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Synthesis of alkaloids
by a diastereoselective allylation of chiral N-sulfinyl imines

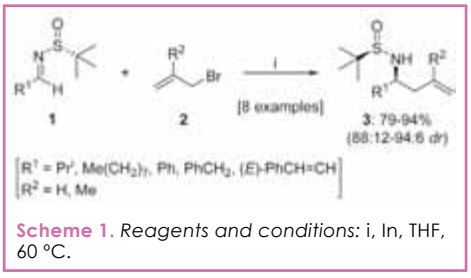
KEYWORDS: Diastereoselective allylation, chiral N-sulfinyl imines, alkaloids, desulfinylation, indium metal.

Abstract The indium-promoted allylation of chiral N-sulfinyl imines represents a useful and versatile procedure to prepare chiral protected homoallyl amines in a diastereoselective manner. Desulfinylation under acidic conditions liberates easily the corresponding enantioenriched homoallyl amines. This type of compounds can be easily manipulated synthetically in order to prepare a series of natural alkaloids in an enantiopure form, using simple transformations.

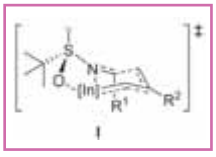
INTRODUCTION

Among the reactions involving the addition of an organometallic reagent to carbonyl compounds or imines, the corresponding allylation offers the advantage of making possible the further manipulation of the allylic moiety. In general, the allylation of imines has been far less studied than the corresponding reaction with carbonyl compounds (1, 2). On the other hand, the asymmetric version of this reaction would afford chiral homoallylic amines, able to be transformed into interesting chiral nitrogen-containing compounds (3, 4). Some years ago (5), we found out that indium metal can promote the allylation of chiral *N-tert*-butylsulfinyl imines **1** with allyl bromides **2** under mild reaction conditions, giving the expected protected homoallyl amines **3** with good yields and diastereoselectivities (Scheme 1).

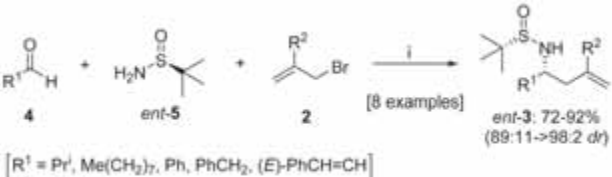
The observed stereochemistry could be easily explained considering a chair-like transition state **I** in which the indium atom is coordinated to both the nitrogen and the oxygen atoms, and the group R^1 is located in a pseudo-antiperiplanar position with respect to the sulfinyl group.



Scheme 1. *Reagents and conditions:* i, In, THF, 60 °C.



An interesting version of the reaction shown in Scheme 1 consists in a three-component reaction (6), which allows the in situ generation of the imine (from the aldehyde **4** and the sulfinamide *ent*-**5**) in the presence of the allylation mixture, so the corresponding protected *N-tert*-butylsulfinyl homoallyl amine is prepared with similar results that those obtained starting from the isolated imine (Scheme 1). Scheme 2 illustrates the one-pot method using the enantiomerically pure commercially available sulfinamide, to yield the enantiomeric products *ent*-**3** (7).



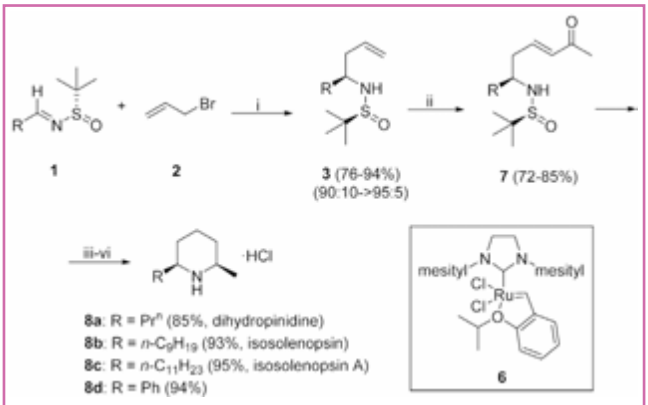
Scheme 2. *Reagents and conditions:* i, $Ti(OEt)_4$, In, THF, 60 °C.

