molbank

MDPI

*Short Note*

# 2-Diphenylphosphinomethyl-3-methylpyrazine

**Tiziana Boccuzzi [1,†], Luciana Cicco [1,†], Andrea Francesca Quivelli [1,†], Paola Vitale [1], Filippo Maria Perna [1], Konstantin Karaghiosoff [2,*] and Vito Capriati [1,*]**

[1] Dipartimento di Farmacia-Scienze del Farmaco, Università di Bari "Aldo Moro", Consorzio C.I.N.M.P.I.S., Via E. Orabona 4, 70125 Bari, Italy; tizianaboccuzzi@live.it (T.B.); luciana.cicco@uniba.it (L.C.); andrea.quivelli@uniba.it (A.F.Q.); paola.vitale@uniba.it (P.V.); filippo.perna@uniba.it (F.M.P.)

[2] Department Chemie, Ludwig-Maximilians-Universität München, Butenandstrasse S-13, Haus D, 81377 München, Germany

* Correspondence: Konstantin.Karaghiosoff@cup.uni-muenchen.de (K.K.); vito.capriati@uniba.it (V.C); Tel.: +49-89-2180-77426 (K.K.); +39-080-5442174 (V.C.)

† Equally contributing authors.

**Abstract:** The lateral metalation-electrophilic trapping reaction of alkyl-substituted pyrazines has always been challenging and poorly regioselective, with the corresponding derivatives often being isolated in moderate yield. In this contribution, we first report on the preparation of an unsymmetrically-substituted pyrazine, that is 2-diphenylphosphinomethyl-3-methylpyrazine, by subjecting to metalation with *n*-BuLi the commercially available 2,3-dimethylpyrazine, followed by interception of the putative lithiated benzyl-type intermediate with $Ph_2PCl$. Such a functionalization has been successfully carried out in the absence of additional ligands, working either in THF at −78 °C or in a more environmentally friendly solvent like cyclopentyl methyl ether at 0 °C, with the desired phosphine derivative being isolated in 70–85% yield. The newly synthesized adduct has been fully characterized by means of multinuclear magnetic resonance spectroscopic techniques, and also by preparing a selenium derivative, which furnished single crystals that were suitable for X-ray analysis.

**Keywords:** pyrazines; lithiation; organophosphorus compounds; heterocycles; X-ray diffraction studies; NMR studies



**Citation:** Boccuzzi, T.; Cicco, L.; Quivelli, A.F.; Vitale, P.; Perna, F.M.; Karaghiosoff, K.; Capriati, V. 2-Diphenylphosphinomethyl-3-methylpyrazine. *Molbank* **2021**, *2021*, M1267. https://doi.org/10.3390/M1267

Academic Editor: Nicholas E. Leadbeater

Received: 28 June 2021
Accepted: 2 August 2021
Published: 5 August 2021



## 1. Introduction

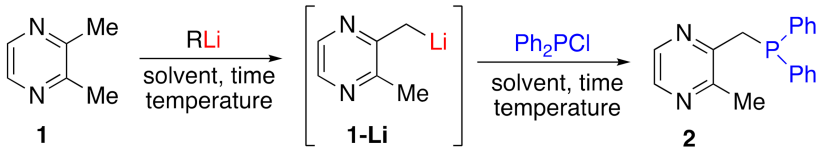
Pyrazine-based skeletons are present in many natural bioactive products and have been extensively incorporated in clinically used drugs and molecules exhibiting noteworthy antibiotic, antifungal, antitubercular, antidepressant, antineoplastic, diuretic, antiulcerogenic, and anti-infective effects [1–6]. Moreover, they can also serve as important building blocks for the preparation of dyes and electroluminescent materials, and were found to act as suitable ligands in coordination chemistry [7–12].

Heteroatom-promoted lateral lithiation of benzylic alkyl groups closest to the heteroatom, followed by trapping reaction with electrophiles, represents a valuable tool to elaborate (hetero)aromatic systems by providing either a chain extension at the benzylic position or the synthesis of fused carbo- and heterocyclic systems via the annulation of chain-extended adducts [13–16].

Among nitrogen-containing heterocyclic systems, lateral metalation of pyrazines-bearing Me groups has largely remained unexplored [17–21]. Kamal and Levine pioneered the use of sodium amide in liquid ammonia to promote acylation, alkylation and hydroxyalkylation reactions of dimethylpyrazines [22,23]. Later on, Houminer et al. prepared 2-(2-hydroxy-2-arylethyl)pyrazines by benzylic lithiation of alkylpyrazines with lithium diisopropylamide (LDA) in ether or diglyme, followed by electrophilic interception of the corresponding anions with aromatic aldehydes, with the desired adducts, however, being isolated in poor-to-moderate yields (25–60%) [24,25].

