# AN APPROACH TO PREPARATION OF *trans*-DHQs VIA RING-OPENING OF *meso-N*-SULFONYLAZIRIDINES

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Received January 18, 2011
Accepted April 6, 2011
Published online June 17, 2011

*Dedicated to Professor Pavel Kočovský on the occasion of his 60th birthday.*

As an approach to the enantioselective synthesis of *trans*-decahydroquinolines (DHQs), desymmetrization of *meso*-aziridine (**5**) with various carbon nucleophiles under catalytic conditions was investigated. By applying TMSCN in the presence of $YbCl_3$ and chiral non-racemic ligands, nitrile **13** was obtained with an ee up to 40%. Nitrile **13** was a key intermediate in a novel route to *trans*-DHQs.

**Keywords**: Desymmetrization; Carbon nucleophiles; *meso*-Aziridines; Yb-catalysis; *trans*-DHQs; Alkaloids; Metathesis; Synthetic methods.

Neotropical poison frogs belonging to the family of *Dendrobatidae* have over the last four decades proven to be a rich source of novel azaheterocyclic compounds[1]. Amongst these, decahydroquinolines (DHQs) functionalised in the 2- and 5-positions constitute a major structural class (Fig. 1)[2]. The combination of very low natural abundance together with marked biological activity has caused considerable attention to be directed towards the

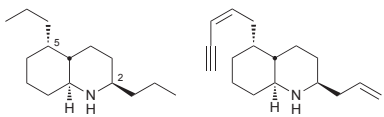



FIG. 1
Structures of selected *trans*-DHQs

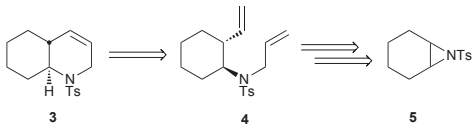


doi:10.1135/cccc2011013

preparation of DHQs. Both the *cis*- and *trans*-fused congeners have been shown to inhibit carbamylcholine elicited sodium flux in pheochromocytoma PC12 cells, as well as to inhibit the binding of the non-competitive blocking agent [$^3$H]perhydrohistrionicotoxin to muscle-type nicotinic acetylcholine receptor-channels in membranes obtained from *Torpedo* electroplax[3]. However, of the many synthetic endeavours reported only few relate to the construction of compounds having a *trans*-configured ring-system[4].

Contributions by Schultz[4a] and Comins[4b] are among the most prominent on the subject. In the first case, the *trans*-fused bicycle is formed through intramolecular condensation between a primary amine and a ketone obtained via Birch reduction of a chiral anthranilic acid derivative. In the second case, the *trans*-fused bicycle is a result of Robinson annulation after iterative elaboration of a chiral 1-acyl-4-methoxypyridinium salt.

Aziridines serving as a β-aminoethyl unit are valuable building blocks for natural products and pharmaceuticals[5]. To investigate a novel strategy towards the synthesis of optically active *trans*-DHQs, we envisioned the desymmetrization of an *N*-sulfonated *meso*-aziridine together with ring-closing metathesis (RCM) as the means to access the *trans*-fused moiety (Scheme 1).

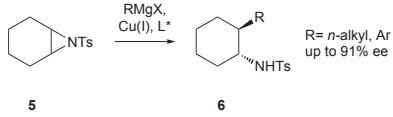



SCHEME 1
Simplified retrosynthetic analysis to access *trans*-DHQs

RCM as a key transformation in the total synthesis of piperedine and pyrrolidine derived alkaloids is well known[6]. However, to the best of our knowledge, this process has not previously been applied to the preparation of the heterocyclic portion of DHQs.

Until very recently, the desymmetrization of *meso*-aziridines with *C*-nucleophiles was almost unknown. In a previous paper one of the present authors has reported desymmetrizations of *N*-sulfonated aziridines with organometallic reagents in the presence of Cu(I) and chiral ligands (Scheme 2). Enantioselectivities of up to 91% could be obtained starting from MeMgBr as source of the nucleophilic reagent[7]. Desymmetrization could also be achieved with Grignard reagents derived from simple *n*-alkyl, aryl and mesityl bromide. However, the products resulting from these reac-

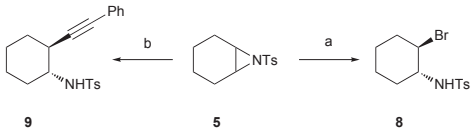
tions do not easily lend themselves to further elaboration into more complex structures, owing to the inertness of the R substituents[8a]. Experiments to extend the procedure to simple vinylic or allylic reagents failed. For example, no ring-opening of aziridine **5** occurred under standard conditions with Grignard reagents derived from acetylene, vinyl or allyl bromide[7b].




SCHEME 2
Enantioselective ring-opening of *meso*-aziridine **5**

## RESULTS AND DISCUSSION

In a first series of experiments, the aziridine **5** (Scheme 3) was exposed to the organolithium or Grignard reagent derived from vinyl bromide and 2-bromopropene, in the absence or the presence of Cu(I) in stoichiometric or catalytic amounts. However, the expected product was not formed, and only the sulfonamide **8**[9] resulting from bromide attack was isolated in yields ranging from 15 to 27%. By employing the corresponding lithium reagent derived from ethylvinylether, both in the presence and absence of $BF_3$, as well as with divinylmagnesium, only decomposition products were observed[10]. From a series of Li-reagents or cuprates derived from 1,3-dithiacyclohexane, dithiophenylmethane and phenylacetylene, only Li-2-phenylacetylide (**7**) afforded a ring-opened product **9** in modest yield, while Cu- and Zn-reagents derived from phenylacetylene were unreactive.



