Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2016, **14**, 6947

Received 26th May 2016,
Accepted 24th June 2016

DOI: 10.1039/c6ob01148a

www.rsc.org/obc

A metal-catalyzed enyne-cyclization step for the synthesis of bi- and tricyclic scaffolds amenable to molecular library production†

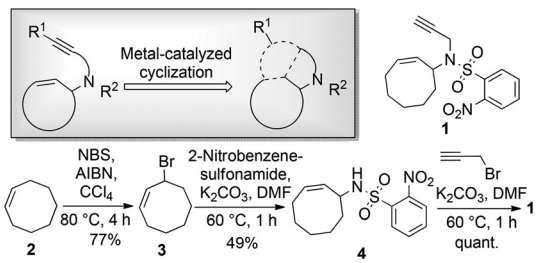
Peng Wu,‡[a] Michael Åxman Petersen,‡[a] A. Emil Cohrt,‡[a] Rico Petersen,[a] Rémy Morgentin,[b] Hugues Lemoine,[b] Carine Roche,[b] Anthony Willaume,[b] Mads H. Clausen*[a,c] and Thomas E. Nielsen*[a,d]

A facile metal-catalyzed diversification step for the synthesis of novel bi- and tricyclic scaffolds from enyne substrates is reported in this study. From a single starting material, topologically diverse scaffolds for library synthesis can be generated and decorated in a few steps. The methodology was used to produce a library of 490 compounds within the European Lead Factory (ELF) Consortium.

Synthetically tractable scaffolds populating unexplored areas of chemical space are highly sought-after in early-stage drug discovery, particularly in the hunt for hits against challenging macromolecular targets.[1] It has been suggested that small-molecule candidates containing fewer aromatic rings and a high fraction of sp^3-hybridized carbon atoms (Fsp^3) exhibit improved molecular solubility and reduced attrition rate.[2,3] On the other hand, aromatic rings are likely to contribute to high binding affinities and potency due to their hydrophobic properties and rigid structures, and compelling correlations between the Fsp^3 value and the hit rate have been elucidated in fragment-based drug discovery analysis.[4] Most FDA-approved small-molecule drugs that are administered orally, including >90% of approved kinase inhibitors,[5,6] have an aromatic ring count value between two and four.[7] Thus, the delicate balance between physicochemical properties and pharmacological potency makes the design of optimal scaffolds a daunting task in drug discovery.

The synthesis of structurally complex and diverse scaffolds from easily accessible building blocks with multiple functional groups is highly sought-after in the current field of library synthesis.[8] In our group, several sp^3-rich scaffolds containing multiple chiral centers have been utilized for the production of molecular libraries of up to 500 compounds.[9–13] Following our previous work within diversity-oriented synthesis, we herein report a facile and scalable metal-catalyzed cyclization approach for the synthesis of bi- and tricyclic scaffolds from enyne substrates. For proof-of-principle, one of the scaffolds was used as a core template for the production of a library containing 490 compounds in the ELF Consortium.[14–16]

Enyne substrates have been studied in various metal-catalyzed reactions, such as the well-investigated enyne metathesis and various cycloisomerization reactions.[17–23] The nosyl-protected enyne compound **1** was designed for use in various cyclization reactions and readily obtained through a straightforward route starting from cyclooctene (Scheme 1). To introduce appendage diversity from any resulting scaffold, a reactive alkenyl halide handle would be highly desirable, *e.g.* for smooth metal-catalyzed cross-coupling reactions. Introduction of a halide prior to a metal-catalyzed enyne-cyclization would be advantageous, particularly if the halide could be retained during several scaffold-generating diversification steps, such as the application of iodoalkynes in cylcoisomerization reactions.[19,20,23] A substantial challenge, however, would be constituted by the inherent reactivity of the halide functionality.



Scheme 1 General strategy (box) and synthesis of enyne **1** from cyclooctene **2**.

