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Synthesis of 2-TIPS-oxazol-5-ylboronic acid pinacol ester: efficient route to 5-(het)aryloxazoles via Suzuki cross-coupling reaction

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ABSTRACT

A facile synthetic route to the new 2-TIPS-oxazol-5-ylboronic acid pinacol ester was described herein. Its reactivity toward Suzuki cross-coupling reaction was studied to provide various 5-(het)aryloxazoles. A wide range of functions on the aryl moiety are tolerated.

1. Introduction

The oxazole ring has widespread application in medicinal, agrochemical, natural products and optical materials such as scintillant molecules and fluorescent dyes.[1] (Hetero)aryl-substituted oxazoles are common features of numerous biologically active natural products and have recently attracted attention in the pharmaceutical community for their therapeutic potential in treating several diseases such as inflammation, cancer and asthma.[2]

5-Aryloxazoles have traditionally been synthesized by the van Leusen reaction which consists of a condensation between carbonyl compounds and tosylmethylisocyanide (TosMIC).[3,4f] Metal-catalyzed direct heterocycle C–H arylation was a relative new method to introduce aryl groups in the 2 or 5 position.[4] However, this straightforward approach is penalized by the regioselectivity difficulties in particular with unsubstituted oxazole at C2 and C5 position.[4d] Direct C5 arylation remains rare with parent oxazole,[4a–c] and they were usually conducted with C-2 substituted oxazoles.[4d–f] It was also possible to access to 5-aryloxazoles with cross-coupling reactions like Stille or Suzuki–Miyaura. Preparation and uses of 5-stannyloxazoles were well described in the literature.[5] Very recently, Smith described for the first time the synthesis of 5-oxazolylboronic acid pinacol ester **1** by a direct C–H borylation[6a] but only one Suzuki cross-coupling reaction using this boronic ester was reported in a recent patent.[7] Other 5-oxazolylboronic acid were mentioned in recent times in a Japanese patent[6b] but all with C-2 position substituted with alkyl or aryl groups. Thus, C-5 Suzuki cross-coupling reactions on oxazole are rare.[8] It must be also pointed out that recent studies have been conducted on the synthesis of oxazole-4-ylboronic esters and they have been engaged in Suzuki cross-coupling reactions.[9] All these recent works attest to the interest shown by the chemical community in the search for new methods to prepare oxazole derivatives.

Within this framework we wish to describe herein a facile synthetic route to the new boronic ester namely 2-triisopropylsilyloxazol-5-ylboronic acid pinacol ester **5** and its use in the Suzuki cross-coupling reaction to afford 5-aryloxazoles.

2. Discussion and results

In the light of the above importance of oxazole compounds, and in continuation of our recent work[10] on the synthesis of 3-aryl-1*H*-pyrazoles, 4(5)-aryl-1*H*-imidazoles and 5-arylthiazoles using respectively 5-pyrazolyl-*N1*-THP-boronic acid pinacol ester **2**, 5-imidazolyl-*N*-THP-boronic acid pinacol ester **3** and 5-thiazolyl boronic acid pinacol ester **4** via Suzuki cross-coupling reaction, it deemed of interest to synthesize 5-aryloxazoles using the same methodology from the appropriate boronic ester **1** (Scheme 1).

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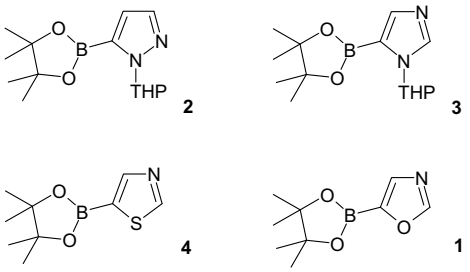
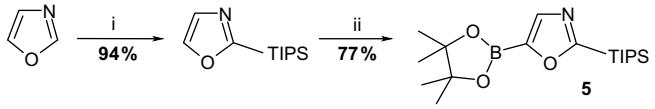


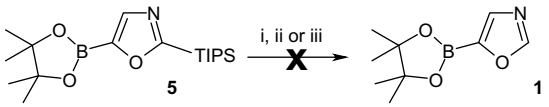
Scheme 1. Boronic species in the azole series.

