The LARGEST library of Bicyclo[1.1.1]pentanes for Drug Discovery enabled by Light

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Dedicated to the people of Ukraine

Abstract. In 2012, bicyclo[1.1.1]pentanes were demonstrated to be bioisosteres of the phenyl ring. Today, after more than a decade, the difficulty in their large-scale preparation is still a problem, that often outweighs the corresponding derivatives to becoming clinical candidates. Here, we report a practical general reaction that gives bicyclo[1.1.1]pentanes on mg- to kg-quantities using *just light*. No additional additives or catalysts are needed. Using this strategy, we have prepared >300 functionalized bicyclo[1.1.1]pentanes on a (multi)gram scale. So far, this is the most general and practical approach to bicyclo[1.1.1]pentanes. Many of these molecules, which were previously commercialized, are already being used in drug discovery by pharmaceutical companies *Gilead Sciences*, *Hoffman-La Roche*, *Idorsia*, *Merck*, *Janssen Pharm.*, *etc*.

This work should ease the transition of bicyclo[1.1.1]pentane-containing bioactive compounds to clinical candidates, and subsequently to drugs.

Introduction. The phenyl ring is the most popular ring in bioactive compounds[1] and natural products.[2]

In 2012, *Stepan* and co-workers demonstrated that bicyclo[1.1.1]pentane (BCP) could mimic the *para*-substituted phenyl ring in biologically active compounds (Figure 1).[3] Since then, bicyclo[1.1.1]pentanes have been playing an important role in chemistry.[4,5,6,7] Synthesis and applications of BCPs are already covered in at least 9 recent reviews.[4,5]

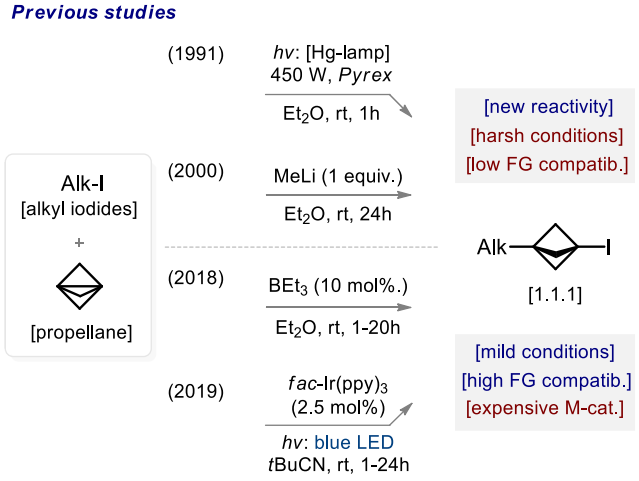
Figure 1. Bicyclo[1.1.1]pentanes (BCPs) as bioisosteres of the phenyl ring.

Despite the numerous studies,[4-7] today, after more than a decade, the lack of scalable methods towards bicyclo[1.1.1]pentanes still often outweighs the corresponding derivatives to becoming clinical candidates. To partially solve this problem, in 2016 pharmaceutical company *Pfizer* initiated a collaboration with *Baran* lab on developing a "strain-release" amination of propellane.[8,9] This study allowed the scalable preparation of *non*-substituted bicyclo[1.1.1]pentyl amines.

In recent years, we received hundreds of requests from pharmaceutical companies regarding the (multi)gram-scale synthesis of unknown functionalized bicyclo[1.1.1]pentanes with an *alkyl substituent*.[10] Aliphatic substituents increase the F(sp^3) content of bioactive molecules, and therefore it is not surprising that medicinal chemists favor using them nowadays.[11]

Results and discussion. ***Optimization***. In a search for a general scalable method for the alkyl-substituted bicyclo[1.1.1]pentanes, we focused our attention on the reaction of alkyl iodides with propellane. In 1991, this reaction was shown to take place under irradiation with a broad-wavelength Hanovia mercury lamp in a Pyrex vessel (Scheme 1).[12] In 2000, it was demonstrated that the addition of an equimolar amount of methyl lithium also promoted the reaction (Scheme 1).[13] The challenges associated with ultraviolet irradiation in Pyrex glassware and the low compatibility of methyl lithium with functional groups lowered the practical potential of both methods and prevented their wide application in the future.[14] In 2018, *Anderson* and colleagues solved the above-mentioned problems by discovering that triethylborane catalyzed the reaction leading to the formation of products in good yields (Scheme 1).[15,16] In 2019, the same authors improved the reaction scope even further by performing the reaction in the presence of *fac*-Ir(ppy)$_3$ catalyst under photoredox conditions.[17,18] The only disadvantage of the latter method was the relatively high price of the metal catalyst.[19,20]

Known approaches towards alkyl-substituted bicyclo[1.1.1]pentanes are depicted in Scheme 1. These reactions were described mostly on a milligram scale. Therefore, we decided to try these protocols in gram quantities with the model methyl iodide. The latter substrate was selected because the methyl radical is the most unstable among all common alkyl radicals. We envisioned that if we could elaborate on a scalable protocol for the reaction of methyl iodide, it would work with other alkyl iodides as well.

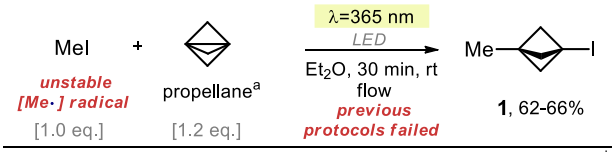


Scheme 1. Approaches to alkyl-substituted bicyclo[1.1.1]pentyl iodides.

The reaction of methyl iodide with the freshly prepared propellane (1.2 eq.) in the presence of methyl lithium[13] or iodine gave only traces of the needed product **1** (Table 1, entries 1, 2). Catalysis with BEt_3[15] gave the product **1** in 31% yield, however, an extensive formation of polymeric products was observed

(entry 3). Catalysis with *fac*-Ir(ppy)$_3$[17] led to the formation of a complex mixture (entries 4, 5). With a double excess of propellane, however, we obtained iodide **1** in 14% yield. Next, we attempted the reaction under various photochemical conditions with no catalysts/additives (entries 7-10). Irradiation of the reaction mixture at 254 nm or 310 nm gave <20% of the needed product (entries 7, 8). Irradiation at 450 nm (blue LED light) did not promote the reaction (entry 10). However, irradiation at 365 nm allowed obtaining the desired product **1** in 43% yield. Moreover, after further optimization, we found that performing this photochemical reaction in flow for thirty minutes allowed increasing the yield to 62%.

Table 1. Optimization of synthesis of bicyclo[1.1.1]pentane **1**.



entry	conditions	yield (%)[b]
1	MeLi (1 eq.), rt, 24h	5
2	I_2 (0.25% mol.), rt, 24h	16
3	BEt_3 (10% mol.), Et_2O, rt, 24h	31
4	*fac*-Ir(ppy)$_3$ (2.5% mol.), Et_2O, 450 nm, 12h	*polym-n*
5	*fac*-Ir(ppy)$_3$ (2.5% mol.), *t*BuCN, 450 nm, 12h	*polym-n*
6	*fac*-Ir(ppy)$_3$ (2.5% mol.), *t*BuCN, 450 nm, 12h, 2 eq. prop-e	14
7	254 nm, Et_2O, rt, 24h	12
8	310 nm, Et_2O, rt, 24h	17
9	365 nm, Et_2O, rt, 24h	43
10	450 nm, Et_2O, rt, 24h	<5
11	365 nm, Et_2O, rt, 30 min, in flow	62 (66)[c]
12	rt, 10 min *(control)*	*n.d.*
13	rt, 12h	*n.d.*
14	rt, 24h	*n.d.*

Scale: 10 g of MeI in each experiment. [a] Solution of propellane (0.7M) in Et_2O-$CH_2(OEt)_2$. [b]Isolated yield. Distillation as a purification method. [c] Crystallization from pentane as a purification method.

Worth noting that all experiments depicted in Table 1 were performed under standardized conditions: methyl iodide (10 grams; 1 eq.), and propellane (1.2 eq.). In each experiment, the product was isolated by distillation under reduced pressure. Under the photochemical conditions in flow (entry 11), isolation of iodide **1** by low-temperature crystallization from pentane gave an even higher yield of the product: 66%. Importantly, having an optimized protocol in hand, we easily synthesized iodide **1** in 855 g amount in one run with almost no additional modifications (Scheme 2; Supporting Information, page S60).

Scope. We also studied the generality of the developed method. First, we tried other primary alkyl iodides (Scheme 2). Given the rise of deuterated compounds in modern drug discovery,[21] we performed an addition of CD_3I to propellane under standard conditions to obtain product D_3-**1** in 68% yield. The reaction worked well with other alkyl iodides (**3**-**7**), oxetane-containing substrates (**8**-**10**), tetrahydrofuran (**11**), and tetrahydropyran-containing molecules (**12**, **13**). *N*-Boc-protected azetidines (**14**), pyrrolidines (**15**), and piperidines (**16**, **17**) performed equally well in the reaction. In addition, BPin (**18**), $PO(OEt)_2$ (**19**), and *t*BuC(O)O groups (**20**) were compatible with the reaction conditions. Given the importance of organofluorine compounds in modern medicinal chemistry,[22] we performed the reaction with various fluorinated alkyl iodides to obtain bicyclo[1.1.1]pentanes **21**-**27** in 69-92% yield. The structure of products **14** and **19** was confirmed by X-ray analysis.[23]

Various labile functional groups, such as nitrile (**28**-**30**), ester (**31**-**33**), active chlorine (**34**), and bromine atoms (**35**), alcohol (**36**, **37**), and NHBoc (**38**-**40**) were compatible with the reaction conditions. Diverse medicinal chemistry-relevant cores including 2-oxabicyclo[2.1.1]hexane[24] (**44**) and oxa-spirocycles[25] (**45**) also gave the desired bicyclo[1.1.1]pentanes **41**-**47** in 41-63% yield.

