Organic Syntheses

Synthesis of [(*R*)-DTBM-SEGPHOS]$NiCl_2$ and Orthoformate Reaction

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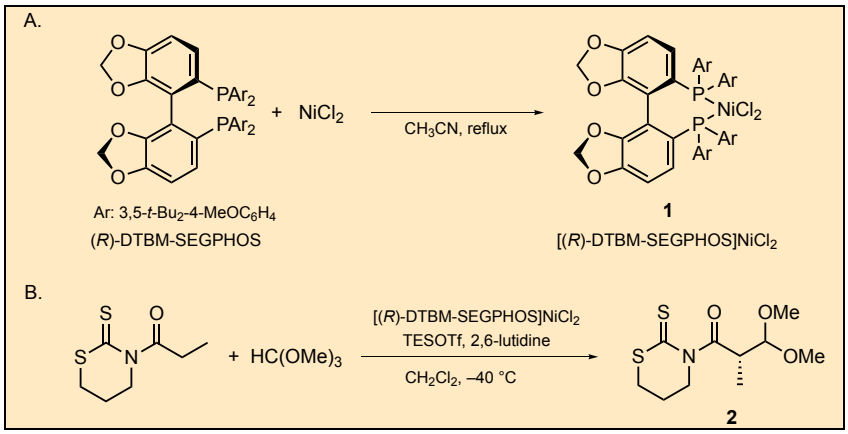


Procedure (Note 1)

A. *[(R)-DTBM-SEGPHOS]$NiCl_2$ (**1**).* An oven dried single-necked 25 mL round-bottomed flask (14/23 joint), equipped with a 1.5-cm Teflon-coated magnetic stirbar, is charged with (*R*)-DTBM-SEGPHOS (1.00 g, 0.85 mmol, 1 equiv) (Note 2) and $NiCl_2$ (110 mg, 0.85 mmol, 1 equiv) (Note 3), and acetonitrile (15 mL) (Note 4). A reflux condenser (14/23 joint) with a rubber septum is attached to the round-bottomed flask and the system is purged for 5 min with N_2, after which a N_2-filled balloon is used to seal the system. The mixture is then heated at reflux in an oil bath for 16 h.

A Number 3 Glass filter funnel connected with a vacuum adaptor to a single-necked 500 mL round-bottomed flask (29/32 joint) is charged with Celite® (25 g) (Note 5). The Celite® is wetted with acetonitrile (70 mL) (Note 4) and allowed to settle. Whilst the reaction mixture is still warm, the contents are poured over the Celite®. Once absorbed, the Celite® is carefully washed (Note 6) with acetonitrile (300 mL) (Note 4) until the color completely passes to the round-bottomed flask. The filtrate is concentrated on a rotary evaporator (30 °C, 12 mmHg pressure). The resulting solid is dissolved in dichloromethane (20 mL) (Note 7) and transferred to a vial (20 mL). The solution is concentrated on a rotary evaporator (30 °C, 12 mmHg pressure) and the resulting solid broken up with a spatula and dried on a high vacuum line (room temperature, 0.1 mmHg pressure) for 4 h giving the title compound **1** (1.10 g, 0.84 mmol, 99% yield) (Note 8) as a fine dark green-black powder.

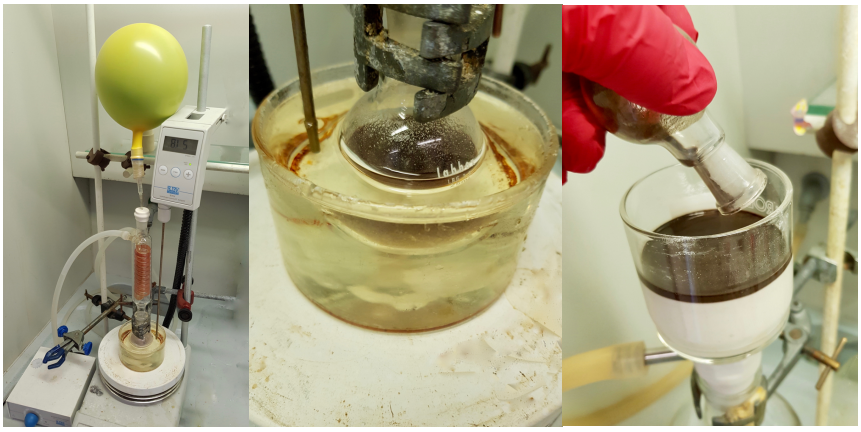


Figure 1. Reaction set-up (left), final color (middle), and Celite® filtration (right)

