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Synthesis of novel triazolopyridylboronic acids and esters. Study of potential application to Suzuki-type reactions

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Abstract—This paper describes a general method for the synthesis of novel [1,2,3]triazolo[1,5-*a*]pyridylboronic acids and esters, and the first results on Suzuki cross-coupling reactions with these new compounds and [1,2,3]triazolo[5,1-*a*]isoquinolylboronic acid, reacting with a variety of aryl halides as a route to 7-aryltriazolopyridines and 5-aryltriazoloisoquinolines.

1. Introduction

During our research on the chemistry of [1,2,3]triazolo[1,5-*a*]pyridines **1** and [1,2,3]triazolo[5,1-*a*]isoquinoline **2**, we discovered a facile route to new bistriazolopyridines and related compounds, which are potential helicating ligands, using compounds **1** and **2** as building blocks.[1–3] The interest of this type of compounds,[4] led us to attempt to widen the scope of their synthesis by alternative routes. The Suzuki reaction would be applicable to the preparation of heteroaryltriazolopyridines and heteroaryltriazoloisoquinolines, which are also potentially interesting in the field of new selective inhibitors of cyclooxygenase 2. In contrast of the many examples of Suzuki coupling reactions between heterocyclic halides and phenyl boronic acids that have appeared in the literature over the past two decades,[5,6] the corresponding reactions involving heterocyclic boronic acids or esters are noticeably fewer,[7] nevertheless interest in heterocyclic boronic derivatives continues to grow and we wish to report here the synthesis of novel [1,2,3]triazolo[1,5-*a*]pyridylboronic acids **3a–c**, esters **4a–c** and **5**, and the first results on Suzuki cross-coupling reactions with these new compounds and [1,2,3]triazolo[5,1-*a*]isoquinolyl boronic acid **6** reacting with a variety of aryl halides.

2. Results and discussion

The starting materials **1a–c**, and **2**, were prepared by procedures described in the literature.[8,2,9] We used the classical preparation of boronic acids which requires the reaction of an organolithium intermediate, generated by deprotonation, with a trialkylborate.[10–12] The corresponding lithium derivatives **7** and **8** were formed in toluene at −40 °C with *n*-BuLi,[13] followed by reaction with triisopropyl borate. The reaction mixture was quenched with slow addition of 5% aqueous NaOH solution and the resulting aqueous layer neutralized by careful addition of concentrated HCl. The new triazolopyridyl boronic acids **3a–c** were stable yellow solids, the triazoloisoquinolyl boronic acid **6** was a stable white solid.[3] All acids were insoluble in usual organic solvents, were relatively easy to handle and purify, could be analyzed by ESI-MS, and were obtained with yields from 40 to 78%. The pinacol esters **4a–c** were obtained using similar conditions to those described previously to obtain pinacol esters from the halopyridyl boronic acids, in an one pot procedure.[14] Compounds **4a–c** are stable and were obtained in high yield. The borolane **5b** was prepared by the procedure described by some of us,[15] from the corresponding boronic acid by reaction with N-methyldiethanolamine in excellent yield (Scheme 1).

The boronic acids were directly subjected to modified Suzuki cross-coupling conditions, (DME/aqueous K_2CO_3/$Pd(PPh_3)_4$/80 °C),[11,16] with 4-iodoanisole. The triazolopyridyl derivatives **3a**,**b** gave protodeboronation as the main result and triazolopyridines **1a**,**b** were recovered from the reaction mixture in almost quantitative yield (Scheme 2).

Keywords: Triazolopyridines; Triazoloisoquinolines; Boronic acids and esters; Suzuki cross-coupling reaction.
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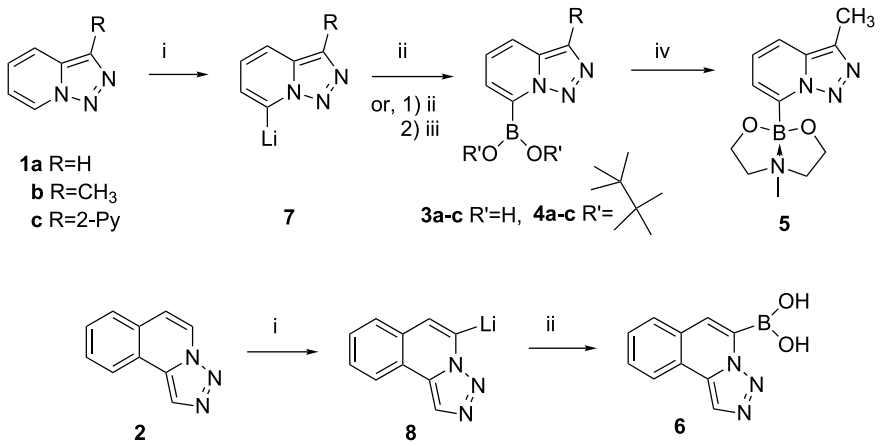
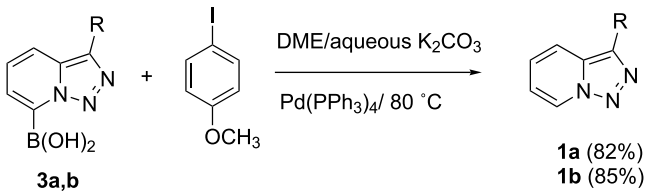


