SYNTHESIS OF VARIOUS SUBSTITUTED BENZO[*c*]-2,7-NAPHTHYRIDINES AND AN APPROACH TOWARDS THE SKELETON OF MERIDINE. CONSIDERATIONS ABOUT THE EFFECT OF COPPER (II)OXIDE

Patrick Björk, Johan Malm, Anna-Britta Hörnfeldt, and Salo Gronowitz*

Organic Chemistry 1, Chemical Center, University of Lund Box 124,
S-221 00 Lund, Sweden

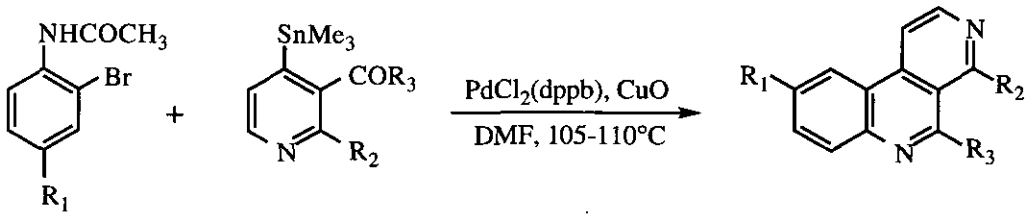
Abstract -Derivatives of benzo[*c*]-2,7-naphthyridines have been prepared in good yields and in one step through the use of the Pd(0)-catalyzed cross couplings of 4-formyl- and 4-acetyl-3-pyridyltrimethylstannanes with *ortho*-bromoacetanilides. Perlolidine, an alkaloids present in perennial rye grass, was readily prepared in a few steps taking advantage of the cross coupling. An approach towards the pentacyclic ring skeleton of meridine has also been made, leading to several new derivatives of benzo[*c*]-2,7-naphthyridine. All cross couplings are greatly promoted by the addition of stoichiometric amounts of copper(II) oxide and a comparison with the use of other catalytic systems in the Pd(0)-catalyzed cross couplings is made.

In connection with our work on the effects of the mode of annelation on physical properties and reactivities of tricyclic heterocyclic systems with the phenanthrene annelation pattern, we have previously described convenient one-pot procedures involving Pd(0)-catalyzed cross couplings for the synthesis of phenanthrene, thieno[*b,c*]quinolines and isoquinolines, dithieno[*b,d*]pyridines and thieno[*b,c*]naphthyridines (for reviews cf. refs.[1,2]).

While preparing the 24 isomers of the thieno[*b* and *c*]-fused naphthyridines we experienced problems with Stille type reactions. We therefore introduced the concept of using a *co-reagent*, in an attempt to raise the yields in these reactions. Silver(I) oxide was the first co-reagent used and good results were obtained both regarding the reaction rate and the yield when applied to low yielding sluggish reactions. [3,4] The usefulness of silver(I) oxide as co-reagent has also been shown by other groups.[5,6] As the yields of the thieno[*b*]-fused naphthyridines[7] still were low, a large amount of other additives were tested whereby copper(II) oxide was found to be an even better co-reagent.[8-10]

The benzo[*c*]-2,7-naphthyridine system has during the last ten years been found in a number of marine natural products.[11] Considering our success in optimizing the synthesis of the thienonaphthyridines, it appeared to us that substituted benzo[*c*]-2,7-naphthyridines could easily be prepared according to the same methodology by a palladium(0)-catalyzed cross coupling of 4-trimethylstannyl-3-pyridinecarboxaldehyde and 2-bromoacetanilide. By varying substituents in these starting materials several substituted benzo[*c*]-2,7-naphthyridines could be prepared[12] (Scheme 1).

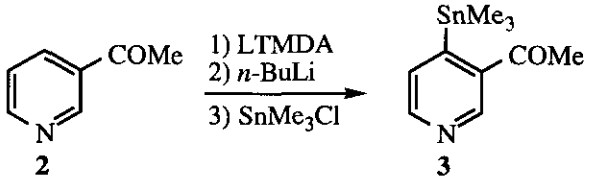
As this seemed to be a viable, high yielding approach, we tried to extend it towards the synthesis of pentacyclic marine natural products.[11] The most easily accessible of these seemed to be the skeleton of meridine. A similiar route towards these natural products was presented after our work began by Quéguiner *et al.*[13-16]



Scheme 1

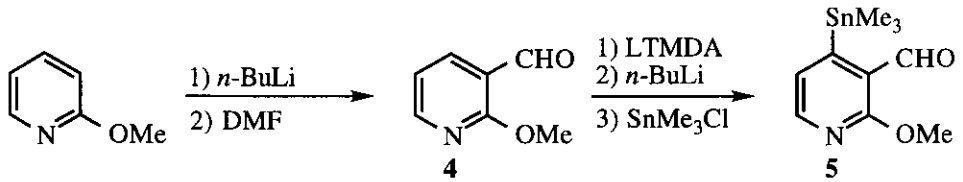
RESULTS AND DISCUSSION

The stannyl derivatives were prepared in one or two steps using convenient *ortho*-metalation techniques. 4-Trimethylstannyl-3-pyridinecarboxaldehyde (**1**) was prepared according to Kelly and Kim.[17] Similar technique using *N'*-lithio-*N,N,N'*-trimethylethylenediamine (LTMDA) as the *ortho*-directing agent was used to metalate 3-acetylpyridine (**2**). This seems to be an interesting extension of the Comins and Killpack[18] method, for the *ortho*-metalation of pyridinecarboxaldehydes, to acetylpyridines (Scheme 2).