Next, we studied the behavior of secondary alkyl iodides (Scheme 3). The protocol efficiently worked for isopropyl (**48**), isobutyl (**49**), and cycloalkyl (**50**-**54**) alkyl iodides. Four-to-six-membered rings with oxygen (**55**-**58**), sulfur (**59**), and *N*-Boc (**60**-**64**) gave the desired products in 30-92% yield. Secondary ($MeCH(I)CO_2tBu$) and tertiary ($Me_2C(I)CO_2tBu$) iodides also reacted with propellane to provide products **65**, **66** in lower yields of 25-36%.[26] Various fluoroalkyl iodides (**67**-**73**)[27] and even bromides (**74**-**78**)[28] were compatible with the reaction conditions. The structure of product **55** was confirmed by X-ray analysis.[23]

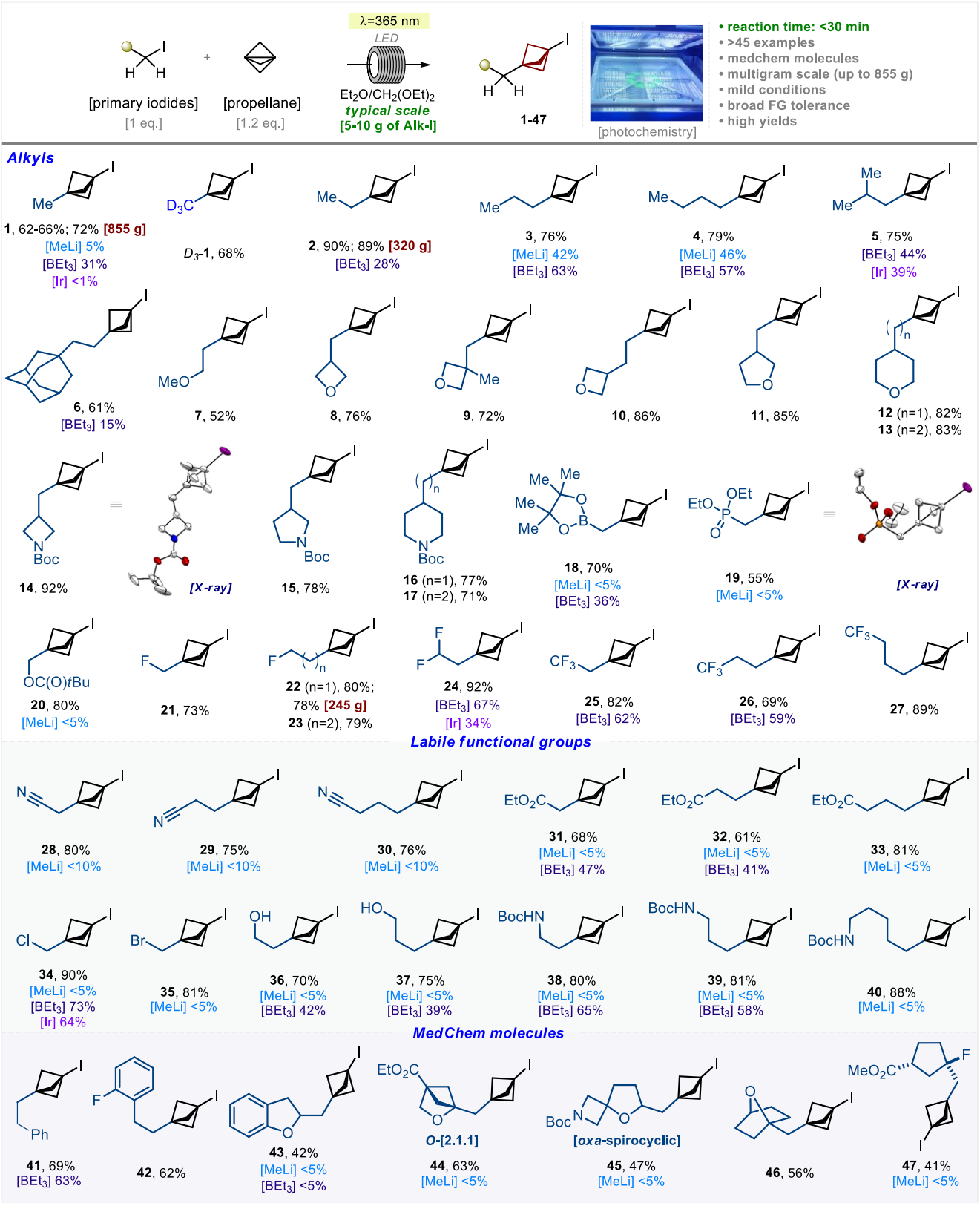
Recently, bicyclo[3.1.1]heptanes were proposed to mimic the *meta*-substituted phenyl ring in bioactive compounds.[29,30] In this context, we studied the reaction of [3.1.1]-propellane with two representative alkyl iodides under the above-developed conditions. Remarkably, the desired bicyclo[3.1.1]heptanes **79** (45%) and **80** (38%) were obtained as a result of these efforts.

From a practical standpoint, most of the syntheses depicted in Schemes 2 and 3 were performed with five to ten grams of the starting alkyl iodides. The typical reaction time was less than thirty minutes. The reaction required no additional catalysts or additives. Only syntheses of bicyclo[1.1.1]pentanes **6**, **40**, **42**-**47** were performed on a smaller scale due to the low availability of the corresponding alkyl iodides.

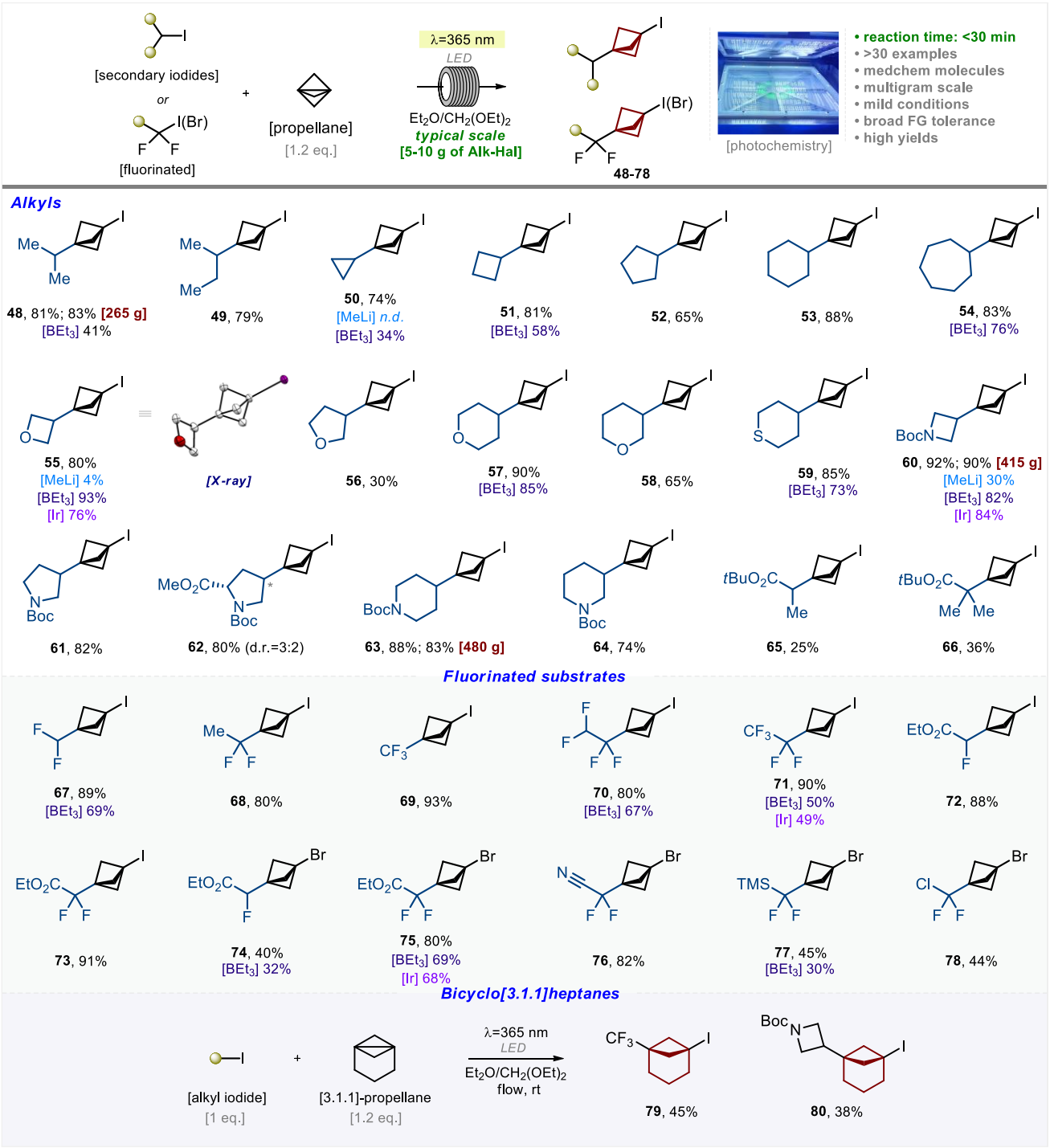
For most examined substrates, we compared the performance of our protocol to prior literature protocols on the same scale (Scheme 2 and 3). Although, MeLi gave poor yields of the desired products bearing functional groups; catalysis with triethylborane often gave good results (**3**-**5**, **55**, **57**, **60**, *etc*). Nonetheless, the photochemical protocol developed here gave the highest yields of products in all examined cases.

We could also repeat the synthesis of bicyclo[1.1.1]pentanes **1**-**3**, **5**, **7**, **14**-**16**, **21**-**27**, **48**, **50**, **55**, **57**, **59**-**63**, **67**-**69**, **71**, **75**, and **77** on 50-800 gram scale with similar yields in one run (Schemes 2 and 3; Supporting Information, pages S60-S68).

