The First Practical and Efficient One-Pot Synthesis of 6-Substituted 7-Azaindoles via a Reissert–Henze Reaction

Thomas Storz,*[a,1] Michael D. Bartberger,[b] Steven Sukits,[b] Chris Wilde,[b] Troy Soukup[c]

[a] Chemical Process R & D, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799, USA
Fax +1(845)6025561; E-mail: storzt@wyeth.com

[b] Molecular Structure & Modelling, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799, USA

[c] Process Analytical Sciences, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799, USA

Received 19 June 2007

Dedicated to Professor Dr. Wolfgang Pfleiderer, Professor Emeritus, University of Konstanz, Germany, on the occasion of his 80th birthday

Abstract: A variety of 6-substituted 7-azaindoles (30 examples) were obtained via selective O-methylation of 7-azaindole-*N*-oxide *m*-chlorobenzoic acid salt and subsequent, base-catalyzed one-pot reaction with a range of *N*-, *O*-, *S*-nucleophiles or cyanide.

Key words: 7-azaindole, pyrrolo[2,3-*b*]pyridine, addition-elimination, oxidation, *N*-oxide, O-methylation

Since its original discovery as a component of coal tar by Kruber in 1943,[2] derivatives of 7-azaindole[3] (1*H*-pyrrolo[2,3-*b*]pyridine) (**1**) have emerged[4] as an important and promising class of bioisosteric pharmacophores[5] for the indole or purine ring system in both agrochemistry and medicinal chemistry[6] (e.g., see Figure 1).[7]

More recently, 7-azaindoles have attracted interest in material sciences for biophysical and photophysical applications due to their optical and metal-ion binding properties.[8]

While a number of strategies for the de novo synthesis of 7-azaindole[3a–d] and its derivatives have been reported,[3e–i] the available methods for *site-selective derivatization* of the parent molecule remain relatively limited. In analogy to known indole chemistry, they target either the pyrrole nitrogen (N1) of **1** (amination,[9] silylation,[10] alkylation, carbamoylation and sulfonation,[11] acylation,[12] arylation,[13] vinylation,[14] Michael addition,[15] urea formation,[16] or glycosylation[17]),[3g,h] or the C3 position (formylation,[18] acylation,[12] aldol condensation,[19] Mannich reaction,[20] Michael addition,[21] alkylation,[21,22] halogenation,[23] nitration,[24] sulfide formation,[25] or oxidation[26]).[3g,h]

Only a few methods are known for the selective modification at C4: from the 7-azaindole-*N*7-oxide (**2**),[27a,b] 4-chloro-7-azaindole[27] and 4-bromo-7-azaindole[28] have been obtained in one synthetic step; whereas 4-amino-7-azaindole[29] and 4-nitro-7-azaindole[29] have been made from **2** in two, and 4-fluoro-7-azaindole[28] in three synthetic steps, respectively.[30] The derivatization of 7-azaindole at C5 is not straightforward[31] and usually better accomplished by de novo-synthesis,[3g,h,32] whereas derivatization at C2 is regarded as more facile.[33]

De novo synthesis has traditionally also been the method of choice for 7-azaindoles substituted at C6.[3g,h] Following the early report of Robison et al.,[34] only one further attempt towards a selective derivatization at C6 was published: Oshiro et al.[35] reported the synthesis of 6-chloro- and 6-bromo-7-azaindole via a Reissert–Henze type reaction[36a] from the *N*-oxide **2**. However, due to π-dona-

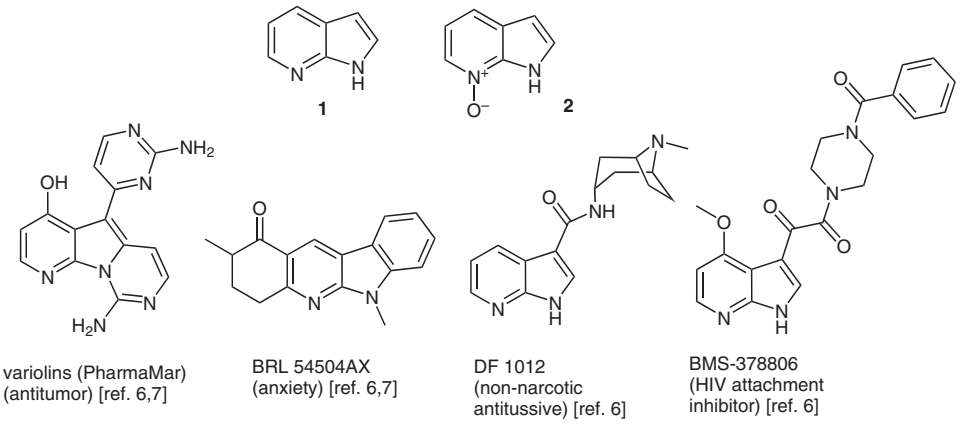
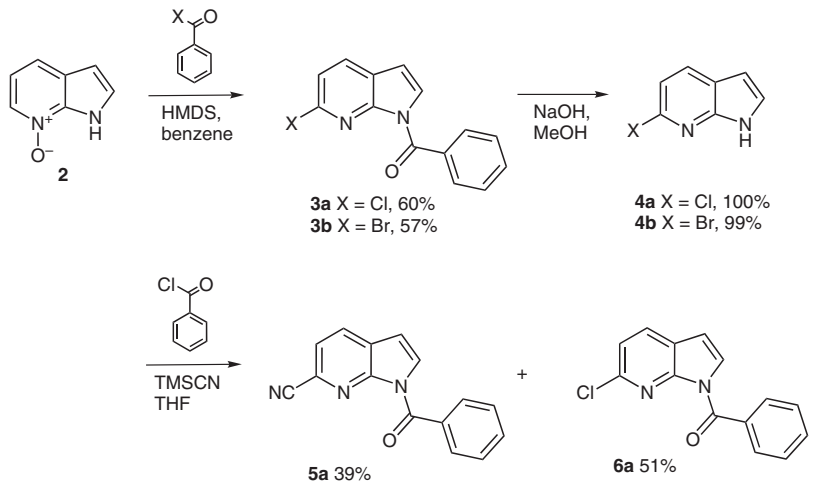


Figure 1 7-Azaindole (1), its N7-oxide 2, and 7-azaindole derivatives in clinical evaluation

SYNTHESIS 2008, No. 2, pp 0201–0214
Advanced online publication: 18.12.2007
DOI: 10.1055/s-2007-1000853; Art ID: M04807SS

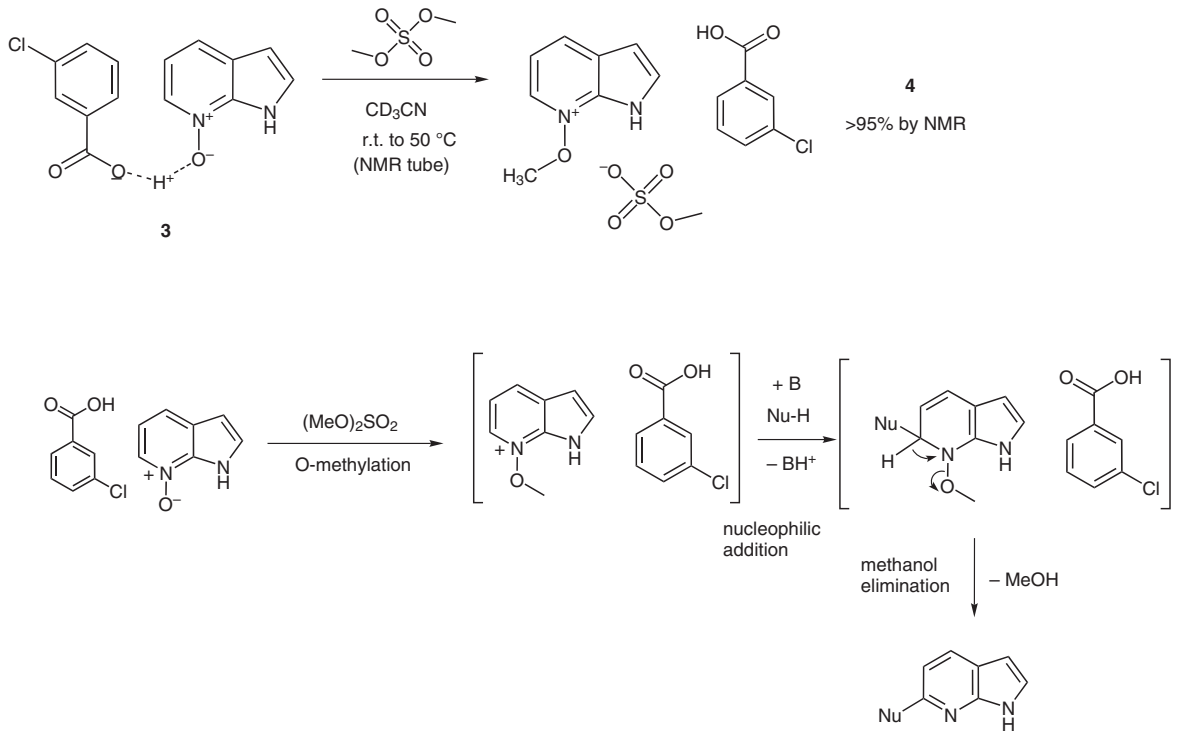


Scheme 1 Selective halogenation and unselective cyanation/halogenation of 7-azaindole at C6 (Ohshiro et al.[35])

tion from N1, electrophilicity at C6 is greatly diminished, so that access to 6-O- and especially 6-N-substituted 7-azaindoles via nucleophilic substitution usually is not practical.[35b,36b,37] Interestingly, attempts by Oshiro et al. to extend their Reissert–Henze reaction variant to the synthesis of 6-cyano- or thiocyanato-7-azaindole met with only limited success due to competing chloride attack at C6 (Scheme 1).[35a]

In the context of a recent development project,[27e,38] we were interested in different syntheses of 4-cyano-[39] and 6-cyano-7-azaindole.[23a] Inspired by the results of Oshiro (Scheme 1), we decided to reinvestigate different variants of the Reissert–Henze reaction[36] of 7-azaindole-*N*-oxide.[40]

To our surprise, O-alkylated derivatives of 7-azaindole-*N*7-oxide (**2**) have not been reported,[41] perhaps because it was felt that, in analogy to the well-known reactivity of **1** towards alkylating agents (vide supra), the same undesirable reaction channels would also predominate in the case of the corresponding *N*-oxide. Gratifyingly, a simple, unambiguous NMR-tube experiment revealed that stoichiometric dimethyl sulfate in acetonitrile does not alkylate the pyrrole nitrogen or C3 of the *N*-oxide MCBA (*m*-chlorobenzoic acid) salt **3**,[42] but, instead, leads to clean formation of O-methylated *N*-oxide methyl sulfate salt **4** (Scheme 2, Figure 2).[43]



Scheme 2 Selective O-methylation of 7-azaindole-*N*7-oxide MCBA salt **3** followed by reaction with a nucleophile; a three-step, one-pot reaction

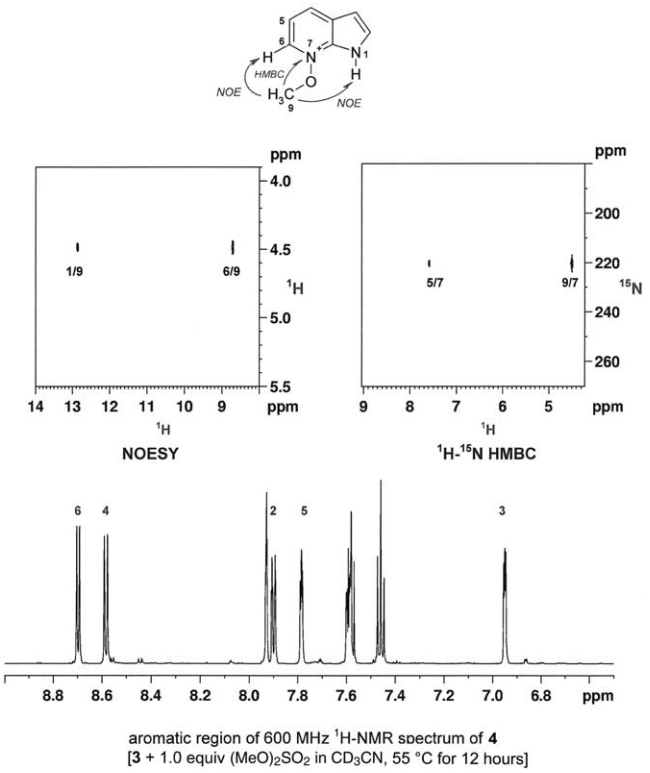
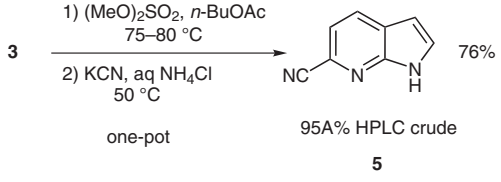


