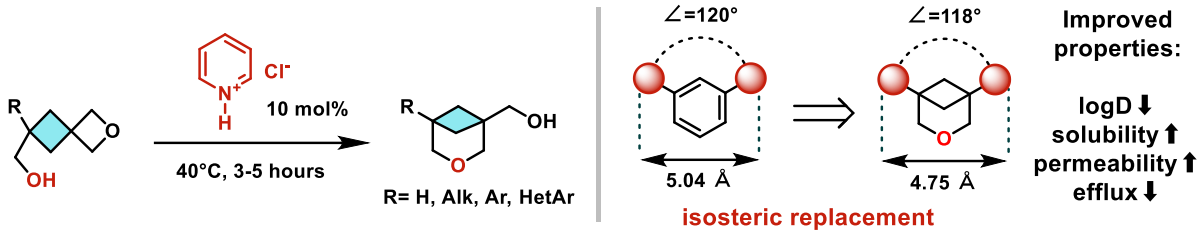
3-Oxabicyclo[3.1.1]heptanes as Isosteres of *meta*-Substituted Benzene Rings

Jennifer Morvan, Evelien Renders, Peter J.J.A. Buijnsters, Pavel Ryabchuk*

Janssen Research & Development, Janssen Pharmaceutica NV, Turnhoutseweg 30, Beerse 2340, Belgium

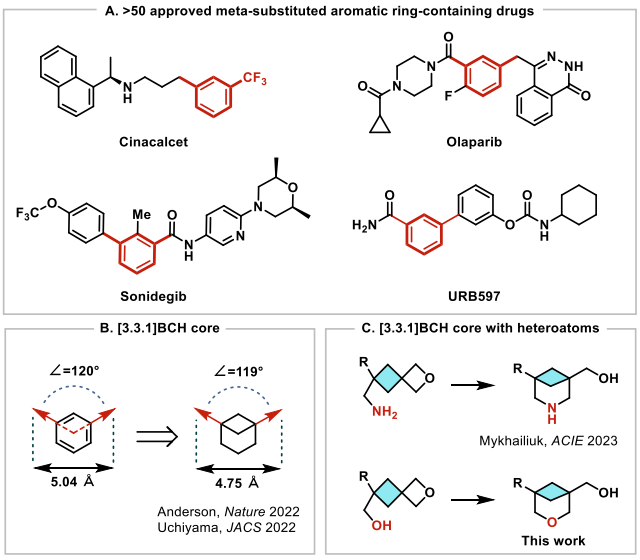
Supporting Information Placeholder



ABSTRACT: Replacement of the aromatic rings in drug candidates with isosteric rigid sp^3-rich scaffolds can improve physicochemical properties and increase the chance of progressing the molecule in the development and open new chemical space. Isosteres of *meta*-substituted benzenes remain challenging due to the difficulty of mimicking the exit vector angles and bond distances. Herein, we report the synthesis of 1,5-disubstituted 3-oxabicyclo[3.1.1]heptanes (oxa-BCHs), which can serve as saturated isosteres of *meta*-substituted phenyl rings, with similar geometric arrangement. This structural motif can be obtained under mild reaction conditions via acid-mediated isomerization of (2-oxaspiro[3.3]heptan-6-yl)methanols using catalytic quantities of pyridinium chloride (PyrHCl). We demonstrate the utility of this methodology by preparing various building blocks for use in medicinal chemistry and incorporating the 3-oxa-BCH into the anticancer drug *Sonidegib*, improving its physicochemical properties, such as permeability, metabolic stability and solubility.

