Synthesis of Indolo[3,2-*c*]quinoline and Pyrido[3',2':4,5][3,2-*c*]quinoline Derivatives

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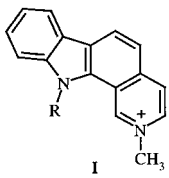
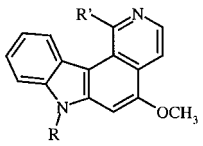
Abstract: Potential antitumoral scaffold indolo[3,2-*c*]quinoline **5a** was obtained by an intramolecular Heck cyclisation from the corresponding 2-iodophenyl-3-indolecarboxamide **4a**. The 7-azaindole analogue **5b** was prepared by the same approach. Triflate displacement of compounds **6** according to Suzuki and Stille reactions gave the 6-substituted derivatives **7**–**10**.

Key words: indole, 7-azaindole, palladium, cyclisation, quinoline

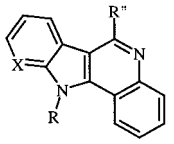
Ellipticine[1] has generated considerable interest because of its potent antitumoral activity in animals and humans. Numerous derivatives have been prepared and their biological activities described.[2,3] Among the structural variations[4] the pyridocarbazole backbone has been investigated. Thus, active 7*H* and 11*H*-pyridocarbazoles[5,6] derivatives **I** or benzocarbazoles[7] have been prepared. Recently compounds **II** have been reported[8] to show anti-HIV and antitumor activities.



I



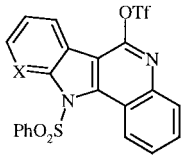
II



III X = CH
IV X = N

As a part of our program is devoted to the search of new anticancer agents,[9-12] we became interested in the preparation of 6-substituted indolo[3,2-*c*]quinoline **III** and 6-substituted pyrido[3',2':4,5][3,2-*c*]quinoline **IV** derivatives through triflates **6**. The latter were obtained from the corresponding amides **5**, which permitted us to introduce a wide range of substituents in position-6 via well-documented palladium-mediated cross-coupling reactions. We included the synthesis of aza-analogue **IV** since the 7-azaindole framework had not been studied as much as its indolic counterpart, despite its promising biological properties.[13-22]

Three general approaches to the synthesis of 11*H*-indolo[3,2-*c*]quinolin-6-one moiety **5** have been described in the literature so far. Photochemical cyclo-deshydrogenation of phenyl 1*H*-3-indolecarboxamide have been reported to generate 11*H*-indolo[3,2-*c*]quinolin-6-one in only



6a X = CH
6b X = N

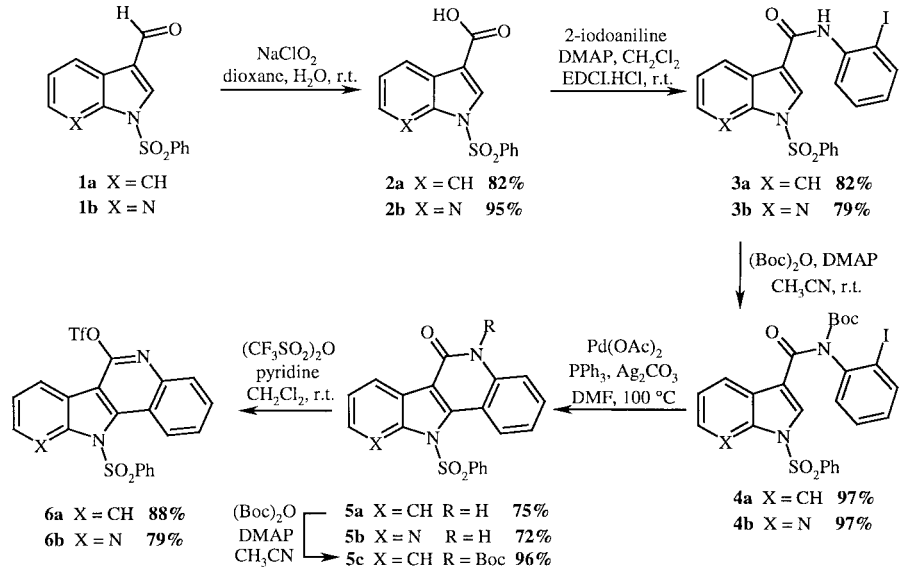
15% yield.[23] Alkylation of oxindole with 2-nitrobenzyl chloride after rearrangement produces three products, two of which possess the same 11*H*-indolo[3,2-*c*]quinoline structure.[24] Cyclisation of 2-(2-aminophenyl)indole occurred with phosgene[25] or in a carefully controlled acidic medium in the presence of benzoyl cyanide or acetyl cyanide[26] to give **5** or 6-phenyl or 6-methyl-11*H*-indolo[3,2-*c*]quinoline. None of these methods were considered satisfactory because of the moderate yields observed.

In addition, the recent publication of two papers concerning: (a) the carbonylative cyclisation of (*o*-aminophenyl)ethynyl derivatives[27] which afforded indolo[3,2-*c*]quinoline compounds of type **9a** in a two step procedure and (b) the synthetic utility of triflate derivatives of β-carbolines,[28] prompted us to report our own results.

We planned to generate the six-membered ring of the quinoline system by an intramolecular Heck reaction[29-32] of *N*-2-iodophenyl-3-indolecarboxamide **3a** and *N*-2-iodophenyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide **3b** prepared in two steps from easily available compounds **1a**–**b**.[33,34]

Compound **2a** was obtained from 1-phenylsulfonyl-3-formylindole **1a** by $NaClO_2$ oxidation in dioxane/water in 82% yield. Similarly, **2b** was prepared from 1-phenylsulfonyl-3-formylpyrido[2,3-*b*]pyridine **1b** in 95% yield. Amidification of **2a**–**b** with 2-iodoaniline in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (EDCI)/ 4-dimethylaminopyridine (DMAP) afforded the corresponding amides **3a**–**b** in 82% and 79% yield, respectively.