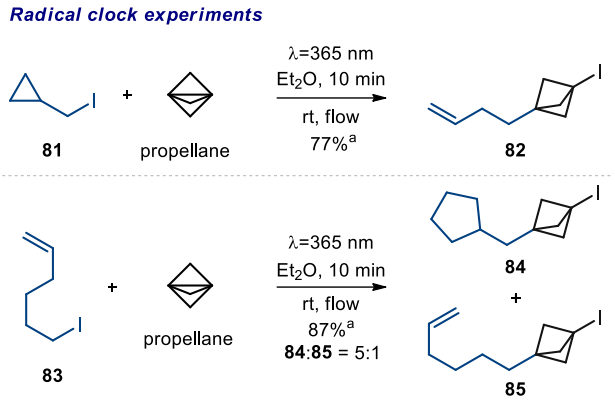
Mechanism. Product **62** (Scheme 3) was obtained from the derivative of the optically pure (2*S*,4*S*)-4-iodoproline as a 3:2 mixture of two diastereomers at *C*(4)-atom (Scheme 3). This observation suggested the radical mechanism of the reaction with the initial formation of the configurationally unstable alkyl radicals. To validate this hypothesis, we performed “radical clock” experiments.[31] Alkyl iodide **81** reacted with propellane under the developed conditions to selectively form the ring-opened alkene **82** (Scheme 4; Supporting Information, pages S69-S74). In the NMR of the crude reaction mixture, we did not observe even traces of signals of the cyclopropane ring. Similarly, the reaction of alkyl iodide **83** with propellane gave mostly the rearranged cyclopentane-containing product **84** with only traces of alkene **85** (**84**:**85**=5:1; Scheme 4; Supporting Information, pages S69, S76). These experiments supported the original hypothesis of the radical pathway of the reaction.



Scheme 2. *Reaction conditions*: A solution of alkyl iodide (1 eq.) and propellane (0.7M in $Et_2O/CH_2(OEt)_2$; 1.2 eq.) in diethyl ether was passed through a coil (irradiated area: 160 mL) with a flow rate 10 mL/min under irradiation with 365 nm LED (radiated power: 420 W). Residence time: 16 min. Typical scale 5-10 g of alkyl iodide. Compounds **1**, **2**, and **22** were additionally obtained on a multigram scale. Synthesis of compounds **6**, **40**, **42**-**47** was performed on 0.1-2 g scale (irradiated coil: 7.6 mL; flow rate: 0.75 mL/min; irradiation: 365 nm LED; radiated power: 257 W; residence time: 10.1 min.). [MeLi]: MeLi (1 eq.), $CH_2(OEt)_2$, 24h, rt. [BEt_3]: BEt_3 (0.1 eq.), Et_2O, 24h, rt; [Ir]. *fac*-Ir(ppy)$_3$ (2.5% mol.), *t*BuCN, 12h, rt. X-ray crystal structure of compounds **14** and **19**. Hydrogen atoms are omitted for clarity.



Scheme 3. *Reaction conditions*: A solution of alkyl iodide (1 eq.) and propellane (0.7M in $Et_2O/CH_2(OEt)_2$; 1.2 eq.) in diethyl ether was passed through a coil (irradiated area: 160 mL) with a flow rate 10 mL/min under irradiation with 365 nm LED (radiated power: 420 W). Residence time: 16 min. Typical scale 5-10 g of alkyl iodide. Compounds **48**, **60**, and **63** were also obtained on a multigram scale. [MeLi]: MeLi (1 eq.), $CH_2(OEt)_2$, 24h, rt; [BEt_3]: BEt_3 (0.1 eq.), Et_2O, 24h, rt; [Ir]: *fac*-Ir(ppy)$_3$ (2.5% mol.), *t*BuCN, 15h, rt. X-ray crystal structure of compound **55**. Hydrogen atoms are omitted for clarity.



Scheme 4. Radical clock experiments with iodides **81** and **83**. [a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

Bicyclo[1.1.1]pentanes for medicinal chemistry. Having a practical and scalable protocol towards alkyl bicyclo[1.1.1]pentyl iodides in hand, we converted them into various BCP-containing building blocks (compounds with one or two functional groups) for medicinal chemistry. Treatment of BCP-iodides with *t*-BuLi in THF followed by trapping of the formed carboanion with (*i*PrO)BPin gave boron pinacolates "**a**" (Scheme 5).[32] The reaction of the latter with potassium fluoride in an acetone/water mixture smoothly gave trifluoroborates "**b**." Oxidation of boron pinacolates with H_2O_2 gave alcohols "**c**."[33]

Lithiation of BCP-iodides followed by the addition of diverse electrophiles was studied in the next step. Reaction with BocN=NBoc followed by acidic *N*-Boc deprotection produced hydrazines "**d**" (Scheme 5).[34] Reaction with sulfur dioxide followed by oxidative chlorination of the intermediate sulfinate salts gave sulfonyl chlorides "**e**".[35] Reaction with hexachloroethane afforded BCP-chlorides "**f**". Analogous reaction with 1,1,2,2-tetrabromo-1,2-difluoroethane provided BCP-bromides "**g**". The addition of CD_3OD followed by *N*-Boc deprotection gave deuterated amines **60h** and **63h**. The addition of ethyl formate gave aldehydes "**i**". Treatment of *C*-anions with methanol followed by optional hydrolysis of the ester group or *N*-Boc deprotection gave *mono*-substituted bicyclo[1.1.1]pentanes: carboxylic acids, amines, and alcohols "**j**". Reaction with dry ice gave carboxylic acids "**k**".[36] Standard Curtius reactions of the latter gave unique amines "**l**".[37]

Using this strategy, during the past five years, we have prepared >200 functionalized bicyclo[1.1.1]pentanes on a (multi)gram scale (Scheme 5). So far, this is the most general and practical approach to bicyclo[1.1.1]pentanes. Many of these molecules (**2k**, **21l**, **55k**, **60i**, **60j**, **60k**, **62j**, **67c**, **67l**, **69c**, **69e**) which were previously commercialized[10] and preparation of which has not been reported before anywhere, are already being used in drug discovery by pharmaceutical companies *Gilead Sciences, Hoffman-La Roche, Idorsia, Merck, Janssen Pharm.*, *etc* (Figure 2; for full details, please, see the Supporting Information, pages S161-S165).[38]

Compounds from this work have also found solid application in research projects by other academic groups: *Hartwig* (**14j**, **61j**, **73j**)[39] and *Gomez* (**21**, **25**, **55**, **57**, **60**, **63**, **67**, **69**).[40] For the details, please, see the Supporting Information, page S166.

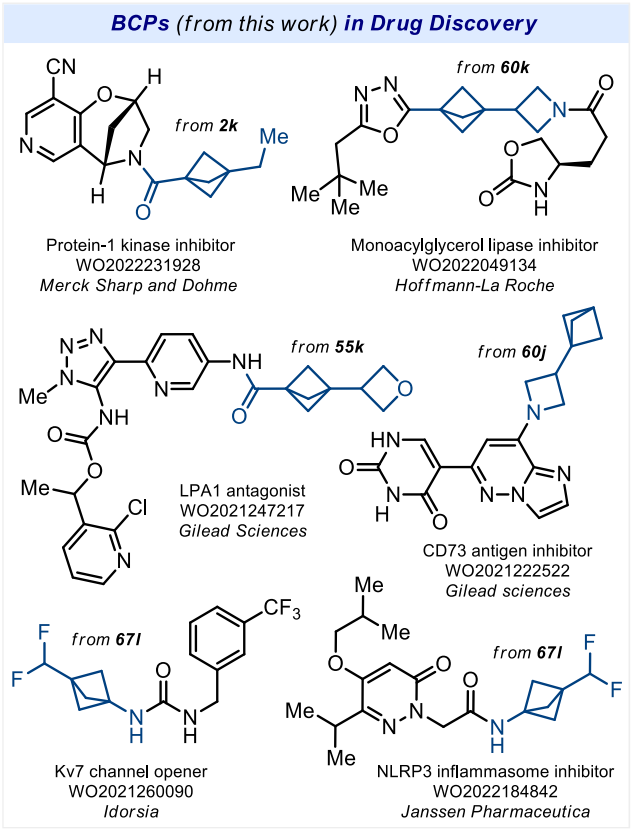
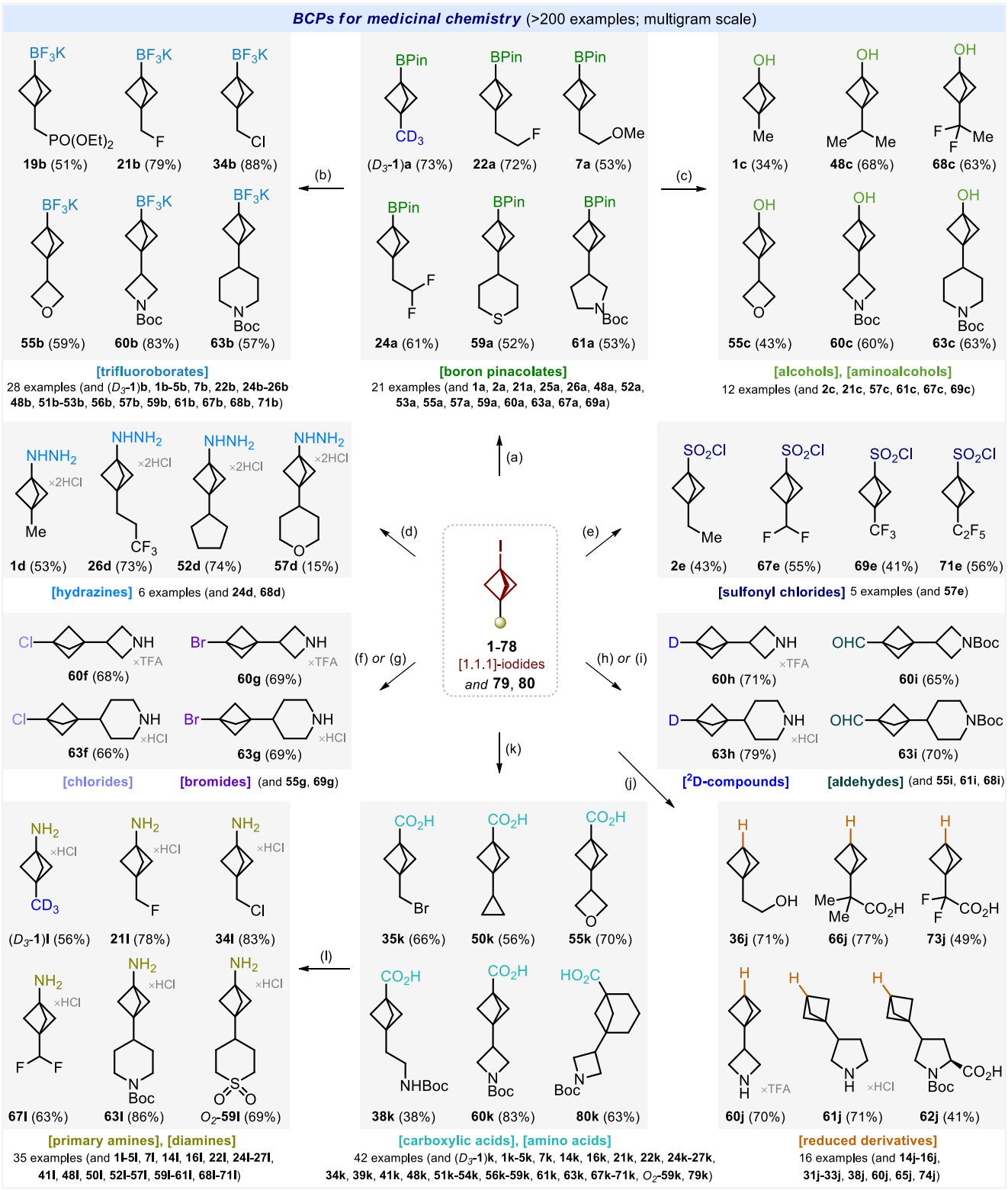