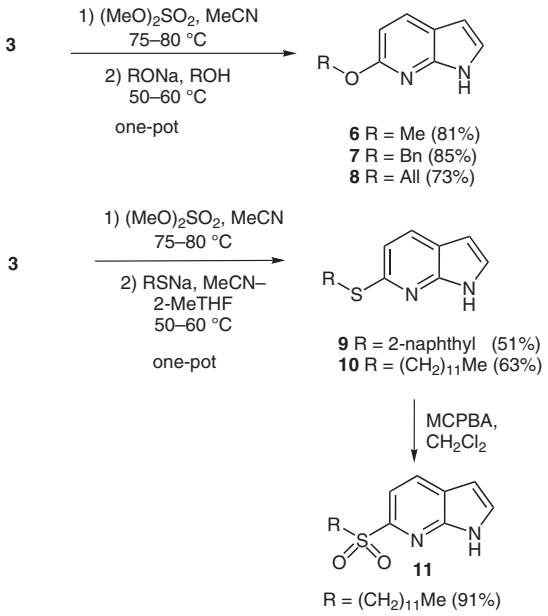
Figure 2 ^{1}H-NOESY and ^{1}H-^{15}N-HMBC NMR data of in situ generated **4** (in CD_3CN)

With the desired *O*-methyl-*N*-oxide salt **4** in hand, we applied a variant of the Okamoto–Tani cyanation conditions[44] known to be selective for the formation of 4-cyano- over 2-cyanopyridine from *O*-methylpyridine-*N*-oxide.[36a,c] The precipitated solid isolated in 76% yield by a simple filtration from the aqueous ammonium chloride/potassium cyanide reaction mixture was 95% pure by HPLC, and turned out to be 6-cyano-7-azaindole (**5**) (Scheme 3).[45–47] No traces of the 4-cyano-regioisomer were detected. To the best of our knowledge, this constitutes the first direct and clean synthesis of a cyano-7-azaindole from the corresponding *N*-oxide and the most practical synthesis of compound **5** to date[23a] (vide supra, Scheme 1).[48,49]



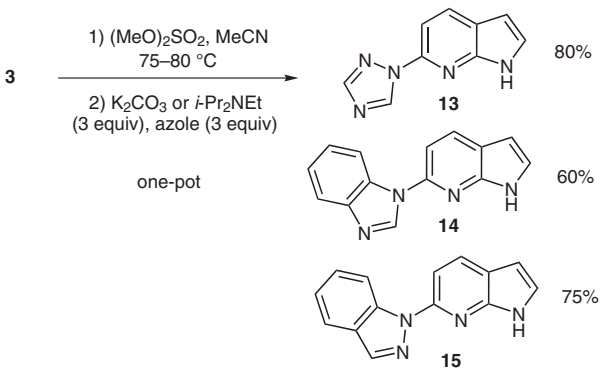
Scheme 3 Reaction of in situ generated *O*-methyl-*N*-oxide salt **4** with aqueous potassium cyanide

Next we subjected **4** to a variety of oxygen and sulfur nucleophiles and found that primary, allylic, and benzylic alcohols reacted cleanly and smoothly with **4** to give exclusively the 6-O-substituted 7-azaindole in good yields (Scheme 4).[50,51] The *N*-oxide salt **4** behaved mainly as an O-methylating agent towards secondary, tertiary, neopentylic alcohols, and phenols, respectively (usually <30% desired product observed, mostly *N*-oxide **2** was obtained back). Likewise, aliphatic thiolates gave the 6-S-substituted 7-azaindole more cleanly than aromatic thiolates; and with heteroaromatic thiols (2-mercaptoazoles, -diazoles and -diazines), S-methylation was again the dominant reaction pathway (>60% formation of the *S*-methylheterocycle and *N*-oxide **2** observed). With MCPBA, the 6-thio-substituted 7-azaindole **10** underwent selective oxidation to the corresponding sulfone (no N-oxidation observed), a potentially interesting, stable building block for introducing further functionality at C6 (Scheme 4).[50,51]



Scheme 4 Reaction of the *O*-methyl-*N*-oxide salt **4** with alcoholates and thiolates

The reaction of **4** with a number of azoles gave predominantly the 6-substituted regioisomer and provides a mild and quick route to previously inaccessible pharmacophores **13**–**15**; only the unsymmetrical (N1) coupling product was obtained with 1,2,4-triazole (**13**) (Scheme 5).[51,52]



Scheme 5 Reaction of the *O*-methyl-*N*-oxide salt **4** with diazoles and triazoles

We found the new reaction to be most useful for the one-pot conversion of the *N*-oxide salt 3 to 6-aminosubstituted 7-azaindoles. Direct regioselective introduction of nitrogen functionality at the 6-position of 7-azaindole was not possible with previous synthetic methodology.[37] Ammonia, primary amines, α-branched and β-branched amines, allylic amines, benzylic/heteroaromatic amines, propargylic amines, secondary acyclic as well as secondary cyclic amines all reacted with in situ generated **4** to the corresponding 6-amino-substituted 7-azaindoles **16**–**24** under mild conditions and in good yields.[53] Furthermore, both primary (1°, 2°) as well as secondary amino alcohols were found to react in a completely chemoselective fashion giving **25**–**27**, respectively; concomitant O-arylation was not observed (Table 1).

Table 1 6-Amino-Substituted 7-Azaindoles **16**–**27** Prepared from **3**

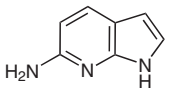
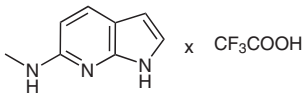
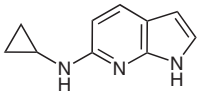
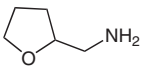
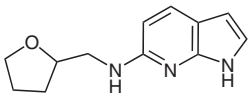
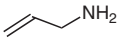
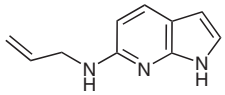
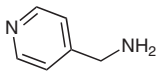
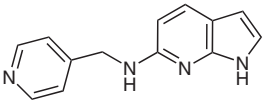
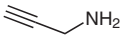
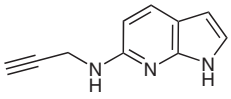
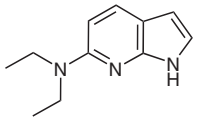
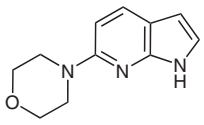
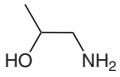
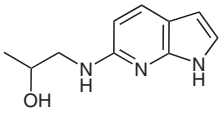
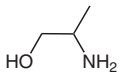
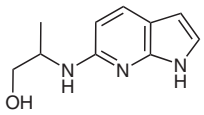
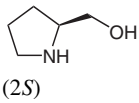
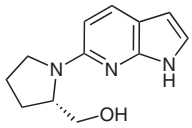
Nitrogen nucleophile	Method[a]	Yield (%)[b]	Product
NH_3	A	65	 **15**
$MeNH_2$	A	71	 **17**
	B	67	 **18**
	B	83	 **19**
	B	70	 **20**
	B	77	 **21**
	B	68	 **22**
Et_2NH	B	87	 **23**

Table 1 6-Amino-Substituted 7-Azaindoles **16**–**27** Prepared from **3** (continued)

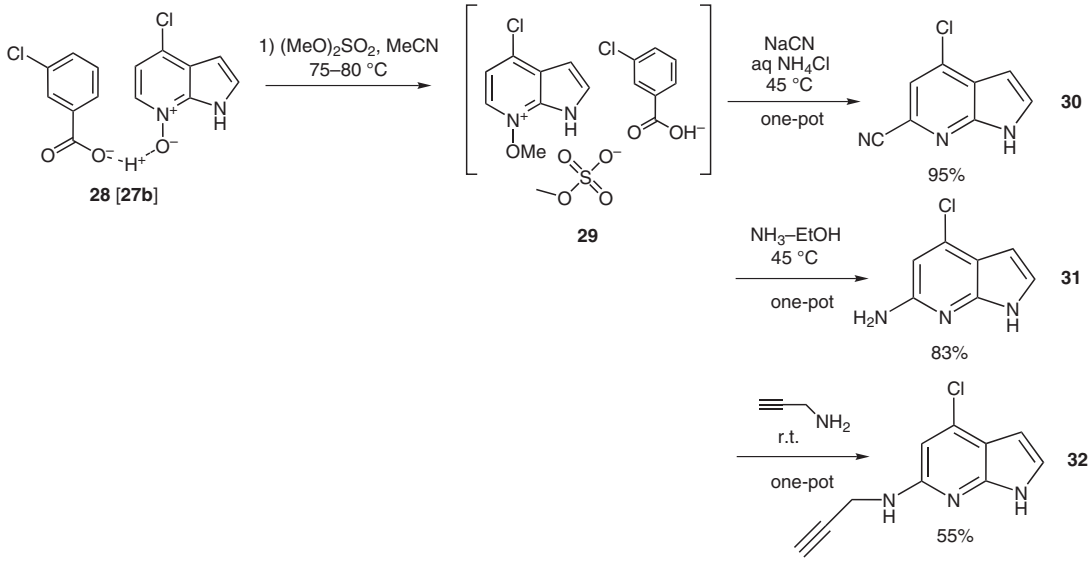
Nitrogen nucleophile	Method[a]	Yield (%)[b]	Product
	B	63	 **24**
 (±)	B	58	 **25** (±)
 (±)	B	72	 **26** (±)
 (2*S*)	B	73	 **27** (2′*S*)

[a] Method A: 1. **3** + dimethyl sulfate (1.05–1.10 equiv), MeCN, 50–60 °C, 8–12 h; 2. NH_3 (10 equiv, or $MeNH_2$ in MeOH or EtOH), 50 °C, 8–12 h. Method B: 1. **3** + dimethyl sulfate (1.05–1.10 equiv), MeCN, 50–60 °C, 8–12 h; 2. add 4–6 equiv of the corresponding amine (in case of value-added amines: add 1.5 equiv of the amine + 3–4 equiv *i*-Pr_2NEt) 40–60 °C; 8–12 h.
[b] Isolated yields after flash chromatography on SiO_2.

This mild reaction sequence also did not disappoint in the one-pot conversion of 4-chloro-7-azaindole-*N*-oxide MCBA salt **28**[54] to the corresponding 6-substituted derivatives **30**–**32** (see Scheme 6): no S_NAr product could be detected.

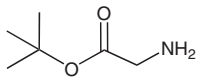
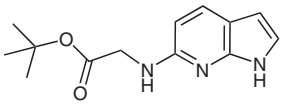
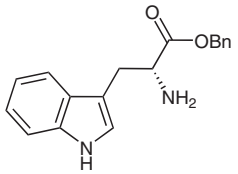
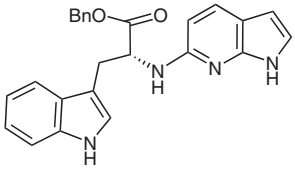
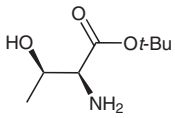
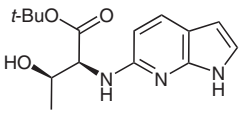
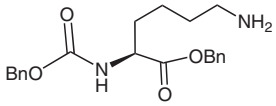
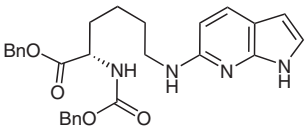
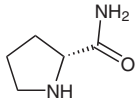
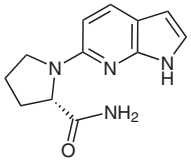
Moreover, the same protocol allows the facile introduction of α- and ω-amino acids as nitrogen substituents at C6 of 7-azaindole with full retention of optical purity. In this way, the new, unnatural 7-azaindolyl amino acid derivatives **33**–**37** (Table 2) were obtained, potentially useful new building blocks for the construction of peptidomimetic drugs.[55]

In general, after aqueous workup, the crude 6-amino-substituted azaindoles were obtained ≥85% pure by HPLC and only require minimal purification. This is remarkable, considering that three separate reaction steps (O-methylation, nucleophilic addition, MeOH-elimination, see Scheme 2) have to occur in this one-pot sequence. According to Katritzky[56] and Abramovitch,[57] the reaction of *N*-alkoxypyridinium salts with nucleophiles can proceed through a number of other reaction channels as well, such as pyridine ring opening, alkylation of the nucleophile by the R-group on the oxygen (vide supra), or deoxygenation of the *N*-oxide with concomitant aldehyde formation.[36a–d]



Scheme 6 Reaction of in situ generated 4-chloro-7-azaindole-*O*-methyl-*N*-oxide salt (**28**) with cyanide, ammonia, or propargylamine, respectively

