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Functionalization of oxazolo[4,5-*b*]pyrazines by deprotometallation

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Abstract: Different 2-arylated oxazolo[4,5-*b*]pyrazines, obtained by palladium(II)-catalysed domino reaction from 2,3-dichloropyrazine and the corresponding carboxamides, were functionalized by deprotometallation. Employing lithium 2,2,6,6-tetramethylpiperidine, in order to form a lithio derivative, and then trapping it by iodolysis, proved to be inefficient. However, the presence of a zinc-based *in situ* trap allowed most substrates to be functionalized. Deprotonation of the pyrazine ring was observed in the presence of tolyl and anisyl groups at the oxazole 2-position. In contrast, with chlorophenyl and thienyl groups in this 2-position, deprotonation rather occurred on these groups either competitively or exclusively. The regioselectivities were discussed in the light of calculated pK_a values of the substrates in THF. Finally, in the case of 2-phenyloxazolo[4,5-*b*]pyrazine, we converted the mixture of 5- and 6-iodinated products into the corresponding 5,6-diiodide which was further functionalized by a double Suzuki coupling.

planar heterocycle is structurally close to benzoxazole and oxazolopyridine, which are key scaffolds of both natural-^[2] and synthetic products,^[3] often endowed with attractive biological activities.^[4] Thus, there is an interest in the medicinal chemistry field for methodologies which can give access to derivatives starting of 2-arylated oxazolo[4,5-*b*]pyrazines (Fig. 1).

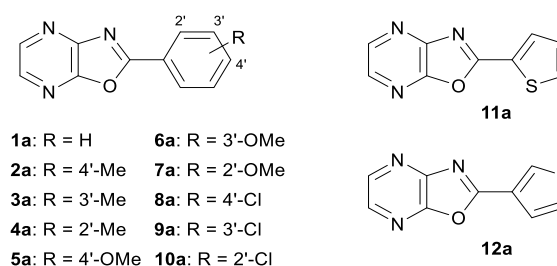


Figure 1. Starting 2-arylated oxazolo[4,5-*b*]pyrazines.

Introduction

The heterocycle oxazolo[4,5-*b*]pyrazine was synthesized for the first time in 2014 by Demmer, Bunch and co-workers.^[1] This

Among the methods used to functionalize aromatic compounds and heterocycles, deprotonative metallation is an efficient strategy.^[5] Nevertheless, due to their low LUMO level, diazines are sensitive to nucleophilic attacks (e.g. to competitively give dimers), and thus hardly compatible with polar organometallics such as aryllithiums.^[6] Consequently, in the absence of a substituent able to stabilize generated diazynyllithiums, by-products are generally observed.^[7]

Within the last two decades, methods have been developed to tackle the chemoselectivity issue of deprotometallation. Lithium-ate bases (e.g. zincates) and 'Turbo' bases (e.g. zinc amides containing LiCl) have been identified as suitable reagents to this date,^[8] but few examples concern diazines without directing/acidifying groups.^[9]

In situ 'trans-metal trapping' is an alternative way to address this issue by intercepting the generated aryllithiums with an electrophilic trap as soon as it is formed.^[10] For the functionalization of bare diazines, methods employing different base-*in situ* trap pairs have been reported. In this vein, the tandem LiTMP-Zn(TMP)₂ (TMP = 2,2,6,6-tetramethylpiperidino) allowed Mongin and co-workers to deprotometallate pyrazine at room temperature in THF (THF = tetrahydrofuran), a result evidenced by subsequent iodolysis.^[11] Mg(TMP)₂·2LiCl-ZnCl₂ also worked for the same purpose under similar conditions,^[12] as well as LiTMP-Ga(CH₂SiMe₃)₃ in hexane at room temperature.^[13]

In the frame of this paper, we report our efforts to functionalize the 2-arylated oxazolo[4,5-*b*]pyrazines **1a-12a** by deprotonative metallation strategies.

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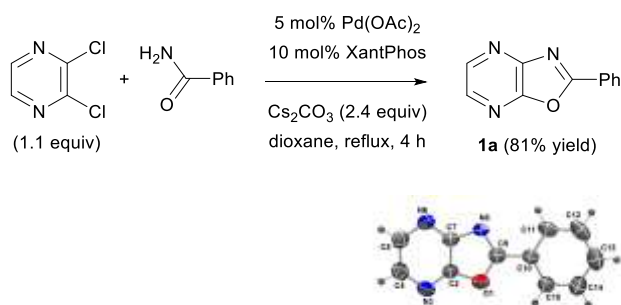
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Results and Discussion

The starting oxazolo[4,5-*b*]pyrazines were synthesized as described previously by a palladium(II)-catalysed domino reaction from 2,3-dichloropyrazine and the corresponding carboxamides.^[1] We chose the phenyl-substituted oxazolo[4,5-*b*]pyrazine **1a** to identify suitable deprotometallation conditions (Table 1). The construction of **1a** using benzamide, initially reported at a 0.61 mmol scale and in 68% yield, was scaled up to 12.4 mmol to give **1a** in 81% yield under efficient stirring (Scheme 1).



Scheme 1. Formation of 2-phenyloxazolo[4,5-*b*]pyrazine (**1a**) and ORTEP diagram (50% probability) of **1a**.

Substrates possessing numerous heteroatoms can be reluctant to LiTMP-mediated deprotometallation.^[14] It proved to be the case from **1a** since the reactions using 1 or 2 equiv of LiTMP in THF at -75 °C for 1 h showed after iodolysis low

Table 1. Optimization of **1a** deprotometallation.

Entry	Base (equiv)	Conditions	Products	Ratio ^[a]	Yields ^[b] (%)
1	LiTMP (1)	-75 °C, 1 h	1a , 1b , 1c	89/5/6	— ^[c]
2	LiTMP (2)	-75 °C, 1 h	1a , 1b , 1c	77/10/13	— ^[c]
3	LiTMP-Zn(TMP) ₂ ^[d] (1 each)	0 °C, 2 h	1a , 1b , 1c	46/36/8 ^[e]	— ^[c]
4	LiTMP-Zn(TMP) ₂ ^[d] (1 each)	20 °C, 2 h	1a , 1b , 1c	9/49/14 ^[e]	34 (1b), 7 (1c)
5	LiTMP (1.5)-ZnCl ₂ ^[f] (1)	-10 °C, 1/4 h	1a , 1b , 1c	20/53/23 ^[e]	44 (1b), 18 (1c)
6	LiTMP (1.5)-ZnCl ₂ ^[f] (1)	-30 °C, 1/4 h	1a , 1b , 1c	17/57/26	50 (1b), 34 (1c)

[a] Estimated by ¹H NMR spectroscopy. [b] After column chromatography over silica gel. [c] Crudes not purified due to the important amount of remaining starting material. [d] Base generated from ZnCl₂-TMEDA (1 equiv) and LiTMP (3 equiv). [e] Diiodides also formed. [f] The TMEDA chelate was employed as *in situ* trap.

conversions to **1b** and **1c** (conversions below 25%; Table 1, entries 1 and 2).

We thus turned to the use of LiTMP-Zn(TMP)₂, generated *in situ* from ZnCl₂-TMEDA (TMEDA = *N,N,N',N'*-tetramethylethylenediamine) and LiTMP in a 1:3 ratio.^[15] Surprisingly, almost no conversion was detected when using 0.5 equiv LiTMP-Zn(TMP)₂ in THF at 0 °C for 2 h. The amount of base was therefore increased to 1 equiv LiTMP-Zn(TMP)₂ (Table 1, entry 3). Unlike previously observed for diazines and their benzo analogues under similar conditions,^[11] no dimer formation was noticed. Thus, the reaction temperature was raised to room temperature to afford a mixture of the 5- and 6-iodo derivatives **1b** and **1c** in 34% and 7% isolated yield, respectively (Table 1, entry 4). Nor were dimers formed at room temperature, but the presence of two diiodinated products increased (possessing a second iodo group on the phenyl group, at the *ortho* position).

We thus decided to attempt the use of LiTMP (1.5 equiv) in the presence of ZnCl₂-TMEDA (1 equiv; more soluble than ZnCl₂) as *in situ* trap, this pair being efficient to ensure accelerated and chemoselective reactions.^[16] When employed at -30 °C, products from dimetallation were not observed, and the iodides **1b** and **1c** were isolated in 50% and 34% yield, respectively (Table 1, entries 5 and 6; Fig. 2).



Figure 2. ORTEP diagrams (50% probability) of **1b** (left) and **1c** (right).