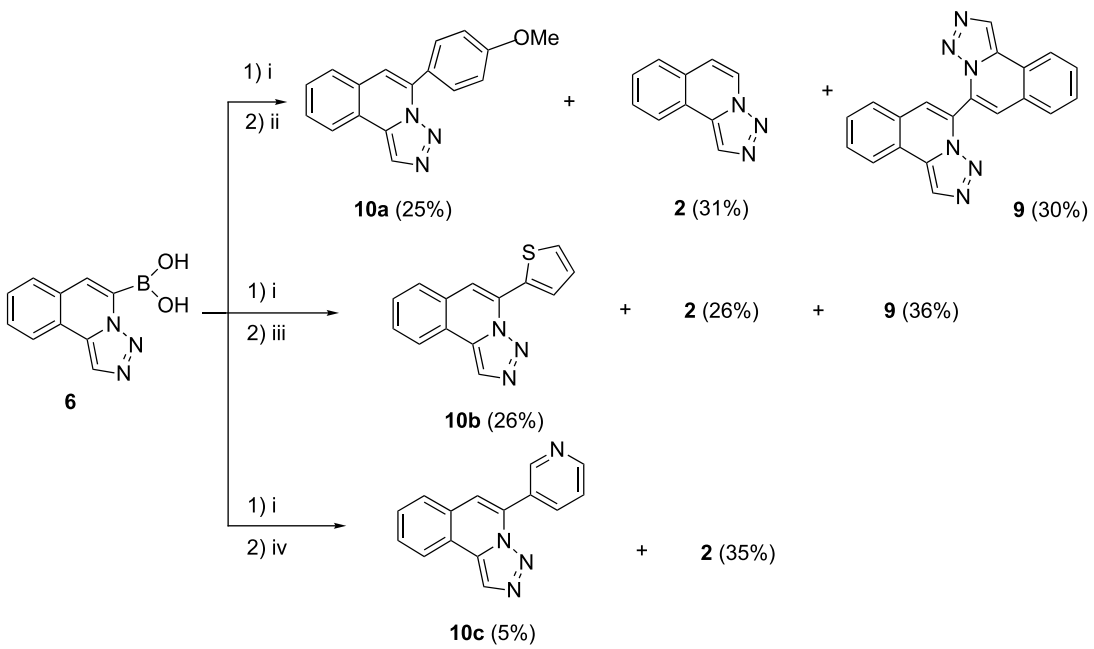
Scheme 1. i, *n*-BuLi/toluene; ii, $B(OiPr)_3$; iii, pinacol; iv, $MgSO_4$/N-methyldiethanolamine (from **3b**).



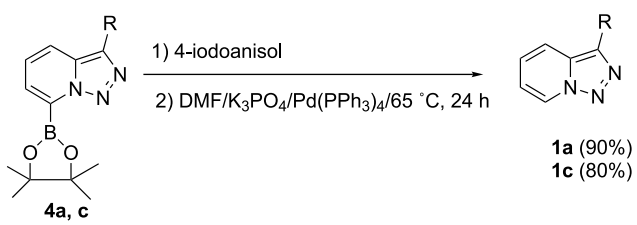
Scheme 2.

The triazoloisoquinoline boronic acid **6** gave a mixture of three compounds that were characterized as triazoloisoquinoline **2** (31%), bistriazoloisoquinoline **9** (30%),[3] and the heterobiaryl derivative **10a** (25%) (Scheme 3).

The pinacol esters **4a** and **4c** gave only protodeboronation (Scheme 4), nevertheless the pinacol ester **4b** under standard Suzuki-type conditions, (DMF/K_3PO_4/$Pd(PPh_3)_4$/65 °C),[14] gave better results furnishing furthermore protodeboronation, the heterobiaryl derivative **11a** but