Isosteric replacement of aromatic rings with rigid saturated analogues has been used in medicinal chemistry to enhance the physicochemical properties and ADME properties of a molecule, such as solubility, lipophilicity, permeability, and pharmacokinetic properties.[1] This approach addresses the intrinsic properties of phenyl rings, which can contribute to the overall poor physicochemical properties of drug candidates, limiting their prospects of being further developed into drugs. Bridged bicyclic saturated hydrocarbons, such as bicyclo[1.1.1]pentanes (BCPs), bicyclo[2.2.2]octanes (BCOs) and cubanes have been successfully used as *para*-substituted aromatic ring replacement.[2] On the other hand, isosteres of *meta*- and *ortho*- substituted benzenes have received less attention due to difficulties with establishing vectorial arrangements similar to corresponding aromatic systems. Recently, the bicyclo[3.1.1]heptane (BCH) scaffold has been suggested as a bioisostere of *meta*-substituted benzenes.[3,4] Its shape mimics the meta-arenes' 3D arrangement of exit vectors (119° vs. 120°). Anderson and co-workers have validated the bioisosteric approach by comparing BCH-containing drug analogues to the parent drugs: *Sonidegib* and *URB597*(Scheme 1, A and B).[3] In both cases, BCH analogues showed reduced clearance rates and improved membrane permeability compared to their arene congeners. However, it did not affect the solubility. Researchers from *Enamine* have shown that replacing one carbon atom with oxygen on saturated para- and ortho-

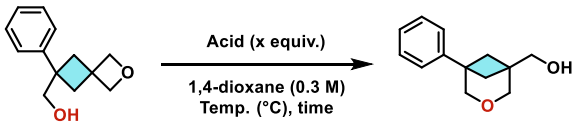
Scheme 1. Prevalence of meta-substituted phenyl rings in drugs and isosteric approaches



isosteres can significantly improve the aqueous solubility of the molecule.[5] Moreover, Mykhailiuk and co-workers reported 3-azabicyclo[3.1.1]heptanes as an isostere of meta-substituted pyridines.[6] We envisioned that incorporating an oxygen atom into the BCH skeleton could also improve the

solubility, permeability and clearance while keeping the 3D space arrangement close to the parent *meta*-aromatic systems. Herein, we report the synthesis of 1,5-disubstituted 3-oxabicyclo[3.1.1]heptanes (oxa-BCH) as isosteric replacements of *meta*-arenes, which can be obtained via a mild acid-catalyzed rearrangement of 6-substituted (2-oxaspiro[3.3]heptan-6-yl)methanols (Scheme 1, C). We demonstrate the scope of the reaction, including acid groups and product diversification into valuable building blocks. Moreover, the effects on some physicochemical properties of the oxa-BCH analog of the anticancer drug *Sonidegib* were investigated.

Table 1. Reaction Optimization



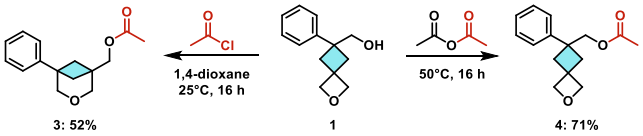
1 2

Entry	Reagent (equiv.)	T, (°C)	Time	LC yield (Isolated yield)
1	HCl (1.0)	20	30 min	99 (85%)
2	PTSA (1.0)	20	30 min	96
3	TFA (1.0)	20	3 days	95
4	AcOH (1.0)	60	24 h	3
5	HCl (0.1)	20	15 min	98 (89%)
6	PTSA (0.1)	20	30 min	97
7	PyrHF (1.0)	20	24 h	99
8	PyrHCl (1.0)	20	24 h	87 (80%)
9	PyrHCl (1.0)	40	1 h	96
10	PyrHCl (0.1)	40	4 h	95
11	Pyridine (1.0)	60	3 days	0
12	LiCl (1.0)	60	24 h	0

For a long time, the synthesis and study of rigid bridgehead bicyclic structures have been of interest to theoretical and physical organic chemists; however, relatively few methods for the preparation of oxabicyclo[3.1.1]heptane (oxa-BCH) scaffolds have been reported. The strategies can be divided into two categories: a) simultaneous formation of cyclobutane and pyrane rings, typically achieved *via* intramolecular [2+2] cycloaddition; and b) construction of a pyrane ring from a substrate already containing a cyclobutane moiety. [7,8] The former methods require the utilization of prefunctionalized bisallyl ethers or 3-oxa-1,6-enynes and harsh reaction conditions, which limit reaction scope. The latter approach is much less explored, and to the best of our knowledge, only 3 single examples have been reported. The pyrane ring is formed through ring-opening or substitution reaction and relies on strongly acidic or basic reagents (HCl, H_2SO_4, KOH), which makes this methodology incompatible with substrates possessing sensitive functional groups.