Figure 2. Representative bicyclo[1.1.1]pentanes **2k**, **55k**, **60k**, **60j**, **67l** from this work in drug discovery projects of pharmaceutical companies.

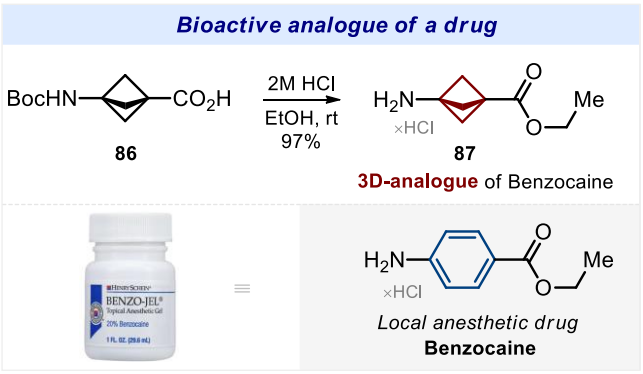
Incorporation into a drug. In addition to existing studies (Figure 1),[3,4] we validated the bicyclo[1.1.1]pentane scaffold as a phenyl ring bioisostere. We incorporated this core into a structure of an FDA-approved local anesthetic drug *Benzocaine* (Scheme 6) instead of the phenyl ring. The compound was synthesized from *N*-Boc amino acid **86**. Acidic *N*-Boc cleavage and the simultaneous esterification of the carboxyl group gave the desired analog **87** as a hydrochloride salt.

Biological activity. We measured the experimental anesthetic activity of *Benzocaine* and its analog **87** *in vivo*. We studied the antinociceptive effect of *Benzocaine* and compound **87** using the "tail flick test"[41] in 2-month-old CD-1 female mice (for details, see the Supporting Information, pages S819-S825).[42] The results are presented in Figures 3 and 4. On one hand, compound **87** was found to be less active compared to the original drug *Benzocaine* - no significant difference in response time to tail flick was present throughout the observation period. On the other hand, analog **87** demonstrated a clear analgesic activity - a significant increase in coverage of analgesia by time (AUC level) compared to that of the vehicle (Figure 4).

This biological experiment corroborated the hypothesis that bicyclo[1.1.1]pentane is an actual bioisostere of the phenyl ring.



Scheme 5. Modifications of bicyclo[1.1.1]pentyl and bicyclo[3.1.1]heptyl iodides. *Reaction conditions*: (a) (*i*PrO)BPin, *t*-BuLi, Et_2O, -100 °C; (b) KHF_2, acetone/water, rt; (c) KH_2PO_4, H_2O_2, THF/water, rt; (d) (i) BocN=NBoc, *t*-BuLi, Et_2O, -100 °C; (ii) dioxane-HCl, rt; (e) (i) *t*-BuLi, SO_2, Et_2O; (ii) Cl_2, CH_2Cl_2/H_2O, 0-5 °C; (f) (i) *t*-BuLi, Cl_3CCCl_3, Et_2O, -100 °C; (ii) deprotection: HCl/dioxane or TFA/CH_2Cl_2; (g) (i) *t*-BuLi, $C_2Br_2F_4$, Et_2O, -100 °C; (ii) deprotection: HCl/dioxane or TFA/CH_2Cl_2; (h) (i) *t*-BuLi, CD_3OD, Et_2O, -100 °C; (ii) deprotection: HCl/dioxane or TFA/CH_2Cl_2; i) *t*-BuLi, ethyl formate, Et_2O, -100 °C; (j) *t*-BuLi, MeOH, Et_2O, -100 °C; (k) *t*-BuLi, CO_2, Et_2O, -80 °C; (l) (i) DPPA, Et_3N, *t*-BuOH, 95 °C; (ii) HCl-dioxane, Et_2O, rt.



Scheme 6. Synthesis of saturated analog of local anesthetic drug *Benzocaine* – compound **87**.

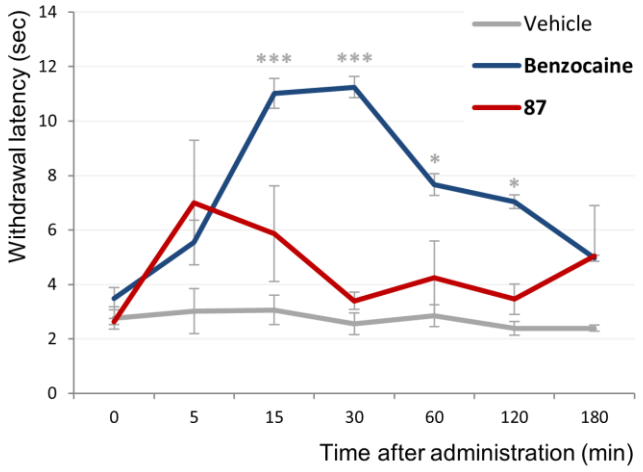


Figure 3. Time course of the antinociceptive effect of *Benzocaine* and its analog **87** in tail flick test. The data were presented as mean ± SEM. * - indicates P < 0.05; and *** - indicates P < 0.001 compared with the control group (vehicle).

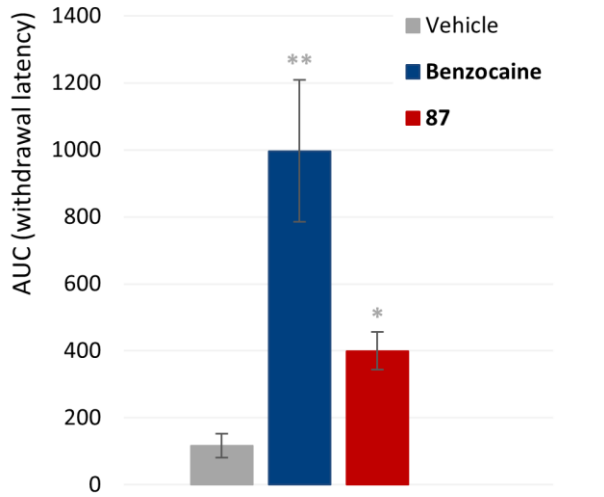


Figure 4. The area under the curve (AUC) of withdrawal latency of *Benzocaine* and its analog **87** in a tail flick test. The data were presented as mean ± SEM. * - indicates P < 0.05; ** - P < 0.01 compared with the control group (vehicle).

Summary. In 2012, bicyclo[1.1.1]pentanes were demonstrated to mimic the phenyl ring in bioactive compounds.[3] Today, after more than a decade, the difficulty in their large-scale preparation is still a problem. Here, we report a general practical reaction between alkyl iodides and propellane that gives alkyl-substituted bicyclo[1.1.1]pentanes in milligram to kilogram quantities. The reaction proceeds under light and requires no additional additives or catalysts. Using this strategy, during the past five years, we have prepared more than three hundred functionalized bicyclo[1.1.1]pentanes on a (multi)gram scale. So far, this is the most general and practical approach towards bicyclo[1.1.1]pentanes. Many of these molecules, which were previously commercialized, are already being used in drug discovery by pharmaceutical companies[38] and academic groups.[39,40]

We expect that this work will ease the transition of bicyclo[1.1.1]pentane-containing bioactive compounds to clinical candidates, and subsequently to drugs.

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Keywords: bicyclo[1.1.1]pentane • BCP • medicinal chemistry • light • drugs

References

[1] (a) R. D. Taylor, M. MacCoss, A. D. G. Lawson. Rings in Drugs. *J. Med. Chem.* **2014**, *57*, 5845-5859. (b) J. Shearer, J. L. Castro, A. D. G. Lawson, M. MacCoss, R. D. Taylor. Rings in Clinical Trials and Drugs: Present and Future. *J. Med. Chem.* **2022**, *65*, 8699-8712.

[2] Y. Chen, C. Rosenkranz, S. Hirte, J. Kirchmair. Ring systems in natural products: structural diversity, physicochemical properties, and coverage by synthetic compounds. *Nat. Prod. Rep.* **2022**, *39*, 1544-1556.

[3] A. F. Stepan, C. Subramanyam, I. V. Efremov, J. K. Dutra, T. J. O`Sullivan, K. J. DiRico, W. S. McDonald, A. Won, P. H. Dorff, C. E. Nolan, S. L. Becker, L. R. Pustilnik, D. R. Riddell, G. W. Kauffman, B. L. Kormos, L. Zhang, Y. Lu, S. H. Capetta, M. E. Green, K. Karki, E. Sibley, K. P. Atchison, A. J. Hallgren, C. E. Oborski, A. E. Robshaw, B. Sneed, C. J. O`Donnell, Application of the Bicyclo[1.1.1]pentane Motif as a Nonclassical Phenyl Ring Bioisostere in the Design of a Potent and Orally Active γ-Secretase Inhibitor. *J. Med. Chem.* **2012**, *55*, 3414-3424.

