

C–H Insertion as a key step to spiro-oxetanes, scaffolds for drug discovery

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Abstract: A new route to spiro-oxetanes, potential scaffolds for drug discovery, is described. The route is based on the selective 1,4-C–H insertion reactions of metallocarbenes, generated from simple carbonyl precursors in flow or batch mode, to give spiro- β -lactones that are rapidly converted into spiro-oxetanes. The three-dimensional and lead like-properties of spiro-oxetanes is illustrated by the conversion of the 1-oxa-7-azaspiro[3,5]nonane scaffold into a range of functionalized derivatives.

Modern drug discovery programs drive an appetite for new, low molecular weight bioactive molecules. In support of the well-established drug discovery process, strategies such as diversity-oriented synthesis (DOS), lead-oriented synthesis (LOS), biology-oriented synthesis (BOS), and fragment based drug discovery (FBDD) have recently emerged as tools to accelerate the search for new drug candidates.^[1] Nevertheless, access to compounds with desirable properties by chemical synthesis remains challenging. For example, the power of transition metal-catalyzed sp^2 - sp^2 cross coupling reactions has inadvertently led to large numbers of (hetero)aromatic-rich fragments, despite evidence that such compounds are susceptible to attrition in the later stages of drug development due to inappropriate physicochemical properties.^[2] As a result, there is now a desire to develop robust synthetic methods that will provide ready access to diverse collections of lead-like, sp^3 -atom rich, low molecular weight and often densely functionalized molecules, ideally creating molecular complexity from simple starting materials in a few steps.

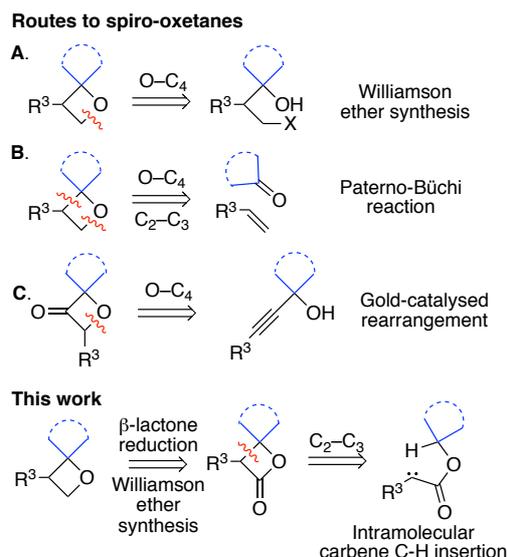
One contemporary initiative, the European Lead Factory (ELF),^[3] was established with the precise goal of identifying compound libraries that fulfil the above criteria. As part of our work under the ELF programme,^[4] we were intrigued by the recent interest in spiro-oxetanes,^[5] and identified the little known 1-oxa-7-azaspiro[3,5]nonane ring system (Figure 1) as an ideal scaffold for drug discovery. Spirocycles incorporating a small ring, such as an oxetane, have relatively rigid structures, and can be densely functionalized, with the substituent vectors clearly defined in their three-dimensional arrangement. Evidence that the 1-oxa-7-azaspiro[3,5]nonane scaffold does indeed allow access to lead-like properties came from analysis of a virtual library generated using the open access LLAMA tool (see Supporting Information for details).^[6] When one functionalization was considered, 42% of the molecules in the virtual library fell within lead-like space (MW < 350, logP < 3) (Figure S1), and all were compliant to Lipinski's 'rule of five'. In addition, current medicinal chemistry space is well populated with "disc-like" molecules. In contrast, the spiro-oxetanes occupy the "rod-like" area of molecular space (see Figure S2).



Figure 1. The 1-oxa-7-azaspiro[3,5]nonane ring system.