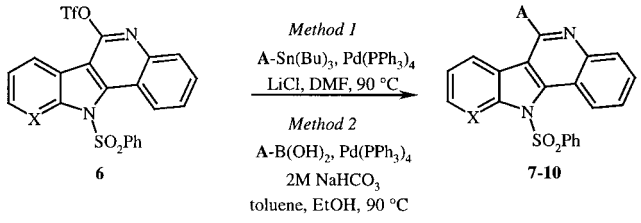
In order to prevent deiodination on the phenyl during the Heck reaction, amides **3a**–**b** were protected[35] with the Boc group to give **4a**–**b**, respectively. It was reported[36] that secondary amides react sluggishly compared to tertiary amides in Heck-type cyclisation. After much experimentation (amount of catalyst, base, ligand, reaction time), optimal cyclisation reactions were carried out on compounds **4a**–**b** with $Pd(OAc)_2$ (20%), triphenylphos-



Scheme 1

phine (40%) and silver carbonate (2 equivalents) in DMF at 100 °C for 24 hours to give tetracyclic derivatives **5a**–**b** in 75% and 72% yield, respectively. It should be noted that the use of less than 20% of $Pd(OAc)_2$ decreased the reaction yield and initial attempts to accomplish Heck reaction of **4** with triethylamine as base were completely unsuccessful. Loss of the Boc group was observed in this synthetic step (since the IR spectrum of **5a** did not show the NH vibration). Thus, **5a** was reacted with Boc_2O/DMAP/CH_3CN to obtain the *N*-Boc derivative **5c** which allowed to establish the presence of the NH bond. Cyclisation on position-2 of the indole ring and not on position-4 was confirmed by 2D-NMR experiments. It should be noted that no 3-spiro-2-oxindoles were formed as reported for palladium-catalysed intramolecular alkene arylation.[37]

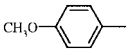
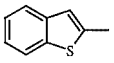
Introduction of the triflate group on compounds **5a**–**b** was accomplished using trifluoromethanesulfonic anhydride in dichloromethane in the presence of pyridine at room temperature to afford **6a**–**b** in good yields (88% and 79%, respectively). A range of palladium-catalysed couplings to **6** was examined to easily introduce various groups on position-6 of the tetracyclic structure (Scheme 2).



Scheme 2

Suzuki and Stille reactions afforded products **7**–**10** in good yields. Stille reaction of **6a** with (1-ethoxyvinyl)tributyltin (1.5 equivalents) in the presence of $Pd(PPh_3)_4$ (6%), LiCl (2.8 equivalents) in DMF at 90 °C for 1.5 hours gave compound **7a**. Similarly, coupling reactions between **6** and (2-furanyl)tributyltin afforded compounds **8a**–**b**. Suzuki reactions of **6** with 4-methoxyphenylboronic acid (1.5 equivalents) or 2-benzo[*b*]thiophene-2-boronic acid (1.5 equivalents) in the presence of $Pd(PPh_3)_4$ (6%) and 2 M aqueous $NaHCO_3$ as base, in a mixture of toluene/ethanol (5:1) at 90 °C for 2 hours afforded compounds **9** and **10**, respectively.

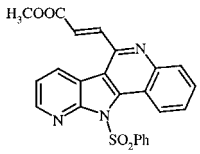
Table 1 Palladium-Catalysed Coupling Reactions of **6**

Method	A	Compound	Yield[a]
1		**7a**; X = CH	77%
1		**8a**; X = CH	76%
1		**8b**; X = N	72%
2		**9a**; X = CH	81%
2		**9b**; X = N	82%
2		**10a**; X = CH	96%
2		**10b**; X = N	89%

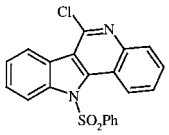
[a] Isolated yield of purified product.

Heck reaction between compound **6b** and methyl acrylate (1.5 equivalents) in the presence of $Pd(OAc)_2$ (20%), triphenylphosphine (40%) and silver carbonate (2 equivalents) was also performed in DMF at 100 °C for 3 hours to afford azadiene **11b** in 51% yield.

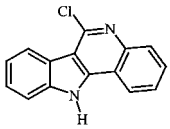
Finally, we tried to prepare potential anticancer agents through the introduction of an aminoalkyl chain on position-6, which is very often encountered in anticancer agents. Thus, 6-chloro derivative **12**, obtained after treat-



11b



12



13

ment of **5a** with $POCl_3$, was tentatively condensed with 2-(diethylamino)ethylamine to afford only unprotected compound **13**.[24] Palladium-catalysed aminations using Buchwald[38] or Hartwig[39] conditions are under progress to obtain the desired derivatives.

To sum up, we have established a convenient method to obtain indolo[3,2-*c*]quinoline **5a** or pyrido[3'2':4,5][3,2-*c*]quinoline **5b** structures through an intramolecular Heck reaction. The 6-substituted derivatives were obtained from the corresponding triflates **6** via Stille or Suzuki reaction.

Mps were determined on a Buchi SMP-20 melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in the indicated solvent on a Brüker Avance DPX250 (250 MHz for proton and 62.9 MHz for carbon). Chemical shifts for ^{1}H are given relative to internal TMS, while the ^{13}C chemical shifts were obtained with the solvent signal set to δ ($CDCl_3$) = 77.16 ppm and δ (DMSO-d_6) = 39.52 ppm. IR spectra were recorded in the range of 4000−600 cm^{-1} on a Perkin−Elmer spectrometer FT PARAGON 1000 PC. MS spectra were recorded under ion spray conditions on a Perkin−Elmer mass spectrometer SCIEX API 300. Column chromatographic separations were performed on Merck silica gel 60 (0.040−0.063 mm) using petroleum ether (40-60°C). Compounds **1a**[32] and **1b**[33] were prepared according to the reported methods. Mp, IR, MS, ^{1}H NMR and ^{13}C NMR data of prepared compounds **2**−**12** are reported in Tables 2−7.

1-Phenylsulfonylindole-3-carboxylic Acid (2a)

To a solution of 1-phenylsulfonyl-3-formylindole **1a** (400 mg, 1.4 mmol) in dioxane (15 mL)/ H_2O (5 mL) was added $NaClO_2$ (164 mg, 1.8 mmol) followed by sulfamic acid (774 mg, 8.0 mmol) at r.t. The reaction was almost instantaneous and was monitored by TLC. Saturated $NaHCO_3$ was added, with precaution, to the solution and then the reaction was stirred for a few minutes. The solution was concentrated and the residue was dissolved in EtOAc and washed with 10% HCl and H_2O. The organic layer was dried ($MgSO_4$) and evaporated in vacuo to give the crude product. Recrystallisation gave **2a** (345 mg, 82%) as white crystals.