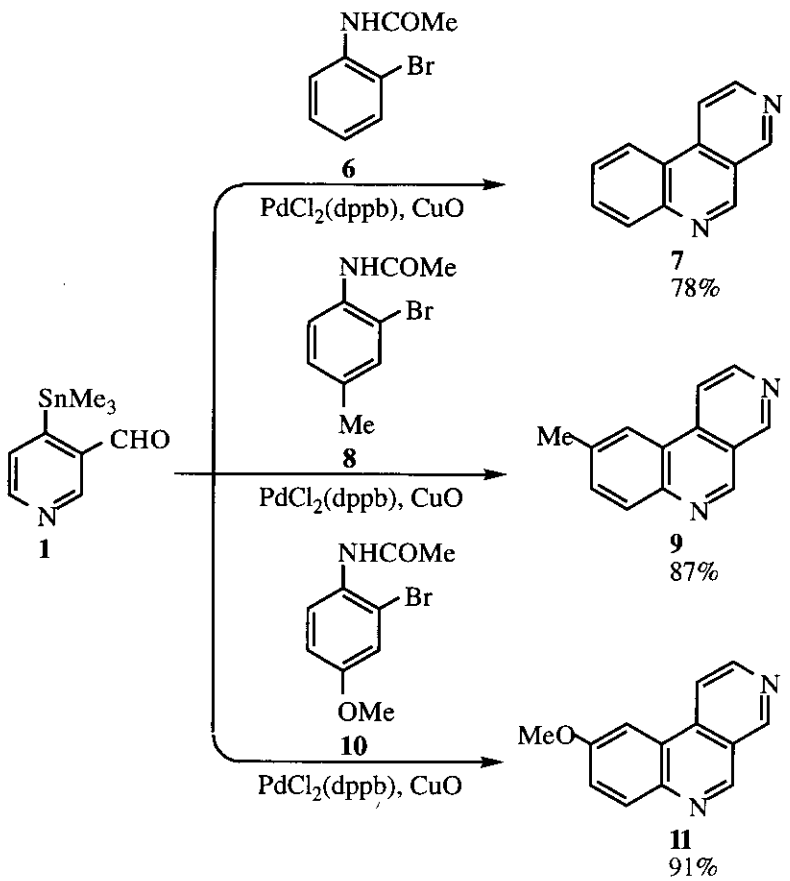
Scheme 2

2-Methoxy-3-pyridinecarboxaldehyde (**4**) was prepared according to literature[19] and then *ortho*-metalated with LTMDA[17,18] to give 2-methoxy-4-trimethylstannyl-3-pyridinecarboxaldehyde (**5**) (Scheme 3).



Scheme 3

The cross couplings were carried out in dimethylformamide, using dichloro[(1,4-bisdiphenylphosphino)-butane]palladium (II) as catalyst and copper(II) oxide as co-reagent. As a test of our copper(II) oxide approach identical runs where done, but with exclusion of the co-reagent. This led to lower yields and much longer reaction times and the comparative yields will be noted in the text. For the reactions to work

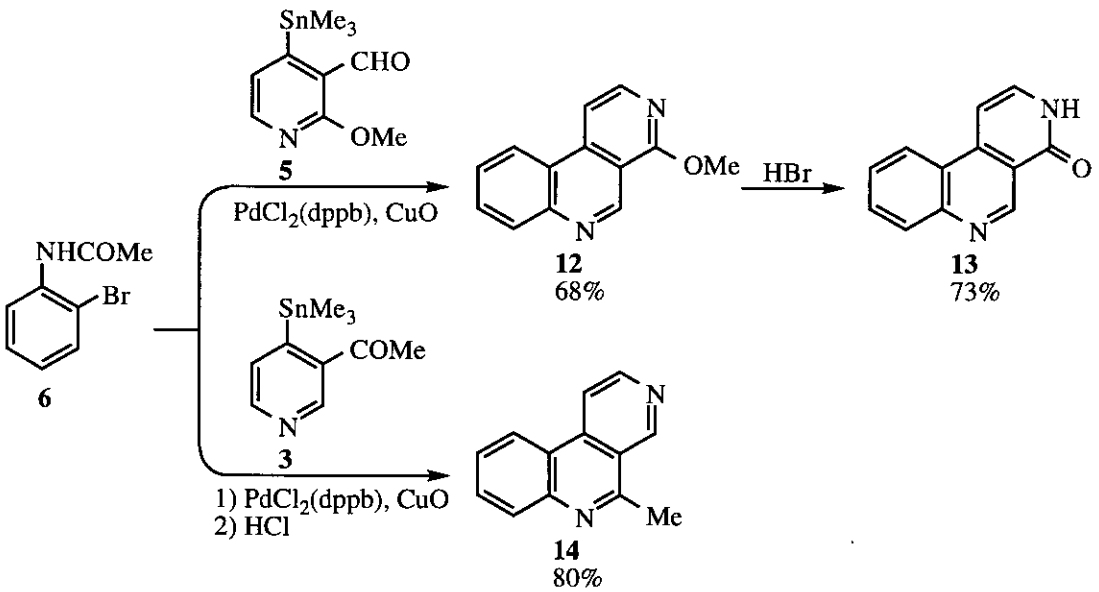


Scheme 4

effectively our normal cross coupling temperature of 100 °C was not high enough, instead we found that a temperature of 105-110 °C had to be used.[20]

2-Bromoacetanilide (**6**) and 4-trimethylstannyl-3-pyridinecarboxaldehyde (**1**) gave benzo[*c*]-2,7-naphthyridine (**7**) in a yield of 78 % while using copper(II) oxide, but only 43 % without it. It was also found that silver(I) oxide, our other co-reagent, had a deteriorating effect on the yield, only giving 18 % of **7**. 2-Bromo-4-methylacetanilide (**8**) and **1** gave 9-methylbenzo[*c*]-2,7-naphthyridine (**9**) in a yield of 87 %. 2-Bromo-4-methoxyacetanilide (**10**) and **1** gave 9-methoxybenzo[*c*]-2,7-naphthyridine (**11**) in 91 % yield in the presence of copper(II) oxide, while using no co-reagent gave a yield of 65 % (Scheme 4).

