Organic Syntheses

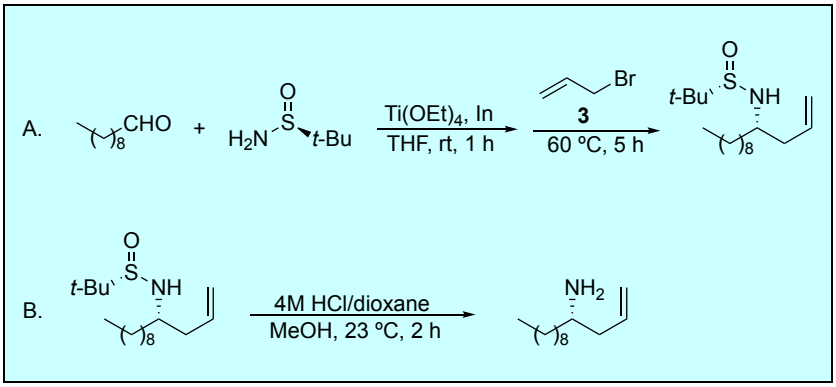
Discussion Addendum for:

Preparation of Enantioenriched Homoallylic Primary Amines

Miguel Yus[*1]

Centro de Innovación en Química Avanzada (ORFEO-CINQA), Universidad de Alicante, 03080 Alicante, Spain

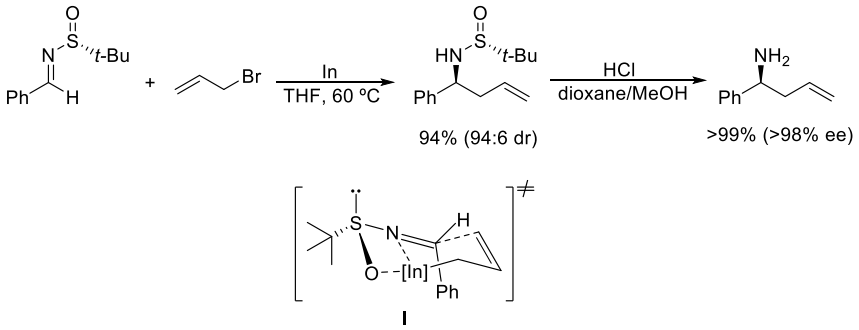
Original Article: González-Gómez, J. C.; Foubelo, F.; Yus, M. Org. Synth. ***2012****, 89, 88–97.*



One of the most efficient methodologies to prepare amines is the addition of organometallic reagents to imines.[2] From a synthetic point of view, the corresponding allylation presents special interest due to the possible transformation of the introduced carbon-carbon double bond into other functionalities.[3] The asymmetric version of this process, both in an enantio-[4] or diastereoselective[5] catalytic fashion, allows the preparation of chiral homoallylic amines, useful starting materials in synthetic organic chemistry.[6] Among different possibilities, one way to activate the C=N bond in imines and at the same time to introduce asymmetric information in the starting material, is the use of *N*-sulfinyl imines (mainly aldimines) as electrophiles in the reaction with allylic organometallic compounds.[7] As activated imines, *N*-

DOI: 10.15227/orgsyn.096.0179 Published on the Web 6/19/2019

tert-butylsulfinyl derivatives[8] have been extensively used, and as metallic components, allylmagnesium,[9] allylzinc[10] and allylindium[11] reagents were successfully employed. Some years ago, we found that a convenient method to allylate *N*-*tert*-butylsulfinyl aldimines in a diastereoselective manner is the use of an allyl bromide and indium metal in THF at 60 ºC.[12] The combination of this methodology with the easy deprotection of the sulfinyl moiety under acidic conditions represents an useful procedure to prepare enantiomerically enriched homoallylic primary amines: Scheme 1 shows an example of this process. The transition state **I** can explain the obtained stereochemical outcome. This procedure was further extended to ketimines with similar results.[13]



I

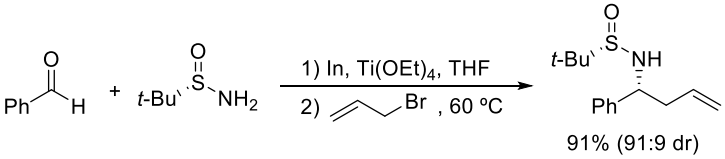
Scheme 1. First In-promoted allylation of *N*-*tert*-butylsulfinyl imines

The most commonly used method to prepare the starting enantiomerically pure *N*-*tert*-butylsulfinyl imines is the direct reaction of the corresponding carbonyl compounds with enantiomerically pure commercially available *tert*-butanesulfinamides and titanium tetraethoxide under thermal[14] or microwave[15] activation. Other procedures starting from epoxides[16] or allylic alcohols and aryl iodides[17] are complementary but not so general.