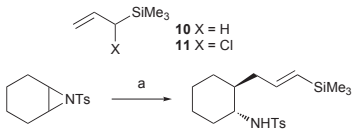

SCHEME 3
Reagents: (a) vinyl bromide or 2-bromopropene in the presence of *n*-BuLi, CuI or Mg; (b) Li-2-phenylacetylide (**7**)

The reaction of Schaumann[11], which involves aziridine opening by the allyltrimethylsilyl anion, was investigated with a view to finding conditions compatible with asymmetric catalysis. In contrast to unsubstituted allyl anions, silylated analogs reacted readily with the aziridine. The anion

was generated by deprotonation of allyl trimethylsilane with *n*-BuLi, and was allowed to react with the aziridine at low temperature under a variety of conditions to afford the desired product **12** in yields of up to 81%. A control experiment carried out at –115 °C showed that even at this low temperature ring-opening could not be entirely suppressed (Table I). Thus, since the anion of deprotonated allyl trimethylsilane proved to be too reactive, and therefore unsuitable for the envisioned asymmetric process, the catalytic approach was abandoned.

An alternative synthetic route was then explored, based on the work of Utimoto, who had reported ring-opening of *N*-sulfonated aziridines by their exposure to TMSCN in conjunction with $YbCl_3$[12]. Accordingly, we have applied this system in combination with a selection of chiral ligands to our

TABLE I
Reaction of aziridine **5** with silylated allyl reagents **10** and **11** in the presence of *n*-BuLi or Mg[a]

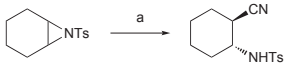



| Entry | X | Reagent | Solvent | Conditions | Yield, % |
|---|---|---|---|---|---|
| 1 | H | BuLi | THF | –78 to –30 °C, 3 h | 34 |
| 2 | H | BuLi | $Et_2O$ | –78 to 25 °C, 24 h | 81 |
| 3 | H | BuLi | $Et_2O$ | –78 to 0 °C, 2.5 h | 37 |
| 4 | H | BuLi | $Et_2O$ | –115 °C, 30 min | 15 |
| 5 | H | *s*-BuLi/$MgBr_2$ | $Et_2O$ | 0 to 25 °C, 6 h | 28 |
| 6 | H | BuLi, 2 eq.; CuI | $Et_2O$ | –40 to 0 °C, 6 h | 0 |
| 7 | Cl | Mg | THF | 0 °C, 2 h | 73 |
| 8 | Cl | Mg | THF | –20 °C, 4 h | 69 |
| 9 | Cl | Mg | $Et_2O$ | –78 to 25 °C, 24 h | 61 |
| 10 | Cl | Mg; CuI, 1 eq. | $Et_2O$ | 0 °C, overnight | 0 |
| 11 | Cl | Mg; CuBr, 1 eq. | $Et_2O$ | 0 °C, 6 h | 0 |

[a] Conditions: 0.80 mmol of **5** in THF or $Et_2O$ (3.0 ml), 1.0 equiv. of reagent. [b] 28% of bromide **8**.

aziridine **5**, and the results are summarized in Table II. The catalytically active species was prepared from $YbCl_3 \cdot 6H_2O$ in THF and the appropriate ligand, and reactions were routinely run in $CHCl_3$ with 25% of catalyst[10]. In the absence of chiral ligand, the reaction proceeded at 65 °C to afford **13** in 66 % yield. A selection of chiral ligands which were available from other projects was screened with variable success (Fig. 2). The highest enantioselectivity (40%) was reached with the pybox catalyst **16b**, but the highest yield (84%) resulted from reaction with **16c**.

TABLE II
Desymmetrization of aziridine **5** with TMSCN/$YbCl_3$[a]




**5** **13**

| Entry | Ligand | Yield, % | ee, %[b] |
|---|---|---|---|
| 1 | – | 65 | – |
| 2 | **14a** | 66 | 0 |
| 3 | **14b** | 22 | 0 |
| 4 | **15** | 33 | 0 |
| 5 | **16a** | 62 | 9 |
| 6 | **16b** | 67 | 40 |
| 7 | **16c** | 84 | 37 |
| 8 | **16d** | 27 | 0 |
| 9 | **17a** | – | – |
| 10 | **17b** | 40 | 26 |
| 11 | **17c** | 52 | 14 |
| 12 | **17d** | 42 | 3 |
| 13 | **18** | 24 | 5 |
| 14 | **19** | 32 | 9 |
| 15 | **20** | 32 | 13 |

[a] Conditions: **5** (0.100 g, 1.0 equiv.) in $CHCl_3$ (1.5 ml), 65 °C; TMSCN (1.2 equiv.); $YbCl_3$ (0.25 equiv.) and L* (0.30 equiv.). [b] Determined by HPLC on OD-H column.

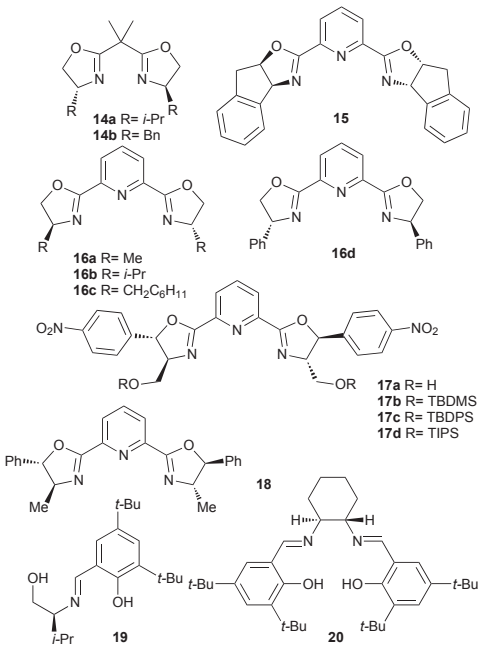
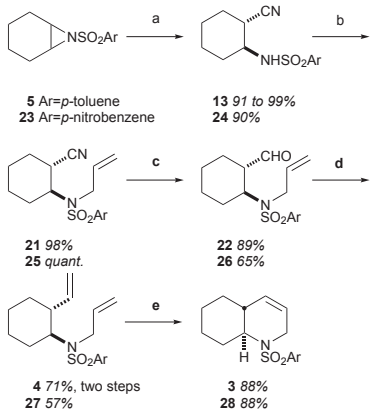



FIG. 2
Ligands used in the desymmetrization of *meso*-aziridine **5**

Clearly, the $YbCl_3$ system needs further optimization which we could not carry out since we were forced to discontinue this part of the project. Nevertheless, the results show that this reagent combination certainly has potential for further development.

