 96:4 hexanes/EtOAc and then 0.2 L of 95:5 hexanes/EtOAc). The product is obtained in fractions 51–83 (R_f 0.42 (hexanes/EtOAc, 9:1), which were concentrated by rotary evaporation (25°C, 10 mmHg). The observed impurity was collected in fractions 44-47 (41 mg, R_f0.50 (hexanes/EtOAc, 9:1). Unreacted **2** (34 mg, 2%, R_f 0.28 (hexanes/EtOAc, 9:1) was recovered from fractions 84-94. The (*R*)-cat was triturated as described above to give a white powder. The purity was determined to be 96% as measured by Quantitative - NMR analysis versus 1,3,5-trimethoxybenzene as an internal standard.
15. Characterization data for **(*R*)-cat**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.35 (br. s, 6H, HC(14) and HC(14′)), 1.45 (br. s, 6H, HC(13) and HC(13′)), 3.09 (d, *J* = 13.8 Hz, 3H, HC(11′)), 3.33 (d, *J* = 12.5 Hz, 3H, HC(11)), 3.64 (br. s, 2H, HC(12) and HC(12′)), 6.97 (d, *J* = 8.6 Hz, 1H, HC(9′)), 7.10 (ddd, *J* = 8.2, 6.7, 1.4 Hz, 1H, HC(8′)), 7.23 (ddd, *J* = 8.4, 6.6, 1.3 Hz, 1H, HC(8)), 7.28 (d, *J* = 7.4 Hz, 1H, HC(9)), 7.35 (t, *J* = 7.4 Hz, 1H, HC(7′)), 7.43 (ddd, *J* = 8.1, 6.6, 1.4 Hz, 1H, HC(7)), 7.66 (d, *J* = 8.9 Hz, 1H, HC(3′)), 7.70 (dd, *J* = 8.9, 1.4 Hz, 1H, HC(3)), 7.86 (d, *J* = 7.6 Hz, 1H, H(C(6′)), 7.91 (t, *J* = 9.3 Hz, 2H, HC(4) and HC(4′)), 7.98 (d, *J* = 8.9 Hz, 1H, HC(6)); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 22.7 (C(14) and C(14′)), 24.9 (C(13) and C(13′)), 36.8 (d, *J* = 6.2 Hz, C(11′)), 37.6 (d, *J* = 12.6 Hz, C(11)), 48.3 (C(12) and C(12′)), 122.8 (C3), 123.0 (d, *J* = 2.6 Hz, C(3′)), 124.8 (C(7′), 125.1 (C(7)), 125.7 (C(8′)), 126.0 (C(8)), 127.4 (C(9′)), 127.7-127.8 ((C(4), C(4′), C(1'), and C(9)), 128.2 (C(1)), 128.3 (C(6′)), 129.0 (d, *J* = 1.9 Hz, C(6)), 130.7 (C(5)), 131.4 (d, *J* = 2.2 Hz, C(5′)), 132.3 (d, *J* = 1.8 Hz, C(10′)), 132.7 (C(10)), 142.2 (d, *J* = 1.8 Hz, C(2′)), 143.4 (d, *J* = 6.1 Hz, C(2)); ^{31}P NMR (121 MHz, $CDCl_3$) δ: 79.7 (br s). IR (KBr): 3062, 2962, 1618, 1594, 1506, 1466, 1367, 1330, 1270, 1260, 1178, 1146, 1087, 982, 931, 848, 813, 750, 698, 634, 604 cm^{-1}. $[\alpha]^{22}_D$ = −418.99 (c = 0.935, $CHCl_3$) [non-linear ORD]; HRMS (ES): *m*/*z* calcd. for $C_{28}H_{33}N_3PSe$ [M+H]: 522.1577, found: 522.1560; mp 148−149 °C.
16. A second reaction on the same scale provided 1.63 g (63%) of the compound **(*R*)-cat** with identical purity.

17. Although the reaction has not been shown to be specifically sensitive to oxygen or air, the reaction was run using anhydrous dichloromethane under N_2. Anhydrous dichloromethane in all sections was obtained by passing through activated alumina under atmosphere of argon (H_2O content <10 ppm, Karl Fisher titration).
18. The internal temperature of the solution was monitored via a thermocouple digital temperature probe. The temperature of the bath temperature fluctuated between –18 to –22 °C while the internal temperature stayed in a smaller window of fluctuation between –19 to –20 °C.
19. Methanesulfonic acid (≥99.5%) was purchased from Sigma-Aldrich Co and was distilled from P_2O_5. Methanesulfonic acid was added neat to the reaction mixture. However, because the melting point of the methanesulfonic acid is 19 °C, it was carefully added dropwise positioning the needle away from the solution to prevent solidifying. The use of a long-neck Synthware Modified Schlenk Tube Flask (purchased from Kemtech America) with a 24/40 joint was found to be necessary to prevent solidifying. Addition of methanesulfonic acid to flasks bearing 14/20 joints resulted in solidifying. Methanesulfonic acid could not be added as a solution in dichloromethane due to the partial phase separation from the dichloromethane over time.
20. The solution is stirred at 600 rpm throughout the reaction. The reaction becomes heterogeneous as it proceeds due to the formation of phthalimide crystals. A reaction previously monitored by TLC and ^{1}H NMR on a smaller scale was found to have reached >95% conversion by 48 h. For this reaction, it was checked at 48 h by TLC on Merck silica gel 60 F254 TLC glass plates and visualized with UV light and ceric ammonium nitrate staining solution. R_f (product): 0.55 (40:1 hexanes/acetone).
21. The crude product was loaded onto a column (silica gel, 300 g, diameter: 60 mm, height: 150 mm) that was dry packed with 1.5 L of 40:1 hexanes:acetone, ca. 50 mL fractions, sample loaded as a suspension on Celite (5.0 g), eluent: 1.5 L of 40:1 hexanes:acetone. The desired product was obtained in fractions 13-26, which was concentrated by rotary evaporation (23 °C, 10 mmHg). The product has been characterized as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.91 (t, J = 7.0 Hz, 3H), 0.93 (t, J = 7.0 Hz, 3H), 1.28 – 1.37 (m, 1H), 1.39 – 1.59 (m, 4H), 1.62 – 1.73 (m, 3H), 3.20 (dt, J = 9.3, 4.0 Hz, 1H), 3.30 (dt, J = 8.2, 4.2 Hz, 1H), 3.38 (s, 3H), 7.20

