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Enantioselective synthesis of (+)(*R*)- and (−)(*S*)-nicotine based on Ir-catalysed allylic amination†

Carolin Welter, Rosa M. Moreno, Stephane Streiff and Günter Helmchen*

Organisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany. E-mail: g.helmchen@urz.uni-heidelberg.de; Fax: 49 6221 544205; Tel: 49 6221 8401

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The synthesis of nicotine with enantiomeric excess of >99% ee was accomplished by asymmetric Ir-catalysed allylic amination followed by ring closing metathesis and racemisation-free double bond reduction.

Nicotine is mainly known in connection with smoking as an addictive substance. However, nicotine itself and several analogues (Fig. 1) have shown therapeutic benefits for a number of deseases caused by nervous system disorders. Examples are Alzheimer's and Parkinson's disease and Tourette's syndrom.[1] Further positive effects of nicotine are pain relief and lowering of anxiety and depression.

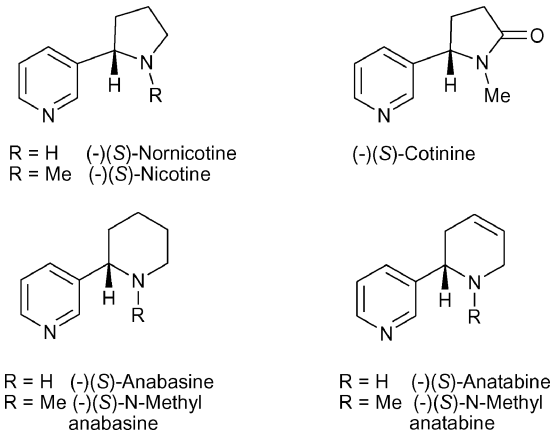
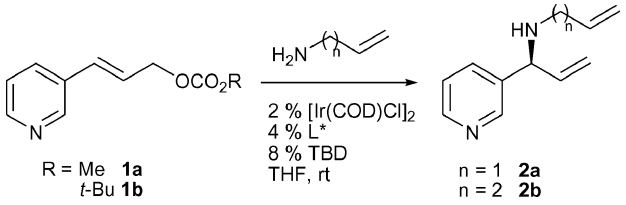


Fig. 1 Tobacco alkaloids.

The remarkable pharmacological profile has aroused interest in the synthetic chemistry of piperidine and pyrrolidine derivatives related to nicotine.[2] As most of the pharmacologically interesting compounds of these series are chiral, enantio- and diastereoselectivity are important aspects. We have now developed new routes on the basis of Ir-catalysed allylic aminations (Scheme 1), which proceed with unusually high regio- and enantioselectivity.



Scheme 1 Iridium-catalysed allylic amination of 3-(3-pyridyl)allyl carbonates (**L*** = **L1**, **L2** or **L3**).

Allyl derivatives can often be transformed into heterocycles by ring closing metathesis (RCM). Elegant syntheses of alkaloids based on domino metathesis sequences starting with cyclic allylamines, derived *inter alia* by Pd-catalysed allylic substitution, have been reported by Blechert *et al*.[3] Evans and Robinson[4] have described syntheses of dihydropyrroles based on a combination of metathesis and stereospecific Rh-catalyzed amination of enantiomerically pure allyl carbonates. Lebreton and co-workers[5] have used asymmetric allylboration of pyridine-3-aldehyde as key step to yield allyl alcohols, which were transformed into allyl amines serving as intermediates on the way to tobacco alkaloids.

The Ir-catalysed asymmetric allylic substitution, *cf.* Scheme 1, is well suited for the routes described above and offers new opportunities, as the precursors of the ring closing metathesis can be assembled in a single step from simple components. Iridium-catalysed intermolecular[6] and intramolecular[7] allylic aminations of a variety of substrates have been studied intensively over the past few years. The best results were achieved with allylic carbonates as substrates and phosphorus amidites[8] as chiral ligands. A particularly active catalyst was obtained by treatment of a solution of $[Ir(COD)Cl]_2$ (0.02 mmol), **L*** (0.04 mmol) in dry THF (0.5 mL) with the base 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD) (0.08 mmol).[7] This procedure was also used here. In our laboratory, the phosphorus amidites **L1**–**L3** (Fig. 2) are routinely used as ligands, with a preference for ligand **L2**, which was introduced by Alexakis and co-workers[9]

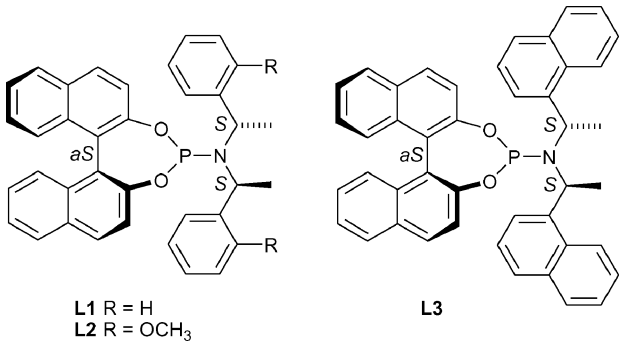


Fig. 2 Ligands used in the allylic amination.