We then focussed on demonstrating that a nitrile group could indeed serve as a vinyl surrogate in the route to *trans*-DHQs outlined in Scheme 1. In the racemic case, ring-opening of **5** with TMSCN has been thoroughly described, either by applying a promoter or a catalyst[12,13], so we chose to work with racemic **13** for "proof of concept".

*N*-allylation of β-amino nitrile **13** followed by DIBAL reduction afforded the labile aldehyde **22** upon aqueous workup (Scheme 4). The subsequent olefination (triphenylphosphonium bromide, KHMDS) was thus generally done on crude **22**, providing diene **4** in 71% yield for the two steps. Finally, ring-closure of diene **4** occurred smoothly in the presence of the Grubbs 1st generation pre-catalyst to furnish racemic *trans*-octahydroquinoline **3** in 88% yield (61% for the five-step sequence).




SCHEME 4

Reagents and conditions: Compounds **3**–**5**, **13**, **21**, **22**; Ar = *p*-toluene. Compounds **23**–**28**; Ar = *p*-nitrobenzene. (a) Refs[13,14]; (b) Allyl bromide, $K_2CO_3$, acetone, Δ; (c) DIBAL, DCM, –78 °C, then water, –78 °C to r.t.; (d) $PPh_3{=}CH_2$, THF, –78 °C to r.t.; (e) Grubbs 1st generation pre-catalyst, DCM, r.t.

In view of the rather harsh conditions usually necessary to detach the *p*-toluenesulfonyl group[14], we also investigated the more easily removable *p*-nitrobenzenesulfonyl group[15]. Both with respect to the reduction of β-amino nitrile **25** to aldehyde **26** (65%) and in the subsequent olefination (57%), the presence of the nitro functionality was detrimental. Thus, even though the other steps went smoothly, the overall yield was lowered substantially (29% for the five-step sequence).

## CONCLUSION

Desymmetrization of *N*-*p*-toluenesulfonylimine **5** with organocuprates in the presence of chiral non-racemic ligands under catalytic conditions was abandoned, based on the initial findings that neither vinylic nor acetylenic reagents effectuated any ring-opening under the applied conditions. Without Cu(I) present, 2-Li-phenylacetylide could bring about the ring-opening in poor yield. In contrast, organolithium and organomagnesium reagents derived from silylated propene reacted at low temperature in good yield, while the corresponding cuprates were found to be unreactive. By switching to cyanide as the carbon nucleophile, desymmetrization of *meso*-aziridine **5** with TMSCN in the presence of $YbCl_3$ and chiral ligands was achieved. In the best case nitrile **13** could be obtained with an ee of 40%.

By elaborating on nitrile **13**, a sequence was developed to access *trans*-DHQs. In five steps, *meso*-aziridine **5** was transformed into racemic *trans*-octahydroquinoline **3** in an overall yield of 61%. Altering the activating/protecting group on the *meso*-aziridine from a *p*-toluenesulfonyl to a *p*-nitrobenzenesulfonyl resulted in lower overall yield (29% for the five-step sequence). In view of the complementary work of Shibasaki[8a] and the efficient synthetic sequence outlined above, enantioselective routes to naturally occurring *trans*-DHQ alkaloids can readily be envisaged.

## EXPERIMENTAL

All moisture- and air-sensitive reactions were carried out under an argon atmosphere using oven-dried or flame-dried glassware. Reaction solvents were distilled prior to use by standard procedures or used as received. $Et_2O$ and THF were distilled under nitrogen from sodium-benzophenone. $CH_2Cl_2$ and $CHCl_3$ were distilled under nitrogen from $CaH_2$. Acetone (HPLC-grade) was purchased from Aldrich and used as received. $^1H$ NMR (200, 300 or 500 MHz) and $^{13}C$ NMR (50, 75 or 125 MHz) spectra were recorded either on a Bruker AC-200 (200 MHz), Varian Mercury 300 (300 MHz), Varian Inova 500 (500 MHz) or a Bruker AMX-500 (500 MHz) spectrometer at ambient temperature. Chemical shifts (δ-scale) are reported in ppm relative to the residual undeuterated solvent signal as internal standard. Coupling constants (*J*) are given in Hz. Optical rotations were measured with a Perkin Elmer 241 Polarimeter at ambient temperature, $[\alpha]_D$ values are given in $10^{-1}$ deg cm$^2$ g$^{-1}$; the concentration (*c*) is given in g per 100 ml. Determination of the enantiomeric excess was performed by analytical high performance liquid chromatography (HPLC) using a Kontron 325 system/Kontron 332 detector with a Daicel (0.46 cm × 25 cm) Chiracel OD-H column. HRMS was recorded on a Jeol HX 110/110 mass spectrometer at the Department of Chemistry, University of Copenhagen, Denmark or on a VG analytical 7070E at the Department of Organic Chemistry, University of Geneva, Switzerland. Melting points were determined on a Heidolph capillary melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) analyses were performed using 0.25 mm Merk Kiselgel aluminium-backed 60 $F_{254}$ silica gel plates. Visualization was achieved by exposure to UV light and dipping in a solution of 5–10% of phosphomolybdic acid in EtOH followed by gentle heating. Merk silica gel 60 (40–63 μm, 230–400 mesh) was used for flash chromatography purification. Microanalyses were performed at the Microanalysis Laboratory, Institute of Physical Chemistry, University of Vienna, Austria.