We aimed to develop an expeditious synthetic methodology that allows access to the oxo-BCH core in a facile fashion and has the possibility of incorporating this moiety into more complex target molecules. Moreover, we envisioned that the oxa-BCH containing a primary alcohol functionality could be converted into a valuable variety of building blocks using conventional oxidation chemistry, substitutions or coupling reactions. For this purpose, we prepared (6-phenyl-2-oxaspiro[3.3]heptan-6-yl)methanol (**1**) from commercially available ethyl 2-phenylacetate in 2 steps (see SI). Using compound **1** as a model substrate, we systematically evaluated the acid-catalyzed 2-oxaspiro[3.3]heptane rearrangement. In the presence of 1 equiv. of strong acids, such as HCl or pTSA in 1,4-dioxane, compound **1** gave the desired product 2 after 30 minutes in >95% yield (Entries 1 and 2). Trifluoroacetic acid gave a similar reaction profile, however, at a much lower rate, and completion was achieved only after 3 days (Entry 3). Treatment of **1** with acetic acid failed to promote the rearrangement, even at higher temperatures (Entry 4). Further exploration revealed that the presence of catalytic quantities of strong acids is sufficient to obtain the desired product in comparable high yields (Entries 5 and 6). We then performed the reaction on a multigram scale using 10 mol% HCl to afford oxa-BCH **2** in 89% isolated yield (Entry 6). Although utilization of HCl gave excellent results, we were interested in finding conditions that would be compatible with acid-sensitive groups. In this context, we have identified pyridinium chloride and fluoride as alternatives; both reagents resulted in full conversion at room temperature after 24 hours, with the latter giving a slightly improved yield of the desired product (Entries 7-9). Due to the corrosive nature of the pyridinium fluoride, which necessitates special glassware and safety concerns, we have chosen pyridinium chloride for further exploration. To our delight, pyridinium chloride gives similar results in catalytic quantities (Entry 10). Control experiments with pyridine and LiCl further supported the acid-catalyzed mechanism of this reaction (entries 11 and 12).

Scheme 2. Acetylation of 1



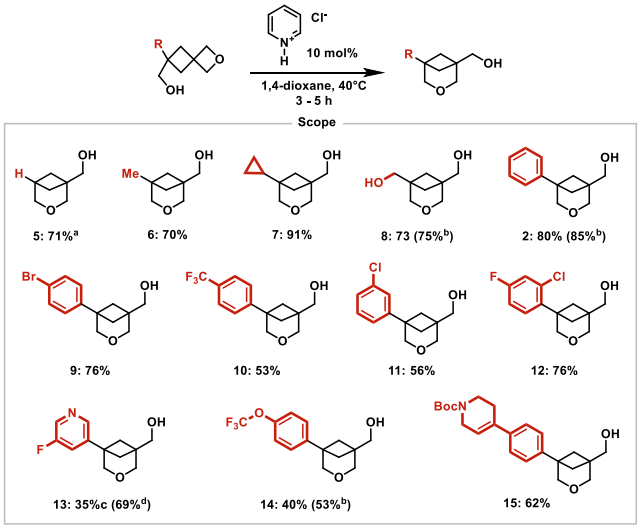
3: 52% 1 4: 71%

We have also evaluated the alternative methods for the oxa-BCH preparation. In this context, we have found that the presence of acetyl chloride substrate **1** gives the acetylated product **3** containing the oxa-BCH core in 52% yield (Scheme 2). Interestingly, treatment of the same starting material **1** in pure acetic anhydride results in clean acetylation of the alcohol with the preservation of oxetane fragment **4**. These results further support the acidic nature of the rearrangement. They are explained by the high acidity of HCl, which can be present in acetic chloride or is generated *in situ* upon acetylation.

