A DIVERSITY-ORIENTED SYNTHESIS OF MACROCYCLIC PEPTIDOMIMETICS WITH UNPRECEDENTED SCAFFOLD DIVERSITY

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1. Introduction

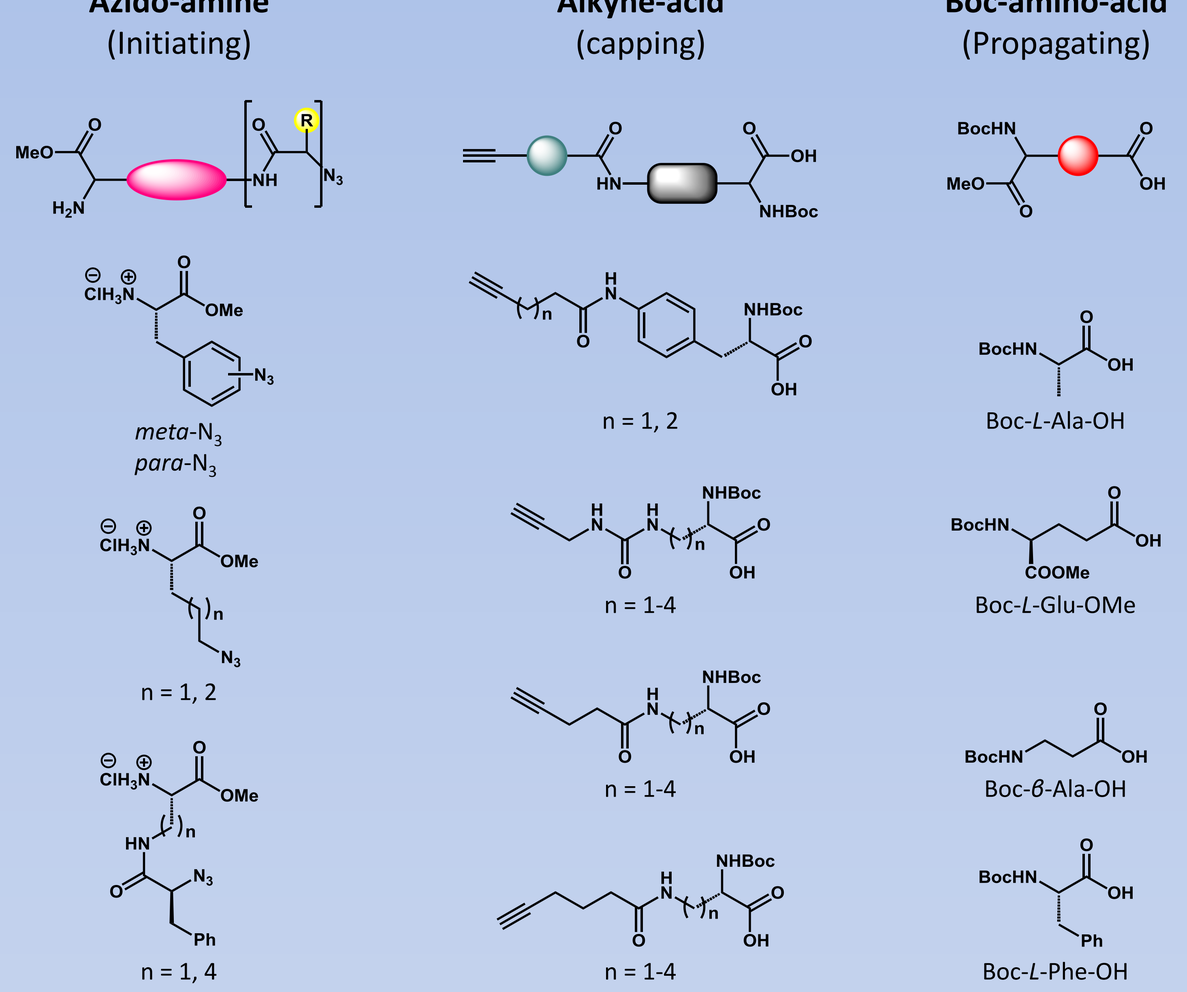
Macrocycles (ring structures of 12 or more atoms) are important core scaffolds that contribute significantly to the overall 3D conformation of molecules and thus how they present chemical information.[1] Macrocyclic peptidomimetics are a subclass of macrocycles that are designed to act as functional substitutes of peptide motifs or proteins, displaying more desirable properties such as improved metabolic and proteolytic stability.[2] Despite their useful properties, macrocyclic peptidomimetics represent an underexplored structural class within drug discovery. This is often attributed to the lack of general synthetic methods for producing collections of macrocycles with high level of structural (scaffold) and thus functional diversity (broad range of biological activities).