B. *N-[(S)-(3,3-Dimethoxy-2-methylpropanoyl)]-1,3-thiazinane-2-thione* (**2**). An oven dried single-necked 50 mL round-bottomed flask (14/23 joint), equipped with a 2-cm Teflon-coated magnetic stirbar, is charged with *N*-propanoyl-1,3-thiazinane-2-thione (1.89 g, 10 mmol, 1 equiv) (Note 9) and **1** (196 mg, 0.15 mmol, 1.5 mol%). The round-bottomed flask is sealed with a rubber septum and purged with N_2 for 5 min, after which a N_2-filled balloon is attached to the system. Freshly distilled dichloromethane (20 mL) (Note 7) is added to the mixture, followed by trimethyl orthoformate (1.3 mL, 12

mmol, 1.2 equiv) (Note 10). The resultant mixture is stirred and cooled to –40 °C with an acetonitrile/liquid N_2 bath. Then, triethylsilyl triflate (3.2 mL, 14 mmol, 1.4 equiv) (Note 11) is added and the mixture is stirred for 5 min. Finally, freshly distilled 2,6-lutidine (1.75 mL, 15 mmol, 1.5 equiv) (Note 12) is added and the resultant mixture is stirred for 2 h at –40 °C.

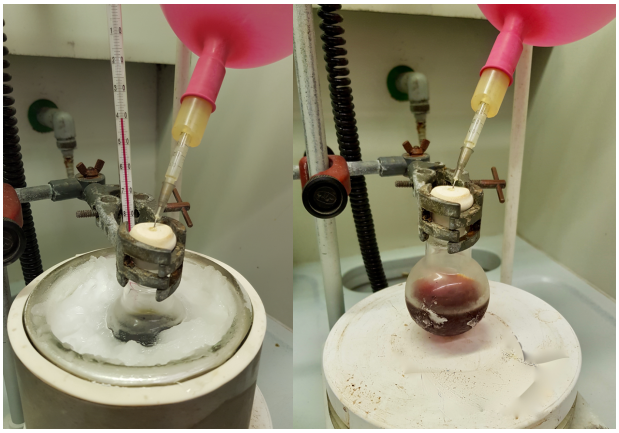


Figure 2. Reaction set-up (left) and final appearance (right)

The reaction is quenched with saturated NH_4Cl aqueous solution (10 mL) and the mixture is transferred to a 250 mL separating funnel. The round-bottomed flask is washed with dichloromethane (2 × 25 mL) (Note 13), which is then transferred to the separating funnel. Deionized water (2 × 25 mL) was used to wash the round-bottomed flask and added to the separating funnel. After shaking vigorously, the lower organic layer is collected and the remaining aqueous layer is further extracted with dichloromethane (50 mL) (Note 13). The combined organic extracts are dried over $MgSO_4$ (30 g) (Note 14) and filtered into a 250 mL round-bottomed flask (29/32 joint); the remaining $MgSO_4$ (Note 14) is further washed with dichloromethane (50 mL) (Note 13) and filtered. The combined filtrates are concentrated on a rotary evaporator (25 °C, 12 mmHg pressure) to produce a yellow–brown oil.

The residue is then submitted to flash column chromatography using a 4.5 cm diameter column with a length of 25 cm of silica gel (60 Å) (Note 15). This is first compacted with 95:5 dichloromethane/triethylamine (500 mL) (Notes 13 and 16), washed once with dichloromethane (500 mL) (Note 13),

and the surface levelled. The residue is dissolved in dichloromethane (10 mL) (Note 13) and transferred onto the compacted column with a pipette. The round-bottomed flask is washed with further dichloromethane (2 × 5 mL) (Note 13) and the washings added to the column. Once adsorbed, thick sand is added to protect the silica. The column is eluted with dichloromethane (*ca* 500 mL) (Note 13) until all of the yellow color has left the column and the eluent runs clear. All pure tubes are collected in a 500 mL round-bottomed flask and concentrated on a rotary evaporator (35 °C, 12 mmHg pressure). Neat dichloromethane (2 × 25 mL) (Note 13) is added and the resultant solution transferred to a vial (20 mL) where it is concentrated on a rotary evaporator (35 °C, 12 mmHg pressure). The resultant solid is kept under high vacuum (0.1 mmHg) at room temperature for 4 h to afford pure product **2** (2.29 g, 87% yield) as a yellow solid (Note 17).