1-Phenylsulfonylpyrrolo[2,3-*b*]pyridine-3-carboxylic Acid (2b)

The same procedure applied to **1b** gave **2b** in 95% yield.

***N*-(2-Iodophenyl)-1-(phenylsulfonyl)-1*H*-indole-3-carboxamide (3a)**

To a suspension of acid **2a** (200 mg, 0.7 mmol) in anhyd CH_2Cl_2 (10 mL) were added, successively, DMAP (161 mg, 1.3 mmol), 2-iodoaniline (219 mg, 1.0 mmol) dissolved in CH_2Cl_2 (2 mL), and EDCI•HCl (151 mg, 0.8 mmol) at 0 °C. The final solution was stirred overnight at r.t. After hydrolysis, the organic layer was dried

Table 2 Mp, IR and MS Data of Compounds **2**–**6**

Compound	Mp (°C)	IR (cm^{-1})	MS *m/z* (M$^+$+1)	Formula
2a	232 (MeOH/PE)	3200–2500 (OH), 1675 (CO)	302	$C_{15}H_{11}NO_4S$ (301.3)
2b	224 (MeOH/PE)	3200–2500 (OH), 1686 (CO)	303	$C_{14}H_{10}N_2O_4S$ (302.3)
3a	192 (Et_2O/PE)	3241 (NH), 1640 (CO)	503	$C_{21}H_{15}IN_2O_3S$ (502.3)
3b	216 (CH_2Cl_2/PE)	3252 (NH), 1637 (CO)	504	$C_{20}H_{14}IN_3O_3S$ (503.3)
4a	84 (Et_2O/PE)	1736 (CO), 1680 (CO)	603	$C_{26}H_{23}IN_2O_5S$ (602.4)
4b	96 (Et_2O/PE)	1737 (CO), 1683 (CO)	604	$C_{25}H_{22}IN_3O_5S$ (603.4)
5a	256 (MeOH/PE)	1667 (CO)	375	$C_{21}H_{14}N_2O_3S$ (374.4)
5b	252 (MeOH/PE)	1667 (CO)	376	$C_{20}H_{13}N_3O_3S$ (375.4)
5c	oil	1769 (CO), 1667 (CO)	475	$C_{26}H_{22}N_2O_5S$ (474.5)
6a	134 (Et_2O/PE)	1598, 1564, 1515, 1448, 1424, 1380, 1212	507	$C_{22}H_{13}F_3N_2O_5S_2$ (506.5)
6b	144 (Et_2O/PE)	1612, 1589, 1557, 1511, 1405, 1370, 1345, 1223	508	$C_{21}H_{12}F_3N_3O_5S_2$ (507.5)

Table 3 Yield, Mp, IR and MS Data of Compounds **7–12**

Compound	Yield	Mp (°C)	IR (cm^{-1})	MS *m/z* (M^++1)	Formula
7a	77%	120 (Et_2O/PE)	2957, 2925, 2854, 1654, 1560, 1447, 1378, 1311	429	$C_{25}H_{20}N_2O_3S$ (428.5)
8a	76%	198 (CH_2Cl_2/Et_2O)	1586, 1563, 1550, 1500, 1446, 1376, 1188	425	$C_{25}H_{16}N_2O_3S$ (424.5)
8b	72%	202 (CH_2Cl_2/PE)	1583, 1560, 1548, 1498, 1376, 1187	426	$C_{24}H_{15}N_3O_3S$ (425.5)
9a	81%	201 (Et_2O/PE)	1608, 1499, 1448, 1440, 1362, 1247, 1187, 1172	465	$C_{28}H_{20}N_2O_3S$ (464.5)
9b	82%	212 (Et_2O/PE)	1606, 1494, 1393, 1380, 1251, 1190, 1171	466	$C_{27}H_{19}N_3O_3S$ (465.5)
10a	96%	224 (CH_2Cl_2/PE)	1574, 1552, 1501, 1449, 1370, 1345, 1189, 1178	491	$C_{29}H_{18}N_2O_2S_2$ (490.6)
10b	89%	212 (CH_2Cl_2/PE)	1565, 1550, 1497, 1393, 1359, 1336, 1186	492	$C_{28}H_{17}N_3O_2S_2$ (491.6)
11b	51%	202 (CH_2Cl_2/PE)	1717 (CO), 1551, 1448, 1433, 1379, 1262, 1187	444	$C_{24}H_{17}N_3O_4S$ (443.5)
12	96%	152 (CH_2Cl_2/PE)	1562, 1503, 1443, 1374, 1347, 1185, 1176	393, 395	$C_{21}H_{13}ClN_2O_2S$ (392.9)