Based on our long lasting interest in the functionalization of heterocycles by direct [26–33], *ortho*- [34,35], and lateral [36,37] lithiation reactions, we became interested in synthesizing a pyrazine derivative incorporating a phosphine unit into its scaffold as transition metal-phosphine complexes are known to be powerful catalytic tools for numerous C–C bond-forming reactions in modern organic synthesis [38–41].

In this Short Note, we report on the synthesis and the structural characterization of a novel, unsymmetrical diphenylphosphinomethyl pyrazine (**2**), by selectively deprotonating one of the methyl group of 2,3-dimethylpyrazine (**1**) with an organolithium compound, followed by trapping of the resulting putative lithium intermediate **1-Li** with diphenylchlorophosphine ($Ph_2PCl$) (Scheme 1). A comparison has been made on the effectiveness of using more eco-friendly solvents in place of traditional volatile organic compounds (VOCs). To date, only symmetrical pyrazine-based aryl- or alkyldiphosphines have been made accessible when using in the deprotonation reaction of the corresponding precursors a mixture of *n*-BuLi and tetramethylethylenediamine (TMEDA) as a privileged ligand, and working in ethereal solutions of VOCs at −78 °C [42].



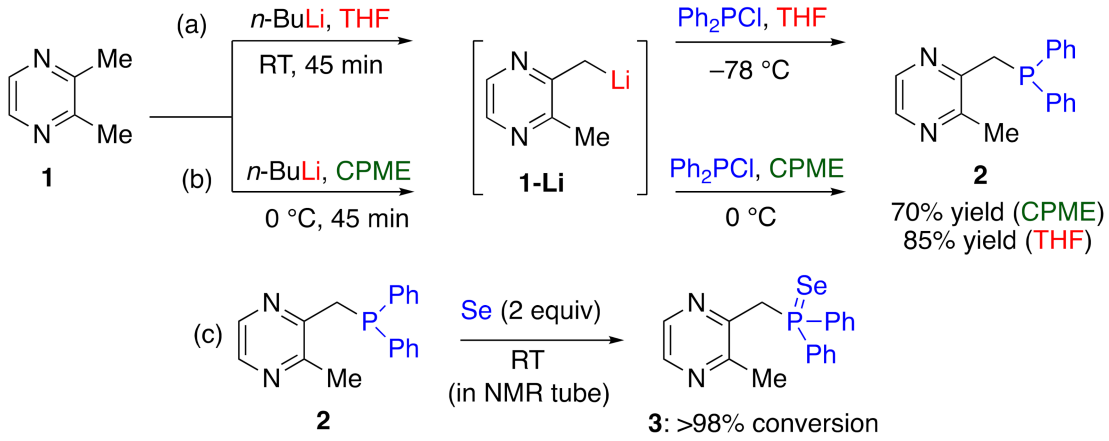

**Scheme 1.** Synthesis of phosphine **2** by deprotonating 2,3-dimethylpyrazine **1** with an organolithium, followed by a trapping reaction of the intermediate **1-Li** with $Ph_2PCl$.

## 2. Results and Discussions

Treatment of a solution of **1** in THF with *n*-BuLi (1 equiv) (1.4 M solution in cyclohexane), under Ar at room temperature (RT), followed by dropwise quenching with $Ph_2PCl$ (1 equiv) in THF after 45 min, gave no reaction. Lowering the temperature to −78 °C was found to be similarly ineffective. Pleasingly, upon first stirring a THF solution of **1** with *n*-BuLi for 45 min at RT under Ar, and then adding dropwise the resulting mixture to a pre-cooled (−78 °C) THF solution of $Ph_2PCl$, adduct **2** could now be isolated in 85% yield (Scheme 2a). The latter was fully characterized by multinuclear ($^1H$, $^{13}C$ and $^{31}P$) magnetic resonance spectroscopy (Supplementary Materials).

Further characterization of **2** came by allowing it to react at RT with chalcogens like selenium (2 equiv) directly in an NMR tube, and subsequently monitoring the appearance of phosphine selenide **3**, which formed with >98% conversion within a few minutes (Scheme 2c). The structure and the connectivity of **3** were unambiguously assigned by means of mono- ($^1H$, $^{13}C$, $^{31}P$ and $^{77}Se$) and two-dimensional (($^1H$-$^1H$)-COSY, ($^1H$-$^{13}C$)-HMBC and HMQC)) NMR techniques (Supplementary Materials), and by X-ray analysis (Figure 1 and Supplementary Materials). The major resonance displayed in the $^{31}P$ NMR spectrum at δ 32.4 ($C_6D_6$) is that typical of phosphine selenides [43]. $^{31}P$-$^{77}Se$ NMR coupling could be seen either in $^{31}P$ NMR spectrum as satellites ($^1J_{P\text{-}Se}$ = 756.3 Hz) or directly in the $^{77}Se$ NMR spectrum (Supplementary Materials).

