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Stereoselective Synthesis of 2,6-Disubstituted Piperidines Using the Iridium-Catalyzed Allylic Cyclization as Configurational Switch: Asymmetric Total Synthesis of (+)-241D and Related Piperidine Alkaloids

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Piperidines are prominent structural units of alkaloids, which often display interesting biological activities.[1] Therefore, the stereoselective synthesis of piperidine derivatives is important for organic and medicinal chemistry.[2]

Many routes for the construction of piperidines involve a ring closure by C–N bond formation. As most alkaloids possess a chirality center at C2 and/or C6 (see examples in Figure 1), stereoselectivity is essential. Indeed, high levels of

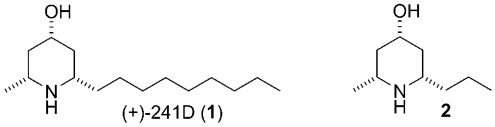
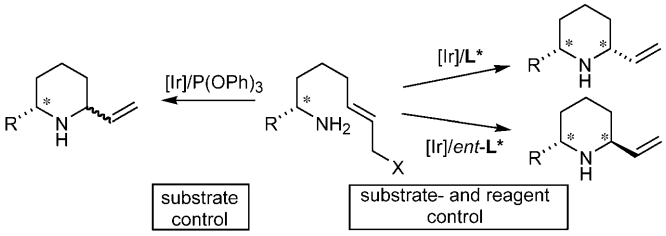


Figure 1. Examples of naturally occurring 2,6-disubstituted 4-hydroxypiperidines.

diastereoselectivity have been achieved by substrate control.[3] A drawback of this approach is that only one of a pair of diastereoisomers can be provided. We have now developed a method based on an Ir-catalyzed asymmetric allylic substitution (see Scheme 1),[4] which allows generation of either diastereomer by external (reagent) control. To the best of our knowledge, such a *configurational switch* to obtain both possible diastereomers with high diastereoselectivity has not been achieved for an allylic substitution,[5] while it has been developed for other reactions, most prominently the Katsuki–Sharpless epoxidation.[6]

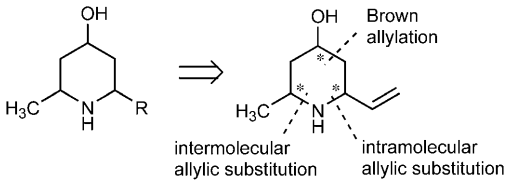
As applications of this approach, we present total syntheses of the dendrobate alkaloid (+)-241D (**1**), its C6-epimer



Scheme 1. Double stereodifferentiation: interplay between substrate- and reagent- induced selectivity ([Ir] = Ir catalyst; **L*** = **L1** or **L2**).

(**12b**) and (2*R*,4*S*,6*S*)-2-methyl-6-propylpiperidin-4-ol (**2**), a spruce alkaloid (Figure 1).

The overall strategy of the syntheses is described in Scheme 2. Key steps are two asymmetric Ir-catalyzed allylic substitutions and an addition of Brown's chiral allylboron reagent $Ipc_2B(allyl)$ to an intermediate aldehyde. Given the availability of both enantiomers of all the chiral reagents, the configurational switch allows preparation of each of the eight stereoisomers with high selectivity.



Scheme 2. Retrosynthetic analysis of 2,6-disubstituted hydroxypiperidines.

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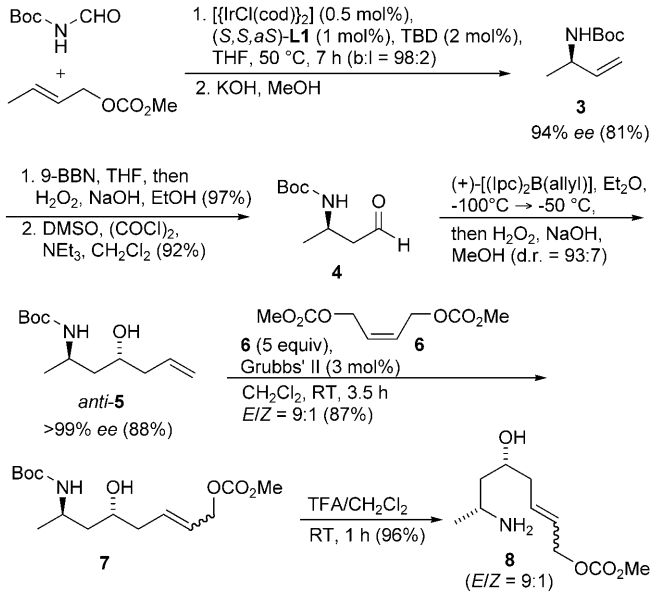
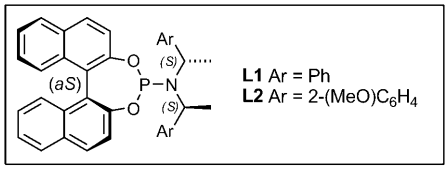
The synthesis of the cyclization precursor **8** started with the known Ir-catalyzed amination of *trans*-crotyl methyl carbonate with HN(CHO)Boc, an ammonia equivalent (Scheme 3).[7] A preparative scale of 77 mmol with a catalyst loading of 1 mol% was employed. The catalyst was pre-