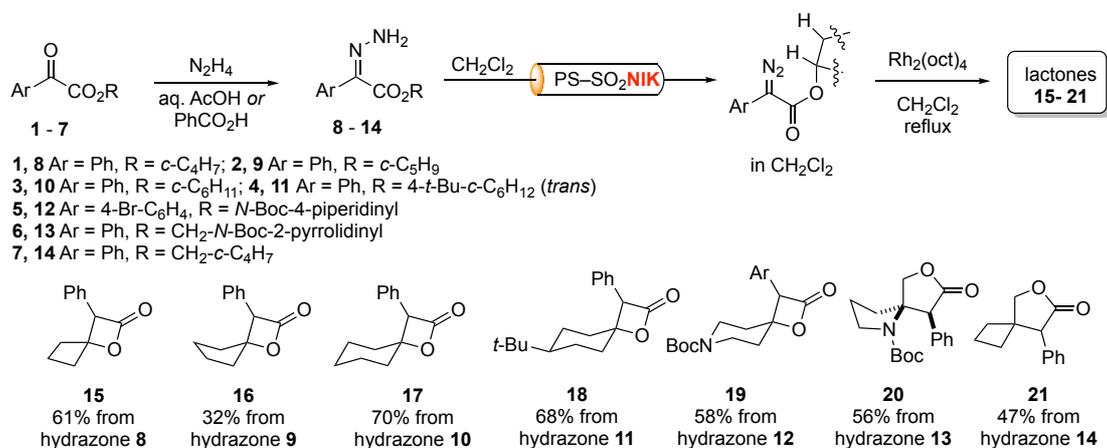
Since the original report highlighting the potential of oxetanes in medicinal chemistry,^[7] this small ring system has attracted considerable attention, not only due to its low steric bulk, but also because of the advantageous effect on physicochemical parameters.^[8] Originally conceived as polar replacements for lipophilic *gem*-dimethyl groups, oxetanes also act as surrogates for carbonyl groups,^[9] and in bioisosteres for morpholine.^[8c] We now report a new approach to spiro-oxetanes, using reactive metallocarbene intermediates, generated from simple ketone precursors *via* diazo compounds, to access high-energy, strained products by selective 1,4-C–H activation.

Access to 2,2-spiro-oxetanes can be achieved by the Williamson ether synthesis or the Paterno-Büchi reaction (Scheme 1A, B),^[8d,10] although recent developments such as the gold-catalyzed rearrangement of propargylic alcohols (Scheme 1C) can also be used.^[11] Some recent approaches to 3,3-spiro-oxetanes are also noteworthy.^[12] Our approach features a selective metal carbene C–H activation strategy to give a key β -lactone intermediate that can be converted into the target oxetane through a short reaction sequence.



Scheme 1. Synthetic approaches to 2,2-spiro-oxetanes.

The reactions of metalcarbenes, readily derived from the metal-catalysed reactions of diazocarbonyl compounds, have become an established tactic in synthesis over the last two decades.^[13] Although such reactions constitute an attractive route to a variety of compound types, significant worries about the hazards involved in preparing and using diazo compounds have precluded their widespread adoption. However, the direct handling of potentially hazardous materials can be minimized by their generation and use in flow chemistry.^[14] We recently described a new protocol for the preparation of diazo compounds by oxidation of hydrazones based on the reagent *N*-iodo *p*-toluenesulfonamide potassium salt (TsNIK),^[15] and based on the efficiency of this method, we developed a recyclable, polystyrene-supported version of the oxidant (PS-TsNIK), and demonstrated its use in the generation of a wide range of diazo compounds under flow conditions.^[16] This method allows the safe generation of highly reactive diazo compounds and enables their use to access higher energy, strained materials such as β -lactones. Therefore we initially investigated the intramolecular C-H activation reactions of aryl diazoacetates derived in flow from ketoesters *via* hydrazones where the ester *O*-alkyl group contains a suitably positioned tertiary C-H bond. The starting hydrazones **8** – **14** were prepared from the corresponding ketoesters **1** – **7** in near-quantitative yields by treatment with hydrazine hydrate under acidic conditions (AcOH or PhCO₂H) as previously described,^[15] and subsequently oxidized in flow as a dichloromethane solution using a column packed with PS-TsNIK. Oxidation of the hydrazones on the resin was fast, with complete conversion being seen with a residence time of 5-10 minutes. The flow output was directly exposed to dirhodium(II) octanoate catalyst in dichloromethane at reflux in standard equipment, resulting in the formation of the desired spiro β -lactones **15** – **19** (Scheme 2). The relative stereochemistry of β -lactone **18** derived from *trans*-4-*tert*-butylcyclohexanol was established by X-ray crystallography (Figure S3, Supporting Information), confirming that, as expected, insertion occurs with retention of stereochemistry into the axial C-H bond. Similarly the hydrazone **12** derived from *N*-Boc-4-hydroxypiperidine gave the spiro β -lactone **19**, the key intermediate in our proposed route to the 1-oxa-7-azaspiro[3,5]nonane core structure.