Firstly, we focused our attention on the synthesis of the key oxazolylboronic ester **1**. It was already described in literature by Smith who used a C–H direct borylation[6a] from the parent oxazole, using pinacolborane, a ligand (4,4′-di-tertbutyl-2,2′-dipyridyl) and an iridium-complex:[Ir(OMe)(COD)]$_2$. Faced to this complexity, we investigated another synthetic route using our laboratory know-how, namely by lithiation, which was previously acquired in azole series. Starting from the commercially available oxazole, it was necessary to protect the more acidic hydrogen in C-2 position to permit a further C-5 lithiation. C-2 Silyl oxazoles were well studied and it was demonstrated that the C-2 oxazole anion could be *C-2* silylated with silyltriflates or *O*-silylated with silylchlorides.[5c,11] Thus, a lithiation on parent oxazole in THF at −30 °C using *n*-BuLi followed by a quench with triisopropylsilyltriflate (TIPSOTf) affords 2-TIPS-oxazole[11] in excellent yield (Scheme 2). With this C-2 protected oxazole, a lithiation was conducted at −30 °C in THF on C-5 position with *n*-BuLi. The C-5 lithio anion was trapped with triisopropylborate and transesterification with pinacol in the presence of AcOH was then achieved at room temperature. After treatment and purification on silica gel, 2-TIPS-5-oxazolylboronic acid pinacol ester **5** was isolated in a very good yield without desilylation (Scheme 2). This compound is stable and can be store at room temperature for long time without degradation.



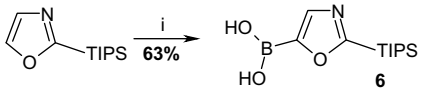
Scheme 2. Synthesis of 2-TIPS-5-oxazolylboronic esters **5**. Reagents and conditions: (i) *n*-BuLi 1.05 equiv, TIPSOTf 1.05 equiv, THF, −30 °C to rt; (ii) *n*-BuLi 1.2 equiv, B(OiPr)$_3$ 1.2 equiv, pinacol 1 equiv, AcOH pH 5, THF, −30 °C to rt.

Afterwards, we looked to cleave the TIPS group while preserving the boronic ester moiety. Unfortunately we have not succeeded and in our hands, the use of HCl 1 M in THF at room temperature cleave both TIPS group and boronic ester (Scheme 3). This problem was already illustrated by Miller[5c] in the case of 5-stannyl-2-TIPS-oxazole which was destannylated. The use of various conditions with tetra-*n*-butylammonium fluoride 1 M in THF (TBAF) remains unsuccessful even by warming. By heating **5** with 2.5 equiv of Na_2CO_3 at 80 °C in a dioxane/water mixture, we observed only the protodeboronation of **5**.



Scheme 3. Desilylation attempts. Reagents and conditions: (i) 1 M HCl, THF, rt, 10 min; (ii) 1 M TBAF, THF, rt or reflux; (iii) Na_2CO_3 2.5 equiv, dioxane/water 3:1, 80 °C.

We have also attempted the synthesis of the boronic acid derivative of **2**. Instead of the transesterification step, a basic hydrolysis was conducted. After extraction with ether, the basic aqueous layer was made acidic by diluted HCl until pH 2. The boronic acid was extracted with EtOAc and it was characterized as 2-TIPS-5-oxazolylboronic acid **6** (Scheme 4). However, **5** is unstable at room temperature and it was partially degraded after 2 days.

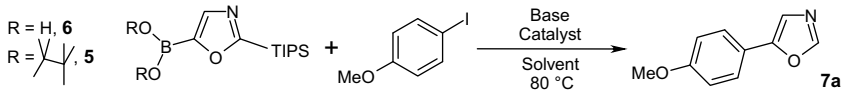


Scheme 4. Synthesis of 2-TIPS-5-oxazolylboronic acid **6**: Reagents and conditions: (i) *n*-BuLi 1.2 equiv, B(OiPr)$_3$ 1.2 equiv, NaOH 2 M then HCl 3 M to pH 2, THF, −30 °C to rt.

Although the presence of TIPS, we have engaged the ester **5** in a Suzuki–Miyaura cross-coupling reaction in order to study its reactivity with 4-iodoanisole. Thus **2** was firstly reacted with 4-iodoanisole under standard conditions (boronic ester 1.1 equiv; Na_2CO_3 2.5 equiv; dioxane/water; 80 °C) and fortunately the reaction furnished directly 5-(4-methoxyphenyl)oxazole **7a** with a excellent yield of 79% (Table 1, entry 1). The C-2 desilylation occurred during the cross-coupling reaction. The use of water-free protocol (boronic ester 1.1 equiv; CsF 2.5 equiv; CuI 0.1 equiv; Pd(PPh$_3$)$_4$ 5 mol %; dry DMF; 80 °C) described for sensitive boronic ester in our previous work[10c] afforded a mixture of **7a** and 2,5-bis(4-methoxyphenyl)oxazole[4e] in equal proportion (Table 1, entry 2). It was not a surprisingly result since copper-catalyzed direct C2–H arylation of oxazole was described.[12] We have also studied the ability of **5** to react toward ligand-free conditions[13] by using Pd(OAc)$_2$. With 5 mol % of Pd(OAc)$_2$ the obtained yield was poor (Table 1, entry 3). We have noted the rapid formation of inactive 'palladium black' which prompted us to reduce the quantity of catalyst. By using 2 mol % of Pd(OAc)$_2$, the yield rose up to 62% (Table 1, entry 4). Even if the boronic acid **6** was not a grade partner due to its instability, it could be coupled with 4-iodoanisole under classical conditions and yielded 47% of **7a** (Table 1, entry 5).