Scheme 3. Synthesis of the cyclization precursor **8**.

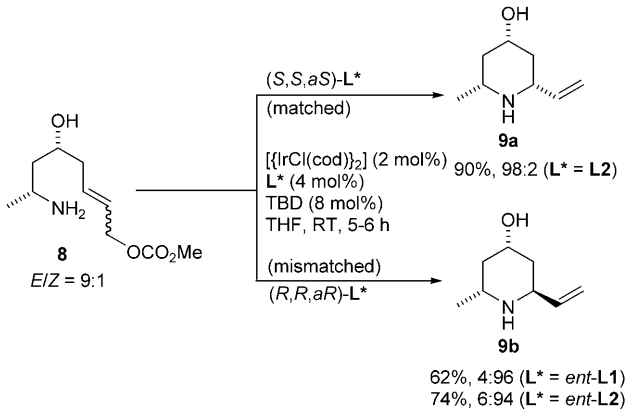
pared from the phosphoramidite ligand **L1**.[8] The formyl group was removed by treatment with KOH to give the Boc-protected amine **3** in 81% yield with 94% *ee*.[9] Hydro-



boration/oxidation and Swern reaction of the resultant primary alcohol[10] furnished the sensitive aldehyde **4** in 89% yield over two steps.[11] This was treated with (+)-*B*-allyldiisopinocampheylborane[12] [(+)-Ipc$_2$B(allyl)] at low temperature. A 93:7 mixture (GC) of the homoallylic alcohols *anti*-**5** and *syn*-**5** was obtained.[13] The diastereoisomers could be separated easily by flash chromatography. The desired alcohol *anti*-**5**[14] was isolated in 88% yield with >99% *ee*.[15] The very high *ee* is a consequence of double asymmetric induction.

Finally, chain prolongation was carried out by cross metathesis (Grubbs' II catalyst) of the homoallylic alcohol *anti*-**5** and the biscarbonate **6** (5 equiv). The allylic carbonate **7** was produced in 87% yield as 9:1 mixture of *E*/*Z* isomers (^{1}H NMR spectroscopy). Cleavage of the Boc group under standard conditions gave the cyclization precursor **8** in 96% yield.

The Ir-catalyzed cyclization of amine **8** (*E*:*Z* = 9:1) proceeded smoothly under standard conditions (4 mol% of catalyst; Scheme 4).[16] With **L2** as ligand,[8] the piperidine **9a** was obtained in 90% yield with an almost perfect diastereoselectivity of **9a**/**9b** = 98:2. Upon use of ligand *ent*-**L2**, the diastereoisomer **9b** was prepared in 74% yield with only



Scheme 4. Ir-catalyzed cyclizations.

slightly reduced selectivity of **9a**/**9b** = 6:94. The yield was slightly lower with ligand *ent*-**L1**, while the diastereoselectivity of 4:96 was even higher than that achieved with *ent*-**L2**. The *Z* isomer in the substrate did not markedly interfere.[17] These results impressively demonstrate the high level of stereocontrol induced by the Ir-catalysts.

In a control experiment P(OPh)$_3$ was used as achiral ligand. The diastereoselectivity in favor of **9a** was 65:35; thus, substrate control is very weak in this system.