(m, 1H), 7.27 (m, 2H), 7.42 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 14.0, 14.1, 19.2, 20.9, 33.0, 33.8, 53.1, 58.4, 83.5, 126.6, 128.9, 131.8, 136.8; IR (neat): 3075, 2957, 2934, 2872, 2826, 1584, 1478, 1465, 1439, 1376, 1300, 1259, 1225, 1191, 1142, 1095, 1025, 1025, 962, 932, 888, 826, 746, 691 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{24}OS$ [M+NH_4] 270.1886, found 270.1878; $[\alpha]^{22}_D$ = –14.8° (c = 1.12, $CHCl_3$). SFC analysis was performed using a Mettler SFC supercritical CO_2 analytical chromatography system (CO_2 = 1450 psi, column temperature = 40 °C, with a Chiralcel IC column (2% *i*PrOH/CO_2, 2.5 mL/min, 210 nm): 98.2:1.8 e.r. (t_R (major) = 3.8 min, t_R (minor) = 6.9 min). The purity was determined to be 96% as measured by Quantitative - NMR analysis versus 1,3,5-trimethoxybenzene.

22. A second reaction on the same scale provided 1.52 g (60%) of the compound with identical purity.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and

its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

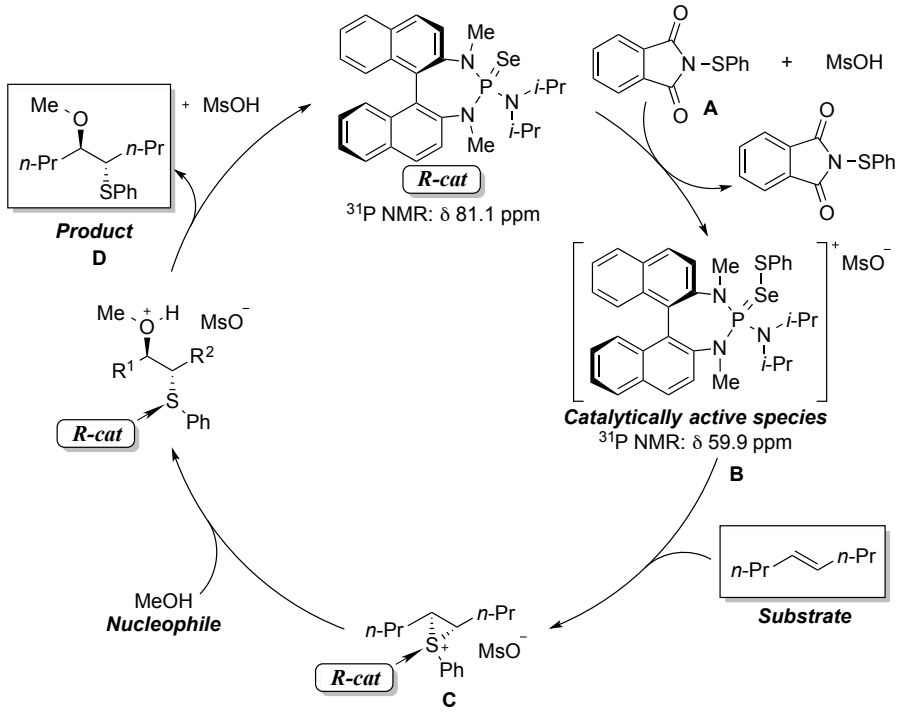
Sulfur-containing groups are frequently found in many pharmaceutical and agricultural agents, as well as in natural products.[2] In addition thioethers have a rich functional group chemistry making them useful sites of manipulation. Introduction of thioethers via alkene sulfenofunctionalization is a very powerful transformation, which results in a simultaneous formation of vicinal stereocenters.[3] Despite the attractiveness of this approach the stereocontrolled transfer of sulfur groups to alkenes remains underdeveloped and, for a long time, only two examples of direct enantioselective sulfenofunctionalization were known, both employing chiral reagents in stoichiometric quantities.[4]

The diastereo- and enantioselective intermolecular sulfenoetherification described herein employs a BINAM-based selenophosphoramide catalyst developed in our laboratories.[5] The reaction proceeds through formation of an enantioenriched thiiranium ion,[6] which is subsequently captured by a nucleophile to afford the product. The stereodetermining step is the formation of the thiiranium ion, which is configurationally stable below 0 °C.[7] Because of the intermediacy of the thiiranium ion, this method exclusively affords *anti* products with exceptional diastereoselectivity.

The catalytic cycle begins with a transfer of a phenylsulfenyl moiety from **A** to the Lewis basic selenium atom and generation of the catalytically active species **B (**Scheme 1). Evidence for theses species is provided by X-ray crystallography and ^{31}P NMR spectroscopy.[5a,g] Transfer of the sulfenium ion from **B** to an alkene forms intermediate thiiranium ion **C**, which is then captured with a nucleophile to afford the corresponding enantioenriched sulfenofunctionalized product **D**.