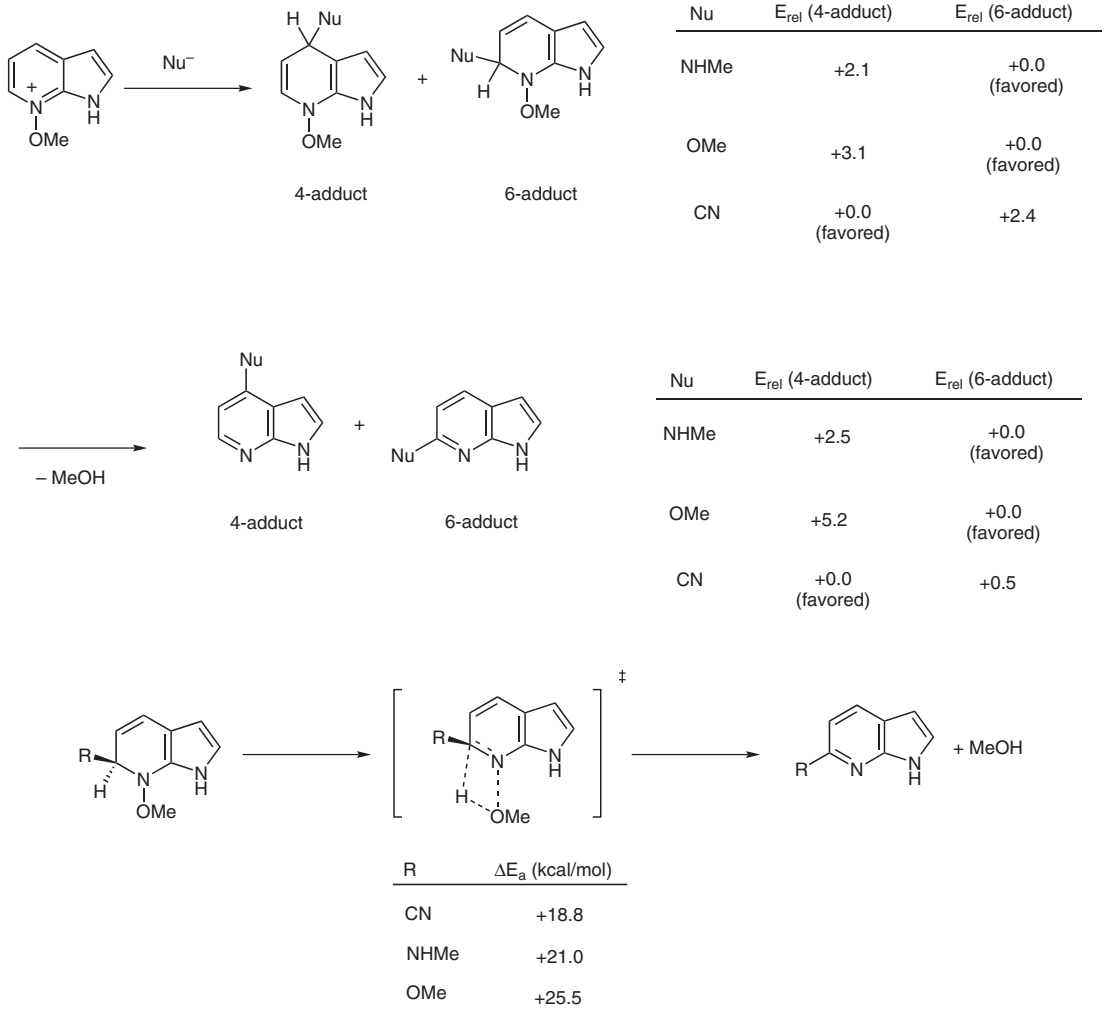
Table 2 6-Aminoacid-Substituted 7-Azaindoles **33–37** Prepared

α-Amino acid	Method[a]	Yield (%)[b]	Product[c]
 (Gly)	C	80	 **33**
 (D-Trp)	C	52	 **34**
 (L-Thr)	C	84	 **35**
 (L-Lys)	C	73	 **36**
 (L-Pro)	C	67	 **37**

[a] Method C: 1. **3** + dimethyl sulfate (1.05 equiv), MeCN, 50–60 °C; 8–12 h; 2. amino acid (1.5–2.0 equiv) + *i*-Pr_2NEt (2–3 equiv), MeCN, r.t. –45 °C; 8–24 h.

[b] Yields are for isolated and chromatographed products.

[c] Optical purity: Amino acid **35** did not show any signs of *erythro*-diastereomer in the NMR and on achiral and chiral stationary phases. For amino acids **34**, **36** and **37**, the opposite enantiomers were made and used as reference standards for chiral HPLC analysis; the enantiomeric purities were in line with the optical purity of the commercial AA building blocks used: **34**: er = 98.8:1.2; **36**: er = 100:0; **37**: er = 99.8:0.2.



Nu	E_{rel} (4-adduct)	E_{rel} (6-adduct)
NHMe	+2.1	+0.0 (favored)
OMe	+3.1	+0.0 (favored)
CN	+0.0 (favored)	+2.4

Nu	E_{rel} (4-adduct)	E_{rel} (6-adduct)
NHMe	+2.5	+0.0 (favored)
OMe	+5.2	+0.0 (favored)
CN	+0.0 (favored)	+0.5

R	ΔE_a (kcal/mol)
CN	+18.8
NHMe	+21.0
OMe	+25.5

Scheme 7 Relative energies (kcal/mol) of intermediate adducts and elimination products (B3LYP/6-31G* + ZPE)

As a rule, softer nucleophiles either react via the O-methylation pathway (phenols, heteroaromatic thiols) or tend to give somewhat lower regioselectivities (aliphatic, aromatic thiols, diazoles) than harder nucleophiles (amines, aliphatic alcoholates), which give the 6-regioisomer almost exclusively. The observed regioselectivity, in accordance with that of the Reissert–Henze reaction of thieno[2,3-*b*]- and furo[2,3-*b*]pyridine (α to the azine ring nitrogen),[58] is rationalized in part on the basis of the thermodynamic stabilities of both the initial intermediates, and final products after MeOH elimination (Scheme 7).[59] B3LYP/6-31G* geometry optimizations were performed on the 4- and 6-substituted intermediates and final products corresponding to addition of methylamine, methanol, and cyanide.

In accord with experimental findings for nitrogen- and oxygen-based nucleophiles, formation of the 6-regioisomers of both intermediate adduct and methanol elimination product are favored in a thermodynamic sense (Scheme 7). Curiously, addition of cyanide at the 4-position is predicted to be thermodynamically preferred, both in terms of the initial adduct intermediate and final eliminated product. We therefore attribute the kinetically-controlled formation of the observed 6-cyano isomer to rapid 1,2-elimination of methanol from the disfavored 6-adduct. B3LYP/6-31G* calculations locate a transition state corresponding to a unimolecular, 1,2-*syn*-elimination of MeOH, lying 18.8 kcal/mol in energy above the initial tetrahedral 6-cyano adduct. This pathway may constitute an additional, thermally accessible avenue, not available to the 4-substituted species, to account for formation of the observed 6-cyano product; however, medium effects, such as general acid-base catalysis and/or hydrogen bonding may also lower the elimination barrier and override the thermodynamic stability in the cyano case.

In summary, the newly discovered 7-*O*-methyl-*N*-oxides of 7-azaindole and 4-chloro-7-azaindole, respectively, lend themselves as versatile and convenient in situ Reissert–Henze intermediates[60] en route to a variety of 6-substituted 7-azaindoles not readily accessible via previous synthetic methodology.[38]

All reactions were carried out under N_2. All reagents were obtained from Aldrich. TLC was performed on silica gel 60 F_{254} (Merck) with detection by UV light and/or staining with anisaldehyde. Flash chromatography (FC) was performed on silica gel 60 (EMD, 40–63

μm). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400, 500 or 600 MHz spectrometer. IR spectra were recorded using a universal ATR sampling unit. All yields are isolated yields for chromatographed (HPLC ≥ 95A%) products (HPLC purity = area% at 254 nm unless otherwise indicated).

6-Cyano-7-azaindole (5)

A suspension of *N*-oxide MCBA salt **3**[27d] (3.5 g, 12.04 mmol) and dimethyl sulfate (1.38 mL, 14.45 mmol) in anhyd BuOAc (17.5 mL) was stirred under N_2 at 75–80 °C overnight. After cooling to 4 °C, the upper BuOAc phase was separated and discarded. The lower, purple phase was washed with cyclohexane (5 mL) and diluted with sat. aq NH_4Cl (25 mL). KCN (2.4 g, 3.0 equiv) was added and the purple mixture was stirred overnight at 50 °C, then cooled to 4 °C and filtered. The filter cake was rinsed with aq sat. $NaHCO_3$ (5 mL) and H_2O (5 mL) and dried in vacuo to afford **5** (1.309 g, 76%) as a slightly yellowish crystalline solid (HPLC: 95A% [245 nm]); mp (DSC) 187.4 °C (Lit.[23a] mp 175–177 °C).

IR (KBr): 2229 cm^{-1} (C≡N).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.25 (br s, 1 H, NH), 8.18 (d, $^3J_{4,5}$ = 8 Hz, 1 H, H-4), 7.83 (t, $^3J_{2,3}$ = $^3J_{2,NH}$ = 3.2 Hz, 1 H, H-2), 7.62 (d, $^3J_{5,4}$ = 8 Hz, 1 H, H-5), 6.63 (dd, $^3J_{3,2}$ = 3.4 Hz, $^4J_{3,NH}$ = 1.9 Hz, 1 H, H-3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 148.3 (C7a), 131.7 (C2), 129.5 (C4), 124.2 (C6), 123.4 (C3a), 120.4 (C5), 119.5 (C≡N).

HRMS (MALDI-TOF): *m*/*z* calcd for $C_8H_6N_3$ [M + H$^+$]: 144.0564; found: 144.0568.

6-Methoxy-7-azaindole (6); Typical Procedure

The procedure given below is not optimized.

A suspension of *N*-oxide MCBA salt **3**[27d] (1.69 g, 5.81 mmol) and dimethyl sulfate (0.6 mL, 6.39 mmol) in anhyd MeCN (15 mL) was stirred overnight under N_2 at 60–65 °C. After cooling to r.t., a soln of NaOMe in MeOH (25 wt%, Aldrich, 6.6 mL) was added, and the turbid mixture was stirred overnight at 60–65 °C. After neutralization with AcOH and diluting with MeOH, the mixture was evaporated to dryness. The residue was taken up in CH_2Cl_2 (20 mL) and washed with aq $NaHCO_3$ (2 × 5 mL). The aqueous layers were extracted with EtOAc (10 mL). The combined organic phases were dried (Na_2SO_4) and evaporated to dryness. Flash chromatography[61] on SiO_2 (hexanes–EtOAc) yielded **6** (695 mg, 81%) as a white crystalline solid; mp (DSC) 89.4 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.40 (br s, 1 H, NH), 7.84 (d, ^3J = 8.4 Hz, 1 H, H-4), 7.18 (dd, ^3J = 3.3, 2.5 Hz, 1 H, H-2), 6.52 (d, ^3J = 8.4 Hz, 1 H, H-5), 6.34 (dd, ^3J = 3.3 Hz, ^4J = 2.5 Hz, 1 H, H-3), 3.86 (s, 3 H, OCH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 160.4, 146.2, 131.8, 122.9, 114.1, 103.7, 100.6, 53.4.

HRMS (MALDI-TOF): *m*/*z* calcd $C_8H_9N_2O$ [M + H$^+$]: 149.07094; found: 149.07122.

6-Benzyloxy-7-azaindole (7)

Yield: 980 mg (85%); slightly yellowish; amorphous solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.46 (br s, 1 H), 7.87 (d, *J* = 8.4 Hz, 1 H), 7.45–7.30 (m, 5 H, C_6H_5), 7.19 (br d, *J* = 2.8 Hz, 1 H), 6.59 (d, *J* = 8.4 Hz, 1 H), 6.36 (br d, *J* = 3.2 Hz, 1 H), 5.38 (s, 2 H, OCH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 159.8, 146.0, 138.1, 132.0, 128.8, 128.3, 128.1, 123.1, 114.4, 103.9, 100.7, 67.1.

HRMS (MALDI-TOF): *m*/*z* calcd for $C_{14}H_{13}N_2O$ [M + H$^+$]: 225.10237; found: 225.10250.

6-Allyloxy-7-azaindole (8)

Yield: 650 mg (73%); off-white crystalline solid; mp (DSC) 69.3 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.44 (br s, 1 H), 7.86 (d, *J* = 8.3 Hz, 1 H), 7.20 (dd, *J* = 2.5, 3.3 Hz, 1 H), 6.55 (d, *J* = 8.3 Hz, 1 H), 6.35 (dd, *J* = 3.3, 1.9 Hz, 1 H), 6.12 (ddd, *J* = 17.2, 10.5, 5.3 Hz, 1 H), 5.39 (dq, *J* = 17.2, 3.2, 1.7 Hz, 1 H), 5.23 (dq, *J* = 10.5, 3.2, 1.4 Hz, 1 H), 4.83 (dt, *J* = 5.3, 1.7, 1.4 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 159.2, 145.6, 134.2, 131.5, 122.6, 116.9, 113.8, 103.3, 100.1, 65.7.

HRMS (MALDI-TOF): *m*/*z* calcd for $C_{10}H_{11}N_2O$ [M + H$^+$]: 175.08659; found: 175.08610.