The configuration of the cyclization products was assigned according to a general rule for the steric course of Ir-catalyzed substitutions[4a] and was verified in the case of **9a** by an X-ray crystal structure analysis (Figure 2).[14]

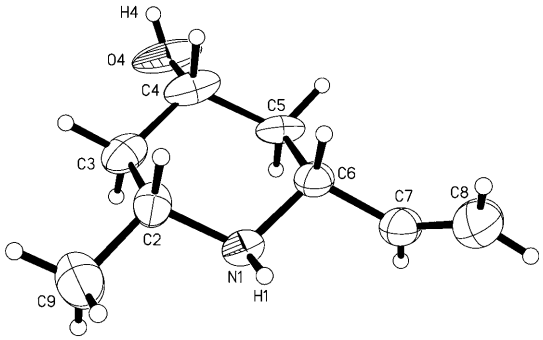
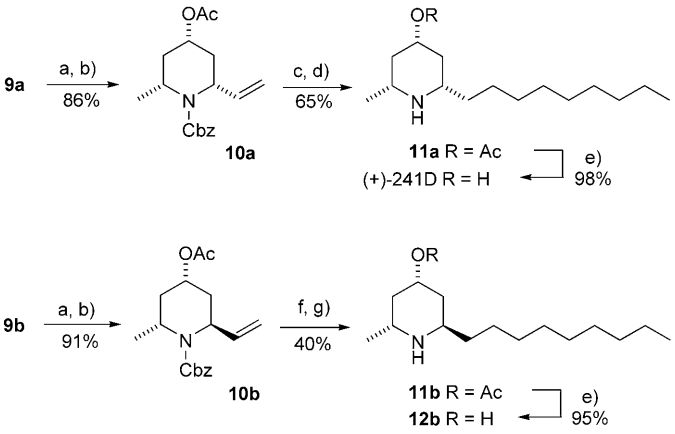


Figure 2. Molecular structure of **9a** from single-crystal X-ray structure analysis.

The alkaloid (+)-241D (**1**) was isolated by Daly et al. from the skin of *Dendrobates speciosus*, a rare poison frog of western Panama.[18] This compound was found to be a potent inhibitor of binding of [^{3}H]perhydrohistrionicotoxin to nicotinic acetylcholine receptor channels.[19] Subsequent to a synthesis of the racemate[19] asymmetric syntheses of (+)-**1** and (−)-**1** as well as syntheses of the C4-epimers were reported.[20]

Our synthesis of **1** is described in Scheme 5. Chain elongation of **9a** by cross metathesis was chosen as key step. Ini-



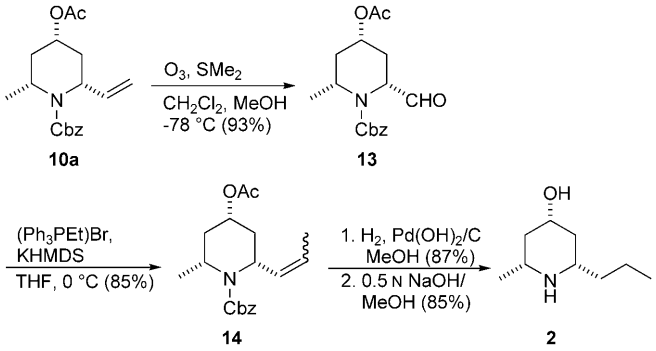
Scheme 5. Synthesis of (+)-241 D (**1**) and its C6-epimer **12b**: a) CbzCl, Na_2CO_3, CH_2Cl_2/H_2O, 0 °C→RT; b) Ac_2O, pyridine; c) 1-Nonene (10 equiv), Grubbs' II catalyst (10 mol %), CH_2Cl_2, 5 h, reflux (71 %, 91 % corr.); d) H_2, Rh/C (5 mol %), MeOH, 1 h, RT (92 %); e) 0.5 N NaOH/MeOH; f) 1-Nonene (10 equiv), Grubbs' II catalyst (10 mol %), CH_2Cl_2, 8 h, reflux (46 %, 99 % corr.); g) H_2, $Pd(OH)_2$/C (5 mol %), MeOH, 1 h, RT (86 %).

tially, N-protection by salt formation was probed. The attempts were not successful, partially because of low solubility of the salts in dichloromethane. Next, protecting groups at both O and N were introduced by using standard procedures. Thus, the carbamate **10a** was prepared and treated with 1-nonene in the presence of Grubbs' II catalyst (10 mol %). The cross metathesis product was obtained in 71 % yield, the starting material was partially recovered (20 %). Catalytic hydrogenation (Rh/C) furnished the free amine **11a** in 92 % yield. No epimerization was found for this step within the limits of detection (^{1}H NMR spectroscopy). Finally, the acetate was hydrolyzed to give the natural product **1**, the spectroscopic properties of which were in full agreement with those reported. An overall yield of 27 % was achieved.