### (±)-*trans*-2-Phenylethynyl-*N*-tosylcyclohexanamine (**9**)

Dry phenylacetylene (0.061 g, 0.07 ml, 0.60 mmol) in dry ether (3.0 ml) was cooled to –78 °C and *n*-BuLi (1.6 M in pentane, 0.40 ml, 0.60 mmol) was added in a dropwise manner during 10 min. The reaction was then slowly heated to –30 °C and stirred for 0.5 h, whereupon 7-tosyl-7-azabicyclo[4.1.0]heptane (**5**; 0.100 g, 0.40 mmol) was added in one portion and the resulting mixture was allowed to warm to 0 °C. After 5 h, the reaction was quenched by addition of aqueous saturated $NH_4Cl$ (10 ml), the phases were separated and the aqueous phase was extracted with ether (3 × 10 ml). The combined organic phases were dried over $MgSO_4$, the solvent was evaporated in vacuo and the residue was purified by flash

chromatography on silica (pentane/EtOAc 4:1 (v/v)) to yield the title compound **9** as a yellow oil (0.033 g, 29%). $^1$H NMR (500 MHz, $CDCl_3$): 7.74 (d, $J$ = 8.1, 2 H), 7.23–7.30 (m, 5 H), 7.11 (d, $J$ = 8.2, 2 H), 4.77 (d, $J$ = 5.1, 1 H), 3.07–3.12 (m, 1 H), 2.43–2.47 (m, 1 H), 2.31 (s, 3 H), 2.26–2.29 (m, 1 H), 2.01–2.04 (m, 1 H), 1.64–1.83 (m, 4 H), 1.47–1.52 (m, 1 H), 1.25–1.33 (m, 1 H). $^{13}$C NMR (125 MHz, $CDCl_3$): 143.1, 137.3, 131.6, 129.5, 128.1, 127.9, 127.1, 123.0, 89.7, 83.0, 56.6, 36.1, 24.3, 23.9, 21.4. HRMS (EI) calculated for $C_{21}H_{23}O_2NS$ [$M^+$] 353.1449, found 353.1445.

(±)-*trans*-2-((*E*)-3-(Trimetylsilyl)allyl)-*N*-tosylcyclohexanamine (**12**)

*General procedure for reaction with allyltrimethylsilane* (**10**): To a solution of allyltrimethylsilane **10** (0.114 g, 0.16 ml, 1.00 mmol) in dry ether (5.0 ml) at 0 °C was added *n*-BuLi (1.6 M in hexanes, 0.63 ml, 1.00 mmol) in a dropwise manner, followed by addition of TMEDA (0.15 ml, 1.00 mmol). The mixture was stirred for 2.5 h at 0 °C and then cooled to the temperatures stated in Table I, whereupon 7-tosyl-7-azabicyclo[4.1.0]heptane (**5**; 0.200 g, 0.80 mmol) was added in one portion. After the stated time had passed aqueous saturated $NH_4Cl$ (10 ml) was added, the phases were separated and the aqueous phase was extracted with ether (3 × 10 ml). The combined organic phases were dried over $Na_2SO_4$, the solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica (hexane/EtOAc 7:3 (v/v)) to afford the title compound 12 as a yellow solid in the yields stated.

*General procedure for the reaction with (1-chloroallyl)trimethylsilane* (**11**): Magnesium (0.194 g, 8.00 mmol) was suspended in dry THF (1.0 ml) followed by addition of (1-chloroallyl)-trimethylsilane (**11**), prepared according to a procedure by Sakurai[16]. The mixture was cooled to 0 °C in an ice-bath and sonicated for 2–3 min, whereupon the resulting reagent was rapidly added via a syringe to a solution of 7-tosyl-7-azabicyclo[4.1.0]heptane (**5**; 0.200 g, 0.80 mmol) in dry THF (2.0 ml) at the temperatures stated in Table I. After the stated time had passed aqueous saturated $NH_4Cl$ (10 ml) was added, the phases were separated and the aqueous phase was extracted with ether (3 × 10 ml). The combined organic phases were dried over $Na_2SO_4$, the solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica (hexane/EtOAc 7:3 (v/v)) to afford the title compound **12** as a yellow solid in the yields stated. M.p. 118 °C. $^1$H NMR (500 MHz, $CDCl_3$): 7.76 (d, $J$ = 8.1, 2 H), 7.29 (d, $J$ = 8.2, 2 H), 5.82 (ddd, $J$ = 18.3, 7.1, 6.1, 1 H), 5.55 (d, $J$ = 18.3, 1 H), 4.54 (d, $J$ = 8.7, 1 H), 2.42 (s, 3 H), 2.81–2.89 (m, 1 H), 2.43–2.48 (m, 1 H), 1.70–1.79 (m, 3 H), 1.57–1.59 (m, 2 H), 1.17–1.27 (m, 1 H), 1.03–1.14 (m, 3 H), 0.83–0.97 (m, 1 H), 0.02 (s, 9 H). $^{13}$C NMR (125 MHz, $CDCl_3$): 144.7, 143.1, 138.5, 132.2, 129.6, 126.9, 57.2, 42.6, 39.9, 34.3, 30.8, 25.1, 21.5, 24.9, –1.2. HRMS (EI) calculated for $C_{19}H_{31}O_2NSSi$ [$M^+$] 365.1845, found 365.1864.