With the optimized conditions, the substrate scope for the acid-catalyzed rearrangement of (2-oxaspiro[3.3]heptan-6-yl)methanols into the corresponding oxa-BCH derivatives was investigated (Scheme 3). The initial focus was to examine substrates containing non-aromatic groups. Alkyl substituents at the 6 position of the (2-oxaspiro[3.3]heptan-6-yl)methanol derivatives, such as methyl, cyclopropyl, and primary alcohols, are well tolerated during the reaction, giving the desired oxa-BCH derivatives in excellent yields (**6-**

8). Alcohol **5**, with R being hydrogen (Scheme 3), could be isolated in a good yield (71%), although a longer reaction time was required. Additionally, compared to the phenyl substituted model substrate **2**, the rearrangement of other aromatic moieties, such as *ortho-, meta* or *para*-halogenated arenes to the oxa-BCH derivatives **9**, **11** and **12**, also works efficiently. Electron withdrawing -CF_3 (**10**) and π-donating - OCF_3 (**14**) groups were tolerated in this transformation. We observed a slightly higher yield for the latter substrate **14** when 10 mol% HCl was used. Oxa-BCH containing pyridine **13** can be prepared; however, it necessitated 50 mol% of PyrHCl, most likely due to the basicity of the pyridine moiety. The best result to reach compound **13** was to use 1.1 equiv. of pTSA, however, a side-product was obtained in both cases, resulting from a competing nucleophilic attack of chloride or tosylate on the oxetane ring (See SI). We assessed how the reactions performed with an acid labile group in the starting material as a final test of the mild conditions. Gratifyingly, we isolated the acid labile Boc-protected amine **15** using PyrHCl, giving the desired product in 62% yield without losing the protecting group.

Scheme 3. Substrate scope

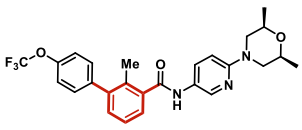


[a]24 hours. [b]10 mol% HCl. 50 mol% PyrHCl. [c]1.1 equiv. pTSA

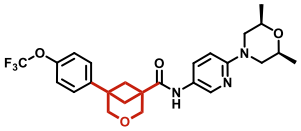
Several representative modifications of oxa-BCH alcohol moiety of compound **2** have been undertaken to show its utility in medicinal chemistry programs (Scheme 4A). Treatment of **2** with Dess-Martin periodinane gave aldehyde **16**, while oxidation with NMO/TPAP yields the tertiary carboxylic acid **22**. Alcohol **2** can be converted into corresponding bromide **21** via Appel reaction or into iodide **20** by displacement of its mesylate analogue **19** with sodium iodide. 4-Fluorophenol can be engaged in a Mitsunobu reaction with **2** giving aryl ether **17**, all in synthetically useful yields. Following the MacMillan deoxygenative Csp^2-Csp^3 coupling procedure with Br-Flumazenil afforded oxa-BCH derivative **18** in 32% yield.[9] Carboxylic acid **22** itself serves as an excellent starting point of diversification: primary and Weinreb amides (**24**, **25**), as well as a redox-active ester (RAE) **26**, can be obtained in a single step (Scheme 4B) in moderate to good yields. Generation of RAE *in situ* using PITU and subsequent with B_2cat_2 under blue LED emission gives tertiary boronic ester **28** in 48% yield.[10] Conversion in tertiary fluoride **27** occurs smoothly using Selectfluor with silver nitrate in 60%. Finally, boc-protected amine **23** can be accessed using Curtius rearrangement. Scheme 4C depicts the synthesis of diester **29**, which, upon lithium hydroxide mediated mono hydrolysis, gives the intermediate **30**. This compound is then further converted into tertiary nitrile **32**, converted to the corresponding primary amide **31** via TFAA dehydration in excellent yield over two steps. Using silica-supported DCC, molecule **30** was converted to the corresponding RAE **33**, which is further engaged in an electrocatalyzed Csp^2-Csp^3 decarboxylative coupling, recently developed by Baran and co-workers, to give product **34** with a promising yield of 21%.[11]