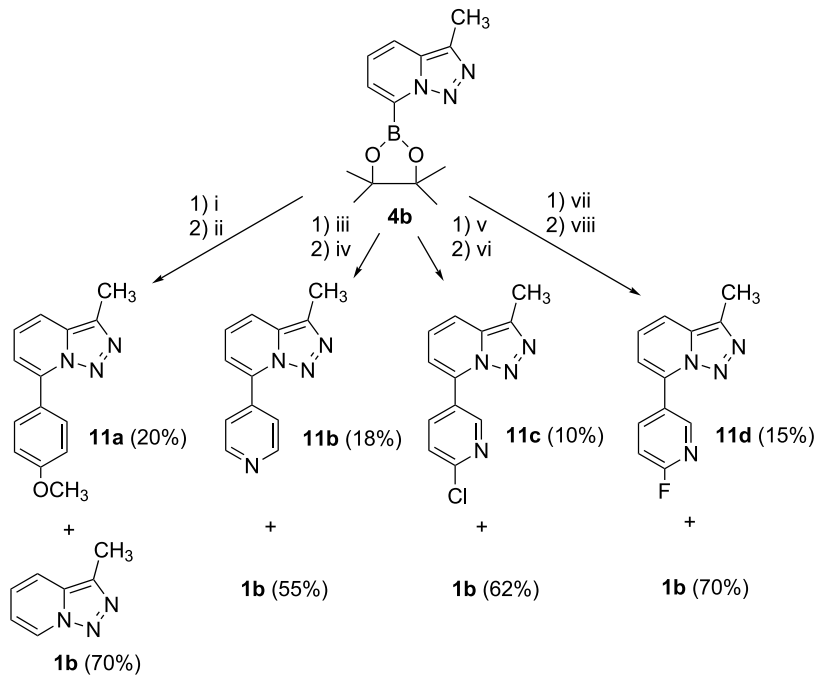
Scheme 3. i, $DME/NaHCO_3/H_2O$, 45 °C, 15 m; ii, 4-iodoanisol/$Pd(PPh_3)_4$/DME/reflux, 6 h; iii, 2-bromothiophene/$Pd(PPh_3)_4$/DME/reflux, 6 h; iv, 3-bromopyridine/$Pd(PPh_3)_4$/DME/reflux, 6 h.



Scheme 4.

only in low yield (20%) (Scheme 5). Such different reactivity is probably due to the better solubility and stability of the compound **4b**.

We followed the research with the boronic ester **4b** and the boronic acid **6**, that underwent Suzuki couplings. We did several attempts to improve the results modifying the reaction conditions, a number of bases (K_2CO_3, Na_3PO_4, K_3PO_4, $NaHCO_3$, KOH, $Ba(OH)_2{\cdot}8H_2O$), solvents



Scheme 5. i, 4-iodoanisol/Pd(PPh$_3$)$_4$/DMF; ii, K$_3$PO$_4$/H$_2$O, 70 °C, 16 h; iii, 4-iodopyridine/Pd(PPh$_3$)$_4$/dioxane; iv, Ba(OH)$_2$.8H$_2$O/H$_2$O/90–100 °C, 20 h; v, 2-chloro-5-iodopyridine/Pd(PPh$_3$)$_4$/dioxane; vi, Ba(OH)$_2$.8H$_2$O/H$_2$O/80–100 °C, 24 h; vii, 5-bromo-2-fluorpyridine/Pd(PPh$_3$)$_4$/dioxane; viii, Ba(OH)$_2$.8H$_2$O/H$_2$O/50–60°C, 72 h.

(DME/H$_2$O, DMF/H$_2$O, toluene, acetone, dioxane), catalysts (Pd(PPh$_3$)$_4$ purchased from commercial sources: Aldrich; Lancaster, Pd/C 10%), and co-reagents (2-bromopyridine, 2-bromothiophene, 3-bromopyridine, 4-iodopyridine, 2-chloro-5-iodopyridine, 2-fluor-5-bromopyridine) were investigated. The boronic derivatives **4b** and **6** coupled to some of these heteroarylhalides in modest to low yield and compounds **11b–d**, and **10b**,**c** were synthesized (Schemes 5 and 3). The reaction of triazoloisoquinoline boronic acid **6** with iodoanisol and with 2-bromothiophen resulted in a competitive formation of homo-coupling derivative **9**. In all reactions studied the protodeboronation is always the main result. The analytical and spectroscopic data for all new compounds are in Tables 1–3.

Protodeboronation is a known issue for heteroarylboronic acids, specifically when the boron is on a carbon adjacent to a heteroatom.[17] Triazolopyridines are easily quaternizated in N2,[18,19] and as Stevens et al. suggest for pyridineboronic

Table 1. ^{1}H NMR shifts (ppm) and *J* values (Hz) for triazolopyridine derivatives