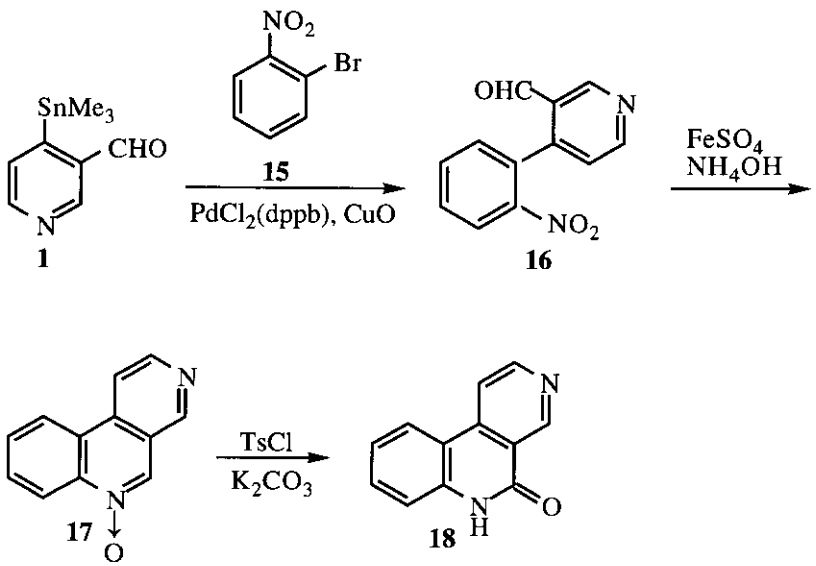
2-Bromoacetanilide (**6**) and 2-methoxy-4-trimethylstannyl-3-pyridinecarboxaldehyde (**5**) gave 4-methoxybenzo[*c*]-2,7-naphthyridine (**12**) in a yield of 68 % when using copper(II) oxide, without it the yield was only 17 %. Acid treatment of **12** induced hydrolysis to benzo[*c*]-2,7-naphthyridin-4(3*H*)-one (perlolidine) (**13**), an alkaloids present in perennial rye grass. [21-24] 2-Bromoacetanilide (**6**) and 4-trimethylstannyl-3-acetylpyridine (**3**) gave 5-methylbenzo[*c*]-2,7-naphthyridine (**14**) in a yield of 80 %, when using copper(II) oxide as co-reagent, but only 10 % without it (Scheme 5).



Scheme 5

In our approach towards the pentacyclic ring system which makes up the skeleton of meridine, we started with a cross coupling between **1** and bromo-2-nitrobenzene (**15**) using our normal copper(II) oxide methodology. The reaction gave us 4-(2-nitrophenyl)-3-pyridinecarboxaldehyde (**16**) in good yield. This biaryl was reductively ring closed by using ferrosulfate in aqueous ammonia,[25] to give benzo[*c*]-2,7-

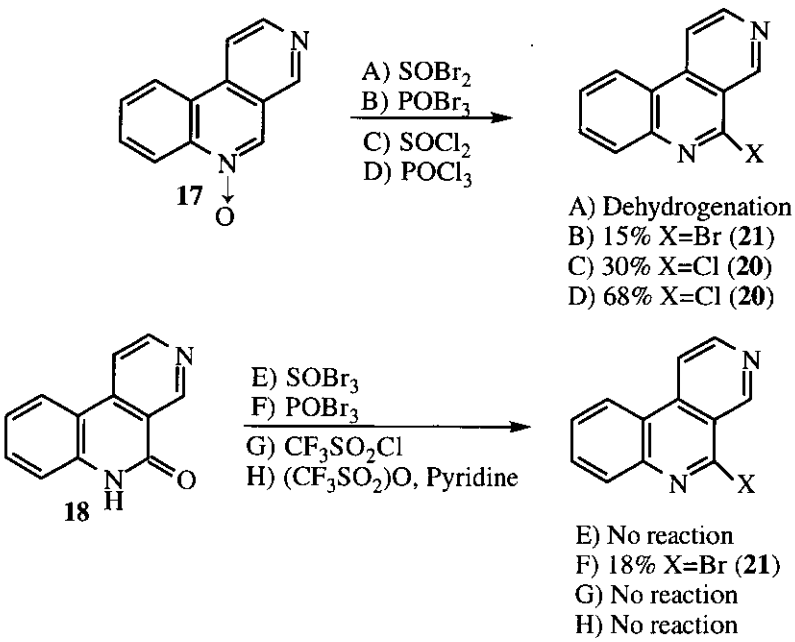
naphthyridine-6-oxide (**17**). This *N*-oxide could be converted to benzo[*c*]-2,7-naphthyridin-5(6*H*)-one (**18**)



Scheme 6

by reaction with *p*-toluenesulfonyl chloride and potassium carbonate in chloroform (Scheme 6).