The results displayed in Table 1 demonstrate that excellent results can be achieved with the (3-pyridyl)allyl derivatives. While selectivities obtained upon use of ligands **L1** and **L3** are typical for allylic aminations,[7a] the selectivities induced by ligand **L2** are truly remarkable, for the *N*-allyl derivative **2a** regioselectivity of >98 : 2 and enantiomeric excess exceeding 99% ee, using either methyl carbonate **1a** (entry 3) or *tert*-butyl carbonate **1b** (entry 8) as starting material. The *N*-homoallyl derivative **2b** was likewise obtained with excellent selectivity. The very high level of enantiomeric excess of 99% ee as well as regioselectity of 99 : 1 was obtained with the *tert*-butyl carbonate **1b** as substrate (entry 11).

Further steps towards tobacco alkaloids caused more difficulties than anticipated. The secondary amines **2** had to

† Electronic supplementary information (ESI) available: preparation of carbonates **1a** and **1b**. See http://dx.doi.org/10.1039/b508634e

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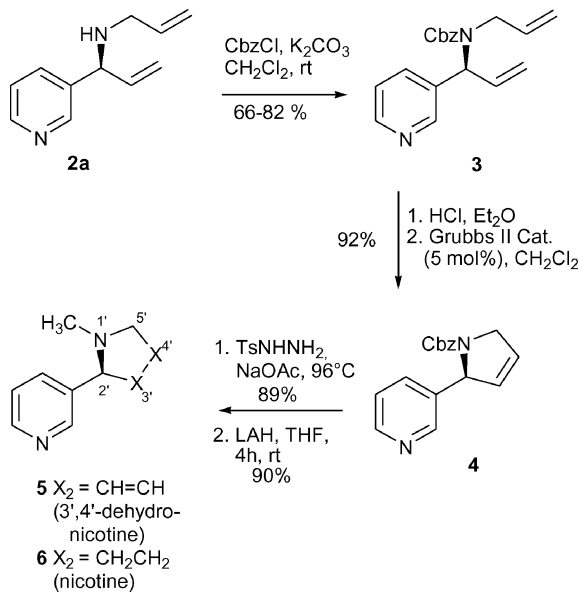
Table 1 Iridium-catalyzed allylic amination[a]

No	Reactant	Product	Ligand	Reaction time/d	Yield[b] (%)	Ratio b : l isomer[c]	Ee (%)[d]
1	**1a**	**2a**	**L1**	1	87	96 : 4	97
2[e]	**1a**	**2a**	**L1**	1	78	99 : 1	96
3[f]	**1a**	**2a**	**L2**	1.1	69	98 : 2	>99
4	**1a**	**2a**	**L3**	3	91	92 : 8	97
5	**1a**	**2b**	**L2**	0.7	68	86 : 14	99
6	**1a**	**2b**	**L3**	4	77	99 : 1	95
7	**1b**	**2a**	**L1**	4	59	99 : 1	97
8[f]	**1b**	**2a**	**L2**	4	69	>99 : 1	>99
9	**1b**	**2a**	**L3**	3	53	98 : 2	96
10	**1b**	**2b**	**L1**	4	59	>99 : 1	92
11	**1b**	**2b**	**L2**	1	70	99 : 1	99
12	**1b**	**2b**	**L3**	1.7	68	>99 : 1	96

[a] All reactions were carried out on a 0.5 mmol scale using 2 mol% of $[Ir(COD)Cl]_2$, 4 mol% of ligand and 2 h of activation with TBD (8 mol%). [b] Yield of isolated product. [c] The designations b and l refer to the branched (Scheme 1; **2a**,**b**) and linear (formula not shown in Scheme 1) substitution products, respectively. [d] Determined by HPLC {column: Daicel Chiralcel AD–H, eluent: *n*-hexane/*i*-PrOH 98 : 2, 250 × 4.6 mm, 5 µm, + guard cartridge 10 × 4 mm, 5 µm, flow = 0.5 mL min^{-1}), t_R[(*S*)-**2a**] = 28.8 min, t_R[(*R*)-**2a**] = 30.9 min, t_R[(*S*)-**2b**] = 24.8 min, t_R[(*R*)-**2b**] = 26.9 min}. [e] The experiment was carried out with (*R*,*R*,*R*)-**L1** as ligand. [f] These reactions were carried out on a 15 (entry 3) or 25 (entry 8) mmol scale.