[4] Reviews on the application of bicyclo[1.1.1]pentanes: P. K. Mykhailiuk. Saturated bioisosteres of benzene: where to go next? *Org. Biomol. Chem.* **2019**, *17*, 2839-2849. b) G. M. Locke, S. S. R. Bernhard, M. O. Senge. Nonconjugated Hydrocarbons as Rigid-Linear Motifs: Isosteres for Material Sciences and Bioorganic and Medicinal Chemistry. *Chem. Eur. J.* **2019**, *25*, 4590-4647. (c) L. K. Macreadie, K. B. Idrees, C. S. Smoljan, O. K. Farha. Expanding Linker Dimensionality in Metal-organic Frameworks for sub-Ångstrom Pore Control for Separation Applications. *Angew. Chem. Int. Ed.* **2023**, e202304094. (d) M. A. M. Subbaiah, N. A. Meanwell. Bioisosteres of the Phenyl Ring: Recent Strategic Applications in Lead Optimization and Drug Design. *J. Med. Chem.* **2021**, *64*, 14046–14128.

[5] Reviews on the synthesis of bicyclo[1.1.1]pentanes: (a) J. Kanazawa, M. Uchiyama Recent Advances in the Synthetic Chemistry of Bicyclo[1.1.1]pentane. *Synlett* **2019**, *30*, 1-11. (b) X. Ma, L. N. Pham, Selected Topics in the Syntheses of Bicyclo[1.1.1]Pentane (BCP) Analogues. *Asian J. Org. Chem.* **2020**, *9*, 8-22. (c) F.-S. He, S. Xie, Y. Yao, J. Wu, Recent advances in the applications of [1.1.1]propellane in organic synthesis. *Chin. Chem. Lett.* **2020**, 3065-3072. (d) J. M. Anderson, N. D. Measom, J. A. Murphy, D. L. Poole, Bridge Functionalisation of Bicyclo[1.1.1]pentane Derivatives. *Angew. Chem. Int. Ed.* **2021**, *60*, 24754-24769. (e) B. R. Shire, E. A. Anderson. Conquering the Synthesis and Functionalization of Bicyclo[1.1.1]pentanes. *JACS Au* **2023**, *in press* (doi.org/10.1021/jacsau.3c00014).

[6] Representative examples of applications of bicyclo[1.1.1]pentanes in medicinal chemistry, peptide studies and supramolecular chemistry: a) K. C. Nicolaou, D. Vourloumis, S. Totokotsopoulos, A. Papakyriakou, H. Karsunky, H. Fernando, J. Gavrilyuk, D. Webb, A. F. Stepan, Synthesis and Biopharmaceutical Evaluation of Imatinib Analogues Featuring Unusual Structural Motifs. *ChemMedChem*, **2016**, *11*, 31-37. b) N. D. Measom, K. D. Down, D. J. Hirst, C. Jamieson, E. S. Manas, V. K. Patel, D. O. Somers. Investigation of a Bicyclo[1.1.1]pentane as a Phenyl Replacement within an $LpPLA_2$ Inhibitor. *ACS Med. Chem. Lett.* **2017**, 8, 43-48. c) Y. L. Goh, Y. T. Cui, V. Pendharkar, V. A. Adsool. Toward Resolving the Resveratrol Conundrum: Synthesis and *in Vivo* Pharmacokinetic Evaluation of BCP–Resveratrol. *ACS Med. Chem. Lett.* **2017**, *8*, 516-520. d) Q. Pu, H. Zhang, L. Guo, M. Cheng, A. C. Doty, H. Ferguson, X. Fradera, C. A. Lesburg, M. A. McGowan, J. R. Miller, P. Geda, X. Song, K. Otte, N. Sciammetta, N. Solban, W. Yu, D. L. Sloman, H. Zhou, A. Lammens, L. Neumann, D. J. Bennett, A. Pasternak, Y. Han. Discovery of Potent and Orally Available Bicyclo[1.1.1]pentane-Derived Indoleamine-2,3-dioxygenase 1 (IDO1) Inhibitors. *ACS Med. Chem. Lett.* **2020**, *11*, 1548–1554. e) P. K. Mikhailiuk, S. Afonin, A. N. Chernega, E. B. Rusanov, M. O. Platonov, G. G. Dubinina, M. Berditsch, A. S. Ulrich, I. V. Komarov. Conformationally Rigid Trifluoromethyl-Substituted α-Amino Acid Designed for Peptide Structure Analysis by Solid-State ^{19}F NMR Spectroscopy. *Angew. Chem. Int. Ed.* **2006**, *45*, 5659-5661. f) S. O. Kokhan, A. V. Tymtsunik, S. L. Grage, S. Afonin, O. Babii, M. Berditsch, A. V. Strizhak, D. Bandak, M. O. Platonov, I. V. Komarov, A. S. Ulrich, P. K. Mykhailiuk Design, Synthesis, and Application of an Optimized Monofluorinated Aliphatic Label for Peptide Studies by Solid-State ^{19}F NMR Spectroscopy. *Angew. Chem. Int. Ed.* **2016**, *55*, 14788-14792. g) B. Yang, K. Niu, N. Cao, N. Grover, W. Zhao, A. Riss, J. Björk, W. Auwärter, J. V. Barth, M. O. Senge. On-Surface Synthesis of Polyphenylene Wires Comprising Rigid Aliphatic Bicyclo[1.1.1]Pentane Isolator Units. *Angew. Chem. Int. Ed.* **2023**, *62*, e202218211. h) N. Grover, M. Cheveau, B. Twamley, C. J. Kingsbury, C. M. Mattern, M. O. Senge. Bicyclo[1.1.1]pentane Embedded in Porphyrinoids. *Angew. Chem. Int. Ed.* **2023**, *62*, e202302771.

[7] 1,2-Disubstituted bicyclo[1.1.1]pentanes: a) X. Ma, Y. Han, D. J. Bennett. Selective Synthesis of 1-Dialkylamino-2-alkylbicyclo-[1.1.1]pentanes. *Org. Lett.* **2020**, *22*, 9133–9138. b) J.-X. Zhao, Y.-X. Chang, C. He, B. J. Burke, M. R. Collins, M. D. Bel, J. Elleraas, G. M. Gallego, T. P. Montgomery, J. J. Mousseau, S. K. Nair, M. A. Perry, J. E. Spangler, J. C. Vantourout, P. S. Baran 1,2-Difunctionalized bicyclo[1.1.1]pentanes: Long–sought-after mimetics for ortho/meta-substituted arenes. *PNAS* **2020**, *118*, e2108881118. (c) Y. Yang, J. Tsien, J. M. E. Hughes, B. K Peters, R. R. Merchant, T. Qin. An intramolecular coupling approach to alkyl bioisosteres for the synthesis of multisubstituted bicycloalkyl boronates. *Nat. Chem.* **2021**, *13*, 950-955. (d) X. Ma, D. L. Sloman, Y. Han, D. J. Bennett. A Selective Synthesis of 2,2-Difluorobicyclo[1.1.1]pentane Analogues: "BCP-F_2" *Org. Lett.* **2019**, *21*, 7199–7203. (e) R. M. Bychek, V. Hutskalova, Y. P. Bas, O. A. Zaporozhets, S. Zozulya, V. V. Levterov, P. K. Mykhailiuk. Difluoro-Substituted Bicyclo[1.1.1]pentanes for Medicinal Chemistry: Design, Synthesis, and Characterization. *J. Org. Chem.* **2019**, *84*, 15106−15117. (f) J. M. Anderson, N. D. Measom, J. A. Murphy, D. L. Poole. Bridge Heteroarylation of Bicyclo[1.1.1]pentane Derivatives. *Org. Lett.* **2023**, *25*, 2053–2057. (g) R. Bychek, P. K. Mykhailiuk. A Practical and Scalable Approach to Fluoro-Substituted

Bicyclo[1.1.1]pentanes. *Angew. Chem. Int. Ed.* **2022**, *61*, e202205103. (h) O. L. Garry, M. Heilmann, J. Chen, Y. Liang, X. Zhang, X. Ma, C. S. Yeung, D. J. Bennett, D. W. C. MacMillan. Rapid Access to 2-Substituted Bicyclo[1.1.1]pentanes. *J. Am. Chem. Soc.* **2023**, *145*, 3092–3100. (i) B. A. Wright, A. Matviitsuk, M. J. Black, P. García-Reynaga, L. E. Hanna, A. T. Herrmann, M. K. Ameriks, R. Sarpong, T. P. Lebold. Skeletal Editing Approach to Bridge-Functionalized Bicyclo[1.1.1]pentanes from Azabicyclo[2.1.1]hexanes. *J. Am. Chem. Soc.* **2023**, *145*, 10960–10966.

[8] R. Gianatassio, J. M. Lopchuk, J. Wang, C.-M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran. Strain-release amination. *Science*, **2016**, *351*, 241-246

[9] J. M. Lopchuk, K. Fjelbye, Y. Kawamata, L. R. Malins, C.-M. Pan, R. Gianatassio, J. Wang, L. Prieto, J. Bradow, T. A. Brandt, M. R. Collins, J. Elleraas, J. Ewanicki, W. Farrell, O. O. Fadeyi, G. M. Gallego, J. J. Mousseau, R. Oliver, N. W. Sach, J. K. Smith, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran. Strain-Release Heteroatom Functionalization: Development, Scope, and Stereospecificity. *J. Am. Chem. Soc.* **2017**, *139*, 3209–3226.

[10] Authors are employees of a chemical supplier Enamine (www.enamine.net).

[11] a) F. Lovering, J. Bikker, C. Humblet. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752-6756. b) F. Lovering. Escape from Flatland 2: complexity and promiscuity. *Med. Chem. Commun.* **2013**, *4*, 515-519.