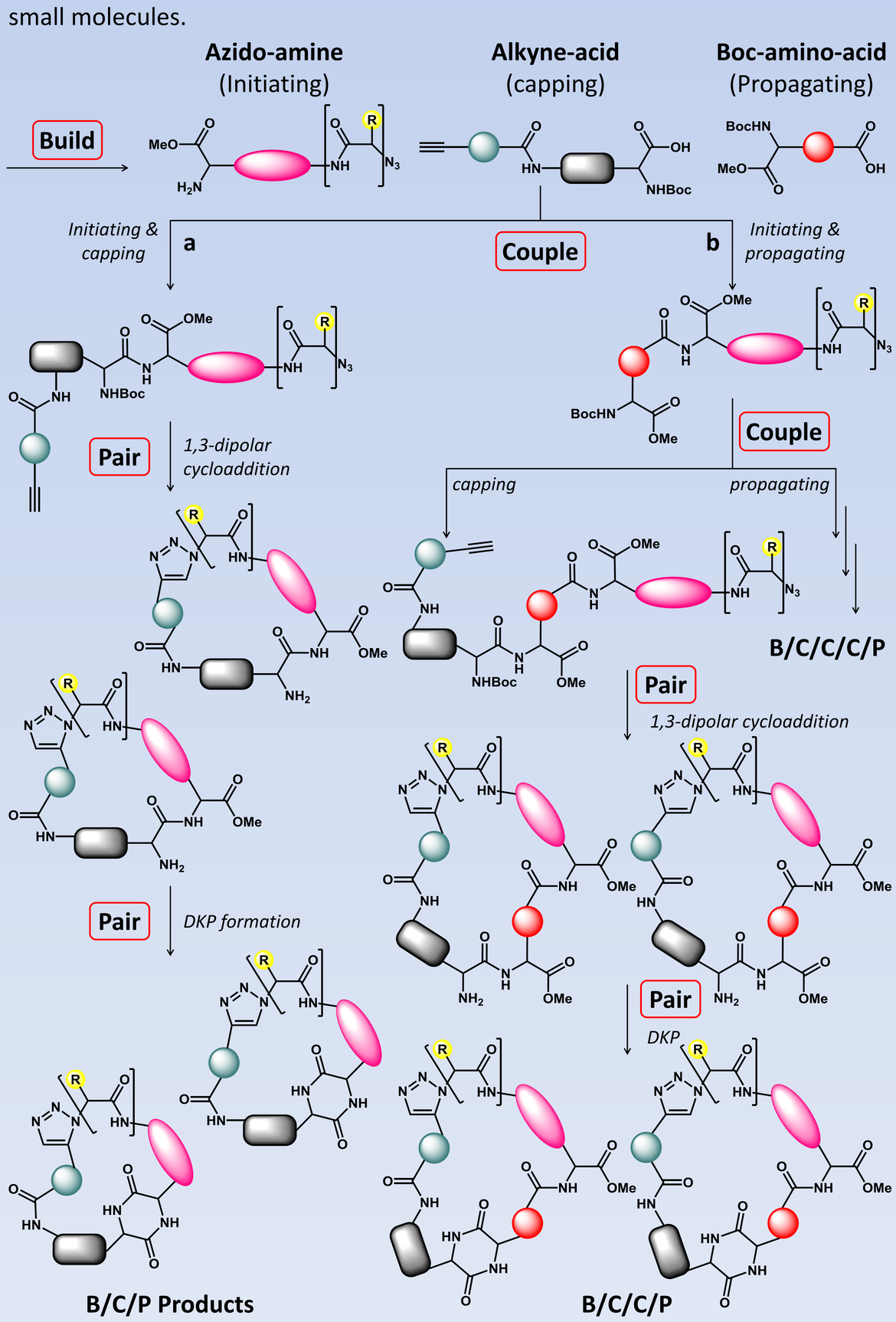
2. Synthesis

In our attempt to address this issue, we adopted and expanded upon the build/couple/pair (B/C/P) synthetic algorithm, which has found extensive application in the field of diversity-oriented synthesis (DOS).[3] In the *build* phase, three general types of chiral building blocks were constructed: six "azido-amines" ("initiating"), 14 "alkyne-acids" ("capping") and four "Boc-amino-acids" ("propagating") (right).

