Chemistry in the Ambient Field of the Alkaloid Epibatidine, 2: Triphenylarsine as an Efficient Ligand in the Pd-Catalyzed Synthesis of Epibatidine and Analogs

Jan Christoph Namyslo and Dieter E. Kaufmann

Technische Universität Clausthal, Institut für Organische Chemie, Leibnizstr. 6, D-38678 Clausthal-Zellerfeld, Germany
Fax +49(0)5323/72-28 34
E-mail: dieter.kaufmann@tu-clausthal.de
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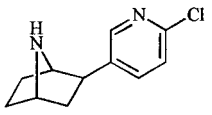
Abstract: The key-step in the original synthesis of the *N*-protected form **4** of the highly analgetic, but also toxic alkaloid epibatidine (**1**) via Pd-catalyzed *Heck*-type hydroarylation gave only a moderate yield. With triphenylarsine as a ligand we obtained **4** in 81% yield and some partly new analogs **5** - **8** in racemic form in 75 to 100% yield. Further attempts to optimize the ligand properties led to the combination of As and N donor centers. The *N*-protected pyrrolidine derivative **10** bearing a diphenylarsino substituent provided **4** in 92% yield.

Keywords: alkaloids, palladium, C-C coupling, heterocycles, ligand

Epibatidine (**1**)[1] was isolated from an Ecuadorian poison frog and characterized by *Daly* in 1992.[2] From a synthetical viewpoint we have focused on a convergent synthesis using the Pd-catalyzed Heck-type hydro(het)arylation of an appropriate bicyclic alkene **2**.



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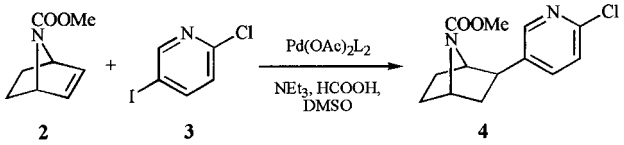


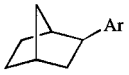
2 **3** **4**

Scheme 1

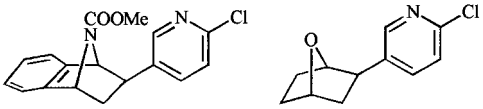
After we had shown that a broad variety of both aryl and hetaryl components[3] can be attached to the bicyclic alkene norbornene by this reaction type we published recently the high-yielding synthesis of the *N*-protected epibatidine **4** and of some analogs[1] applying a modified hydroarylation procedure of *Clayton and Regan*.[4] For example, with triphenylphosphine as a ligand in the key-step we obtained *N*-methoxycarbonyl protected epibatidine **4** in up to 77% yield. Herein, we report the synthesis of **4** in yields up to 92% using ligands with arsine donor centers in the hydroarylation procedure. To the best of our knowledge, this synthetic pathway is hitherto the shortest route to the novel alkaloid **1** and together with our preliminary published synthesis of the azabicyclic alkene **2**[1], epibatidine **1** is now obtainable in 59% overall yield starting from bis(trimethylsilyl)acetylene.

Apart from a few exceptions the use of arsine ligands in Pd-catalyzed reactions is a new synthetic procedure. An early application, for example, was published in 1989 by *Trost and co-workers* who used triphenylarsine in a Pd-mediated cyclization of an allylic enyne.[5] *Farina et al.*[6] found an acceleration of the *Stille*-coupling and other recent examples also deal with *Stille*-[7] and *Suzuki*-type[8] coupling reactions. The Pd-catalyzed cross-coupling reaction between organozinc halides and vinyl or aryl halides has been investigated by *Rossi et al.*[9] During our investigations *Shibasaki* documented *Heck* reactions performed with arsine ligands.[10]

Using triphenylarsine as a ligand, the C-C coupling step of 2-chloro-5-iodopyridine (**3**) with **2** was completed within 2 hours.[11] We were very pleased to note that the undesired reduction of the aryl derivative[3] was driven back in favour of the reductive hetarylation. With different carbo-, aza- and oxabicyclic alkenes we obtained the corresponding racemic hydroarylation products **5 – 8**[12] in yields ranging from 75 to 100%[13] (Scheme 2, Table 1).



5 Ar = 6'-chloro-3'-pyridyl
6 Ar = phenyl



7 **8**

Scheme 2

Thus, triphenylarsine is a soft ligand, suitable for *Heck*-type hydro-arylations, which enables high yields and short reaction times. We should emphasize that in the case of the benzo-anellated azabicyclic compound **7** the prelimi-

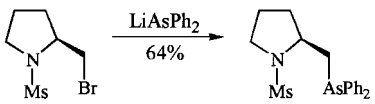
nary observed opening of the nitrogen bridge (accompanied by rearomatization into a naphthylamine and in the presence of a hydride source into a 1,2-dihydronaphthyl derivative, respectively)[14,15], did not occur using an arsine ligand.