[12] P. Kaszynski, N. D. McMurdie, J. Michl. Synthesis of Doubly Bridgehead Substituted Bicyclo[1.1.1]pentanes. Radical Transformations of Bridgehead Halides and Carboxylic Acids. *J. Org. Chem.* **1991**, *56*, 307-316.

[13] M. Messner, S. I. Kozhushkov, A. de Meijere. Nickel- and Palladium-Catalyzed Cross-Coupling Reactions at the Bridgehead of Bicyclo[1.1.1]pentane Derivatives – A Convenient Access to Liquid Crystalline Compounds Containing Bicyclo[1.1.1]pentane Moieties. *Eur. J. Org. Chem.* **2000**, 1137-1155.

[14] (a) P. Kaszynski, A. C. Friedli, J. Michl. Toward a molecular-size tinkertoy construction set. Preparation of terminally functionalized [n]staffanes from [1.1.1]propellane. *J. Am. Chem. Soc.* **1992**, *114*, 601–620. (b) K. B. Wiberg, N. McMurdie. Formation and Reactions of Bicyclo[1.1.1]pentyl-1 Cations. *J. Am. Chem. Soc.* **1994**, *116*, 11990–11998. (c) V. K. Vyas, G. J. Clarkson, M. Wills. Enantioselective Synthesis of Bicyclopentane-Containing Alcohols via Asymmetric Transfer Hydrogenation. *Org. Lett.* **2021**, *23*, 3179–3183. (d) Paul I. Dron, K. Zhao, J. Kaleta, Y. Shen, J. Wen, R. K. Shoemaker, C. T. Rogers, J. Michl. Bulk Inclusions of Pyridazine-Based Molecular Rotors in Tris(o-phenylenedioxy)cyclotriphosphazene (TPP). *Adv. Funct. Mater.* **2016**, *26*, 5718-5732. (e) J. Kaleta, M. Nečas, C. Mazal. 1,3-Diethynylbicyclo[1.1.1]pentane, a Useful Molecular Building Block. *Eur. J. Org. Chem.* **2012**, *25*, 4783-4796.

[15] D. F. J. Caputo, C. Arroniz, A. B. Dürr, J. J. Mousseau, A. F. Stepan, S. J. Mansfield, E. A. Anderson, Synthesis and applications of highly functionalized 1-halo-3-substituted bicyclo[1.1.1]pentanes. *Chem. Sci.* **2018**, *9*, 5295−5390.

[16] (a) M. L. J. Wong, J. J. Mousseau, S. J. Mansfield, E. A. Anderson. Synthesis of Enantioenriched α-Chiral Bicyclo[1.1.1]pentanes. *Org. Lett.* **2019**, *21*, 2408−2411. (b) J. Nugent, B. R. Shire, D. F. J. Caputo, H. D. Pickford, F. Nightingale, I. T. T. Houlsby, J. J. Mousseau, E. A. Anderson. Synthesis of All-Carbon Disubstituted Bicyclo[1.1.1]pentanes by Iron-Catalyzed Kumada Cross-Coupling. *Angew. Chem. Int. Ed.* **2020**, *59*, 11866−11870. (c) H. D. Pickford, J. Nugent, B. Owen, J. J. Mousseau, R. C. Smith, E. A. Anderson, Twofold Radical-Based Synthesis of N,C-Difunctionalized Bicyclo[1.1.1]pentanes. *J. Am. Chem. Soc.* **2021**, *143*, 9729-9736.

[17] J. Nugent, C. Arroniz, B. R. Shire, A. J. Sterling, H. D. Pickford, M. L. J. Wong, S. J. Mansfield, D. F. J. Caputo, B. Owen, J. J. Mousseau, F. Duarte, E. A. Anderson, A General Route to Bicyclo[1.1.1]pentanes through Photoredox Catalysis. *ACS Catal.* **2019**, *9*, 9568–9574.

[18] Recently, *Crane* and *Molander* also used $Ru(bpy)_3(PF_6)_2$ as a catalyst in the reaction of alkyl iodides with propellane (originally it was used by Anderson and colleagues during the optimization of the [Ir]-catalyzed reaction – Ref. 17): E. Yen-Pon, L. Li, G. Levitre, J. Majhi, E. J. McClain, E. A. Voight, E. A. Crane, G. A. Molander. On-DNA Hydroalkylation to Introduce Diverse Bicyclo[1.1.1]pentanes and Abundant Alkyls via Halogen Atom Transfer. *J. Am. Chem. Soc.* **2022**, *144*, 12184–12191.

[19] Price of *fac*-$Ir(ppy)_3$ (Aldrich): 811€ for 250 mg. https://www.sigmaaldrich.com/UA/en/product/aldrich/694924

[20] In the reaction of Alk-I (MW = 200) with propellane on a 10 g scale, one needs 813 mg (2.5% mol) of *fac*-$Ir(ppy)_3$ (MW = 655) with a total price of 2636 €.

[21] (a) T. Pirali, M. Serafini, S. Cargnin, A. A. Genazzani. Applications of Deuterium in Medicinal Chemistry. *J. Med. Chem.* **2019**, *62*, 5276–5297. (b) R. M. C. Di Martino, B. D. Maxwell, T. Pirali. Deuterium in drug discovery: progress, opportunities and challenges. *Nat. Rev. Drug. Discov.* **2023**, *in press* (https://doi.org/10.1038/s41573-023-00703-8).

[22] (a) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315–8359. (b) N. A. Meanwell. Fluorine and Fluorinated Motifs in the Design and

Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61*, 5822–5880. (c) M. Inoue, Y. Sumii, N. Shibata. Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020**, *5*, 10633–10640.

[23] Cambridge Crystallographic Data Center (CCDC) deposition numbers: 2260408 (**14**), 2244857 (**19**), 2244859 (**55**), 2237112 (**2k**), 2244856 (**21k**).

[24] V. V. Levterov, Y. Panasyuk, V. O. Pivnytska, P. K. Mykhailiuk. Water-Soluble Non-Classical Benzene Mimetics. *Angew. Chem. Int. Ed.* **2020**, *59*, 7161-7167.

[25] K. Fominova, T. Diachuk, D. Granat, T. Savchuk, V. Vilchynskyi, O. Svitlychnyi, V. Meliantsev, I. Kovalchuk, E. Litskan, V. V. Levterov, V. R. Badlo, R. I. Vaskevych, A. I. Vaskevych, A. V. Bolbut, V. V. Semeno, R. Iminov, K. Shvydenko, A. S. Kuznetsova, Y. V. Dmytriv, D. Vysochyn, V. Ripenko, A. A. Tolmachev, O. Pavlova, H. Kuznietsova, I. Pishel, P. Borysko, P. K. Mykhailiuk. Oxa-spirocycles: synthesis, properties and applications. *Chem. Sci.* **2021**, *12*, 11294-11305.

[26] Recently, [Fe]-catalyzed reaction between *t*BuI and propellane was described: A. Rentería-Gómez, W. Lee, S. Yin, M. Davis, A. R. Gogoi, O. Gutierrez. General and Practical Route to Diverse 1-(Difluoro)alkyl-3-aryl Bicyclo[1.1.1]pentanes Enabled by an Fe-Catalyzed Multicomponent Radical Cross-Coupling Reaction. *ACS Catal.* **2022**, *12*, 11547−11556.

[27] CF_3I is known to react with propellane in the dark without any catalysis. The reaction time in that case is 72 hours, however: J. L. Adcock, A. A. Gakh. Nucleophilic substitution in 1-substituted 3-iodobicyclo[1.1.1]pentanes. A new synthetic route to functionalized bicyclo[1.1.1]pentane derivatives. *J. Org. Chem.* **1992**, *57*, 6206–6210.

[28] Compounds RCF_2Br were recently shown to react with propellane also under [Fe]-catalysis (Ref. 26) and photoredox-catalysis: S. Cuadros, G. Goti, G. Barison, A. Raulli, T. Bortolato, G. Pelosi, P. Costa, L. Dell'Amico. A General Organophotoredox Strategy to Difluoroalkyl Bicycloalkane (CF_2-BCA) Hybrid Bioisosteres. *Angew. Chem. Int. Ed.* **2023**, *in press*, e202303585.

[29] N. Frank, J. Nugent, B. R. Shire, H. D. Pickford, P. Rabe, A. J. Sterling, T. Zarganes-Tzitzikas, T. Grimes, A. L. Thompson, R. C. Smith, C. J. Schofield, P. E. Brennan, F. Duarte, E. A. Anderson. Synthesis of meta-substituted arene bioisosteres from [3.1.1]propellane. *Nature* **2022**, *611*, 721–726.

[30] Other approaches to bicyclo[3.1.1]heptanes: (a) T. Iida, J. Kanazawa, T. Matsunaga, K. Miyamoto, K. Hirano, M. Uchiyama. Practical and Facile Access to Bicyclo[3.1.1]heptanes: Potent Bioisosteres of meta-Substituted Benzenes. *J. Am. Chem. Soc.* **2022**, *144*, 21848–21852. (b) Y. Zheng, W. Huang, R. K. Dhungana, A. Granados, S. Keess, M. Makvandi, G. A. Molander. Photochemical Intermolecular [3σ + 2σ]-Cycloaddition for the Construction of Aminobicyclo[3.1.1]heptanes. *J. Am. Chem. Soc.* **2022**, *144*, 23685–23690. (c) T. Yu, J. Yang, Z. Wang, Z. Ding, M. Xu, J. Wen, L. Xu, P. Li. Selective [2σ + 2σ] Cycloaddition Enabled by Boronyl Radical Catalysis: Synthesis of Highly Substituted Bicyclo[3.1.1]heptanes. *J. Am. Chem. Soc.* **2023**, *145*, 4304–4310.

[31] D. Griller, K. U. Ingold. Free-radical clocks. *Acc. Chem. Res.* **1980**, *13*, 317–323.