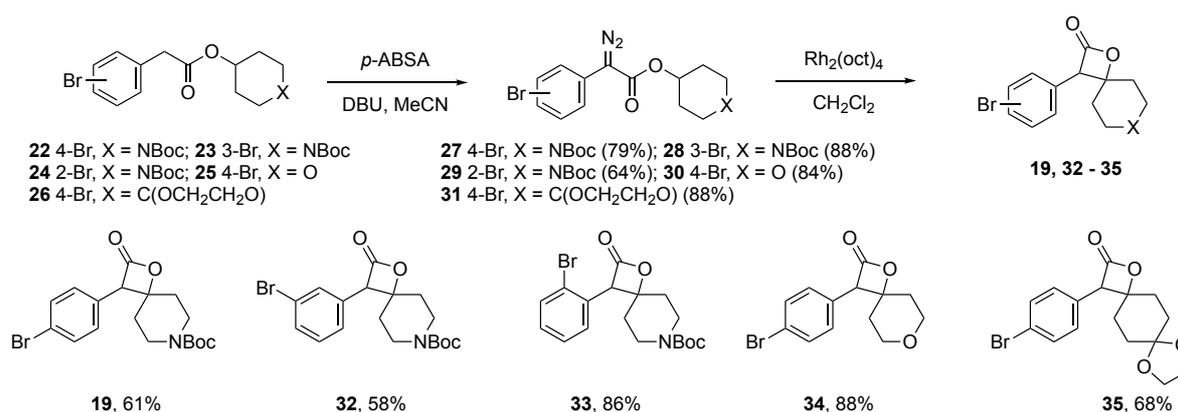


Scheme 2. [oct = octanoate; Ar = 4-bromophenyl] Synthesis of diazoesters from oxidation of hydrazones in flow and subsequent intramolecular C–H insertion reactions to give spiro- β - and γ -lactones.

The selectivity of intramolecular metalcarbene C–H insertion reactions has been widely studied, and although the formation of 5-membered rings is generally favoured, the presence of heteroatoms or suitably positioned tertiary C–H bonds can often override this preference and lead to the formation of 4-membered rings. This has been exemplified by β -lactone formation, following the early work by Lee *et al.*^[17] using dirhodium(II) catalysis.^[18] Hence our synthesis of spiro- β -lactones follows the expected selectivity trends for preferential insertion into a tertiary C–H bond rather than a CH₂ group. In accord with this selectivity, oxidation of the prolinol-derived hydrazone **13** and treatment with the dirhodium(II) catalyst gave the spiro- γ -lactone **20**, isolated as a single diastereomer. The structure and stereochemistry were confirmed by X-ray crystallography (Figure S4, Supporting Information). Likewise, the hydrazone **14** derived from cyclobutylmethanol gave the spiro- γ -lactone **21** (47%) (Scheme 2), again emphasizing the preference for insertion into tertiary C–H bonds.

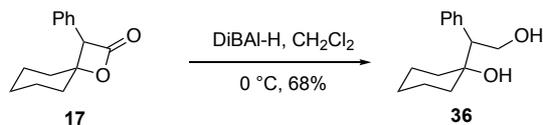
The diazoesters can be also be formed by more conventional diazo transfer protocols as illustrated for the aryl diazoacetates **27** – **31**, and their subsequent conversion into β -lactones (Scheme 3). Using this route, the synthesis of β -lactones **19** and **32** – **35** was undertaken starting from the corresponding arylacetates on multi-gram scale, and the product isolated without chromatography over the 3-step sequence.