Having secure a good access to **7a**, we examined the scope and limitations of the use of our oxazolyl boronic ester **5** in Suzuki cross-coupling reactions. Thus, **5** was coupled with a variety of (het)aryl halides using standard aqueous reaction conditions (Table 1, entry 1). The yields were satisfactory and our methodology using the new oxazol-5-ylboronic pinacol ester allows the synthesis of 5-aryloxazoles bearing sensitive groups such as nitriles, esters or aldehydes positioned in any position of the phenyl group (Table 2). In the case of aldehydes, our method is very interesting since it permits the access in one step to the corresponding aldehydes in mild conditions (entries 7–9) advantageously toward the van Leusen method which permit only to realize a three steps synthesis from the corresponding methyl 4-formylbenzoate to afford **7g**.[14] The first step is the condensation with TosMIC followed by reduction with $LiAlH_4$ and a final Swern oxidation is conducted to afford the 4-(oxazol-5-yl)benzaldehyde **7g**. Even in the presence of a free amino group, Suzuki cross-coupling occurred with a good yield (Table 2, entry 3). Heteroaryl bromides were also suitable reactants in this reaction. 2 or 3-Bromopyridine and 5-bromofurfural gave respectively **7l**, **7k** and **7m** in moderate to good yields (Table 2, entries 11–13). Moreover, it must be pointed out that is was possible to performed cross-coupling with chlorimine[15] (Table 2, entry 14). In the case of entry 15, we observed that the *N*-Boc was cleaved during the cross-coupling and yielded 22% of **7o**. The other isolated products were *N*-deprotected unreacted bromocarbazole. Due to the emerging C–H arylation interest, we have compared this methodology with two of our examples. The conditions used by Kuo et al.[4b] (aryl halide, oxazole 3 equiv, KOAc 1.5 equiv, Pd(PPh$_3$)$_4$ 5 mol %, DMA, 80 °C) with 4-bromobenzonitrile as substrate lead to only 36% of **7d**. We have also tried ligand free conditions inspired from Roger et al.[16] (aryl halide, oxazole 2 equiv, KOAc 2 equiv, Pd(OAc)$_2$ 1 mol %, DMA, 80 °C) starting from 4-iodoanisole. In this

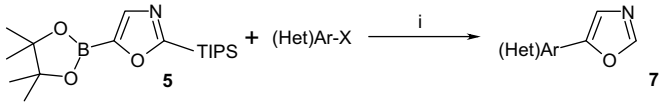
Table 1
Cross-coupling reaction optimization of **5** and **6** with 4-iodoanisole



Entry	Boronic (equiv)	Base	Catalyst	mol %	Solvent	Yield[a] (%)
1	**5** (1.1 equiv)	Na_2CO_3 (2.5 equiv)	$Pd(PPh_3)_4$	5	Dioxane/H_2O 3:1	79
2	**5** (1.1 equiv)	CsF (2.5 equiv), CuI (0.1 equiv)	$Pd(PPh_3)_4$	5	DMF	Mixture
3	**5** (1.1 equiv)	Na_2CO_3 (2.5 equiv)	$Pd(OAc)_2$	5	Dioxane/H_2O 3:1	31
4	**5** (1.1 equiv)	Na_2CO_3 (2.5 equiv)	$Pd(OAc)_2$	2	Dioxane/H_2O 3:1	62
5	**6** (1.1 equiv)	Na_2CO_3 (2.5 equiv)	$Pd(PPh_3)_4$	5	Dioxane/H_2O 3:1	47

[a] Isolated yield.

Table 2
Suzuki cross-coupling reactions of ester **5** with various halides



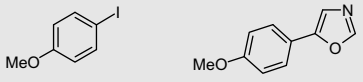
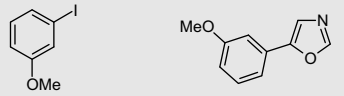
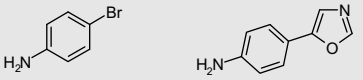
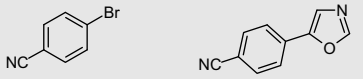
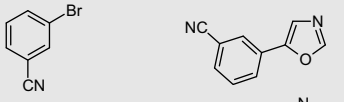
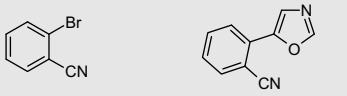
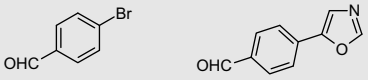
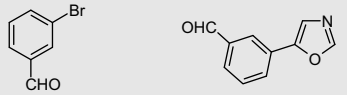
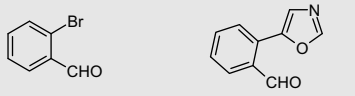
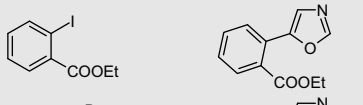
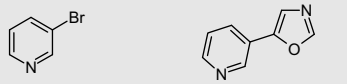
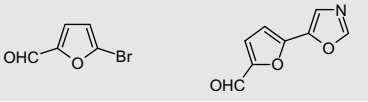
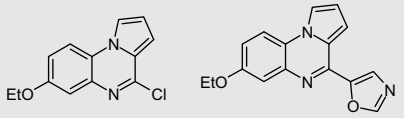
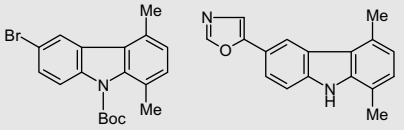
Entry	Halide	Product	Yield[a] (%)
1		**7a**	79
2		**7b**	90
3		**7c**	62
4		**7d**	64[b]
5		**7e**	75
6		**7f**	72
7		**7g**	71
8		**7h**	67
9		**7i**	74
10		**7j**	53
11		**7k**	69
12		**7l**	42
13		**7m**	71