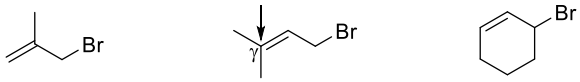
In-promoted allylation of *N*-*tert*-butylsulfinyl imines[18]

The method shown in Scheme 1 has been further improved without the need of isolating the starting imine. Thus, after reacting an aldehyde and the chiral sulfinamide in the presence of titanium tetraethoxide and indium powder for one hour, allyl bromide is added and the mixture heated at 60 ºC. In this one-pot procedure the anticipated protected homoallylamine is

obtained as illustrated in Scheme 2.[19] The reaction is rather general concerning the starting aldehyde and has been applied to other allylic bromides with good yields (82–89%) and high diastereoselectivities (90:10–>99:1). It is remarkable that in the case of prenyl bromide[20] only γ -attack was observed.

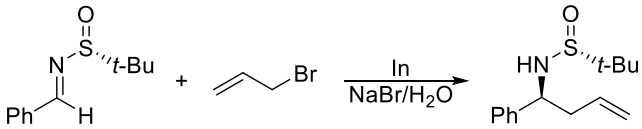


Other allylic bromides:



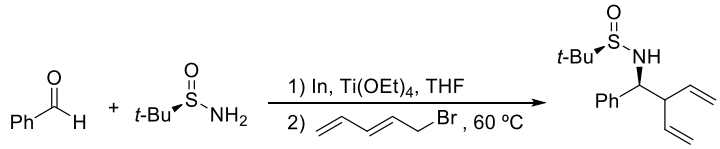
Scheme 2. One-pot procedure to allylate in situ generated sulfinyl imines

Another version of the reaction depicted in Scheme 1 has been performed under aqueous conditions.[11b] An example is shown in Scheme 3 for the allylation of the same imine using a saturated solution of sodium bromide at room temperature.



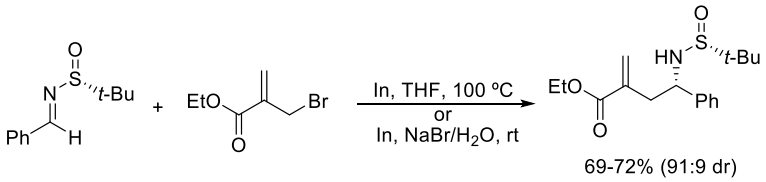
Scheme 3. In-promoted allylation of a chiral *N-tert*-butylsulfinyl imine under aqueous conditions

When the one-pot procedure described in Scheme 2 was applied to pentadienyl bromide a γ -attack was also observed giving the corresponding pentadienyl product in low yield as shown in Scheme 4 for the same imine.[21]



Scheme 4. One-pot In-promoted pentadienylation of an in situ generated *N-tert*-butylsulfinyl imine

In addition, the allylic bromide component can bear an ester group and the reaction works in the same way as allyl bromide giving multifunctionalized amines as exemplified in Scheme 5 for the reaction in THF[22] or under aqueous conditions.[23]

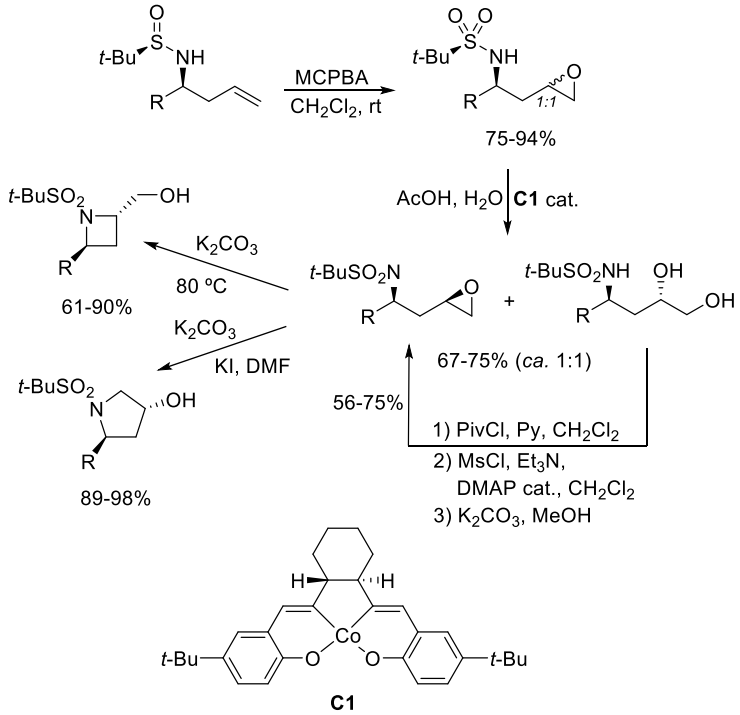


Scheme 5. In-promoted allylation of an *N*-*tert*-butylsulfinyl aldimine with ethyl 2-(bromoethyl)acrylate

Finally, the same protocol described for the In-promoted allylation of chiral *N*-*tert*-butylsulfinyl imines has been successfully applied to propargyl bromides to access diastereo- and regioselectively to homopropargylic amines.[24]