However, problems were encountered when we tried to convert benzo[*c*]-2,7-naphthyridine 6-oxide (**17**)



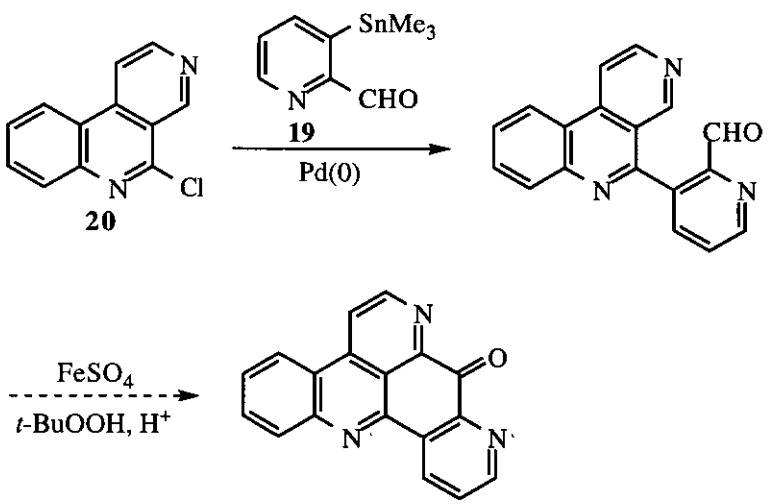
Scheme 7

and benzo[*c*]-2,7-naphthyridin-5(6I)-one (**18**) to 5-halo derivatives, suitable for cross coupling with 3-trimethylstannyl-2-pyridinecarboxaldehyde (**19**).[9] 5-Chlorobenzo[*c*]-2,7-naphthyridine (**20**) could be isolated in a yield of 68 % by reacting benzo[*c*]-2,7-naphthyridine 6-oxide (**17**) with phosphoryl chloride. The better cross coupling partner 5-bromobenzo[*c*]-2,7-naphthyridine (**21**) could only be isolated in 18 % from the reaction between benzo[*c*]-2,7-naphthyridin-5(6H)-one (**18**) and phosphoryl bromide. Attempts to prepare the triflate also failed giving none of the triflated compound (Scheme 7).

As only very low yields of 5-bromobenzo[*c*]-2,7-naphthyridine (**21**) could be obtained, we decided to continue with 5-chlorobenzo[*c*]-2,7-naphthyridine (**20**) as the coupling partner for 3-trimethylstannyl-2-pyridinecarboxaldehyde (**19**). We had some hopes about this reaction as we had previously managed to couple 2-tributylstannylpyridine and 4-chloropyridine in 44 % yield[8] and 2-chloro-3-pyridine-carboxaldehyde *N*-oxide with *t*-butyl-*N*-(2-bromo-3-thienyl)carbamate in 35 % yield.[26] This time though, our approach using copper(II) oxide as co-reagent failed utterly, giving us none of the desired coupled product.

We therefore sought to find other conditions which could manage to execute this coupling. Couplings were tried with slow addition of the tin derivative to avoid its decomposition, at elevated temperatures in boiling dimethylformamide, with dichloro[(1,3-bisdiphenylphosphino)propane] nickel(II)as catalyst[27,28] and with tris(dibenzylideneacetone)dipalladium(0) as catalyst and tri-2-furylphosphine as ligand,[29] but none of these conditions were able to make 5-chlorobenzo[*c*]-2,7-naphthyridine (**20**) to react.

To see if the reason for the inertness in the coupling was due to steric hindrance, we attempted to cross

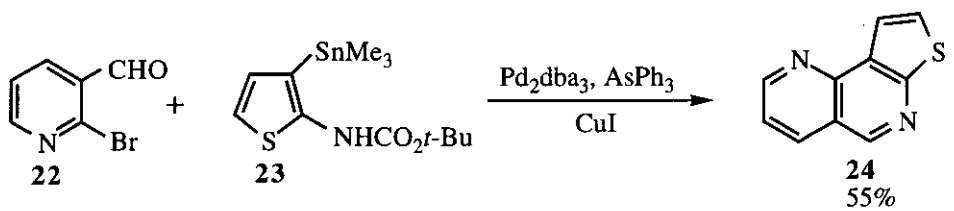


Scheme 8

couple **20** with 2-trimethylstannylpyridine, but no product was formed. An attempt to convert the chloro compound to the iodide with acetyl iodide[30] also failed. The final step would otherwise have been a radical ring closure,[31] but this remains yet to be tried (Scheme 8).

This work, though not leading to the desired target compound, still shows the tremendous utility of the copper(II) oxide co-reagent concept as a way of achieving good yields in Stille type cross coupling reactions. The question is of course if this is the same kind of "copper effect" which has been observed and studied by Liebeskind,[32] Echavarren[33] and others.[34] In a recent paper by Farina *et al.*[35] an attempt has been made to explain the effect of copper(I) iodide in Stille cross couplings. Two mechanistic proposals were made about its role. The role of copper could be to scavenge free ligands which hinder the transmetalation, in this case the ratio ligand:copper(I) iodide would be of importance with a maximum found at 20 %:10 %. This mechanism was found to be applicable only for ethereal solvents. This first proposal seems unlikely for our approach as we use stoichiometric amounts of copper(II) oxide, which according to Farina *et al.* would extract ligand from the catalyst and cause it to decompose. We are also using a non-ethereal solvent. The other role of copper(I) iodide could be a Sn/Cu transmetalation, where the formed organocuprate then would transmetalate to palladium. This second proposal was only found to be feasible in highly polar solvents (NMP) and in the absence of strong ligands. Trying to apply this idea on our own methodology, we find that this second proposal falls as we use phosphines which are strong ligands instead of arsines. The comparison between the catalytic systems is probably difficult to make as our methodology gives rise to a highly heterogenic system. One can also wonder how much the difference in oxidation states matters.