Table 1. Hydroarylation products obtained with arsine donor ligands compared to triphenylphosphine

product	aryl compound	isolated yield using tpp[a] [%]	isolated yield using tpa[b] [%]
4	2-chloro-5-iodopyridine (**3**)	45 77[c]	81 (92)[d]
5	**3**	59	81
6	phenyl triflate	83	100
7	**3**	18	75
8	**3**	50	96

[a]tpp = triphenylphosphine, [b]tpa = triphenylarsine. Reaction conditions: 1.00 mmol bicyclic alkene, 1.50 mmol aryl compound, 3.50 mmol triethylamine, 3.00 mmol formic acid, 2.5 mol% $Pd(OAc)_2$, 5.5 mol% ligand, solvent: 1.5 mL DMSO, 65° C. [c]obtained in DMF at 50° C, [d]the yield in brackets results from ligand **10** instead of triphenylarsine

These results prompted us to develop arsine ligands with a chiral backbone to render the reductive coupling enantioselective. Although numerous arsine ligands with a chiral arsine donor atom are known, arsine ligands with a chiral backbone are rare.[16] One of the latter kind is DIARSOP[17], the arsino pendant to *Kagan*'s DIOP.[18] Very recent examples of chiral arsine ligands were published by *Shibasaki*, who worked with BINAP-like, atropisomeric arsine ligands.[10] We have introduced a diphenylarsino center into chiral aliphatic systems using an appropriate organic bromide **9** and lithium diphenylarsenide.[19,20] It is noteworthy that the organoarsines with phenyl groups are more stable than the corresponding phosphines, although the tendency of the higher homologues to be oxidized increases in the case of aliphatic substituents.[21] The known optically pure (*S*)-prolinol bismesylate[22] gave the *N*-protected bromide **9** by *Finkelstein* reaction which afterwards was converted into the new ligand (*S*)-Ms-ProDPAs **10**.



9 **10**

Scheme 3

With this As,N ligand in hand we obtained the protected epibatidine **4** in 92% yield. Unfortunately, the asymmetric induction was low (11 % ee). The results of further studies on arsine ligands, in particular with chiral backbones, will be published soon.

Acknowledgment

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(11) *General procedure for hydroarylation reactions:* 5.6 mg (25 µmol) palladium(II) acetate and 55 µmol of the arsine ligand were dissolved in 1.5 ml dry dimethylsulfoxide and stirred at 65 °C for 15 min. 1.00 mmol of the bicyclic alkene, 1.50 mmol of the aryl compound, 488 µl (3.60 mmol) triethylamine, and 3.00 mmol of formic acid were added rapidly in one portion. After stirring until conversion was completed (usually 2 hrs) the reaction mixture was partioned between water and ethyl acetate. The aqueous layer was extracted three times with ethyl acetate. The resulting organic layer was dried over magnesium sulfate and the solvent finally evaporated. The crude products **4** - **8** were purified by flash column chromatography (SiO_2, 40-64 µm).
(12) With comparable amounts of triphenylphosphine **7** was obtained in 18% yield: J. Klinge, Diploma thesis, TU Clausthal 1997. The aforementioned conditions gave **8** in 50% yield: H.-M. Richter, Ph.D. thesis, TU Clausthal 1998.
(13) *Selected data for the epibatidine analogs **5**, **7**, **8**, and the pyrrolidine-As,N ligand* **10**: *2-(6'-Chloro-3'-pyridyl)-nor-bornane* (**5**): m.p. 86 °C; R_f = 0.46 (SiO_2, petroleum ether/ AcOEt 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.15–1.65 (m, 7 H), 1.78 (ddd, J = 12.3, 9.0, 1.8 Hz, 1 H, 3-H_{endo}), 2.31 and 2.36 (s, 2 H, 1,4-H), 2.69 (dd, J = 8.8, 5.5 Hz, 1 H, 2-H_{endo}), 7.19 (d, J = 8.0 Hz, 1 H, 5'-$H_{pyridyl}$), 7.45 (dd, J = 8.0, 2.4 Hz, 1 H, 4'-$H_{pyridyl}$), 8.20 (d, J = 2.4 Hz, 1 H, 2'-$H_{pyridyl}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 28.6 (–), 30.3 (–), 35.9 (–), 36.8 (+), 38.9