We evaluated the effect of replacing a meta-substituted benzene ring with a 2-oxabicyclo[3.1.1]heptane core on physiochemical and ADME properties (Table 2). For this purpose, we have prepared molecule **36**, an oxa-BCH-containing analogue of the anti-cancer drug Sonidegib **35** (See SI for details). Both molecules **35** and **36** have similar molecular weights and topological polar surface areas. Replacement of *meta*-arene with oxa-BCH decreased the experimental CHI logD value by 0.5 units. Next, we observed that isosteric substitution resulted in a slight decrease of human microsomal stability: 26 uL/min/mg for Sonidegib **36** vs 35 uL/min/mg for oxa-BCH analogue **35** Moreover, the intrinsic permeability was increased for oxa-BCH-Sonidegib, as evident in the MDCK-MDR1 permeability assay, along with reduced the efflux ratio. Finally, a > 2-fold increase in solubility was observed for the saturated analogue **36**, compared to the parent drug **35**: 6.61 vs 2.51 μM in the FaSSIF assay.

Table 2. Physicochemical and metabolic profile of Sonidegib 35 and oxa-BCH-Sonidegib 36



Sonidegib
35

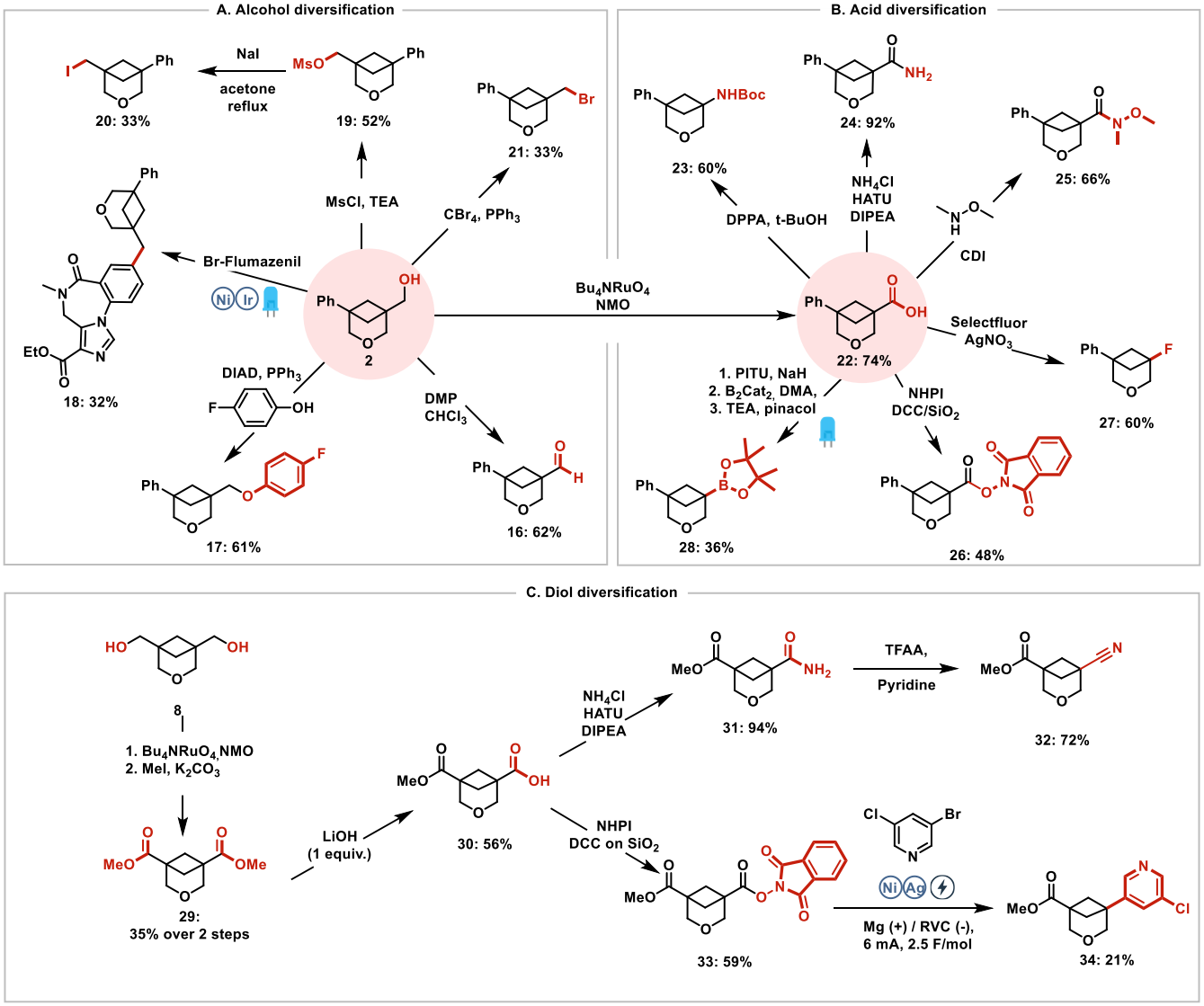


Oxa-BCH-Sonidegib
36

	MW	logD[a]	TPSA[b]	CL_{int} [c]	$t_{1/2}$[d]	P_{app} A>B[e],	P_{app} B>A /A>B[f]	Sol.[g]
35	485	4.1	63.7	26.6	52	0.051	9.47	2.51
36	491	3.54	72.9	35.4	39	7.44	1.72	6.61