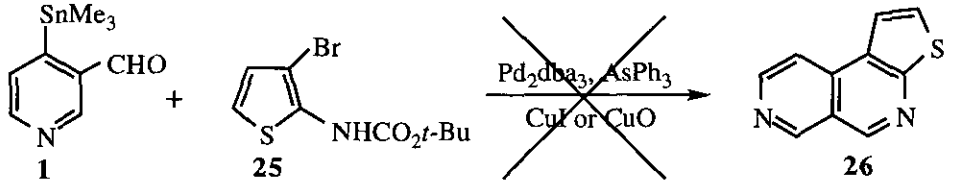
In an attempt to see if copper(I) iodide was as effective as copper(II) oxide in making our type of compounds, we reacted 2-bromo-3-pyridinecarboxaldehyde (**22**) with *t*-butyl-*N*-(3-trimethylstannyl-2-thienyl)carbamate (**23**). This gave a 55 % yield of thieno[2,3-*b*]-2,5-naphthyridine (**24**), which is comparable with what we obtained using copper(II) oxide[10] (Scheme 9).



Scheme 9

We also tried copper(I) iodide in the more sluggish and unfavourable reaction between 4-trimethyl-

stannyl-3-pyridinecarboxaldehyde (**1**) and *t*-butyl-*N*-(3-bromo-2-thienyl)carbamate (**25**) and did not obtain any of the desired thieno[2,3-*b*]-2,7-naphthyridine (**26**). By using $PdCl_2$(dppb) as catalyst and CuO as co-reagent compound (**26**) was obtained in 25 % yield.[9] In an attempt to react **1** with **25** using Pd_2dba_3, $AsPh_3$ as catalyst and either CuI or CuO as co-reagent instead of copper(I) iodide, no product was obtained (Scheme 10).



Scheme 10

EXPERIMENTAL

The nmr spectra were recorded on a Varian XL-300 spectrometer. The mass spectra were recorded on a JEOL JMS SX 102 spectrometer (70 eV). The ir spectra were taken on a Perkin-Elmer 298 spectrophotometer. All melting points are uncorrected.

Tetrahydrofuran and ether used were distilled over sodium wire and benzophenone. Chloroform was distilled over phosphorous pentoxide prior to use. Petroleum ether (60-70), ethyl acetate, dimethylformamide, *n*-heptane and dichloromethane were distilled over 4 Å molecular sieves prior to use. The substances were purified by flash-chromatography on Merck silica gel 60 (0.040-0.063 mm) or by chromatography on a silica gel Dynamax HPLC column, 500x10 mm. Tlc analyses were done on Merck silica 60 F_{254} precoated aluminium sheets. All coupling reactions and *ortho*-metalation reactions were performed under nitrogen. *N,N,N'*-Trimethylethylenediamine and 1-bromo-2-nitrobenzene were purchased from Janssen. Trimethyltin chloride, 3-acetylpyridine and *p*-toluenesulfonyl chloride were purchased from Aldrich. Triphenylarsine, phosphoryl chloride, phosphoryl bromide and ferrous sulfate heptahydrate were purchased from Merck. Copper(I) iodide[36] was purchased from BDH. The catalysts, dichloro[1,4-bis(diphenylphosphino)butane]palladium(II)[37] and tris(dibenzylideneacetone)dipalladium(0) chloroform,[38] and the organic compounds, 2-methoxy-3-pyridinecarboxaldehyde (**4**),[39] 2-bromoacetanilide (**6**)[40], 4-trimethylstannyl-3-pyridinecarboxaldehyde (**1**),[17] 2-bromo-4-methylacetanilide (**8**),[40] 2-bromo-4-methoxyacetanilide (**10**),[41] 2-bromo-3-pyridinecarboxaldehyde,[42,43] *t*-butyl-*N*-(3-tri-methylstannyl-2-thienyl)carba-

mate (**23**)[10] and *t*-butyl-*N*-(3-bromo-2-thienyl)carbamate[44] (**25**) were prepared according to published procedures.

4-Trimethylstannyl-3-pyridyl methyl ketone (3).

To a stirred solution of *N,N,N'*-trimethylethylenediamine (1.55 ml, 12.2 mmol) in anhydrous tetrahydrofuran (25 ml), butyllithium (6 ml, 11.5 mmol, 1.92 M in cyclohexane) was added at -78 °C. After 15 min, 3-acetylpyridine (1.2 g, 9.9 mmol) was added, the mixture was stirred at -78 °C for 15 min, butyllithium (11.0 ml, 21.1 mmol, 1.92 M in cyclohexane) was added and the stirring was continued for 2 h at -42 °C. After cooling to -78 °C, trimethyltin chloride (4.2 g, 21.2 mmol) in anhydrous tetrahydrofuran (25 ml) was added over a couple of minutes. The reaction mixture was allowed to attain room temperature overnight, quenched with saturated cold brine (50 ml) and extracted with ether (3x80 ml). The organic phase was dried over potassium carbonate and concentrated at reduced pressure. The crude product was purified by hplc using chloroform/2-propanol (99:1) as eluent, leaving 1.30 g (46 %) of the title compound as a pale yellow oil. Ir (film): 2950, 2910 (CH), 1740 (CO); ^{1}H nmr ($CDCl_3$): δ 0.28 (s, 9H, CH_3), 2.71 (s, 3H, $COCH_3$), 7.66 (dd, 1H, H_5, J = 0.9, 4.6 Hz), 8.67 (d, 1H, H_6, J = 4.6 Hz), 9.20 (d, 1H, H_2, J = 0.9 Hz; ms: m/z (%) 270 (100, M^+-CH_3), 268 (75, M^+-CH_3-2), 264 (40), 240 (60), 238 (50), 236 (30). HRms found: 286.0247; calcd for $C_{10}H_{15}NOSn$ $[M+H]^+$: 286.0253.

2-Methoxy-4-trimethylstannyl-3-pyridinecarboxaldehyde (5).