6-(2-Naphthylthio)-7-azaindole (9)

This compound was prepared via a similar procedure as for the alcohols **6**–**8**, except that the sodium thiolate solution (5 equiv thiol + 5 equiv NaH) was generated in 2-methylteterahydrofuran; yield: 268 mg (51%); off-white crystalline solid; mp (DSC) 196.3 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.67 (br s, 1 H), 8.14 (s, 1 H), 7.96–7.92 (m, 3 H), 7.88 (d, *J* = 8.2 Hz, 1 H), 7.58–7.55 (m, 2 H), 7.53 (dd, *J* = 8.6, 1.4 Hz, 1 H), 7.41 (br t, *J* = 3, 2 Hz, 1 H), 6.92 (d, *J* = 8.2 Hz, 1 H), 6.42 (br d, *J* = 2 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 150.2, 148.4, 133.4, 132.3, 131.8, 130.4, 130.3, 129.4, 128.9, 127.6, 127.5, 126.7, 126.0, 117.8, 115.4, 100.1.

HRMS (MALDI-TOF): *m*/*z* calcd for $C_{17}H_{13}N_2S$ [M + H$^+$]: 277.07940; found: 277.07957.

6-Dodecylthio-7-azaindole (10)

Yield: 1.0 g (63%); slightly pinkish crystalline solid; mp (DSC) 77.3 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.56 (br s, 1 H), 7.80 (d, *J* = 8.2 Hz, 1 H), 7.31 (dd, *J* = 3.5, 2.5 Hz, 1 H), 6.92 (d, *J* = 8.2 Hz, 1 H), 6.37 (br dd, *J* = 2, 3.3 Hz, 1 H), 3.16 (t, *J* = 7.3 Hz, 2 H), 1.68–1.61 (m, 2 H), 1.44–1.37 (m, 2 H), 1.32–1.16 (m, 16 H), 0.85 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 150.5, 148.3, 128.8, 124.4, 116.4, 114.2, 100.0, 31.3, 29.6, 29.1, 29.0, 28.95, 28.7, 28.6, 28.3, 22.1, 14.0.

HRMS (MALDI-TOF): *m*/*z* calcd for $C_{19}H_{31}N_2S$ [M + H$^+$]: 319.22025; found: 319.21952.

6-Dodecylsulfonyl-7-azaindole (11)

To a soln of the thioether **10** (860 mg, 2.69 mmol) in CH_2Cl_2 (30 mL) was added MCPBA (1.1 g, 5.40 mmol) at 0 °C. The resulting lemon-yellow suspension was allowed overnight to reach r.t. and quenched at 0 °C by adding aq 0.2 M $Na_2S_2O_3$ (5 mL). After dilution with CH_2Cl_2 (30 mL), phases were separated and the organic phase was washed with aq $NaHCO_3$ (15 mL) and brine (15 mL). The organic phases were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. After FC on SiO_2, **11** was obtained (855 mg, 91%) as a slightly yellowish crystalline solid; mp (DSC) 87.1 °C.

IR (KBr): 1324/1310, 1149/1110 cm^{-1} (O=S=O).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.32 (br s, 1 H), 8.26 (d, *J* = 8.1 Hz, 1 H), 7.84 (br t, *J* = 3 Hz, 1 H), 7.74 (d, *J* = 8.1 Hz, 1 H), 6.66 (br dd, *J* = 1.7, 3.2 Hz, 1 H), 3.41–3.37 (m, 2 H), 1.58–1.52 (m, 2 H), 1.32–1.10 (m, 18 H), 0.84 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 149.1, 147.6, 131.6, 129.9, 123.5, 113.7, 101.1, 52.3, 31.8, 29.5, 29.3, 29.2, 29.1, 28.8, 27.9, 22.6, 22.5, 14.4.

HRMS (MALDI-TOF): *m/z* calcd for $C_{19}H_{30}N_2O_2SNa$ [M + Na^+]: 373.19202; found: 373.19269.

6-(1,2,4-Triazol-2-yl)-7-azaindole (13); Typical Procedure

A suspension of *N*-oxide MCBA salt **3**[27d] (2.5 g, 8.60 mmol) and dimethyl sulfate (1.0 mL, 10.32 mmol) in anhyd MeCN (15 mL) was stirred under N_2 at 60 °C overnight. The purple solution was divided up into five equal aliquots. To one of the aliquots was added 1,2,4-triazole (360 mg, 5.2 mmol) and anhyd K_2CO_3 (1.2 g, 8.6 mmol). After stirring overnight at 60 °C and cooling to r.t., the suspension was neutralized with aq AcOH and evaporated to dryness. The solid residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq Na_2CO_3 (3 mL), and the combined organic layers washed with brine (3 mL) and H_2O (3 mL). After drying ($MgSO_4$) and evaporating to dryness, flash chromatography[61] of the crude product with hexanes–EtOAc afforded **13** (255 mg, 80%) as an off-white crystalline solid; mp (DSC) 225.5 °C. Trace amounts of the 4-isomer are readily removed during purification; purity: ≥95A% HPLC.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.95 (br s, 1 H, NH), 9.26 (s, 1 H), 8.27 (s, 1 H), 8.20 (d, *J* = 8.3 Hz, 1 H), 7.61 (d, *J* = 8.3 Hz, 1 H), 7.56 (br t, *J* = 3 Hz, 1 H), 6.55 (d, *J* = 3 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6) δ: 152.5, 146.0, 143.4, 141.3, 131.4, 127.4, 119.7, 105.2, 100.5.

HRMS (MALDI-TOF): *m/z* calcd for $C_9H_8N_5$ [M + H^+]: 186.07742; found: 186.07732.

6-(Benzimidazol-1-yl)-7-azaindole (14)

Prepared by adding benzimidazole (615 mg, 5.2 mmol) to one of the aliquots obtained in the typical procedure described above; yield: 244 mg (60%); off-white crystalline solid; mp (DSC) 210.8 °C. Trace amounts of the 4-isomer are readily removed during purification; purity: ≥95A% HPLC.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.96 (br s, 1 H), 8.91 (s, 1 H), 8.33 (d, *J* = 8.0 Hz, 1 H), 8.22 (d, *J* = 8.4 Hz, 1 H), 7.78 (d, *J* = 7.9 Hz, 1 H), 7.58 (d, *J* = 8.4 Hz, 1 H), 7.55 (d, *J* = 3.4 Hz, 1 H), 7.39 (m, 1 H), 7.33 (m, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 147.1, 144.5, 144.4, 142.8, 132.6, 131.6, 127.2, 123.9, 123.4, 120.2, 118.7, 114.0, 107.6, 100.8.

HRMS (MALDI-TOF): *m/z* calcd for $C_{14}H_{11}N_4$ [M + H^+]: 235.09782; found: 235.09801.

(Indazol-1-yl)-7-azaindole (15)

Prepared by adding indazole (615 mg, 5.2 mmol) to one of the aliquots obtained in the typical procedure described above; yield: 302 mg (75%); white crystalline solid; mp (DSC) 215.2 °C. Trace amounts of the 4-isomer are readily removed during purification; purity: ≥95A% HPLC.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.81 (br s, 1H), 8.91 (dd, *J* = 8.6, 0.6 Hz, 1 H), 8.41 (s, 1 H), 8.15 (d, *J* = 8.45 Hz, 1 H), 7.91 (d, *J* = 8 Hz, 1 H), 7.77 (d, *J* = 8.45 Hz, 1 H), 7.57 (m, 1 H), 7.48 (br d, *J* = 3.3 Hz, 1 H), 7.32 (br t, *J* = 7.45 Hz, 1 H), 6.51 (d, *J* = 3.3 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 148.6, 146.3, 138.3, 136.7, 131.4, 127.9, 126.0, 125.9, 122.6, 121.5, 117.3, 115.1, 106.2, 100.9.

HRMS (MALDI-TOF): *m/z* calcd for $C_{14}H_{11}N_4$ [M + H^+]: 235.09785; found: 235.09758.

Amino Adducts 16–27; Typical Procedures

Procedure A: A suspension of *N*-oxide MCBA salt **3**[27d] (1.23 g, 4.24 mmol) and dimethyl sulfate (0.45 mL, 4.63 mmol) in anhyd MeCN (9 mL) was stirred under N_2 at 55–60 °C for 14 h. After transferring the mixture to a 25 mL glass pressure tube and cooling to 0–4 °C, a soln of ammonia in MeOH (Aldrich, 7 M, anhyd, 10 mL) was added slowly. The mixture was stirred overnight in the sealed tube at 50–55 °C. After cooling to r. t., the suspension was evaporated to dryness, and the solid residue partitioned between CH_2Cl_2 (10 mL) and 10% aq Na_2CO_3 (2.5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were washed with 10% aq Na_2CO_3 (3 mL), brine (3 mL), and H_2O (3 mL). After drying ($MgSO_4$) and evaporating to dryness, flash chromatography[61] of the crude product (84A% HPLC) with toluene–EtOAc afforded **16**[35b] (373 mg, 65%) as an amber crystalline solid (99.5A% HPLC, 230 nm). Anhyd $MeNH_2$ in EtOH (33 wt%, 5.8 mL) was used for the preparation of **17** (860 mg, 71%, TFA-salt [isolated by preparative RP-HPLC on a C18-phase, MeCN–H_2O, 1% TFA]).

Procedure B: A suspension of *N*-oxide MCBA salt **3**[27d] (1.50 g, 5.15 mmol) and dimethyl sulfate (0.55 mL, 5.65 mmol) in anhyd MeCN (10 mL) was stirred overnight under N_2 at 55–60 °C. After cooling to r.t., DL-2-aminopropan-1-ol (2.0 mL, 25.5 mmol) was added slowly and the mixture was stirred overnight under N_2 at 50–55 °C. After cooling to r. t., the suspension was concentrated under reduced pressure, and the residue partitioned between CH_2Cl_2 (10 mL) and 10% aq Na_2CO_3 (2.5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were washed with 10% aq Na_2CO_3 (3 mL), brine (3 mL), H_2O (3 mL), and dried ($MgSO_4$). After concentrating to dryness, flash chromatography[61] of the crude evaporated residue (900 mg, 82A% HPLC, 230 nm) with CH_2Cl_2–MeOH afforded **26** (710 mg, 72%) as a caramel-colored solid. Similarly compounds **18**–**25** and **27** were prepared using 3–6 equiv of the corresponding amine nucleophile.

6-Amino-7-azaindole (16)

Yield: 373 mg (65%); crystalline solid; mp (DSC) 126.7 °C (Lit.[35b] mp 118–119 °C).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.79 (br s, 1 H, NH), 7.54 (d, $^3J_{4,5}$ = 8.4 Hz, 1 H, H-4), 6.91 (dd, $^3J_{2,3}$ = 3.0 Hz, $^3J_{2,NH}$ = 2.4 Hz, 1 H, H-2), 6.25 (d, $^3J_{5,4}$ = 8.4 Hz, 1 H, H-5), 6.16 (dd, $^3J_{3,2}$ = 3.3 Hz, $^4J_{3,NH}$ = 2.4 Hz, 1 H, H-3), 5.56 (br s, 2 H, NH_2).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 155.7, 147.5, 129.8, 119.9, 110.7, 102.7, 99.95.

HRMS (MALDI-TOF): *m/z* calcd for $C_7H_8N_3$ [M + H^+]: 134.07127; found: 134.07150.

6-Methylamino-7-azaindole Trifluoroacetic Acid Salt (17)

Yield: 860 mg (71%); off-white crystalline solid; mp (DSC) 99.6 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.79 (br s, 1 H), 8.04 (br d, *J* = 8.85 Hz, 1 H), 7.10 (m, 1 H), 6.56 (br d, *J* = 8.85 Hz, 1 H), 6.44 (m, 1 H), 2.96 (br s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = {159.1, 158.9, 158.7, 158.4} (C=O [CF_3COO^-]), 151.4, 136.9, 136.4, 121.4, {119, 117, 115, 113} (CF_3 [CF_3COO^-]), 111.3, 103.2, 102.2, 28.7.

HRMS (MALDI-TOF): *m/z* calcd for $C_8H_9N_3Na$ (free base) [M + Na^+]: 170.06887; found: 170.06837.

6-Cyclopropylamino-7-azaindole (18)

Yield: 542 mg (67%); brownish crystalline solid; mp (DSC) 115.3 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.0 (br s, 1 H), 7.60 (d, *J* = 8.4 Hz, 1 H), 6.94 (m, 1 H), 6.47 (br s, 1 H), 6.37 (d, *J* = 8.4 Hz, 1 H), 6.18 (m, 1 H), 2.56 (m, 1 H), 0.68 (m, 2 H), 0.42 (m, 2 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 156.0, 147.7, 129.5, 120.0, 110.9, 101.8, 99.8, 24.1, 6.8.

HRMS (MALDI-TOF): *m/z* calcd for $C_{10}H_{12}N_3$ [M + H^+]: 174.10257; found: 174.10205.