It is worthy to note that the desulfinylation of compounds **3** is a very simple process, taking place by simple treatment with hydrochloric acid in an organic solvent.

SYNTHESIS OF ALKALOIDS

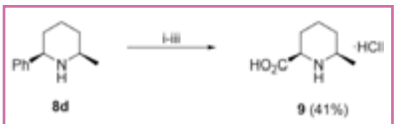
The allylation of (*S*)-*N-tert*-butylsulfinyl imines **1** with allyl bromide **2** in the presence of indium metal gave the expected products **3** with high yields and diastereoselectivities.

Treatment of these compounds with methyl vinyl ketone (MVK) and the ruthenium catalyst **6** yielded the corresponding unsaturated ketones **7**. Successive hydrogenation of the carbon-carbon double bond using the Wilkinson catalyst followed by desulfinylation and final reduction afforded spontaneously the corresponding *cis*-piperidines **8**, isolated as their hydrochlorides (Scheme 3) (8).



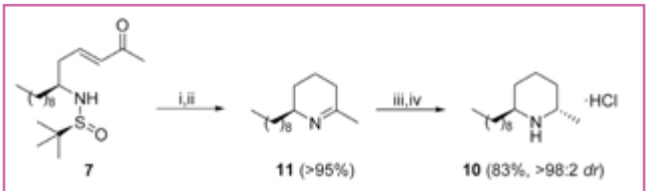
Scheme 3. *Reagents and conditions:* i, In, THF, 60 °C; ii, MVK, **6** cat., CH_2Cl_2, 45 °C; iii, H_2 (1 atm), $(Ph_3P)_3RhCl$ cat., EtOH, rt; iv, 4 M HCl, dioxane, MeOH, 0 °C; v, $NaBH_3CN$, buffer pH 5, rt; vi, HCl, Et_2O.

Among compounds **8** prepared, it is dihydropinidine (**8a**), a defense alkaloid of the Mexican bean beetle *Epilachna varivestis* (9, 10), as well as isosolenopsins **8c**,**d**, venom alkaloids of fire ants (*Solenopsis*) (11). Structurally related *cis*-6-methylpipecolic acid **9** is an interesting key constituent of several bioactive molecules (12-14). It can be easily prepared by oxidation of the precursor **8d** under standard conditions (Scheme 4).



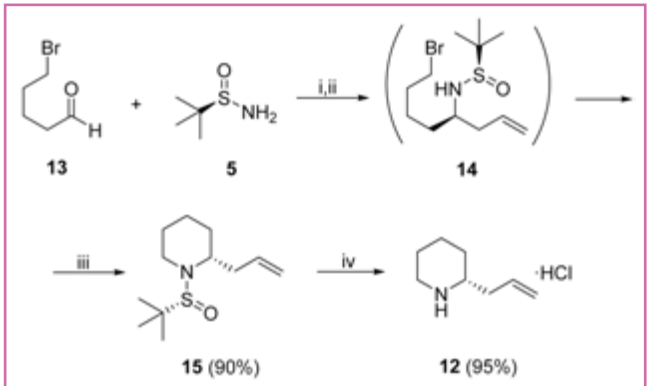
Scheme 4. *Reagents and conditions:* i, TFAA, Et_3N; ii, $RuCl_3·H_2O$ cat., $NaIO_3$; iii, K_2CO_3, MeOH, then 1M HCl.

The corresponding *trans*-derivatives of the type **8** could be prepared changing the final reduction step shown in Scheme 3. One example is the preparation of (+)-solenopsine **10**, another natural alkaloid isolated from the fire ants (11) (Scheme 5). After preparing the intermediate **7**, it was hydrogenated and cyclized under acidic conditions to yield the tetrahydropyridine **11**, which was submitted finally to a reduction using the mixture of $AlMe_3/LiAlH_4$ at low temperature to yield the expected *trans*-configurated alkaloid **10** (15).