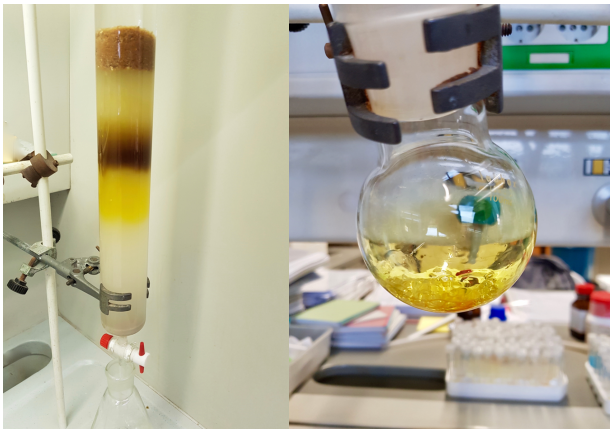


Figure 3. Column chromatography (left) and final product (right)

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 trimethyl orthoformate, triethylsilyl triflate, 2,6-lutidine, triethylamine, Celite®, silica gel, acetonitrile, and dichloromethane.

2. (*R*)-DTBM-SEGPHOS (> 99%) was purchased from TCI Europe and used as received.
3. $NiCl_2$ (99%) was purchased from Sigma-Aldrich and used as received.
4. Acetonitrile (99%) was purchased from VWR International and used as received.
5. Celite@ was purchased from Fluorochem and used as received.
6. It is important to wash the Celite® surface carefully to minimally stir up the solid.
7. Dichloromethane (99%) was purchased from Acros Organics and was freshly distilled from CaH_2.
8. [(*R*)-DTBM-SEGPHOS]$NiCl_2$ (**1**) has the following physical and spectroscopic properties: mp 255–257 °C; IR (ATR): 2955, 1439, 1407, 1391, 1223, 11135, 1112, 1049, 1002, 844, 805 cm^{-1}; HRMS (+ESI) *m*/*z* calcd for $C_{74}H_{100}ClNiO_8P$ $[M - Cl]^+$ 1271.5930, found 1271.5919.
9. *N*-Propanoyl-1,3-thiazinane-2-thione has been reported in the preceding paper.
10. Methyl orthoformate (99%) was purchased from Sigma-Aldrich and used as received.
11. Triethylsilyl triflate (> 98%) was purchased from Fluorochem and used as received. Importantly, triethylsilyl triflate must be new and fresh. It is imperative that it resembles a clear liquid.
12. 2,6-Lutidine (98%) was purchased from Sigma-Aldrich and freshly distilled over CaH_2.
13. Dichloromethane (99%) was purchased from Acros Organics and used as received.

14. Anhydrous $MgSO_4$ was purchased from Panreac and used as received.
15. Silica gel was purchased from Sigma-Aldrich and used as received.
16. Triethylamine (> 99%) was purchased from Sigma-Aldrich and used as received.
17. *N*-[(*S*)-(3,3-Dimethoxy-2-methylpropanoyl)]-1,3-thiazinane-2-thione (**2**) has the following physical and spectroscopic properties: R_f 0.40 (CH_2Cl_2); chiral HPLC (Phenomenex Lux® Amylose-2 column, 10% *i*-PrOH in hexane, flow 1 mL min^{-1}] R_t 11.4 min [R_t minor 18.9 min], 99% *ee*; mp 56–57 °C; $[\alpha]_D^{20}$ +352 (*c* 1.00, $CHCl_3$); IR (ATR): 2936, 2823, 1704, 1460, 1374, 1344, 1289, 1127, 1096, 1047, 992 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.30 (d, *J* = 6.7 Hz, 3H), 2.15–2.35 (m, 2H), 2.97–3.14 (m, 2H), 3.30 (s, 3H), 3.33 (s, 3H), 3.48 (ddd, *J* = 13.3, 9.3, 4.2 Hz, 1H), 3.95 (dq, *J* = 8.1, 6.7 Hz, 1H), 4.13 (dt, *J* = 13.3, 5.0 Hz, 1H), 4.41 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 13.8 (CH_3), 22.5 (CH_2), 31.8 (CH_2), 45.8 (CH), 47.6 (CH_2), 52.0 (CH_3), 55.2 (CH_3), 107.4 (CH), 181.4 (C), 201.1 (C); HRMS (+ESI) *m*/*z* calcd for $C_9H_{14}NO_2S_2$ $[M - OMe]^+$ 232.0460, found 232.0462.