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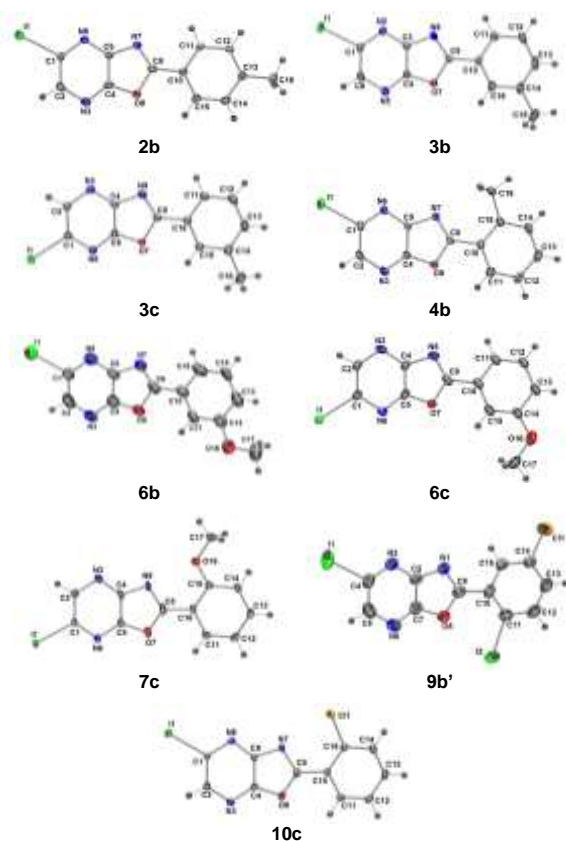


Figure 3. ORTEP diagrams (50% probability) of **2b**, **3b**, **3c**, **4b**, **6b**, **6c**, **7c**, **9b'** and **10c**.

We next studied the effect of a substituent on the phenyl ring by employing the 2-arylated oxazolo[4,5-*b*]pyrazines **2a–7a** in

Table 2. Deprotometallation-iodolysis sequence from **2a–7a**.

$ \begin{array}{c} \text{5} \\ \text{6} \end{array} \begin{array}{c} \text{N} \\ \text{N} \end{array} \begin{array}{c} \text{O} \\ \text{O} \end{array} \begin{array}{c} \text{2'} \\ \text{3'} \\ \text{4'} \end{array} \text{R} $ <p style="text-align: center;">a</p>				
1) $\text{ZnCl}_2 \cdot \text{TMEDA}$ (1 equiv) 2) LiTMP (1.5 equiv) THF, -30°C , 0.25 h 3) I_2 , THF				
$ \begin{array}{c} \text{I} \end{array} \begin{array}{c} \text{N} \\ \text{N} \end{array} \begin{array}{c} \text{O} \\ \text{O} \end{array} \begin{array}{c} \text{R} \end{array} $ <p style="text-align: center;">b</p>				
$ \begin{array}{c} \text{I} \end{array} \begin{array}{c} \text{N} \\ \text{N} \end{array} \begin{array}{c} \text{O} \\ \text{O} \end{array} \begin{array}{c} \text{R} \end{array} $ <p style="text-align: center;">c</p>				
Entry	Substrate (R)	Products	Ratio ^[a]	Yields ^[b] (%)
1	2a (4'-Me)	2a , 2b , 2c	15/59/26	40 (2b), 15 ^[c] (2c)
2	3a (3'-Me)	3a , 3b , 3c	29/50/21	47 (3b), 21 (3c)
3	4a (2'-Me)	4a , 4b , 4c	22/61/17	52 (4b), 12 ^[c] (4c)
4	5a (4'-OMe)	5a , 5b , 5c	61/27/12	34 ^[c] (5b), 8 ^[c] (5c)
5	6a (3'-OMe)	6a , 6b , 6c	53/30/16	32 (6b), 21 (6c)
6	7a (2'-OMe)	7a , 7b , 7c	30/47/23	24 ^[c] (7b), 18 ^[c] (7c)

[a] Estimated by ^1H NMR spectroscopy. [b] After column chromatography over silica gel.

[c] Estimated from a mixture with the other regioisomer.

the deprotometallation-iodolysis sequence. Under the conditions optimized from **1a**, the monoiodides **2b–7b** and **2c–7c** were obtained with similar **b/c** ratios (Table 2, Fig. 3). No competitive reactions were observed on the aryl group.

However, product distribution became more complex when the reaction conditions were applied to the 2-(chlorophenyl)oxazolo[4,5-*b*]pyrazines **8a–10a** (Table 3). From **8a** and **9a**, analysis of the crudes showed the presence of diiodides containing an additional halogen on the chlorophenyl ring (entries 1 and 2). The reactions were carried out in the presence of an *in situ* trap ($\text{ZnCl}_2 \cdot \text{TMEDA}$), which can impede the isomerization of the initially formed lithio compound to a more stable one. However, such isomerizations are extremely fast,^[17] and the experimental procedure favours thermodynamic control of anion formation (slow addition of base to the substrate). Thus, to try to understand this result, and why it differs from **10a** (entry 3; Fig. 3), the pK_a values in THF (Fig. 4) were calculated within DFT framework by using earlier elaborated approach.^[18]

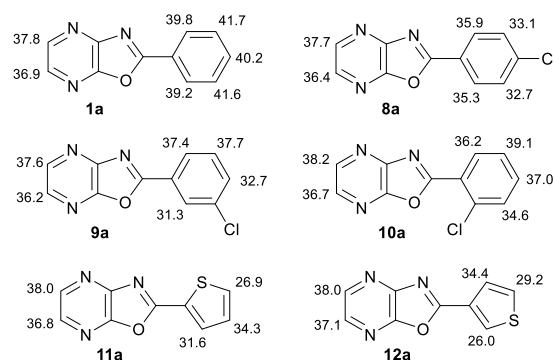
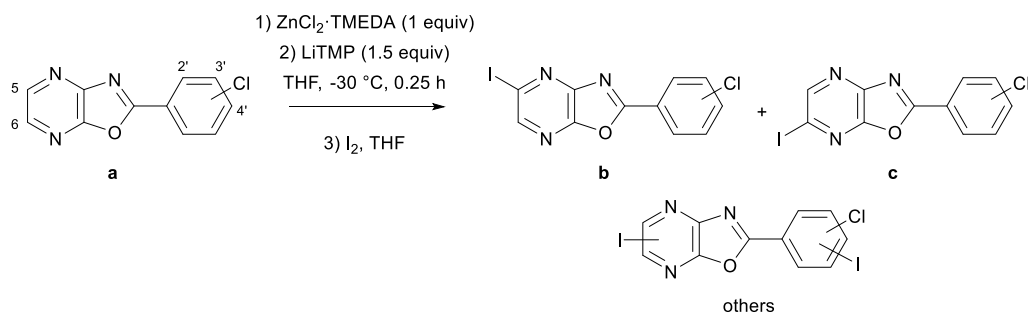


Figure 4. Calculated $\text{pK}_\text{a}(\text{THF})$ values of **1a**, **8a–10a**, **11a** and **12a**.

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Table 3. Deprotometallation-iodolysis sequence from **8a-10a**.

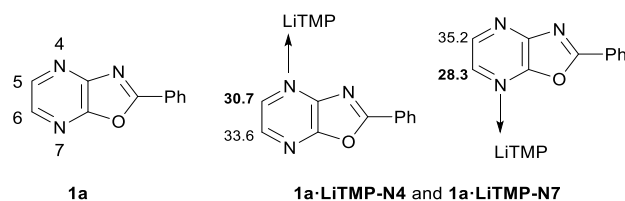
Entry	Substrate	Products	Ratio ^[a]	Yields ^[b] (%)
1	8a (4'-Cl)	8a , 8b , 8c , others	52/24/12/13	18 (8b), 4 ^[c] (8c)
2	9a (3'-Cl)	9a , 9b , 9c , others ^[d]	10/60/25/5	56 ^c (9b), 19 ^[c] (9c)
3	10a (2'-Cl)	10a , 10b , 10c	45/37/19	31 (10b), 18 ^[c] (10c)

[a] Estimated by ¹H NMR spectroscopy. [b] After column chromatography over silica gel. [c] Estimated from a mixture with the other regioisomer. [d] For example, 2-(5-chloro-2-iodophenyl)-5-iodooxazolo[4,5-*b*]pyrazine (**9b'**; Fig. 3) was isolated in 3% yield.