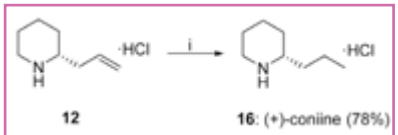
Scheme 5. *Reagents and conditions:* i, H_2 (1 atm), $(Ph_3P)_3RhCl$ cat., EtOH; ii, HCl, dioxane, 0 °C; iii, $AlMe_3/LiAlH_4$, -78 to 0 °C; iv, HCl, Et_2O.

One interesting molecule that can be further elaborated to give alkaloids in a chiral form is 2-allylpiperidine **12**. 5-Bromopentanal (**13**) was submitted to the tandem formation of the corresponding chiral imine and allylated to give the non-isolated protected homoallyl amine **14**, which by treatment with potassium hexamethyldisilazide (KHMDS) gave the sulfinyl derivative **15**, easily deprotected under acidic conditions to afford compound **12** as its hydrochloride (Scheme 6) (16).



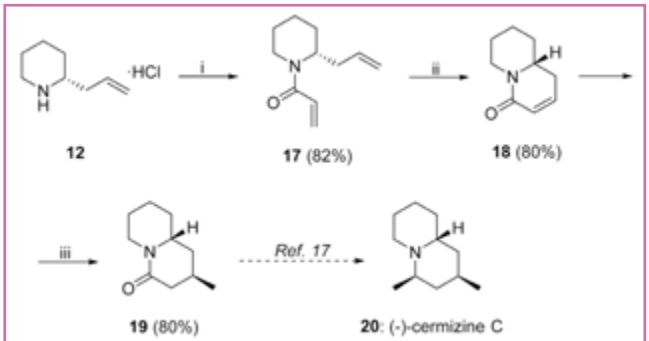
Scheme 6. *Reagents and conditions:* i, $Ti(OEt)_4$, THF; ii, CH_2=$CHCH_2Br$, In, 60 °C; iii, KHMDS, THF, 0 °C; iv, HCl, MeOH, dioxane.

The simple hydrogenation of compound **12** yielded (+)-coniine (**16**), the major alkaloid extracted from poison hemlock and responsible of its toxicity, as its hydrochloride (Scheme 7) (16).



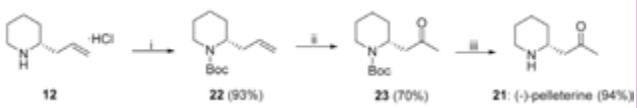
Scheme 7. *Reagents and conditions:* i, H_2 (1 atm), Pd/C cat., MeOH.

The same starting material was treated with acryloyl chloride under basic conditions to give compound **17**, ready to get a ring-closing metathesis in the presence of the catalyst **6** giving the bicyclic system **18**. Final methylation at the conjugate position using a lithium cuprate (17) afforded compound **19** in a stereoselective manner (16). This bicyclic derivative has been reported (18, 19) to be the precursor of the alkaloid (-)-cermizine C (**20**), so this method represents a formal synthesis of this alkaloid (Scheme 8).



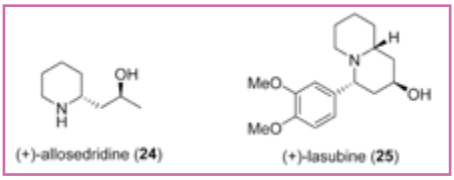
Scheme 8. *Reagents and conditions:* i, CH_2=$CHCOCl$, CH_2Cl_2, NaOH; ii, **6** cat., CH_2Cl_2 reflux; iii, Me_2CuLi, $BF_3·OEt_2$.

Another application of compound **12** was the synthesis of (-)-pelleterine **21** (20) a key intermediate in the biomimetic synthesis of natural alkaloids. Thus, once compound **12** was protected as its Boc derivative **22** (the corresponding sulfinyl derivative failed in the oxidation), it was submitted to the Wacker oxidation to give the ketone **23** that after final deprotection gave the expected alkaloid **21** (Scheme 9) (16).

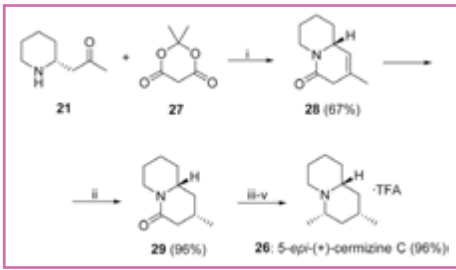


Scheme 9. *Reagents and conditions:* i, Boc_2O, CH_2Cl_2, NaOH; ii, O_2, $PdCl_2$ cat., $Cu(OAC)_2$, DMF; iii, HCl.