Table 4 ^{1}H NMR Data of Compounds **1–6**

Compound	^{1}H NMR (ppm) δ, *J* (Hz)
2a[a]	7.34–7.46 (m, 2 H, H_{Ar}), 7.60–7.77 (m, 3 H, H_{Ar}), 7.97–8.16 (m, 4 H, H_{Ar}), 8.38 (s, 1 H, H_2), 13.02 (br s, 1 H, OH)
2b[a]	7.41 (dd, 1 H, *J* = 4.8, 7.8, H_{Pyr}), 7.61–7.78 (m, 3 H, H_{Ar}), 8.23 (br d, 2 H, *J* = 8.2, H_{Ar}), 8.36 (d, 1 H, *J* = 7.8, H_{Pyr}), 8.42 (s, 1 H, H_2), 8.44 (d, 1 H, *J* = 4.8, H_{Pyr}), 13.14 (br s, 1 H, OH)
3a[b]	6.90 (t, 1 H, *J* = 7.5, H_{Ar}), 7.35–7.63 (m, 6 H, H_{Ar}), 7.83 (dd, 1 H, *J* = 1.3, 7.8, H_{Ar}), 7.95–8.04 (m, 3 H, H_{Ar}), 8.08 (br s, 1 H, NH), 8.21 (dd, 1 H, *J* = 1.9, 7.0, H_{Ar}), 8.24 (s, 1 H, H_2), 8.38 (dd, 1 H, *J* = 1.3, 8.2, H_{Ar})
3b[b]	6.62 (t, 1 H, *J* = 7.5, H_{Ar}), 6.99–7.14 (m, 2 H, H_{Ar} + H_{Pyr}), 7.23–7.39 (m, 3 H, H_{Ar}), 7.55 (dd, 1 H, *J* = 1.0, 7.8, H_{Ar}), 7.77 (br s, 1 H, NH), 7.99–8.07 (m, 3 H, H_{Ar}), 8.09 (s, 1 H, H_2), 8.23–8.28 (m, 2 H, H_{Pyr})
4a[b]	1.26 (s, 9 H, CH_3), 7.06–7.13 (m, 1 H, H_{Ar}), 7.30–7.60 (m, 7 H, H_{Ar}), 7.88–8.02 (m, 5 H, H_{Ar}), 8.05 (s, 1 H, H_2)
4b[b]	1.34 (s, 9 H, CH_3), 7.12 (br t, 1 H, *J* = 7.2, H_{Ar}), 7.25–7.34 (m, 2 H, H_{Ar}), 7.41–7.64 (m, 4 H, H_{Ar} + H_{Pyr}), 7.95 (br d, 1 H, *J* = 7.8, H_{Ar}), 8.15 (s, 1 H, H_2), 8.20 (br d, 2 H, *J* = 8.1, H_{Ar}), 8.36 (dd, 1 H, *J* = 1.6, 7.8, H_{Pyr}), 8.44 (dd, 1 H, *J* = 1.6, 4.7, H_{Pyr})
5a[a]	7.29–7.62 (m, 10 H, H_{Ar}), 8.19 (d, 2 H, *J* = 8.2, H_{Ar}), 8.55 (d, 1 H, *J* = 8.2, H_{Ar}), 12.16 (s, 1 H, NH)
5b[a]	7.32–7.71 (m, 7 H, H_{Ar} + H_{Pyr}), 7.90 (d, 2 H, *J* = 7.8 Hz, H_{Ar}), 8.42–8.51 (m, 3 H, H_{Ar} + H_{Pyr}), 12.26 (br s, 1 H, NH)
5c[b]	1.73 (s, 9 H, CH_3), 7.12–7.50 (m, 9 H, H_{Ar}), 7.26–7.56 (m, 1 H, H_{Ar}), 8.22–8.27 (m, 2 H, H_{Ar}), 8.81 (d, 1 H, *J* = 8.8, H_{Ar})
6a[b]	7.08–7.19 (m, 4 H, H_{Ar}), 7.33–7.40 (m, 1 H, H_{Ar}), 7.45–7.62 (m, 2 H, H_{Ar}), 7.71–7.86 (m, 2 H, H_{Ar}), 7.99 (br d, 1 H, *J* = 7.9, H_{Ar}), 8.13 (br d, 1 H, *J* = 8.1, H_{Ar}), 8.41 (br d, 1 H, *J* = 8.1, H_{Ar}), 9.08 (br d, 1 H, *J* = 8.5, H_{Ar})
6b[b]	7.37–7.44 (m, 3 H, H_{Ar} + H_{Pyr}), 7.51–7.58 (m, 1 H, H_{Ar}), 7.71–7.87 (m, 2 H, H_{Ar}), 7.91–7.96 (m, 2 H, H_{Ar}), 8.15 (dd, 1 H, *J* = 1.0, 8.2, H_{Ar}), 8.36 (dd, 1 H, *J* = 1.6, 7.9, H_{Pyr}), 8.60 (dd, 1 H, *J* = 1.6, 5.4, H_{Pyr}), 8.95 (dd, 1 H, *J* = 1.3, 8.5, H_{Ar})

[a] In DMSO-d_6.
[b] In $CDCl_3$.

($MgSO_4$) and evaporated. The crude residue was purified by flash chromatography on silica gel (CH_2Cl_2) to give **3a** (228 mg, 82%) as crystals.

***N*-(2-Iodophenyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide (3b)**
The same procedure applied to **2b** afforded **3b** in 79% yield.

***tert*-Butyl *N*-(2-Iodophenyl)-*N*-4{[1-(phenylsulfonyl)-1*H*-3-indolyl]carbonyl}carbamate (4a)**
A solution of amide **3a** (480 mg, 1.0 mmol), DMAP (117 mg, 1.0 mmol), Et_3N (0.14 mL, 1.0 mmol) and Boc_2O (251 mg, 1.2 mmol) in CH_3CN (15 mL) was stirred at r.t. for 16 h. The solvent was removed in vacuo. The crude residue was purified by flash chromatography on silica gel (PE/EtOAc, 1:3) to afford **4a** (560 mg, 97%) as crystals.

***tert*-Butyl *N*-(2-Iodophenyl)-*N*-4{[1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]carbonyl}carbamate (4b)**
The same procedure applied to **3b** afforded **4b** in 97% yield.

11-(Phenylsulfonyl)-6,11-dihydro-5*H*-indolo[3,2-*c*]quinolin-6-one (5a)
To a solution of indole **4a** (460 mg, 0.76 mmol) in DMF (10 mL) was added $Pd(OAc)_2$ (34 mg, 0.15 mmol), triphenylphosphine (84 mg, 0.3 mmol) and silver carbonate (419 mg, 1.5 mmol). The mixture was then stirred at 100 °C for 1 day. After cooling, the solvent was evaporated. The residue was dissolved in CH_2Cl_2 and washed 3 times with water. The organic layer was dried ($MgSO_4$) and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (PE/EtOAc, 1:1) to afford **5a** (213 mg, 75%) as crystals.

11-(Phenylsulfonyl)-6,11-dihydro-5*H*-pyrido[3',2':4,5]pyrrolo-[3,2-*c*]quinolin-6-one (5b)
The same procedure applied to **4b** afforded **5b** in 72% yield.

***tert*-Butyl 11-(Phenylsulfonyl)-6-oxo-6,11-dihydro-5*H*-indolo-[3,2-*c*]quinoline-5-carboxylate (5c)**
Same procedure as for compound **4a** starting from compound **5a**, afforded **5c** in 96% yield.

