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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.

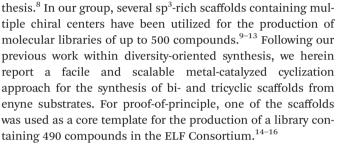
Synthetically tractable scaffolds populating unexplored areas of chemical space are highly sought-after in early-stage drug discovery, particularly in the hunt for hits against challenging macromolecular targets.¹ It has been suggested that smallmolecule candidates containing fewer aromatic rings and a high fraction of sp³-hybridized carbon atoms (Fsp³) 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 Fsp³ value and the hit rate have been elucidated in fragment-based drug discovery analysis.⁴ Most FDAapproved 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-

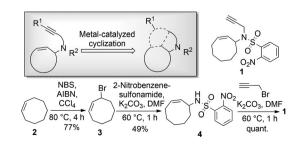
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Envne substrates have been studied in various metal-catalyzed reactions, such as the well-investigated enyne metathesis and various cycloisomerization reactions.¹⁷⁻²³ The nosyl-protected envne compound 1 was designed for use in various cyclization 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 envne-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.



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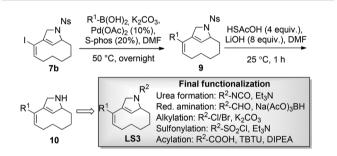
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In this context, we decided to synthesize iodoenyne 5 and subject this substrate to metal-catalyzed cyclization reactions that allow the formation of new scaffolds without compromising the halide handle. In a successful embodiment, metal-catalyzed cyclization could then be followed by appendage diversifying cross-coupling reactions, ideally providing substituted sp³-rich scaffolds (clog *P* value <3) of low molecular weight (<300 Da) (Scheme 2).§

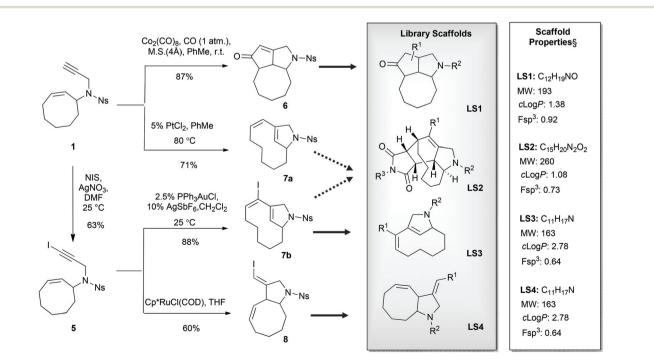
When iodoenyne 5 was subjected to ruthenium-based metathesis conditions, only complex reaction mixtures were obtained. Whereas the platinum-catalyzed metathesis reaction of 1 gave the expected product 7a using $PtCl_2$ ²⁴ the iodinated analogue 5 did not undergo metathesis under these conditions. In further synthetic studies on compound 5, it was discovered that the bicyclic product 7b could be synthesized in excellent yield using PPh₃AuCl/AgSbF₆ 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 iodoenvne 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 Fsp³ 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

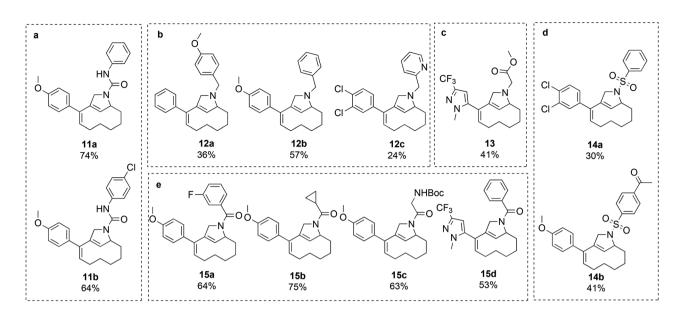
Diels-Alder products impossible irrespective of the dienophile. It was therefore decided to bring scaffold LS3 forward as a library core structure based on compound 7b, which has two potential diversification handles. The R¹ group could selectively be varied using different boronic acids in Suzuki crosscoupling 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 any 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 7**b** (75 g) from 550 mmol of cyclooctene 2 (70 g) in the indicated 5 steps. Functionalization of the R^1 group of 7**b** 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 metalcatalyzed 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

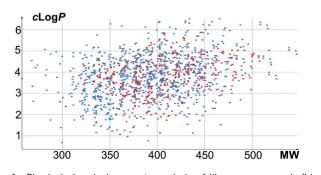


Fig. 1 Physical chemical property analysis of library compounds (blue spots: 903 enumerated compounds; red spots: 490 validated compounds), clog *P* vs. MW.

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).

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