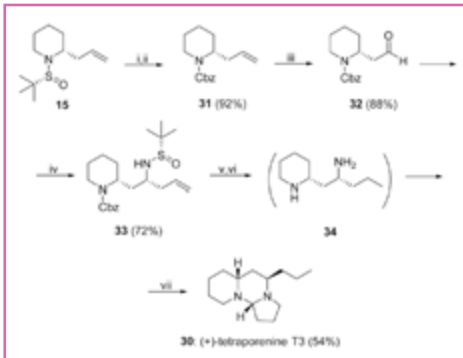
In addition, stereoselective reduction of (-)-pelletierine (**21**) allowed the preparation of (+)-allosedridine (**24**) (21), as well as the two-step transformation into (+)-lasubine (**25**) (22).



Another application of (-)-pelletrine (**21**) is the preparation of 5-*epi*-(+)-cermizine C (**26**). Condensation of compound **21** with the Meldrum acid (**27**) in the presence of acetic acid afforded the bicyclic compound **28**, which was hydrogenated easily to give **29** with high diastereoselectivity (13:1 *dr*). Final transformation into the desired alkaloid, isolated as its trifluoroacetate, was achieved in a one-pot process by addition of methylmagnesium bromide followed by in situ reduction and final treatment with trifluoroacetic acid (Scheme 10) (16).



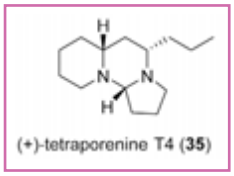
Scheme 10. *Reagents and conditions:* i, AcOH, EtOH, 60 °C; ii, H_2 (4 atm), PtO_2 cat., EtOH; iii, MeMgBr, THF, 65 °C; iv, $NaBH_3CN$, AcOH; v, TFA, MeOH.



Scheme 11. *Reagents and conditions:* i, HCl, THF; ii, CbzCl, CH_2Cl_2, NaOH; iii, OsO_4 cat.; $NaIO_4$, lutidine; iv, **5**, $Ti(OEt)_4$, **2**, In THF, 60 °C; v, HCl, THF; vi, H_2 (4 atm), Pd/C, MeOH; vii, $Br(CH_2)_3CHO$, K_2CO_3, CH_2Cl_2.

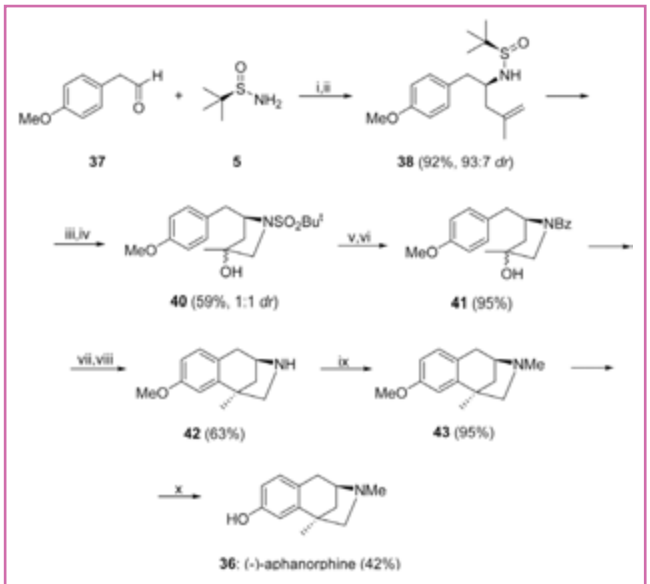
It is worth noting that starting from *ent*-**21**, easily available from *ent*-**12**, the corresponding alkaloid *ent*-**26** could be easily obtained. In addition, protonation of compound **26** should render a stereogenic nitrogen via equilibration to the most stable *trans*-quinolizidine conformation of the free amine. As a consequence, all four diastereomers of cermizine C could be prepared following the methodology shown in Scheme 10.
A little bit more sophisticated structurally is the alkaloid (+)-tetraporenine T3 (**30**), one of the components of a family of alkaloids that Pseudomyrmecine ants (of the genus *Tetraponera*) segregate against their enemies (23). The starting material was compound **15**, which after protection exchange gave the benzoxycarbonyl (Cbz) derivative **31**.