be *N*-protected prior to RCM in order to prevent catalyst deactivation. Unexpectedly, the reaction of CbzCl with amine **2a** was accompanied by polymerisation. A good yield was obtained by carrying out the reaction in a suspension of potassium carbonate in dichloromethane and addition of a polymerisation inhibitor (5 mol% of 2,6-di-*tert*-butylbenzene-1,4-diol) to the reaction mixture.[10] The protected amine **3** was obtained in 66–82% yield.[11] RCM with the hydrochloride of **3** using Grubbs' II catalyst[12] was uneventful and yielded the 3,4-dihydropyrrole derivative **4** in >90% yield. However, the seemingly simple final reduction steps caused problems. Thus, reaction of **4** with lithium aluminium hydride (LAH) under a variety of conditions produced mixtures of 3′,4′-dehydronicotine and nicotine (GC/MS). We did not find conditions leading to either of the pure compounds (Scheme 2).



Scheme 2 Synthesis of (−)(*S*)-nicotine (**6**).

Accordingly, we decided to reduce the double bond first. This turned out to be another problematic step, in that transition metal-catalysed hydrogenation is generally prone to inducing epimerisation in an allylic position.[13] We had previously encountered this problem in conjunction with syntheses of cyclopentanoid *Archaea* lipids and then solved it by using diimide reduction.[14] Gratifyingly, the reduction of **4** with diimide generated from $TsNHNH_2$ proceeded in 89% yield. Subsequent reduction with LAH furnished (−)(*S*)-nicotine (**6**) in 95% yield.

The route described above was also used to prepare (+)(*R*)-nicotine (*cf.* Table 1, entry 2). The enantiomeric purity (HPLC[15]) of the final product **6** was identical to that of the starting material **2a**, *i.e.* racemisation had not occurred in any of the steps.

In conclusion, we have developed a short route to prepare nicotine of very high enantiomeric purity. The route can be readily extended to a variety of other tobacco alcaloids, for example anabasine, and analogs of interest in medicinal chemistry.

Experimental

General procedure for the allylic amination of carbonates 1

Success with the following procedure requires dry THF (<35 µg of H_2O per mL, Karl Fischer titration). Under argon, a solution of $[Ir(COD)Cl]_2$ (0.02 mmol) and **L*** (0.04 mmol) in dry THF (0.5 mL) was treated with TBD (0.08 mmol). After stirring for 2 h at room temperature the allylic carbonate **1** (1.0 mmol) was added, and the mixture was stirred for 5 min at rt. Then the nucleophile (1.1–5 mmol) was added and the mixture was stirred until TLC indicated complete conversion. The solvent was removed under reduced pressure and the residue analysed with respect to the content of branched and linear product by ^1H NMR. The pure reaction products were obtained by flash chromatography.

(*S*)-Benzyl allyl(1-pyridin-3-ylprop-2-en-1-yl)carbamate (3)

A solution of amine (−)(*S*)-**2a** (1.15 g, 6.6 mmol, 99%ee) in dry dichloromethane (50 mL) was treated with 5 mol% of 2,6-di-*tert*-butylbenzene-1,4 diol and cooled to 0 °C. Then K_2CO_3 (1.82 g, 13.2 mmol) and CbzCl (1.46 g, 8.6 mmol) were added. The mixture was allowed to warm to room temperature and air was bubbled through for 2 min. After 24 h of stirring saturated aqueous $NaHCO_3$ was added and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography (petroleum ether–ethyl acetate 1 : 1) yielded carbamate (*S*)-**3** (1.67 g, 82%) as a pale yellow oil. ^1H NMR ($CDCl_3$, 250 MHz): δ 3.72–3.91 (m, 2 H), 4.99–5.05 (m, 2 H), 5.17 (s, 2 H), 5.23 (d, J = 17.2 Hz, 1 H), 5.40 (d, J = 10.3 Hz, 1 H), 5.65–5.76 (m, 2 H), 6.18 (ddd, J = 17.0 Hz, J = 3.8 Hz, J = 10.4 Hz, 1 H), 7.23–7.34 (m, 6 H), 7.58 (m, 1 H), 8.53–8.56 (m, 2 H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 53.3, 60.5, 67.5, 116.2, 119.2, 123.2, 127.8, 128.0, 128.4, 134.2, 134.4, 135.0, 135.2, 136.3, 148.8, 149.4, 155.9. HRMS: *m*/*z* (FAB) calc. for $C_{19}H_{21}N_2O_2$ ($M + H^+$) 309.1603, found 309.1618.