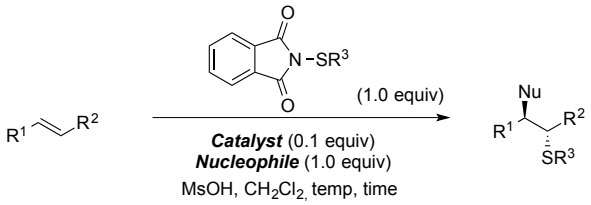
The origin for the improved selectivity of above described diisopropylamine substituted catalyst over the other previously developed selenophosphoramide catalysts could be attributed to the increased steric interactions.[5a,g] Enhanced steric interactions with the diisopropylamino group leads to better differentiated transition states of alkene and catalytically active species during the formation of thiiranium ion. Previously

reported intermolecular sulfenylation of 4-octene employing a less sterically demanding azepane substituted selenophosphoramide catalyst afforded phenylthio methyl ether with a lower er (Table 1, entry 2). Introducing even greater steric interaction by substitution on the 2,6-position of the phenyl on the sulfenylating reagent with bulkier isopropyl groups showed further enhanced enantioselectivity (entry 4). Thiofunctionalization of the same substrate with a new sulfenylating agent was exceptionally selective even at elevated temperatures.[5g] The suitability of a terminal double bond was also showcased in an intermolecular functionalization with 1-octene and MeOH as the nucleophile (entries 5 and 6). Other oxygen-based nucleophiles were tested in the described transformation; for example, acetic acid was an effective nucleophile for the intermolecular thiofunctionalization giving corresponding 4-(5-phenylthio)octyl acetate in good yield and er (entry 3).

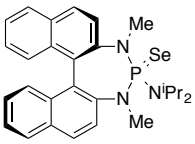


Scheme 1. Proposed catalytic cycle of Lewis-base catalyzed sulfenofunctionalization.

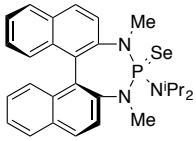
Table 1. Intermolecular sulfenofunctionalization.



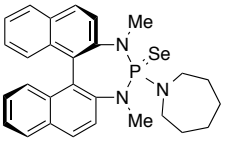
entry	R^1	R^2	R^3	Catalyst	Nucleophile	temp, ºC	time, h	yield, %	e.r.
1	*n*-Pr	*n*-Pr	Ph	(*R*)-cat	MeOH	–20	48	91	98.4:1.6
2	*n*-Pr	*n*-Pr	Ph	(*R*)-azepane-cat	MeOH	–20	48	93	92:8
3	*n*-Pr	*n*-Pr	Ph	(*R*)-azepane-cat	AcOH	–20	48	77	91.4:8.6
4	*n*-Pr	*n*-Pr	2,6-*i*-$Pr_2C_6H_3$	(*R*)-cat	MeOH	0	36	85	99.2:0.8
5	*n*-Hex	H	Ph	(*R*)-azepane-cat	MeOH	23	48	77	82.2:17.8
6	*n*-Hex	H	2,6-*i*-$Pr_2C_6H_3$	(*R*)-cat	MeOH	23	24	84	98.6:1.4



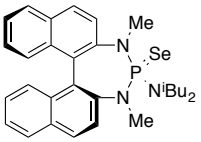
(*R*)-cat



(*S*)-cat



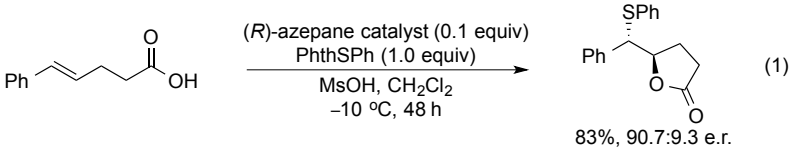
(*R*)-azepane-cat



(*S*)-*i*-Bu_2-cat

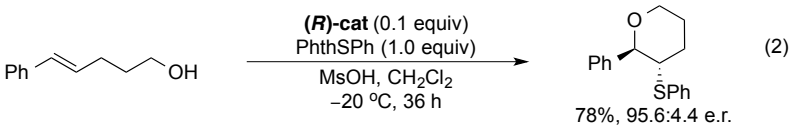
The scope of the sulfenofunctionalization has been further extended to intramolecular sulfenofunctionalization by employing oxygen-,[5a,g] nitrogen-,[5d] and carbon-based[5b,c,e] nucleophiles tethered to the unactivated alkenes. Various enantiomerically enriched tetrahydropyrans, − furans and lactones can be constructed from corresponding acids and alcohols (eq 1-3). Nitrogen-containing heterocycles, such as piperidines, pyrrolidines and azepanes can be accessed via sulfenoamination of corresponding tosyl-protected amines (eq 4-5). Finally, sulfenofunctionalization can also incorporate aromatic nucleophiles in intramolecular carbosulfenylation yielding enantioenriched decalins (eq 6).

Finally, the selenophosphoramide catalyst has also been used in enantioselective sulfenylation of silyl enol ethers to afford α-sulfenylated ketones (eq 7).[5f] For this transformation a new sulfenylating agent that did not require additional Brønsted acid activation is employed. *N*-Phenylthiosaccharin successfully transfers the *S*-phenyl moiety to the substrate under acid-free conditions, avoiding acidic hydrolysis of the silyl enol ether.



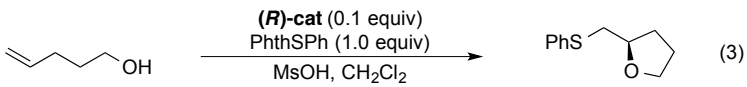
(1)

83%, 90.7:9.3 e.r.



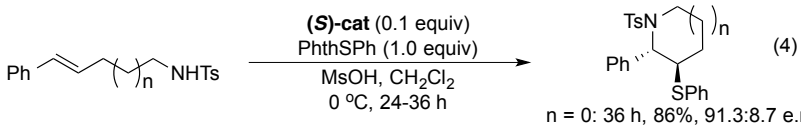
(2)

78%, 95.6:4.4 e.r.



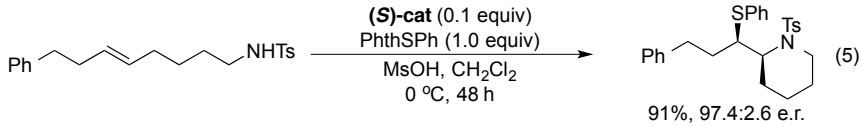
(3)

83%, 88.9:11.1 e.r.