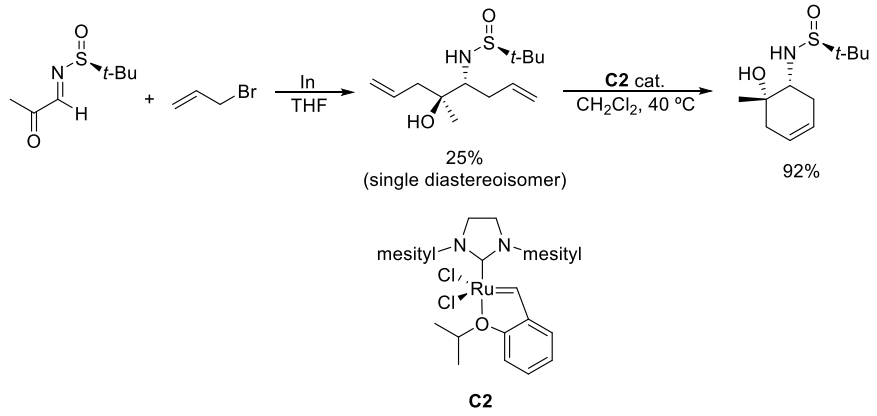
Synthetic applications of chiral *N*-sulfinyl homoallylic amines[25]

Once chiral *N*-*tert*-butylsulfinyl homoallylic amines were prepared, their oxidation with *meta*-chloroperbenzoic acid (MCPBA) yielded the corresponding sulfonyl epoxides as a *ca.* 1:1 mixture of diastereoisomers concerning the new stereocenter formed. The application of the Jacobsen kinetic resolution[26] to the mixture of epoxides gave a *ca.* 1:1 mixture of enantiomerically pure diols and epoxides, which were easily separated by column chromatography. The transformation of the diols into the epoxides can be easily performed by standard methodologies: (1) protection of the terminal alcohols as their pivalates, (2) mesylation of the secondary alcohols, and (3) deprotection of the primary alcohols and epoxidation under basic conditions. The enantiomerically pure epoxides were transformed into azetidines or pyrrolidines by treatment with potassium carbonate and potassium iodide in the second case (involving an iodohydrin intermediate) (Scheme 6).[27]



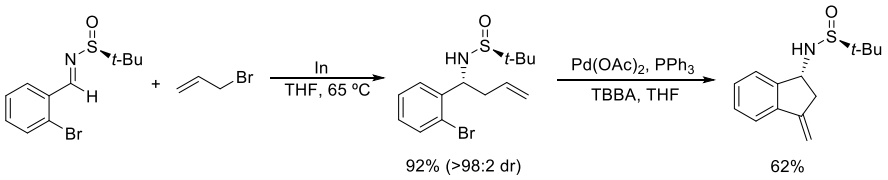
Scheme 6. Preparation of chiral azetidines and pyrrolidines from *N*-*tert*-butylsulfinyl imines by a tandem epoxidation/kinetic resolution/cyclization

N-*tert*-Butylsulfinyl imines derived from α-keto aldehydes[28a] or α-keto esters[28b] have been allylated in the presence of indium powder to give the corresponding allylated products in a diastereoselective manner. In the first case, using an excess of the allylic component resulted in diallylation giving a diene that by ring-closing metathesis gave the expected chiral *N*-protected 2-aminocyclohexanol, as it is illustrated in Scheme 7.



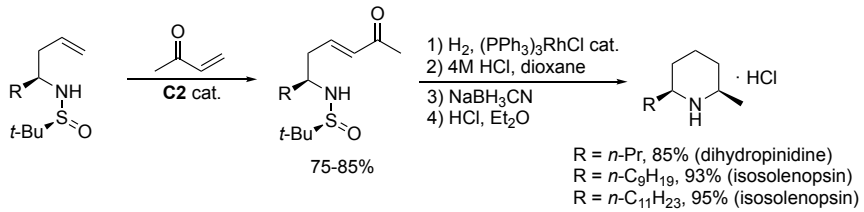
Scheme 7. Diallylation of an α -keto *N*-*tert*-butylsulfinyl imine and ring-closing metathesis

When *N*-*tert*-butylsulfinyl imines derived from *ortho*-bromo carbonyl compounds were allylated in the presence of In, the protected amines were obtained with high yields and stereoselectivities. These compounds were submitted to a Heck-type reaction to yield chiral *exo*-methylenic indenylamines. An example is illustrated in Scheme 8.[29]



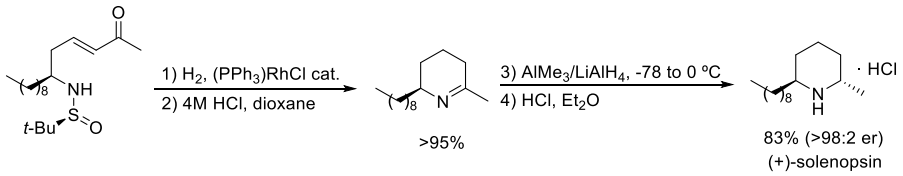
Scheme 8. Tandem allylation/Heck-type reaction of an *o*-bromo sulfinyl imine