6-(Tetrahydrofuran-2-ylmethyl)amino-7-azaindole (19)
Yield: 925 (83%); yellow amorphous solid.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.91 (br s, 1 H), 7.52 (d, *J* = 8.4 Hz, 1 H), 6.88 (dd, *J* = 2.4, 3.2 Hz, 1 H), 6.32 (d, *J* = 8.4 Hz, 1 H), 6.26 (t, *J* = 5.8 Hz, 1 H), 6.15 (dd, *J* = 2.0, 3.2 Hz, 1 H), 4.02 (m, 1 H), 3.79 (m, 1 H), 3.62 (m, 1 H), 3.38–3.30 (m, 2 H), 1.95–1.55 (m, 4 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 155.3, 147.4, 129.5, 119.5, 110.1, 103.2, 100.0, 77.3, 67.0, 45.2, 28.8, 25.2.

HRMS (MALDI-TOF): *m*/*z* calcd for $C_{12}H_{16}N_3O$ [M + H$^+$]: 218.12879; found: 218.12904.

6-Allylamino-7-azaindole (20)
Yield: 625 (70%); slightly pinkish crystalline solid; mp (DSC) 71.2 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.92 (br s, 1 H), 7.54 (d, *J* = 8.3 Hz, 1 H), 6.89 (dd, *J* = 2.4, 3.3 Hz, 1 H), 6.38 (t, *J* = 5.75 Hz, 1 H), 6.31 (d, *J* = 8.3 Hz, 1 H), 6.15 (dd, *J* = 2.0, 3.3 Hz, 1 H), 5.96 (m, 1 H), 5.20 (m, 1 H), 5.05 (m, 1 H), 3.92 (m, 2 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 155.1, 147.5, 136.9, 129.6, 119.6, 114.6, 110.3, 103.1, 100.0, 43.4.

HRMS (MALDI-TOF): *m*/*z* calcd for $C_{10}H_{12}N_3$ [M + H$^+$]: 174.10257; found: 174.10201.

6-(Pyridin-4-ylmethyl)amino-7-azaindole (21)
Yield: 890 mg (77%); reddish oil.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.94 (br s, 1 H), 8.46 (d, *J* = 5.9 Hz, 2 H), 7.59 (d, *J* = 8.6 Hz, 1 H), 7.32 (d, *J* = 5.9 Hz, 1 H), 6.96 (br t, *J* = 8.1 Hz, 1 H), 6.90 (dd, *J* = 2.5, 3.2 Hz, 1 H), 6.38 (d, *J* = 8.6 Hz, 1 H), 6.17 (dd, *J* = 2.0, 3.4 Hz, 1 H), 4.55 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 154.9, 150.6, 149.3, 147.4, 129.9, 122.2, 119.9, 110.7, 103.1, 100.1, 43.4.

HRMS (MALDI-TOF): *m*/*z* calcd for $C_{13}H_{13}N_4$ [M + H$^+$]: 225.11347; found: 225.11397.

6-Propargylamino-7-azaindole (22)
Yield: 400 (68%); yellowish crystalline solid; mp (DSC) 104.7 °C.

IR (KBr): 2106 cm^{-1} (C≡C).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.05 (br s, 1 H), 7.59 (d, *J* = 8.4 Hz, 1 H), 6.95 (dd, *J* = 2.5, 3.2 Hz, 1 H), 6.59 (br t, *J* = 5.9 Hz, 1 H), 6.33 (d, *J* = 8.4 Hz, 1 H), 6.18 (dd, *J* = 2.0, 3.2 Hz, 1 H), 4.06 (dd, *J* = 5.9, 2.5 Hz, 2 H), 2.98 (s, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 154.3, 147.3, 129.7, 120.1, 110.8, 103.3, 100.0, 83.1, 72.1, 30.3.

HRMS (MALDI-TOF): *m*/*z* calcd for $C_{10}H_{10}N_3$ [M + H$^+$]: 172.08692; found: 172.08679.

6-Diethylamino-7-azaindole (23)
Yield: 825 mg (87%); yellowish crystalline solid; mp (DSC) 67.4 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.93 (br s, 1 H), 7.63 (d, *J* = 8.6 Hz, 1 H), 6.93 (dd, *J* = 2.4 Hz, 1 H), 6.38 (d, *J* = 8.6 Hz, 1 H), 6.18 (dd, *J* = 2.0, 3.0 Hz, 1 H), 3.50 (q, *J* = 7.0 Hz, 4 H), 1.12 (t, *J* = 7.0 Hz, 6 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 153.8, 147.9, 129.9, 120.1, 109.9, 100.0, 99.7, 42.0, 13.1.

HRMS (MALDI-TOF): *m*/*z* calcd for $C_{11}H_{16}N_3$ [M + H$^+$]: 190.13387; found: 190.13359.

6-(Morpholin-4-yl)-7-azaindole (24)
Yield: 416 mg (63%); yellowish crystalline solid; mp (DSC) 161.1 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.09 (br s, 1 H), 7.75 (d, *J* = 8.6 Hz, 1 H), 7.08 (dd, *J* = 2.4, 3.3 Hz, 1 H), 6.64 (d, *J* = 8.6 Hz, 1 H), 6.25 (dd, *J* = 2.0, 3.3 Hz, 1 H), 3.73 (m, 2 H), 3.41 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.9, 147.1, 130.0, 121.9, 112.1, 101.5, 99.7, 66.1, 46.4.

HRMS (MALDI-TOF): *m*/*z* calcd for $C_{11}H_{14}N_3O$ [M + H$^+$]: 204.11314; found: 204.11319.

(±)-6-(Propan-2-ol-3-yl)amino-7-azaindole (25)
Yield: 510 mg (58%); brownish crystalline solid; mp (DSC) 160.2 °C.

IR (KBr): 3312, 3242 (s) cm^{-1} (O–H).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.90 (br s, 1 H, exch. D_2O), 7.53 (d, *J* = 8.4 Hz, 1 H), 6.88 (t, *J* = 2.8 Hz, 1 H), 6.31 (d, *J* = 8.4 Hz, 1 H), 6.18 (br t, *J* = 5.6 Hz, exch. D_2O, 1 H), 6.15 (br d, *J* = 1.9 Hz, 1 H), 4.82 (br s, 1 H, exch. D_2O), 3.82 (m, 1 H), 3.25–3.17 (m, 2 H), 1.10 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 155.6, 147.4, 129.6, 119.5, 110.1, 103.2, 100.0, 65.5, 49.2, 21.5.

^{15}N NMR (60.8 MHz, DMSO-d_6): δ = 218.5, 137.1, 75.2.

HRMS (MALDI-TOF): *m*/*z* calcd for $C_{10}H_{14}N_3O$ [M + H$^+$]: 192.11314; found: 192.11222.

(±)-6-(Propan-1-ol-2-yl)amino-7-azaindole (26)
Yield: 634 mg (72%); yellowish crystalline solid; mp (DSC) 108.9 °C.

IR (KBr): 3377 (s) cm^{-1} (O–H).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.89 (br s, 1 H), 7.51 (d, *J* = 8.5 Hz, 1 H), 6.88 (dd, *J* = 2.6, 3.1 Hz, 1 H), 6.27 (d, *J* = 8.5 Hz, 1 H), 6.14 (dd, *J* = 2.0, 3.3 Hz, 1 H), 5.94 (d, *J* = 7.7 Hz, 1 H), 4.72 (br s, 1 H), 3.96 (m, 1 H), 3.51 (m, 1 H), 3.33 (m, 1 H), 1.14 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 155.5, 147.9, 130.0, 119.9, 110.5, 103.9, 100.5, 65.5, 48.3, 18.2.

HRMS (MALDI-TOF): *m*/*z* calcd for $C_{10}H_{14}N_3O$ [M + H$^+$]: 192.11314; found: 192.11259.

(*S*)-6-(2-Hydroxymethylpyrrolidin-1-yl)-7-azaindole (27)
Yield: 840 mg (73%); light-yellow crystalline solid; mp (DSC) 118.4 °C.

IR (KBr): 3178 (s) cm^{-1} (O–H).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.04 (br s, 1 H), 7.67 (d, *J* = 8.8 Hz, 1 H), 6.95 (dd, *J* = 2.4, 3.3 Hz, 1 H), 6.31 (d, *J* = 8.8 Hz, 1 H), 6.20 (dd, *J* = 1.8, 3.3 Hz, 1 H), 4.94 (br t, *J* = 4 Hz, 1 H, OH), 4.03 (m, 1 H), 3.62 (m, 1 H), 3.48 (m, 1 H), 3.35–3.20 (m, 2 H), 2.05–1.83 (m, 4 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 153.9, 147.6, 129.9, 120.4, 110.5, 101.1, 99.9, 62.1, 59.5, 48.0, 27.8, 23.0.

^{15}N NMR (60.8 MHz, DMSO-d_6): δ = 222.7, 136.8, 92.5.

HRMS (MALDI-TOF): *m*/*z* calcd for $C_{12}H_{16}N_3O$ [M + H$^+$]: 218.12879; found: 218.12874.

4-Chloro-7-azaindole-7-oxide MCBA Salt 28
To a vigorously stirred suspension of 4-chloroazaindole[27a] (22.7 g, 148.77 mmol) in butyl acetate–heptane (3:5, 800 mL) was added portionwise MCPBA (37.65 g, 163.65 mmol) under cooling in an ice bath. The suspension was vigorously stirred and allowed overnight to reach r.t. Suction filtration of the resulting white suspen-

sion, followed by washing the filter cake with heptane (4 × 100 mL) provided, after drying in vacuo, **28** as an off-white powdery solid (42.72 g, 88%; 98.4% HPLC, 220 nm); mp (DSC) 151.9 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 13.37 (br s, 1 H), 12.90 (br s, 1 H), 8.15 (d, *J* = 6.6 Hz, 1 H), 7.89 (m, 2 H) 7.68 (d, *J* = 8.0 Hz, 1 H), 7.56 (d, *J* = 3.1 Hz, 1 H), 7.52 (t, *J* = 8.1 Hz, 1 H), 7.20 (d, *J* = 6.6 Hz, 1 H), 6.58 (d, *J* = 3.1 Hz, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 166.6, 133.8, 133.5, 133.1, 132.3, 131.1, 129.3, 128.4, 128.0, 123.9, 122.5, 116.5, 101.1.

HRMS (MALDI-TOF): *m*/*z* calcd for $C_7H_6ClN_2O$ [M + H$^+$]: 169.01632; found: 169.01594.

4-Chloro-6-cyano-7-azaindole (30)

Using the synthetic procedure for **5** (vide supra), 4-chloro-7-azaindole-*N*-oxide MCBA salt **28** (1.3 g, 3.98 mmol) gave **30** (675 mg, 95%) as slightly yellowish crystalline solid; mp (DSC) 213.0 °C.

IR (KBr): 2232 (C≡N).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.67 (br s, 1 H), 7.98 (d, *J* = 3.4 Hz, 1 H), 7.89 (s, 1 H), 6.70 (d, *J* = 3.4 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 148.1, 134.4, 132.3, 124.3, 121.8, 119.5, 117.9, 99.0.

HRMS (MALDI-TOF): *m*/*z* calcd for $C_8H_5ClN_3$ [M + H$^+$]: 178.01665; found: 178.01655.

6-Amino-4-chloro-7-azaindole (31)

Following the synthetic procedure for **16** [vide supra, using 2 M NH_3/EtOH (8 equiv) instead of NH_3/MeOH], 4-chloro-7-azaindole-*N*-oxide MCBA salt **28** (1.6 g, 4.92 mmol) gave **31** (690 mg, 83%) as an amber crystalline solid; mp (DSC) 140.0 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.14 (br s, 1 H), 7.02 (dd, *J* = 2.3, 3.3 Hz, 1 H), 6.36 (s, 1 H), 6.22 (dd, *J* = 3.3, 2.3 Hz, 1 H), 5.85 (br s, 2 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 156.4, 148.3, 135.1, 121.0, 109.9, 101.7, 98.0.

HRMS (MALDI-TOF): *m*/*z* calcd for $C_7H_7ClN_3$ [M + H$^+$]: 168.03230; found: 168.03218.

4-Chloro-6-propargylamino-7-azaindole (32)

Applying the typical procedure B for **26** (vide supra, using 3 equiv propargylamine overnight at r.t.), **32** was obtained from of 4-chloro-7-azaindole-*N*7-oxide MCBA-salt **28** (vide supra, 925 mg, 2.84 mmol); yield: 320 mg (55%); slightly yellowish crystalline solid; mp (DSC) 110.6 °C.

IR (KBr): 2111 cm^{-1} (C≡C).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.44 (br s, 1 H), 7.06 (dd, *J* = 3.4, 2.4 Hz, 1 H), 6.88 (br t, *J* = 2.3 Hz), 6.45 (s, 1 H), 6.25 (dd, *J* = 2.3, 3.4 Hz, 1 H), 4.07 (dd, *J* = 5.7, 2.3 Hz), 3.05 (t, *J* = 2.3 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 154.9, 148.0, 135.2, 121.3, 110.1, 102.3, 98.2, 82.6, 72.5, 30.4.

HRMS (MALDI-TOF): *m*/*z* calcd $C_{10}H_9ClN_3$ [M + H$^+$]: 206.04795; found: 206.04778.