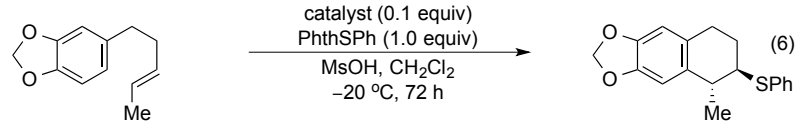
(4)

n = 0: 36 h, 86%, 91.3:8.7 e.r.
n = 1: 24 h, 93%, 93.6:6.4 e.r.
n = 2: 36 h, 84%, 92.6:7.3 e.r.



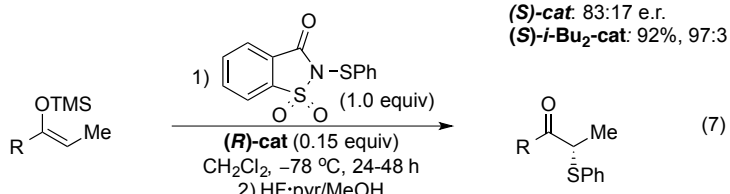
(5)

91%, 97.4:2.6 e.r.



(6)

(S)-cat: 83:17 e.r.
(*S*)-*i*-Bu$_2$-cat: 92%, 97:3 e.r.



(7)

R = Ph: 24 h, 72%, 93:7 e.r.
R = *t*-Bu: 24 h, 74%, 98:2 e.r.
R = *N*-Boc-4-piperidinyl: 48 h, 78%, 94:6 e.r.

References

1. Department of Chemistry, Roger Adams Laboratory, University of Illinois at Urbana-Champaign. Urbana, IL, 61801, email: sdenmark@illinois.edu, ORCID: 0000-0002-1099-9765.
2. (a) Metzner, P. & Thuillier, A. *Sulfur Reagents in Organic Synthesis* (Academic Press, 1994). (b) Page, P. (ed.) *Organosulfur Chemistry*: *Synthetic Aspects* (Academic Press, 1995). (c) Prinsep, M. R. Sulfur-containing natural products from marine invertebrates. *Stud. Nat. Prod. Chem*. **2003**, *28*, 617–751.
3. de la Mare, P. B. D. & Bolton, R. (eds) in *Electrophilic Additions to Unsaturated Systems* 2nd edn, Vol. *9*, 198–246 (Elsevier, **1982**).
4. (a) Archer, N. J., Rayner, C. M., Bell, D.; Miller, D. *Synlett*., **1994**, 617–619. (b) Lucchini, V., Modena, G. & Pasquato, L. *J. Chem. Soc. Chem. Commun.* **1994**, 1565–1566.
5. (a) Denmark, S. E.; Kornfilt, D. J.-P.; Vogler, T. *J. Am. Chem. Soc.* **2011**, *133*, 15308−15311. (b) Denmark, S. E.; Jaunet, A. *J. Am. Chem. Soc*. **2013**, *135*, 6419−6422. (c) Denmark, S. E.; Jaunet, A. *J. Org. Chem.* **2014**, *79*, 140−171. (d) Denmark, S. E.; Chi, H. M. *J. Am. Chem. Soc.* **2014**, *136*, 3655−3663. (e) Denmark, S. E.; Chi, H. M. *J. Am. Chem. Soc.* **2014**, *136*, 8915−8918. (f) Denmark, S. E.; Rossi, S.; Webster, M. P.; Wang, H. *J. Am. Chem. Soc.* **2014**, *136*, 13016–13028. (g) Denmark, S. E.; Hartmann, E.; Kornfilt, D. J. P.; Wang, H. *Nat. Chem*., **2014**, 6, 1056−1064
6. (a) Smit, W. A., Zefirov, N. S., Bodrikov, I. V.; Krimer, M. Z. *Acc. Chem. Res.* **1979**, *12*, 282–288. (b) Rayner, C. M. in *Organosulfur Chemistry:* Synthetic Aspects (ed. Page, P.) Ch. 3 (Academic Press, **1995**).
7. Denmark, S. E.; Vogler, T. *Chem. Eur. J*. **2009**, *15*, 11737−11745.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

Phosphorus trichloride: Phosphorus trichloride; (7719-12-2)
Diisopropylamine: diisopropylamine; (108-18-9)
1,1-Dichloro-N,N-diisopropylphosphanamine: Dichloro-N,N-diisopropylamino-phosphane; (921-26-6)
(*R*)-*N*,*N*″ -dimethyl-1,1′-binaphthyl-2,2′-diamine: [1,1'-Binaphthalene]-2,2'-diamine, N2,N2'-dimethyl-, (1R)-; (93713-30-5)

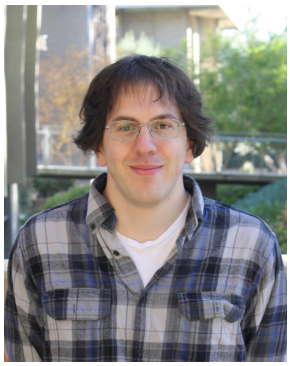
n-Butyllithium: Lithium, butyl-; (109-72-8)
Selenium: Selenium (7782-49-2)
(R)-4-(Diisopropylamino)-3,5-dimethyl-4,5-dihydro-3H-dinaphtho[2,1-d:1′,2′-f][1,3,2]diazaphosphepine-4-selenide) (***R*-cat**): 4H-Dinaphtho[2,1-d:1',2'-f] [1,3,2]diazaphosphepin-4-amine, 3,5-dihydro-3,5-dimethyl-N,N-bis(1-methylethyl)-, 4-selenide, (11bR)- ; (1627528-49-7)
Phenylthiophthalimide: 1*H*-Isoindole-1,3 (2*H*)-dione, 2-(phenylthio)- (14204-27-4)
trans-4-Octene: 4-Octene, (4E)- ;(14850-23-8)
Methanol: Methanol (67-56-1)
MsOH: Methanesulfonic acid; (75-75-2)
[(1*S*,2*R*)-2-Methoxy-1-propylpentyl]thiobenzene: [(1*S*,2*R*)-2-Methoxy-1-propylpentyl]thiobenzene; (1202357-37-6)

Scott E. Denmark was born in Lynbrook, New York on 17 June 1953. He obtained an S.B. degree from MIT in 1975 and his D.Sc.Tech. (with Albert Eschenmoser) from the ETH Zürich in 1980. That same year he began his career at the University of Illinois. He was promoted to associate professor in 1986, to full professor in 1987 and since 1991 he has been the Reynold C. Fuson Professor of Chemistry. His research interests include the invention of new synthetic reactions, organoelement chemistry and the origin of stereocontrol in fundamental carbon-carbon bond forming processes.