[a] Experimental CHI logD at pH7.4; [b] Calculated topological polar surface area, $Å^2$; [c] Intrinsic clearance, human liver microsomes, uL/min/mg; [d] metabolic half-life, min; [e] Cyprotex MDCK-MDR1-KO permeability assay, 10^{-6} cm/sec; [f] Efflux ratio; [g] FASSIF thermodynamic solubility assay, μM.

Scheme 4. Product diversification



In summary, we have developed 3-oxabicyclo[3.1.1]heptanes as novel isosteres of *meta*-substituted phenyl rings, which closely mimic the exit vectors and bond distances of the parent aromatic systems. The oxa-BCH core can be obtained from 2-oxaspiro[3.3]heptan-6-yl methanols under mild conditions using catalytic quantities of pyridinium chloride, has a broad scope and is compatible with acid-sensitive functional groups. We have demonstrated that using this methodology, a variety of building blocks suitable for medicinal chemistry programs can be easily accessed. Finally, we observed the improvement of physicochemical and ADME properties, such as logD, solubility, permeability and efflux ratio, upon incorporation of the oxa-BCH core in the analogue of anticancer drug *Sonidegib*.[12]

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds, along with copies of spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

Pavel Ryabchuk - *Janssen Research & Development, Janssen Pharmaceutica NV, Turnhoutseweg 30, Beerse 2340, Belgium*
ORCID: https://orcid.org/0000-0003-2859-3867
Email: pryabchu@its.jnj.com.