There is no data on the acidity of oxazolo[4,5-*b*]pyrazines in literature. The most related experimental studies deal with equilibrium CH acidities of benzoxazole, benzofuran, benzothiazole, *N*-methylindole in THF,^[19] and benzoxazole, benzothiazole in DMSO.^[20] The deprotonation of **1a-12a** can proceed at both the pyrazine ring or the aryl group. The by far most acidic position of bare oxazolo[4,5-*b*]pyrazine is blocked in **1a-12a** with an aryl moiety. When generalizing our previous data on CH acidities of azoles and azines,^[18,21] one should firmly expect to find the most acidic site in pyrazine ring in case of **1a-7a**. But when turned to electron-withdrawing substituents (**8a-12a**), competitive *pK_a* values could be found within them (Fig. 4) and deprotonation can proceed at the aryl group.

The results point to the aryl hydrogens of **8a** and **9a** being more acidic, when compared with those of **1a** and **10a**. We believe this explains the observed iodination of the phenyl ring.

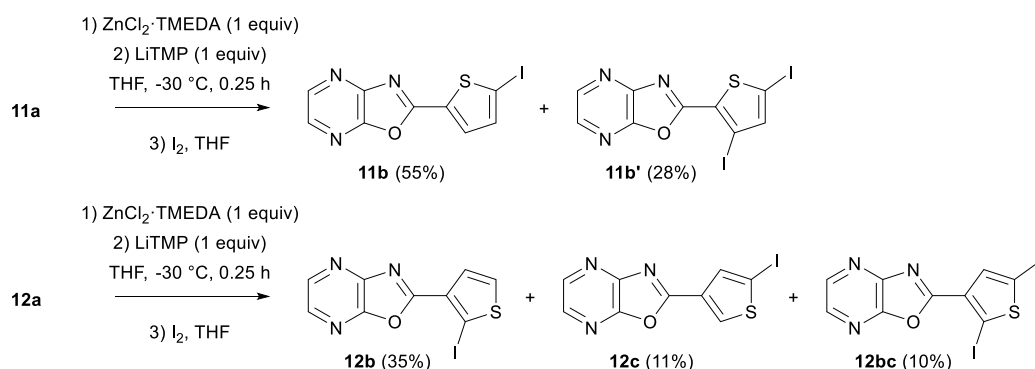
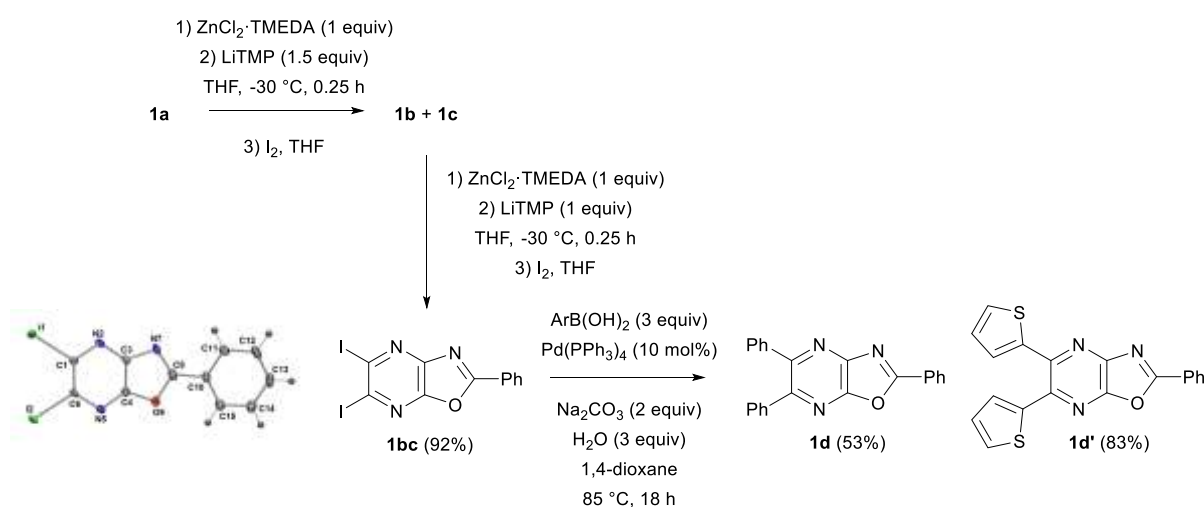
The *pK_a* calculations also help understand why mixtures of 5- and 6-iodinated oxazolo[4,5-*b*]pyrazines are systematically formed by deprotometallation. To understand why deprotonation at the pyrazine ring could not be avoided in favour of more acidified sites at the aryl ring (e.g. in the case of **9a**), we decided to consider possible coordination of the pyrazine heteroatoms onto lithium (Fig. 5). Coordination of pyrazine nitrogens to metals presumably takes place in premetallation complexes and transition structures, and will increase the acidity of the neighbouring hydrogens considerably, making this proton abstraction competitive with that of activated aryl groups. In addition, whereas coordination of N₇ to lithium (complex **1a-LiTMP-N7**) seems to contribute more efficiency to acidification in favour of a deprotonation at C₆, **1a-LiTMP-N4** was predicted to be slightly more stable in favour of a deprotonation at C₅.

**Figure 5.** Calculated *pK_a*(THF) values of **1a-LiTMP** (coordination of N₄ or N₇).

In view of the low *pK_a* values of the thienyl groups in **11a** and **12a** (Fig. 4), reactions are expected to occur at this five-membered ring. Indeed, when **11a** was submitted to LiTMP (1 equiv) in the presence of ZnCl₂·TMEDA (1 equiv) in THF at -30 °C, subsequent iodolysis led to the 5-iodo derivative **11b**; however, it could not be separated from the diiodide **11b'** also formed in the reaction. An inseparable mixture of two moniodides (**12b** and **12c**) and one diiodide (**12bc**) was obtained when **12a** was treated similarly (Scheme 2).

Because we could not regioselectively functionalize the aryl-substituted oxazolo[4,5-*b*]pyrazines, we considered the introduction of a second iodine from the mixture of **1b** and **1c**, generated by deprotometallation-iodolysis of **1a**, in order to converge towards a single product. It has been shown in literature that iodopyrazine can be deprotolithiated at -78 °C upon treatment by LiTMP in THF.^[22] Using ZnCl₂·TMEDA as *in situ* trap, we could avoid products arising from diazine formation,^[23] and isolate the 5,6-diiodo derivative **1bc** in 92% yield. Subsequent functionalization by double Suzuki coupling led to the triarylated derivatives **1d** and **1d'** (Scheme 3). Direct formation of **1bc** by dideprotometallation of **1a** using an excess of base^[18b,21] did not work in this case.

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Scheme 2. Deprotometallation-iodolysis sequence from **11a** and **12a**.Scheme 3. Deprotometallation-iodolysis sequence from **1b-1c** mixture and double Suzuki coupling from **1bc**; ORTEP diagrams (50% probability) of **1bc**.

Conclusions

Probably because they possess numerous heteroatoms, deprotometallation of oxazolo[4,5-*b*]pyrazines by classical hindered lithium amides are sluggish reactions. Recourse to *in situ* trapping was efficient in pushing the formation of arylmetals to completion, but a poor regioselectivity was noticed due to the high chemical similarity of the 5 and 6 pyrazine positions. It proved possible to convert the mixture of 5- and 6-iodo derivatives **1b** and **1c** into the corresponding 5,6-diiodide **1bc**, thereby opening the door to subsequent functionalizations of this heterocycle.

Experimental Section

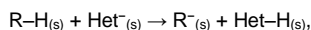
General synthetic and analytical details. All reactions were performed under an argon atmosphere. THF was distilled over sodium-benzophenone. Column chromatography separations were achieved on silica gel (40-63 μm). Melting points were measured on a Kofler apparatus. IR spectra were collected on a Perkin-Elmer Spectrum 100 spectrometer. ^1H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance III spectrometer at 300 MHz and 75 MHz, respectively. ^1H chemical shifts (δ) are given in ppm relative to the solvent residual peak and ^{13}C chemical shifts are relative to the central peak of the solvent signal.^[24] Chemical shifts are expressed in δ ppm. Microanalyses were performed on a Flash 1112 Thermo Fisher elemental analyser. Compounds **1a-12a** were obtained as reported before.¹ $\text{ZnCl}_2 \cdot \text{TMEDA}$ was prepared as described previously.^[15c]

General crystallographic details. The X-ray diffraction data were collected either using an APEXII Bruker-AXS diffractometer (graphite monochromatized Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$)) for the compounds **1a**, **6b** and **9b'**, or using a D8 VENTURE Bruker AXS diffractometer (multilayer monochromatized Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$)) for **2a**, **1b**, **1c**, **2b**, **3b**, **3c**, **4b**, **6c**, **7c**, **10c** and **1bc**. Except for **1c**, for which the

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structure was solved by direct methods using *SIR97*,^[25] all the structures were solved by dual-space algorithm using the *SHELXT* program.^[26] Structural refinements were performed with full-matrix least-square methods based on F^2 (*SHELXL-2014*).^[27] All non-hydrogen atoms were refined with anisotropic atomic displacement parameters and finally, H atoms were included in their calculated positions. The molecular diagrams were generated by ORTEP-3 (version 2.02).^[28]

Computational details. All calculations were performed within the DFT framework by using an approach elaborated earlier.^[18b] Geometries were fully optimized at the B3LYP/6-31G(d) level of theory without any symmetry constraints implied. Vibrational frequencies were calculated at the same level of theory in order to characterize stationary points and to calculate zero-point vibrational energies (ZPVE) and thermal corrections. The single point energies were obtained using the B3LYP/6-311+G(d,p) level and tight convergence criteria. The solvent effects were treated using the polarized continuum model (PCM) with the default parameters for THF. The pK_a values were obtained from the Gibbs energy of the homodesmotic reaction between the studied (RH) and a probe (HetH) aromatic substrates:

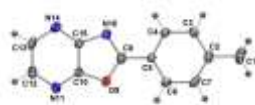


where *N*-methylindole with pK_a (THF) = 38.1^[19] was used as the probe.