	H3	H4	H5	H6	Others
3a[a]	7.90, s	7.53, d, *J*=8, 7 Hz	7.17, dd, J_1=8.7 Hz, J_2=6.7 Hz	6.98, d, *J*=6.7 Hz	
3b[a]	—	7.59, d, *J*=8.7 Hz	7.28, dd, J_1=8.7 Hz, J_2=6.6 Hz	7.15, d, *J*=6.6 Hz	2.54, s, (CH_3)
3c[b]	—	8.75, d, *J*=8.9 Hz	7.52, dd, J_1=8.9 Hz, J_2=6.8 Hz	7.66, d, *J*=6.8 Hz	8.59, d, *J*=4.8 Hz, H6′; 8.22, d, *J*=8.1 Hz, H3′; 7.82, dd, J_1=7.7 Hz, J_2=8.1 Hz, H4′; 7.23, dd, J_1=4.8 Hz, J_2=7.7 Hz, H5′
4a[c]	8.04, s	7.73, d, *J*=8.9 Hz	7.13, dd, J_1=8.9 Hz, J_2=6.6 Hz	7.43, d, *J*=6.6 Hz	1.38, s, 4(CH_3)
4b[c]	—	7.60, d, *J*=8.9 Hz	7.05, dd, J_1=8.9 Hz, J_2=6.6 Hz	7.40, d, *J*=6.6 Hz	1.37, s, 4(CH_3)
4c[c]	—	8.76, d, *J*=8.9 Hz	7.26, dd, J_1=8.9 Hz, J_2=6.6 Hz	7.46, d, *J*=6.6 Hz	8.59, d, *J*=4.9 Hz, H6′; 8.32, d, *J*=7.9 Hz, H3′; 7.72, t, *J*=7.7 Hz, H4′; 7.14, dd, J_1=4.9 Hz, J_2=7.5 Hz, H5′
5[c,d]	—	7.51, d, *J*=8.7 Hz	7.12, dd, J_1=8.7 Hz, J_2=6.3 Hz	7.36, d, *J*=6.3 Hz	4.27, m, 4H; 3.61, m, 2H; 3.32, m, 2H; 2.70, s, 3H; 2.59, s, 3H
11a[c]	—	7.50, d, *J*=8.8 Hz	7.17, dd, J_1=8.8 Hz, J_2=6.9 Hz	6.89, d, *J*=6.9 Hz	7.92, d, *J*=9.0 Hz, H2′+H6′; 7.00, d, *J*=9.0 Hz, H3′+H5′; 3.83, s, (OCH_3); 2.59, s, (CH_3)
11b[c,d]	—	7.71, d, *J*=8.8 Hz	7.31, dd, J_1=8.8 Hz, J_2=6.8 Hz	7.14, d, *J*=6.8 Hz	8.82, d, *J*=5.6 Hz, H2′+H6′; 7.99, d, *J*=5.6 Hz, H3′+H5′; 2.68, s, (CH_3)
11c[c,d]	—	7.69, d, *J*=8.8 Hz	7.30, dd, J_1=8.8 Hz, J_2=6.8 Hz	7.07, d, *J*=6.8 Hz	8.88, d, *J*=2.3 Hz, H6′; 8.55, dd, J_1=8.4 Hz, J_2=2.3 Hz, H4′; 7.53, d, *J*=8.4 Hz, H3′; 2.68, s, (CH_3)
11d[c,d]	—	7.68, d, *J*=8.9 Hz	7.30, dd, J_1=8.9 Hz, J_2=6.8 Hz	7.05, d, *J*=6.8 Hz	8.72, d, *J*=2.5 Hz, H6′; 8.67, ddd, J_{HF}=9.0 Hz, J_1=8.6 Hz, J_2=2.5 Hz; 7.14, dd, J_{HF}=2.8 Hz, *J*=8.6 Hz; 2.68, s, (CH_3)

[a] Solvent: D$_2$O/NaOH.
[b] Solvent: CD_3COCD_3.
[c] Solvent: Cl_3CD.
[d] NMR spectrum 400 MHz.

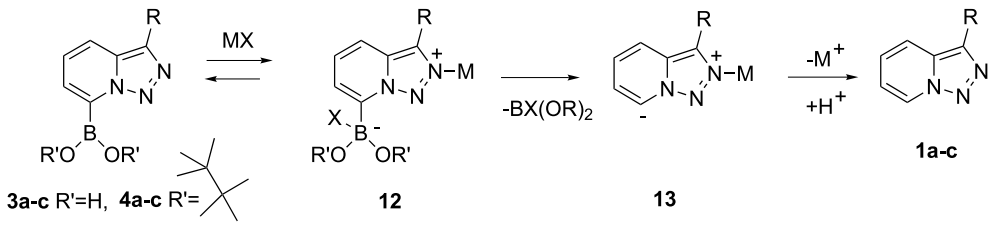
Table 2. ^{1}H NMR shifts (ppm) and J values (Hz) for triazoloisoquinoline derivatives

	H1	H6	H7	H8	H9	H10	Others
6[a]	8.36, s	7.20, s	7.66, d, J=7.3 Hz	⟨7.48–7.36, m⟩		7.96, d, J=7.6 Hz	
10a[b]	8.45, s	7.15, s	7.76, dd, J_1=7.4 Hz, J_2=2.9 Hz	⟨7.62–7.49, m⟩		8.12, dd, J_1=7.4 Hz, J_2=2.9 Hz	7.87, d, J=8.7 Hz, 2H; 7.20, d, J=8.7 Hz, 2H; 3.8, s, 3H
10b[b]	8.47, s	7.47, s	7.78–7.75 m	⟨7.58–7.55, m⟩		8.11–8.08, m	8.23, dd, J_1=3.7 Hz, J_2=1.5 Hz; 7.48, dd, J_1=5.1 Hz, J_2=1.5 Hz; 7.18, dd, J_1=5.1 Hz, J_2=3.7 Hz
10c[b]	8.47, s	7.28, s	7.81, dd, J_1=7.5 Hz, J_2=2.2 Hz	⟨7.68–7.59, m⟩		8.14, dd, J_1=7.5 Hz, J_2=2.2 Hz	9.08, s_{br}; 8.71, dd, J_1=4.5 Hz, J_2=1.5 Hz; 8.48, ddd, J_1=7.5 Hz, J_2=1.5 Hz, J_3=1.5 Hz; 7.47, dd, J_1=7.5 Hz, J_2=4.5 Hz

[a] Solvent: D_2O/NaOH.
[b] Solvent: Cl_3CD.