The synthesis of the C6-epimer of **1** through an analogous route was straightforward. Protection of **9b** gave **10b** in good yield. However, **10b** was significantly less reactive than **10a** in the cross metathesis reaction. After testing several reaction conditions we had to settle with incomplete conversion and a moderate isolated yield of 46 %; fortunately, the starting material was fully recovered (53 %). Similarly, hydrogenation of **10b** by using Rh/C as catalyst was not possible; $Pd(OH)_2$ on charcoal was used instead, and amine **11b** was obtained in 86 % yield. Other than anticipated, no epimerization occurred (^{1}H NMR spectroscopy). Hydrolysis gave the amino alcohol **12b** in 95 % yield.[14] This concluded the first synthesis of the C6-epimer of the alkaloid (+)-241 D (**1**). The overall yield was 15 %.

The piperidine derivative **2** has been identified as a trace alkaloid in extracts from Colorado blue spruce (*Picea pungens*) by Stermitz et al.[21] Its structure was deduced from GC/MS data and on the basis of analogy to similar alkaloids and was verified by a synthesis of the racemic compound. The absolute configuration and optical rotation were unknown. The assignment shown in Figure 1 is based on the observation that, with one exception (euphococcinine), 2,6-disubstituted piperidines occurring in conifers possess the same absolute configuration at the methylated center C2.[21]

Our synthesis of **2** started with the vinypiperidine **10a** (Scheme 6). Oxidative cleavage of the double bond (O_3/SMe_2) gave the aldehyde **13**, which was subjected to a Wittig olefination to complement the C_3 side chain. The olefin **14** was obtained in 81 % yield as a mixture of isomers (Z/E = 87:13, ^{1}H NMR spectroscopy). Catalytic hydrogenation with $Pd(OH)_2$/C as catalyst and subsequent hydrolysis furnished **2** in the form of colorless polyhedra ($[\alpha]_D^{20} = +8.8$, $c = 0.43$ in MeOH, >99 % *ee*)[14] in an overall yield of 24 %.



Scheme 6. Synthesis of the spruce alkaloid **2**.

In conclusion, we are presenting the first example of a *configurational switch* for Ir-catalyzed allylic cyclizations, which allows both possible diastereoisomeric products to be generated with very high selectivity. The application of this method to an asymmetric synthesis of the alkaloid (+)-241 D (**1**) and to the first asymmetric synthesis of its C6-epimer **12b** are reported. Furthermore, the first stereoselective synthesis of the spruce alkaloid (2*R*,4*S*,6*S*)-2-methyl-6-propylpiperidin-4-ol (**2**) is presented. Extension of our method to syntheses of *Prosopis* alkaloids is under active investigation.

Experimental Section

General procedure for Ir-catalyzed cyclization reactions: Success with the following procedures requires dry THF (<30 mg L^{-1} of H_2O, Karl–Fischer titration). A Schlenk tube was dried under argon with a heat gun and charged with a solution of $[\{IrCl(cod)\}_2]$ (13.4 mg, 0.02 mmol) and **L1**/**L2** (0.04 mmol) in anhydrous THF. Anhydrous 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD; 11.1 mg, 0.08 mmol) was added, and the mixture was stirred for 5 min (**L2**) or 1 h (**L1**). Then the carbonate **8** (217.3 mg, 1 mmol) was added and the mixture was stirred until control by TLC (CH_2Cl_2/MeOH 4:1, R_f(**8**) = 0.4, R_f(**9a**) = 0.3, R_f(**9b**) = 0.3) revealed complete conversion. The mixture was concentrated and analyzed by GC with respect to the ratio of diastereomers.[16] The crude product was subjected to flash column chromatography (silica gel, CH_2Cl_2/MeOH 4:1 to 3:1). Analytically pure samples were obtained by sublimation under reduced pressure.