Starting aromatic substrates.

2-Phenyloxazolo[4,5-b]pyrazine (1a). Pd(OAc)₂ (0.14 g, 5 mol%), XantPhos (0.71 g, 10 mol%), Cs₂CO₃ (9.6 g, 2.4 equiv) and benzamide (1.5 g, 12.4 mmol) were placed in a dried flask with a large magnetic stir bar. 1,4-Dioxane (40 mL, 0.3 M) and 2,3-dichloropyrazine (1.4 mL, 1.1 equiv) were added to the flask through a septum. The septum was replaced by a condenser flushed with argon, connected to a source of positive argon pressure. Under vigorous stirring, the reaction mixture was heated to reflux for 4 h. The reaction mixture was diluted with EtOAc (60 mL) and filtered, before evaporating the solvent. The crude was purified by flash column chromatography (heptane-EtOAc 3:1) to yield the pure compound (1.91 g, 81%). ¹H-NMR (CDCl₃): δ 7.54-7.62 (m, 2H), 7.62-7.69 (m, 1H), 8.30 (d, 1H, *J* = 2.8 Hz), 8.34-8.40 (m, 2H), 8.58 (d, 1H, *J* = 2.8 Hz); ¹³C NMR (CDCl₃): δ 125.9 (C), 128.7 (2CH), 129.3 (2CH), 133.6 (CH), 138.8 (CH), 142.2 (CH), 149.6 (C), 153.1 (C), 166.6 (C). The spectral data are as described previously.^[1] Crystal data for **1a**. C₁₁H₇N₃O, *M* = 197.20, *T* = 295(2) K, monoclinic, *P* 2₁/c, *a* = 7.4626(4), *b* = 10.3742(5), *c* = 12.3870(6) Å, β = 105.435(3)°, *V* = 924.40(8) Å³, *Z* = 4, *d* = 1.417 g·cm⁻³, μ = 0.096 mm⁻¹. A final refinement on F^2 with 2114 unique intensities and 136 parameters converged at ω(R^2) = 0.1348 ($R(F)$ = 0.0464) for 1381 observed reflections with *I* > 2σ(*I*). CCDC 1828127.

2-(4-Tolyl)oxazolo[4,5-b]pyrazine (2a).^[1] Crystal data for **2a**. C₁₂H₉N₃O, *M* = 211.22, *T* = 150(2) K, triclinic, *P* -1, *a* = 7.2090(11), *b* = 8.8617(13), *c* = 16.029(2) Å, α = 79.827(6), β = 85.402(6), γ = 86.473(6)°, *V* = 1003.5(3) Å³, *Z* = 4, *d* = 1.398 g·cm⁻³, μ = 0.094 mm⁻¹. A final refinement on F^2 with 4629 unique intensities and 291 parameters converged at ω(R^2) = 0.1644 ($R(F)$ = 0.0663) for 3452 observed reflections with *I* > 2σ(*I*). CCDC 1828131.



Synthesis of the iodides from 1a-10a.

General procedure 1. A solution of LiTMP (prepared by adding BuLi (about 1.6 M hexanes solution, 1.5 mmol) to a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.5 mmol) in THF (3 mL) and stirring for 5 min) cooled at -30 °C was slowly transferred to a solution of the required heterocycle (1.0 mmol) and ZnCl₂-TMEDA (0.25 g, 1.0 mmol) in THF (3 mL) at the same temperature. The resulting mixture was stirred for 15 min at -30 °C and then cooled to -70 °C. A solution of I₂ (0.38 g, 1.5 mmol) in THF (5 mL) was introduced to the reaction mixture and it was stirred for 1.5 h at room temperature. The reaction was quenched with sat. aq. Na₂S₂O₃ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography on silica gel (eluent: heptane-Et₂O 9:1) to yield the product.

5-Iodo-2-phenyloxazolo[4,5-b]pyrazine (1b). The general procedure 1 using 2-phenyloxazolo[4,5-b]pyrazine (**1a**, 0.20 g) gave **1b** in 50% yield (0.16 g) as an off-white solid: mp 178-180 °C; *R*_f = 0.29 (heptane-Et₂O 9:1); IR (ATR): 690, 709, 928, 1044, 1111, 1214, 1265, 1373, 1449, 1479, 1500, 1608, 1654, 2853, 2922, 3055, 3343 cm⁻¹; ¹H NMR (CDCl₃) δ 7.55-7.62 (m, 2H), 7.64-7.70 (m, 1H), 8.37-8.32 (m, 2H), 8.54 (s, 1H); ¹³C NMR (CDCl₃) δ 111.6 (C), 125.4 (C), 128.8 (2CH), 129.4 (2CH), 134.0 (CH), 146.1 (CH), 150.7 (C), 152.5 (C), 167.1 (C). Anal. Calcd for C₁₁H₆IN₃O (323.09): C, 40.89; H, 1.87; N, 13.01. Found: C, 41.11; H, 2.04; N, 12.89. Crystal data for **1b**. C₁₁H₆IN₃O, *M* = 323.09, *T* = 150(2) K, triclinic, *P* -1, *a* = 5.2803(5), *b* = 7.4980(7), *c* = 13.7959(13) Å, α = 100.213(3), β = 98.362(3), γ = 98.357(3)°, *V* = 523.56(9) Å³, *Z* = 2, *d* = 2.049 g·cm⁻³, μ = 3.038 mm⁻¹. A final refinement on F^2 with 2372 unique intensities and 145 parameters converged at ω(R^2) = 0.0641 ($R(F)$ = 0.0264) for 2148 observed reflections with *I* > 2σ(*I*). CCDC 1828128.

6-Iodo-2-phenyloxazolo[4,5-b]pyrazine (1c). The general procedure 1 using 2-phenyloxazolo[4,5-b]pyrazine (**1a**, 0.20 g) gave **1c** in 34% yield (0.11 g) as an off-white solid: mp 170-172 °C; *R*_f = 0.21 (heptane-Et₂O 9:1); IR (ATR): 688, 708, 782, 897, 926, 1019, 1119, 1181, 1196, 1278, 1324, 1369, 1450, 1479, 1523, 1590, 1608, 2852, 2923, 3056 cm⁻¹; ¹H NMR (CDCl₃) δ 7.54-7.63 (m, 2H), 7.63-7.71 (m, 1H), 8.29-8.38 (m, 2H), 8.82 (s, 1H); ¹³C NMR (CDCl₃) δ 108.2 (C), 125.4 (C), 128.8 (2CH), 129.4 (2CH), 133.9 (CH), 148.4 (C), 149.9 (CH), 152.7 (C), 166.3 (C). Anal. Calcd for C₁₁H₆IN₃O (323.09): C, 40.89; H, 1.87; N, 13.01. Found: C, 41.02; H, 2.01; N, 12.93. Crystal data for **1c**. C₁₁H₆IN₃O, *M* = 323.09, *T* = 150(2) K, monoclinic, *P* 2₁/n, *a* = 4.4223(2), *b* = 21.6629(7), *c* = 11.3085(4) Å, β = 104.3400(10)°, *V* = 1054.12(7) Å³, *Z* = 4, *d* = 2.036 g·cm⁻³, μ = 3.017 mm⁻¹. A final refinement on F^2 with 2409 unique intensities and 145 parameters converged at ω(R^2) = 0.0496 ($R(F)$ = 0.0237) for 2083 observed reflections with *I* > 2σ(*I*). CCDC 1828130.