Upon switching THF for an environmentally friendly solvent such as cyclopentyl methyl ether (CPME) (relatively high boiling point, non-inflammability, low toxicity and low peroxide formation rate, and stability under acidic and basic conditions) [44], compound **2** could be isolated in 70% yield when a CPME solution of **1-Li** (prepared by reacting **1** with *n*-BuLi (1.4 M in cyclohexane, 1 equiv) and aging the resulting solution at 0 °C for 45 min) was cannulated into a solution of $Ph_2PCl$ (1 equiv) in CPME, which was kept at 0 °C (Scheme 2b).




**Scheme 2.** (a) Synthesis of phosphine **2** by deprotonation of **1** and reaction of **1-Li** with $Ph_2PCl$ in THF; (b) synthesis of phosphine **2** by deprotonation of **1** and reaction of **1-Li** with $Ph_2PCl$ in CPME; (c) synthesis of phosphine selenide **3** by reacting **2** with Se.

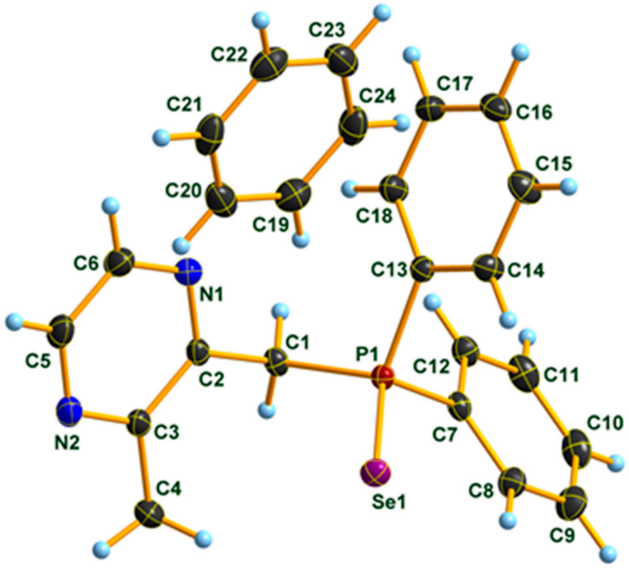



**Figure 1.** Molecular structure of compound **3** · $C_6H_6$ in the crystal, DIAMOND [45] representation, thermal ellipsoids are drawn at 50% probability level.

## 3. Materials and Methods

Tetrahydrofuran (THF) and cyclopentyl methyl ether (CPME) were dried over sodium/benzophenone ketyl under argon, and distilled prior to use. All reactions involving air-sensitive reagents were performed under argon in oven-dried glassware using syringe-septum cap technique.

GC-MS analyses were performed on a HP 5995C model. High-resolution mass spectrometry (HRMS) analyses were performed using a Bruker microTOF QII mass spectrometer equipped with an electrospray ion source (ESI). Reagents and solvents, unless otherwise specified, were purchased from Sigma-Aldrich (Sigma-Aldrich, St. Louis, MO, USA) and used without any further purification. Ethyl acetate was used as the solvent in the work-up procedures. *n*-BuLi (1.4 M in cyclohexane) was used as the lithiating agent.

NMR spectra were recorded on a Jeol EX 400 Eclipse spectrometer operating at 400.182 MHz ($^1$H), 100.626 MHz ($^{13}$C), 161.997 MHz ($^{31}$P) and 76.321 MHz ($^{77}$Se). Chemical shifts are reported in parts per million (δ) using the following standards $Me_4Si$ ($^1$H, $^{13}$C), 85% $H_3PO_4$ ($^{31}$P), $Me_2Se$ ($^{77}$Se). Coupling constants are expressed in Hz using $C_6D_6$ as

the solvent. The following abbreviations have been used to explain the multiplicities: s = singlet, d = doublet, dd = double of doublets, quin = quintuplet, m = multiplet.

### *3.1. X-ray Diffraction Studies on Compound* **3 · $C_6D_6$**

A suitable crystal of **3** immersed in perfluorinated oil was mounted and measured by means of an Oxford Diffraction Excalibur diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, using MoKα radiation (λ = 0.71073 Å). Data collection was performed with the program CrysAlis CCD. Data reduction was carried out with the program CrysAlis RED (CrysAlis RED, 2006) [46]. The intensities were corrected for Lorentz and polarization effects, and an absorption correction based on the multi-scan method using SCALE3 ABSPACK [47] in CrysAlisPro was applied. The structure was solved by direct methods using the program SIR97 [48], refined by means of full matrix least-squares based on F2 using the program SHELXL-97 [49], and checked with PLATON [50]. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms involved in hydrogen bonds were located in the Fourier difference map. Data collection and refinement parameters are given in Tables S1–S4 (Supplementary Material). Interactions between selenium and the neighbouring protons are shown in Figure S13 (Supplementary Informations). Illustrations of the molecular structure were drawn with DIAMOND [45]. CCDC-2092648 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif [51].