Table 2 (*continued*)

Entry	Halide	Product	Yield[a] (%)
14		**7n**	43
15		**7o**	22

Conditions: boronic ester 1.1 equiv; aryl halide 1 equiv; Na_2CO_3 2.5 equiv; $Pd(PPh_3)_4$ 5 mol %; dioxane/water 3:1; 80 °C.
[a] Isolated yields.
[b] This compound was obtained with 17% yield from direct arylation of 2-TIPS-oxazole and 37% from parent oxazole.

case only 18% of **7a** was recovered. Finally, we have also conducted direct arylations of 2-TIPS-oxazole with 4-iodoanisole and 4-bromobenzonitrile. With 4-iodoanisole only traces of the expected anisyloxazole **7a** were detected and with 4-benzonitrile, compound **7d** was recovered with a poor 17% yield (Table 2, entry 4). These poor results are due to the formation of complex mixtures contrarily to direct arylation of parent oxazole which gave cleaner results and rather better yields.

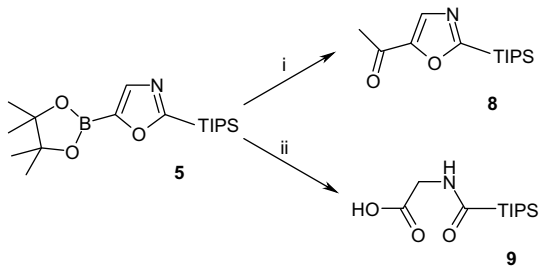
3. Conclusion and perspectives

In conclusion we have performed an efficient synthesis of the 2-TIPS-5-oxazolylboronic acid pinacol ester **5**. This latter is stable in the Suzuki cross-coupling reactions and allows the facile synthesis of various 5-(het)aryloxazoles under mild conditions. We are now studying the usefulness of **5** in other reactions. In one hand we have not found the good conditions to perform Chan–Lam coupling reaction[17] due to the rapid deboronation of **5** in the presence of cupric salts. But in the other hand, our first results leading to the yet unknown 5-acetyloxazole **8** (obtained by reaction of **5** with acetic anhydride in the presence of $Pd(PPh_3)_4$ according to the method of Gooβen and Ghosh[18]) and to the new *N*-protected glycine **9** (obtained by oxidation of **5** with hydrogen peroxide) are very encouraging for further explorations in the oxazole chemistry (Scheme 5).

4. Experimental

4.1. General procedures

Commercial reagents were used as received without additional purification. Melting points were determined on a Köfler melting



Scheme 5. New reactions starting from **5**: Reagents and conditions: (i) boronic ester **5** 1.2 equiv, Ac_2O 1 equiv, $Pd(PPh_3)_4$ 5 mol %, 60 °C, 20 h, 18% (ii) (1) boronic ester **5**, NaOH 2 M, rt; (2) H_2O_2 35% 10 equiv, rt; (3) HCl 3 M; 68%.

point apparatus and are uncorrected. IR spectra were taken with a Perkin–Elmer Spectrum BX FT-IR-ATR System spectrometer. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL Lambda 400 Spectrometer. Chemicals shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. The mass spectra (MS) were taken on a JEOL JMS GCMate spectrometer at a ionizing potential of 30 eV. Thin layer chromatographies (TLC) were performed on 0.2 mm precoated plates of silica gel 60F-264 (Merck). Visualization was made with ultraviolet light (234 nm). Column chromatographies were carried out using silica gel 60 (0.063–0.2 mm) (Merck). Elemental analyses for new compounds were performed at the 'Institut de Recherche en Chimie Fine' (Rouen).