From a synthetic point of view the most important application of allylated *N*-*tert*-butylsulfinyl imines is the preparation of alkaloids.[25] Scheme 9 shows a simple access to piperidine-derived natural products: the starting homoallyl amines were treated with methyl vinyl ketone in the presence of catalyst **C2** to give enones, that after (1) hydrogenation, (2) deprotection and (3) reduction suffer cyclization to afford natural venom alkaloids of fire ants, isolated as their hydrochlorides.[30]



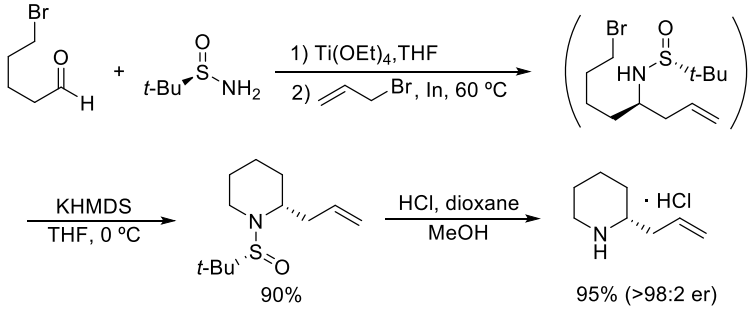
Scheme 9. Preparation of chiral *cis*-2,6-disubstituted piperidines

The corresponding *trans*-2,6-disubstituted piperidines were prepared just changing the reduction step in Scheme 9. One example depicted in Scheme 10 is the synthesis of (+)-solenopsin, an alkaloid also isolated from fire ants: after isolation of the tetrahydropyridine intermediate it was reduced diastereoselectively with $AlMe_3/LiAlH_4$ at low temperature to give the mentioned alkaloid.[31]



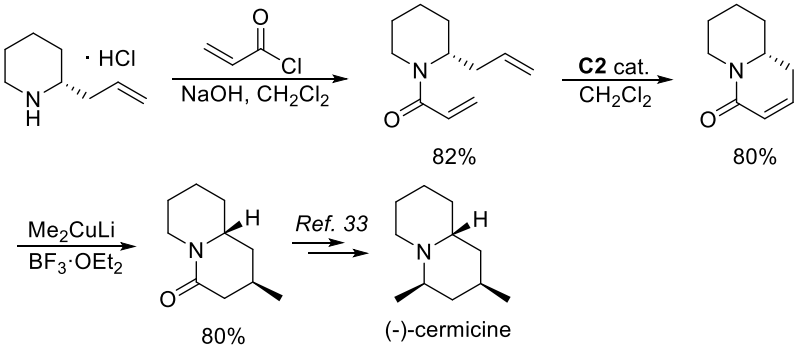
Scheme 10. Synthesis of (+)-solenopsin

One interesting compound that can be further elaborated in order to prepare natural alkaloids is chiral 2-allylpiperidine. For this purpose δ-bromopentanal was allylated and cyclized in situ to give the expected *N*-*tert*-butylsulfinyl 2-allylpiperidine, which was easily deprotected to afford the corresponding amine hydrochloride (Scheme 11).[32]



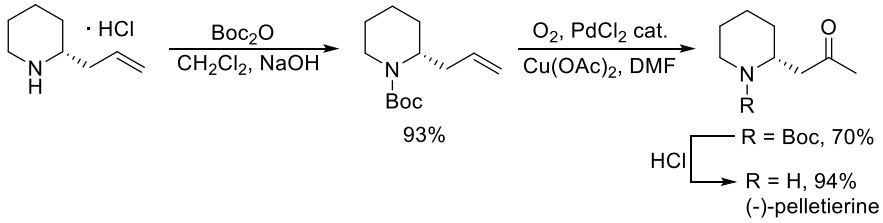
Scheme 11. Preparation of chiral 2-allylpiperidine

The simple hydrogenation (H_2, Pd/C cat., MeOH) of the prepared chiral 2-allylpiperidine afforded (+)-coniine (78%), the major alkaloid extracted from poison hemlock. The same starting material was transformed into the corresponding *N*-acryloyl derivative and then submitted to a ring-closing metathesis in the presence of catalyst **C2**. Thus, a bicyclic compound was isolated that was easily converted in its methylated derivative, a precursor of (-)-cermicine C,[32] as reported previously[33] (Scheme 12).