### *3.2. Synthetic Procedure for the Synthesis of* **2** *in THF*

To a solution of **1** (18.55 mmol) in 30 mL of dry THF, *n*-BuLi (1 equiv) (13.25 mL of a solution 1.4 M in cyclohexane) was rapidly added under Ar at RT. The resulting dark red mixture was vigorously stirred for 45 min. This solution was then cannulated into a pre-cooled (−78 °C) THF solution of $Ph_2PCl$ (1 equiv) (18.55 mmol in 20 mL of dry THF) under Ar. The mixture was allowed to warm to RT. After 4 h, the organic layer was filtered through a silica pad under Ar, using ethyl acetate as the eluent. The solvent was removed under reduced pressure to provide the desired product **2** in 85% yield.

### *3.3. Synthetic Procedure for the Synthesis of* **2** *in CPME*

To a solution of **1** (1 mmol) in 1 mL of dry CPME, *n*-BuLi (1 equiv) (0.7 mL of a solution 1.4 M in cyclohexane) was rapidly added under Ar at 0 °C. The resulting dark red mixture was vigorously stirred for 45 min. This solution was then cannulated into a pre-cooled (0 °C) CPME solution of $Ph_2PCl$ (1 equiv) (1 mmol in 1 mL of dry CPME) under Ar. The mixture was allowed to warm to RT. After 4 h, the organic layer was filtered through a silica pad under Ar, using ethyl acetate as the eluent. The solvent was removed under reduced pressure to provide the desired product **2** in 70% yield.

*2-Diphenylphosphinomethyl-3-methylpyrazine* (**2**). $^1$H NMR (400.182, $C_6D_6$): δ 2.35 (s, 3 H, $CH_3$), 3.48 (s, 2 H, $CH_2$), 7.04–7.11 (m, 6 H, arom-H), 7.42–7.49 (m, 4 H, arom-H), 7.88–7.91 (m, 2 H, arom-H); $^{13}$C NMR (100.626 MHz, $C_6D_6$): δ 21.9 (d, $^4J_{C\text{-}P}$ = 4.9 Hz, $CH_3$), 36.0 (d, $^1J_{C\text{-}P}$ = 18.1 Hz, $CH_2$), 128.4 (d, $^3J_{C\text{-}P}$ = 6.4 Hz, CH), 128.8 (s, CH), 133.1 (d, $^2J_{C\text{-}P}$ = 19.4 Hz, CH), 134.4 (d, $^1J_{C\text{-}P}$ = 12.7 Hz, C), 138.7 (d, $^2J_{C\text{-}P}$ = 15.6 Hz, C), 141.3 (d, $^3J_{C\text{-}P}$ = 7.6 Hz, C), 152.6 (d, $J$ = 0.8 Hz, CH), 152.7 (s, CH); $^{31}$P NMR (161.997 MHz, $C_6D_6$) δ = −14.8 (quin, $^3J_{PH}$ = 5.9 Hz); GC-MS (70 ev) *m/z* (%): 292 (36), 277 (1), 215 (3), 183 (100), 152 (8), 133 (3), 107 (13), 91 (1), 77 (4); HR-MS (ESI), (M.W.:292): *m/z* [M + $H^+$] calculated for $C_{18}H_{18}N_2P$: 293.1114, found: 293. 1171.

### *3.4. Synthetic Procedure for the Synthesis of* **3**

In an NMR tube containing a solution of **2** in $C_6D_6$, 2 equiv. of selenium were added at RT. The reaction was monitored by NMR. After a few minutes, phosphine selenide **3** was obtained with 98% conversion. Single crystals were obtained directly from the NMR tube by slow evaporation of the solvent, and were subjected to X-ray diffraction studies.