[32] For other approaches to bicyclo[1.1.1]pentanes with organoboron substituents, see: (a) A. Fawcett, J. Pradeilles, Y. Wang, T. Mutsuga, E. L. Myers, V. K. Aggarwal. Photoinduced decarboxylative borylation of carboxylic acids. *Science* **2017**, *357*, 283-286. (b) J. Wang, M. Shang, H. Lundberg, K. S. Feu, S. J. Hecker, T. Qin, D. G. Blackmond, P. S. Baran. Cu-Catalyzed Decarboxylative Borylation. *ACS Catal.* **2018**, *8*, 9537−9542. (c) M. Kondo, J. Kanazawa, T. Ichikawa, T. Shimokawa, Y. Nagashima, K. Miyamoto, M. Uchiyama. Silaboration of [1.1.1]Propellane: Storable Feedstock for Bicyclo[1.1.1]pentane Derivatives. *Angew. Chem. Int. Ed.* **2020**, *59*, 1970-1974. (d) Q. Zhang, X. Li, W. Zhang, S. Ni, Y. Wang, Y. Pan. Decarboxylative Borylation of Stabilized and Activated Carbon Radicals. *Angew. Chem. Int. Ed.* **2020**, *59*, 21875-21879. (e) M. D. VanHeyst, J. Qi, A. J. Roecker, J. M. E. Hughes, L. Cheng, Z. Zhao, J. Yin. Continuous Flow-Enabled Synthesis of Bench-Stable Bicyclo[1.1.1]pentane Trifluoroborate Salts and Their Utilization in Metallaphotoredox Cross-Couplings. *Org. Lett.* **2020**, *22*, 1648–1654. (f) R. A. Shelp, A. Ciro, Y. Pu, R. R. Merchant, J. M. E. Hughes, P. J. Walsh. Strain-release 2-azaallyl anion addition/borylation of [1.1.1]propellane: synthesis and functionalization of benzylamine bicyclo[1.1.1]pentyl boronates. *Chem. Sci.* **2021**, *12*, 7066. (g) C. Zarate, M. Ardolino, G. J. Morriello, K. M. Logan, W. P. Kaplan, L. Torres, D. Li, M. Chen, H. Li, J. Su, P. Fuller, M. L. Maddess, Z. Jake Song. Development of Scalable Routes to 1-Bicyclo[1.1.1]pentylpyrazoles. *Org. Process Res. Dev.* **2021**, *25*, 642–647. (h) L. M. Barton, L. Chen, D. G. Blackmond, P. S. Baran. Electrochemical borylation of carboxylic acids. *PNAS* **2021** *118*, e2109408118. (i) W. Dong, E. Yen-Pon, L. Li, A. Bhattacharjee, A. Jolit, G. A. Molander. Exploiting the sp^2 character of bicyclo[1.1.1]pentyl radicals in the transition-metal-free multi-component difunctionalization of [1.1.1]propellane. *Nat. Chem.* **2022**, *14*, 1068–1077.

[33] For a recent example of *O*-substituted bicyclo[1.1.1]pentanes, see: E. M. Alvarez, Z. Bai, S. Pandit, N. Frank, L. Torkowski, T. Ritter. O-, N- and C-bicyclopentylation using thianthrenium reagents. *Nat. Synth*. **2023**, *2*, 548–556.

[34] For another previous to bicyclo[1.1.1]pentane hydrazines, see: (a) K. D. Bunker, N. W. Sach, Q. Huang, P. F. Richardson. Scalable Synthesis of 1-Bicyclo[1.1.1]pentylamine via a Hydrohydrazination Reaction. *Org. Lett*. **2011**, *13*, 4746-4748. (b) J. Kanazawa, K. Maeda, M. Uchiyama. Radical Multicomponent Carboamination of [1.1.1]Propellane. *J. Am. Chem. Soc*. **2017**, *139*, 17791–17794.

[35] For other approaches to bicyclo[1.1.1]pentanes with *S*-substituents, see: (a) R. M. Bär, S. Kirschner, M. Nieger, S. Bräse. Alkyl and Aryl Thiol Addition to [1.1.1]Propellane: Scope and Limitations of a Fast Conjugation Reaction. *Chem. Eur. J.* **2018**, *24*, 1373-1382. (b) Y. Kraemer, C. Ghiazza, A. N. Ragan, S. Ni, S. Lutz, E. K. Neumann, J. C. Fettinger, N. Nöthling, R. Goddard, J. Cornella, C. R. Pitts. Strain-Release Pentafluorosulfanylation and Tetrafluoro(aryl)sulfanylation of [1.1.1]Propellane: Reactivity and Structural Insight. *Angew. Chem. Int. Ed.* **2022**, *61*, e202211892. (c) S. Livesley, B. Trueman, C. M. Robertson, W. R. F. Goundry, J. A. Morris, C. Aïssa. Synthesis of Sulfur-Substituted Bicyclo[1.1.1]pentanes by Iodo-Sulfenylation of [1.1.1]Propellane. *Org. Lett.* **2022**, *24*, 7015−7020. (d) H. D. Pickford, V. Ripenko, R. E. McNamee, S. Holovchuk, A. L. Thompson, R. C. Smith, P. K. Mykhailiuk, E. A. Anderson. Rapid and Scalable Halosulfonylation of Strain-Release Reagents. *Angew. Chem. Int. Ed.* **2023**, *62*, e202213508. (e) W. Dong, S. Keess, G. A. Molander. Nickel-mediated alkyl-, acyl-, and sulfonylcyanation of [1.1.1]propellane. *Chem. Catalysis* **2023**, *3*, 100608.

[36] For alternative approaches to bicyclo[1.1.1]pentanes with *C*-substituents, see: (a) I. S. Makarov, C. E. Brocklehurst, K. Karaghiosoff, G. Koch, P. Knochel. Synthesis of Bicyclo[1.1.1]pentane Bioisosteres of Internal Alkynes and *para*-Disubstituted Benzenes from [1.1.1]Propellane. *Angew. Chem. Int. Ed.* **2017**, *56*, 12774 –12777. (b) R. A. Shelp, P. J. Walsh. Synthesis of BCP Benzylamines From 2-Azaallyl Anions and [1.1.1]Propellane. *Angew. Chem. Int. Ed.* **2018**, *57*, 15857-15861. (c) N. Trongsiriwat, Y. Pu, Y. Nieves-Quinones, R. A. Shelp, M. C. Kozlowski, P. J. Walsh. Reactions of 2-Aryl-1,3-Dithianes and [1.1.1]Propellane. .*Angew. Chem. Int. Ed.* **2019**, *58*, 13416-13420. (d) S. Yu, C. Jing, A. Noble, V. K. Aggarwal. 1,3-Difunctionalizations of [1.1.1]Propellane via 1,2-Metallate Rearrangements of Boronate Complexes. *Angew. Chem. Int. Ed.* **2020**, *59*, 3917-3921. (e) K. Schwärzer, H. Zipse, K. Karaghiosoff, P. Knochel. Highly Regioselective Addition of Allylic Zinc Halides and Various Zinc Enolates to [1.1.1]Propellane. *Angew. Chem. Int. Ed.* **2020**, *59*, 20235–20241. (f) Z. J. Garlets, J. N. Sanders, H.Malik, C. Gampe, K. N. Houk, H. M. L. Davies. Enantioselective C–H functionalization of bicyclo[1.1.1]pentanes. *Nat. Catal.* **2020**, *3*, 351–357. (g) S. Yu, C. Jing, A. Noble, V. K. Aggarwal. Iridium-Catalyzed Enantioselective Synthesis of α-Chiral Bicyclo[1.1.1]pentanes by 1,3-Difunctionalization of [1.1.1]Propellane. *Org. Lett.* **2020**, *22*, 5650–5655. (h) C. Andersen, V. Ferey, M. Daumas, P. Bernardelli, A.Guérinot, J. Cossy. Copper-Catalyzed Cross-Coupling between Alkyl (Pseudo)halides and Bicyclopentyl Grignard Reagents. *Org. Lett.* **2020**, *22*, 6021–6025. (i) M. L. J. Wong, A. J. Sterling, J. J. Mousseau, F. Duarte, E. A. Anderson. Direct catalytic asymmetric synthesis of α-chiral bicyclo[1.1.1]pentanes. *Nat. Commun.* **2021**, *12*, 1644. (j) V. C. Polites, S. O. Badir, S. Keess, A. Jolit, G. A. Molander. Nickel-Catalyzed Decarboxylative Cross-Coupling of Bicyclo[1.1.1]pentyl Radicals Enabled by Electron Donor−Acceptor Complex Photoactivation. *Org. Lett.* **2021**, *23*, 4828−4833. (k) J. Nugent, A. J. Sterling, N. Frank, J. J. Mousseau, E. A. Anderson. Synthesis of *α*-Quaternary Bicyclo[1.1.1]pentanes through Synergistic Organophotoredox and Hydrogen Atom Transfer Catalysis. *Org. Lett.* **2021**, *23*, 8628–8633. (l) J. J. Mousseau, M. A. Perry, M. W. Bundesmann, G. M. Chinigo, C. Choi, G. Gallego, R. W. Hicklin, S. Hoy, D. C. Limburg, N. W. Sach, Y. Zhang. Automated Nanomole-Scale Reaction Screening toward Benzoate Bioisosteres: A Photocatalyzed Approach to Highly Elaborated Bicyclo[1.1.1]Pentanes. *ACS Catal.* **2022**, *12*, 600−606. (m) W. Huang, S. Keess, G. A. Molander. One step synthesis of unsymmetrical 1,3-disubstituted BCP ketones via nickel/photoredoxcatalyzed [1.1.1]propellane multicomponent dicarbofunctionalization. *Chem. Sci.* **2022**, *13*, 11936. (n) W. Huang, S. Keess, G. A. Molander. Dicarbofunctionalization of [1.1.1]Propellane Enabled by Nickel/Photoredox Dual Catalysis: One-Step Multicomponent Strategy for the Synthesis of BCP-Aryl Derivatives. *J. Am. Chem. Soc.* **2022**, *144*, 12961−12969. (o) R. Shelp, R. R. Merchant, J. M. E. Hughes, P.J. Walsh. Enantioenriched BCP Benzylamine Synthesis via Metal Hydride Hydrogen Atom Transfer/Sulfinimine Addition to [1.1.1]Propellane. *Org. Lett.* **2022**, *24*, 110−114. (p) Q. Li, L. Li, Q.-L. Xu, F. Pan. Radical Acylation of [1.1.1]Propellane with Aldehydes: Synthesis of Bicyclo[1.1.1]pentane Ketones. *Org. Lett.* **2022**, *24*, 4292–4297. (q) W. Huang, S. Keess, G. A. Molander. A General and Practical Route to Functionalized BCP-Heteroaryls Enabled by Photocatalytic Multicomponent Heteroarylation of [1.1.1]Propellane. *Angew. Chem. Int. Ed.* **2023**, *62*, e202302223. (r) Y. Gao, Z. Zheng, Y. Zhu, W. Xu, Y. Zhou, C.Yu, X. Jiang. Visible light-induced synthesis of 1,3-disubstituted bicyclo[1.1.1]pentane ketones via cooperative photoredox and N-heterocyclic carbene catalysis. *Green Chem.* **2023**, *25*, 3909-3915. (s) W. Huang, Y. Zheng, S. Keess, G. A. Molander. A General and Modular Approach to BCP Alkylamines via Multicomponent Difunctionalization of [1.1.1]Propellane. *J. Am. Chem. Soc.* **2023**, *145*, 5363−5369.