Authors

Jennifer Morvan - *Janssen Research & Development, Janssen Pharmaceutica NV, Turnhoutseweg 30, Beerse 2340, Belgium*
Evelien Renders - *Janssen Research & Development, Janssen Pharmaceutica NV, Turnhoutseweg 30, Beerse 2340, Belgium*
Peter Buijnsters - *Janssen Research & Development, Janssen Pharmaceutica NV, Turnhoutseweg 30, Beerse 2340, Belgium*

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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REFERENCES

1. (a) Subbaiah, M. A. M.; Meanwell, N. A. Bioisosteres of phenyl ring: recent strategic applications in lead optimization and drug design. *J. Med. Chem.* **2021**, *64*, 14046−14128.; (b) Mykhailiuk, P. K. Saturated bioisosteres of benzene: where to go next? *Org. Biomol. Chem.* **2019**, *17*, 2839−2849.
2. (a) Tsien, J.; Hu, C.; Merchant, R. R.; Qin, T. Three-dimensional saturated C(sp3)-rich bioisosteres for benzene. *Nat. Rev.Chem*. **2024**, *8*, 605−627.; (b) Diepers,H. E.; Walker, J. C. L. (Bio)isosteres of ortho- and meta-substitutedbenzenes. *Beilstein J. Org. Chem.* **2024**, *20*, 859−890.; (c) S. Nagasawa, Y. Iwabuchi, Recent Progress in Accessing Multi-functionalized Caged Hydrocarbons: En Route to Highly Functionalized Saturated (Bio)isosteres of Benzene Rings *Synthesis* **2024**, *56*, 10.1055/a-2360-8218.
3. Frank, N.; Nugent, J.; Shire, B. R.; Pickford, H. D.; Rabe, P.;Sterling, A. J.; Zarganes-Tzitzikas, T.; Grimes, T.; Thompson, A. L.;Smith, R. C.; et al. Synthesis of meta-substituted arene bioisosteresfrom [3.1.1]propellane. *Nature* **2022**, *611*, 721−772.
4. Iida, T.;Kanazawa, J.; Matsunaga, T.; Miyamoto, K.; Hirano, K.; Uchiyama,M. Practical and Facile Access to Bicyclo[3.1.1]heptanes: PotentBioisosteres of meta-Substituted Benzenes. *J. Am. Chem. Soc.* **2022**, *144*, 21848−21852.
5. (a) Fominova, K.; Diachuk, T.;Granat, D.; Savchuk, T.; Vilchynskyi, V.; Svitlychnyi, O.; Meliantsev,V.; Kovalchuk, I.; Litskan, E.; Levterov, V. V.; Badlo, V. R.;Vaskevych, R. I.; Vaskevych, A. I.; Bolbut, A. V.; Semeno, V. V.;Iminov, R.; Shvydenko, K.; Kuznetsova, A. S.; Dmytriv, Y. V.;Vysochyn, D.; Ripenko, V.; Tolmachev, A. A.; Pavlova, O.;Kuznietsova, H.; Pishel, I.; Borysko, P.; Mykhailiuk, P. K. Oxa-spirocycles: synthesis, properties and applications. *Chem. Sci.* **2021**, *12*, 11294−11305.; (b) Levterov, V. V.; Panasyuk, Y.; Pivnytska, V. O.; Mykhailiuk, P. K.Water-Soluble Non-Classical Benzene Mimetics. *Angew. Chem., Int. Ed.* **2020**, *59*, 7161−7167.; (c) Levterov, V. V.; Panasiuk, Y.; Shablykin, O.; Stashkevych, O.; Sahun, K.; Rassokhin, A.; Sadkova, I.; Lesyk, D.; Anisiforova, A.; Holota, Y.; Borysko, P.; Bodenchuk, I.; Voloshchuk, N. M.; Mykhailiuk, P. K. 2-Oxabicyclo[2.1.1]hexanes: Synthesis, Properties, and Validation as Bioisosteres of ortho- and meta-Benzenes. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202319831.