*[(3-Methylpyrazin-2-yl)methyl]diphenylphosphine selenide* (**3**). $^{1}$H NMR (400.182 MHz, $C_6D_6$): δ 2.46 (s, 3 H, $CH_3$), 3.98 (d, $^{2}J_{PH}$ = 12.0 Hz, 2 H, $CH_2$), 6.95–6.98 (m, 6 H, *m*-H, *p*-H), 7.67 (d, $^{3}J_{HH}$ = 4.0 Hz, 1 H, pyrazine-H), 7.80 (dd, $^{3}J_{HH}$ = 4.0 Hz, $^{5}J_{PH}$ = 4.0 Hz, 1 H, pyrazine-H), 7.85–7.91 (m, 4 H *o*-H); $^{13}$C NMR (100.626 MHz, $C_6D_6$): δ 23.0 (d, $^{4}J_{PC}$ = 4.0 Hz, $CH_3$), 39.7 (d, $^{1}J_{PC}$ = 43.2 Hz, $CH_2$), 128.2 (d, $^{3}J_{PC}$ = 12.1 Hz, CH-*m*), 131.2 (d, $^{4}J_{PC}$ = 3.0 Hz, CH-*p*), 132.2 (d, $^{2}J_{PC}$ = 13.1 Hz, CH-*o*), 132.9 (d, $^{1}J_{PC}$ = 19.1 Hz, C-*i*), 140.9 (d, $^{5}J_{PC}$ = 3.0 Hz, CH-3), 142.1 (d, $^{4}J_{PC}$ = 4.0 Hz, CH-4), 148.6 (d, $^{3}J_{PC}$ = 8.0 Hz, C-2), 154.9 (d, $^{2}J_{PC}$ = 5.0 Hz, C-1); $^{31}$P NMR (161.997 MHz, $C_6D_6$): δ 32.35 (s, $^{1}J_{PSe}$ = 755.9 Hz);$^{77}$Se NMR (76.321 MHz, $C_6D_6$): δ-316.45 (d, $^{1}J_{PSe}$ = 756 Hz).

## 4. Conclusions

The preparation of an unsymmetrically substituted pyrazine, 2-diphenylphosphinomethyl-3-methylpyrazine, was presented, by subjecting to lithiation the commercially available 2,3-dimethyl pyrazine followed by an electrophilic interception of the putative benzyl-type intermediate with $Ph_2PCl$. The chemical structure of the synthesized adduct was unambiguously secured by using NMR and mass techniques, and by preparing a selenium derivative, which furnished single crystals that were suitable for X-ray analysis. The described lateral lithiation/functionalization was proven to be regioselective in the absence of additional ligands, and was successfully achieved either working in a VOC such as THF at −78 °C (85% yield) or in an environmentally friendly solvent like CPME at 0 °C (70% yield). Further investigation is in progress to prepare transition-metal complexes of such a P,N-heterocyclic phosphine motif to investigate their biological properties and their applications as auxiliary ligands in organometallic catalysis.

**Supplementary Materials:** The following are available online at: copies of $^{1}$H-, $^{13}$C- and $^{31}$P-NMR spectra of compound **2**; copies of $^{1}$H-, $^{13}$C-, $^{31}$P- and $^{77}$Se-NMR spectra of compound **3**; copies of 2D $^{1}$H-$^{1}$H-COSY, 2D $^{1}$H-$^{13}$C HMQC, 2D $^{1}$H-$^{13}$C HMBC spectra of compound **3**; crystallographic data, geometric parameters and bond angles for compound **3 · $C_6D_6$**; X-ray ellipsoid plot of compound **3 · $C_6D_6$** showing interactions between selenium and the neighbouring protons.

**Author Contributions:** Conceptualization, K.K. and V.C.; methodology, all authors; validation, T.B., L.C. and A.F.Q.; formal analysis, T.B., L.C., A.F.Q., F.M.P. and P.V.; investigation, K.K., F.M.P. and P.V.; resources, K.K. and V.C.; data curation, F.M.P. and P.V.; writing—original draft preparation, V.C.; writing—review and editing, all authors; supervision, K.K. and V.C.; funding acquisition, V.C. and K.K. All authors have read and agreed to the published version of the manuscript.

**Funding:** This work was carried out under the framework of the National PRIN project "Unlocking Sustainable Technologies Through Nature-Inspired Solvents" (Code: 2017A5HXFC_002) and financially supported by the University of Bari.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** The data presented in this study are available in this article and in its Supplementary Materials. The X-ray data are deposited at CCDC as stated above.

**Acknowledgments:** University of Bari and Ludwig-Maximilians-Universität München are gratefully acknowledged for participating in an Erasmus scholarship programme.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Miniyar, P.B.; Murumkar, P.R.; Patil, P.S.; Barmade, M.A.; Bothara, K.G. Unequivocal role of pyrazine ring in medicinally important compounds: A review. *Mini. Rev. Med. Chem.* **2013**, *13*, 1607–1625. [CrossRef]
2. Asif, M. Piperazine and Pyrazine containing molecules and their diverse pharmacological activities. *Int. J. Adv. Sci. Res.* **2015**, *1*, 5–11. [CrossRef]
3. Dolezal, M.; Zitko, J. Pyrazine derivatives: A patent review (June 2012–present). *Expert Opin. Ther. Pat.* **2015**, *25*, 33–47. [CrossRef] [PubMed]