Scheme 12. Preparation of a precursor of (-)-cermicine C

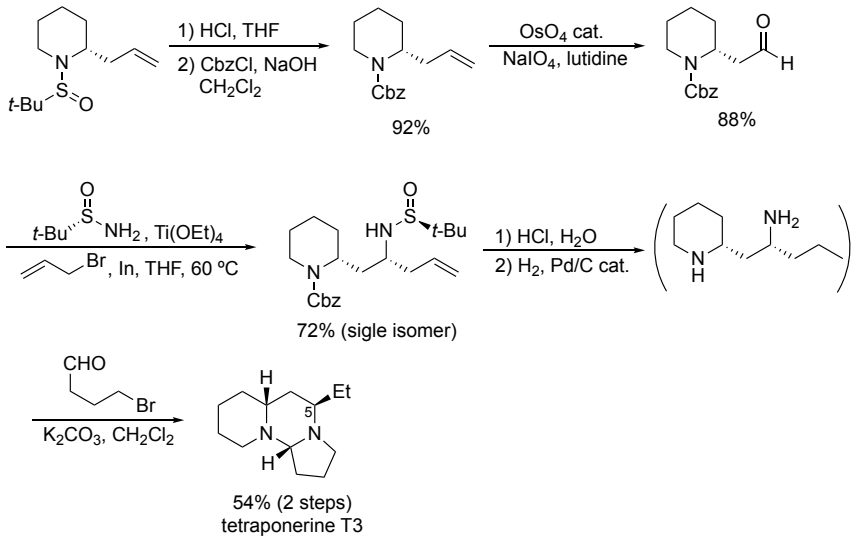
The straightforward synthesis of (-)-pelletierine, shown in Scheme 13, starts from the same material: after introducing the Boc protection at the nitrogen atom, a Wacker-type oxidation followed by deprotection yielded the expected alkaloid.[32] On the other hand, (*R*)-*N*-Boc-pelletierine has been used for the direct preparation of (+)-allosedrine[34] and its (*S*)-enantiomer for (-)-lausibine II.[35]



Scheme 13. Synthesis of (-)-pelletierine

Another synthetic application of enantiopure 2-allyl-*N*-*tert*-butylsulfinylpiperidine is the preparation of tetraponerine T3 as depicted in Scheme 14. After changing the protecting group to Cbz, the oxidative

cleavage of the carbon-carbon double bond affords the expected aldehyde. This was transformed into its *N*-*tert*-butylsulfinyl imine and allylated in situ (iterative process) to yield the corresponding protected homoallyl amine. Its tandem deprotection/hydrogenation and in situ treatment with γ-bromobutanal gave tetraponerine T3 as a single isomer (Scheme 14).[36]

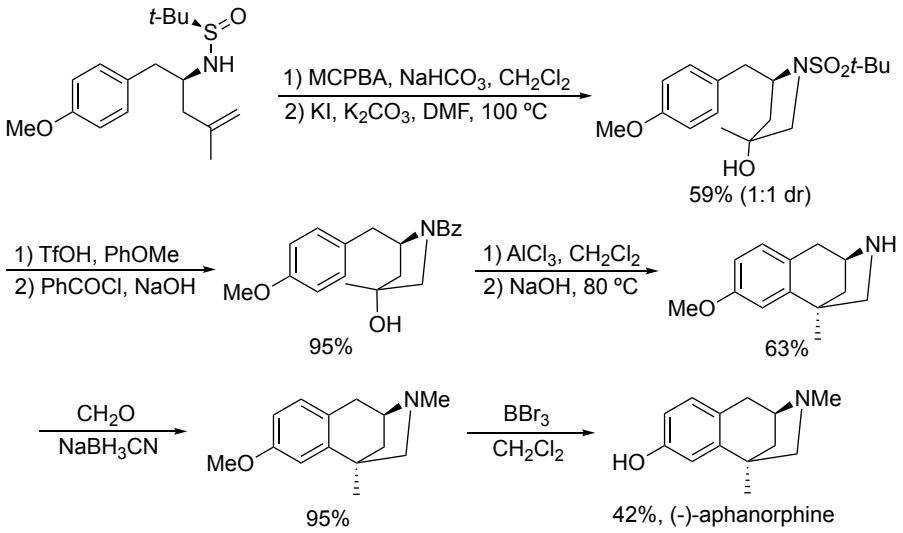


Scheme 14. Total synthesis of tetraponerine T3

By changing the stereochemistry of the *tert*-butanesulfinamide in the reaction with the aldehyde in Scheme 14, the corresponding 5-epimer (tetraponerine T4) was obtained.[36] Following a similar synthetic strategy the other members of the tetraponerine family (T1, T2, T5-T8), components of Pseudomymecine ants (of the genus *Tetraponera*) secreted against enemies, have been synthesized and studied for their antiproliferative activity.[37]