4.2. 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-2-triisopropylsilyloxazole (5)

To a stirred solution under nitrogen of 2-triisopropylsilyloxazole[11] (3.2 g, 14.2 mmol) in dry THF (100 mL) cooled to −30 °C, was added *n*-BuLi (2.5 M) (6.8 mL, 17.1 mmol, 1.2 equiv) over a period of 10 min. After 20 min of stirring at this temperature was added triisopropyl borate (3.9 mL, 17.1 mmol, 1.2 equiv). The resulting mixture was allowed to react at this temperature for 2 h and then left to warm to room temperature over a course of 45 min. A solution of pinacol (1.68 g, 14.2 mmol, 1 equiv) in THF (10 mL) was added and after 5 min, glacial acetic acid was added until the pH reached 5 (a drop of the mixture was put down on pH-indicator paper with a drop of water). After 1 h of stirring at room temperature, the mixture was diluted with ether, filtered and concentrated under vacuum. Cyclohexane was added to the residue, the resulting mixture was triturated and the solvent was removed by evaporation. This operation was conducted three times. Purification by column chromatography on silica gel was performed (cyclohexane/EtOAc 7:3) to furnish 5 (3.84 g, 77%) as a pale yellow oil which slowly crystallizes on standing. Mp <50 °C. IR (KBr) ν 2944, 2868, 1569, 1462, 1332, 1122, 970, 883, 854 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.74 (s, 1H, H4), 1.44 (sept, *J*=7.8 Hz, 3H, CH TIPS), 1.35 (s, 12H), 1.14 (d, *J*=7.8 Hz, 18H, CH_3 TIPS). ^{13}C NMR ($CDCl_3$): δ 173.2 (C2), 139.4 (C5), 84.3 (2 O-*C*(CH_3)$_3$), 24.6 (4 CH_3), 18.3 (6 CH_3), 10.9 (3 CH),(the boron-carrying C-5 did not appear). HRMS (EI) *m*/*z* Calcd: 351.24010, Found: 351.23997.

4.3. 2-(Triisopropylsilyl)oxazol-5-ylboronic acid (6)

To a stirred solution under nitrogen of 2-triisopropylsilyloxazole[11] (2.0 g, 8.9 mmol) in dry THF (80 mL) cooled to −30 °C, was added *n*-BuLi (2.5 M) (4.3 mL, 10.7 mmol, 1.2 equiv) over a period of 10 min. After 20 min of stirring at this temperature was added triisopropylborate (2.5 mL, 10.7 mmol, 1.2 equiv). The resulting mixture was allowed to react at this temperature for 1 h and then left to warm to room temperature. The solution was quenched with NaOH 4 N and extracted two times with ether. The basic aqueous layer was made acidic with HCl 3 N until pH 2. The mixture was extracted three times with EtOAc, dried over $MgSO_4$ and concentrated. The residue was triturated with ether and filtered to give **6** as a white solid (1.50 g, 63%). Mp >250 °C. ^1H NMR (D_2O): δ 6.82 (s, 1H, H4), 1.27 (sept, *J*=7.8 Hz, 3H, CH TIPS), 0.96 (d, *J*=7.8 Hz, 18H, CH_3 TIPS).

4.4. Typical procedure for the Suzuki cross-coupling reaction

To a mixture of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole **5** (500 mg, 1.4 mmol, 1.1 equiv), aryl halide (1.3 mmol, 1 equiv) in a mixture of dioxane and water 3:1 (20 mL) under argon was added Na_2CO_3 (343 mg, 3.2 mmol, 2.5 equiv) and $Pd(PPh_3)_4$ (75 mg, 0.06 mmol, 0.05 equiv). The reaction mixture was heated at 80 °C and the consumption of halocompound was followed by TLC (6–18 h). The reaction mixture was then diluted with EtOAc and filtered trough a pad of Celite®. The filtrate was washed three times with brine. The organic layer was dried on $MgSO_4$, filtered and evaporated under vacuum. The crude product was purified using column chromatography on silica gel (cyclohexane/EtOAc).

*4.4.1. 5-(4-Methoxyphenyl)oxazole (**7a**)[4f,19]*

White solid (79%), using 4-iodoanisole as halocompound. Mp 58 °C. IR (KBr) ν 3099, 2937, 1619, 1510, 1490, 1251, 1176, 811 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.87 (s, 1H, H_2), 7.58 (dd, *J*=2.0 and 6.8 Hz, 2H, H_{Ar}), 7.23 (s, 1H, H_4), 6.95 (d, *J*=6.8 Hz, 2H, H_{Ar}), 3.84 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 159.8, 151.4, 149.8, 125.8, 120.5, 119.9, 114.2, 55.2. Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 64.78; H, 4.93; N, 7.78.

*4.4.2. 5-(3-Methoxyphenyl)oxazole (**7b**)*

Pale yellow oil (90%), using 3-iodoanisole as halocompound. IR (KBr) ν 3126, 2941, 1693, 1575, 1489, 1290, 1218, 1034, 948, 778, 688 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.88 (s, 1H, H_2), 7.33 (s, 1H, H_4), 7.30 (t, *J*=7.8 Hz, 1H, H_{Ar}), 7.23–7.16 (m, 2H, H_{Ar}), 6.87 (dd, *J*=2.9 and 7.8 Hz, 1H, H_{Ar}), 3.82 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 159.7, 151.2, 150.2, 129.8, 128.7, 121.4, 116.6, 114.1, 109.6, 55.0. HRMS (EI) *m*/*z* Calcd: 175.06333, Found: 175.06326.