(1*R*,2*R*)-*trans*-2-(Tosylamino)cyclohexanecarbonitrile (**13**)

*General procedure for the desymmetrization with TMSCN*: $YbCl_3 \cdot 6H_2O$ (0.039 g, 0.10 mmol) was suspended in dry THF (3.0 ml) and the resulting suspension was sonicated for 5 min. The appropriate ligand **14–20** (0.12 mmol) was added to the homogenised suspension and the resulting mixture was stirred for 2 h at r.t. Dry $CHCl_3$ (2.0 ml) was added to obtain a clear solution containing some white precipitate of uncomplexed $YbCl_3$. After being stirred for a further 0.5 h at r.t., the solution was filtered through a small plug of cotton. The filtrate was then concentrated in vacuo (1 torr) for 15 min. The resulting white solid was

re-dissolved in $CHCl_3$ (1.5 ml), whereupon 7-tosyl-7-azabicyclo[4.1.0]heptane (**5**; 0.100 g, 0.40 mmol) and TMSCN (0.048 g, 0.06 ml, 0.48 mmol) was added in succession. The resulting mixture was heated to reflux for 12 h and upon cooling treated with aqueous saturated $NH_4Cl$ (10 ml). The phases were separated, the aqueous phase was extracted with EtOAc (3 × 10 ml) and the combined phases were dried over $Na_2SO_4$. Upon evaporation of the solvent in vacuo, the residue was purified by flash chromatography on silica (pentane/EtOAc 4:1) to yield the title compound **13** as a colourless solid with the enantioselectivities and yields stated in Table II. M.p. 113–114 °C; $[\alpha]_D^{25}$ –1.6 (*c* 1.03, EtOH) for 40% ee. $^1$H NMR (500 MHz, $CDCl_3$): 7.82 (d, *J* = 8.2, 2 H), 7.36 (d, *J* = 8.2, 2 H), 5.52 (d, *J* = 7.9, 1 H), 3.30–3.50 (m, 1 H), 2.60–2.90 (m, 1 H), 2.40 (s, 3 H), 1.85–2.20 (m, 2 H), 1.55–1.78 (m, 3 H), 1.20–1.52 (s, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): 143.8, 136.9, 129.8, 127.3, 120.3, 52.7, 34.5, 22.9, 22.7, 22.6, 21.5. HRMS (EI) calculated for $C_{14}H_{18}O_2NS$ [$M^+$] 278.1089, found 278.1094.

(±)-*trans*-2-(*N*-Allyl-*N*-tosylamino)cyclohexanecarbonitrile (**21**)

(±)-*trans*-2-(Tosylamino)cyclohexanecarbonitrile (**13**; 0.142 g, 0.51 mmol) was dissolved in dry acetone (10 ml) under argon, whereupon $K_2CO_3$ (0.564 g, 4.08 mmol) and allyl bromide (0.247 g, 0.18 ml, 2.04 mmol) was added in sequence. The resulting heterogeneous mixture was heated to reflux and kept at this temperature overnight. After 12 h the heating was discontinued and the solvent evaporated in vacuo to yield a semisolid residue, which was treated with a mixture of water (10 ml) and EtOAc (20 ml). The phases were separated and the aqueous phase was extracted with EtOAc (5 × 10 ml). The combined organic phases were washed with brine, dried over $MgSO_4$ and evaporated in vacuo to yield a yellow oil as the crude. Purification by flash chromatography on silica (hexane, followed by hexane/EtOAc 10:1 to 5:1 (v/v)) afforded the title compound **21** as a clear, faintly yellow oil, which solidified upon standing (0.159 g, 98%). $R_F$ 0.18 (heptane/EtOAc 2:1 (v/v)); m.p. 86.0–88.0 °C. $^1$H NMR (300 MHz, $CDCl_3$): 7.72 (d, *J* = 8.3, 2 H), 7.23 (d, *J* = 8.0, 2 H), 5.74 (tdd, *J* = 16.9, 10.1, 6.5, 1 H), 5.14 (ddd, *J* = 17.1, 2.6, 1.3, 1 H), 5.06 (ddd, *J* = 10.3, 2.4, 1.1, 1 H), 3.82 (dd, *J* = 16.1, 6.0, 1 H), 3.62 (dd, *J* = 16.1, 6.9, 1.1, 2 H), 3.00–2.76 (m, 1 H), 2.33 (s, 3 H), 2.16–2.05 (m, 1 H), 1.80–1.41 (m, 4 H), 1.31–0.95 (m, 3 H). $^{13}$C NMR (75 MHz, $CDCl_3$): 143.5, 137.1, 134.6, 129.8, 127.4, 120.4, 118.4, 59.3, 34.0, 30.5, 30.1, 25.0, 24.0, 21.3. For $C_{17}H_{22}N_2O_2S$ (318.44) calculated: 64.12% C, 6.96% H, 8.80% N; found: 64.22% C, 7.14% H, 8.69% N.

(±)-*trans*-2-(*N*-Allyl-*N*-tosylamino)cyclohexanecarbaldehyde (**22**)

(±)-*trans*-2-(*N*-Allyl-*N*-tosylamino)cyclohexanecarbonitrile (**21**; 0.159 g, 0.50 mmol) was dissolved in dry DCM (10 ml) and cooled to –78 °C. DIBAL (1.0 M in DCM, 0.80 ml, 0.80 mmol) was added in a dropwise manner during 10 min. With continued cooling, the reaction was monitored by TLC and after 1 h more DIBAL (1.0 M in DCM, 0.30 ml, 0.30 mmol) was added. After a further 10 min, the intermediate aldimine was quenched by addition of an aqueous saturated solution of Rochelle salt (1.0 ml). The reaction mixture was brought to r.t., diluted with DCM (50 ml) and successively washed with an aqueous saturated solution of Rochelle salt (10 ml) and brine (10 ml). The organic phase was dried over $Na_2SO_4$, the solvent was evaporated in vacuo and the oily residue was purified by flash chromatography on silica gel (heptane, followed by heptane 5:1 (v/v)) to afford the title