4. Kiran, G.S.; Priyadharsini, S.; Sajayan, A.; Ravindran, A.; Selvin, J. An antibiotic agent pyrrolo [1,2-*a*] pyrazine-1,4-dione, hexahydro isolated from a marine bacteria *Bacillus tequilensis* MSI45 effectively controls multi-drug resistant *Staphilococcus Aureus*. *RSC Adv.* **2018**, *8*, 17837–17846. [CrossRef]
5. Srinivasarao, S.; Nandikolla, A.; Suresh, A.; Van Calster, K.; De Voogt, L.; Cappoen, D.; Ghosh, B.; Aggarwal, H.; Murugesan, S.; Sekhar, K.V.G.C. Seeking potent anti-tubercolar agents: Design and synthesis of substituted-*N*-(6-(4-(pyrazine-2-carbonyl)piperazine/homopiperazine-1-yl)pyridin-3-yl)benzamide derivatives as anti-tubercolar agents. *RSC Adv.* **2020**, *10*, 12272–12288. [CrossRef]
6. Patel, A.; Kumar, A.; Sheoran, N.; Kumar, M.; Sahu, P.K.; Ganeshan, P.; Ashajyothi, M.; Gopalakrishnan, S.; Gogoi, R. Antifungal and defense elicitor activities of pyrazines identified in endophytic *Pseudomonas putida* BP25 against fungal blast incited by *Magnaporthe oryzae* in rice. *J. Plant Dis. Protect.* **2021**, *128*, 261–272. [CrossRef]
7. Achelle, S.; Baudequin, C.; Plé, N. Luminescent materials incorporating pyrazine or quinoxaline moieties. *Dye. Pigment.* **2013**, *98*, 575–600. [CrossRef]
8. Walton, R.A.; Matthewa, R.W. Coordination compounds of silver(II). Preparation and characterization of new pyrazine and pyrazine carboxylate complexes and some related silver(I), copper(II), cobalt(II) and nichel(II) derivatives. *Inorg. Chem.* **1971**, *10*, 1433–1438. [CrossRef]
9. Fitchett, C.M.; Steel, P.J. Chiral heterocyclic ligands. XII. Metal complexes of a pyrazine ligand derived from camphor. *Arkivoc* **2006**, *3*, 218–225. [CrossRef]
10. Ogyzek, M.; Chylewska, A.; Królicka, A.; Banasiuk, R.; Turecka, K.; Lesiak, D.; Nidzworski, D.; Makowski, M. Coordination chemistry of pyrazine derivatives analogues of PZA: Design, synthesis, characterization and biological activity. *RSC Adv.* **2016**, *6*, 52009–52025. [CrossRef]
11. Wang, W.-Z.; Xu, Y.-C.; Wang, L.; Li, L.-L.; Jia, X.-G.; Lee, G.-H.; Peng, S.-M. Transition metal complexes with pyrazine amine ligand: Preparation, structure and carbon dioxide copolymerization behavior. *J. Mol. Struct.* **2019**, *1193*, 280–285. [CrossRef]
12. Zheng, X.; Chen, Y.; Ran, J.; Li, L. Synthesis, crystal structure, photoluminescence and catalytic properties of a novel cuprous complex with 2,3-pyrazinedicarboxylic acid ligands. *Sci. Rep.* **2020**, *10*, 6723. [CrossRef]
13. Clark, R.D.; Jahangir, A. Lateral Lithiation Reactions Promoted by Heteroatomic Substituents. In *Organic Reactions*; Paquette, L.A., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 1995; Volume 47, Chapter 1; pp. 1–314. [CrossRef]
14. Clayden, J. Organolithiums: Selectivity for Synthesis. In *Tetrahedron Organic Chemistry Series*; Pergamon: Amsterdam, The Netherlands, 2002; Volume 23.
15. Luisi, R.; Capriati, V. *Lithiums Compounds in Organic Synthesis—From Fundamentals to Applications*; Wiley-VCH: Weinheim, Germany, 2014.