Pavel Ryabchuk was born in Moscow, Russia in 1986. He received his diploma in chemistry from Moscow State University in 2008. He obtained his Ph.D. in chemistry in 2013 for research conducted under Professor Michael Rubin. He was a postdoctoral researcher with Professor Scott E. Denmark at University of Illinois at Urbana-Champaign from 2014-2016 and is currently a postdoctoral research associate with Professor Matthias Beller at the Leibniz Institute in Rostok.

Hyung Min Chi was born in Champaign, IL in 1984. He received his Bachelor's degree in chemistry from Seoul National University in 2009 and his Ph.D. with Professor Scott E. Denmark's at University of Illinois at Urbana-Champaign in 2016 on the enantioselective, catalytic sulfenoamination and carbosulfenylation reactions of unactivated olefins with selenophosphoramide catalysts. He is currently a postdoctoral research associate with Prof. Scott Snyder at the University of Chicago.

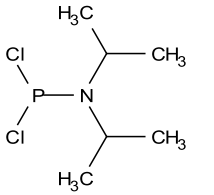
Anastassia Matviitsuk was born in Narva, Estonia in 1989. She received her BSc and MSc degrees in chemistry from Humboldt University of Berlin (with Professor Rainer Mahrwald). She obtained her Ph.D. in chemistry in 2018 from University of St Andrews for research conducted under the supervision of Professor Andrew D. Smith. She is currently a postdoctoral researcher in Professor Scott E. Denmark's research laboratory at University of Illinois at Urbana-Champaign.



Michael Rombola was born in Rochester, NY in 1989. He received a B.S. in biology from Cornell University in 2011. He earned a Ph.D. in organic chemistry from the University of Chicago in 2018 working in the lab of Prof. Viresh H. Rawal. He is currently a postdoctoral researcher in the lab of Prof. Sarah E. Reisman at the California Institute of Technology.

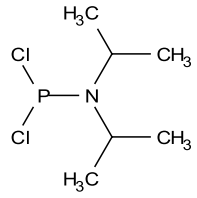
PROTON01
MR_2_67_A

^{1}H NMR spectrum of **1** ($CDCl_3$)



CARBON01
MR_2_67_A

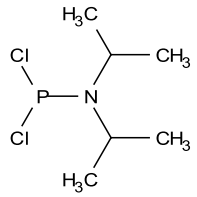
^{13}C NMR spectrum of **1** ($CDCl_3$)



PHOSPHORUS01
MR_2_67_A

169.51

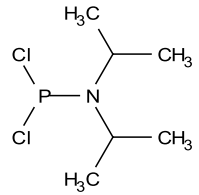
^{31}P NMR spectrum of **1** ($CDCl_3$)

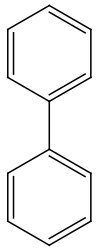


MR_OS1_Q.1.fid

internal standard (biphenyl)

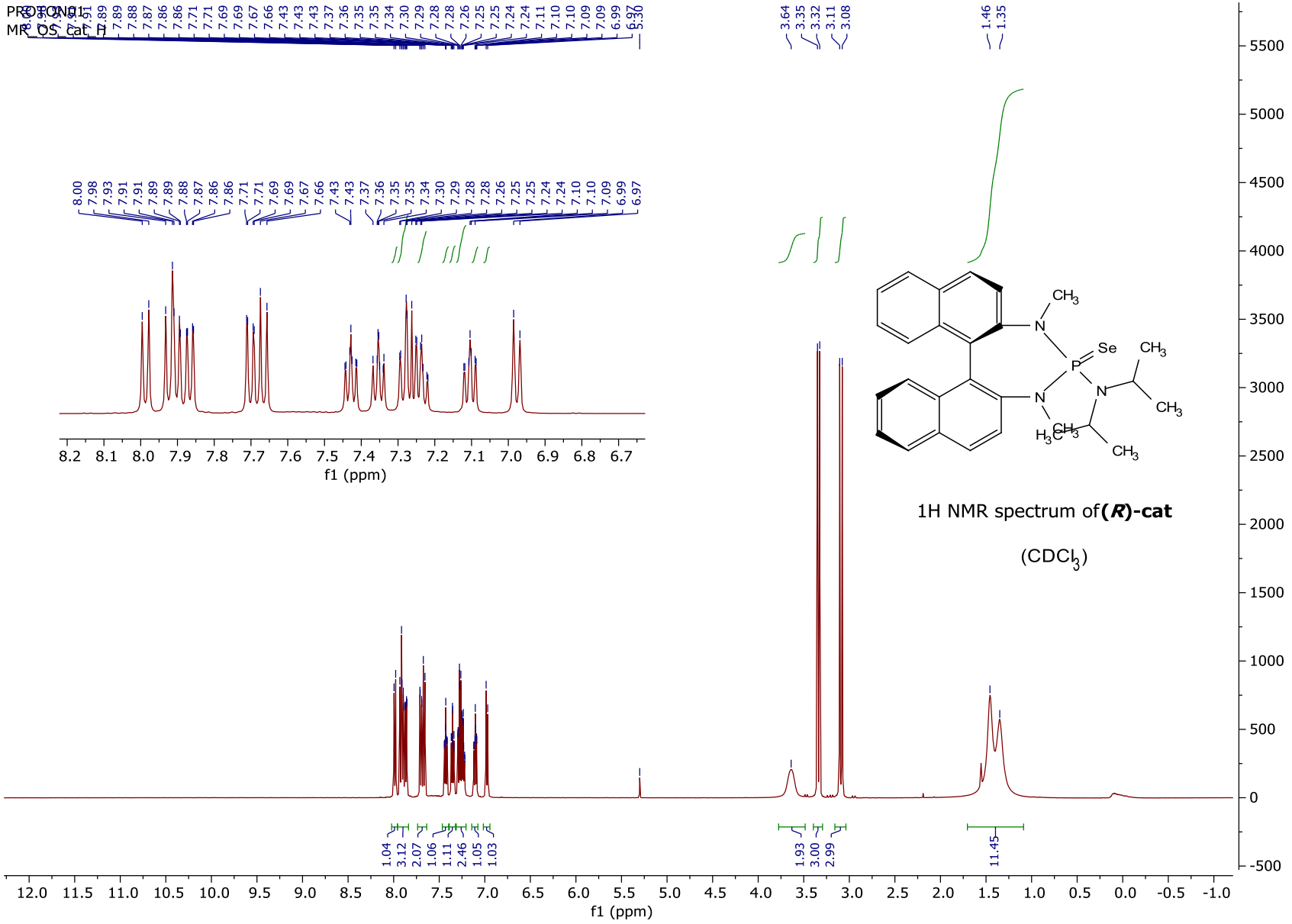
Product (1)