Chiral Amino Acid Adducts 33–37

***N*-(7-Azaindol-6-yl)glycine *tert*-Butyl Ester (33); Typical Procedure**

A suspension of *N*-oxide MCBA salt **3** (vide supra) (875 mg, 3.0 mmol) and dimethyl sulfate (0.303 ml, 3.16 mmol) in anhyd MeCN (5 mL) was stirred overnight under N_2 at 55–60 °C. After cooling the resulting dark purple soln to r.t., glycine *tert*-butyl ester (790 mg, 6.0 mmol) and Hünig's base (1.05 mL, 6.0 mmol) were added slowly and the mixture was stirred overnight under N_2 at r.t. The suspension was concentrated under reduced pressure, and the residue partitioned between CH_2Cl_2 (20 mL) and 10% aq Na_2CO_3 (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were washed with 10% aq Na_2CO_3 (3 mL), brine (3 mL), H_2O (3 mL), and dried ($MgSO_4$). After concentrating to dryness, flash chromatography[61] (toluene–EtOAc) of the crude evaporated residue yielded **33** (600 mg, 80%) as a light yellow crystalline solid; mp (DSC) 114.4 °C.

Similarly compounds **34**–**37** were prepared at reaction temperatures from r.t. to 45 °C. The yields given are isolated yields for chromatographed (HPLC ≥94A%, 230 nm) products.

Optical purity was checked either via analytical HPLC on a Chiralcel OJ-H column (4.6 × 250mm, 5 µm, mobile phase: *i*-PrOH–hexane), or via analytical SFC on a Chiralpak AD-H column [4.6 × 250 mm, 5 µm, mobile phase: MeOH (0.1% *i*-PrNH_2)/scCO_2], using the opposite enantiomer as reference standards.

IR (KBr): 3406 (NH), 1731 cm^{-1} (C=O).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.95 (br s, 1 H), 7.57 (d, *J* = 8.5 Hz, 1 H), 6.92 (m, 1 H), 6.65 (br t, *J* = 6.3 Hz, 1 H), 6.35 (d, *J* = 8.5 Hz, 1 H), 6.18 (m, 1 H), 3.93 (d, *J* = 6.4 Hz, 2 H), 1.41 (s, 9 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 171.4, 155.2, 147.7, 130.1, 120.4, 111.1, 103.7, 100.4, 80.4, 44.0, 28.3.

^{15}N NMR (60.8 MHz, DMSO-d_6): δ = 271.0, 188.1 ($^1J_{N,H}$ = 90 Hz), 120.8 ($^1J_{N,H}$ = 90 Hz).

HRMS (MALDI-TOF): *m*/*z* calcd for $C_{13}H_{17}N_3O_2Na$ [M + Na$^+$]: 270.12130; found: 270.12192.

(*S*)-N_α-(7-Azaindol-6-yl)tryptophan Benzyl Ester (34)

Reaction temperature: 45 °C; yield: 725 mg (52%); brownish viscous oil.

IR (KBr): 3406 (s) (NH), 1728 (s) cm^{-1} (C=O).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.95 (br s, 1 H), 10.88 (br s, 1 H), 7.59–7.53 (m, 2 H), 7.37 (d, *J* = 8.1 Hz, 1 H), 7.32–7.08 (m, 7 H), 7.00 (t, *J* = 7.1 Hz, 1 H), 6.92 (dd, *J* = 2.6, 3.1 Hz, 1 H), 6.77 (br d, *J* = 8.2 Hz, 1 H), 6.40 (d, *J* = 8.6 Hz, 1 H), 6.18 (dd, *J* = 1.9, 3.3 Hz, 1 H), 5.07–5.00 (m, 2 H), 4.87 (q, *J* = 7.4 Hz, 1 H), 3.27 (dd, *J* = 6.3 Hz, 1 H), 3.19 (dd, *J* = 8.0, 14.1 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 174.5, 154.8, 147.5, 137.8, 136.7, 136.6, 130.1, 129.4, 128.7, 128.5, 128.1, 127.8, 127.6, 127.1, 126.9, 125.8, 124.3, 121.4, 120.5, 118.9, 118.6, 111.9, 111.3, 110.6, 103.9, 100.5, 65.9, 55.6, 28.4.

^{15}N NMR (50.7 MHz, DMSO-d_6): δ = 320.8, 137.8, 131.4, 83.8.

HRMS (MALDI-TOF): *m*/*z* calcd for $C_{25}H_{23}N_4O_2$ [M + H$^+$]: 411.18155; found: 411.18202.

(*S*)-*N*-(7-Azaindol-6-yl)threonine *tert*-Butyl Ester (35)

Reaction temperature 45 °C; yield: 1.3 g (84%); brownish viscous oil.

IR (KBr): 3383 (s/br) (OH/NH), 1727 cm^{-1} (C=O).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.90 (br s, 1 H, exch. D_2O), 7.57 (d, *J* = 8.5 Hz, 1 H), 6.91 (br t, *J* = 2.8 Hz, 1 H), 6.47 (d, *J* = 8.5 Hz, 1 H), 6.17 (dd, *J* = 1.9, 3.3 Hz, 1 H), 6.10 (br d, *J* = 9.0 Hz, 1 H, exch. D_2O), 4.87 (d, *J* = 6.15 Hz, 1 H, exch. D_2O), 4.37 (dd, *J* = 3.7, 9.0 Hz, 1 H), 4.14 (m, 1 H), 1.38 (s, 9 H), 1.17 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 172.1, 155.4, 147.5, 130.1, 120.4, 111.2, 104.1, 100.4, 80.2, 67.6, 60.7, 28.2, 21.4.

^{15}N NMR (50.7 MHz, DMSO-d_6): δ = 136.7 (NH), 75.1 (NH).

HRMS (MALDI-TOF): *m*/*z* calcd for $C_{15}H_{22}N_3O_3$ [M + H$^+$]: 292.16557; found: 292.16619.

(*S*)-N_α-Cbz-N_ω-(7-Azaindol-6-yl)lysine Benzyl Ester (36)
Reaction temperature: 30 °C; yield: 1.72 g (73%); brownish crystalline solid; mp (DSC) 95.7 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.91 (br s, 1 H, exch. D_2O), 7.82 (d, *J* = 7.7 Hz, 1 H, exch. D_2O), 7.51 (d, *J* = 8.5 Hz, 1 H), 7.39–7.23 (m, 10 H), 6.88 (dd, *J* = 2.5, 3.2 Hz, 1 H), 6.24 (d, *J* = 8.5 Hz, 1 H), 6.21 (br t, *J* = 5.5 Hz 1 H, exch. D_2O), 6.14 (dd, *J* = 1.9, 3.3 Hz, 1 H), 5.13 (s, 2 H), 5.03 (AB system, 2 H), 4.11 (m, 1 H), 3.20 (AB system, 2 H), 1.76–1.61 (m, 2 H), 1.53 (m, 2 H), 1.40 (m, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 172.9, 156.7, 155.9, 148.1, 137.4, 136.4, 129.9, 128.9, 128.8, 128.5, 128.3, 128.2, 119.9, 110.4, 103.6, 100.5, 66.4, 66.0, 54.6, 41.3, 31.0, 29.1, 23.7.

^{15}N NMR (50.7 MHz, DMSO-d_6): δ = 269.4 (N7), 186.8 (N1), 138.0 (Lys-α-N), 128.9 (Lys-ω-N).

HRMS (MALDI-TOF): *m/z* calcd for $C_{28}H_{31}N_4O_4$ [M + H^+]: 487.23398; found: 487.23452.

(*S*)-N_α-(7-Azaindol-6-yl)prolinecarboxamide (37)
Reaction temperature: 40 °C; yield: 690 mg (67%); yellowish viscous oil.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.05 (br s, 1 H), 7.68 (d, *J* = 8.5 Hz, 1 H), 7.26 (br s, 1 H), 6.97 (dd, *J* = 3.1, 2.5 Hz, 1 H), 6.94 (br s, 1 H), 6.24 (d, *J* = 8.5 Hz, 1 H), 6.21 (dd, *J* = 3.1, 1.9 Hz, 1 H), 4.25 (dd, *J* = 9.4, 10.2 Hz, 1 H), 3.68 (m, 1 H), 3.35 (m, 1 H), 2.14 (m, 1 H), 1.99–1.91 (m, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 175.7, 153.4, 147.5, 129.7, 120.7, 110.9, 101.1, 99.8, 61.1, 47.9, 30.6, 23.7.

^{15}N NMR (60.8 MHz, DMSO-d_6): δ = 223.6, 136.7, 103.2 ($CONH_2$, $^1J_{N,H}$ = 87.9, 88.4 Hz), 91.6.

HRMS (MALDI-TOF): *m/z* calcd for $C_{12}H_{15}N_4O$ [M + H^+]: 231.12404; found: 231.12440.

Acknowledgment

We are grateful to Dr. Paul Schnier for exact mass determinations. Dr. J. Preston is thanked for DSC measurements and Mr. Milan Petkovic for IR spectroscopic data.

References

(1) New address: Wyeth Research, 401 N. Middletown Road, Pearl River, NY 109, USA.
(2) Kruber, O. *Ber. Dtsch. Chem. Ges.* **1943**, *76*, 128.
(3) (a) First synthesis of 7-azaindole: Clemo, G. R.; Swan, G. A. *J. Chem. Soc.* **1945**, 603. Improved versions: (b) Robison, M.; Robison, B. *J. Am. Chem. Soc.* **1955**, *77*, 457. (c) See also: Lorenz, R. R.; Tullar, B. F.; Koelsch, C. F.; Archer, S. *J. Org. Chem.* **1965**, *30*, 2531. (d) See also: Hands, D.; Bishop, B.; Cameron, M.; Edwards, J. S.; Cottrell, I. F.; Wright, S. H. B. *Synthesis* **1996**, 877. For reviews, see: (e) Willette, R. E. *Adv. Heterocycl. Chem.* **1968**, *9*, 27. (f) Yakhontov, L. N. *Khim. Geterotsikl. Soedin.* **1982**, 1155. (g) Mérour, J.-Y.; Benoît, J. *Curr. Org. Chem.* **2001**, *5*, 471. (h) Popowycz, F.; Routier, S.; Benoît, J.; Mérour, J.-Y. *Tetrahedron* **2007**, *63*, 1031. (i) For a review on synthetic methodology for (partially) hydrogenated pyrrolopyridines, see: Varlamov, A. V.; Borisova, T. N.; Voskressensky, L. G. *Synthesis* **2002**, 155.
(4) Jachontow, L. N. *Pharmazie* **1963**, *18*, 317, and references cited therein.
(5) (a) Kidder and co-workers were the first to report that 7-azaindoles can act as antimetabolites for the corresponding indole compounds in biological pathways: Kidder, G. W.; Dewey, V. C. *Biochim. Biophys. Acta* **1955**, *17*, 288. (b) For an early review on studies of biological activity of 7-azaindoles, see: Yakhontov, L. N.; Prokopov, A. A. *Russ. Chem. Rev. (Engl. Transl.)* **1980**, *49*, 428.
(6) Especially since the year 2000, the medicinal chemistry literature on pharmaceutically active 7-azaindole derivatives has increased exponentially; among others, their use has been reported in the following categories: (a) As constituents of anti-inflammatories: Saify, Z. N. *Pakistan J. Pharmacol.* **1985**, *2*, 43. (b) See also: Henry, J. R.; Dodd, J. H. *Tetrahedron Lett.* **1998**, *39*, 8763. (c) As anxiolytics: Meade, E. A.; Beauchamp, L. M. *J. Heterocycl. Chem.* **1996**, *33*, 303. (d) As plant antifungals: Minakata, S.; Hamada, T.; Komatsu, M.; Tsuboi, H.; Kikuta, H.; Ohshiro, Y. *J. Agric. Food Chem.* **1997**, *45*, 2345. (e) As corticotropin releasing hormone antagonists: Hodge, C. N.; Aldrich, P. E.; Wasserman, Z. R.; Fernandez, C. H.; Nemeth, G. A.; Arvanitis, A.; Cheeseman, R. S.; Chorvat, R. J.; Ciganek, E.; Christos, T. E.; Gilligan, P. J.; Krenitsky, P.; Scholfield, E.; Strucely, P. *J. Med. Chem.* **1999**, *42*, 819. (f) As antipsychotic agents: Kulagowski, J. J.; Broughton, H. B.; Curtis, N. R.; Mawer, I. M.; Ridgill, M. P.; Baker, R.; Emms, F.; Freedmann, S. B.; Marwood, R.; Patel, S.; Ragan, C. I.; Leeson, P. D. *J. Med. Chem.* **1996**, *39*, 1941. (g) As antitussive agents: Allegretti, M.; Anacardio, R.; Cesta, M. C.; Curti, R.; Mantovanini, M.; Nano, G.; Topai, A.; Zampella, G. *Org. Process Res. Dev.* **2003**, *7*, 209. (h) As antivirals/anti-HIV agents: Soundararajan, N.; Benoit, S.; Gingras, S. US Patent Appl. 2004/0044025, **2004**. (i) See also: Reeves, J. D.; Piefer, A. J. *Drugs* **2005**, *65*, 1747. (j) See also: Yang, A.; Zadjura, L.; D'Arienzo, A. M.; Santone, K.; Llunk, L.; Green, D.; Lin, P.-F.; Colonno, R.; Wang, T.; Neanwell, N.; Hansel, S. *Biopharm. Drug Dispos.* **2005**, *26*, 387. (k) As PPARγ modulators: Dropinski, J. F.; Akiyama, T.; Einstein, M.; Habulihaz, B.; Doebber, T.; Berger, J. P.; Meinke, P. T.; Shi, G. Q. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5035. (l) As inhibitors of various kinases (FAK, KDR, Tie2, Aurora, JNK): Tabart, M.; Bacque, E.; Halley, F.; Ronan, B.; Desmazeau, P.; Viviani, F.; Souaille, C. French Patent 2884821, **2006**. (m) See also: Patel, V. F.; Askew, B.; Booker, S.; Chen, G.; Dipietro, L. V.; Germain, J.; Habgood, G. J.; Huang, Q.; Kim, T.; Li, A.; Nishimura, N.; Nomak, R.; Riahi, B.; Yuan, C. C.; Elbaum, D. US Patent Appl. 2003/3203922, **2003**. (n) See also: Rodgers, J. D.; Wang, H.; Combs, A. P.; Sparks, R. B. PCT Int. Appl. WO 2006069080, **2006**. (o) See also: Graczyk, P.; Khan, A.; Bhatia, G.; Limura, Y. PCT Int. Appl. WO 2004078756, **2004**. (p) As dopamine D-4 receptor ligands: Le Hyaric, M.; de Almeida, M. V.; de Souza, M. V. N. *Quim. Nova* **2002**, *25*, 1165. (q) As gonadotropin releasing hormone antagonists: Ujjainwalla, F.; Walsh, T. F. *Tetrahedron Lett.* **2001**, *42*, 6441. (r) As GSK-3β inhibitors: O'Neill, D. J.; Shen, L.; Prouty, C.; Conway, B. R.; Westover, L.; Xu, J. Z.; Zhang, H.-C.; Maryanoff, B. E.; Murray, W. V.; Demarest, K. T.; Kuo, G.-H. *Bioorg. Med. Chem.* **2004**, *12*, 3167. (s) As p38 MAP kinase inhibitors: *Expert Opin. Ther. Pat.* **2004**, *15*, 227. (t) As Rho kinase inhibitors: Ishizaki, T.; Uehata, M.; Tamechika, I.; Keel, J.; Nonomura, K.; Maekawa, M.; Narumiya, S. *Mol. Pharm.* **2000**, *57*, 976. (u) As CDK1 inhibitors: Huang, S.; Li, R.; Connolly, P. J.; Emanuel, S.; Middleton, S. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4818. (v) As cannabimimetics: Gluszok, S.; Goossens, L.; Depreux, P.; Barbry, D.; Hénichart, J.-P. *Synth. Commun.* **2006**, *36*, 2797. (w) As antihistamines: Fonquerna, S.; Miralpeix, M.; Pagès, L.; Puig, C.; Cardús, A.; Antón, F.; Vilella, D.; Aparici, M.; Prieto, J.; Warrellow,