*4.4.3. 4-(Oxazol-5-yl)aniline (**7c**)[20]*

White solid (62%) using 4-iodoaniline as halocompound. Mp 156 °C. IR (KBr) ν 3424, 3306, 3205, 1640, 1610, 1490, 1286, 806 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.83 (s, 1H, H_2), 7.45 (dd, *J*=2.0 and 8.8 Hz, 2H, H_{Ar}), 7.15 (s, 1H, H_4), 6.71 (dd, *J*=2.0 and 8.8 Hz, 2H, H_{Ar}), 3.85 (br s, 2H, NH_2). ^{13}C NMR ($CDCl_3$): δ 152.0, 149.4, 146.9, 125.8, 119.0, 118.3, 115.0. HRMS (EI) *m*/*z* Calcd: 160.06366, Found: 160.06372.

*4.4.4. 4-(Oxazol-5-yl)benzonitrile (**7d**)[21a,b]*

White solid (64%), using 4-bromobenzonitrile as halocompound. Mp 133 °C. IR (KBr) ν 3122, 2223, 1615, 1504, 1485, 1107, 1096, 943, 835 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.00 (s, 1H, H_2), 7.78–7.72 (m, 4H, H_{Ar}), 7.52 (s, 1H, H_4). ^{13}C NMR ($CDCl_3$): δ 149.8, 148.0, 131.0, 129.9, 122.9, 122.4, 116.6, 110.2. Anal. Calcd for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.49; H, 3.31; N, 16.47.

*4.4.5. 3-(Oxazol-5-yl)benzonitrile (**7e**)*

White solid (75%), using 3-bromobenzonitrile as halocompound. Mp 135 °C. IR (KBr) ν 3119, 2230, 1695, 1502, 1473, 1097, 949, 845, 801, 684 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.99 (s, 1H, H_2), 7.94 (s, 1H, H_4), 7.89 (dd, *J*=2.0 and 7.8 Hz, 1H, H_{Ar}), 7.63 (d, *J*=2.0 and 7.8 Hz, 1H, H_{Ar}), 7.57 (t, *J*=7.8 Hz, 1H, H_{Ar}), 7.47 (s, 1H, H_{Ar}). ^{13}C NMR ($CDCl_3$): δ 151.1, 149.2, 131.7, 129.8, 128.8, 128.2, 127.6, 123.0, 118.0, 113.3. Anal. Calcd for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.41; H, 3.35; N, 16.46.

*4.4.6. 2-(Oxazol-5-yl)benzonitrile (**7f**)*

White solid (72%), using 2-bromobenzonitrile as halocompound. Mp 100 °C. IR (KBr) ν 3122, 2223, 1615, 1485, 1108, 943, 836 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.03 (s, 1H, H_2), 7.95 (s, 1H, H_4), 7.87 (d, J=7.8 Hz, 1H, $H_{6'}$), 7.76 (d, J=7.8 Hz, 1H, $H_{3'}$), 7.69 (t, J=7.8 Hz, 1H, $H_{5'}$), 7.45 (t, J=7.8 Hz, 1H, $H_{4'}$). ^{13}C NMR ($CDCl_3$): δ 151.2 (C2), 147.7 (C5), 134.1 (C3′), 133.2 (C5′), 130.4 (C1′), 128.5 (C4′), 126.3 (C6′), 126.0 (C4), 118.2 (CN), 107.8 (C2′). Anal. Calcd for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.32; H, 3.42; N, 16.22.

*4.4.7. 4-(Oazol-5-yl)benzaldehyde (**7g**)[14]*

White solid (71%), using 2-bromobenzaldehyde as halocompound. Mp 104 °C. IR (KBr) ν 3125, 2836, 1694, 1608, 1209, 1109, 1093, 828 cm^{-1}. ^1H NMR ($CDCl_3$): δ 10.03 (s, 1H, CHO), 8.00 (s, 1H, H2), 7.95 (d, J=8.4 Hz, 2H, H_{Ar}), 7.83 (d, J=8.4, 2H, H_{Ar}), 7.53 (s, 1H, H2). ^{13}C NMR ($CDCl_3$): δ 191.3, 151.5, 150.3, 136.0, 133.0, 130.4, 124.7, 124.1. Anal. Calcd for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.19; H, 3.89; N, 8.00.