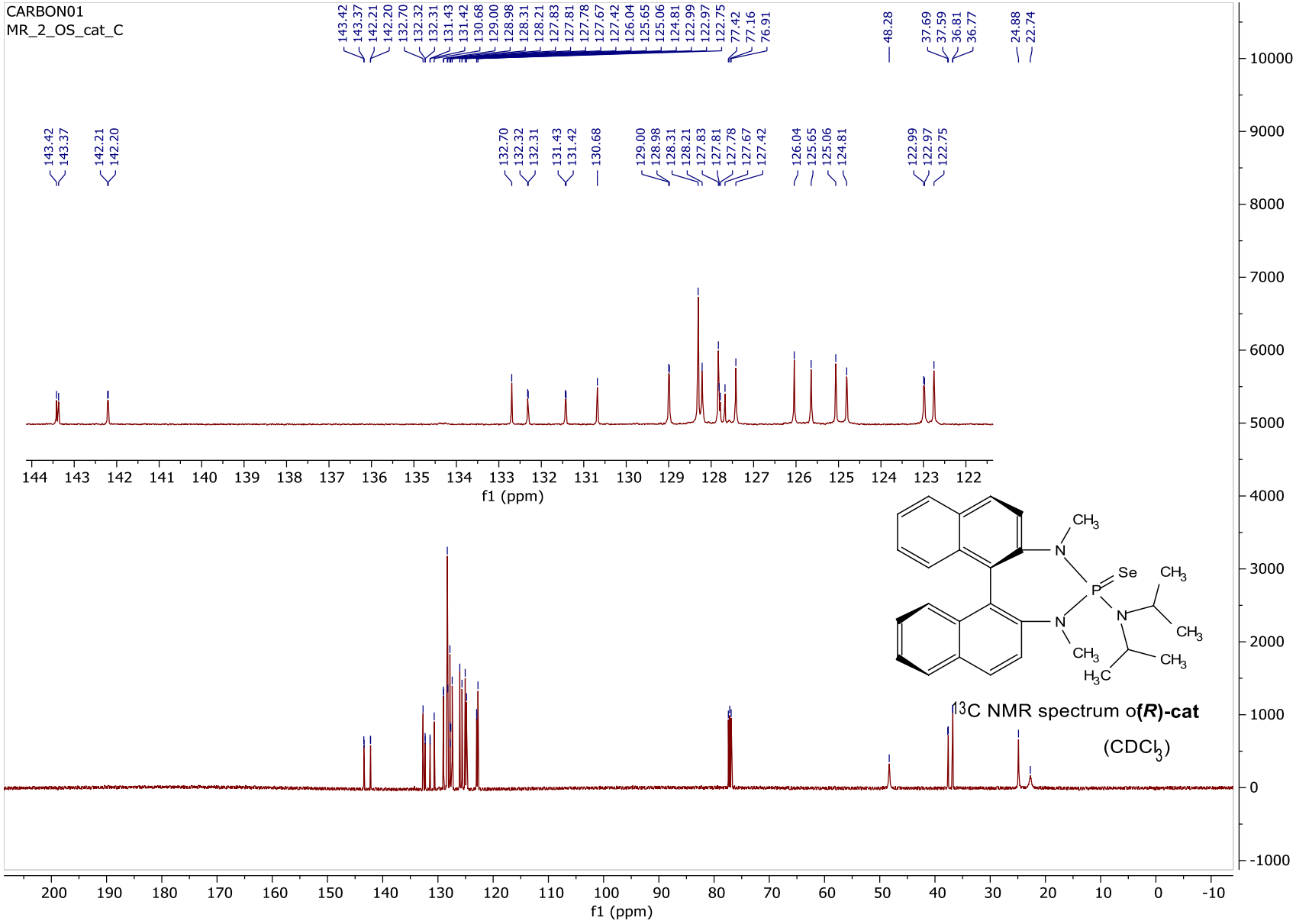




purity: 97% solvent: $CDCl_3$

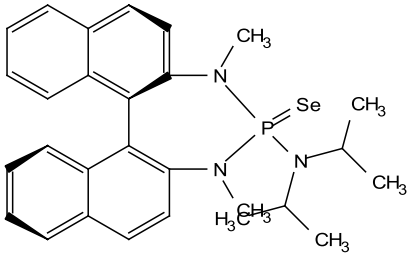
	Product	Internal Standard (biphenyl)
MW	202.06	154.21
Amount	58.2 mg	53.4 mg
Area	0.8068	2.0000