(–), 42.6 (+), 44.2 (+), 123.6 (+, $C_{pyridyl}$-5'), 137.2 (+, $C_{pyridyl}$-4'), 141.5 ($C_{quat.}$, $C_{pyridyl}$-3'), 148.3 (+, $C_{pyridyl}$-2'), 148.7 ($C_{quat.}$, $C_{pyridyl}$-6'); MS (70 eV), *m/z (%)* = 207 (46) [M^+], 164 (11), 153 (7), 140 (100) [ClPy–CH=CH_2^+], 127 (27), 114 (12), 104 (16); HRMS $C_{12}H_{14}ClN$ requires: 207.0815; found: 207.0815. *N-(Methoxycarbonyl)-2,3-benzo-5-(6'-chloro-3'-pyridyl)-7-aza-bicyclo[2.2.1]hept-2-ene* (**7**): m.p. 165 °C; R_f = 0.28 (SiO_2 petroleum ether/AcOEt 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.98 (dd, J = 11.7, 8.7 Hz, 1 H, 6-H_{endo}), 2.13 (dd, J = 12.2, 4.6 Hz, 1 H, 6-H_{endo}), 2.85 (dd, J = 8.7, 4.1 Hz, 1 H, 5-H_{endo}), 3.60 (s, 3 H, OCH_3), 5.07 (br s, 1 H, 4-H), 5.33 (br s, 1 H, 1-H), 7.18–7.22 (m, 2 H, H_{aryl}), 7.28–7.36 (m, 3 H, H_{aryl}), 7.74 (dd, J = 8.3, 2.3 Hz, 1 H, 4'-$H_{pyridyl}$), 8.31 (d, J = 2.0 Hz, 1 H, 2'-$H_{pyridyl}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 37.9 (–, C–6), 42.7 (+, C–5), 52.7 (+, OMe), 61.3 (+, C-1), 67.0 (+, C-4), 119.9 and 120.2 (+, 2 C, C_{aryl}), 124.3 (+, $C_{pyridyl}$-5'), 126.9 and 127.1 (+, 2 C, C_{aryl}), 137.3 (+, $C_{pyridyl}$-4'), 138.6 ($C_{quat.}$, $C_{pyridyl}$-3'), 144.8 and 145.4 ($C_{quat.}$, 2 C, C-2,3), 149.0 (+, $C_{pyridyl}$-2'), 149.7 ($C_{quat.}$, $C_{pyridyl}$-6'), 156.5 ($C_{quat.}$, C=O); MS (70 eV), *m/z (%)* = 15 (100) [M^+ +1], 176 (26) [M^+ –ClPy–CH=CH_2^+], 140 (18) [ClPy–CH=CH_2^+]; HRMS $C_{17}H_{15}ClN_2O_2$ requires: 314.0822; found: 314.0822. *2-(6'-Chloro-3'-pyridyl)-7-oxabicyclo[2.2.1]heptane* (**8**): m.p. 74.5 °C; R_f = 0.32 (SiO_2, petroleum ether/AcOEt 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.48–1.84 (m, 5 H), 2.09 (dd, J = 12.2, 8.9 Hz, 1 H, 3-H_{endo}), 2.88 (dd, J = 8.9, 4.5 Hz, 1 H, 2-H_{endo}), 4.38–4.42 (m, 1 H, 1-H), 4.68–4.78 (m, 1 H, 4-H), 7.23 (d, J = 8.2 Hz, 1 H, 5'-$H_{pyridyl}$), 7.67 (dd, J = 8.2, 2.4 Hz, 1 H, 4'-$H_{pyridyl}$), 8.23 (d, J = 2.4 Hz, 1 H, 2'-$H_{pyridyl}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 29.5 (–), 30.1 (–), 41.8 (–), 45.6 (+), 76.3 (+), 82.3 (+), 124.2 (+, $C_{pyridyl}$-5'), 137.5 (+, $C_{pyridyl}$-4'), 140.8 ($C_{quat.}$, $C_{pyridyl}$-3'), 148.5 (+, $C_{pyridyl}$-2'), 149.2 ($C_{quat.}$, $C_{pyridyl}$-6'); MS (70 eV), *m/z (%)* = 209 (22) [M^+], 180 (7) [M^+–C_2H_5], 165 (100), 130 (45); HRMS $C_{11}H_{12}ClNO$ requires: 209.0607; found: 209.0607.*(S)-2-(Diphenylarsinomethyl)-1-methylsulfonyl-pyrrolidine, (S)-Ms-ProDPAs* (**10**): 500 mg (64%); m.p. 97 °C; R_f = 0.23 (SiO_2, petroleum ether/AcOEt 2:1); $[\alpha]_D^{23}$ = –104.2° (c = 1.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.77–2.09 (m, 4 H, CH_2CH_2), 2.20 (dd, J = 12.7, 10.7 Hz, 1 H, *H*CHAs), 2.72 (s, 3 H, SO_2CH_3), 2.77 (dd, J = 12.7, 3.7 Hz, 1 H, HC*H*As), 3.29–3.42 (m, 2 H, NCH_2), 3.85–3.93 (m, 1 H, NC*H*), 7.28–7.38 (m, 6 H, H_{aryl}), 7.40–7.45 (m, 2 H, H_{aryl}), 7.51–7.56 (m, 2 H, H_{aryl}); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.7 and 32.7 (–, 2 C, CH_2CH_2), 35.4 (–, CH_2As), 35.7 (+, SO_2Me), 48.9 (–, NCH_2), 58.9 (+, CHN), 128.4, 128.6, 128.7, 132.8, and 133.2 (+, 10 C, C_{aryl}), 138.9 and 140.3 ($C_{quat.}$, 2 C, C_{aryl}); $C_{18}H_{22}AsNO_2S$ (391.36): calcd. C 55.24 H 5.67 N 3.58 S 8.19 found C 55.33 H 5.79 N 3.30 S 8.00.

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