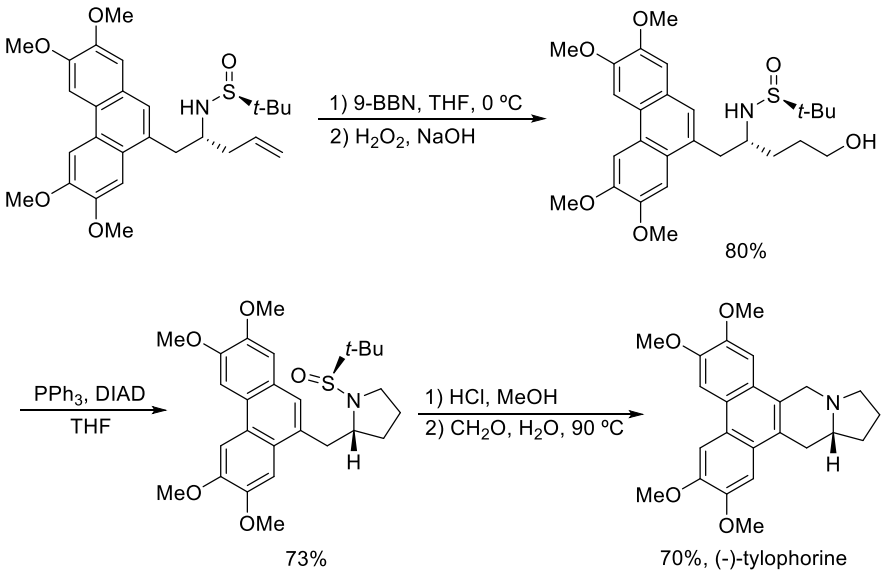
(-)-Aphanorphine, which was isolated from the fresh-water blue-green alga *Aphanizomenon* flos-aquae, incorporates a 3-benzazepine scaffold that resembles benzomorphane analgesics. The total synthesis of the natural alkaloid starts from the *N*-*tert*-butylsulfinyl imine derived from 4-methoxyphenylacetaldehyde, which was reacted with methallyl bromide under standard conditions. Its oxidation afforded the expected epoxide -with concomitant oxidation of the sulfinamide to sulfonamide- that in the presence of KI suffered opening to give the corresponding tertiary alcohol as a 1:1 mixture of diastereoisomers. The required cyclization of this alcohol under

different reaction conditions failed, so it was necessary to change the protection at the nitrogen to the corresponding benzoyl derivative. Treatment of this compound with $AlCl_3$ gave a Friedel-Crafts reaction yielding the corresponding tricycle; further deprotection, methylation at the nitrogen atom and final demethylation at the oxygen atom afforded the expected natural product (Scheme 15).[38]



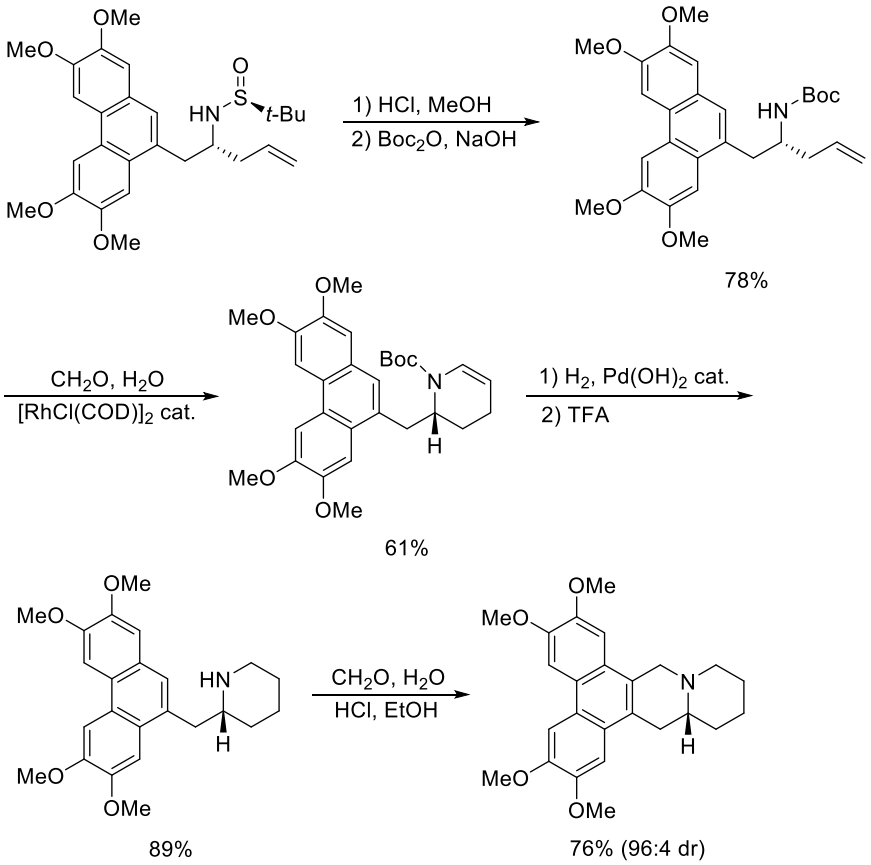
Scheme 15. Total synthesis of (-)-aphanorphine

The indium-promoted diastereoselective allylation of the corresponding aldehyde allows the preparation of a homoallyl amine, starting material for (-)-tylophorine, used in traditional medicine due to its antiasthmatic, antiviral and anti-inflammatory properties. After hydroboration and oxidation the expected primary alcohol is obtained, which suffers an intramolecular Mitsunobu reaction to give a *N*-*tert*-butylsulfinylpyrrolidine that after deprotection and treatment with formaldehyde yielded the natural alkaloid (Scheme 16).[39]



Scheme 16. Total synthesis of (-)-tylophorine

The same starting material shown in Scheme 16 was used for the synthesis of 7-methoxycryptopleurine, following the reactions depicted in Scheme 17. After exchange of the protecting group to Boc, treatment with formalin in the presence of a Rh catalyst gave a six-membered ring, which after hydrogenation and formylation afforded the expected alkaloid derivative.[40]



Scheme 17. Total synthesis of 7-methoxycryptopleurine

Other synthetic methodologies from our research group starting from chiral *N*-*tert*-butylsulfinyl imines involving hydrogen transfer,[41] homoallyl amine oxidation,[42] addition of organomagnesium,[43] organolithium compounds[44] or enolates,[45] and reaction with nitro compounds[46] have been used for the preparation of a series of chiral enantioenriched nitrogen-containing natural and unnatural compounds, including several heterocyclic compounds.