(*S*)-Benzyl 2-pyridin-3-yl-2,3-dihydro-1*H*-pyrrole-1-carboxylate (4)

A 1 M solution of HCl in Et_2O (3 mL) was added to a solution of amine (*S*)-**3** (300 mg, 0.97 mmol) in dry Et_2O (6 mL). After 10 min the solvent was evaporated, and the colourless, oily residue was dissolved in dry, degassed CH_2Cl_2 (13 mL) and the solution added to a solution of Grubbs' II catalyst[16] (43 mg, 0.05 mmol) in dry, degassed CH_2Cl_2 (7 mL). The resulting mixture was heated at reflux under argon. After 4 h, saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were concentrated *in vacuo*. The residue was subjected to flash chromatography (petroleum ether–ethyl acetate 1 : 1) to give (*S*)-**4** (250 mg, 92%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 250 MHz):[17] δ 4.26–4.44 (m, 2 H), 5.02 (s, 2 H), 5.53–5.61 (m, 1 H), 5.74–5.83 (m, 1 H), 5.98–6.04 (m, 1 H), 7.02–7.04 (m, 1 H), 7.18–7.65 (m, 6 H), 8.49–8.59 (m, 2 H). ^{13}C NMR ($CDCl_3$, 62.5 MHz):[17] δ 53.5, 54.0, 65.4, 65.9, 66.7, 66.9, 123.2, 123.2, 125.5, 125.7, 127.6, 127.7, 127.8, 128.1, 128.3, 129.6, 129.8, 134.2, 134.6, 135.9, 136.0, 136.6, 136.8, 148.5, 148.7, 148.8, 154.1. HRMS: *m*/*z* (FAB) calc. for $C_{17}H_{17}N_2O_2$ ($M + H^+$) 281.129, found 281.1317.

(*S*)-3-(1-Methyl-2,3-dihydro-1*H*-pyrrol-2-yl)pyridine (5)

A solution of (*S*)-**4** (118 mg, 0.42 mmol) and $TsNHNH_2$ (3.91 g, 21 mmol) in dimethylformamide (8 mL) was stirred at 96 °C. After 30 min a solution of sodium acetate (3.44 g, 42 mmol) in water (24 mL) was added slowly. After 20 h the reaction mixture was cooled to room temperature. Water was added and the mixture was extracted four times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The residue was subjected to flash chromatography (petroleum ether–ethyl acetate 2 : 1) to give (*S*)-**5** (60 mg, 89%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.85–2.01 (m, 3 H), 2.39–2.45 (m, 1 H), 3.50–3.71 (m, 2 H), 5.02–5.13 (m, 3 H), 6.91–7.00 (m, 1 H), 7.23–7.48 (m, 6 H), 7.81 (d, J = 4.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 21.4, 35.1, 36.8, 60.5, 68.0, 125.2, 127.2, 128.6, 128.9, 129.3, 129.5, 130.5, 135.6, 148.0, 148.5.

(*S*)-3-(1-Methylpyrrolidine-2-yl)pyridine, (*S*)-nicotine (6)

Under an atmosphere of argon, a solution of (*S*)-**5** (87 mg, 0.54 mmol) in dry THF (6 mL) was added dropwise with a syringe to a cold (0 °C) suspension of lithium aluminium hydride (1.09 g, 28.7 mmol) in dry diethyl ether (17 mL). The mixture was stirred for 4 h at room temperature, then cooled to 0 °C and dropwise treated with water (1.1 mL), NaOH solution (1.1 mL, 15% in water) and again water (3.3 mL). The mixture was stirred until the precipitate could be conveniently filtered off. The filtrate was concentrated under reduced pressure. The residue was subjected to flash chromatography (silica, CH_2Cl_2–MeOH 95 : 5) to give **6** (79 mg, 90%) as colourless oil. $[\alpha]_D^{20} = -127$ (*c* 1.0, EtOH). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.68–1.92 (m, 4 H), 2.20 (s, 3 H), 2.32–2.45 (m, 1 H), 3.10 (t, J = 9.0 Hz, 1 H), 3.27 (dt, J = 2.4 Hz, J = 11.2 Hz, 1 H), 7.25–7.30 (m, 1 H), 7.67–7.73 (m, 1 H), 8.51–8.55 (m, 2 H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 22.6, 35.2, 40.4, 57.0, 68.9, 123.6, 134.9, 138.6, 148.7, 149.5. HRMS: *m*/*z* (EI), calc. for $C_{10}H_{14}N_2$ (M^+) 162.1157, found 162.1152.

The hydrochloride **6**·2HCl[18] was prepared by treatment of (*S*)-**6** with an excess of 1 M HCl, concentration *in vacuo* and crystallisation from EtOH–Et_2O: mp 159–161 °C. The same melting point was displayed by a sample prepared from commercial (*S*)-nicotine.

Acknowledgements

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