11-(Phenylsulfonyl)-11*H*-indolo[3,2-*c*]quinolin-6-yl trifluoromethanesulfonate (6a)
To a stirred solution of **5a** (200 mg, 0.5 mmol) in CH_2Cl_2 (20 mL) under Ar at 0 °C was added pyridine (0.5 mL, 6.2 mmol) followed by trifluoromethanesulfonic anhydride (0.18 mL, 1.1 mmol). The solution was stirred at r.t. for 3 h., then washed with sat. $NaHCO_3$ (30 mL) and H_2O (20 mL), dried ($MgSO_4$) and evaporated in vacuo.

Table 5 ^{13}C NMR Data of Compounds **1–6**

Compound	^{13}C NMR (ppm) δ, *J* (Hz)
2a[a]	113.2 (CH), 114.1 (C), 121.8 (CH), 124.5 (CH), 125.5 (CH), 127.2 (2CH), 127.5 (C), 130.1 (2CH), 131.9 (CH), 134.1 (C), 135.2 (CH), 136.4 (C), 164.3 (CO)
2b[a]	111.2 (C), 120.1 (CH), 120.5 (C), 128.1 (2CH), 129.7 (2 CH), 130.6 (CH), 131.5 (CH), 135.3 (CH), 136.7 (C), 145.6 (CH), 146.3 (C), 163.9 (CO)
3a[b]	90.3 (C), 113.7 (CH), 118.0 (C), 121.8 (CH), 122.2 (CH), 124.7 (CH), 126.0 (CH), 126.3 (CH), 127.2 (2CH), 127.5 (C), 128.3 (CH), 129.5 (CH), 129.8 (2CH), 134.7 (CH), 135.1 (C), 137.6 (C), 138.2 (C), 139.0 (CH), 161.5 (CO)
3b[b]	90.5 (C), 114.6 (C), 120.2 (CH), 120.5 (C), 122.3 (CH), 126.4 (CH), 127.4 (CH), 128.6 (2CH), 129.3 (2CH), 129.5 (CH), 130.8 (CH), 134.8 (CH), 137.6 (C), 138.0 (C), 139.0 (CH), 146.3 (CH), 147.1 (C), 160.9 (CO)
4a[b]	28.0 ($3CH_3$), 84.1 (C), 99.8 (C), 113.5 (CH), 118.2 (C), 122.1 (CH), 124.5 (CH), 125.6 (CH), 127.2 (2CH), 128.3 (C), 129.4 (CH), 129.6 (2CH), 129.9 (CH), 130.0 (CH), 131.1 (CH), 134.4 (C), 134.5 (CH), 137.7 (C), 139.9 (CH), 142.0 (C), 152.0 (CO), 165.1 (CO)
4b[b]	27.8 ($3CH_3$), 84.3 (C), 99.8 (C), 114.7 (C), 120.1 (CH), 121.2 (C), 128.5 (2CH), 129.3 (2CH), 129.5 (CH), 130.0 (CH), 130.1 (CH), 130.9 (CH), 131.2 (CH), 134.7 (CH), 137.7 (C), 140.0 (CH), 141.8 (C), 146.0 (CH), 146.6 (C), 151.9 (CO), 164.6 (CO)
5a[a]	112.7 (C), 116.2 (CH), 117.2 (C), 117.4 (CH), 121.5 (CH), 121.6 (CH), 126.0 (CH), 126.3 (2CH), 126.8 (CH), 126.9 (CH), 127.3 (C), 129.3 (2CH), 130.2 (CH), 134.8 (CH), 134.9 (C), 138.6 (C), 139.4 (C), 142.9 (C), 158.5 (CO)
5b[a]	112.3 (C), 113.7 (C), 116.3 (CH), 119.3 (C), 121.3 (CH), 121.4 (CH), 127.3 (3CH), 129.4 (2CH), 130.0 (CH), 130.5 (CH), 134.8 (CH), 137.3 (C), 139.0 (C), 142.5 (C), 145.9 (CH), 151.8 (C), 158.4 (CO)
5c[b]	28.0 ($3CH_3$), 87.6 (C), 114.1 (C), 114.3 (CH+C), 117.9 (CH), 122.6 (CH), 122.9 (CH), 126.3 (CH), 126.8 (2CH), 127.1 (CH), 127.7 (C), 128.9 (3CH), 130.5 (CH), 134.3 (CH), 135.5 (C), 136.2 (C), 140.4 (C), 143.8 (C), 150.9 (CO), 157.3 (CO)
6a[a]	113.3 (C), 118.7 (CH), 118.7 (q, CF_3, *J* = 320), 120.2 (C), 121.7 (CH), 123.8 (C), 126.5 (2CH), 126.6 (CH), 126.8 (CH), 127.4 (CH), 128.3 (CH), 128.8 (2CH), 129.2 (CH), 130.4 (CH), 134.4 (CH), 135.2 (C), 140.9 (C), 144.9 (C), 146.3 (C), 148.5 (C)
6b[a]	109.3 (C), 115.9 (C), 118.7 (q, CF_3, *J* = 320), 119.4 (C), 121.3 (CH), 127.3 (2CH), 128.0 (2CH), 129.1 (2CH), 129.5 (CH), 130.3 (CH), 130.8 (CH), 134.7 (CH), 137.8 (C), 145.1 (C), 145.4 (C), 147.8 (CH), 148.7 (C), 152.7 (C)

[a] In DMSO-d_6.
[b] In $CDCl_3$.

The crude residue was purified by flash chromatography on silica gel (PE/EtOAc, 8:2) to give **6a** (236 mg, 88%) as crystals.

11-(Phenylsulfonyl)-11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*c*]quinolin-6-yl Trifluoromethanesulfonate (6b)
The same procedure applied to **5b** afforded **6b** in 79% yield.

Stille Reactions of 6a–b with Tin Derivatives; Method 1
To a mixture of LiCl (19 mg, 0.45 mmol) and freshly prepared $Pd(PPh_3)_4$ (11 mg, 0.01 mmol) in DMF (10 mL) under Ar, triflate **6** (0.16 mmol), (1-ethoxyvinyl)tributyltin (0.24 mmol) or (2-furanyl)tributyltin (0.24 mmol) in DMF (5 mL) were added. The stirred solution was heated at 90 °C for 2 h. The solvent was then removed in vacuo and the crude residue was purified by flash chromatography on silica gel (PE/EtOAc, 1:3) to give **7**–**8**.