[a]*Department of Chemistry, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark. E-mail: ten@sund.ku.dk*
[b]*EDELRIS, 115 Avenue Lacassagne, 69003 Lyon, France*
[c]*Center for Nanomedicine and Theranostics, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark*
[d]*Singapore Centre on Environmental Life Science Engineering, Nanyang Technological University, 637551, Singapore*

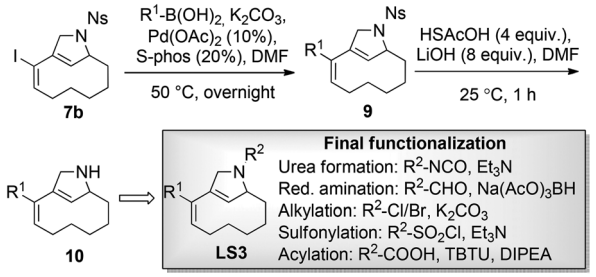
†Electronic supplementary information (ESI) available: General methods, experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c6ob01148a

‡These authors contributed equally to this work.

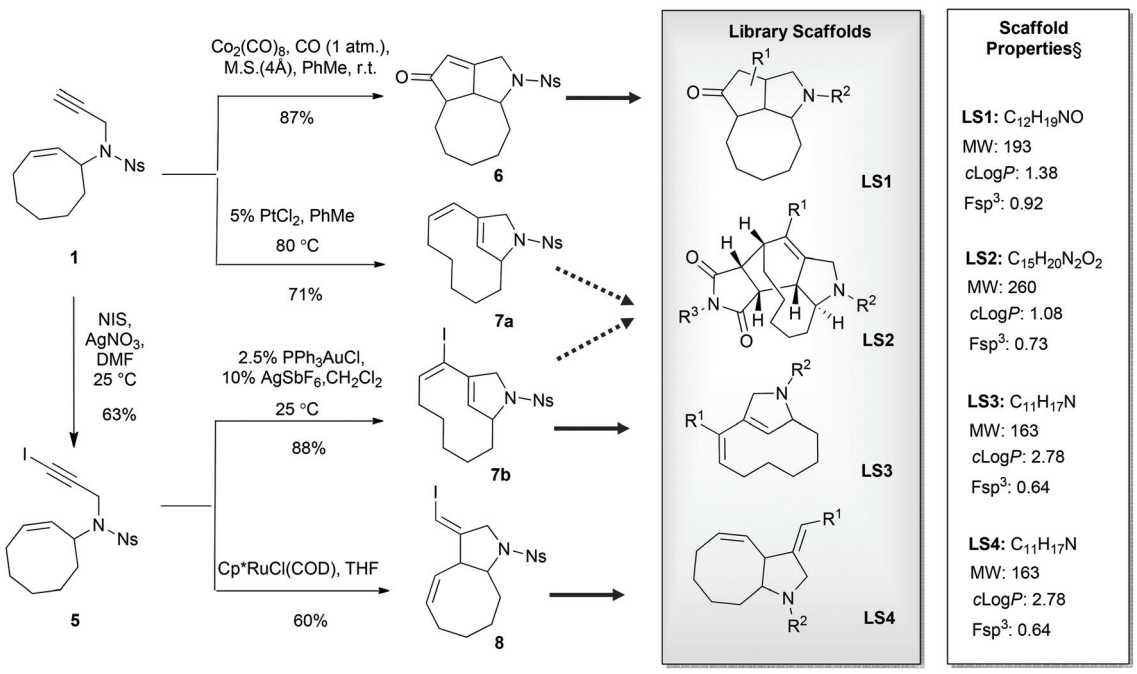
In this context, we decided to synthesize iodoenyne **5** and subject this substrate to metal-catalyzed cyclization reactions that allow the formation of new scaffolds without compromising the halide handle. In a successful embodiment, metal-catalyzed cyclization could then be followed by appendage diversifying cross-coupling reactions, ideally providing substituted sp^3-rich scaffolds (clog *P* value <3) of low molecular weight (<300 Da) (Scheme 2).§