Table 3. Mass spectroscopic data, melting points, and preparative yields for new compounds

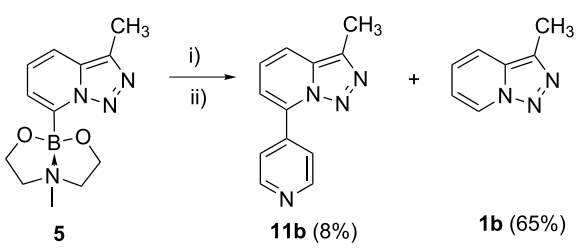
	Formula	MS	Mp (°C)	Yield %
3a	$C_6H_6BN_3O_2$	ESI 163, MW 163	>300	66
3b	$C_7H_8BN_3O_2$	ESI 177, MW 177	>300	40
3c	$C_{11}H_9BN_4O_2$	ESI 240, MW 240	>300	78
4a	$C_{12}H_{16}BN_3O_2$	HRMS found 245.1340, calcd 245.1335	72–74	65
4b	$C_{13}H_{18}BN_3O_2$	HRMS found 259.1243, calcd 259.1492	77–79	55
4c	$C_{17}H_{19}BN_4O_2$	HRMS found 322.1602, calcd 322.1601	185–187	31
5	$C_{12}H_{17}BN_4O_2$	HRMS found 260.0804, calcd 260.1441	130–132	90
11a	$C_{14}H_{13}N_3O$	HRMS found 239.1134, calcd 239.1059	134–136	20
11b	$C_{12}H_{10}N_4$	HRMS found 210.0941, calcd 210.0905	132–134	18
11c	$C_{12}H_9ClN_4$	HRMS found 244.0337, calcd 244.0516	178–180	10
11d	$C_{12}H_9FN_4$	HRMS found 228.0596, calcd 228.0811	206–208	15
10a	$C_{17}H_{13}N_3O$	HRMS found 275.1059, calcd 275.1056	117–120	25
10b	$C_{14}H_9N_3S$	HRMS found 251.0517, calcd 251.0518	131–132	26
10c	$C_{15}H_{10}N_4$	HRMS found 246.0905, calcd 246.0912	208–209	5



Scheme 6.

ester,[20] it is possible that the boronic derivatives **3** and **4** coordinate to Lewis acids and bases present in solution forming the zwitterions **12** that through ylides **13** gave triazolopyridines (Scheme 6).

In another hand, the ester **5** possess a tetra-coordinated boron which can no interact with other atom, for this we thought it could be better substrate for coupling reactions.[21]



Scheme 7. i, 4-iodopyridine/$Pd(PPh_3)_4$/dioxane; ii, $Ba(OH)_2.8H_2O$/H_2O/H_2O/90–100 °C, 20 h.

We tried the reaction of **5** with 4-iodopyridine using the best conditions found in the reaction of **4b** with the same co-reagent, nevertheless compound **11b** was obtained in smaller yield (8%) and triazolopyridine **1b** was also formed (65% yield) (Scheme 7).

3. Conclusion

In summary, we have successfully formed and characterized some 7-triazolopyridylboronic acids and esters, that are stable solids when have been stored, as well as 5-triazolo-isoquinolylboronic acid. Nevertheless, in solution under the various Suzuki reaction conditions experimented they are not very stable and underwent protodeboronation. 7-Triazolopyridylboronic acids are the most unstable compounds. Still we were able to synthesize some new 7-aryltriazolopyrines and 5-aryltriazolisoquinolines in modest to low yields, as result of Suzuki type cross-coupling reactions. Investigations are continuing on boronic

esters to improve these yields by study of the recently developed methodologies, a solventless Suzuki coupling reaction,[21] and an in situ formation and reaction of heteroarylboronic esters.[20,22]

4. Experimental

Melting points were determined on a Kofler heated stage and are uncorrected. NMR spectra were recorded on a Bruker AC300 MHz or on a JEOL Lambda 400 MHz spectrometers. HRMS (EI) determinations were made using a VG Autospec Trio 1000 (Fisons). ESI-MS was performed using an ion trap mass spectrometer (Esquire 3000 Plus, Bruker) coupled to a liquid chromatograph (Agilet LC 1100 Chemstation), the ionization method was electrospray with positive ion polarity (ESI+). Samples were dissolved in acetonitrile/water (2/3) containing 0.5% formic acid. Infrared spectra were recorded in KBr discs on a Bio-Rad FTS-7. Chromatography was performed on a Chromatotron, using 2 cm plates of silica Merck Pf254. $Pd(PPh_3)_4$ supplier Lancaster.