compound **22** as a semi-viscous, colourless oil (0.143 g, 89%). $R_F$ 0.26 (heptane/EtOAc 2:1 (v/v)). $^1$H NMR (300 MHz, $CDCl_3$): 9.42 (d, *J* = 4.2, 1 H), 7.65 (d, *J* = 8.1, 2 H), 7.25 (d, *J* = 8.4, 2 H), 5.72 (dddd, *J* = 17.1, 10.1, 7.2, 5.7, 1 H), 5.14 (dd, *J* = 17.1, 1.5, 1 H), 5.07 (dd, *J* = 10.2, 1.5, 1 H), 4.01–3.83 (m, 2 H), 3.66 (tdd, *J* = 16.1, 7.2, 1.1, 1 H), 2.46 (tt, *J* = 12.0, 3.9, 1 H), 2.37 (s, 3 H), 1.83–1.63 (m, 3 H), 1.50–1.40 (m, 2 H), 1.40–1.00 (m, 3 H). $^{13}$C NMR (75 MHz, $CDCl_3$): 203.4, 143.3, 137.6, 135.4, 129.6, 126.9, 117.7, 57.5, 47.1, 29.5, 26.8, 25.2, 23.8, 21.4.

(±)-*trans*-(*N*-Allyl-*N*-tosyl)-2-vinylcyclohexanamine (**4**)

Dried methyltriphenylphosphonium bromide (0.314 g, 0.88 mmol) was suspended in dry THF (10 ml) at r.t. and KHMDS (0.5 M in toluene, 1.80 ml, 0.90 mmol) was added in a dropwise manner, resulting in a bright yellow suspension. The ylide solution was stirred at r.t. for an additional 1 h and then cooled to –78 °C. Crude (±)-*trans*-2-(*N*-Allyl-*N*-tosylamino)cyclohexanecarbaldehyde (**22**; 0.160 g, 0.50 mmol) was dissolved in dry THF (5 ml) and was then added to the ylide during 10 min. With continued cooling, the resulting mixture was monitored by TLC. After 2 h excess ylide was decomposed by addition of methanol (2 ml). The mixture was brought to r.t., diluted with ether (30 ml) and poured into aqueous saturated Rochelle salt (10 ml). The phases were separated and the aqueous phase was extracted with ether (3 × 10 ml). The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo to yield a pale yellow oil as the crude. The residue was purified by flash chromatography on silica gel (hexane, followed by hexane/EtOAc 10:1 to 5:1 (v/v)) to afford the title compound **4** as a colourless oil (0.113 g, 71% over two steps). $R_F$ 0.54 (hexane/EtOAc 2:1). $^1$H NMR (500 MHz, $CDCl_3$): 7.67 (d, *J* = 11.4, 2 H), 7.25 (d, *J* = 11.4, 2 H), 5.81 (dd, *J* = 17.5, 10.8, 1 H), 5.51 (dt, *J* = 19.1, 1 H), 5.15 (d, *J* = 17.8, 1 H), 5.04 (d, *J* = 10.2, 1 H), 4.94 (d, *J* = 19.1, 1 H), 4.86 (d, *J* = 10.8, 1 H), 3.83 (dd, *J* = 17.7, 7.6, 1 H), 3.75 (dd, *J* = 17.7, 7.6, 1 H), 3.59–3.49 (m, 1 H), 2.40 (s, 3 H), 2.23–2.09 (m, 1 H), 1.78–1.53 (m, 4 H), 1.53–1.38 (m, 1 H), 1.31–1.07 (m, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): 142.7, 141.2, 138.7, 136.6, 129.3, 127.2, 116.3, 114.8, 61.8, 45.8, 33.4, 31.7, 25.9, 25.1, 21.4.

(±)-(4a*R*,8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-1-tosylquinoline (**3**)

Dry DCM under argon was frozen in liquid nitrogen and then reheated to allow melting in vacuo. Deoxygenation by this process was carried out thrice. (±)-*trans*-(*N*-allyl-*N*-tosyl)-2-vinylcyclohexanamine (**4**; 0.110 g, 0.34 mmol) was dissolved in degassed DCM (10 ml) after having been repetitively purged by evacuation and flushing with argon. The Grubbs 1st generation pre-catalyst (0.028 g, 0.034 mmol) was added in one portion at r.t. to yield a homogeneous yellow solution, which turned light pink within 2 min after the addition. The reaction mixture was stirred at r.t and the progress was monitored by TLC. After 15 min, the solvent was evaporated in in vacuo and the oily purple residue was purified by flash chromatography on silica gel (hexane, followed by hexane/EtOAc 10:1 to 5:1 (v/v)) to afford the title compound **3** as clear, colourless oil (0.088 g, 88%). $R_F$ 0.50 (heptane/EtOAc 2:1 (v/v)). $^1$H NMR (300 MHz, $CDCl_3$): 7.67 (d, *J* = 8.3, 2 H), 7.24 (d, *J* = 8.0, 2 H), 5.58 (tdd, *J* = 9.9, 4.6, 2.4, 1 H), 5.39 (qd, *J* = 10.0, 2.1, 1 H), 4.33 (tdd, *J* = 17.7, 4.3, 2.2, 1 H), 3.72 (tdd, *J* = 17.7, 3.7, 2.2, 1 H), 2.72 (ddd, *J* = 11.9, 10.1, 3.3, 1 H), 2.39 (s, 3 H), 2.24–2.13 (m, 1 H), 1.99–1.84 (m, 1 H), 1.84–1.52 (m, 4 H), 1.30–1.06 (m, 2 H), 1.04–0.80 (m, 1 H). $^{13}$C NMR (75 MHz, $CDCl_3$): 142.9, 138.5, 131.5, 129.4, 127.1, 123.1, 62.8, 47.9, 40.0, 32.0, 31.0, 26.3, 25.3, 21.4. HRMS (EI) calculated for $C_{16}H_{21}NO_2S$ [$M^+$] 291.1293, found 291.1287.