Suzuki Reactions of 6a–b with Boronic Acids; Method 2
To a stirred solution of triflate **6** (0.2 mmol) in toluene (5 mL) under Ar was added freshly prepared $Pd(PPh_3)_4$ (14 mg, 0.012 mmol). The mixture was allowed to stir for 30 min r.t. Boronic acid (0.3 mmol) (4-methoxyphenylboronic acid or benzo[*b*]thiophene-2-boronic acid) in ethanol (2 mL) was then added, followed immediately by sat. $NaHCO_3$ (2 mL). The heterogeneous solution was stirred at 90 °C for 2 h. Brine solution was then added, the two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The crude residue was purified by flash chromatography on silica gel (PE/EtOAc, 8:2) to give compounds **9**–**10**.

Methyl (*E*)-3-[11-Phenylsulfonyl-11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*c*]quinolin-6-yl]prop-2-enoate (11b)
Triflate **6b** (100 mg, 0.2 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), triphenylphosphine (21 mg, 0.08 mmol), silver carbonate (110 mg, 0.4 mmol) and methyl acrylate (26 mg, 0.3 mmol) were stirred in DMF (10 mL) at 100 °C for 3 h. After filtration, the mixture was evaporated in vacuo, then the crude oil was diluted in CH_2Cl_2 (30 mL). The organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated. The crude residue was purified by flash column chromatography (PE/EtOAc, 8:2) to afford **11b** (45 mg, 51%) as a solid.

6-Chloro-11-(phenylsulfonyl)-11*H*-indolo[3,2-*c*]quinoline (12)[24]
Compound **5a** (120 mg, 0.32 mmol) was dissolved in toluene (10 mL) / DMF (1 mL), phosphorus oxychloride (53 mg, 0.38 mmol) was added at 0 °C and then the mixture was stirred at r.t. for 4 h. Evaporation of the mixture in vacuo followed by hydrolysis, neutralisation with sat. $NaHCO_3$, extraction with EtOAc and drying ($MgSO_4$) afforded a solid; The crude solid was quickly purified by flash column chromatography (PE/EtOAc, 8:2) to afford **12** (120 mg, 96%) as a solid.

References

(1) Woodward, R. B.; Iacobucci, G. A.; Hochtein, F. A. *J. Am. Chem. Soc.* **1959**, *81*, 4434.
(2) Pratviel, G.; Bernadou, J.; Ha, T.; Meunier, G.; Cros, S.; Meunier, B.; Gillet, B.; Guittet, E. *J. Med. Chem.* **1986**, *29*, 1350.
(3) Guillonneau, C.; Pierré, A.; Charton, Y.; Guilbaud, N.; Kraus-Berthier, L.; Léonce, S.; Michel, A.; Bisagni, E.; Atassi, G. *J. Med. Chem*. **1999**, *42*, 2191.

Table 6 ^1H NMR ($CDCl_3$) Data of Compounds **7–12**

Compound	^1H NMR (ppm) δ, *J* (Hz)
7a	0.92 (t, 3H, *J* = 7.5, CH_3), 4.01 (q, 2 H, *J* = 7.5, CH_2), 4.61 (d, 1 H, *J* = 2.5, =CH_2), 4.64 (d, 1 H, *J* = 2.5, =CH_2), 7.04–7.7 (m, 4 H, H_{Ar}), 7.25–7.40 (m, 2 H, H_{Ar}), 7.45–7.52 (td, 1 H, *J* = 2.8, H_{Ar}), 7.71–7.86 (m, 3 H, H_{Ar}), 8.24 (br d, 1 H, *J* = 8.1, H_{Ar}), 8.33 (br d, 1 H, *J* = 8.1, H_{Ar}), 8.95 (br d, 1 H, *J* = 8.5, H_{Ar})
8a	6.63-6.67 (m, 1 H, H_{Ar}), 7.08–7.15 (m, 5 H, H_{Ar}), 7.25–7.35 (m, 2 H, H_{Ar}), 7.45–7.52 (m, 2 H, H_{Ar}), 7.65–7.76 (m, 2 H, H_{Ar}), 7.78 (br d, 1H, *J* = 7.9, H_{Ar}), 8.23 (br d, 1H, *J* = 8.1, H_{Ar}), 8.36 (br d, 1H, *J* = 8.1, H_{Ar}), 8.95 (br d, 1H, *J* = 8.5, H_{Ar})
8b	6.70–6.72 (m, 1 H, H_{Ar}), 7.23–7.51 (m, 5 H, H_{Ar} + H_{Pyr}), 7.63–7.75 (m, 3 H, H_{Ar}), 7.80 (br d, 2 H, *J* = 7.5, H_{Ar}), 8.22 (d, 1 H, *J* = 8.2, H_{Ar}), 8.42 (dd, 1 H, *J* = 1.2, 8.0, H_{Pyr}), 8.51 (dd, 1 H, *J* = 1.2, 4.7, H_{Pyr}), 8.79 (d, 1 H, *J* = 7.9, H_{Ar})
9a	3.90 (s, 3 H, CH_3), 7.03 (br d, 2 H, *J* = 8.8, H_{Ar}), 7.08–7.19 (m, 7 H, H_{Ar}), 7.33–7.40 (m, 1 H, H_{Ar}), 7.45 (br d, 2 H, *J* = 8.8, H_{Ar}), 7.69 (t, 1 H, *J* = 6.9, H_{Ar}), 7.78 (t, 1 H, *J* = 6.9, H_{Ar}), 8.24 (d, 1 H, *J* = 8.5, H_{Ar}), 8.34 (d, 1 H, *J* = 8.2, H_{Ar}), 8.97 (d, 1 H, *J* = 8.5, H_{Ar})
9b	3.92 (s, 3 H, CH_3), 7.05–7.12 (m, 3 H, H_{Ar} + H_{Pyr}), 7.34–7.40 (m, 2 H, H_{Ar}), 7.48–7.55 (m, 1 H, H_{Ar}), 7.61–7.70 (m, 4 H, H_{Ar}+H_{Pyr}), 7.75–7.88 (m, 3 H, H_{Ar}), 8.25 (dd, 1 H, *J* = 1.0, 8.2, H_{Ar}), 8.49 (dd, 1 H, *J* = 1.6, 5.0, H_{Pyr}), 8.83 (dd, 1 H, *J* = 1.0, 8.5, H_{Ar})
10a	7.08–7.25 (m, 5 H, H_{Ar}), 7.35–7.46 (m, 4 H, H_{Ar}), 7.50 (br s, 1 H, H_{Ar}), 7.66 (d, 1 H, *J* = 8.1, H_{Ar}), 7.70–7.84 (m, 3 H, H_{Ar}), 7.92–7.96 (m, 1 H, H_{Ar}), 8.25 (d, 1 H, *J* = 8.5, H_{Ar}), 8.36 (d, 1 H, *J* = 8.5, H_{Ar}), 8.98 (d, 1 H, *J* = 8.5, H_{Ar})
10b	7.15 (dd, 1 H, *J* = 5.0, 8.0, H_{Pyr}), 7.31–7.58 (m, 5 H, H_{Ar}), 7.66–8.00 (m, 7 H, H_{Ar}), 8.10 (dd, 1 H, *J* = 1.9, 8.0, H_{Pyr}), 8.28 (dd, 1 H, *J* = 1.0, 8.4, H_{Ar}), 8.52 (dd, 1 H, *J* = 1.9, 5.0, H_{Pyr}), 8.83 (dd, 1 H, *J* = 1.0, 8.4, H_{Ar})
11b	3.89 (s, 3 H, OCH_3), 7.29–7.52 (m, 5 H, H_{Ar}+ H_{Pyr} + CH=), 7.66–7.84 (m, 4 H, H_{Ar}), 8.23 (dd, 1 H, *J* = 1.0, 8.5, H_{Ar}), 8.38 (dd, 1 H, *J* = 1.6, 7.9, H_{Pyr}), 8.43 (d, 1 H, *J* = 15.3, CH=), 8.56 (dd, 1 H, *J* = 1.6, 4.7, H_{Pyr}), 8.83 (dd, 1 H, *J* = 1.0, 8.5, H_{Ar})
12	7.05–7.15 (m, 4 H, H_{Ar}), 7.25–7.35 (m, 1 H, H_{Ar}), 7.40–7.58 (m, 2 H, H_{Ar}), 7.65–7.80 (m, 2 H, H_{Ar}), 8.10 (d, 1 H, *J* = 1.3, 8.2, H_{Ar}), 8.36 (t, 2 H, *J* = 8.2, H_{Ar}), 8.97 (dd, 1 H, *J* = 1.3, 8.2, H_{Ar})