With a range of spiro- β -lactones available, their conversion into the corresponding oxetanes was investigated. The conversion of β -lactones into the corresponding oxetanes in a *single* step is an unknown chemical transformation. Although a number of protocols are available for the direct reduction of higher lactones to the corresponding cyclic ether in one step,^[19] these failed to give any oxetane products when applied to our β -lactones. Therefore, we used a procedure involving reduction and etherification.^[20] Reduction of β -lactone **17** to the corresponding diol **36** proved more difficult than expected, and common reduction conditions led to decomposition of the



Scheme 3. Synthesis of spiro- β -lactones in batch mode (yields for diazoesters are over two steps from the aryl acetic acid).

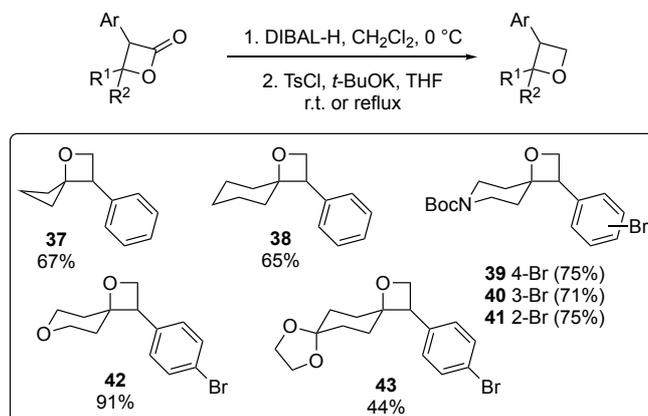
substrates, mainly *via* a retro-aldol reaction. A number of reaction conditions were investigated (Table S1, Supporting Information) including borane reduction of the carboxylic acid hydrolysis product of **17**, reduction using lithium triethylborohydride, lithium aluminium hydride or diisobutylaluminium hydride (DIBAL-H). Optimization of the reaction conditions using β -lactone **17** led to diol **36** in 68% yield when DIBAL-H was used in dichloromethane (Scheme 4).



Scheme 4. Reduction of β -lactone **17** to diol **36**.

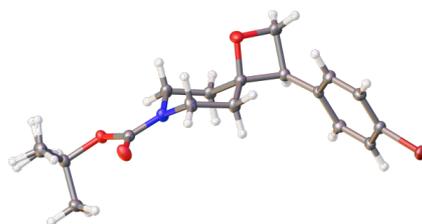
Cyclization of the diol **36** to the oxetane **38** proceeded readily using tosyl chloride and potassium *tert*-butoxide in THF at reflux, presumably *via* an initial sulfonylation of the primary alcohol, followed by the alkylation of the tertiary alcohol. Alternatively the diol can be briefly isolated, and without purification, simply treated with tosyl chloride to give oxetanes **37** and **39** – **43** in 44 – 80% yield (Scheme 5). The structure of oxetanes **39** and **43** were confirmed by X-ray crystallography (Figure 2).

The aforementioned analysis of the three-dimensional and lead like-properties of compounds based on the 1-oxa-7-aza-spiro[3,5]nonane spiro-oxetane core highlighted the potential of the scaffold as a platform for drug discovery. Therefore a number of transformations were carried out on oxetane **39** (Scheme 6) to exemplify the range of functionality that could be incorporated. Initially Suzuki-Miyaura and Buchwald-Hartwig coupling reactions of the aryl bromide gave the spiro-oxetanes **44** and **49** in excellent yield, whilst conversion into the carboxylic acid **46** was efficiently achieved by palladium-catalyzed carbonylation reaction with phenyl formate followed by hydrolysis of the ester **45** (Scheme 6).^[21] Amides **50** – **52** were prepared from carboxylic acid **46** under standard conditions, and further functionalized at the piperidine nitrogen to give **53** – **55**.