16. Di Nunno, L.; Scilimati, A.; Vitale, P. Regioselective synthesis and side-chain metallation and elaboration of 3-alkyl-5-alkylisoxazoles. *Tetrahedron* **2002**, *58*, 2659–2665. [CrossRef]
17. Kaiser, E.M. Lateral Metallation of Methylated Nitrogenous Heterocycles. *Tetrahedron* **1983**, *39*, 2055–2064. [CrossRef]
18. Smith, K.; El-Hiti, G.A.; Alshammari, M.B.; Fekri, A. Control of Site of Lithiation of 3-(Aminomethyl)pyridine derivatives. *Synthesis* **2013**, *45*, 3426–3464. [CrossRef]
19. Palao, E.; de la Moya, S.; Agarrabeitia, A.R.; Esnal, I.; Bañuelos, J.; López-Arbeloa, I.; Ortiz, M.J. Selective Lateral Lithiation of Methyl BODIPYs: Synthesis, Photophysics, and Electrochemistry of New Meso Derivatives. *Org. Lett.* **2014**, *16*, 4364–4367. [CrossRef]
20. Zhang, C.Y.; Tou, J.M. Synthesis of Highly Functionalized Pyrazines by *Ortho*-Lithiation Reactions. Pyrazine Ladder Polymers. *J. Am. Chem. Soc.* **1999**, *121*, 8783–8790. [CrossRef]
21. El-Hiti, G.A.; Smith, K.; Hegazy, A.S.; Alshammari, M.B.; Masmali, A.M. Directed lithiation of simple aromatics and heterocycles for synthesis of substituted derivatives. *Arkivoc* **2015**, *4*, 19–47. [CrossRef]
22. Kamal, M.; Levine, R. Chemistry of Pyrazine and Its Derivatives. V. Acylation and Alkylation of 2,6-Dimethylpyrazine and Certain Other Pyrazine Derivatives. *J. Org. Chem.* **1962**, *27*, 1355–1359. [CrossRef]
23. Kamal, M.; Levine, R. The Chemistry of Pyrazine and Its Derivatives. VI. The Synthesis of Carbinols Containing the Pyrazine Nucleus. *J. Org. Chem.* **1962**, *27*, 1360–1363. [CrossRef]
24. Bassfield, R.; Houminer, Y. Selectivity in the Metalation of Polymethylpyrazines. *J. Org. Chem.* **1983**, *48*, 2130–2133. [CrossRef]
25. Houminer, Y.; Fenner, R.A.; Secor, H.V.; Seeman, J.I. Steric Effects on Pyrolysis Reactions. The Thermal Retro-Ene Reaction of Pyrazineethanols. *J. Org. Chem.* **1987**, *52*, 3971–3974. [CrossRef]
26. Capriati, V.; Florio, S.; Luisi, R.; Perna, F.M.; Spina, A. 2-Lithio-3,3-dimethyl-2-oxazolinyloxirane: Carbanion or Azaenolate? Structure, Configurational Stability, and Stereodynamics in Solution. *J. Org. Chem.* **2008**, *73*, 9552–9564. [CrossRef] [PubMed]
27. Capriati, V.; Florio, S.; Perna, F.M.; Salomone, A.; Abbotto, A.; Amedjkouh, M.; Nilsson Lill, S.O. On the Dichotomic Reactivity of Lithiated Styrene Oxide: A Computational and Multinuclear Magnetic Resonance Investigation. *Chem. Eur. J.* **2009**, *15*, 7958–7979. [CrossRef]
28. Capriati, V.; Florio, S.; Perna, F.M.; Salomone, A. Lithiated Fluorinated Styrene Oxides: Configurational Stability, Synthetic Applications, and Mechanistic Insight. *Chem. Eur. J.* **2010**, *16*, 9778–9788. [CrossRef]
29. Perna, F.M.; Salomone, A.; Dammacco, M.; Florio, S.; Capriati, V. Solvent and TMEDA Effects on the Configurational Stability of Chiral Lithiated Aryloxiranes. *Chem. Eur. J.* **2011**, *17*, 8216–8225. [CrossRef]