(4) Molina, A.; Vaquero, J. J.; Garcia-Navio, J. L.; Alvarez-Builla, J.; Pascual-Tereza, B.; Gago, F.; Rodrigo, M. M. *J. Org. Chem*. **1999**, *64*, 3907.
(5) Lescot, E.; Muzard, G.; Markovits, J.; Belleney, J.; Rocques, B. P.; Le Pecq, J. B. *J. Med. Chem*. **1986**, *29*, 1731.
(6) De Silva, O.; Snieckus, V. *Synthesis* **1971**, 254.
(7) Bair, K. W.; Webster A. C.; Tuttle, R. L.; Knick, V. C.; Cory, M.; Mc Knee, D. D. *J. Med. Chem* **1991**, *34*, 1983.
(8) Hirata, K.; Ito, C.; Furukawa, H.; Itoigawa, M.; Cosentino, L. M.; Lee, K. -H. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 119.
(9) Joseph, B.; Cornec, O.; Mérour, J. -Y.; Solans, X.; Font-Bardia, M. *J. Heterocycl. Chem.* **1997**, *34*, 525.
(10) Joseph, B.; Chapellier, V.; Mérour, J. -Y.; Léonce, S. *Heterocycles* **1998**, *48*, 1423.
(11) Joseph, B.; Cornec, O.; Mérour, J. -Y. *Tetrahedron* **1998**, *54*, 7765.
(12) Joseph, B.; Alagille, D.; Rousseau, C.; Mérour, J. -Y. *Tetrahedron* **1999**, *55*, 4341.
(13) Alvarez, M.; Fernández, D.; Joule, J. *Synthesis* **1999**, 615.
(14) Urögdi, L.; Barta-Szalai, G.; Kisfaludy, L.; Domany, G.; Csehi, A. *Heterocycles* **1994**, *37*, 1807.
(15) Dormoy, J. R.; Heymes, A. *Tetrahedron* **1993**, *49*, 2885.
(16) Desarbre, E.; Coudret, S.; Meheust, C.; Mérour, J. -Y. *Tetrahedron* **1997**, *53*, 3637.
(17) Curtis, N. L.; Kulagowski, J. J.; Leeson, P. D.; Ridgill, M. P.; Emns, F.; Freedman, S. B.; Patel, S. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 585.
(18) Kelly, T. A.; McNeil, D. W.; Rose, J. M.; David, E.; Shih, C. -K.; Grob, P. M. *J. Med. Chem.* **1997**, *40*, 2430.
(19) Lorenz, R. R.; Tullar, B. F.; Koelsch, C. F.; Archer, S. *J. Org. Chem*. **1965**, *30*, 2531.
(20) Estel, L.; Marsais, F.; Guéguiner, G. *J. Org. Chem*. **1988**, *53*, 2740.
(21) Levacher, V.; Benoit, R.; Duflos, J.; Dupas, G.; Bourguignon, J.; Quéguiner, G. *Tetrahedron* **1991**, *47*, 429.
(22) Kulagowski, J. J.; Broughton, H. B.; Curtis, N. R.; Mawer, I. M.; Ridgill, M. P.; Baker, R.; Emms, F.; Freedman, S. B.; Marwood, R.; Patel, S.; Patel, S.; Ragan, C.I.; Leeson, P. D. *J. Med. Chem*. **1996**, *39*, 1941.
(23) Winterfeld, E.; Altmann, H. J. *Angew. Chem., Int. Ed. Engl*. **1968**, *7*, 466.
(24) Dave, V.; Warnhoff, E. W. *Tetrahedron* **1975**, *31*, 1255.
(25) Bergman, J.; Carlsson, R.; Sjöberg, B. *J. Heterocycl. Chem*. **1977**, *12*, 1123.
(26) Kiang, A. K.; Mann, F. G.; Prior, A. F.; Topham, A. *J. Chem. Soc*. **1956**, 1319.
(27) Cacchi, S.; Fabrizi, G.; Pace, P.; Marinelli, F. *Synlett* **1999**, 620.
(28) Busacca, C. A.; Eriksson, M. C.; Dong, Y.; Prokopowicz, A. S.; Salvagno, A. M.; Tschantz, M. A. *J. Org. Chem*. **1999**, *64*, 4564.
(29) Negishi, E. -I.; Coperet, C.; Ma, S.; Liou, S. -Y.; Liu, F. *Chem. Rev*. **1996**, *96*, 365.
(30) Ames, D. E.; Opalko, A. *Tetrahedron* **1984**, *40*, 1919.
(31) Harayma, T.; Akiyama, T.; Nakano, Y. *Chem. Pharm. Bull.* **1997**, *45*, 1723.
(32) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003.
(33) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem*. **1982**, *47*, 757.