Oxidative carbon-carbon double bond cleavage afforded the aldehyde **32**, which was submitted to an iterative process using the sulfinamide **5** and allyl bromide (**2**). The obtained sulfinyl derivative **33** was deprotected and hydrogenated to give the diamine **34**, that without isolation was condensed with 4-bromobutanal under basic conditions yielding finally the expected alkaloid (+)-tetraporenine T3 (**30**) (Scheme 11) (24).



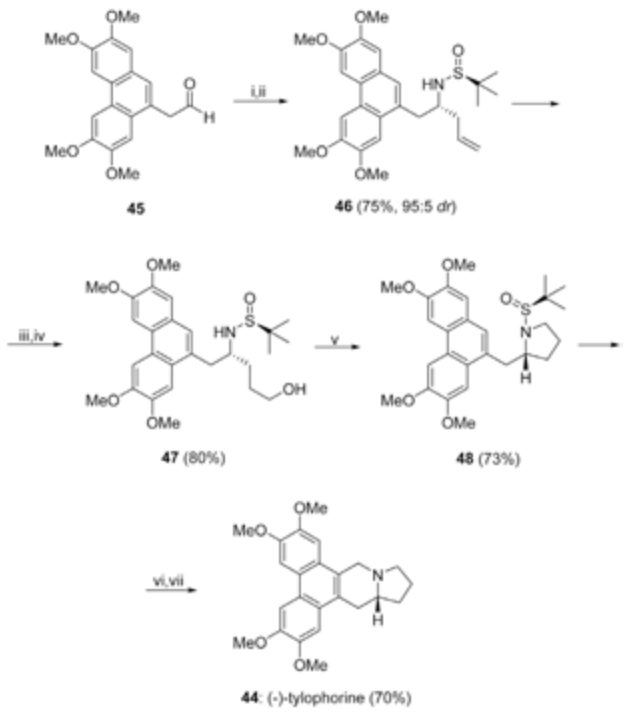
When the aldehyde **32** was treated with *ent*-**5** under the same reaction conditions the final product was its epimer (+)-tetraponerine T4 (**35**) (24). A DFT study could explain the obtained stereochemistry. In addition, other members of the family, namely tetraponerines T1, T2 and T5-T8 were also synthesized following the methodology shown in Scheme 11, and studied their antiproliferative activity (25).

(-)-Aphanorphine (**36**), that was isolated from the fresh-water blue-green alga *Aphanizomenon flos-aquae* (26), incorporates a 3-benzazepine scaffold that resembles benzomorphane analgesics. For its synthesis the protected homomethallyl amine **38** was prepared starting from 4-methoxyphenylacetaldehyde (**37**) and the sulfinamide **5** under the standard conditions shown above, but using methallyl bromide (**39**) as the allylation component. Oxidation of compound **38** with *m*-chloroperbenzoic acid (*m*CPBA) under basic conditions afforded an epoxide with concomitant oxidation of the sulfur atom, which by treatment with potassium iodide gave the alcohol **40** as a 1:1 diastereomeric mixture at the newly created stereocenter. The Friedel-Crafts cyclization of this alcohol was not possible under different acidic conditions. Therefore, it was transformed into the corresponding *N*-benzoyl derivative **41**, which then was cyclized and deprotected to yield the bicyclic compound **42**. Final *N*-methylation to give compound **43** followed by *O*-demethylation, in both cases under standard conditions, afforded the expected alkaloid **36** (Scheme 12) (27).