(±)-*trans*-2-(Nosylamino)cyclohexanecarbonitrile (**24**)

7-Nosyl-7-azabicyclo[4.1.0]heptane (**23**; 2.094 g, 7.42 mmol) was dissolved in dry THF (50 ml) under argon at r.t., whereupon TMSCN (0.736 g, 0.93 ml, 7.42 mmol) and TBAF (1.0 M in THF, 1.48 ml, 1.48 mmol) were added in succession. The resulting reaction mixture was warmed to 40 °C and the progress was monitored by TLC. After 20 h, the heating was discontinued, the solvent was evaporated in vacuo and the solid residue was purified by flash chromatography on silica gel (DCM, followed by DCM/EtOAc 20:1 to 5:1 (v/v)) to afford the title compound **24** as a granular, white solid (2.055 g, 90%). $R_F$ 0.15 (hexane/EtOAc 2:1 (v/v)); m.p. 198.0 °C. $^1$H NMR (200 MHz, $CD_3CN$): 6.93 (d, $J$ = 11.4, 2 H), 6.67 (d, $J$ = 11.4, 2 H), 6.29 (d, $J$ = 5.7, 1 H), 3.53–3.24 (m, 1 H), 2.55 (dt, $J$ = 8.6, 2.9, 1 H), 2.15–1.98 (m, 1 H), 1.75–1.44 (m, 4 H), 1.38–1.01 (m, 3 H). $^{13}$C NMR (50 MHz, $CDCl_3$): 151.1, 148.1, 129.1, 125.4, 121.6, 55.0, 36.2, 33.3, 29.8, 24.1, 24.2. For $C_{13}H_{15}N_3O_4S$ (309.35) calculated: 50.48% C, 4.89% H, 13.58% N; found: 50.44% C, 4.80% H, 13.51% N.

(±)-*trans*-2-(*N*-Allyl-*N*-nosylamino)cyclohexanecarbonitrile (**25**)

(±)-*trans*-2-(Nosylamino)cyclohexanecarbonitrile (**24**; 0.200 g, 0.65 mmol) was dissolved in dry acetone (15 ml) under argon, whereupon $K_2CO_3$ (0.713 g, 5.17 mmol) and allyl bromide (3.15 g, 2.25 ml, 26 mmol) were added in sequence. The resulting heterogeneous mixture was heated to reflux and kept at this temperature overnight. After 12 h the heating was discontinued and the solvent evaporated in vacuo to yield a solid residue, which was treated with a mixture of water (10 ml) and EtOAc (30 ml). The phases were separated and the aqueous phase was extracted with EtOAc (10 × 10 ml). The combined organic phases were washed with brine, dried over $MgSO_4$ and evaporated in vacuo to yield a yellow solid as the crude. Purification by flash chromatography on silica (hexane, followed by hexane/EtOAc 10:1 to 5:1 (v/v)) afforded the title compound **25** as a faintly yellow solid (0.225 g, quantitative). $R_F$ 0.29 (hexane/EtOAc 2:1 (v/v)); m.p. 108.5–110.0 °C. $^1$H NMR (300 MHz, $CDCl_3$): 8.35 (d, $J$ = 9.0, 2 H), 8.10 (d, $J$ = 8.9, 2 H), 5.79 (tdd, $J$ = 16.7, 10.0, 6.5, 1 H), 5.26 (ddd, $J$ = 17.1, 2.6, 1.4, 1 H), 5.19 (qd, $J$ = 10.0, 1.1, 1 H), 3.95 (tdd, $J$ = 16.0, 6.5, 1.2, 1 H), 3.83 (tdd, $J$ = 16.2, 6.5, 1.4, 1 H), 3.78–3.61 (m, 1 H), 3.00–2.70 (m, 1 H), 2.28–2.15 (m, 1 H), 1.96–1.50 (m, 5H), 1.44–1.04 (m, 3 H). $^{13}$C NMR (75 MHz, $CDCl_3$): 150.1, 146.0, 134.0, 128.8, 124.3, 120.2, 119.4, 60.1, 48.6, 33.8, 31.2, 30.5, 25.1, 24.1.

(±)-*trans*-2-(*N*-Allyl-*N*-nosylamino)cyclohexanecarbaldehyde (**26**)

(±)-*trans*-2-(*N*-Allyl-*N*-nosylamino)cyclohexanecarbonitrile (**25**; 0.306 g, 0.88 mmol) was dissolved in dry DCM (10 ml) and cooled to –78 °C. DIBAL (1.0 M in DCM, 1.92 ml, 1.92 mmol) was added in a dropwise manner during 10 min. With continued cooling, the reaction was monitored by TLC and after 1 h, the intermediate aldimine was quenched by addition of an aqueous saturated solution of Rochelle salt (1.0 ml). The reaction mixture was brought to r.t., diluted with DCM (50 ml) and successively washed with an aqueous saturated solution of Rochelle salt (2 × 10 ml) and brine (10 ml). The organic phase was dried over $Na_2SO_4$, the solvent was evaporated in vacuo and the oily residue was purified by flash chromatography on silica gel (heptane, followed by heptane 5:1 (v/v)) to afford the title compound **26** as an opaque, colourless oil (0.200 g, 65%). $R_F$ 0.22 (heptane/EtOAc 2:1). $^1$H NMR (200 MHz, $CDCl_3$): 9.49 (d, $J$ = 2.9, 1 H), 8.37 (d, $J$ = 11.4, 2 H), 8.03 (d, $J$ = 11.4, 2 H), 5.67 (tdd, $J$ = 18.0, 12.0, 4.0, 1 H), 5.24 (d, $J$ = 17.2, 1 H), 5.17 (d, $J$ = 11.4, 1 H), 4.17–3.69 (m, 3 H),

2.74–2.40 (m, 1 H), 1.97–1.69 (m, 3 H), 1.69–1.47 (m, 1 H), 1.47–1.00 (m, 4 H). $^{13}$C NMR (50 MHz, $CDCl_3$): 202.3, 149.8, 146.6, 134.4, 128.4, 124.2, 118.8, 57.9, 53.2, 47.5, 30.3, 26.8, 25.3, 23.8.