Physical data for selected compounds:

*(−)-(2R,4S,6R)-2-Methyl-6-vinylpiperidin-4-ol (**9a**)*: $R_f = 0.3$ (CH_2Cl_2/MeOH 4:1); colorless needles; m.p. 82–83 °C; $[\alpha]_D^{20} = -4.7$ ($c = 0.34$ in acetone, >99 % *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.82$ (ddd, $J = 17.1$, 10.5, 6.6 Hz, 1H; =CH), 5.16 (ddd, $J = 17.3$, 1.3, 1.3 Hz, 1H; $=CH_EH_Z$), 5.04 (ddd, $J = 10.4$, 1.1, 1.1 Hz, 1H; $=CH_EH_Z$), 3.69 (dddd, $J = 11.1$, 11.1, 4.6, 4.6 Hz, 1H; C*H*OH), 3.20–3.13 (m, 1H; 6-H), 2.80–2.69 (m, 1H; 2-H), 2.11 (brs, 2H; NH, OH), 2.01–1.90 (m, 2H; 3-H_aH_b, 5-H_aH_b), 1.22–0.99 (m, 2H; 3-H_aH_b, 5-H_aH_b), 1.13 ppm (d, $J = 6.2$ Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 140.28$ (d, =CH), 114.96 (t, $=CH_2$), 68.99 (d, CHOH), 57.74 (d, C-6), 50.26 (d, C-2), 43.33, 41.16 (2t, C-3, C-5), 22.36 ppm (q, CH_3); HRMS (EI+): *m/z* calcd for $C_8H_{15}NO^+$: 141.1148; found: 141.1142 $[M]^+$.

*(+)-(2R,4S,6S)-2-Methyl-6-vinylpiperidin-4-ol (**9b**)*: $R_f = 0.3$ (CH_2Cl_2/MeOH 4:1); colorless solid, m.p. 38–40 °C; $[\alpha]_D^{20} = +69.2$ ($c = 0.27$ in acetone, >99 % *ee*); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.97$ (ddd, $J = 17.3$, 10.8, 5.6 Hz, 1H; =CH), 5.13 (ddd, $J = 17.4$, 1.4, 1.4 Hz, 1H; $=CH_EH_Z$), 5.12 (ddd, $J = 10.5$, 1.4, 1.4 Hz, 1H; $CH=CH_EH_Z$), 3.84 (dddd, $J = 11.0$, 11.0, 4.5, 4.5 Hz, 1H; C*H*OH), 3.80–3.76 (m, 1H; 6-H), 3.01–2.94 (m, 1H; 2-H), 2.05–1.98 (m, 3H; 5-H_aH_b, OH, NH), 1.95–1.91 (m, 1H; 3-H_aH_b), 1.58 (ddd, $J = 12.4$, 11.3, 5.5 Hz, 1H; 5-H_aH_b), 1.10–1.02 (m, 1H; 3-H_aH_b), 1.08 ppm (d, $J = 6.4$ Hz, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 140.06$ (d, =CH), 115.20 (t, $=CH_2$), 65.52 (d, CHOH), 54.46 (d, C-6), 44.93 (d, C-2), 44.18 (t, C-3), 38.68 (t, C-5), 22.76 ppm (q, CH_3); HRMS (EI+): *m/z* calcd for $C_8H_{15}NO^+$: 141.1148; found: 141.1167 $[M]^+$.

*(+)-(2R,4S,6S)-2-Methyl-6-nonylpiperidin-4-ol [(+)-241D] (**1**)*: Colorless needles, m.p. 108–109 °C, $[\alpha]_D^{20} = +5.9$ ($c = 0.65$ in MeOH, >99 % *ee*); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.66$ (dddd, $J = 11.0$, 11.0, 4.6, 4.6 Hz, 1H; C*H*OH), 2.71 (dqd, $J = 11.1$, 6.3, 2.3 Hz, 1H; 2-H), 2.56 (dddd, $J = 11.0$, 6.4, 6.4, 2.2 Hz, 1H; 6-H), 2.01–1.93 (m, 4H; 3-H_{eq}, 5-H_{eq}, NH, OH), 1.49–1.37 (m, 2H; 1′-H), 1.36–1.21 (m, 14H; $CH_{2(n\text{-nonyl})}$), 1.14 (d, $J = 6.4$ Hz, 3H; C*H*$_3$CHN), 1.05 (ddd, $J = 11.6$, 11.6, 11.6 Hz, 1H; 3-H_{ax}), 1.00 (ddd, $J = 11.5$, 11.5, 11.5 Hz, 1H; 5-H_{ax}), 0.88 ppm (t, $J = 7.0$ Hz, 3H; C*H*$_3$CH$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 69.43$ (d, CHOH), 55.02 (d, C-6), 50.36 (d, C-2), 43.86 (t, C-3), 41.63 (t, C-5), 36.73 (t, C-1′), 32.04, 29.87, 29.71, 29.69, 29.46, 26.15 (6t, $CH_{2(n\text{-nonyl})}$), 22.81 (t, *C*H$_2$CH$_3$), 22.41 (q, *C*H$_3$CHN), 14.26 ppm (q, *C*H$_3$CH$_2$); HRMS (FAB+): *m/z* calcd for $C_{15}H_{32}NO^+$: 242.2478; found: 242.2453 $[M+H]^+$.

