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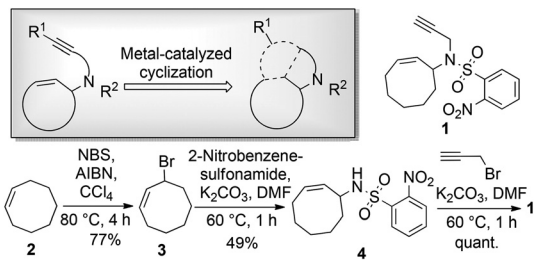
A facile metal-catalyzed diversification step for the synthesis of novel bi- and tricyclic scaffolds from enyne substrates is reported in this study. From a single starting material, topologically diverse scaffolds for library synthesis can be generated and decorated in a few steps. The methodology was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

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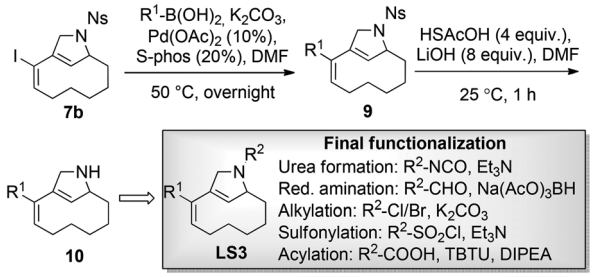
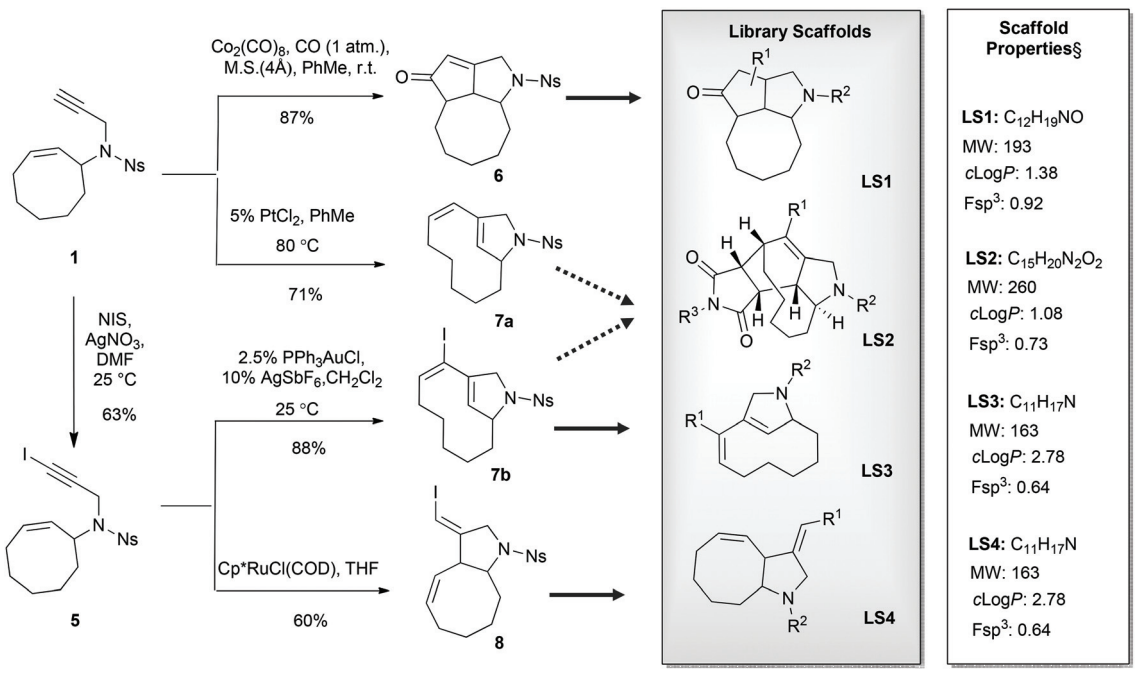
In this context, we decided to synthesize iodoenyne **5** and subject this substrate to metal-catalyzed cyclization reactions that allow the formation of new scaffolds without compromising the halide handle. In a successful embodiment, metal-catalyzed cyclization could then be followed by appendage diversifying cross-coupling reactions, ideally providing substituted 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]

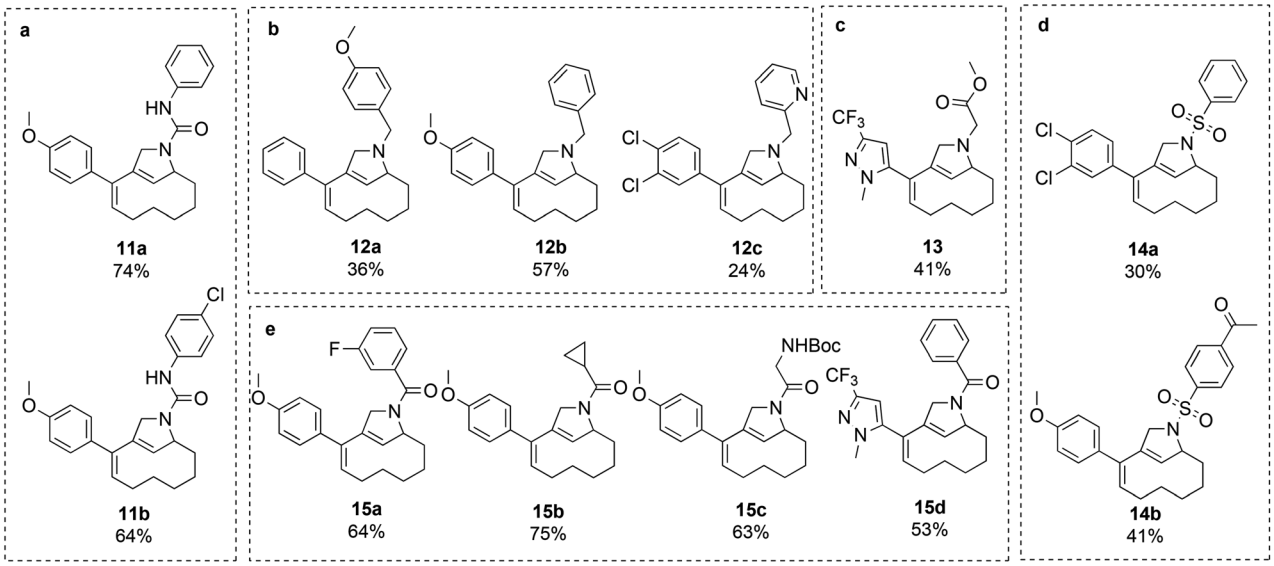
Attempts were made to form the tetracyclic scaffold **LS2** from **7a** and **7b** *via* maleimide Diels–Alder reactions. With a high Fsp^3 value and a substantial number of chiral centers and appendage diversification handles, **LS2** represents an interesting scaffold for library synthesis. Presumably, 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.

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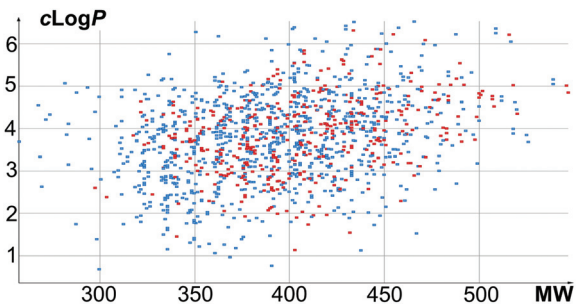

Fig. 1 Physical chemical property analysis of library compounds (blue spots: 903 enumerated compounds; red spots: 490 validated compounds), clog *P vs.* MW.

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).

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