PROTON01
MR OS cat H
8.00 7.98 7.93 7.91 7.91 7.89 7.89 7.88 7.87 7.86 7.86 7.71 7.71 7.69 7.69 7.67 7.66 7.43 7.43 7.37 7.36 7.35 7.35 7.34 7.30 7.29 7.28 7.28 7.26 7.25 7.25 7.24 7.24 7.11 7.10 7.10 7.09 7.09 6.99 6.97
3.64 3.35 3.32 3.11 3.08
1.46 1.35
8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7
f1 (ppm)
CH3
N
P
Se
CH3
N
N
CH3
H3C
CH3
CH3
1H NMR spectrum of(R)-cat
(CDCl3)
1.04 3.12 2.07 1.06 1.11 2.46 1.05 1.03
1.93 3.00 2.99
11.45
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)
5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 -500

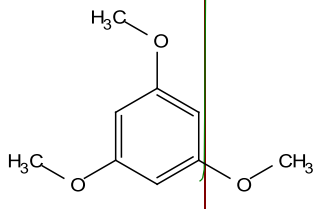

CARBON01
MR_2_OS_cat_C
143.42
143.37
142.21
142.20
132.70
132.32
132.31
131.43
131.42
130.68
129.00
128.98
128.31
128.21
127.83
127.81
127.78
127.67
127.42
126.04
125.65
125.06
124.81
122.99
122.97
122.75
77.42
77.16
76.91
48.28
37.69
37.59
36.81
36.77
24.88
22.74
f1 (ppm)
f1 (ppm)
CH3
N
P
Se
N
N
CH3
CH3
CH3
CH3
CH3
H3C
13C NMR spectrum of(R)-cat
(CDCl3)

MR_OS2_Q_A.1.fid

Product **(R)-cat)**



internal standard
(1,3,5-trimethoxybenzene)



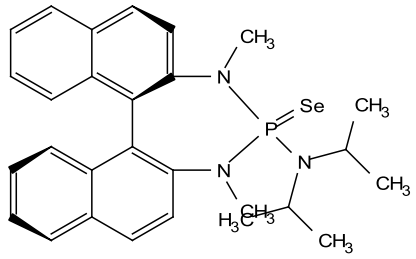
purity: 96%

solvent: $CDCl_3$

	Product	Internal Standard (1,3,5-trimethoxybenzene)
MW	520.53	168.19
Amount	21.56 mg	15.64 mg
Area	0.4289	1.0000