G.; Beleta, J.; Ryder, H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1165. (x) As melatonin analogues: Larraya, C.; Guillard, J.; Renard, P.; Audinot, V.; Boutin, J. A.; Delegrange, P.; Bennejean, C.; Viaud-Massuard, M.-C. *Eur. J. Med. Chem.* **2004**, *39*, 515. (y) As staurosporin analogues: Routier, S.; Ayerbe, N.; Mérour, J.-Y.; Coudert, G.; Bailly, C.; Pierré, A.; Pfeifer, B.; Caignard, D.-H.; Renard, P. *Tetrahedron* **2002**, *58*, 6621. (z) As rebeccamycin analogues: Messaoudi, S.; Anizon, F.; Pfeiffer, B.; Prudhomme, M. *Tetrahedron* **2005**, *61*, 7304. (aa) As PDE-4 inhibitors: Hofgen, N.; Egerland, U.; Kronbach, T.; Marx, D.; Szelenyi, S.; Kuss, H.; Polymeropoulos, E. US Patent Appl. 2006/258700, **2006**. (bb) As COX-2 inhibitors: Beswick, P.; Gleave, R.; Swarbrick, M. PCT Int. Appl. WO 2005016924, **2005**.

(7) (a) Rodriguez, J.; Feraud, M. *Spec. Chem. Mag.* **2005**, *25*, 16. (b) Popowycz, F.; Routier, S.; Joseph, B.; Mérour, J.-Y. *Tetrahedron* **2007**, *63*, 1031.

(8) (a) Kim, Y. K.; Lee, S. J.; Ko, J. J.; Lee, T. G.; Jung, I.; Song, K. H. (Samsung) Korean Patent Appl. KR 2006/001405, **2006**. (b) Catalan, J. *Chem. Phys. Lett.* **2006**, *423*, 395. (c) Wu, P.-W.; Hsieh, W.-T.; Cheng, Y.-M.; Wei, C.-Y.; Chou, P.-T. *J. Am. Chem. Soc.* **2006**, *128*, 14426. (d) Huang, W.-H.; Jia, W.-L.; Wang, S. *Can. J. Chem.* **2006**, *84*, 477. (e) Tani, K.; Sakurai, H.; Fujii, H.; Hirao, T. *J. Organomet. Chem.* **2004**, *689*, 1665.

(9) Hynes, J. Jr.; Doubleday, W. W.; Dyckman, A. J.; Godfrey, J. D. Jr.; Grosso, J. A.; Kiau, S.; Leftheris, K. *J. Org. Chem.* **2004**, *69*, 1368.

(10) Yokoyama, M.; Nomura, M.; Togo, H.; Seki, H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2145.

(11) (a) Galvez, C.; Viladomes, P. *J. Heterocycl. Chem.* **1984**, *21*, 421. (b) Alvarez, M.; Fernandez, D.; Joule, J. A. *Synthesis* **1999**, 615. (c) Cai, Z.; Feng, J.; Guo, Y.; Li, P.; Shen, Z.; Chu, F.; Guo, Z. *Bioorg. Med. Chem.* **2006**, *14*, 866.

(12) (a) Galvez, C.; Viladoms, P. *J. Heterocycl. Chem.* **1982**, *19*, 665. (b) Shadrina, L. P.; Dormidontov, Y. P.; Ponomarev, V. G.; Lapkin, I. I. *Khim. Geterotsikl. Soedin.* **1987**, 1206. (c) Song, D.; Liu, S.-F.; Wang, R.-Y.; Wang, S. *J. Organomet. Chem.* **2001**, *631*, 175. (d) Zhang, Z.; Yang, Z.; Wong, H.; Zhu, J.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *J. Org. Chem.* **2002**, *67*, 6226. (e) Allegretti, M.; Anacardio, R.; Cesta, M. C.; Curti, R.; Mantovanini, M.; Nano, G.; Topai, A.; Zampella, G. *Org. Process Res. Dev.* **2003**, *7*, 209. (f) Helgen, C.; Bochet, C. G. *Heterocycles* **2006**, *67*, 797.

(13) (a) Wu, Q.; Hook, A.; Wang, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 3933. (b) Tani, K.; Sakurai, H.; Fujii, H.; Hirao, T. *J. Organomet. Chem.* **2004**, *689*, 1665.

(14) Reisch, J.; Dittmann, S. *J. Heterocycl. Chem.* **1993**, *30*, 379.

(15) (a) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J.; Sebastião, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3317. (b) Rolland-Fulcrand, V.; Haroune, N.; Roumestant, M.-L.; Martinez, J. *Tetrahedron: Asymmetry* **2000**, *11*, 4719. (c) Huck, J.; Duru, C.; Roumestant, M.-L.; Martinez, J. *Synthesis* **2003**, 2165.

(16) Ahaidar, A.; Fernandez, D.; Danelon, G.; Cuevas, C.; Manzanares, I.; Albericio, F.; Joule, J. A.; Alvarez, M. *J. Org. Chem.* **2003**, *68*, 10020.

(17) Wang, K.; Stringfellow, S.; Dong, S.; Jiao, Y.; Yu, H. *Spectrochim. Acta, Part A* **2002**, *58*, 2595.

(18) (a) Verbiscar, A. J. *J. Med. Chem.* **1972**, *15*, 149. (b) Oh, S.-J.; Lee, K. C.; Lee, S.-Y.; Ryu, E. K.; Saji, H.; Choe, Y. S.; Chi, D. Y.; Kim, S. E.; Lee, J.; Kim, B.-T. *Bioorg. Med. Chem.* **2004**, *12*, 5505.

(19) Mewshaw, R. E.; Meagher, K. L.; Zhou, P.; Zhou, D.; Shi, X.; Scerni, R.; Smith, D.; Schechter, L. E.; Andree, T. H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 307.

(20) (a) Robison, M. M.; Robison, B. L. *J. Am. Chem. Soc.* **1955**, *77*, 457. (b) Eskola, O.; Bergman, J.; Lehikoinen, P.; Haaparanta, M.; Grönroos, T.; Forsback, S.; Solin, O. *J. Labelled Compd. Radiopharm.* **2002**, *45*, 687.

(21) Alfonsi, M.; Arcadi, A.; Bianchi, G.; Marinelli, F.; Nardini, A. *Eur. J. Org. Chem.* **2006**, 2393.

(22) (a) Sloan, M. J.; Phillips, R. S. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1053. (b) Routier, S.; Ayerbe, N.; Merour, J.-Y.; Coudert, G.; Bailly, C.; Pierre, A.; Pfeiffer, B.; Caignard, D.-H.; Renard, P. *Tetrahedron* **2002**, *58*, 6621. (c) Henon, H.; Messaoudi, S.; Hugon, B.; Anizon, F.; Pfeiffer, B.; Prudhommer, M. *Tetrahedron* **2005**, *61*, 5599.

(23) (a) Chlorination: Minakata, S.; Hamada, T.; Komatsu, M.; Tsuboi, H.; Kikuta, H.; Ohshiro, Y. *J. Agric. Food Chem.* **1997**, *45*, 2345. (b) Bromination of *N*1-unprotected **1** is unknown. For a high-yielding C3 bromination on *N*1-benzenesulfonyl protected **1**, see: Huang, S.; Li, R.; Connolly, P. J.; Emanuel, S.; Middleton, S. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4818. (c) For regioselective C3 bromination of 2-substituted 7-azaindoles, see: Gallou, F.; Reeves, J. T.; Tan, Z.; Song, J. J.; Yee, N. K.; Harcken, C.; Liu, P.; Thomson, D.; Senanayake, C. H. *Synlett* **2007**, 211. (d) Iodination: *N*1-unprotected 3-iodo-7-azaindole is unstable; selective C3 iodination of *N*1-BOC-protected **1** is possible: Herbert, R.; Wibberley, D. G. *J. Chem. Soc. C* **1969**, 1505. (e) See also: Kelly, T. A.; McNeil, D. W.; Rose, J. M.; David, E.; Shih, C.-K.; Grob, P. M. *J. Med. Chem.* **1997**, *40*, 2430.

(24) (a) Robison, M. M.; Robison, B. L.; Butler, F. P. *J. Am. Chem. Soc.* **1959**, *81*, 743. (b) Yizun, J.; Adams, G. E.; Parrick, J.; Stratford, I. J. *Eur. J. Med. Chem.* **1989**, *24*, 511.

(25) Minakata, S.; Itoh, S.; Komatsu, M.; Ohshiro, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2992.

(26) (a) *N*1-Protected 7-azaindolin-3-one was obtained from Bayer–Villiger oxidation of the corresponding 3-formyl compound, see: Desarbre, E.; Mérour, J.-Y. *Tetrahedron Lett.* **1994**, *35*, 1995. (b) *N*1-(Me, Et, Bn)-substituted 7-azaisatin was obtained from the parent azaindole via oxidation with NBS/DMSO, see: Tatsugi, J.; Zhiwei, T.; Amano, T.; Izawa, Y. *Heterocycles* **2000**, *53*, 1145.

(27) (a) Clark, B. A. J.; Parrick, J. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2270. (b) Schneller, S. W.; Luo, J.-K. *J. Org. Chem.* **1980**, *45*, 4045. (c) Chen, C.-C.; Chang, C.-P.; Yu, W.-S.; Hung, F.-T.; Liu, Y.-I.; Wu, G.-R.; Chou, P.-T. *J. Phys. Chem. A* **2003**, *107*, 1459. (d) Soundararajan, N.; Benoit, S.; Gingras, S. US Patent Appl. US 2004/0044025, **2004**. (e) Wang, X.; Zhi, B.; Baum, J.; Chen, Y.; Crockett, R.; Huang, L.; Eisenberg, S.; Ng, J.; Larsen, R.; Martinelli, M.; Reider, P. *J. Org. Chem.* **2006**, *71*, 4021.

(28) Thibault, C.; L'Heureux, A.; Bhide, R. S.; Ruel, R. *Org. Lett.* **2003**, *5*, 5023.

(29) Antonini, I.; Claudi, F.; Cristalli, G.; Franchetti, P.; Grifantini, M.; Martelli, S. *J. Med. Chem.* **1982**, *25*, 1258.