To a stirred solution of *N,N,N'*-trimethylethylenediamine (1.35 ml, 10.6 mmol) in anhydrous tetrahydrofuran (30 ml), butyllithium (5.04 ml, 9.7 mmol, 1.92 M in cyclohexane) was added at -78 °C. After 15 min, 2-methoxy-3-pyridinecarboxaldehyde (**4**) (1.21 g, 8.8 mmol) was added, and the mixture was stirred at -78 C° for 15 min, butyllithium (9.17 ml, 17.6 mmol, 1.92 M in cyclohexane) was added and the stirring was continued for 3 h at -42 °C. After cooling to -78 °C, trimethyltin chloride (3.67 g, 18.5 mmol) in anhydrous tetrahydrofuran (20 ml) was added over a couple of min. The reaction mixture was allowed to reach room temperature, quenched with cold brine (50 ml) and extracted with ether (3x60 ml). The organic phase was dried over potassium carbonate and concentrated at reduced pressure. The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (95:5) as eluent, leaving 1.40 g

(53%) of the title compound as a pale yellow oil. Ir (film): 2950, 2910, 2870 (CH), 1730 (CO); ^{1}H nmr ($CDCl_3$): δ 0.27 (s, 9H, CH_3), 4.06 (s, 3H, OCH_3), 7.21 (dd, 1H, H_5, J = 0.9, 4.7 Hz), 8.29 (d, 1H, H_6, J = 4.7 Hz), 10.44 (d, 1H, CHO, J = 0.9 Hz); ms: m/z (%) 286 (100, M^+-CH_3), 284 (85, M^+-CH_3-2), 282 (80, M^+-CH_3-4), 256 (80), 254 (60), 254 (40). HRms found: 302.0205; calcd for $C_{10}H_{15}NO_2Sn$ $[M+H]^+$: 302.0203.

General procedure for the palladium catalyzed coupling reactions (preparation of compounds 7, 9, 11, 12 and 14).

A mixture of the appropriate halogen compound (1.0 mmol), dichloro[1,6-bis(diphenylphosphino)-butane]palladium(II) (30 mg, 0.05 mmol) and copper(II) oxide (80 mg, 1.0 mmol) in dimethylformamide (4 ml) was stirred at 105-110°C. After 1 min the appropriate tin compound (1.5 mmol) dissolved in dimethylformamide (1 ml) was added. After the halogen compound was consumed, the reaction mixture was allowed to attain room temperature, the precipitate was filtered off and the filtrate was concentrated at reduced pressure. The residue was subjected to hplc-chromatography. Eluents for the chromatography are given below.

Benzo[c]-2,7-naphthyridine (7).

This compound was obtained by the coupling of 2-bromoacetanilide (**6**) (214 mg, 1.0 mmol) with 4-trimethylstannyl-3-pyridinecarboxaldehyde (**1**) (405 mg, 1.5 mmol). After 1 h the reaction was stopped, worked up as above and subjected to chromatography using first chloroform/2-propanol (95:5) and then chloroform/2-propanol (97:3) as eluent. This gave 141 mg (78%) of the title compound with identical spectroscopic properties as the known compound.[45] mp: 145-146 °C (lit.,[45] mp 140-142 °C).

9-Methylbenzo[*c*]-2,7-naphthyridine (9).

This compound was obtained by the coupling of 2-bromo-4-methylacetanilide (**8**) (228 mg, 1.0 mmol) with 4-trimethylstannyl-3-pyridinecarboxaldehyde (**1**) (405 mg, 1.5 mmol). After 1.5 h the reaction was stopped, worked up as above and subjected to chromatography using chloroform/2-propanol (90:10) as eluent. This gave 168 mg (87 %) of the title compound with identical spectroscopic properties as the known

compound.[46] mp: 187-189 C°(lit.,[46] mp 187-189 °C).

9-Methoxybenzo[c]-2,7-naphthyridine (11).

This compound was obtained by coupling of 2-bromo-4-methoxiacetanilide (**10**) (244 mg, 1.0 mmol) with 4-trimethylstannyl-3-pyridinecarboxaldehyde (**1**) (405 mg, 1.5 mmol). After 2 h the reaction was stopped, worked up as above and subjected to chromatography using chloroform/2-propanol (95:5) as eluent. This gave 191 mg (91 %) of the title compound with identical spectroscopic properties as the known compound.[46] mp: 145-146 °C (lit.,[46] mp 144-146°C).

4-Methoxybenzo[*c*]-2,7-naphthyridine (12).

This compound was obtained by coupling of 2-bromoacetanilide (**6**) (214 mg, 1.0 mmol) with 2-methoxy-4-trimethylstannyl-3-pyridinecarboxaldehyde (**5**) (453 mg, 1.5 mmol). After 2 h the reaction was stopped, worked up as above and subjected to chromatography using chloroform/2-propanol (95:5) as eluent. This gave 143 mg (68 %) of the title compound as white crystals. mp: 139-141 °C; ^{1}H nmr ($CDCl_3$): δ 7.68-8.25 (m, 3H, H_8-H_{10}), 7.93 (d, 1H, H_1, J = 5.9 Hz), 8.43 (d, 1H, H_2, J = 5.9 Hz), 8.49 (m, 1H, H_7), 9.67 (s, 1H, H_5); ^{13}C nmr (DMSO-d_6): δ 59.28, 115.20, 129.28, 132.94, 134.93, 151.8, 166.52; ms: m/z (%) 210 (100, M^+), 209 (56, M^+-1), 181 (33), 180 (27), 179 (28). HRms found: 210.0793; calcd for $C_{13}H_{10}N_2O$ $[M]^+$: 210.0793.

Benzo[*c*]-2,7-naphthyridine-4(3*H*)-one (Perlolidine) (13).