5-Iodo-2-(4-tolyl)oxazolo[4,5-b]pyrazine (2b). The general procedure 1 using 2-(4-tolyl)oxazolo[4,5-b]pyrazine (**2a**, 0.21 g) gave **2b** in 40% yield (0.135 g) as an off-white solid: mp 190-192 °C; *R*_f = 0.29 (heptane-Et₂O 9:1); IR (ATR): 732, 835, 899, 928, 1109, 1183, 1208, 1269, 1370, 1410, 1491, 1608, 2851, 2911, 3059 cm⁻¹; ¹H NMR (CDCl₃) δ 2.46 (s, 3H), 7.36 (d, 2H, *J* = 7.9 Hz), 8.20 (d, 2H, *J* = 8.1 Hz), 8.49 (s, 1H); ¹³C NMR (CDCl₃) δ 22.1 (CH₃), 111.4 (C), 122.6 (C), 128.8 (2CH), 130.2 (2CH), 145.1 (C), 145.7 (CH), 150.9 (C), 152.5 (C), 167.4 (C). Anal. Calcd for C₁₂H₉IN₃O (337.12): C, 42.75; H, 2.39; N, 12.46. Found: C, 42.84; H, 2.53; N, 12.22. Crystal data for **2b**. C₁₂H₉IN₃O, *M* = 337.11, *T* = 150(2) K, triclinic, *P* -1, *a* = 5.6141(7), *b* = 7.5340(10), *c* = 13.9577(15) Å, α = 85.340(4), β = 85.011(4), γ = 77.111(4)°, *V* = 572.15(13) Å³, *Z* = 2, *d* = 1.957 g·cm⁻³, μ = 2.784 mm⁻¹. A final refinement on F^2 with 2452 unique intensities and 156 parameters converged at ω(R^2) = 0.1274 ($R(F)$ = 0.0504) for 2334 observed reflections with *I* > 2σ(*I*). CCDC 1828132.

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6-Iodo-2-(4-tolyl)oxazolo[4,5-b]pyrazine (2c). The general procedure 1 using 2-(4-tolyl)oxazolo[4,5-b]pyrazine (**2a**, 0.21 g) gave **2c** in an estimated 15% yield (51 mg) in a mixture with **2b**: $R_f = 0.21$ (heptane-Et₂O 9:1). It was identified by NMR: ¹H NMR (CDCl₃) δ 2.46 (s, 3H), 7.36 (d, 2H, $J = 7.9$ Hz), 8.20 (d, 2H, $J = 8.1$ Hz), 8.77 (s, 1H).

5-Iodo-2-(3-tolyl)oxazolo[4,5-b]pyrazine (3b). The general procedure 1 using 2-(3-tolyl)oxazolo[4,5-b]pyrazine (**3a**, 0.21 g) gave **3b** in 47% yield (0.16 g) as an off-white solid: mp 147–149 °C; $R_f = 0.32$ (heptane-Et₂O 9:1); IR (ATR): 687, 728, 797, 911, 933, 1108, 1192, 1275, 1366, 1473, 1515, 1601, 2855, 2924 cm⁻¹; ¹H NMR (CDCl₃) δ 2.47 (s, 3H), 7.45 (d, 2H, $J = 5.2$ Hz), 8.08–8.15 (m, 2H), 8.51 (s, 1H); ¹³C NMR (CDCl₃) δ 21.5 (CH₃), 111.5 (C), 125.3 (C), 126.1 (CH), 129.3 (CH), 129.3 (CH), 134.8 (CH), 139.4 (C), 146.0 (CH), 150.8 (C), 152.5 (C), 167.4 (C). Anal. Calcd for C₁₂H₈IN₃O (337.12): C, 42.75; H, 2.39; N, 12.46. Found: C, 42.80; H, 2.46; N, 12.31. Crystal data for **3b**. C₁₂H₈IN₃O, $M = 337.11$, $T = 150(2)$ K, monoclinic, $P 2_1/n$, $a = 14.2075(5)$, $b = 12.2360(4)$, $c = 14.2507(4)$ Å, $\beta = 109.336(2)^\circ$, $V = 2337.64(13)$ Å³, $Z = 8$, $d = 1.916$ g·cm⁻³, $\mu = 2.726$ mm⁻¹. A final refinement on F^2 with 5324 unique intensities and 309 parameters converged at $\omega R(F^2) = 0.0569$ ($R(F) = 0.0272$) for 4446 observed reflections with $I > 2\sigma(I)$. CCDC 1828133.

6-Iodo-2-(3-tolyl)oxazolo[4,5-b]pyrazine (3c). The general procedure 1 using 2-(3-tolyl)oxazolo[4,5-b]pyrazine (**3a**, 0.21 g) gave **3c** in 21% yield (70 mg) as an off-white solid: mp 158–160 °C; $R_f = 0.25$ (heptane-Et₂O 9:1); IR (ATR): 687, 727, 798, 894, 915, 930, 1118, 1178, 1284, 1295, 1362, 1412, 1472, 1528, 1599, 2853, 2923 cm⁻¹; ¹H NMR (CDCl₃) δ 2.49 (s, 3H), 7.45–7.49 (m, 2H), 8.14 (dd, 2H, $J = 9.2$ and 4.4 Hz), 8.81 (s, 1H). Anal. Calcd for C₁₂H₈IN₃O (337.12): C, 42.75; H, 2.39; N, 12.46. Found: C, 42.97; H, 2.48; N, 12.39. Crystal data for **3c**. C₁₂H₈IN₃O, $M = 337.11$, $T = 150(2)$ K, orthorhombic, $P n m a$, $a = 13.1929(19)$, $b = 6.5142(8)$, $c = 13.5650(18)$ Å, $V = 1165.8(3)$ Å³, $Z = 4$, $d = 1.921$ g·cm⁻³, $\mu = 2.733$ mm⁻¹. A final refinement on F^2 with 1448 unique intensities and 103 parameters converged at $\omega R(F^2) = 0.0522$ ($R(F) = 0.0208$) for 1362 observed reflections with $I > 2\sigma(I)$. CCDC 1828134.

5-Iodo-2-(2-tolyl)oxazolo[4,5-b]pyrazine (4b). The general procedure 1 using 2-(2-tolyl)oxazolo[4,5-b]pyrazine (**4a**, 0.21 g) gave **4b** in 52% yield (0.175 g) as a pale yellow solid: mp 166–168 °C; $R_f = 0.39$ (heptane-Et₂O 9:1); IR (ATR): 734, 782, 904, 930, 1108, 1181, 1210, 1367, 1483, 1506, 2853, 2922 cm⁻¹; ¹H NMR (CDCl₃) δ 2.87 (s, 3H), 7.41 (dt, 2H, $J = 6.8$ and 3.1 Hz), 7.49–7.57 (m, 1H), 8.27–8.33 (m, 1H), 8.55 (s, 1H); ¹³C NMR (CDCl₃) δ 22.9 (CH₃), 111.3 (C), 124.2 (C), 126.6 (CH), 130.7 (CH), 132.6 (CH), 133.3 (CH), 141.2 (C), 146.1 (CH), 150.7 (C), 152.0 (C), 167.4 (C). Anal. Calcd for C₁₂H₈IN₃O (337.12): C, 42.75; H, 2.39; N, 12.46. Found: C, 42.83; H, 2.49; N, 12.30. Crystal data for **4b**. C₁₂H₈IN₃O, $M = 337.11$, $T = 150(2)$ K, monoclinic, $P 2_1/c$, $a = 7.3996(9)$, $b = 15.0365(18)$, $c = 10.3727(15)$ Å, $\beta = 99.424(5)^\circ$, $V = 1138.5(3)$ Å³, $Z = 4$, $d = 1.967$ g·cm⁻³, $\mu = 2.798$ mm⁻¹. A final refinement on F^2 with 2614 unique intensities and 155 parameters converged at $\omega R(F^2) = 0.0460$ ($R(F) = 0.0202$) for 2297 observed reflections with $I > 2\sigma(I)$. CCDC 1828135.

6-Iodo-2-(2-tolyl)oxazolo[4,5-b]pyrazine (4c). The general procedure 1 using 2-(2-tolyl)oxazolo[4,5-b]pyrazine (**4a**, 0.21 g) gave **4c** in an estimated 12% yield (45 mg) in a mixture with **4b**: $R_f = 0.34$ (heptane-Et₂O 9:1). It was identified by NMR: ¹H NMR (CDCl₃) δ 2.86 (s, 3H), 7.30 (t, 1H, $J = 7.4$ Hz), 7.36–7.46 (m, 2H), 8.24–8.34 (m, 1H), 8.82 (s, 1H).