*4.4.8. 3-(Oxazol-5-yl)benzaldehyde (**7h**)*

White solid (67%), using 3-bromobenzaldehyde as halocompound. Mp 87 °C. IR (KBr) ν 3103, 1683, 1576, 1179, 1114, 959, 850, 797, 686 cm^{-1}. ^1H NMR ($CDCl_3$): δ 10.08 (s, 1H, CHO), 8.17 (s, 1H, H2), 7.98 (s, 1H, H4), 7.92 (d, J=7.8 Hz, 1H, H_{Ar}), 7.86 (d, J=7.8 Hz, 1H, H_{Ar}), 7.62 (t, J=7.8 Hz, 1H, H_{Ar}), 7.48 (s, 1H, H_{Ar}). ^{13}C NMR ($CDCl_3$): δ 191.7, 151.0, 150.3, 137.0, 129.9, 129.8, 129.7, 128.8, 125.2, 122.7. Anal. Calcd for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.22; H, 3.91; N, 7.86.

*4.4.9. 2-(Oxazol-5-yl)benzaldehyde (**7i**)*

White solid (74%), using 2-bromobenzaldehyde as halocompound. Mp 85 °C. IR (KBr) ν 3118, 1689, 1601, 1436, 1201, 1106, 825, 767 cm^{-1}. ^1H NMR ($CDCl_3$): δ 10.33 (s, 1H, CHO), 8.06–8.02 (m, 2H, H_2+H_{Ar}), 7.71–7.67 (m, 2H, H_{Ar}), 7.57–7.53 (m, 1H, H_{Ar}), 7.39 (s, 1H, H_4). ^{13}C NMR ($CDCl_3$): δ 190.9, 151.7, 148.5, 133.9, 133.3, 129.6, 129.4, 128.9, 128.8, 126.6. Anal. Calcd for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.20; H, 3.87; N, 7.92.

*4.4.10. Ethyl 2-(oxazolyl-5-yl)benzoate (**7j**)*

Yellow oil (53%), using ethyl 2-iodobenzoate as halocompound. IR (KBr) ν 2982, 1716, 1286, 1258, 1127, 1092, 943, 760 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.96 (s, 1H, H_2), 7.81 (d, J=7.8 Hz, 1H, H_{Ar}), 7.60–7.52 (m, 2H, H_{Ar}), 7.45 (t, J=7.8 Hz, 1H, H_{Ar}), 7.31 (s, 1H, H_4), 4,30 (q, J=6.8 Hz, 2H, CH_2), 1.27 (t, J=6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 167.6 (C=O), 150.6, 150.1, 131.3, 130.5, 129.8, 129.0, 128.9, 126.9, 124.2, 61.4, 14.0. HRMS (EI) m/z Calcd: 217.07389, Found: 217.07371.

*4.4.11. 3-(Oxazol-5-yl)pyridine (**7k**)[22]*

White solid (69%), using 3-bromopyridine as halocompound. Mp 64 °C. IR (KBr) ν 3096, 1689, 1498, 1465, 1428, 1105, 1019, 939, 810, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.94 (d, J=2.0 Hz, 1H, H_{Ar}), 8.59 (d, J=4.9 Hz, 1H, H_{Ar}), 7.99 (s, 1H, H_2), 7.93 (dt, J=2.0 and 5.8 Hz, 1H, H_{Ar}), 7.46 (s, 1H, H_4), 7.37 (dd, J=4.9 and 7.8 Hz, 1H, H_{Ar}). ^{13}C NMR ($CDCl_3$): δ 151.1, 149.5, 148.8, 145.7, 131.4, 123.9, 123.6, 122.7. HRMS (EI) m/z Calcd: 146.04801, Found: 146.04788.

*4.4.12. 2-(Oxazol-5-yl)pyridine (**7l**)[22b,23]*

Tan oil (42%), using 2-bromopyridine as halocompound. ^1H NMR ($CDCl_3$): δ 8.64 (d, J=3.8 Hz, 1H, H_{Ar}), 8.02 (s, 1H, H_2), 7.77 (dt, J=1.9 and 7.8 Hz, 1H, H_{Ar}), 7.72 (s, 1H, H_4), 7.67 (d, J=7.8 Hz, 1H, H_{Ar}), 7.25 (m, 1H, H_{Ar}). ^{13}C NMR ($CDCl_3$): δ 151.2, 151.1, 150.0, 147.1, 136.9, 124.9, 123.1, 119.4. HRMS (EI) m/z Calcd: 146.04801, Found: 146.04815.

*4.4.13. 5-(Oxazol-5-yl)furan-2-carbaldehyde (**7m**)*

Pale yellow solid (71%), using 5-bromofurfural as halocompound. Mp 122 °C. IR (KBr) ν 3118, 2230, 1682, 1502, 1108, 949, 895, 795 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.69 (s, 1H, CHO), 7.97 (s, 1H, H_2), 7.54 (s, 1H, H_4), 7.33 (d, J=3.6 Hz, 1H, H_{Ar}), 6.83 (d, J=3.6 Hz, 1H, H_{Ar}). ^{13}C NMR ($CDCl_3$): δ 177.3, 152.4, 151.3, 148.1, 142.6, 125.2, 122.4, 109.5. Anal. Calcd for $C_8H_5NO_3$: C, 58.90; H, 3.09; N, 8.59. Found: C, 58.69; H, 2.92; N, 8.52.