A mixture of 4-methoxybenzo[*c*]-2,7-naphthyridine (100 mg, 0.476 mmol) (**12**) and aqueous hydrobromic acid (1 ml, 48 %) was stirred at room temperature for 90 min. The reaction mixture was neutralized with a saturated solution of sodium hydrogen carbonate and left in the refrigerator overnight. The crude product was collected by filtration and recrystallized from ethanol. This gave 68 mg (73 %) of the title compound with identical spectroscopic properties as the known compound.[13] mp: >300 °C (lit., mp[24] 336-340 °C).

5-Methylbenzo[*c*]-2,7-naphthyridine (14).

This compound was obtained by the coupling of 2-bromoacetanilide (**6**) (214 mg, 1.0 mmol) with 4-trimethylstannyl-3-pyridyl methyl ketone (**3**) (429 mg, 1.5 mmol). After 2 h hydrochloric acid (5 ml, 2 M)

was added to the reaction mixture, which was heated at 100 °C for 1 h, allowed to reach room temperature and neutralized with sodium hydroxide solution (5 ml, 2 M). The reaction mixture was then worked up as above and subjected to chromatography using chloroform/2-propanol (95:5) as eluent. This gave 155 mg (80 %) of the title compound with identical spectroscopic properties as the known compound.[47] mp: 116-117 °C (lit.,[47] mp 110-112 °C).

4-(2-Nitrophenyl)-3-pyridinecarboxaldehyde (16).

A mixture of 1-bromo-2-nitrobenzene (2.26 g, 11.2 mmol) (**15**), dichloro[1,4-bis(diphenylphosphino)-butane]palladium(II) (336 mg, 0.56 mmol) and copper(II) oxide (896 mg, 11.2 mmol) in dimethylformamide (56 ml) was stirred at 110 °C under nitrogen. After 5 min, 4-trimethylstannyl-3-pyridinecarboxaldehyde (**1**) (4.2g, 15.6 mmol) in dimethylformamide (14 ml) was added all at once to the reaction mixture. After 90 min, the reaction mixture was allowed to reach room temperature, the precipitate was filtered off and the filtrate was evaporated. Flash-chromatography of the residue, using heptane/ethyl acetate (50:50) as eluent, gave 2.02 g (79 %) of the title compound as white crystals. mp: 98-100 °C; ir (KBr): 1690 (CO), 1525, 1345 (NO_2); ^{1}H nmr ($CDCl_3$): δ 7.23 (d, 1H, H_5 pyridine, J = 5.1 Hz), 7.28-8.27 (m, 4H, H_3-H_6 benzene), 8.86 (d, 1H, H_6 pyridine, J = 5.1 Hz), 9.14 (s, 1H, H_2 pyridine), 9.96 (s, 1H, CHO); ^{13}C nmr (DMSO-d_6): δ 129.67, 129.97, 135.35, 136.81, 139.20, 158.22, 159.30, 197.10; ms (CI-NH_3): 229 (100, M+H$^+$). HRms found: 229.0607; calcd for $C_{12}H_9N_2O_3$ [M+H]$^+$: 229.0613.

Benzo[*c*]-2,7-naphthyridine 6-oxide (17).

A 50 ml three-necked flask equipped with condenser and mechanical stirrer was charged with 4-(2-nitrophenyl)-3-pyridinecarboxaldehyde (**16**) (300 mg, 1.32 mmol), water (9 ml), ferrous sulfate (3.67 g, 13.2 mmol) and hydrochloric acid (2 ml, 12 M). The reaction mixture was heated at 100 °C. After 5 min the temperature was lowered to 60 °C, aqueous ammonia (11 ml, 25 %) was added and the reaction mixture was stirred for 1 h. The reaction mixture was extracted with chloroform, using an apparatus for continuous extraction. The chloroform extract was evaporated and the residue was subjected to flash-chromatography using dichloromethane/methanol (95:5) as eluent. This gave 190 mg (73 %) of the title compound as white crystals. mp: 190-194°C; ^{1}H nmr ($CDCl_3$): δ 7.86-8.63 (m, 3H, H_8-H_{10}), 8.27 (d, 1H, H_1, J = 5.7 Hz), 8.85 (d, 1H, H_2, J = 5.7 Hz), 8.94 (s, 1H, H_5), 8.97 (m, 1H, H_7), 9.16 (s, 1H, H_4); ^{13}C nmr (DMSO-d_6): δ 121.00, 125.08, 129.88, 135.21, 137.17, 152.47, 154.27; ms: m/z (%) 196 (100, M$^+$), 180

(50, M^+-O), 168 (45), 140 (40). HRms found: 196.0638; calcd for $C_{12}H_8N_2O$ $[M]^+$: 196.0637.

Benzo[*c*]-2,7-naphthyridin-5(6*H*)-one (18).

Benzo[*c*]-2,7-naphthyridine 6-oxide (**17**) (196 mg, 1.0 mmol), potassium carbonate (5 ml, 10 % solution) and 10 ml of chloroform were mixed, whereupon *p*-toluenesulfonyl chloride (230 mg, 1.2 mmol) was added. The reaction mixture was shaken for 8 h at room temperature. The product was filtered off, washed with water, taken up in anhydrous ether (5 ml) and dried over magnesium sulfate. This gave 134 mg (68 %) of the title compound as white crystals. mp: 285-290 °C (lit.,[45] mp 300 decomp.); ^{1}H nmr (DMSO-d_6): δ 7.29-7.66 (m, 3H, H_8-H_{10}), 8.42 (br, 1H, H_1), 8.46 (m, 1H, H_7), 8.95 (br, 1H, H_2), 9.48 (br, 1H, H_4), 11.91 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 121.62, 127.83, 129.52, 137.09, 143.44, 155.40, 157.10; ms: m/z 196 (100, M^+), 195 (15, M^+-1), 168 (5), 140 (15). HRms found: 196.0634; calcd for $C_{12}H_8N_2O$ $[M]^+$: 196.0637.

