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

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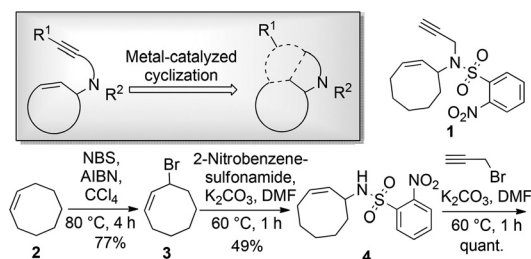
A facile metal-catalyzed diversification step for the synthesis of novel bi- and tricyclic scaffolds from enyne substrates is reported in this study. From a single starting material, topologically diverse scaffolds for library synthesis can be generated and decorated in a few steps. The methodology was 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 (F_{sp^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 F_{sp^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 syn-

thesis.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 cycloisomerization 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**.

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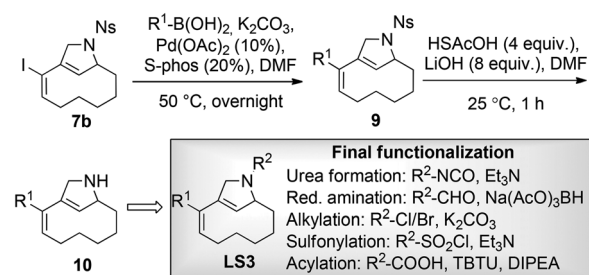


In this context, we decided to synthesize iodoenynone **5** and subject this substrate to metal-catalyzed cyclization reactions that allow the formation of new scaffolds without compromising the halide handle. In a successful embodiment, metal-catalyzed cyclization could then be followed by appendage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

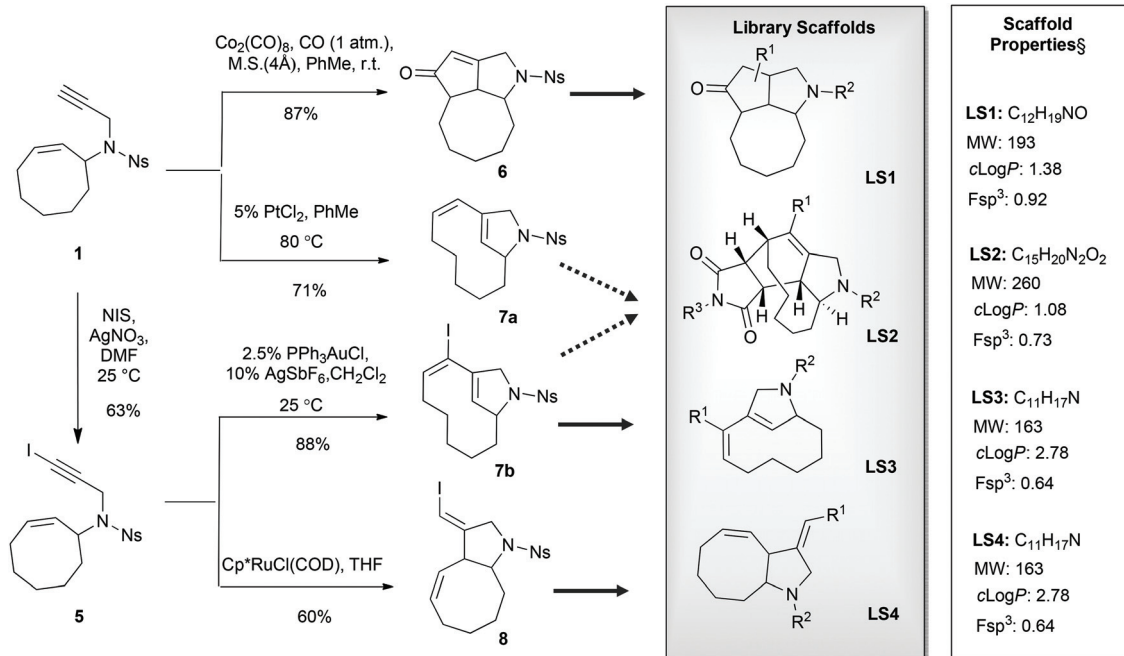
When iodoenynone **5** was subjected to ruthenium-based metathesis conditions, only complex reaction mixtures were obtained. Whereas the platinum-catalyzed metathesis reaction of **1** gave the expected product **7a** using $PtCl_2$,²⁴ the iodinated analogue **5** did not undergo metathesis under these 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 iodoenynone **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

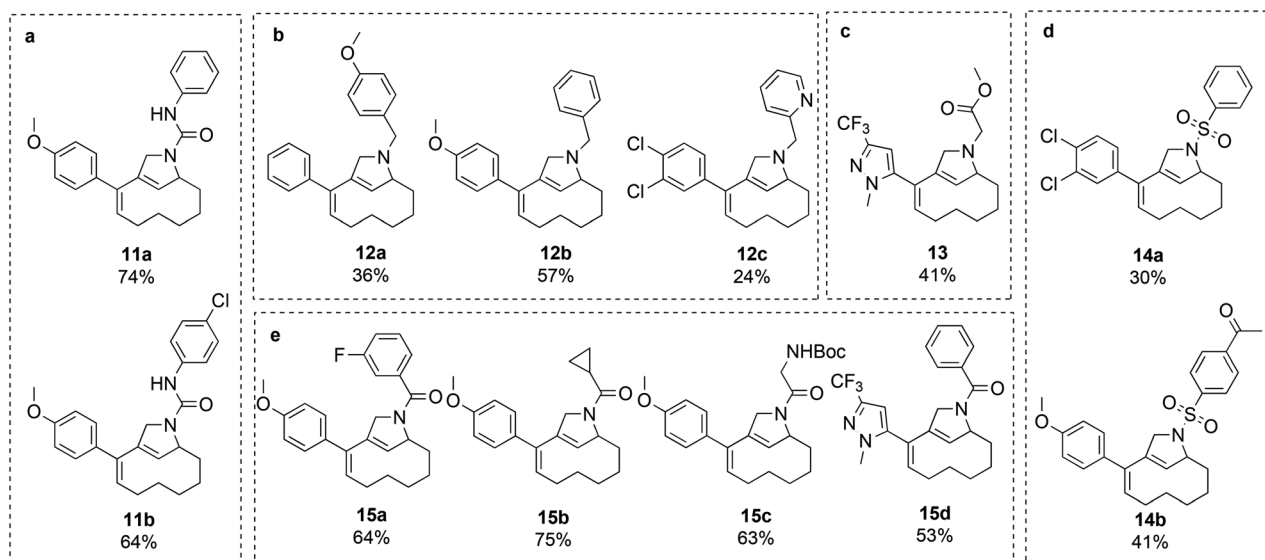


Scheme 3 Synthetic strategy to access library scaffold **LS3**.



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 iodoenone. 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.

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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).

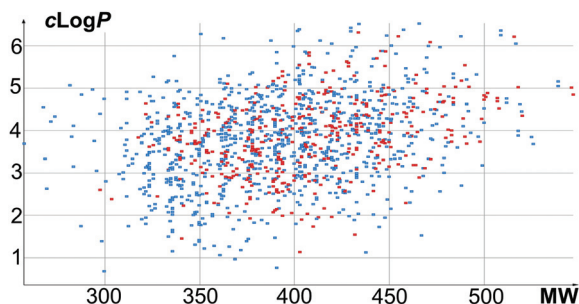
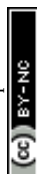


Fig. 1 Physical chemical property analysis of library compounds (blue spots: 903 enumerated compounds; red spots: 490 validated compounds), $\text{clog } P$ vs. MW.

- 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.