Scheme 5. Conversion of β -lactones into oxetanes.

A



B

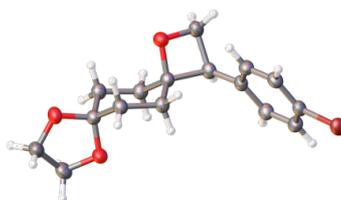
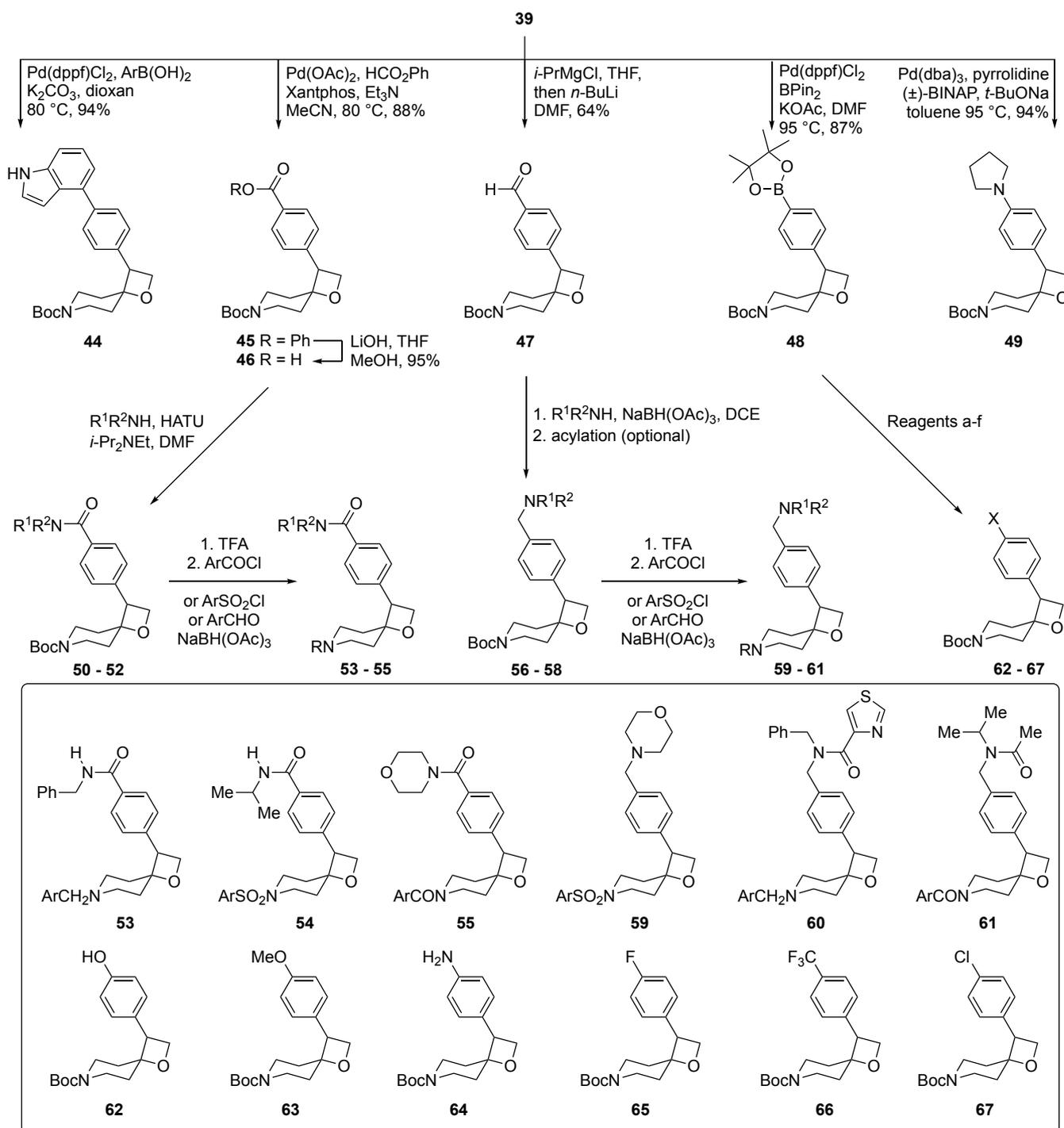


Figure 2. X-ray crystal structure of spiro-oxetanes (A) **39** and (B) **43**.