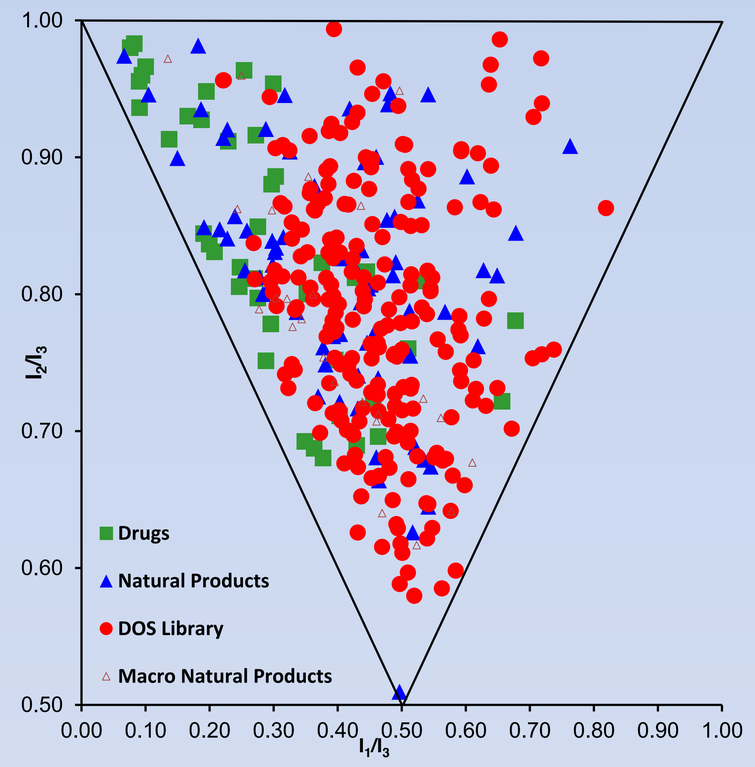
An amide coupling of the "initiating" and "capping" building blocks afforded linear peptides containing both a terminal alkyne and an azide (below, pathway **a**). The *pair* phase was comprised of two cyclization steps. In the first, a regioselective metal-catalysed 1,3-dipolar cycloaddition ("click") selectively afforded regioisomeric macrocycles containing 1,4- or 1,5-disubstituted triazoles (copper and ruthenium catalysed, respectively). The triazole moiety acts as a peptide bond mimic. A subsequent cyclization reaction between the amine and carbonyl groups introduced the diketopiperazine moiety (DKP), an important motif in drug discovery.

Our advanced DOS strategy (pathway **b**) involved iterative *couple* steps (B/C/C/P and even B/C/C/C/P), allowing for step-economical access to a diverse range of larger peptidomimetic scaffolds. These may be better suited to targeting extended binding interfaces, such as those associated with protein-protein interactions, which are traditionally viewed as being difficult to modulate using small molecules.





A PMI plot illustrates that our DOS compounds exhibit almost the same range of shape diversity as the natural products, whilst also overlapping to a substantial extent with the top-selling brand-name drugs and macrocyclic natural products. Thus, the library can be said to have a high level of shape diversity.



3. Conclusion

Overall, this advanced DOS algorithm allowed for the efficient synthesis of 219 structurally diverse macrocyclic peptidomimetics from a small set of simple building blocks. This represents an unprecedented level of scaffold diversity in a synthetically-derived library of compounds.

4. References

(1) Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. *Nat. Rev. Drug Discovery* **2008**, *7*, 608.

(2) Isidro-Llobet, A.; Murillo, T.; Bello, P.; Cilibrizzi, A.; Hodgkinson, J. T.; Galloway, W. R. J. D.; Bender, A.; Welch, M.; Spring, D. R. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 6793.

(3) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 48.

5. Acknowledgements

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