5-Iodo-2-(4-methoxyphenyl)oxazolo[4,5-b]pyrazine (5b). The general procedure 1 using 2-(4-methoxyphenyl)oxazolo[4,5-b]pyrazine (**5a**, 0.23 g) gave **5b** in an estimated 34% yield (0.12 g) as a mixture with **5c**: $R_f = 0.11$ (heptane-Et₂O 9:1). It was identified by NMR: ¹H NMR (CDCl₃) δ 3.93 (s, 3H), 7.04–7.10 (m, 2H), 8.26–8.32 (m, 2H), 8.47 (s, 1H); ¹³C NMR

(CDCl₃) δ 55.7 (CH₃), 94.2 (C), 114.8 (2CH), 117.6 (C), 130.2 (C), 130.8 (2CH), 145.1 (CH), 151.0 (C), 160.7 (C), 164.3 (C).

6-Iodo-2-(4-methoxyphenyl)oxazolo[4,5-b]pyrazine (5c). The general procedure 1 using 2-(4-methoxyphenyl)oxazolo[4,5-b]pyrazine (**5a**, 0.23 g) gave **5c** in an estimated 8% yield (28 mg) as a mixture with **5b**: $R_f = 0.07$ (heptane-Et₂O 9:1). It was identified by NMR: ¹H NMR (CDCl₃) δ 3.90 (s, 3H), 7.04–7.10 (m, 2H), 8.26–8.32 (m, 2H), 8.76 (s, 1H).

5-Iodo-2-(3-methoxyphenyl)oxazolo[4,5-b]pyrazine (6b). The general procedure 1 using 2-(3-methoxyphenyl)oxazolo[4,5-b]pyrazine (**6a**, 0.23 g) gave **6b** in 32% yield (0.11 g) as a white solid: mp 159–161 °C; $R_f = 0.20$ (heptane-Et₂O 9:1); IR (ATR): 733, 922, 1031, 1176, 1242, 1282, 1294, 1312, 1365, 1490, 1530, 1571, 1597, 2836, 2941, 3062 cm⁻¹; ¹H NMR (CDCl₃) δ 3.92 (s, 3H), 7.19 (ddd, 1H, $J = 8.3$, 2.7 and 1.0 Hz), 7.47 (t, 1H, $J = 8.0$ Hz), 7.84 (dd, 1H, $J = 2.6$ and 1.5 Hz), 7.93 (ddd, $J = 7.7$, 1.6 and 1.0 Hz, 1H), 8.53 (s, 1H); ¹³C NMR (CDCl₃) δ 55.8 (CH₃), 111.6 (C), 112.9 (CH), 120.8 (CH), 121.3 (CH), 126.5 (C), 130.5 (CH), 146.2 (CH), 150.7 (C), 152.5 (C), 160.2 (C), 167.0 (C). Anal. Calcd for C₁₂H₈IN₃O₂ (353.12): C, 40.82; H, 2.28; N, 11.90. Found: C, 40.69; H, 2.43; N, 11.75. Crystal data for **6b**. C₁₂H₈IN₃O₂, $M = 353.11$, $T = 150(2)$ K, monoclinic $P 2_1/c$, $a = 11.5887(8)$, $b = 15.4356(11)$, $c = 13.7074(10)$ Å, $\beta = 102.173(3)^\circ$, $V = 2396.8(3)$ Å³, $Z = 8$, $d = 1.957$ g·cm⁻³, $\mu = 2.669$ mm⁻¹. A final refinement on F^2 with 5469 unique intensities and 327 parameters converged at $\omega R(F^2) = 0.0886$ ($R(F) = 0.0590$) for 3169 observed reflections with $I > 2\sigma(I)$. CCDC 1828136.

6-Iodo-2-(3-methoxyphenyl)oxazolo[4,5-b]pyrazine (6c). The general procedure 1 using 2-(3-methoxyphenyl)oxazolo[4,5-b]pyrazine (**6a**, 0.23 g) gave **6c** in 21% yield (73 mg) as a yellow solid: mp 174–176 °C; $R_f = 0.14$ (heptane-Et₂O 9:1); IR (ATR): 734, 922, 1031, 1051, 1173, 1242, 1281, 1312, 1369, 1490, 1531, 1571, 1595, 2835, 2939, 2957 cm⁻¹; ¹H NMR (CDCl₃) δ 3.92 (s, 3H), 7.19 (ddd, 1H, $J = 8.3$, 2.7 and 1.0 Hz), 7.48 (ddd, 1H, $J = 8.3$, 7.7 and 0.4 Hz), 7.83 (dd, 1H, $J = 2.6$ and 1.5 Hz), 7.91 (ddd, 1H, $J = 7.7$, 1.6 and 1.0 Hz), 8.81 (s, 1H); ¹³C NMR (CDCl₃) δ 55.8 (CH₃), 108.3 (C), 112.8 (CH), 120.8 (CH), 121.2 (CH), 126.6 (C), 130.6 (CH), 148.3 (C), 150.0 (CH), 152.7 (C), 160.3 (C), 166.2 (C). Anal. Calcd for C₁₂H₈IN₃O₂ (353.12): C, 40.82; H, 2.28; N, 11.90. Found: C, 40.71; H, 2.49; N, 11.76. Crystal data for **6c**. C₁₂H₈IN₃O₂, $M = 353.11$, $T = 150(2)$ K, monoclinic $P 2_1/n$, $a = 9.620(2)$, $b = 12.945(3)$, $c = 9.5996(18)$ Å, $\beta = 93.204(8)^\circ$, $V = 1193.5(5)$ Å³, $Z = 4$, $d = 1.965$ g·cm⁻³, $\mu = 2.680$ mm⁻¹. A final refinement on F^2 with 2683 unique intensities and 110 parameters converged at $\omega R(F^2) = 0.1050$ ($R(F) = 0.0487$) for 1816 observed reflections with $I > 2\sigma(I)$. CCDC 1828137.

5-Iodo-2-(2-methoxyphenyl)oxazolo[4,5-b]pyrazine (7b). The general procedure 1 using 2-(2-methoxyphenyl)oxazolo[4,5-b]pyrazine (**7a**, 0.23 g) gave **7b** in an estimated 24% yield (85 mg) as a mixture with **7c**: $R_f = 0.05$ (heptane-Et₂O 9:1). It was identified by NMR: ¹H NMR (CDCl₃) δ 4.03 (s, 3H), 7.09–7.18 (m, 2H), 7.61 (ddd, 1H, $J = 8.4$, 7.4 and 1.8 Hz), 8.26 (dd, 1H, $J = 7.8$ and 1.8 Hz), 8.52 (s, 1H).

6-Iodo-2-(2-methoxyphenyl)oxazolo[4,5-b]pyrazine (7c). The general procedure 1 using 2-(2-methoxyphenyl)oxazolo[4,5-b]pyrazine (**7a**, 0.23 g) gave **7c** in an estimated 18% yield (64 mg) as a mixture with **7b**: $R_f = 0.02$ (heptane-Et₂O 9:1). It was identified by NMR: ¹H NMR (CDCl₃) δ 4.03 (s, 3H), 7.09–7.18 (m, 2H), 7.61 (ddd, 1H, $J = 8.4$, 7.4 and 1.8 Hz), 8.25 (dd, 1H, $J = 7.8$ and 1.8 Hz), 8.80 (s, 1H). Crystal data for **7c**. C₁₂H₈IN₃O₂, $M = 353.11$, $T = 150(2)$ K, triclinic $P -1$, $a = 9.2794(9)$, $b = 14.9145(14)$, $c = 18.3826(16)$ Å, $\alpha = 88.818(3)^\circ$, $\beta = 76.164(3)^\circ$, $\gamma = 75.954(3)^\circ$, $V = 2394.5(4)$ Å³, $Z = 8$, $d = 1.959$ g·cm⁻³, $\mu = 2.672$ mm⁻¹. A final refinement on F^2 with 10944 unique intensities and 653 parameters converged at $\omega R(F^2) = 0.0540$ ($R(F) = 0.0236$) for 10197 observed reflections with $I > 2\sigma(I)$. CCDC 1828138.

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2-(4-Chlorophenyl)-5-iodooxazolo[4,5-b]pyrazine (8b). The general procedure 1 using 2-(4-chlorophenyl)oxazolo[4,5-b]pyrazine (**8a**, 0.23 g) gave **8b** in 18% yield (64 mg) as a white solid: mp 244–246 °C; R_f = 0.32 (heptane-Et₂O 9:1); IR (ATR): 736, 844, 905, 931, 1112, 1206, 1268, 1372, 1410, 1468, 1605, 2927, 3078 cm⁻¹; ¹H NMR (CDCl₃) δ 7.54–7.60 (m, 2H), 8.25–8.31 (m, 2H), 8.55 (s, 1H).