Likewise, non-cryogenic metallation of the bromide followed by quenching with DMF gave the aldehyde **47**.^[22] Aldehyde **47** was used in reductive amination chemistry followed by optional acylation to give **56** – **58**, which were further functionalized at the piperidine nitrogen to exemplify potential library synthesis reactions with compounds **59** – **61**.



Scheme 6. [Ar = 4-bromophenyl] Synthesis of an array of spiro-oxetane-piperidines. Reagents and conditions: **62** a.) H₂O₂, aq. NaOH, THF, r.t., 3 h, quant; b.) **63** from **62**, MeI, K₂CO₃, DMF, r.t., 15 h, 80%; **64** c.) hydroxylamine-*O*-sulfonic acid, aq. NaOH, MeCN, r.t., 16 h, 69%; **65** d.) i. AgOTf, NaOH, MeOH, 0 °C, 0.5 h; ii. Selectfluor[®], 3A MS, acetone, r.t., 1 h, 69%; **66** e.) Cu(phen)CF₃, KF, DMF, 50 °C, 18 h, 94%; **67** f.) CuCl₂, H₂O:MeOH (1:1), 90 °C, 5 h, 74%.

Miyaura borylation^[23] gave the pinacol boronate **48** that could be functionalized to further increase molecular diversity of the scaffold. Hydrolysis of boronate **48** under standard conditions (H₂O₂/NaOH) provided the phenol **62**, which was readily alkylated with methyl iodide to scaffold **63**. The corresponding aniline **64** was prepared utilizing the transition metal-free conditions developed by Voth *et al.* using hydroxylamine-*O*-sulfonic acid,^[24] providing the aniline **64** in 95% yield. Pinacol boronate **48** can also be readily converted into two fluorinated scaffolds. Metallation of the pinacol boronate to the organosilver followed by treatment with Selectfluor[®] yielded the aryl fluoride **65** in 69% yield.^[25] Trifluoromethylation was achieved using the conditions developed by Hartwig using (1,10-phenanthroline)(trifluoromethyl)copper(I).^[26] This exquisite transformation provided the trifluoromethyl oxetane **66** in 94% yield. Copper-catalyzed chlorination was also performed under Hartwig conditions to give the aryl chloride **67**.^[27] These diverse transformations highlight the robustness of the scaffold to further functionalization to provide a wide range of functional groups of interest for medicinal chemistry as illustrated by the analysis of the virtual library.

Under the auspices of the European Lead Factory (ELF),^[3] the spiro-oxetane scaffolds prepared herein have been developed for inclusion in the Joint European Compound Library (JECL).^[28] A total of 478 compounds was synthesized by our ELF partner Sygnature Discovery Ltd.

In conclusion, we have described a short route to spiro-oxetanes that features a selective metallocarbene C–H insertion to generate β -lactones as a key step. Diazocarbonyl compound precursors were either generated in-flow and used without isolation or prepared by batch methods. Conversion of β -lactones into oxetanes was readily carried out, and the whole sequence was amendable to scale up. A number of functional group interconversions on the spiro-oxetane products illustrates the potential of this motif as a fragment of interest in drug development programmes.

Experimental Section

For full details of all experiments, and copies of ¹H and ¹³C NMR spectra, see the Supporting Information.