30. Mansueto, R.; Mallardo, V.; Perna, F.M.; Salomone, A.; Capriati, V. Gated access to α-lithiated phenyltetrahydrofuran: Functionalisation via direct lithiation of the parent oxygen heterocycle. *Chem. Commun.* **2013**, *49*, 10160–10162. [CrossRef] [PubMed]
31. Cicco, L.; Addante, V.; Temperini, A.; Donau, C.A.; Karaghiosoff, K.; Perna, F.M.; Capriati, V. Toward Customized Tetrahydropyran Derivatives through Regioselective α-Lithiation and Functionalization of 2-Phenyltetrahydropyran. *Eur. J. Org. Chem.* **2016**, *2016*, 3157–3161. [CrossRef]
32. Di Nunno, L.; Vitale, P.; Scilimati, A. Effect of the aryl group substituent in the dimerization of 3-arylisoxazoles to *syn* 2,6-diaryl-3,7-diazatricyclo[4.2.0.0$^{2,5}$]octan-4,8-diones induced by LDA. *Tetrahedron* **2008**, *64*, 11198–11204. [CrossRef]
33. Di Nunno, L.; Scilimati, A.; Vitale, P. 5-Hydroxy-2-phenyl-5-vinyl-2-isoxazoline and 3-phenyl-5-vinylisoxazole: Synthesis and reactivity. *Tetrahedron* **2005**, *61*, 11270–11278. [CrossRef]
34. Coppi, D.I.; Salomone, A.; Perna, F.M.; Capriati, V. Exploiting the Lithiation-Directing Ability of Oxetane for the Regioselective Preparation of Functionalized 2-Aryloxetane Scaffolds under Mild Conditions. *Angew. Chem. Int. Ed.* **2012**, *30*, 7650–7654. [CrossRef]
35. Perna, F.M.; Falcicchio, A.; Salomone, A.; Milet, A.; Rizzi, R.; Hamdoun, G.; Barozzino-Consiglio, G.; Stalke, D.; Oulyadi, H.; Capriati, V. First Direct Evidence of an *ortho*-Lithiated Aryloxetane: Solid and Solution Structure, and Dynamics. *Eur. J. Org. Chem.* **2019**, *2014*, 5549–5556. [CrossRef]
36. Mansueto, R.; Perna, F.M.; Salomone, A.; Perrone, S.; Florio, S.; Capriati, V. Efficient Regioselective Synthesis of 3,4,5-Trisubstituted 1,2,4-Triazoles on the Basis of a Lithiation-Trapping Sequence. *Eur. J. Org. Chem.* **2014**, *2014*, 6653–6657. [CrossRef]
37. Sassone, F.C.; Perna, F.M.; Salomone, A.; Florio, S.; Capriati, V. Unexpected lateral-lithiation-induced alkylative ring opening of tetrahydrofurans in deep eutectic solvents: Synthesis of functionalized primary alcohols. *Chem. Commun.* **2015**, *51*, 9459–9462. [CrossRef] [PubMed]
38. Tsuji, J. *Palladium in Organic Synthesis*; Springer: Berlin, Germany, 2005. [CrossRef]
39. Tsuji, J. *Palladium Reagents and Catalysts-New Perspectives for the 21st Century*; Wiley: Chichester, UK, 2004.
40. Hartwig, J. *Organotransition Metal Chemistry*; University Science Books: Sausalito, CA, USA, 2010; pp. 745–824.
41. Konrad, T.M.; Fuentes, J.A.; Slawin, A.M.Z.; Clarke, M.L. Highly Enantioselective Hydroxycarbonylation and Alkoxycarbonylation of Alkenes using Dipalladium Complexes as Precatalysts. *Angew. Chem. Int. Ed.* **2010**, *49*, 9197–9200. [CrossRef]
42. Pews-Davtyan, A.; Fang, X.; Jackstell, R.; Spannenberg, A.; Baumann, W.; Franke, R.; Beller, M. Synthesis of New Diphosphine Ligands and their Application in Pd-Catalyzed Alkoxycarbonylation Reactions. *Chem. Asian J.* **2014**, *9*, 1168–1174. [CrossRef] [PubMed]
43. Duddeck, H. Sulfur, Selenium, and Tellurium NMR. In *Encyclopedia of NMR*, 2nd ed.; Harris, R.K., Wasylishen, R.E., Eds.; John Wiley & Sons, Ltd.: Chichester, UK, 2012; Volume 8, pp. 4920–4933.
44. Azzena, U.; Carraro, M.; Pisano, L.; Monticelli, S.; Bartolotta, R.; Pace, V. Cyclopentyl Methyl Ether (CPME): A Versatile Eco-friendly Solvent for Applications in Biotechnology and Biorefineries. *ChemSusChem* **2019**, *12*, 2083–2097. [CrossRef]
45. Brandenburg, K. *Diamond 3.2 h*; Crystal Impact GbR: Bonn, Germany, 2012.
46. *CrysAlis RED*; Version 1.171.27p5 beta; Oxford Diffraction Ltd: Abingdon, UK, 2005.
47. *SCALE3 ABSPACK—An Oxford Diffraction Program*; Version 1.0.4, gui: 1.0.3 (C); Oxford Diffraction, Ltd: Abingdon, UK, 2005.
48. Altomare, A.; Burla, M.C.; Camalli, M.; Cascarano, G.L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A.G.G.; Polidori, G.; Spagna, R. SIR97: A new tool for crystal structure determination and refinement. *J. Appl. Cryst.* **1999**, *32*, 115–119. [CrossRef]
49. Sheldrick, G.M. *SHELXS-97: Program for Crystal Structure Solution*; University of Göttingen: Wilhelmsplatz, Germany, 1997.
50. Spek, A.L. *PLATON: A Multipurpose Crystallographic Tool*; Utrecht University: Utrecht, The Netherlands, 1999.
51. The Cambridge Crystallographic Data Centre (CCDC). Available online: https://www.ccdc.cam.ac.uk/data_request/cif (accessed on 3 August 2021).