[37] For previous approaches to bicyclo[1.1.1]pentanes with *N*-substituents, see Refs. 8, 9 and (a) R. A. Shelp, P. J. Walsh. Synthesis of BCP Benzylamines From 2-Azaallyl Anions and [1.1.1]Propellane. *Angew. Chem. Int. Ed.* **2018**, *57*, 15857-15861. (b) J. M. E. Hughes, D. A. Scarlata, A. C.-Y. Chen, J. D. Burch, J. L. Gleason. Aminoalkylation of [1.1.1]Propellane Enables Direct Access to High-Value 3-Alkylbicyclo[1.1.1]pentan-1-amines. *Org. Lett.* **2019**, *21*, 6800–6804. (c) J. H. Kim, A. Ruffoni, Y. S. S. Al-Faiyz, N. S. Sheikh, D. Leonori. Divergent Strain-Release Amino-Functionalization of [1.1.1]Propellane with Electrophilic Nitrogen-Radicals. *Angew. Chem. Int. Ed.* **2020**, *59*, 8225–8231. (d) X. Zhang, R. T. Smith, C. Le, S. J. McCarver, B. T. Shireman, N. I. Carruthers, D. W. C. MacMillan. Copper-mediated synthesis of drug-like bicyclopentanes. *Nature* **2020**, *580*, 220–226. (e) S. Shin, S. Lee, W. Choi, N. Kim, S. Hong. Visible-Light-Induced 1,3-Aminopyridylation of [1.1.1]Propellane with *N*-Aminopyridinium Salts. *Angew. Chem. Int. Ed.* **2021**, *60*, 7873–7879. (f) S. Livesley, A. J. Sterling, C. M. Robertson, W. R. F. Goundry, J. A. Morris, F. Duarte, C. Aïssa. Electrophilic Activation of [1.1.1]Propellane for the Synthesis of Nitrogen-Substituted Bicyclo[1.1.1]pentanes. *Angew. Chem. Int. Ed.* **2022**, *61*, e202111291.

[38] At least 17 patents describe application of bicyclo[1.1.1]pentanes **2k**, **21l**, **55k**, **60i**, **60j**, **60k**, **62j**, **67c**, **67l**, **69c**, **69e** from this work, synthesis of which was not reported before: (a) L. D. Arnold, A. Jennings, W. Keung. Inhibitors of cysteine proteases and methods of use thereof. *Pardes Biosciences Inc.* US11124497. (b) J. Benz, U. Grether, B. Hornsperger, C. Kroll, B. Kuhn, R. E. Martin, F. O'hara, B. Puellmann, H. Richter, M. Ritter. Heterocyclic compounds. *Hoffmann-La Roche.* WO2022049134. (c) B. P. Bestvater, Z. Du, J. Farand, J. A. Kaplan, D. T. Tang, C. Venkataramani, P. Wang, K. S. Yang, A. Zagorska, B. W. Phillips. LPA receptor antagonists and uses thereof. *Gilead Sciences.* WO2021247217. (d) G. Gavory, M. Ghandi, A. Chicas, M. Warmuth. Treatment of myc-driven cancers with GSPT1 degraders. *Monte Rosa Therapeutics*. WO2022152822. (e) B. Fasching, T. Ryckmans, A. Flohr, A. Ritzén, F. Harvey, L. Mcallister. Isoindolinone compounds. *Monte Rosa Therapeutics*. WO2022152821. (f) G. L. Trainor, M. Obdulia, R. Gracia, L. Fourmois, O. Gherbovet, F. Cachoux. Substituted cyclic modulators of protein phosphatase 2A (PP2A) and methods using same. *Rappta Therapeutics*. WO2022167867. (g) M. Amoussa, J. Benz, N. K. Brian, K. Friston, M. Giroud, U. Grether, K. G. Zbinden, B. Hornsperger, C. Kroll, B. Kuhn, C. J. Leake, R. E. Martin, D. F. E. Nippa, F. S. O'hara, B. Puellmann, H. Richter, M. Ritter, D. Rombach, P. C. Schmid, S. Zhang. Heterocyclic compounds. *Hoffmann-La Roche.* WO2022223750. (h) A. W. Buesking, R. B. Sparks, A. P. Combs, B. Douty, N. Falahatpisheh, L. Shao, S. Shepard, E. W. Yue. Heterocyclic compounds as PI3K-γ inhibitors. *Incyte Corp*. WO2017223414. (i) B. P. Bestvater, Z. Du, J. Farand, C. Venkataramani, K. S. Yang, A. Zagorska. LPA receptor antagonists and uses thereof. *Gilead Sciences.* WO2022241023. (j) D. Oehlrich, N. van Opdenbosch, M. Lamkanfi, M. E. Muratore, D. van Rompaey, M. L. Linares De La Morena, M. J. Alcázar-Vaca, M. L. M. van Gool. 4-Alkoxy-6-oxo-pyridazine derivatives modulating NLRP3. *Janssen Pharm.* WO2022184842. (k) N. S. Gray, J. M. Hatcher. Cyano-pyrimidine inhibitors of EGFR/HER2. *Dana-Farber Cancer Institute*. WO2021141960. (l) O. Bezencon, C. Deymier, J.-U. Peters, R. Siegrist, J.-P. Surivet. Cyclobutyl-urea derivatives. *Idorsia Pharm.* WO2021260090. (m) H. Miao, W. Yizhe, L. Xingguo, Z. Xinglu. Potassium channel modulator, composition and application. Hangzhou Healzen Therapeutics. WO2023025276. (n) R. Jones, A. Bajji, N. Monck, S. O'Connor, R. Rathmell, W. Gardiner, R. Townsend, A. Pita, M. Brunavs, A. Shaikh, J. Shine, I. Wigginton, J. Richards, M. Mastandrea, A. Davenport, B. Moyer, M. Poslusney, J. Barrow. Methyl-substituted pyridine and pyridazine compounds, derivatives thereof, and methods of their use. Latigo Biotherapeutics. WO2022192487. (o) M. Bartlett, G. Chin, M. Clarke, J. Cosman, D. Ensan, B. Goyal, S. Ho, H. Hui, R. Mackman, M. Mish, S. Schroeder, N. Shapiro, D. Siegel, D. Tanz, H. Yang. CD73 inhibiting 2,4-dioxopyrimidine compounds. Gilead sciences. WO2021222522. (p) E. Dimauro, X. Fradera, P. Fuller, M. Lu, J. Methot, M. Mitcheltree, A. Musacchio, P. Siliphaivanh, J. Su. RIPK1 inhibitors and methods of use. Merck Sharp and Dohme. WO2022231928. (q) B. Fasching, T. Ryckmans, O. Eidam, A. Flohr, L. A. Mcallister, A. Ritzén. Compounds that mediate protein degradation and uses thereof. Monte Rosa. WO2023069708.

[39] I. F. Yu, J. L. Manske, A. Diéguez-vázquez, A. Misale, A. E. Pashenko, S. V. Ryabukhin, D. M. Volochnyuk, J. F. Hartwig. Catalytic undirected borylation of tertiary C–H bonds in bicyclo[1.1.1]pentanes and bicyclo[2.1.1]hexanes. *Nat. Chem.* **2023**, *15*, 685–693.

[40] M. Alonso, S. Cañellas, F. Delgado, M. Serrano, A. Diéguez-Vázquez, J. E. Gómez. Accelerated Synthesis of Bicyclo[1.1.1]pentylamines: A High-Throughput Approach. *Org. Lett.* **2023**, *25*, 771–776.

[41] O. L. Davies, J. Raventós, A. L. Walpole A method for the evaluation of analgesic activity using rats. *Br. J. Pharmacol Chemother.* **1946**, 255-264.

[42] Study design, animal selection, handling and treatment were in accordance with Bienta Animal Care and Use Guidelines, and European Union directive 2010/63/EU.

Abstract

The LARGEST library of Bicyclo[1.1.1]pentanes for Drug Discovery enabled by Light

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In 2012, bicyclo[1.1.1]pentanes were demonstrated to be bioisosteres of the phenyl ring. Today, after more than a decade, the difficulty in their large-scale preparation is still a problem, that often outweighs the corresponding derivatives to becoming clinical candidates. Here, we report a practical general reaction that gives bicyclo[1.1.1]pentanes on mg- to kg-quantities using *just light*. No additional additives or catalysts are needed. Using this strategy, we have prepared >300 functionalized bicyclo[1.1.1]pentanes on a (multi)gram scale. So far, this is the most general and practical approach to bicyclo[1.1.1]pentanes. Many of these molecules, which were previously commercialized, are already being used in drug discovery by pharmaceutical companies *Gilead Sciences*, *Hoffman-La Roche*, *Idorsia*, *Merck*, *Janssen Pharm.*, *etc*.

This work should ease the transition of bicyclo[1.1.1]pentane-containing bioactive compounds to clinical candidates, and subsequently to drugs.