When iodoenyne **5** was subjected to ruthenium-based metathesis conditions, only complex reaction mixtures were obtained. Whereas the platinum-catalyzed metathesis reaction of **1** gave the expected product **7a** using $PtCl_2$,[24] the iodinated analogue **5** did not undergo metathesis under these conditions. In further synthetic studies on compound **5**, it was discovered that the bicyclic product **7b** could be synthesized in excellent yield using $PPh_3AuCl/AgSbF_6$ as the catalytic system.[25] During screening of different transition metal catalysts and reagents,[26] it was also shown that compound **1** could be cyclized to the tricyclic compound **6** in a Pauson–Khand reaction using carbon monoxide in the presence of $Co_2(CO)_8$. Unfortunately, the iodoenyne **5** could not be converted to the corresponding tricyclic compound under the same conditions. In addition, compound **5** could be smoothly rearranged to the bicyclic compound **8** using the ruthenium-based catalyst precursor Cp*RuCl(COD).[27,28]

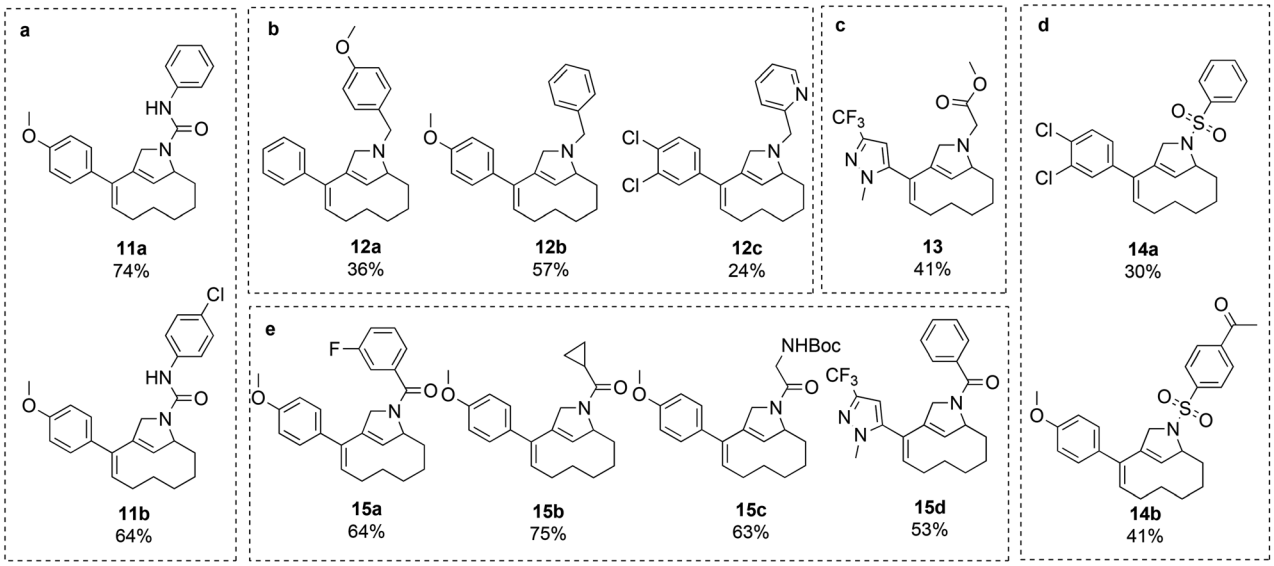
Attempts were made to form the tetracyclic scaffold **LS2** from **7a** and **7b** *via* maleimide Diels–Alder reactions. With a high Fsp^3 value and a substantial number of chiral centers and appendage diversification handles, **LS2** represents an interesting scaffold for library synthesis. Presumably, the twisted nature of the diene moiety of **7** makes the formation of Diels–Alder products impossible irrespective of the dienophile. It was therefore decided to bring scaffold **LS3** forward as a library core structure based on compound **7b**, which has two potential diversification handles. The R^1 group could selectively be varied using different boronic acids in Suzuki cross-coupling reactions. The obtained *N*-nosyl compounds **9** were deprotected to give amines **10**, which were subjected to a final functionalization step to introduce R^2 groups of diverse nature (Scheme 3). Numerous compounds were prepared during library production. For example, compound **10** was treated with aryl isocyanates in the presence of triethylamine to give ureas **11a** and **11b**; reductive amination with aryl aldehydes afforded compounds **12a**, **12b**, and **12c**; alkylation of compound **10** with methyl chloroacetate led to compound **13**; sulfonylation with sulfonyl chlorides gave compounds **14a** and **14b**; and acylation of compound **10** under TBTU-mediated coupling conditions afforded compounds **15a–d** (Scheme 4). The above-validated synthetic route was scaled up to 160 mmol