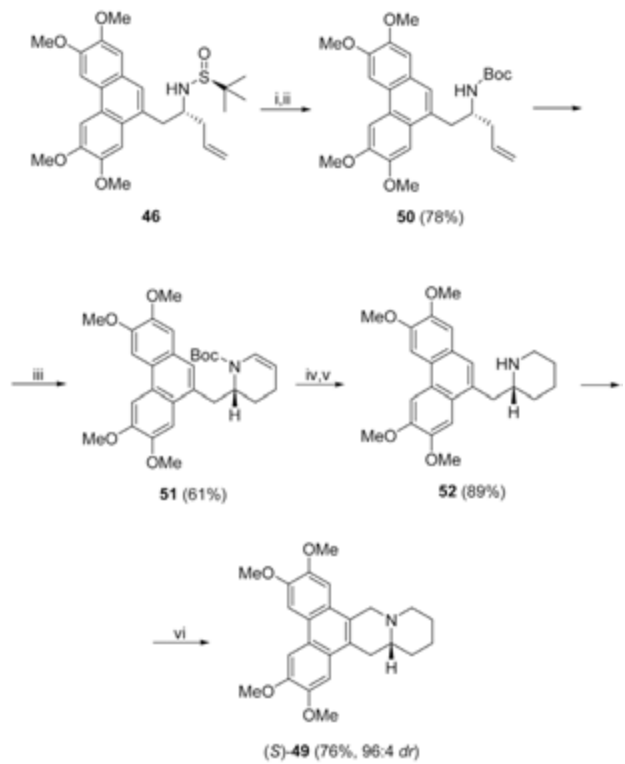


Scheme 12. *Reagents and conditions:* i, In, $Ti(OEt)_4$, THF; ii, CH_2=$CMeCH_2Br$ (**39**), 60 °C; iii, *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C; iv, KI, K_2CO_3, DMF, 100 °C; v, TfOH, PhOMe; vi, PhCOCl, NaOH: vii, $AlCl_3$, CH_2Cl_2; viii, NaOH, 80 °C; ix, CH_2O, $NaBH_4CN$; x, BBr_3, CH_2Cl_2.

The same set of reactions shown in Scheme 12, applied to the starting *ent*-**5** allowed the preparation of (+)-aphanorphine. This chemistry is important in order to assign unequivocally the structure of both enantiomers (28).



Scheme 13. *Reagents and conditions:* i, **5**, $Ti(OEt)_4$, In, THF, rt; ii, **2**, THF, 65 °C; iii, 9-BBN, THF, 0 °C to rt; iv, H_2O_2, NaOH; v, Ph_3P, DIAD, THF; vi, HCl, MeOH, 0 °C to rt; vii, CH_2O, H_2O, 90 °C.

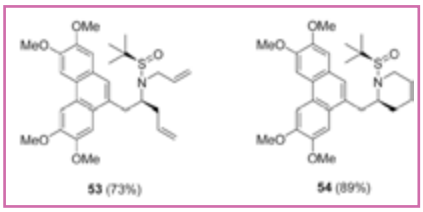


Scheme 14. *Reagents and conditions:* i, HCl, MeOH; ii, Boc_2O, NaOH; iii, $[RhCl(cod)]_2$ cat., CH_2O, H_2O, BIPHEP, Ni-Xantphos, PhMe, 90 °C; iv, H_2 (1 atm), $Pd(OH)_2/C$; v, TFA; vi, CH_2O, H_2O, HCl, EtOH, 90 °C.

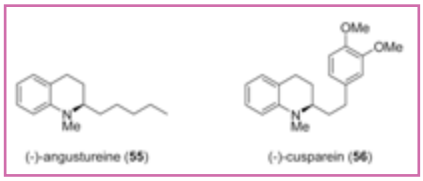
The indium-promoted diastereoselective allylation was the key step in the preparation of the alkaloid (-)-tylophorine (**44**), isolated from the plant Tylophora indica, used in traditional medicine due to its antibacterial, antiasthmatic, antiviral and anti-inflamatory properties (29, 30). This chemistry was applied to the aldehyde **45** to yield the corresponding homoallylic amine **46** with high diastereoselectivity (95:5 *dr*). Tandem hydroboration/oxidation under standard conditions gave the alcohol **47** that was cyclized under Mitsunobu conditions to yield the pyrrolidine **48**, which without purification was transformed into the alkaloid **44** (Scheme 13) (31).