*(+)-(2R,4S,6R)-2-Methyl-6-nonylpiperidin-4-ol (**12b**)*: Colorless needles; m.p. 89 °C; $[\alpha]_D^{20} = +10.0$ ($c = 0.57$ in MeOH, >99 % *ee*); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 3.87$ (dddd, $J = 10.7$, 10.7, 4.5, 4.5 Hz, 1H; C*H*OH), 3.13–3.10 (m, 1H; 6-H), 2.94–2.88 (m, 1H; 2-H), 1.97–1.93 (m, 1H; 3-H_aH_b), 1.88–1.84 (m, 1H; 5-H_aH_b), 1.82 (brs, 2H; NH, OH), 1.55–1.45 (m, 1H; 1′-H_aH_b), 1.48 (ddd, $J = 11.9$, 11.6, 5.2 Hz, 1H; 5-H_aH_b), 1.44–1.38 (m, 1H; 1′-H_aH_b), 1.30–1.22 (m, 14H; $CH_{2(n\text{-nonyl})}$), 1.08 (d, $J = 6.3$ Hz, 3H; C*H*$_3$CHN), 1.03 (ddd, $J = 11.4$, 11.4, 11.4 Hz, 1H; 3-H_aH_b), 0.87 ppm (t, $J = 7.0$ Hz, 3H; C*H*$_3$CH$_2$); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 65.71$ (d, CHOH), 52.50 (d, C-6), 44.27 (d, C-2), 44.16 (t, C-3), 38.65 (t, C-5), 32.44 (t, C-1′), 32.02, 29.76, 29.76, 29.71, 29.45, 27.16 (6t, $CH_{2(n\text{-nonyl})}$), 22.91 (t, *C*H$_2$CH$_3$), 22.81 (q, *C*H$_3$CHN), 14.25 ppm (q, *C*H$_3$CH$_2$); HRMS (ESI+): *m/z* calcd for $C_{15}H_{32}NO^+$: 242.2478; found: 242.2483 $[M+H]^+$.

*(+)-(2R,4S,6S)-2-Methyl-6-propylpiperidin-4-ol (**2**)*: Colorless polyhedra; m.p. 94–95 °C; $[\alpha]_D^{20} = +8.8$ ($c = 0.43$ in MeOH, >99 % *ee*); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.63$ (dddd, $J = 11.0$, 11.0, 4.6, 4.6 Hz, 1H; C*H*OH), 2.68 (dqd, $J = 11.0$, 6.3, 2.3 Hz, 1H; 2-H), 2.58–2.53 (m, 1H; 6-H), 1.98–1.90 (m, 2H; 3-H_aH_b, 5-H_aH_b), 1.85 (brs, 2H; NH, OH), 1.43–1.30 (m, 4H; CH_2CH_2), 1.11 (d, $J = 6.3$ Hz, 3H; C*H*$_3$CHN), 1.05–0.93 (m, 2H; 3-H_aH_b, 5-H_aH_b), 0.90 ppm (t, $J = 7.1$ Hz, 3H; C*H*$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 69.34$ (d, CHOH), 54.66 (d, C-6), 50.28 (d, C-2), 44.00 (t, C-3), 41.78 (t, C-5), 39.06 (t, *C*H$_2$CH$_2$CH$_3$), 22.55 (q, *C*H$_3$CHN), 19.29 (t, *C*H$_2$CH$_3$), 14.28 ppm (*C*H$_3$CH$_2$); HRMS (ESI+): *m/z* calcd for $C_9H_{20}NO^+$: 158.1539; found: 158.1539 $[M+H]^+$.

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Keywords: alkaloids · allylic amination · heterocycles · iridium · total synthesis

[1] G. M. Strunz, J. A. Findlay in *The Alkaloids, Vol. 26* (Ed.: A. Brossi), Academic Press, New York, **1985**, pp. 89–183.