*4.4.14. 7-Ethoxy-4(oxazol-5-yl)pyrrolo[1,2-a]quinoxaline (**7n**)*

Yellow solid (43%). Following typical procedure using 4-chloro-7-ethoxypyrrolo[1,2-*a*]quinoxaline[15] as halocompound. Mp 154 °C. IR (KBr) ν 3120, 1478, 1357, 1237, 1050, 804, 741, 715. ^1H NMR ($CDCl_3$): δ 8.13 (s, 1H), 7.96 (s, 1H), 7.89 (d, J=3.0 Hz, 1H), 7.72 (d, J=8.8 Hz, 1H), 7.42 (d, J=3,0 Hz, 1H), 7.27–7.24 (m, 1H), 7.11 (dd, J=3.0 and 9.8 Hz, 1H), 6.89 (dd, J=2.0 and 4.0 Hz, 1H), 4.13 (q, J=6.8 Hz, 2H), 1.47 (t, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 156.6, 151.8, 149.4, 141.4, 136.4, 128.2, 122.5, 121.3, 118.0, 114.5, 114.4, 114.0, 111.6, 107.1, 63.9, 14.8. Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.42; H, 4.39; N, 14.89.

*4.4.15. 1,4-Dimethyl-6-(oxazol-5-yl)-9H-carbazole (**7o**)*

Pale yellow solid (22%), using *tert*-butyl 6-bromo-1,4-dimethyl-9*H*-carbazole-9-carboxylate[24] as halocompound. Mp 237 °C. IR (KBr) ν 3164, 1586, 1447, 1308, 1269, 1097, 799, 687. ^1H NMR (DMSO-d_6): δ 11.39 (s, 1H, NH), 8.38 (s, 1H), 8.36 (s, 1H), 7.73 (d, J=8.8 Hz, 1H), 7.61 (s, 1H), 7.57 (d, J=8.8 Hz, 1H), 7.09 (d, J=6.8 Hz, 1H), 6.86 (d, J=6.8 Hz, 1H), 2.79 (s, 3H, CH_3), 2.47 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 152.0, 150.9, 139.8, 139.5, 130.0, 126.4, 123.6, 121.6, 120.5, 120.3, 119.9, 119.8, 118.3, 117.8, 111.5, 20.3, 16.7. Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.61; H, 5.13; N, 10.55.

4.5. 1-(2-Triisopropylsilyl)oxazole-5-yl)ethanone (8)

A round bottomed flask was charged with $Pd(PPh_3)_4$ (82 mg, 0.07 mmol, 0.05 equiv), boronic ester 5 (600 mg, 1.71 mmol, 1.2 equiv), acetic anhydride (145 mg, 1.42 mmol, 1 equiv). Subsequently, THF (10 mL) and water (64 μL, 3.56 mmol, 2.5 equiv) were added. The reaction vessel was purged with argon and then heated at 60 °C overnight. After cooling, the volatiles were removed under vacuum and the residue was taken up with EtOAc and washed three times with brine. The organic layer was dried on $MgSO_4$, filtered and evaporated under vacuum. The crude product was purified using column chromatography on silica gel (cyclohexane/EtOAc) and afforded **8** as colorless oil (70 mg, 18%). ^1H NMR ($CDCl_3$): δ 7.83 (s, 1H, H4), 2.52 (s, 3H, $COCH_3$), 1.44 (sept, J=7.8 Hz, 3H, CH TIPS), 1.15 (d, J=7.8 Hz, 18H, CH_3 TIPS). ^{13}C NMR ($CDCl_3$): δ 186.1, 173.1, 151.7, 132.9, 26.9, 18.2, 10.9.

4.6. 2-((Triisopropylsilyl)formamido)acetic acid (9)

To a solution of NaOH 2% (10 mL) was added boronic ester **5**, and the mixture was stirred at room temperature until complete dissolution of **5** (approx. 1 h). Then, H_2O_2 35% (1 mL, 10 equiv) was added a 0 °C and the solution was allowed to stir at room temperature for the night. A solution of HCl 3 N was then added to neutralize the mixture and a precipitate was formed. It was filtrated and washed with water. After drying it afforded **9** as a white solid (200 mg, 68%). Mp 118 °C. ^1H NMR ($CDCl_3$): δ 4.13 (d, J=4.9 Hz, 2H, CH_2), 1.27 (sept, J=7.8 Hz, 3H, CH TIPS), 1.13 (d, J=7.8 Hz, 1H, CH_3 TIPS). ^{13}C NMR ($CDCl_3$): δ 187.4, 172.6, 40.4,

18.4, 10.6. MS(ESI): Calcd for $C_{12}H_{25}NO_3Si$ [M^+] 159, found: [MH^+] 160.

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