The final level of complexity comes with appendage diversification. This can either be employed on a diverse set of scaffolds (vide supra) or simply serve as diversification of a single scaffold as found in lead optimization procedures. In the latter case, common reagent-based routes are followed to explore the chemical

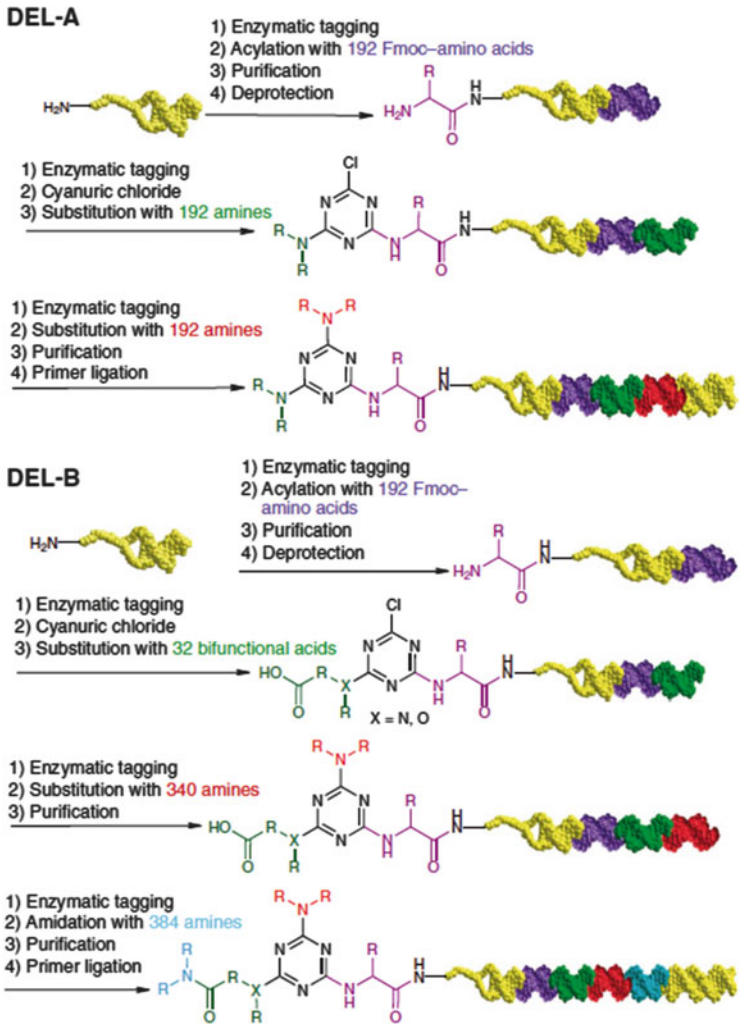

Fig. 6 Target-oriented high-throughput synthesis of two DNA-encoded small-molecule libraries DEL-A and DEL-B. A DNA duplex headpiece is conjugated with a 4,7,10,13-tetraoxapentadecanoic acid (AOP) as a spacer, and following deprotection, the resulting amine allows further diversification. This diversification is then encoded in the DNA utilizing the non-linked two-base 3′ overhang as attachment site for a 7-base variable stretch. DEL-B incorporates an additional p38 kinase pharmacophore, the 3-amino-4-methyl-*N*-methoxybenzamide (AMMB) fragment. Adapted by permission from Clark et al. (2009). Copyright © 2009 Macmillan Publishers Ltd: Nature Chemical Biology