Scheme 3 Synthetic strategy to access library scaffold **LS3**.



Scheme 2 Metal-catalyzed cyclization of enynes for the synthesis of diverse scaffolds for library synthesis.



Scheme 4 Validated compounds for the library establishment based on the **LS3** scaffold. (a) Urea formation; (b) reductive amination; (c) alkylation; (d) sulfonylation; (e) acylation.

scale for the intermediate core scaffold **7b** (75 g) from 550 mmol of cyclooctene **2** (70 g) in the indicated 5 steps. Functionalization of the R^1 group of **7b** through Suzuki-coupling, followed by nosyl-deprotection, and a final amine-substitution step yielded a library of 490 compounds for the European Lead Factory Consortium.¶

A total of 654 new screening compounds, most of which are compliant with the Lipinski's Rule of Five (Fig. 1), were selected amongst the enumerated library and synthesized in 9 production campaigns with an overall success rate of 75% after purification under the optimized conditions.

In this study, we have demonstrated the feasibility of metal-catalyzed cyclizations for the synthesis of structurally diverse bi- and tricyclic scaffolds from a readily available iodoenyne. From a single starting material, topologically diverse scaffolds for library synthesis can be generated and decorated in a few steps. Scaffold **LS3** with two appendage functionalization handles was selected as a proof-of-concept for the synthesis of a library of 490 compounds, which will be screened against a range of biological targets within the ELF Consortium. Further library productions based on other scaffolds from this study will be reported in due course.

Acknowledgement is made to the Innovative Medicines Initiative Grant (115489, FP7/2007–2013), the Lundbeck Foundation (R141-2013-13835), and the Technical University of Denmark. We also thank Jennifer Mehlen, Julie Raud, Guillaume Ranty, and Caroline Gurcel at Edelris for assistance in the purification of the final library compounds.

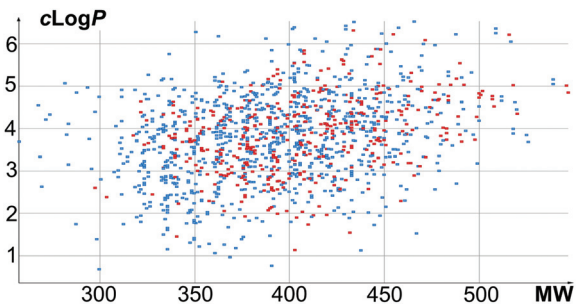


Fig. 1 Physical chemical property analysis of library compounds (blue spots: 903 enumerated compounds; red spots: 490 validated compounds), clog *P vs.* MW.

Notes and references

§The physicochemical properties were calculated based on scaffolds with all R groups counted as hydrogen atoms.

¶One major challenge for the production of this library lies in the apolar nature of the scaffold **LS3**, which resulted in lower success rates in the initial production attempts since standard purification conditions relying on preparative HPLC/MS proved to be unsuitable. After investigating various combinations of stationary and mobile phases, the best result was obtained by using a C_{18} column eluting with a gradient starting from 70% acetonitrile in aqueous ammonia (10 mM).