4.1. General procedure for preparation of boronic acids

To a 2.5 M solution of *n*-BuLi (1.2 equiv.) in hexane, cooled to −40 °C, was added a solution of the corresponding triazoloazine (1 equiv.) in dry toluene and the solution kept at this temperature 4 h. A solution of triisopropyl borate (1.2 equiv.) in toluene was then added and the mixture was allowed to react at this temperature for over 2 h, and then allowed to warm to room temperature. The mixture was quenched by slow addition of 5% aqueous NaOH solution. The resulting aqueous layer was collected and acidified to pH=5 by dropwise addition of concentrated HCl, keeping the internal temperature below 5 °C. Extraction with ethyl acetate, evaporation of the organic layer and washing with ether gave the corresponding boronic acids.

4.1.1. 7-[1,2,3]Triazolo[1,5-*a*]pyridylboronic acid 3a. Yellow solid. IR ν_{max} (KBr) (cm^{-1}) 3201, 1352, 822, 756. ^{13}C NMR δ (D_2O/NaOH) 130.00 (C), 126.79 (CH), 124.96 (CH), 119.00 (C), 118.23 (CH), 115.32 (CH). MS *m*/*z* 163, 145, 135.

4.1.2. 7-(3-Methyl-[1,2,3]triazolo[1,5-*a*]pyridyl)boronic acid 3b. Yellow solid. IR ν_{max} (KBr) (cm^{-1}) 3423, 1316, 868, 772. ^{13}C NMR δ (D_2O/NaOH) 133.80 (CH), 132.08 (C), 125.52 (CH), 118.09 (CH), 117.00 (C), 114.81 (CH), 9.49 (CH_3). MS *m*/*z* 177, 159, 149, 131.

4.1.3. 7-[3-(2-Pyridyl)-[1,2,3]triazolo[1,5-*a*]pyridyl]-boronic acid 3c. Yellow solid. IR ν_{max} (KBr) (cm^{-1}) 3368, 1316, 830, 753. MS *m*/*z* 240, 212, 194.

4.1.4. [1,2,3]Triazolo[5,1-*a*]isoquinolylboronic acid 6. Prepared as described.[3]

4.2. General procedure for preparation of boronic pinacol esters

To a 2.5 M solution of *n*-BuLi (1.2 equiv.) in hexane, cooled to −40 °C, was added a solution of the corresponding triazoloazine (1 equiv.) in dry toluene and the solution kept at this temperature 4 h. A solution of triisopropyl borate (1.2 equiv.) in toluene was then added and the mixture was allowed to react at this temperature for over 2 h, and then allowed to warm to 0−5 °C. A solution of anhydrous pinacol (1.3 equiv.) in toluene was added and, after 5 min, a solution of glacial acetic acid (1.05 equiv.). The mixture was filtered through Celite, and extracted with 5% aqueous NaOH solution. The resulting aqueous layer was collected and acidified to pH=5 by dropwise addition of concentrated HCl, keeping the internal temperature below 5 °C. Extraction with dichloromethane, evaporation of the organic layer and washing with ether/hexane gave the corresponding dioxaborolanes.

4.2.1. 2-(7-[1,2,3]Triazolo[1,5-*a*]pyridyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane 4a. Yellow solid. IR ν_{max} (KBr) (cm^{-1}) 3477, 1366, 1150, 979, 758. ^{13}C NMR δ ($CDCl_3$) 134.00 (C), 126.17 (CH), 125.84 (CH), 124.37 (CH), 120.92 (CH), 110.00 (C), 85.70 (C)×2, 24.20 (CH_3)×4. MS *m*/*z* 245, 217, 216, 118.

4.2.2. 2-(3-Methyl-7-[1,2,3]triazolo[1,5-*a*]pyridyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane 4b. Yellow solid. IR ν_{max} (KBr) (cm^{-1}) 3410, 1329, 1134, 978, 738. ^{13}C NMR δ ($CDCl_3$) 133.57 (C), 131.02 (C), 125.08 (CH), 124.84 (CH), 123.04 (CH), 120.52 (CH), 84.51 (C×2), 24.64 (CH_3×4), 9.96 (CH_3). MS *m*/*z* 259, 231, 216, 188, 172, 149, 132.

4.2.3. 2-[3-(2-Pyridyl)-7-[1,2,3]Triazolo[1,5-*a*]pyridyl]-4,4,5,5-tetramethyl[1,3,2]dioxaborolane 4c. Yellow solid. IR ν_{max} (KBr) (cm^{-1}) 3468, 1378, 1179, 846, 739. ^{13}C NMR δ ($CDCl_3$) 153.00 (C), 149.44 (C), 137.09 (CH), 132.23 (C), 127.00 (C), 126.18 (CH), 125.65 (CH), 124.13 (CH), 122.27 (CH), 121.12 (CH), 96.94 (C), 85.69 (C×2), 23.45 (CH_3×4). MS *m*/*z* 322, 295, 195, 168.