7-Methoxycryptopleurine (**49**), an analogue of compound **44** could be prepared as it is depicted in Scheme 14. Starting from the aldehyde **45** and using **5** as the sulfinamide component the homoallyl amine **46** was prepared. After Boc exchange as protecting group (to give **50**), formylation of this material under rhodium and nickel-catalyzed conditions afforded compound **51**, which after a tandem hydrogenation/deprotection gave the piperidine **52**. Final treatment of this compound with aqueous formaldehyde under acidic conditions gave the expected alkaloid (*S*)-**49** (Scheme 14) (32).

The synthesis of the enantiomer (*R*)-**49** involved allylation of *ent*-**46** to give compound **53**, ready to suffer ring-closing metathesis with the Grubs-II catalyst to afford the corresponding piperidine **54** after hydrogenation. Final deprotection and cyclization with formaldehyde (as shows Scheme 14) gave the expected product (*R*)-**49** (32). Citotoxicity studied for both enantiomers demonstrated that the (*R*)-enantiomer is much more potent than its enantiomer against four cancer lines examined.



N-Sulfinyl imines derived from 3-(2-bromophenyl) propanal have been used in the reaction with two Grignard reagents as the key step for the straightforward synthesis of the alkaloids (-)-angustureine (**55**) or (-)-cusparein (**56**) (33). In the case of the alkaloid **55**, the above mentioned indium-promoted allylation of the same sulfinyl imine was also used as the key step for its synthesis: after allylation and intramolecular *N*-arylation, a cross-metathesis with (*Z*)-3-hexene and final hydrogenation led to the desired molecule (34).



Apart from the application of the indium-promoted diastereoselective allylation of chiral *N*-sulfinyl imines to the synthesis of alkaloids, this technology has been successfully used in the asymmetric synthesis of substituted azetidines and pyrrolidines (35, 36), α-methylene-γ-lactams (37, 38), bicyclic benzolactams (34, 39), α-methylenebenzocycloalkenes (40), and functionalized homoallyl amines (41). In addition, recently the indium-promoted allylation of chiral ketimines generating quaternary stereocenters (42), and the same process applied to the propargylation (43) and allenylation (44) of chiral aldimines, as well as the reaction with other electrophiles (45-47) has been reported.

ACKNOWLEDGEMENTS

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Fira de Barcelona, Gran Via, Barcelona, Spain

THE INTERNATIONAL CONTRACT SERVICES EXPO (ICSE):
A new marketplace for outsourcing solutions

ICSE, co-located with CPhI Worldwide, connects the world of Contract Services in Pharma. Attendees can network with industry professionals from across the globe to establish the best outsourcing partners, the latest manufacturing capabilities and the best opportunities to streamline product portfolios.

"A chance to network with professionals from around the globe."

[illegible]

"80-90% of our key customers show up in the 3 days. Otherwise efficient. It was great."

[illegible]

"I've been in the industry for over 20 years. You learn something new every day. CPhI is a great place to do just that."

[illegible]

WHAT VISITORS SAID ABOUT 2015 SHOW

87% rate CPhI Worldwide as the **leading global gathering** of the pharmaceutical industry

85% agree that CPhI Worldwide is **the most important show** in the pharmaceutical industry's calendar

80% agree that CPhI Worldwide **is the best place** to find new suppliers and products

WHY ATTEND ICSE

- Join **36,000** pharma professionals from **150+** countries; network, source suppliers, develop new and existing relationships and do business in pharma.
- **Find companies** across key sectors
- **Attend multiple product zones** within ICSE Barcelona
- Meet companies from around the world: this is the most efficient and effective way to meet suppliers from major and **emerging markets** including the **US, China, India, Turkey** and **Russia**
- Keep abreast of the latest industry developments: stay up-to-date on market news with free sessions in the **Exhibitor Showcases** (Previously Speakers' Corner), and the **Pharma Insight Briefings**
- **Free access** to all co-located events: your registration will also be valid for CPhI, P-MEC, FDF and InnoPack

Register now: gotocphi.com/icse

SOME OF OUR EXHIBITORS

Organised by UBM