Table 7 ^{13}C NMR ($CDCl_3$) Data of Compounds **7**–**12**

Compound	^{13}C NMR (ppm) δ
7a	14.3 (CH_3), 63.8 (CH_2), 87.9 (CH_2=), 119.0 (CH), 120.6 (C), 120.9 (C), 122.5 (CH), 125.8 (CH), 126.7 (CH), 126.8 (3CH), 126.8 (CH), 127.3 (C), 128.3 (2CH), 129.3 (CH), 130.0 (CH), 133.8 (CH), 134.7 (C), 141.4 (C), 143.9 (C), 147.2 (C), 150.6 (C), 159.9 (C)
8a	112.2 (CH), 112.4 (CH), 119.2 (CH), 120.4 (C), 120.9 (C), 122.7 (CH), 125.7 (CH), 125.9 (CH), 126.7 (CH), 126.9 (2CH), 127.0 (CH), 127.5 (CH), 128.4 (2CH), 129.6 (CH), 129.7 (CH), 134.0 (CH), 134.5 (C), 141.4 (C), 143.7 (2C), 144.4 (C), 144.7 (C), 152.8 (C)
8b	112.6 (CH), 112.7 (CH), 116.4 (C), 119.2 (C), 119.4 (C), 120.6 (CH), 126.4 (CH), 127.3 (CH), 127.9 (2CH), 128.9 (2CH), 129.7 (CH), 130.0 (CH), 131.8 (CH), 134.2 (CH), 137.6 (C), 143.4 (C), 143.7 (CH), 144.2 (C), 146.8 (CH), 147.8 (C), 153.2 (C), 153.5 (C)
9a	55.5 (CH_3), 114.2 (2CH), 119.4 (CH), 120.2 (C), 121.3 (C), 121.9 (CH), 125.7 (CH), 126.4 (CH), 126.8 (CH), 127.0 (2CH), 127.3 (CH), 128.1 (C), 128.3 (2CH), 129.5 (CH), 129.6 (CH), 130.5 (2CH), 132.1 (C), 133.9 (CH), 134.5 (C), 141.5 (C), 144.4 (C), 147.7 (C), 154.9 (C), 160.7 (C)
9b	55.6 (CH_3), 114.4 (2CH), 117.1 (C), 119.1 (C), 119.7 (C), 120.3 (CH), 126.2 (CH), 127.0 (CH), 127.8 (2CH), 128.8 (2CH), 129.8 (CH), 129.9 (CH), 130.3 (CH), 130.5 (2CH), 131.9 (C), 134.2 (CH), 137.7 (C), 142.8 (C), 146.8 (CH), 148.1 (C), 153.6 (C), 155.0 (C), 160.8 (C)
10a	119.5 (CH), 120.5 (C), 121.2 (C), 121.8 (CH), 122.6 (CH), 124.4 (CH), 124.7 (CH), 125.2 (CH), 125.4 (CH), 125.9 (CH), 126.8 (CH), 126.9 (2CH), 127.0 (2CH), 127.5 (C), 127.7 (CH), 128.4 (2CH), 129.8 (CH), 134.0 (CH), 134.5 (C), 139.7 (C), 141.0 (C), 141.5 (C), 142.0 (C), 144.5 (C), 147.5 (C), 148.4 (C)
10b	119.1 (C), 119.5 (C), 120.4 (CH), 122.7 (CH), 124.5 (CH), 124.9 (CH), 125.2 (CH), 125.6 (CH), 126.9 (CH), 127.1 (CH), 128.0 (2CH), 128.9 (3CH), 130.1 (C), 130.2 (CH), 130.3 (CH), 134.3 (CH), 137.8 (C), 139.7 (C), 141.1 (C), 142.0 (C), 143.0 (C), 147.1 (CH), 147.9 (C), 148.8 (C), 153.5 (C)
11b	52.3 (CH_3), 117.6 (C), 118.6 (C), 119.8 (C), 120.9 (CH), 125.9 (CH), 127.0 (CH), 127.3 (CH), 127.9 (2CH), 128.9 (2CH), 130.2 (CH), 130.3 (CH), 130.8 (CH), 134.3 (CH), 137.7 (C), 139.6 (CH), 142.6 (C), 147.0 (CH), 147.9 (C), 148.1 (C), 153.4 (C), 167.1 (CO)
12	118.7 (CH), 119.8 (C), 120.4 (C), 122.4 (CH), 125.9 (C), 126.2 (CH), 126.7 (2CH), 126.8 (CH), 127.0 (CH), 127.9 (CH), 128.6 (2CH), 128.8 (CH), 130.1 (CH), 134.2 (CH), 135.1 (C), 140.1 (C), 144.5 (2C), 147.0 (C)

(34) Kruber, O. *Ber*. **1943**, 143.
(35) We have also observed in other indolic series the complete deiodination with palladium catalysts of substrates containing the secondary amide group.
(36) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem*. **1987**, *52*, 4130.
(37) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488 and references therein.
(38) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem*. **1997**, *62*, 1264.
(39) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 2046.

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