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- [1] (a) S. Wetzel, R. S. Bon, K. Kumar, H. Waldmann, *Angew. Chem., Int. Ed.* **2011**, *50*, 10800-10826; (b) D. E. Scott, A. G. Coyne, S. A. Hudson, C. Abell, *Biochemistry* **2012**, *51*, 4990-5003; (c) A. Nadin, C. Hattotuwigama, I. Churcher, *Angew. Chem., Int. Ed.* **2012**, *51*, 1114-1122.
- [2] T. J. Ritchie, S. J. F. Macdonald, R. J. Young, S. D. Pickett, *Drug Discovery Today* **2011**, *16*, 164-171.
- [3] A. Karawajczyk, F. Giordanetto, J. Benningshof, D. Hamza, T. Kalliokoski, K. Pouwer, R. Morgentin, A. Nelson, G. Muller, A. Piechot, D. Tzalis, *Drug Discovery Today* **2015**, *20*, 1310-1316.
- [4] (a) A. Nortcliffe, C. J. Moody, *Bioorg. Med. Chem.* **2015**, *23*, 2730-2735; (b) A. T. Murray, E. Packard, A. Nortcliffe, W. Lewis, D. Hamza, G. Jones, C. J. Moody, *Eur. J. Org. Chem.* **2017**, 138-148; (c) A. Nortcliffe, G. D. S. Milne, D. Hamza, C. J. Moody, *Bioorg. Med. Chem.* **2017**, *25*, 2218-2225.
- [5] (a) G. Wuitschik, M. Rogers-Evans, A. Buckl, M. Bernasconi, M. Marki, T. Godel, H. Fischer, B. Wagner, I. Parrilla, F. Schuler, J. Schneider, A. Alker, W. B. Schweizer, K. Muller, E. M. Carreira, *Angew. Chem., Int. Ed.* **2008**, *47*, 4512-4515; (b) E. M. Carreira, T. C. Fessard, *Chem. Rev.* **2014**, *114*, 8257-8322.
- [6] I. Colomer, C. J. Empson, P. Craven, Z. Owen, R. G. Doveston, I. Churcher, S. P. Marsden, A. Nelson, *Chem. Commun.* **2016**, *52*, 7209-7212.
- [7] G. Wuitschik, M. Rogers-Evans, K. Muller, H. Fischer, B. Wagner, F. Schuler, L. Polonchuk, E. M. Carreira, *Angew. Chem., Int. Ed.* **2006**, *45*, 7736-7739.
- [8] (a) G. Wuitschik, E. M. Carreira, B. Wagner, H. Fischer, I. Parrilla, F. Schuler, M. Rogers-Evans, K. Mueller, *J. Med. Chem.* **2010**, *53*, 3227-3246; (b) J. A. Burkhard, G. Wuitschik, M. Rogers-Evans, K. Mueller, E. M. Carreira, *Angew. Chem., Int. Ed.* **2010**, *49*, 9052-9067; (c) M. Rogers-Evans, H. Knust, J. M. Plancher, E. M. Carreira, G. Wuitschik, J. Burkhard, D. B. Li, C. Guerot, *Chimia* **2014**, *68*, 492-499; (d) J. A. Bull, R. A. Croft, O. A. Davis, R. Doran, K. F. Morgan, *Chem. Rev.* **2016**, *116*, 12150-12233.
- [9] (a) J. A. Burkhard, G. Wuitschik, J. M. Plancher, M. Rogers-Evans, E. M. Carreira, *Org. Lett.* **2013**, *15*, 4312-4315; (b) G. P. Moller, S. Muller, B. T. Wolfstadter, S. Wolfrum, D. Schepmann, B. Wunsch, E. M. Carreira, *Org. Lett.* **2017**, *19*, 2510-2513.
- [10] O. A. Davis, J. A. Bull, *Synlett* **2015**, *26*, 1283-1288.
- [11] L. W. Ye, W. M. He, L. M. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8550-8551.