(±)-*trans*-(*N*-Allyl-*N*-nosyl)-2-vinylcyclohexanamine (**27**)

Dried methyltriphenylphosphonium bromide (0.434 g, 1.21 mmol) was suspended in dry THF (10 ml) at r.t. and KHMDS (0.5 M in toluene, 2.42 ml, 1.21 mmol) was added in a dropwise manner, resulting in a bright yellow suspension. The ylide solution was stirred at r.t. for an additional 1 h and then cooled to –78 °C. Freshly prepared (±)-*trans*-2-(*N*-allyl-*N*-nosylamino)cyclohexanecarbaldehyde (**26**; 0.195 g, 0.55 mmol) was dissolved in dry THF (5 ml) and was then added to the ylide during 10 min. With continued cooling, the resulting mixture was monitored by TLC. After 2 h excess ylide was decomposed by addition of methanol (2 ml). The mixture was brought to r.t., diluted with ether (30 ml) and poured into aqueous saturated Rochelle salt (10 ml). The phases were separated and the aqueous phase was extracted with ether (5 × 10 ml). The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo to yield a pale yellow oil as the crude. The residue was purified by flash chromatography on silica gel (heptane, followed heptane/EtOAc 10:1 to 5:1 (v/v)) to afford the title compound **27** as a colourless oil (0.110 g, 57%). $R_F$ 0.46 (heptane/EtOAc 2:1 (v/v)). $^1$H NMR (300 MHz, $CDCl_3$): 8.30 (d, $J$ = 8.7, 2 H), 7.97 (d, $J$ = 8.7, 2 H), 5.73 (tdd, $J$ = 16.7, 10.1, 6.5, 1 H), 5.40 (ddd, $J$ = 17.3, 10.2, 8.6, 1 H), 5.19 (qd, $J$ = 17.3, 1.4, 1 H), 5.08 (qd, $J$ = 10.1, 1 H), 4.94 (d, $J$ = 17.2, 1 H), 4.81 (dd, $J$ = 10.3, 1.6, 1 H), 3.91 (tdd, $J$ = 16.2, 6.5, 1.3, 1 H), 3.75 (tdd, 16.4, 6.5, 1.3, 1 H), 3.57 (dt, $J$ = 11.2, 3.3 Hz, 1 H), 2.16 (dd, $J$ = 18.5, 8.1, 1 H), 1.80–1.39 (m, 4 H), 1.35–1.01 (m, 4 H). $^{13}$C NMR (75 MHz, $CDCl_3$): 149.5, 147.3, 140.5, 135.4, 128.3, 124.0, 117.8, 115.4, 62.4, 46.8, 45.8, 33.2, 32.0, 25.8, 24.9. HRMS (EI) calculated for $C_{17}H_{22}N_2O_4S$ [$M^+$] 350.1300, found 350.1301.

(±)-(4a*R*,8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-1-nosylquinoline (**28**)

Dry DCM under argon was frozen in liquid nitrogen and then reheated to allow melting in vacuo. Deoxygenation by this process was carried out thrice. (±)-*trans*-(*N*-Allyl-*N*-nosyl)-2-vinylcyclohexanamine (**27**; 0.117 g, 0.33 mmol) was dissolved in degassed DCM (10 ml) after having been repetitively purged by evacuation and flushing with argon. The Grubbs 1st generation pre-catalyst (0.027 g, 0.033 mmol) was added in one portion at r.t., to yield a homogeneous yellow solution, which turned light pink within 2 min after the addition. The reaction mixture was stirred at r.t and the progress was monitored by TLC. After 5 min, the solvent was evaporated in vacuo and the oily, black residue was purified by flash chromatography on silica gel (heptane, followed by heptane/EtOAc 10:1 to 5:1 (v/v)) to afford the title compound **28** as clear, colourless oil that solidified upon standing (0.094 g, 88%). $R_F$ 0.41 (heptane/EtOAc 2:1 (v/v)); m.p. 82.5–83.0 °C. $^1$H NMR (300 MHz, $CDCl_3$): 8.31 (d, $J$ = 9.0, 2 H), 7.99 (d, $J$ = 9.0, 2 H), 5.62 (tdd, $J$ = 9.8, 4.6, 2.4, 1 H), 5.43 (qd, $J$ = 9.9, 1.9, 1 H), 4.41 (complex d, $J$ = 17.8, 1 H), 3.83 (tdd, $J$ = 17.8, 3.6, 2.2, 1 H), 2.85 (ddd, $J$ = 12.1, 10.3, 3.3, 1 H), 2.16–2.05 (m, 1 H), 1.98–1.69 (m, 4 H), 1.69–1.60 (m, 1 H), 1.35–1.10 (m, 2 H), 1.09–0.91 (m, 1 H). $^{13}$C NMR (75 MHz, $CDCl_3$): 149.7, 147.8, 131.9, 128.3, 124.1, 123.0, 63.3, 48.1, 40.0, 31.9, 30.9, 26.3, 25.3.

*Financial support from the Technical University of Denmark (J.N.) and the Swiss National Science Foundation (Projects Nos 20-52581.97 and 2027-048156) (D.R.) is gratefully acknowledged. Support and sponsorship concerted by COST Action D24 "Sustainable Chemical Processes: Stereoselective Transition Metal-Catalysed Reactions" are also kindly acknowledged (P.M.). The authors (D.R. and P.M.) are indebted to A. Pinto and J.-P. Saulnier for the NMR spectra and D. Klink for the mass spectra.*

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