In summary, chiral *N*-*tert*-butylsulfinyl homoallyl amines were easily prepared with diastereocontrol by allylation of *N*-*tert*-butylsulfinyl imines with indium metal under mild reaction conditions. These compounds are useful starting materials for the preparation of chiral natural or unnatural nitrogen-containing compounds, especially biologically active alkaloids. It is

worth noting that both enantiomeric starting imines are easily accessible from commercially available compounds. In addition, the final desulfinylation of the obtained products is easily performed with hydrochloric acid in an organic solvent. Finally, the chiral auxiliary can be recycled and reused following reported procedures.[47]

References

1. Centro de Innovación en Química Avanzada (ORFEO-CINQA), Universidad de Alicante, 03080 Alicante, Spain. Email: yus@ua.es
2. (a) Kobayashi, S.; Ishatami, H. *Chem. Rev.* **1999**, *99*, 1069-1094; (b) Alvaro, G.; Savoia, D. *Synlett* **2002**, 651–673.
3. Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis*; Wiley-VCH: Weinheim, Germany, 2009; pp 651-673.
4. (a) Kanai, M.; Wada, R.; Shibuguchi, T.; Shibasaki, M. *Pure Appl. Chem.* **2008**, *80*, 1055-1062; (b) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774–7854.
5. (a) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815–2829; (b) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595–5698.
6. Ochoa-Puentes, C.; Kouznetsov, V. *J. Heterocl. Chem.* **2002**, *39*, 595–614.
7. (a) Davis, F. A.; Zhou, P.; Chen, B. C. *Chem. Soc. Rev.* **1998**, *27*, 13–18; (b) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995; (c) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39–46; (d) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003–8030.
8. Robak, M. Y.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600–3740.
9. Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883–8904.
10. (a) Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979–4982; (b) Colodney, G.; Skulte, G.; Perrone, S.; Knochel, P.; Marek, I. *Angew. Chem. Int. Ed.* **2007**, *46*, 9291–9294.
11. (a) Cooper, I. R.; Grigg, R.; MacLachlan, W. S.; Thornton-Pett, M.; Sridharan, V. *Chem. Commun.* **2002**, 1372–1373; (b) Sun, X.-W.; Liu, M.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 1259–1262.
12. Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3823–3825.
13. Sirvent, J. A.; Foubelo, F.; Yus, M. *Chem. Commun.* **2010**, *48*, 2543–2545.
14. Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278–1284.

15. Collados, J. F.; Toledano, E.; Guijarro, D.; Yus, M. *J. Org. Chem.* **2012**, *77*, 5744–5750.
16. Lahosa, A.; Foubelo, F.; Yus, M. *Eur. J. Org. Chem.* **2016**, 4067–4076.
17. Ikhlef, S.; Behloul, C.; Lahosa, A.; Foubelo, F.; Yus, M. *Eur. J. Org. Chem.* **2018**, 2609–2614.
18. For reviews, see. (a) Foubelo, F.; Yus, M. *Eur. J. Org. Chem.* **2014**, 485–491; (b) Foubelo, F.; Yus, M. *Russ. Chem. Bull.* **2016**, *65*, 1667–1686.
19. González-Gómez, J. C.; Medjahdi, M.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2010**, *75*, 6308–6311.
20. See, also: Bosque, I.; Foubelo, F.; González-Gómez, J. C. *Org. Biomol. Chem.* **2013**, *11*, 7507–7515.
21. Bosque, I.; Bagdatli, E.; Foubelo, F.; González-Gómez, J. C. *J. Org. Chem.* **2014**, *79*, 1796–1804.
22. Dema, H. K.; Foubelo, F.; Yus, M. *Heterocycles* **2010**, *80*, 125–131.
23. (a) Dema, H. K.; Foubelo, F.; Yus, M. *Heterocycles* **2011**, *82*, 1411–1421; (b) Dema, H. K.; Foubelo, F.; Yus, M. *Jordan J. Chem.* **2011**, *6*, 247–255; (c) Sirvent, J. A.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2014**, *79*, 1356–1367.
24. (a) García-Muñoz, M. J.; Zacconi, F.; Foubelo, F.; Yus, M. *Eur. J. Org. Chem.* **2013**, 1287–1295; (b) García-Muñoz, M. J.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2016**, *81*, 10214–10226; (c) García-Muñoz, M. J.; Sirvent, A.; Foubelo, F.; Yus, M. *An. Acad. Bras. Cienc.* **2018**, *90*, 1059–1072.
25. For a review, see: Foubelo, F.; Yus, M. *Chem. Today* **2016**, *34*, 45–49.
26. Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938.
27. Medjahdi, M.; González-Gómez, J. C.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2009**, *74*, 7859–7865.
28. (a) Maciá, E.; Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2017**, *28*, 1407–1413; (b) Maciá, E.; Foubelo, F.; Yus, M. *Tetrahedron* **2016**, *72*, 6001–6010.
29. Sirvent, J. A.; Foubelo, F.; Yus, M. *Eur. J. Org. Chem.* **2013**, 2461–2471.
30. González-Gómez, J. C.; Foubelo, F.; Yus, M. *Synlett* **2008**, 2777–2780.
31. Medjahdi, M.; González-Gómez, J. C.; Foubelo, F.; Yus, M. *Heterocycles* **2012**, *86*, 727–734.
32. Bosque, I.; González-Gómez, J. C.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2012**, *77*, 780–784; Corrigendum: Bosque, I.; González-Gómez, J. C.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2012**, *77*, 4190.
33. Snider, B. B.; Grabowski, J. F. *J. Org. Chem.* **2007**, *72*, 1039–1042.
34. Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, *65*, 10192–10213.