- [12] (a) A. Monleon, F. Glaus, S. Vergura, K. A. Jorgensen, *Angew. Chem., Int. Ed.* **2016**, *55*, 2478-2482; (b) B. A. Chalyk, A. A. Isakov, M. V. Butko, K. V. Hrebenuik, O. V. Savych, O. V. Kucher, K. S. Gavrilenko, T. V. Druzhenko, V. S. Yarmolchuk, S. Zozulya, P. K. Mykhailiuk, *Eur. J. Org. Chem.* **2017**, DOI: 10.1002/ejoc.201700536.
- [13] (a) H. M. L. Davies, A. R. Dick, *Top. Curr. Chem.* **2010**, *292*, 303-345; (b) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981-10080; (c) F. J. Lombard, M. J. Coster, *Org. Biomol. Chem.* **2015**, *13*, 6419-6431; (d) B. Wang, D. Qiu, Y. Zhang, J. B. Wang, *Beilstein J. Org. Chem.* **2016**, *12*, 796-804.
- [14] (a) S. T. R. Muller, D. Smith, P. Hellier, T. Wirth, *Synlett* **2014**, *25*, 871-875; (b) S. T. R. Muller, T. Wirth, *ChemSusChem* **2015**, *8*, 245-250; (c) B. J. Deadman, S. G. Collins, A. R. Maguire, *Chem. Eur. J.* **2015**, *21*, 2298 – 2308.
- [15] S. M. Nicolle, C. J. Moody, *Chem. Eur. J.* **2014**, *20*, 4420-4425.
- [16] S. M. Nicolle, C. J. Hayes, C. J. Moody, *Chem. Eur. J.* **2015**, *21*, 4576-4579.
- [17] E. Lee, K. W. Jung, Y. S. Kim, *Tetrahedron Lett.* **1990**, *31*, 1023-1026.
- [18] (a) M. P. Doyle, E. J. May, *Synlett* **2001**, *2001*, 967-969; (b) J. C. Wang, Y. Zhang, Z. J. Xu, V. K. Y. Lo, C. M. Che, *ACS Catalysis* **2013**, *3*, 1144-1148; (c) M. Wamser, T. Bach, *Synlett* **2014**, *25*, 1081-1084; (d) L. B. Fu, H. B. Wang, H. M. L. Davies, *Org. Lett.* **2014**, *16*, 3036-3039.
- [19] (a) G. R. Pettit, T. R. Kasturi, *J. Org. Chem.* **1960**, *25*, 875-876; (b) G. A. Kraus, K. A. Frazier, B. D. Roth, M. J. Taschner, K. Neuenschwander, *J. Org. Chem.* **1981**, *46*, 2417-2419; (c) M. C. Hansen, X. Verdagner, S. L. Buchwald, *J. Org. Chem.* **1998**, *63*, 2360-2361; (d) M. Yato, K. Homma, A. Ishida, *Tetrahedron* **2001**, *57*, 5353-5359.
- [20] (a) Y. Q. Feng, M. M. Majireck, S. M. Weinreb, *J. Org. Chem.* **2014**, *79*, 7-24; (b) A. T. Davies, A. M. Z. Slawin, A. D. Smith, *Chem. Eur. J.* **2015**, *21*, 18944-18948.
- [21] T. Ueda, H. Konishi, K. Manabe, *Org. Lett.* **2012**, *14*, 3100-3103.
- [22] F. Gallou, R. Haenggi, H. Hirt, W. Marterer, F. Schaefer, M. Seeger-Weibel, *Tetrahedron Lett.* **2008**, *49*, 5024-5027.
- [23] T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508-7510.
- [24] S. Voth, J. W. Hollett, J. A. McCubbin, *J. Org. Chem.* **2015**, *80*, 2545-2553.
- [25] T. Furuya, T. Ritter, *Org. Lett.* **2009**, *11*, 2860-2863.
- [26] N. D. Litvinas, P. S. Fier, J. F. Hartwig, *Angew. Chem., Int. Ed.* **2012**, *51*, 536-539.
- [27] J. M. Murphy, X. Liao, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 15434-15435.
- [28] J. Besnard, P. S. Jones, A. L. Hopkins, A. D. Pannifer, *Drug Discovery Today* **2015**, *20*, 181-186.