4.3. 2-(3-Methyl-7-[1,2,3]triazolo[1,5-*a*]pyridyl)-1,3,6-dioxazaborolane 5

To a mixture of 3-methyl-7-triazolopyridylboronic acid **3a** (516 mg, 2.91 mmol) and $MgSO_4$ (ca. 1 g per mmol) in dry dichloromethane (50 mL) was added dropwise a solution of N-methyldiethanolamine (365 mg, 3.08 mmol) in dichloromethane. The mixture was allowed to react under stirring at room temperature for 48 h. Then the mixture was filtered under reduced pressure. The filtrate was dried over $MgSO_4$ and concentrated to dryness. A yellow oil was obtained that was precipitate by ethyl acetate/ether, after filtration compound **5** was obtained almost pure as a yellow solid (655 mg, 87%). ^{13}C NMR δ ($CDCl_3$) 133.11 (C), 131.90 (C), 123.58 (CH), 121.28 (CH), 116.46 (CH), 62.58 (CH_2×2), 61.16 (CH_2×2), 44.46 (CH_3), 10.36 (CH_3). MS *m*/*z* 260, 259, 232, 231, 217, 216, 132, 128, 127, 104.

4.4. General procedure for preparation of 5-aryl-[1,2,3]triazolo[5,1-*a*]isoquinolines

A mixture of 5-[1,2,3]triazolo[5,1-*a*]isoquinolylboronic acid **6** (85 mg, 0.4 mmol), DME (10 mL), sodium hydrogen carbonate (100 mg, 1.2 mmol) and water (5 mL), was heated at 45 °C under nitrogen atmosphere with vigorous

stirring (15 min). A solution of the corresponding co-reactive (0.3 mmol), and $Pd[PPh_3]_4$ (23 mg, 0.039 mmol) in DME (5 mL) was added. The reaction mixture was heated to reflux with vigorous stirring under nitrogen atmosphere, the rate of reaction was followed by TLC. (6 h). Water was added (50 mL) and the mixture was extracted with dichloromethane (3×50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The reaction crude was purified by chromatotron using ethyl acetate/hexane in increasing amounts as eluent.

4.4.1. 5-(4-Methoxyphenyl)-[1,2,3]triazolo[5,1-*a*]isoquinoline 10a. The co-reactive was 4-iodoanisol (58 mg). The isolated products were: [1,2,3]triazolo[5,1-*a*]isoquinoline **2** (21 mg, 31%), 5-(4-methoxyphenyl)-[1,2,3]triazolo[5,1-*a*]isoquinoline **10a** (27 mg, 25%). ^{13}C NMR δ ($CDCl_3$) 160.62 (C), 135.75 (C), 133.20 (C), 130.64 (CH), 129.65 (CH), 128.92 (CH), 128.02 (CH), 127.16 (CH), 125.89 (C), 124.31 (CH), 123.66 (CH), 121.93 (C), 114.59 (CH), 113.83 (CH), 55.24 (OCH_3). MS *m*/*z* 275, 247, 232, 203, and 5,5′-bi[1,2,3]triazolo[5,1-*a*] isoquinoline **9** (20 mg, 30%).

4.4.2. 5-(2-Thienyl)-[1,2,3]triazolo[5,1-*a*]isoquinoline 10b. The co-reactive was 2-bromothiophene (57 mg). The isolated products were: [1,2,3]triazolo[5,1-*a*]isoquinoline **2** (18 mg, 26%), 5-(2-thienyl)-[1,2,3]triazolo[5,1-*a*]isoquinoline **10b** (26 mg, 26%). ^{13}C NMR δ ($CDCl_3$) 132.15 (C), 132.14 (C), 128.89 (CH), 128.57 (CH), 128.33 (CH), 127.54 (CH), 127.29 (CH), 126.82 (CH), 126.53 (CH), 125.21 (CH), 122.91 (C), 121.96 (C), 112.58 (CH). MS *m*/*z* 251, 223, 222, 190, and 5,5′-bi[1,2,3]triazolo[5,1-*a*]isoquinoline **9** (25 mg, 36%).

4.4.3. 5-(3-Pyridyl)-[1,2,3]triazolo[5,1-*a*]isoquinoline 10c. The co-reactive was 3-bromopyridine (78 mg). The isolated products were: triphenylphosphine oxide (18 mg), [1,2,3]triazolo[5,1-*a*]isoquinoline **2** (23 mg, 35%), 5-(3-pyridyl)-[1,2,3]triazolo[5,1-*a*] isoquinoline **10c** (5 mg, 5%). ^{13}C NMR δ (Cl_3CD) (DEPT) 148.44 (CH), 148.21 (CH), 138.14 (CH), 130.20 (CH), 129.71 (CH), 129.62 (CH), 128.79 (CH), 128.28 (CH), 124.43 (CH), 116.84 (CH). MS *m*/*z* 246, 218.

4.5. General procedure for preparation of 7-aryl-3-methyl-[1,2,3]triazolo[1,5-*a*] pyridines

A mixture of 2-(3-methyl-7-[1,2,3]triazolo[1,5-*a*]pyridyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane **4b** (mg, mmol), the corresponding co-reactive (mmol), and $Pd[PPh_3]_4$ as catalyst (mg, %) was dissolved in the appropriate solvent (mL), then a base (g, mmol) dissolved in water (mL) was added and the mixture was heated (°C) with vigorous stirring (h), the rate of reaction was followed by TLC, and then was cooled to room temperature. Water was added (mL) and the mixture was extracted with a organic solvent. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The reaction crude was purified by chromatotron or column chromatography using ethyl acetate/hexane in increasing amounts as eluent.