[2] Reviews: a) M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 1701–1729; b) F.-X. Felpin, J. Lebreton, *Eur. J. Org. Chem.* **2003**, 3693–3712.

[3] a) H. Yokoyama, H. Ejiri, M. Miyazawa, S. Yamaguchi, Y. Hirai, *Tetrahedron: Asymmetry* **2007**, *18*, 852–856; b) H. Makabe, L. K. Kong, M. Hirota, *Org. Lett.* **2003**, *5*, 27–29; c) K. Takao, Y. Nigawara, E. Nishino, I. Takagi, K. Maeda, K. Tadano, S. Ogawa, *Tetrahedron* **1994**, *50*, 5681–5704; d) Y. Hirai, J. Watanabe, T. Nozaki, H. Yokoyama, S. Yamaguchi, *J. Org. Chem.* **1997**, *62*, 776–777.

[4] Reviews: a) G. Helmchen, A. Dahnz, P. Dübon, M. Schelwies, R. Weihofen, *Chem. Commun.* **2007**, 675–691; b) R. Takeuchi, S. Kezuka, *Synthesis* **2006**, 3349–3366; c) H. Miyabe, Y. Takemoto, *Synlett* **2005**, 1641–1655.

[5] Sequential Ir-catalyzed inter- and intramolecular aminations of bisallylic substrates only yield the *trans*-diastereomer with high selectivity: C. Welter, A. Dahnz, B. Brunner, S. Streiff, P. Dübon, G. Helmchen, *Org. Lett.* **2005**, *7*, 1239–1242. For other intramolecular Ir- and Pd-catalyzed allylic substitutions see: C. Welter, O. Koch, G. Lipowsky, G. Helmchen, *Chem. Commun.* **2004**, 896–897 and B. M. Trost, M. J. Krische, R. Radinov, G. Zanoni, *J. Am. Chem. Soc.* **1996**, *118*, 6297–6298, respectively. Recently, Miyabe and Takemoto and co-workers reported a highly stereoselective Ir-catalyzed double allylation of guanidines: H. Miyabe, K. Yoshida, V. K. Reddy, Y. Takemoto, *J. Org. Chem.* **2009**, *74*, 305–311.

[6] R. A. Johnson, K. B. Sharpless, *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: I. Ojima), Wiley-VCH, Weinheim, **2000**, pp. 231–280.

[7] S. Förster, G. Helmchen, *Synlett* **2008**, 831–836.

[8] a) Preparation of **L1**: B. L. Feringa, *Acc. Chem. Res.* **2000**, *33*, 346–353. b) Preparation of **L2**: K. Tissot-Croset, D. Polet, S. Gille, C. Hawner, A. Alexakis, *Synthesis* **2004**, 2586–2590.

[9] The enantiomer of amine **3** has previously been prepared by other routes: a) T. Fujisawa, S. Odake, Y. Ogawa, J. Yasuda, Y. Morita, T. Morikawa, *Chem. Pharm. Bull.* **2002**, *50*, 239–252; b) T. Moriwake, S. Hamano, S. Saito, S. Torii, S. Kashino, *J. Org. Chem.* **1989**, *54*, 4114–4120.

[10] The enantiomer of this alcohol has been already described: a) A. Rae, A. E. Aliev, J. E. Anderson, J. L. Castro, J. Ker, S. Parsons, M. Stchedroff, S. Thomas, A. B. Tabor, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1933–1941; b) P. Casara, C. Danzin, B. Metcalf, M. Jung, *J. Chem. Soc. Perkin Trans. 1* **1985**, 2201–2207.

[11] The aldehyde *ent*-**4** has been synthesized before: M. Alcón, M. Canas, A. Moyano, M. A. Pericàs, A. Riera, *Tetrahedron Lett.* **1994**, *35*, 1589–1592.

[12] a) H. C. Brown, P. K. Jadhav, *J. Am. Chem. Soc.* **1983**, *105*, 2092–2093; b) U. S. Racherla, H. C. Brown, *J. Org. Chem.* **1991**, *56*, 401–404.

[13] The diastereoselectivity of the allylation was determined by GC [HP-1 (cross-linked methylsilicon gum), 25 m × 0.2 mm × 0.33 μm, 140 °C isothermal, injector temperature 250 °C, detector temperature 280 °C]: t_R(*anti*-**5**) = 17.6 min, t_R(*syn*-**5**) = 19.0 min.