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

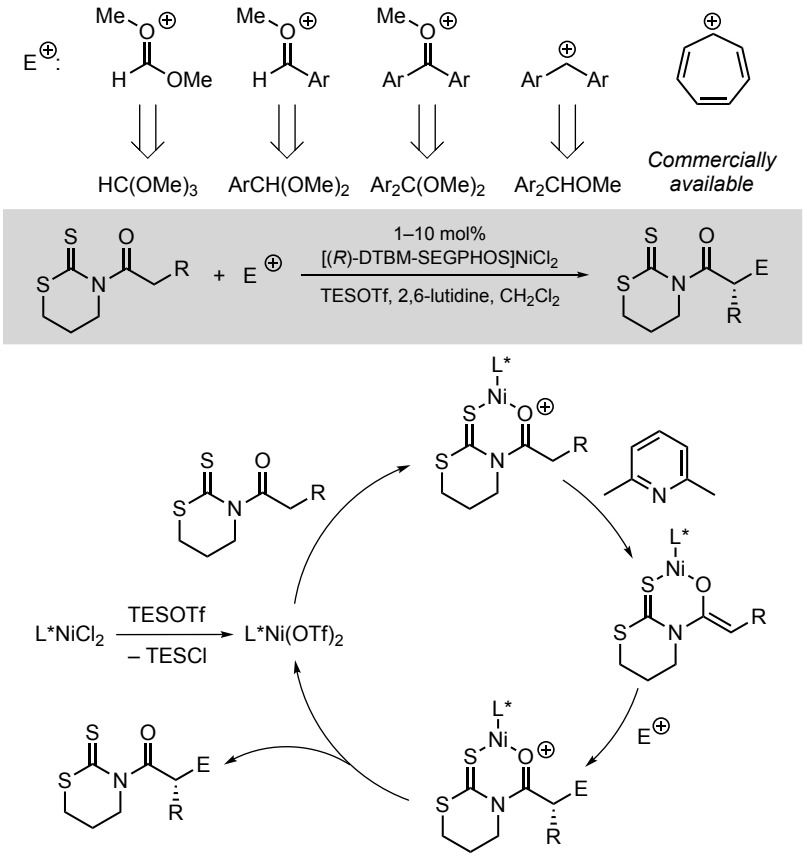
and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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

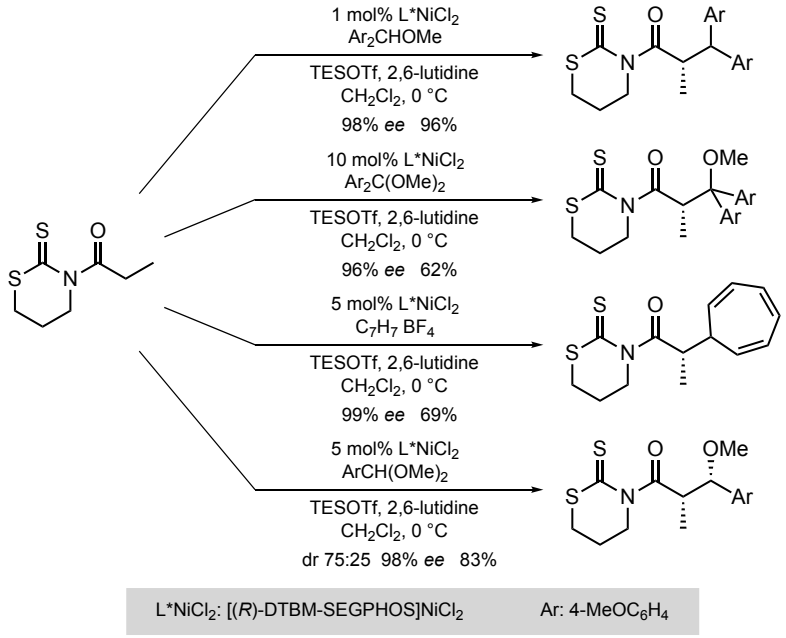
The enantioselective and catalytic construction of carbon–carbon bonds from enolates has attracted much attention in recent years.[2] Indeed, Evans,[3] Shibasaki,[4] and Trost[5] have described insightful approaches taking advantage of privileged scaffolds and chiral nickel(II), copper(II), or zinc complexes. Regardless the outcome of such transformations, availability and easily handled catalysts are important issues to make them useful to be applied to the asymmetric synthesis of natural products.