4.5.1. 7-(4-Methoxyphenyl)-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine 11a. Starting material **4b** (100 mg, 0.4 mmol), 4-iodoanisol as co-reactive (0.32 mmol), catalyst (33 mg, 5%), DMF as solvent (7 mL), K_3PO_4 as base (103 mg, 0.48 mmol), water (7 mL), temperature (70 °C), time (16 h), water (5 mL), extraction solvent ethyl acetate. Purified by chromatotron, the isolated products were: triphenylphosphine oxide (17 mg), 3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **1b** (37 mg, 70%), 7-(4-methoxyphenyl)-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **11a** (19 mg, 20%). IR ν_{max} (KBr) (cm^{-1}) 1636, 1606, 1505, 1283. ^{13}C NMR δ ($CDCl_3$) 161.25 (C), 138.46 (C), 134.85 (C), 133.07 (C), 130.97 (CH×2), 129.00 (C), 124.95 (CH), 124.48 (CH), 115.84 (CH), 114.51 (CH×2), 55.52 (CH_3), 10.92 (CH_3). MS *m*/*z* 239, 227, 211, 196, 185, 168.

4.5.2. 7-(4-Pyridyl)-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine 11b. Starting material **4b** (205 mg, 0.8 mmol), 4-iodopyridine as co-reactive (0.7 mmol), catalyst (40 mg, 5%), dioxane as solvent (25 mL), $Ba(OH)_2.8H_2O$ as base (224 mg, 0.71 mmol), water (4 mL), temperature (90–100 °C), time (20 h), water (5 mL), extraction solvent dichloromethane. Purified by column chromatography, the isolated products were: 3-methyl-[1,2,3]triazolo[1,5-*a*]-pyridine **1b** (58 mg, 55%), 7-(4-pyridyl)-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **11b** (30 mg, 18%). IR ν_{max} (KBr) (cm^{-1}) 1606,1572, 1553, 1424, 1401, 783. ^{13}C NMR δ ($CDCl_3$) 150.38 (CH×2), 139.49 (C), 135.40 (C), 135.19 (C), 132.61 (C), 123.81 (CH), 123.00 (CH×2), 117.97 (CH), 115.87 (CH), 10.48 (CH_3). MS *m*/*z* 210, 182, 181, 155, 78.

4.5.3. 7-(2-Chloro-5-pyridyl)-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine 11c. Starting material **4b** (315 mg, 1.21 mmol), 2-chloro-5-iodopyridine as co-reactive (310 mg, 1.3 mmol), catalyst (60 mg, 4%), dioxane as solvent (40 mL), $Ba(OH)_2{\cdot}8H_2O$ as base (400 mg), water (8 mL), temperature (80–100 °C), time (24 h), water (5 mL), extraction solvent dichloromethane. Purified by column chromatography, the isolated products were: 3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **1b** (100 mg, 62%), 7-(2-chloro-5-pyridyl)-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **11c** (30 mg, 10%). IR ν_{max} (KBr) (cm^{-1}) 1633,1588, 1556, 1112, 783. ^{13}C NMR δ ($CDCl_3$) 152.62 (C), 149.29 (CH), 139.27 (CH), 135.26 (C), 133.76 (C), 132.53 (C), 127.24 (C), 124.03 (CH), 123.89 (CH), 117.55 (CH), 115.33 (CH), 10.46 (CH_3). MS *m*/*z* 246, 244, 218, 217, 216, 215, 191, 189, 181, 78.

4.5.4. 7-(2-Fluor-5-pyridyl)-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine 11d. Starting material **4b** (400 mg, 1.54 mmol), 5-bromo-2-fluorpyridine as co-reactive (246 mg, 1.4 mmol), catalyst (80 mg, 5%), dioxane as solvent (20 mL), $Ba(OH)_2{\cdot}8H_2O$ as base (2.8 mmol), water (4 mL), temperature (50–60 °C), time (72 h), water (5 mL), extraction solvent dichloromethane. Purified by column chromatography using cyclohexane/ethyl acetate/methanol in increasing amounts as eluent, the isolated products were: 3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **1b** (143 mg, 70%), 7-(2-fluor-5-pyridyl)-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **11d** (53 mg, 15%). IR ν_{max} (KBr) (cm^{-1}) 1635,1598, 1486, 1257, 793. ^{13}C NMR δ ($CDCl_3$) 164.00 (C) (d, $^1J_{CF}$=241.90 Hz), 147.89 (CH) (d, $^3J_{CF}$=14.96 Hz), 142.13 (CH) (d, $^3J_{CF}$=8.33 Hz), 135.25 (C), 133.88 (C), 132.56 (C), 126.48 (C) (d, $^4J_{CF}$=4.92 Hz),

123.96 (CH), 117.36 (CH), 115.19 (CH), 109.50 (CH) (d, $^2J_{CF}$=37.95 Hz), 10.49 (CH_3). MS *m*/*z* 228, 200, 199, 173.

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