(30) 4-Halo-7-azaindoles have been used as intermediates for other 4-substituted and also polysubstituted 7-azaindoles, for recent examples, see: (a) Allegretti, M.; Arcadi, A.; Marinelli, F.; Nicolini, L. *Synlett* **2001**, 609. (b) L'Heureux, A.; Thibault, C.; Ruel, R. *Tetrahedron Lett.* **2004**, *45*, 2317. (c) Thutewohl, M.; Schirok, H.; Bennabi, S.; Figueroa-Pérez, S. *Synthesis* **2006**, 629. (d) For a more comprehensive overview, see Refs. 3c,d.

(31) (a) 5-Bromo-7-azaindole (four steps from **1**): Mazéas, D.; Guillaumet, G.; Viaud, M.-C. *Heterocycles* **1999**, *50*, 1065. (b) For a synthesis of 4,5-disubstituted 7-azaindoles from 4-substituted 7-azaindoles via directed *ortho*-metalation, see ref. 30b.

(32) See the recent comparison of synthetic routes for 5-amino-7-azaindole: Pearson, S. E.; Nandan, S. *Synthesis* **2005**, 2503.
(33) (a) Metalation and quenching with electrophiles of *N*1-arylsulfonyl-protected 7-azaindole: Desarbre, E.; Coudret, S.; Meheust, C.; Mérour, J.-Y. *Tetrahedron* **1997**, *53*, 3637. (b) See also: Joseph, B.; Da Costa, H.; Mérour, J.-Y.; Léonce, S. *Tetrahedron* **2000**, *56*, 3189. (c) Arylation of *N*1-SEM-protected 7-azaindole: Touré, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979.
(34) Robison et al. had obtained 6-oxo-7-azaindole via dehydrogenation, followed by acetyl group hydrolysis, of a mixture of 5- and 6-acetoxy-1-acetyl-7-azaindoline: Robison, M. M.; Robison, B. L.; Butler, F. P. *J. Am. Chem. Soc.* **1959**, *81*, 743.
(35) (a) Minakata, S.; Komatsu, M.; Ohshiro, Y. *Synthesis* **1992**, 661. The 6-halo-7-azaindoles described have been used as starting materials for various transition metal-catalyzed C–C coupling reactions, see: (b) Minakata, S.; Itoh, S.; Komatsu, M.; Ohshiro, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2992. (c) See also ref. 30a. (d) Recently, a seven-step de novo synthesis of a new cross coupling-reagent, *N*1-benzyl-6-triflyloxy-7-azaindole, has been reported, see: Kerr, M.; Zheng, X. *Org. Lett.* **2006**, *8*, 3777.
(36) (a) Henze, M. *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 1566. (b) Katritzky, A. R.; Lagowski, J. M. *Chemistry of the Heterocyclic N-Oxides*; Academic Press: New York, **1971**, 300–303. (c) Hayashi, E.; Higashino, T. *Heterocycles* **1979**, *12*, 837. (d) Fife, W. K.; Scriven, E. F. V. *Heterocycles* **1984**, *22*, 2375; and references cited therein. (e) Yakhontov, L. N.; Krasnokutskaya, D. M.; Akalaev, A. N.; Palant, I. N.; Vainshtein, Yu. I. *Khim. Geterotsikl. Soedin.* **1971**, 789. (f) Fife, W. K.; Boyer, B. D. *Heterocycles* **1984**, *22*, 1121. (g) Comins, D. L.; Joseph, S. P. In *Comprehensive Heterocyclic Chemistry II*, Vol. 5; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: London, **1996**, 70–78.
(37) Indirect syntheses of 6-amino-substituted 7-azaindoles have been achieved by: (1) reacting the corresponding 6-halo-7-azaindole with ammonia or amines, but, as a rule, require extended autoclaving at high temperatures/pressures,[35a,b] and (2) by extended heating at high temperatures of the corresponding 6-chloro-7-azaindoline with amines and subsequent oxidation to the azaindole, see: (a) Yakhontov, L. N.; Krasnokutskaya, D. M.; Akalaev, A. N. *Dokl. Akad. Nauk SSSR* **1970**, *192*, 118. (b) See also: Yutilov, Yu. M.; Svertilova, I. A. *Khim. Geterotsikl. Soedin.* **1986**, 91. (c) Oxidation/cyclization/elimination/decarboxylation of a 2,6-diaminosubstituted pyridyl-3-β-keto ester: Sanders, W. J.; Zhang, X.; Wagner, R. *Org. Lett.* **2004**, *6*, 4527.
(38) Germain, J.; Askew, B. C.; Bauer, D.; Choquette, D.; Dipietro, L. V.; Graceffa, R.; Harmanage, J.-C.; Huang, Q.; Kim, J. L.; La, D.; Li, A.; Nishimura, N.; Nomack, R.; Patel, V.; Potashman, M.; Riahi, B.; Storz, T.; Van der Plas, S.; Yang, K.; Yuan, C. PCT Int. Appl. WO 2007/048070, **2007**.
(39) Cox, P. J.; Majid, T. N.; Lai, J. Y. Q.; Morley, A. D.; Amendola, S.; Deprets, S.; Edlin, C. PCT Int. Appl. WO 2001047922, **2001**.
(40) Shiotani, S.; Taniguchi, K. *J. Heterocycl. Chem.* **1997**, *34*, 493.
(41) CAS & Beilstein online searches, June 2007.
(42) The MCBA salt **3** is the most practical way to isolate the *N*-oxide **2** as it readily precipitates from a number of nonpolar solvents during the oxidation of **1** with MCPBA (cf. refs. 27b,d,e). On the other hand, upon freebasing, 20%[27d] to 50%[27e] loss is typically incurred due to the high water solubility of **2**.
(43) Methyl ester formation of MCBA was also not observed.
(44) (a) Ochiai and Nakayama were the first to report the formation of a cyanopyridine (2-cyano-4-chloropyridine) from the reaction of cyanide with the corresponding *O*-alkyl pyridinium salt: Ochiai, E.; Nakayama, I. *Yakugaku Zasshi* **1945**, *65*, 7; *Chem. Abstr.* **1945**, *45*, 49933. The reaction was rediscovered and expanded independently by Okamoto/Tani and Feely/Beavers: (b) Okamoto, T.; Tani, H. *Chem. Pharm. Bull* **1959**, *7*, 130. (c) See also: Okamoto, T.; Tani, H. *Chem. Pharm. Bull* **1959**, *7*, 925. (d) See also: Okamoto, T.; Tani, H. *Chem. Pharm. Bull* **1959**, *7*, 930. (e) See also: Feely, W. E.; Beavers, E. M. *J. Am. Chem. Soc.* **1959**, *81*, 4004. For later reports, see: (f) Matsumura, E.; Ariga, M.; Ohfuji, T. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3210. (g) Botteghi, C.; Schionato, A.; Chelucci, G.; Brunner, H.; Kürzinger, A.; Obermann, U. *J. Organomet. Chem.* **1989**, *370*, 17. (h) Ashimori, A.; Ono, T.; Uchida, T.; Ohtaki, Y.; Fukaya, C.; Watanabe, M.; Yokoyama, K. *Chem. Pharm. Bull.* **1990**, *38*, 2446. (i) Hibino, S.; Sugino, E. *J. Heterocycl. Chem.* **1990**, *27*, 1751. (j) See also reviews cited in ref. 36.
(45) A solvent screen for the O-methylation of **3** with dimethyl sulfate (data not shown) revealed MeCN(homogeneous) and butyl acetate(biphasic) as the most favorable solvents. In MeCN, the O-methylation is very clean and proceeds at a somewhat lower (55–60 °C) temperature than in butyl acetate (85–90 °C). On the other hand, butyl acetate results in a clear biphasic mixture with a lower, purple *N*-oxide salt phase ('ionic liquid layer'), that can be readily separated and employed for reaction with nucleophiles in other solvents, and a clear, upper phase (butyl acetate) containing most of the *m*-chlorobenzoic acid. Although the cyanide reaction also proceeds under nonaqueous conditions, NH_4Cl-buffered aqueous cyanide provides the cleanest reaction and highest yield. A 'blank reaction' with NH_4Cl alone did not yield the 6-chloro product, in accordance with the observations made with tetraalkylammonium halides under forcing conditions (vide infra).[48]
(46) Increasing the steric bulk of the alkylating agent (EtI, *i*-PrI) did not change the regioselectivity. Other cyanating reagents [BzCN, TMSCN,[62] $(EtO)_2P{=}O(CN)$[63]] did not lead to cyanated azaindole (data not shown).
(47) As clearly evidenced by $^3J_{4,5}$ (8 Hz), which is the typical coupling observed between the *m*-, and *p*-protons in *ortho*-substituted pyridines.[64]
(48) Contrary to Ohshiro's report[35] (vide supra, Scheme 1), 6-chloroazaindole was not observed as a side-product under our conditions. In test reactions of **4** with TBACl, TBABr and TBAI under forcing conditions (data not shown), no reaction occurred with the chloride, whereas the bromide and iodide reacted via the demethylation pathway (formation of MeBr and MeI, respectively). Thus, it appears the nature of the leaving group at N7 strongly determines the site of nucleophilic attack at the ambident electrophile **4**.
(49) (a) Vorbrüggen, H.; Krolikiewicz, K. *Synthesis* **1983**, 316. (b) Fife, W. K. *J. Org. Chem.* **1983**, *48*, 1375.
(50) In pyridine chemistry, 2-(alkyl/aryl)sulfonyl groups are often used to introduce heteroatom substituents *ortho* to the ring nitrogen; as a rule, they are more reactive than the corresponding 2-halo compounds, see: Furukawa, N.; Ogawa, S.; Kawai, T.; Oae, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1839.
(51) The reactivity of the *O*-methyl-7-azaindole-*N*-oxide salt **4** towards alcoholates, thiolates and azoles was somewhat surprising considering the earlier unsuccessful attempts to obtain the same types of addition products from Reissert–Henze reactions of *N*-methoxypyridinium salts, see:

Kiselyov A. S., Strekowski L.; *J. Heterocycl. Chem.*; **1993**, *30*: 1361.
(52) In the absence of a stronger base (typically Hünig base or K_2CO_3), N-methylation of the azoles dominates (data not shown). 6-*N*-(Heteroaromatic)-substituted 7-azaindoles have not been reported (CAS/Beilstein, July 2007). Trace amounts of the 4-isomer are readily removed during purification; all yields are isolated yields for chromatographed products (typically ≥95A% HPLC).
(53) Crude 6-amino adducts are typically ~85A% LC-pure already and require minimal purification.
(54) It is more convenient to isolate the hitherto unknown MCBA complex **28** of 4-chloro-7-azaindole-*N*-oxide than the free base, since the isolation of the latter typically leads to reduced yields.[27b,28] A convenient protocol is given in the experimental part (vide supra).
(55) Chiral *N*-(7-azaindolyl)-α-amino acids have not been reported (CAS/Beilstein searches July 2007).
(56) Katritzky, A. R.; Lunt, E. *Tetrahedron* **1969**, *25*, 4291.
(57) Abramovitch, R. A.; Smith, E. M. *Chem. Heterocycl. Comp.* **1974**, *14 (Suppl. 2)*, 1.
(58) Contrary to the behavior of the corresponding *N*,*O*- and *N*,*S*-isosters of pyrrolo[2,3-*b*]pyridine, where both thieno[2,3-*b*]-[65] as well as furo[2,3-*b*]pyridine-*N*-oxide[40] have been reported to give the α-cyanated product in good yields in the Reissert–Henze reaction with benzoyl chloride and cyanide.
(59) For pyridinium salts, regioselectivity of nucleophilic attack to yield either 1,2- or 1,4-dihydropyridines has been explained by the formation of charge-transfer complexes,[62] by Pearson's HSAB-concept,[66] and by kinetic versus thermodynamic control;[67] for a review, see: Poddubnyi, I. S. *Chem. Heterocycl. Comp.* **1995**, *31*, 682.
(60) To the best of our knowledge, no other reports on Reissert–Henze type reactions of 7-azaindole-*N*-oxide have appeared in the literature (CAS/Beilstein searches June 2007). On the other hand, Popp et al. had reported on a failed attempt to obtain cyanated azaindole via the classical Reissert reaction conditions: Veeraraghavan, S.; Popp, F. D. *J. Heterocycl. Chem.* **1981**, *18*, 909.
(61) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(62) Kosower, E. M. *J. Am. Chem. Soc.* **1956**, *78*, 3497.
(63) Harusawa, S.; Hamada, Y.; Shioiri, T. *Heterocycles* **1981**, *15*, 981.
(64) Pretsch, E.; Seibl, J.; Clerc, T.; Simon, W. *Spectral Data for Structure Determination of Organic Compounds*; Springer-Verlag: Heidelberg, **1989**, 2nd ed., H275.
(65) Klemm, L. H.; Muchiri, D. R. *J. Heterocycl. Chem.* **1983**, *20*, 213.
(66) Lyle, R. E.; Gauthier, G. J. *Tetrahedron Lett.* **1965**, *6*, 4615.
(67) Damji, S. W. H.; Fyfe, C. A.; Smith, D.; Sharom, F. J. *J. Org. Chem.* **1979**, *44*, 1761.