1 C. M. Marson, *Chem. Soc. Rev.*, 2011, **40**, 5514.
2 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752.
3 T. J. Ritchie and S. J. F. Macdonald, *Drug Discovery Today*, 2009, **14**, 1011.
4 M. Hansson, J. Pemberton, O. Engkvist, I. Feierberg, L. Brive, P. Jarvis, L. Zander-Balderud and H. Chen, *J. Biomol. Screening*, 2014, **19**, 727.
5 P. Wu, T. E. Nielsen and M. H. Clausen, *Drug Discovery Today*, 2016, **21**, 5.
6 P. Wu, T. E. Nielsen and M. H. Clausen, *Trends Pharmacol. Sci.*, 2015, **36**, 422.

7 R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845.
8 D. J. Foley, R. G. Doveston, I. Churcher, A. Nelson and S. P. Marsden, *Chem. Commun.*, 2015, **51**, 11174.
9 R. Petersen, A. E. Cohrt, M. Å. Petersen, P. Wu, M. H. Clausen and T. E. Nielsen, *Bioorg. Med. Chem.*, 2015, **23**, 2646.
10 M. Å. Petersen, M. A. Mortensen, A. E. Cohrt, R. Petersen, P. Wu, N. Fleury-Brégeot, R. Morgentin, C. Lardy, T. E. Nielsen and M. H. Clausen, *Bioorg. Med. Chem.*, 2015, **23**, 2695.
11 P. Wu, M. Å. Petersen, R. Petersen, M. O. Rasmussen, K. Bonnet, T. E. Nielsen and M. H. Clausen, *Eur. J. Org. Chem.*, 2015, 5633.
12 P. Wu, M. Å. Petersen, A. E. Cohrt, R. Petersen, M. H. Clausen and T. E. Nielsen, *Eur. J. Org. Chem.*, 2015, 2346.
13 P. Wu, M. A. Petersen, R. Petersen, T. Flagstad, R. Guilleux, M. Ohsten, R. Morgentin, T. E. Nielsen and M. H. Clausen, *RSC Adv.*, 2016, **6**, 46654.
14 A. Mullard, *Nat. Rev. Drug Discovery*, 2013, **12**, 173.
15 J. Besnard, P. S. Jones, A. L. Hopkins and A. D. Pannifer, *Drug Discovery Today*, 2015, **20**, 181.
16 A. Karawajczyk, F. Giordanetto, J. Benningshof, D. Hamza, T. Kalliokoski, K. Pouwer, R. Morgentin, A. Nelson, G. Müller, A. Piechot and D. Tzalis, *Drug Discovery Today*, 2015, **20**, 1310.
17 H. Villar, M. Frings and C. Bolm, *Chem. Soc. Rev.*, 2007, **36**, 55.
18 V. Michelet, P. Y. Toullec and J.-P. Genêt, *Angew. Chem., Int. Ed.*, 2008, **47**, 4268.
19 P. Morán-Poladura, E. Rubio and J. M. González, *Angew. Chem., Int. Ed.*, 2015, **54**, 3052.
20 A. Furstner, A. Schlecker and C. W. Lehmann, *Chem. Commun.*, 2007, 4277.
21 B. M. Trost, A. C. Gutierrez and E. M. Ferreira, *J. Am. Chem. Soc.*, 2010, **132**, 9206.
22 P. R. Walker, C. D. Campbell, A. Suleman, G. Carr and E. A. Anderson, *Angew. Chem., Int. Ed.*, 2013, **52**, 9139.
23 P. Nösel, T. Lauterbach, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Chem. – Eur. J.*, 2013, **19**, 8634.
24 A. Fürstner, H. Szillat and F. Stelzer, *J. Am. Chem. Soc.*, 2000, **122**, 6785.
25 C. Obradors and A. M. Echavarren, *Acc. Chem. Res.*, 2014, **47**, 902.
26 H. Pellissier and H. Clavier, *Chem. Rev.*, 2014, **114**, 2775.
27 N. Saito, D. Tanaka, M. Mori and Y. Sato, *Chem. Rec.*, 2011, **11**, 186.
28 J. Le Paih, D. Cuervo Rodríguez, S. Dérien and P. H. Dixneuf, *Synlett*, 2000, 95.