6. Dibchak, D.;Snisarenko, M.; Mishuk, A.; Shablykin, O.; Bortnichuk, L.; Klymenko-Ulianov, O.; Kheylik, Y.; Sadkova, I. V.; Rzepa, H. S.; Mykhailiuk, P.K. General Synthesis of 3-Azabicyclo[3.1.1]heptanes and Evaluationof Their Properties as Saturated Isosteres. *Angew. Chem.Int. Ed*. **2023**, *62*, No. e202304246.
7. (a) Kim, K. H.; Lim, J. W.; Lee, J.; Go, M. J.; Kim, J. N. ThermalIntramolecular [2 + 2] Cycloaddition: Synthesis of 3-Azabicyclo[3.1.1]heptanes from Morita−Baylis−Hillman Adduct-Derived 4,4-Diaryl-1,3-dienes. *Adv. Synth. Catal.* **2014**, *356*, 3363−3369. 10.1002/adsc.201400571.; (b) Hang, X.; Li, X.; Li, J.-L.; Wang, Q.-W.; Zou, W.-L.; Liu, Y.-Q.; Jia, Z.-Q.; Peng, F.; Han, B. Regiodivergent construction of medium-sized heterocycles from vinylethylene carbonates andallylidenemalononitriles. *Chem. Sci.* **2020**, *11*, 2888−2894.10.1039/c9sc06377c.; (c) Chen, Z.; Zheng, D.; Wu, J. *Org. Lett.* **2011**, *13*, 848. (d) Li, B.-S.; Yang, B.-M.; Wang, S.-H.; Zhang, Y.-Q.; Cao, X.-P.; Tu, Y.-Q. Copper(i)-catalyzed intramolecular [2 + 2] cycloaddition of 1,6-enyne-derived ketenimine: an efficient construction of strained and bridged 7-substituted-3-heterobicyclo[3.1.1]heptan-6-one, *Chem. Sci.* **2012**, 3, 1975 /10.1039/C2SC20109G.
8. (a) W. P. Cochrane, P. L. Pauson, T. S. Stevens. Synthesis of 3-oxabicyclo[3.1.1]heptanes by rearrangement of 3-oxaspiro[3,3]heptanes. *J. Chem. Soc. C*, **1969**, 2346-2348.; (b) Hopkins, B.; Ma, B. I. N.; Marx, I.; Schulz, J.; Vandeveer, G.; Prince, R.; Nevalainen, M.; Chen, T.; Yousaf, Z.; Himmelbauer, M.; et al. Pyrazolo[1,5-A]pyrazine Derivatives as BTK Inhibitors. *WO WO 2022/104079 A1*, **2022**.
9. Dong, Z.; MacMillan, D. W. C. Metallaphotoredox-enabled deoxygenative arylation of alcohols. *Nature* **2021**, *598*, 451−456.
10. Fawcett, A.; Pradeilles, J.; Wang, Y.; Mutsuga, T.; Myers, E.;Aggarwal, V. Photoinduced Decarboxylative Borylation of CarboxylicAcids. *Science*, **2017**, 357, 283−286.
11. Palkowitz, M. D.; Laudadio, G.; Kolb, S.; Choi, J.;Oderinde, M. S.; Ewing, T. E.-H.; Bolduc, P. N.; Chen, T.; Zhang, H.;Cheng, P. T. W.; Zhang, B.; Mandler, M. D.; Blasczak, V. D.; Richter,J. M.; Collins, M. R.; Schioldager, R. L.; Bravo, M.; Dhar, T. G. M.;Vokits, B.; Zhu, Y.; Echeverria, P.-G.; Poss, M. A.; Shaw, S. A.; Clementson, S.; Petersen, N. N.; Mykhailiuk, P. K.; Baran, P. S. Overcoming Limitations in Decarboxylative Arylation via Ag−Ni Electrocatalysis. *J. Am. Chem. Soc.* **2022**, *144*, 17709−17720.
12. During the preparation of this manuscript a preprint on this subject appeared: Dibchak D, Mykhailiuk P. Water-soluble Bioisosteres of meta-Benzenes. ChemRxiv. 2024; doi:10.26434/chemrxiv-2024-j5wcs.