[14] The relative configuration was verified by X-ray crystal structure analysis. Selected crystallographic data for **9a**: colorless needles, $C_8H_{15}NO$, $M = 141.21$, dimensions $0.68 \times 0.05 \times 0.04$ mm^3, orthorombic, space group $P2_12_12_1$, $Z = 4$, $a = 6.3274(5)$, $b = 8.7135(8)$, $c =$

15.5742(13) Å, $\alpha=90$, $\beta=90$, $\gamma=90°$, $V=858.66(13)$ Å^3, $\rho_{calcd}=1.092$ g cm^{-1}, $T=200(2)$ K, $\theta_{max}=20.79°$, radiation $Mo_{K\alpha}$ ($\lambda=0.71073$ Å), 0.3° ω scans with CCD area detector, covering a whole sphere in reciprocal space; 4611 reflections collected, 895 unique ($R_{int}=0.1046$), 643 observed [$I>2\sigma(I)$]; intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS[22] based on the Laue symmetry of the reciprocal space, $\mu=0.07$ mm^{-1}, min/max transmission = 0.95/1.00, structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm by using the SHELXTL-PLUS (6.10) software package,[23] 99 parameters refined, hydrogen atoms were treated using appropriate riding models, except of H1 and H4 at the hetero atoms N1 and O4, which were refined isotropically or restrained, Flack absolute structure parameter −4(5), goodness of fit 1.07 for observed reflections, final residual values $R1(F)=0.054$, $wR2(F^2)=0.103$ for observed reflections, residual electron density −0.13 to 0.14 e Å^{-3}. CCDC-704949 (*anti*-**5**), CCDC-704950 (**9a**), CCDC-704951 (**12b**) and CCDC-704952 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] The enantiomeric excess of *anti*-**5** was determined by GC using a chiral column (Chrompack permethyl-β-cyclodextrin, 25 m × 0.25 mm × 25 μm, 125 °C isothermal, injector temperature 200 °C, detector temperature 250 °C): t_R[(*R*,*R*)-**5**] = 42.0 min, t_R[(*S*,*S*)-**5**] = 45.8 min.

[16] The diastereoselectivity of the cyclizations was determined by GC as above (column: HP-1), 90 °C isothermal: t_R(**9a**) = 15.5 min, t_R(**9b**) = 18.2 min.

[17] In intermolecular Ir-catalyzed allylic substitutions, (*Z*)-allylic carbonates are known to give linear substitution products, R. Takeuchi, M. Kashio, *J. Am. Chem. Soc.* **1998**, *120*, 8647–8655; when enriched (*Z*)-**8** (*Z*:*E* = > 90:10) was treated according to Scheme 4, with (*S*,*S*,*aS*)-**L2** as ligand, the cyclization to give **9a** was slow and nonselective (**9a**/**9b** = 63:37, 20 %).

[18] a) M. W. Edwards, J. W. Daly, *J. Nat. Prod.* **1988**, *51*, 1188–1197; b) J. W. Daly, C. W. Myers, N. Whittaker, *Toxicon* **1987**, *25*, 1023–1095.

[19] M. W. Edwards, H. M. Garaffo, J. W. Daly, *Synthesis* **1994**, 1167–1170.

[20] a) R. Chênevert, M. Dickmann, *J. Org. Chem.* **1996**, *61*, 3332–3341; b) S. Ciblat, P. Calinaud, J.-L. Canet, Y. Troin, *J. Chem. Soc. Perkin Trans. 1* **2000**, 353–357; c) D. Ma, H. Sun, *Org. Lett.* **2000**, *2*, 2503–2505; d) F. A. Davis, B. Chao, A. Rao, *Org. Lett.* **2001**, *3*, 3169–3171; e) J. Monfray, Y. Gelas-Mialhe, J.-C. Gramain, R. Remuson, *Tetrahedron: Asymmetry* **2005**, *16*, 1025–1034.

[21] J. N. Tawara, P. Lorenz, F. R. Stermitz, *J. Nat. Prod.* **1999**, *62*, 321–323.

[22] G. M. Sheldrick, Bruker Analytical X-ray-Division, Madison, Wisconsin **2006**.

[23] G. M. Sheldrick, Bruker Analytical X-ray-Division, Madison, Wisconsin **2001**.

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