5-Chlorobenzo[*c*]-2,7-naphthyridine (20).

Method C: Benzo[*c*]-2,7-naphthyridine 6-oxide (**17**) (98 mg, 0.5 mmol) and 1.25 ml of thionyl chloride were mixed and stirred at room temperature for 12 h. The reaction mixture was cooled in an ice bath and neutralized with saturated acqueous sodium bicarbonate. The acqueous phase was extracted with chloroform (3x30 ml), the combined chloroform phases were dried over magnesium sulfate and concentrated at reduced pressure. Flash chromatography of the residue, using chloroform/methanol (95:5) as eluent, gave 33 mg (30%) of the title compound as white crystals and 34 mg (38 %) of benzo[*c*]-2,7-naphthyridine. mp: 153-155 °C; ^{1}H nmr (DMSO-d_6): δ 7.78–8.12 (m, 3H, H_8-H_{10}), 8.89 (d, 1H, H_1, J = 5.5 Hz), 8.94 (m, 1H, H_7), 9.37 (d, 1H, H_2, J = 5.5 Hz), 9.91 (s, 1H, H_4); ^{13}C nmr (DMSO-d_6): δ 115.18, 126.89, 132.94, 134.93, 136.16, 150.94, 151.74; MS: m/z (%) 216 (30, M^++2), 214 (100, M^+), 179 (M^+-Cl), 152 (23). HRms found: 214.0296; calcd. for $C_{12}H_7N_2Cl$ $[M]^+$: 214.0298.

Method D: A mixture of 50 mg (0.25 mmol) of **16** and 2.5 ml (26 mmol) of phosphoryl chloride was stirred at room temperature for 12 h. The work-up procedure above was followed and the residue was subjected to chromatography using dichloromethane/methanol (97.5:2.5) as eluent. This gave 37 mg (68 %) of the title compound as white crystals. mp: 153-155 °C.

5-Bromobenzo[*c*]-2,7-naphthyridine (21).

Method A: A mixture of benzo[*c*]-2,7-naphthyridin-5(6*H*)-one (**18**) (50 mg, 0.25 mmol) and phosphoryl bromide (1.4 g, 5 mmol) were mixed in a sealed tube and heated at 160 °C for 24 h. The reaction mixture was neutralized with acqueous sodium bicarbonate and extracted with chloroform (3x30 ml). The combined chloroform phases were dried over magnesium sulfate and concentrated at reduced pressure. The residue was chromatographed using chloroform/methanol (90:10) as eluent, giving 12 mg (18 %) of the title compound and 22 mg (44 %) of recovered starting material. mp: 142-144 °C; ^{1}H nmr ($CDCl_3$): δ 7.75-8.20 (m, 3H, H_8-H_{10}), 8.34 (d, 1H, H_1, J = 5.7 Hz), 8.54 (m, 1H, H_7), 9.02 (d, 1H, H_2, J = 5.7), 9.76 (s, 1H, H_4, J = 1.2, 8.3); ms: m/z (%) 260 (66, M^++2), 258 (65, M^+), 179 (100, M^+-O), 152 (40), 125 (15). HRms found: 257.9796; calcd for $C_{12}H_7N_2Br$ $[M]^+$: 257.9793.

Method B: A mixture of benzo[*c*]-2,7-naphthyridine 6-oxide (**17**) (50 mg, 0.25 mmol) and phosphoryl bromide (1.4 g, 5 mmol) were mixed in a sealed tube and heated at 160 °C for 40 h. The work-up procedure above was followed and gave 10 mg (15 %) of the title compound.

Thieno[2,3-*b*]-2,5-naphthyridine (24).

The compound was prepared according to ref.[32] In a 25 ml round-bottomed flask equipped with a side arm nitrogen inlet were combined tris(dibenzylideneacetone)dipalladium(0) chloroform (15 mg, 0.025 mmol) and triphenylarsine (61 mg, 0.20 mmol) in 2 ml of dimethylformamide. After one min 2-bromo-3-pyridinecarboxaldehyde (**22**) (186 mg, 1.0 mmol) in 4 ml of dimethylformamide was added. The reaction was heated to 60 °C for 2 min and *t*-butyl-*N*-(3-trimethylstannyl-2-thienyl)carbamate (522 mg, 1.5 mmol) (**23**) in 3 ml of dimethylformamide was added followed by copper(I) iodide (95 mg, 0.5 mmol). After the halogen compound was consumed (2 h), the reaction mixture was allowed to attain room temperature, the precipitate was filtered off and the filtrate evaporated. The residue was subjected to chromatography using ethyl acetate/heptane (50:50) as eluent. After flash chromatography 103 mg (55 %) of the title compound was isolated, with identical spectroscopical properties as the known compound.[4]

Attempted preparation of thieno[3,2-c]-2,5-naphthyridine (26).

The compound was prepared according to the procedure above from *t*-butyl-*N*-(3-bromo-2-thienyl)-

carbamate (**25**) (278 mg, 1 mmol) and 4-trimethylstannyl-3-pyridinecarboxaldehyde (**1**) (405 mg, 1.5 mmol). After 6 h the starting materials were consumed, but the desired product could not be detected on glc or tlc.

In another attempt to prepare the compound copper(I) iodide was exchanged for copper(II) oxide (80 mg, 1 mmol), but otherwise the reaction was executed as above. After 4 h the starting materials were consumed, but the desired product could not be detected on glc or tlc.

ACKNOWLEDGEMENT

Grants from the Swedish National Science Research Council to S.G. and A.-B.H are gratefully acknowledged.

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Received, 19th February, 1996