2-(4-Chlorophenyl)-6-iodooxazolo[4,5-b]pyrazine (8c). The general procedure 1 using 2-(4-chlorophenyl)oxazolo[4,5-b]pyrazine (**8a**, 0.23 g) gave **8c** in an estimated 4% yield (14 mg) as a mixture with **8b**: R_f = 0.23 (heptane-Et₂O 9:1). It was identified by NMR: ¹H NMR (CDCl₃) δ 7.54–7.60 (m, 2H), 8.25–8.31 (m, 2H), 8.83 (s, 1H).

2-(3-Chlorophenyl)-5-iodooxazolo[4,5-b]pyrazine (9b). The general procedure 1 using 2-(3-chlorophenyl)oxazolo[4,5-b]pyrazine (**9a**, 0.23 g) gave **9b** in an estimated 56% yield (0.20 g) as a mixture with **9c**: R_f = 0.30 (heptane-Et₂O 9:1). It was identified by NMR: ¹H NMR (CDCl₃) δ 7.54 (t, 1H, J = 8.0 Hz), 7.61–7.67 (m, 1H), 8.24 (dt, 1H, J = 7.7 and 1.4 Hz), 8.33 (t, 1H, J = 1.9 Hz), 8.58 (s, 1H).

2-(3-Chlorophenyl)-6-iodooxazolo[4,5-b]pyrazine (9c). The general procedure 1 using 2-(3-chlorophenyl)oxazolo[4,5-b]pyrazine (**9a**, 0.23 g) gave **9c** in an estimated 19% yield (68 mg) as a mixture with **9b**: R_f = 0.23 (heptane-Et₂O 9:1). It was identified by NMR: ¹H NMR (CDCl₃) δ 7.54 (t, 1H, J = 8.0 Hz), 7.64 (ddd, 1H, J = 8.1, 2.2 and 1.2 Hz), 8.20–8.26 (m, 1H), 8.31–8.34 (m, 1H), 8.85 (s, 1H).

2-(5-Chloro-2-iodophenyl)-5-iodooxazolo[4,5-b]pyrazine (9b'). The general procedure 1 using 2-(3-chlorophenyl)oxazolo[4,5-b]pyrazine (**9a**, 0.23 g) gave **9b'** in 3% yield (12 mg) as a pale yellow solid: R_f = 0.30 (heptane-Et₂O 9:1); ¹H NMR (CDCl₃) δ 7.26 (dd, 1H, J = 8.4 and 2.6 Hz), 8.08 (d, 1H, J = 8.5 Hz), 8.15 (d, 1H, J = 2.5 Hz), 8.64 (s, 1H). Crystal data for **9b'**: C₁₁H₄ClI₂N₃O, M = 483.42, T = 295(2) K, orthorhombic, $Pbca$, a = 14.9016(8), b = 7.8289(4), c = 22.1258(13) Å, V = 2581.3(2) Å³, Z = 8, d = 2.488 g·cm⁻³, μ = 5.070 mm⁻¹. A final refinement on F^2 with 2945 unique intensities and 163 parameters converged at $\omega R(F^2)$ = 0.0791 ($R(F)$ = 0.0378) for 1847 observed reflections with $I > 2\sigma(I)$. CCDC 1828139.

2-(2-Chlorophenyl)-5-iodooxazolo[4,5-b]pyrazine (10b). The general procedure 1 using 2-(2-chlorophenyl)oxazolo[4,5-b]pyrazine (**10a**, 0.23 g) gave **10b** in 31% yield (0.11 g) as a pale yellow solid: mp 155–157 °C; R_f = 0.21 (heptane-Et₂O 9:1); ¹H NMR (CDCl₃) δ 7.48 (ddd, 1H, J = 7.8, 7.2 and 1.6 Hz), 7.53–7.60 (m, 1H), 7.60–7.65 (m, 1H), 8.26–8.32 (m, 1H), 8.61 (s, 1H); ¹³C NMR (CDCl₃) δ 111.9 (C), 124.4 (C), 127.3 (CH), 132.1 (CH), 132.5 (CH), 133.9 (CH), 134.8 (C), 146.9 (CH), 149.9 (C), 152.1 (C), 165.1 (C). Anal. Calcd for C₁₁H₅ClIN₃O (357.54): C, 36.95; H, 1.41; N, 11.75. Found: C, 36.93; H, 1.52; N, 11.62.

2-(2-Chlorophenyl)-6-iodooxazolo[4,5-b]pyrazine (10c). The general procedure 1 using 2-(3-chlorophenyl)oxazolo[4,5-b]pyrazine (**10a**, 0.23 g) gave **10c** in an estimated 18% yield (64 mg) as a mixture with **10b**: R_f = 0.16 (heptane-Et₂O 9:1). It was identified by NMR: ¹H NMR (CDCl₃) δ 7.48 (ddd, 1H, J = 7.8, 7.2 and 1.6 Hz), 7.53–7.60 (m, 1H), 7.60–7.65 (m, 1H), 8.26–8.32 (m, 1H), 8.88 (s, 1H); ¹³C NMR (CDCl₃) δ 109.3 (C), 124.4 (C), 127.4 (CH), 132.1 (CH), 132.5 (CH), 133.8 (CH), 134.7 (C), 147.6 (C), 150.3 (CH), 152.3 (C), 164.3 (C). Crystal data for **10c**: C₁₁H₅ClIN₃O, M = 357.53, T = 150(2) K, monoclinic $P2_1/c$, a = 7.4151(7), b = 16.2642(9), c = 9.6553(5) Å, β = 105.929(4)°, V = 1119.72(14) Å³, Z = 4, d = 2.121 g·cm⁻³, μ = 3.083 mm⁻¹. A final refinement on F^2 with 2569 unique intensities and 155 parameters converged at $\omega R(F^2)$ = 0.0526 ($R(F)$ = 0.0215) for 2440 observed reflections with $I > 2\sigma(I)$. CCDC 1828140.

Synthesis of the iodides from 11a and 12a.

General procedure 2. A solution of LiTMP (prepared by adding BuLi (about 1.6 M hexanes solution, 1.0 mmol) to a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.0 mmol) in THF (2 mL) and stirring for 5 min) cooled at -30 °C was slowly transferred to a solution of the required heterocycle (1.0 mmol) and ZnCl₂-TMEDA (0.25 g, 1.0 mmol) in THF (3 mL) at the same temperature. The resulting mixture was stirred for 15 min at -30 °C and then cooled to -70 °C. A solution of I₂ (0.25 g, 1.0 mmol) in THF (4 mL) was introduced to the reaction mixture and it was stirred for 1.5 h at room temperature. The reaction was quenched with sat. aq. Na₂S₂O₃ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography on silica gel (eluent: heptane-Et₂O 9:1) to yield the mixture of iodides.

2-(5-Iodo-2-thienyl)oxazolo[4,5-b]pyrazine (11b). The general procedure 2 using 2-(2-thienyl)oxazolo[4,5-b]pyrazine (**11a**, 0.20 g) gave **11b** in an estimated 55% yield (0.19 g). The compound was identified by NMR: ¹H NMR (CDCl₃) δ 7.40 (d, 1H, J = 4.0 Hz), 7.71 (d, 1H, J = 3.9 Hz), 8.26 (d, 1H, J = 2.8 Hz), 8.54 (d, 1H, J = 2.8 Hz).

2-(3,5-Diiodo-2-thienyl)oxazolo[4,5-b]pyrazine (11b'). The general procedure 2 using 2-(2-thienyl)oxazolo[4,5-b]pyrazine (**11a**, 0.20 g) gave **11b'** in an estimated 28% yield (97 mg). The compound was identified by NMR: ¹H NMR (CDCl₃) δ 7.48 (s, 1H), 8.31 (d, 1H, J = 2.8 Hz), 8.58 (d, 1H, J = 2.8 Hz).

2-(2-Iodo-3-thienyl)oxazolo[4,5-b]pyrazine (12b). The general procedure 2 using 2-(3-thienyl)oxazolo[4,5-b]pyrazine (**12a**, 0.20 g) gave **12b** in an estimated 35% yield (0.12 g). The compound was identified by NMR: ¹H NMR (CDCl₃) δ 7.60 (d, 1H, J = 5.7 Hz), 7.68 (d, 1H, J = 5.7 Hz), 8.33 (d, 1H, J = 2.9 Hz), 8.59 (d, 1H, J = 2.9 Hz); ¹³C NMR (CDCl₃) δ 81.5 (C), 129.5 (CH), 131.4 (C), 133.1 (CH), 139.1 (CH), 142.4 (CH), 149.1 (C), 152.5 (C), 162.1 (C).