In this context, we have recently reported the reaction of *N*-acyl-1,3-thiazinane-2-thione with a range of electrophiles in the presence of 1–10 mol% of [(*R*)-DTBM-SEGPHOS]$NiCl_2$.[6,7] Evidence suggests that such a complex is activated *in situ* with TESOTf to produce the true catalytic species, [(*R*)-DTBM-SEGPHOS]$Ni(OTf)_2$, whose coordination with the *N*-acyl thiazinanethione makes possible the Cα deprotonation with 2,6-lutidine (Scheme 1). In turn, TESOTf is also necessary to generate *in situ* the electrophilic reacting species from methyl orthoformate, acetals, ketals, or benzhydryl methyl ethers. Then, the resultant chiral nickel(II) enolate approaches the electrophilic intermediate through an open transition state to produce the corresponding adduct containing a new carbon–carbon bond and up to two new stereogenic centers (Scheme 1).



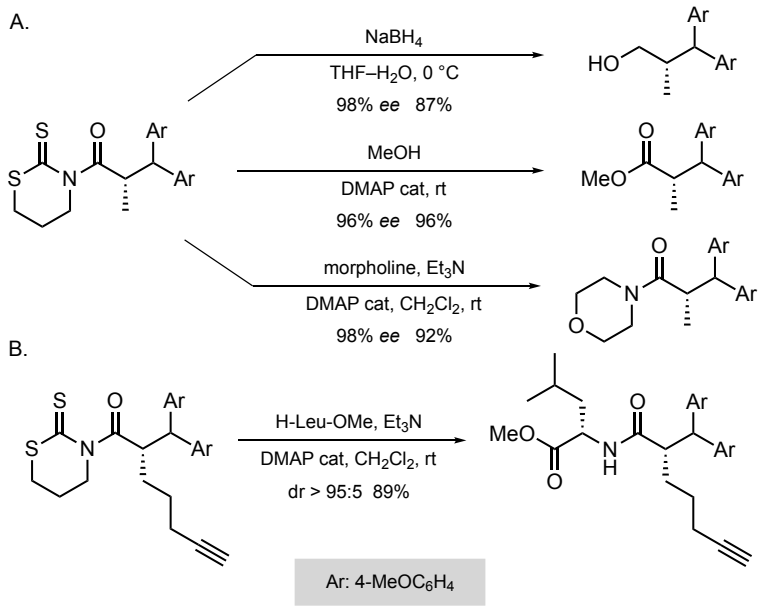
Scheme 1. Enantioselective carbon–carbon bond forming reactions from *N*-acyl-1,3-thiazinane-2-thiones and [(*R*)-DTBM-SEGPHOS]$NiCl_2$

Such a process turns out to be successful and may provide alkylated and aldol-like products in high yields and excellent stereocontrol. Indeed, aside from the 3,3-dimethoxy derivative described before, it is possible to obtain the adducts represented in Scheme 2 as a single enantiomer (ee ≥ 96%) in good to high yields.