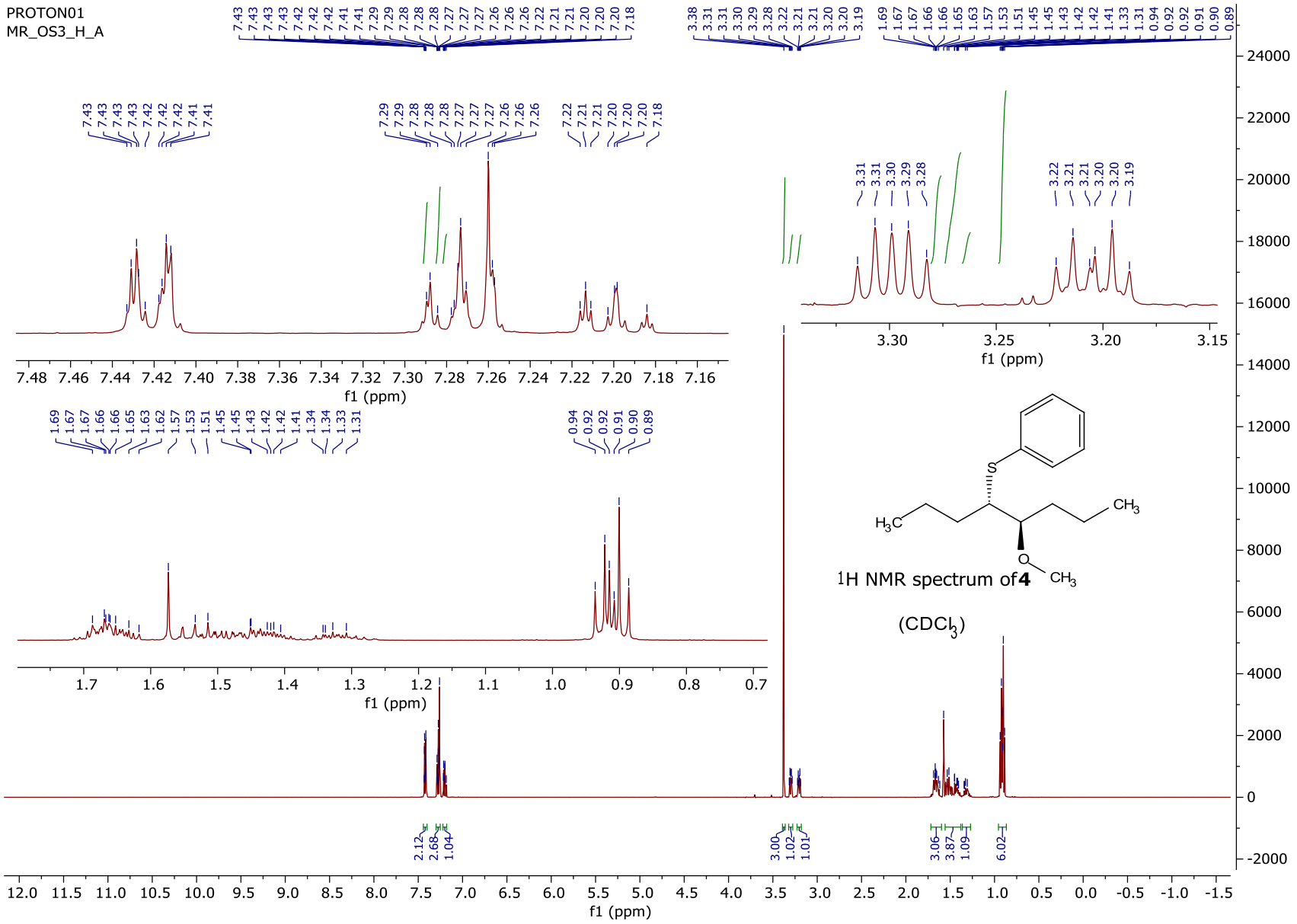
PHOSPHORUS01
MR_2_OS_cat_P

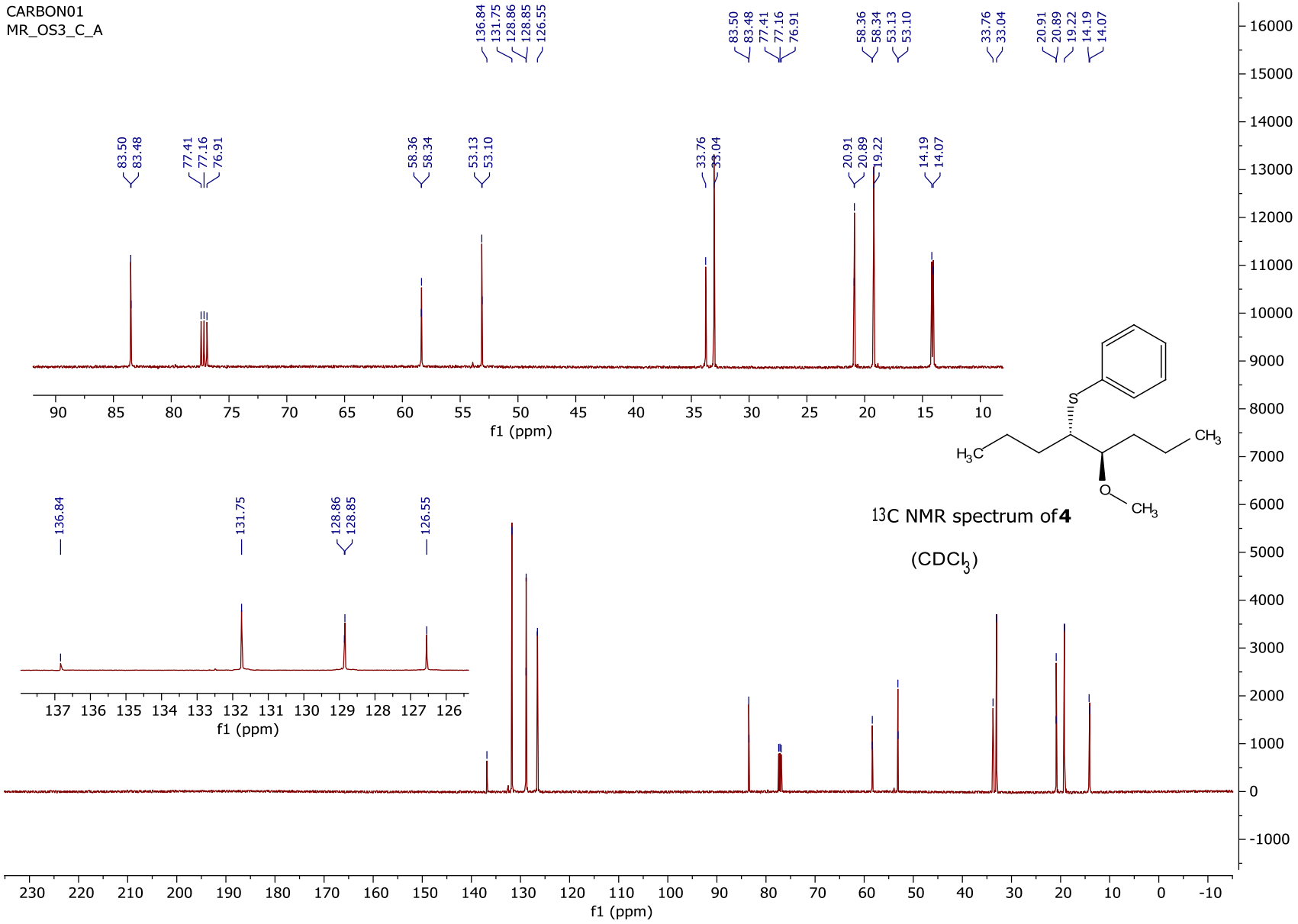
79.74



^{31}P NMR spectrum of **(*R*)-cat**

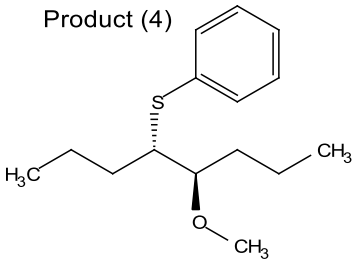
($CDCl_3$)


PROTON01
MR_OS3_H_A
f1 (ppm)
1H NMR spectrum of 4
(CDCl3)
H3C
CH3
O
CH3
S

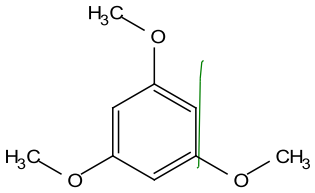

CARBON01
MR_OS3_C_A
136.84
131.75
128.86
128.85
126.55
83.50
83.48
77.41
77.16
76.91
58.36
58.34
53.13
53.10
33.76
33.04
20.91
20.89
19.22
14.19
14.07
f1 (ppm)
S
CH3
H3C
O
CH3
13C NMR spectrum of 4
(CDCl3)

MR_OS3_Q.1.fid

Product (4)



internal standard
(1,3,5-trimethoxybenzene)



purity: 96%

solvent: $CDCl_3$

	Product	Internal Standard (1,3,5-trimethoxybenzene)
MW	252.42	168.19
Amount	35.36 mg	10.71 mg
Area	2.1104	1.0000