2-(5-Iodo-3-thienyl)oxazolo[4,5-b]pyrazine (12c). The general procedure 2 using 2-(3-thienyl)oxazolo[4,5-b]pyrazine (**12a**, 0.20 g) gave **12c** in an estimated 11% yield (38 mg). The compound was identified by NMR: ¹H NMR (CDCl₃) δ 8.01 (d, 1H, J = 1.4 Hz), 8.29 (d, 1H, J = 2.8 Hz), 8.40 (d, 1H, J = 1.4 Hz), 8.57 (d, 1H, J = 2.8 Hz).

2-(2,5-Diiodo-3-thienyl)oxazolo[4,5-b]pyrazine (12bc). The general procedure 2 using 2-(3-thienyl)oxazolo[4,5-b]pyrazine (**12a**, 0.20 g) gave **12bc** in an estimated 10% yield (46 mg). The compound was identified by NMR: ¹H NMR (CDCl₃) δ 7.82 (s, 1H), 8.34 (d, 1H, J = 2.8 Hz), 8.60 (d, 1H, J = 2.8 Hz); ¹³C NMR (CDCl₃) δ 79.1 (C), 84.5 (C), 133.3 (C), 138.7 (CH), 139.3 (CH), 142.6 (CH), 148.8 (C), 152.4 (C), 162.5 (C).

Synthesis of 5,6-diiodo-2-phenyloxazolo[4,5-b]pyrazine (1bc).

A solution of LiTMP (prepared by adding BuLi (about 1.6 M hexanes solution, 2.0 mmol) to a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.33 mL, 2.0 mmol) in THF (3 mL) and stirring for 5 min) cooled at -30 °C was slowly transferred to a solution of the mixture of iodo-2-phenyloxazolo[4,5-b]pyrazines **1b** and **1c** (1.0 mmol, 0.32 g; obtained from **1a** by using the procedure 1) and ZnCl₂-TMEDA (0.25 g, 1.0 mmol) in THF (3 mL) at the same temperature. The resulting mixture was stirred for 15 min at -30 °C and then cooled to -70 °C. A solution of I₂ (0.51 g, 2.0 mmol) in THF (5 mL) was introduced to the reaction mixture which was stirred for 1.5 h at room temperature. The reaction was quenched with sat. aq. Na₂S₂O₃ (10 mL) and extracted with EtOAc (3 x

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10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography on silica gel (eluent: heptane-Et₂O 9:1) to yield **1bc** in 92% yield (0.41 g) as a white solid: mp 245–246 °C; R_f = 0.45 (heptane-Et₂O 9:1); IR (ATR): 707, 836, 906, 933, 1021, 1045, 1161, 1270, 1317, 1338, 1366, 1450, 1473, 1511, 1600, 2851, 2920 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.55–7.64 (m, 2H), 7.64–7.72 (m, 1H), 8.29–8.35 (m, 2H); ^{13}C NMR (CDCl_3) δ 120.9 (C), 124.6 (C), 125.2 (C), 129.0 (2CH), 129.5 (2CH), 134.2 (CH), 151.1 (C), 166.0 (C), 167.1 (C). Anal. Calcd for $\text{C}_{11}\text{H}_5\text{I}_2\text{N}_3\text{O}$ (448.99): C, 29.43; H, 1.12; N, 9.36. Found: C, 29.56; H, 1.39; N, 9.44. Crystal data for **1bc**. $\text{C}_{11}\text{H}_5\text{I}_2\text{N}_3\text{O}$, M = 448.98, T = 150(2) K, monoclinic $P 2_1/n$, a = 11.4355(12), b = 8.5536(9), c = 13.3468(15) Å, β = 114.453(3)°, V = 1188.4(2) Å³, Z = 4, d = 2.509 $\text{g}\cdot\text{cm}^{-3}$, μ = 5.278 mm^{-1} . A final refinement on F^2 with 2729 unique intensities and 154 parameters converged at $\omega R(F^2)$ = 0.0632 ($R(F)$ = 0.0279) for 2376 observed reflections with $I > 2\sigma(I)$. CCDC 1828129.

Suzuki coupling of the diiodide **1bc**.

General procedure 3. 5,6-Diiodo-2-phenyloxazolo[4,5-*b*]pyrazine (**1bc**, 0.11 g, 0.25 mmol), $\text{Pd}(\text{PPh}_3)_4$ (29 mg, 10 mol%), Na_2CO_3 (55 mg, 0.52 mmol) and the corresponding arylboronic acid (3.0 equiv) were dissolved in 1,4-dioxane (5 mL) and water (12.5 μL). The reaction mixture was stirred vigorously at 85 °C overnight. The reaction mixture was allowed to cool to room temperature. It was diluted with dichloromethane (60 mL) and washed with water (3 x 10 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4 , and the solvent was removed under reduced pressure before purification by flash column chromatography on silica gel (heptane-Et₂O 9:1) to yield the product.

2,5,6-Triphenyloxazolo[4,5-*b*]pyrazine (1d**).** The general procedure 3 using phenylboronic acid (91 mg, 0.75 mmol) gave **1d** in 53% yield (46 mg) as an off-white solid: mp 208–210 °C; R_f = 0.25 (heptane-Et₂O 9:1); IR (ATR): 699, 779, 906, 1022, 1171, 1324, 1354, 1367, 1450, 1482, 1531, 1611, 2853, 2923, 3059 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.29–7.39 (m, 6H), 7.49 (td, 4H, J = 6.2 and 2.2 Hz), 7.63 (dd, 3H, J = 11.6 and 7.1 Hz), 8.36–8.45 (m, 2H); ^{13}C NMR (CDCl_3) δ 126.2 (C), 128.3 (2CH), 128.4 (2CH), 128.6 (2CH), 128.6 (CH), 128.8 (CH), 129.4 (2CH), 130.3 (2CH), 130.35 (2CH), 133.4 (CH), 138.5 (C), 138.8 (C), 147.6 (C), 148.2 (C), 151.4 (C), 151.7 (C), 167.0 (C). Anal. Calcd for $\text{C}_{23}\text{H}_{15}\text{N}_3\text{O}$ (349.39): C, 79.07; H, 4.33; N, 12.03. Found: C, 79.19; H, 4.40; N, 12.21.

2-Phenyl-5,6-di(2-thienyl)oxazolo[4,5-*b*]pyrazine (1d'**).** The general procedure 3 using 2-thienylboronic acid (96 mg, 0.75 mmol) gave **1d'** in 83% yield (75 mg) as a bright yellow solid: mp 200–202 °C; R_f = 0.17 (heptane-Et₂O 9:1); IR (ATR): 689, 706, 843, 903, 1168, 1313, 1323, 1367, 1429, 1449, 1481, 1529, 1609, 2925, 3093 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.03 (ddd, 2H, J = 5.0, 4.3 and 3.8 Hz), 7.23 (ddd, 2H, J = 6.6, 3.7 and 1.2 Hz), 7.47 (ddd, 2H, J = 5.1, 1.1 and 0.7 Hz), 7.55–7.69 (m, 3H), 8.34–8.41 (m, 2H); ^{13}C NMR (CDCl_3) δ 126.0 (C), 127.6 (2CH), 127.8 (2CH), 128.7 (2CH), 129.0 (CH), 129.0 (CH), 129.4 (2CH), 133.6 (CH), 140.7 (C), 140.8 (C), 141.8 (C), 144.7 (C), 147.3 (C), 151.1 (C), 167.3 (C). Anal. Calcd for $\text{C}_{19}\text{H}_{11}\text{N}_3\text{OS}_2$ (361.44): C, 63.14; H, 3.07; N, 11.63; S, 17.74. Found: C, 63.25; H, 3.28; N, 11.64; S, 17.63.

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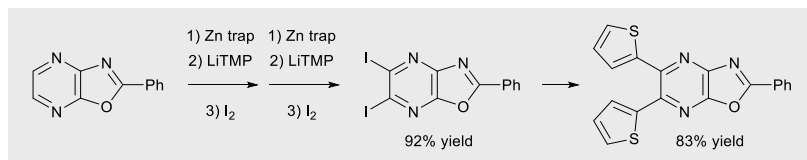
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Entry for the Table of Contents

Key topic: Oxazolo[4,5-*b*]pyrazines

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Functionalizations of 2-arylated oxazolo[4,5-*b*]pyrazines are reported. Access to the corresponding iodides was investigated, and deprotolithiation in the presence of a zinc-based *in situ* trap proved to be the most efficient approach. The observed regioselectivities were analysed in the light of the calculated pK_a values. Triarylated oxazolo[4,5-*b*]pyrazines were synthesized from a diiodo derivative obtained by iterative deprotonation-iodolysis.

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Functionalization of oxazolo[4,5-*b*]pyrazines by deprotometallation