35. Chen, G.; Wang, X.; Su, D.; Liu, H.; Liu, F.; Hu, Y. *J. Org. Chem.* **2010**, *75*, 1911–1916.
36. Bosque, I.; González-Gómez, J. C.; Guijarro, A.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2012**, *77*, 10340–10346.
37. Bosque, I.; González-Gómez, J. C.; Loza, M. I.; Brea, J. *J. Org. Chem.* **2014**, *79*, 3982–3991.
38. Medjahdi, M.; González-Gómez, J. C.; Foubelo, F.; Yus, M. *Eur. J. Org. Chem.* **2011**, 2230–2234.
39. (a) Anton-Torrecillas, C.; González-Gómez, J. C. *Org. Biomol. Chem.* **2014**, *12*, 7018–7025; (b) Anton-Torrecillas, C.; Loza, M. I.; Brea, J.; González-Gómez, J. C. *Org. Biomol. Chem.* **2016**, *14*, 2264–2271.
40. Anton-Torrecillas, C.; Bosque, I.; González-Gómez, J. C.; Loza, M. I.; Brea, J. *J. Org. Chem.* **2015**, *80*, 1284–1290.
41. (a) For a review, see: Foubelo, F.; Yus, M. *Chem. Rec.* **2015**, *15*, 907–924; (b) Pablo, O.; Guijarro, D.; Kovács, G.; Lledós, A.; Ujaque, J.; Yus, M. *Chem. Eur. J.* **2012**, *18*, 1969–1983; (c) Guijarro, D.; Pablo, O.; Yus, M. *J. Org. Chem.* **2013**, *78*, 3647–3650; (d) Pablo, O.; Guijarro, D.; Yus, M. *J. Org. Chem.* **2013**, *78*, 9181–9189; (e) Pablo, O.; Guijarro, D.; Yus, M. *Eur. J. Org. Chem.* **2014**, 7034–7038.
42. Sirvent, J. A.; Soler, T.; Foubelo, F.; Yus, M. *Chem. Commun.* **2017**, *53*, 2701–2704.
43. (a) Sirvent, J. A.; Foubelo, F.; Yus, M. *Heterocycles* **2014**, *88*, 1163–1174; (b) Mendes, J. A.; Merino, P.; Soler, T.; Salustiano, E. J.; Costa, P. R. R.; Yus, M.; Foubelo, F.; Buarque, C. D. *J. Org. Chem.* **2019**, *84*, 2219–2233.
44. García, D.; Moreno, B.; Soler, T.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **2009**, *50*, 4710-4713.
45. (a) Dema, H. K.; Foubelo, F.; Yus, M. *Helv. Chim. Acta* **2012**, *95*, 1790–1798; (b) Lahosa, A.; Soler, T.; Arrieta, A.; Cossío, F. P.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2017**, *82*, 7481–7491.
46. (a) García-Muñoz, M. J.; Dema, H. K.; Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2014**, *25*, 362–372; (b) García-Muñoz, M. J.; Foubelo, F.; Yus, M. *Heterocycles* **2015**, *90*, 1419–1431; (c) Benlahrech, M.; Lahosa, A.; Behloul, C.; Foubelo, F.; Yus, M. *Heterocycles* **2018**, *97*, 1191–1202.
47. (a) Wakayama, M.; Ellman, J. A. *J. Org. Chem.* **2009**, *74*, 2646–2650; (b) Aggarwal, V. K.; Barbero, N.; McGarrigle E. M.; Mickle, G.; Navas, R.; Suárez, J. R.; Unthank, M. G.; Yar, M. *Tetrahedron Lett.* **2009**, *50*, 3482–3484.

Miguel Yus received his PhD in Chemistry at the University of Saragossa in 1973. After postdoctoral studies at the Max Planck Institute für Kohlenforshung (Mülheim Ruhr) he joined the University of Oviedo becoming full Professor in 1987. In 1988 Miguel moved to a chair in Organic Chemistry at the University of Alicante where he has developed is academic carrier ever since. He has published more than 600 papers in international journals, 73 being his h factor (05/2019).