Scheme 2. Enantioselective carbon–carbon bond forming reactions from *N*-propanoyl-1,3-thiazinane-2-thione catalyzed by [(*R*)-DTBM-SEGPHOS]$NiCl_2$

Finally, the thiazinanethione scaffold can be easily removed under mild experimental conditions to afford enantiomerically pure alcohols, esters, or amides as shown in Part A of Scheme 3. Interestingly, the thiazinanethione may also act as a coupling reagent and permits the synthesis of a diastereomerically pure *N*-acyl amino acid by simple addition of methyl (*S*) leucinate to the corresponding adduct with an 89%yield (Part B Scheme 3).[8]



Scheme 3. Removal of the thiazinanethione scaffold

References

1. Secció de Química Orgànica, Departament de Química Inorgànica i Orgànica & Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona, 08028 Barcelona, Catalonia, Spain. Email: pedro.romea@ub.edu; felix.urpi@ub.edu. Financial support from the Spanish Ministerio de Ciencia, Innovación y Universidades (MCIU)/Agencia Estatal de Investigación (AEI)/Fondo Europeo de Desarrollo Regional (FEDER, UE) (Grant No. PGC2018-094311-B-I00), and the Generalitat de Catalunya (2017SGR 271) as well as a doctorate studentship to S. C. D. K. (FI, Generalitat de Catalunya) are acknowledged.
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6. Kennington, S. C. D.; Taylor, A. J.; Romea, P.; Urpí, F.; Aullón, G.; Font-Bardia, M.; Ferré, L.; Rodrigalvarez, J. *Org. Lett.* **2019**, *21*, 305–309.
7. The preparation of [(*R*)-DTBM-SEGPHOS]$NiCl_2$ has been adapted from that reported for [(*R*)-Tol-BINAP]$NiCl_2$. See reference 3b.
8. For a related example proving the synthetic potential of such an approach for the synthesis of peptides, see: Fernández-Valparís, J.; Romea, P.; Urpí, F. *Eur. J. Org. Chem.* **2019**, 2745–2752.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

[(*R*)-DTBM-SEGPHOS]: Phosphine, 1,1'-(4*R*)-[4,4'-bi-1,3-benzodioxole]-5,5'-diylbis[1,1-bis[3,5-bis(1,1-dimethylethyl)-4-methoxyphenyl]-; (566940-03-2)

N-Propanoyl-1,3-thiazinane-2-thione: 1-Propanone, 1-(dihydro-2-thioxo-2H-1,3-thiazin-3(4H)-yl)-; (2138126-72-2)

Trimethyl orthoformate: Methane, trimethoxy-; (149-73-5)

Triethylsilyl triflate: Methanesulfonic acid, 1,1,1-trifluoro-, triethylsilyl ester; (79271-56-0)

2,6-Lutidine: Pyridine, 2,6-dimethyl-; (108-48-5)

N-[(*S*)-3,3-Dimethoxy-2-methylpropanoyl]-1,3-thiazinane-2-thione: 1-Propanone, 1-(dihydro-2-thioxo-2H-1,3-thiazin-3(4H)-yl)-3,3-dimethoxy-2-methyl-, (2*S*)-; (2270858-10-9)

Stuart C. D. Kennington, born in 1992 in Cambridgeshire, England, received his MChem degree from the University of Warwick in 2015. He is currently carrying out his PhD Thesis under the supervision of Prof. Fèlix Urpí and Pedro Romea at the University of Barcelona with a FI scholarship from the Generalitat de Catalunya. His research focuses on new catalyzed asymmetric synthesis methodologies and their application to the total synthesis of natural products.

Pedro Romea completed his B.Sc. in Chemistry at the University of Barcelona and followed PhD studies from 1987 to 1991 under the supervision of Professor Jaume Vilarrasa at the same University of Barcelona. Then, he joined the group of Professor Ian Paterson at the University of Cambridge (UK), where he participated in the total synthesis of oleandolide. Back to the University of Barcelona, he became Associate Professor in 1993. His research interests have focused on the development of new synthetic methodologies and their application to the stereoselective synthesis of naturally occurring molecular structures.

Felix Urpí received his B.Sc. in Chemistry at the University of Barcelona and completed PhD studies under the guidance of Professor Jaume Vilarrasa at the University of Barcelona in 1988. He then worked as a NATO postdoctoral research associate in titanium enolate chemistry with Professor David A. Evans, at Harvard University in Cambridge, MA. He moved back to the University of Barcelona and he became Associate Professor in 1991, where he holds a chair of Full Professor in Organic Chemistry since 2017. His research interests have focused on the development of new synthetic methodologies and their application to the stereoselective synthesis of naturally occurring molecular structures.