Template-Assisted Click Chemistry as a Method for Discovering Therapeutic Agents for Myotonic Dystrophy type 1 (DM1)

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Fragment-based drug discovery and target-guided synthesis represent two novel strategies for developing new therapeutics for RNA-mediated diseases. We have incorporated the major components of these strategies along with the use of click-chemistry to develop a selection assay for RNA- and DNA-binding ligands, whereby the nucleic acid target synthesizes its own inhibitor. Thus, this strategy can be used to find single- or multi-target agents for a number of diseases, including our model system, Myotonic Dystrophy type 1 (DM1). This assay combines a number of DNA- and RNA-targeting ligands with azide and alkyne functionalities with specific nucleic acid targets to find covalent products using MALDI-TOF mass spectrometry as the analytical detection method. Through an initial study, we discovered several inhibitors capable of forming click products on template. We further elucidated the necessary properties to afford more covalent products, including optimal linker length and binding affinities, while further studying the complexes that are formed by dimeric ligands. From this information we used computational modeling and structure-based design to find new lead compounds for the treatment of DM1 and other RNA-mediated diseases.

Asymmetric Allylic C—H Alkylation *via* Pd-*cis*ArSOX Catalysis

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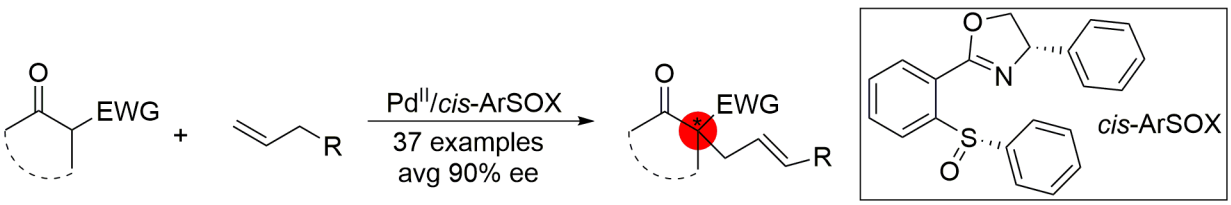
Asymmetric C—H functionalization, which can install both stereochemistry and functionality at unactivated C—H bonds, has the potential to streamline the synthesis of small molecule therapeutics, complex natural products, and agrochemicals. The following work highlights the development of a versatile asymmetric allylic C—H alkylation of terminal olefins with various prochiral carbon nucleophiles under Pd(II)/*cis*-aryl-sulfoxide-oxazoline (*cis*-ArSOX) catalysis. The modular and oxidatively stable *cis*-ArSOX ligand in conjunction with a Lewis Acid catalyst was critical for achieving high levels of enantioinduction. The enantioenriched products have multiple functional group handles for downstream manipulation. This method has been extended to challenging aliphatic olefins with preinstalled stereochemistry, achieving the first highly diastereoselective allylic C—H alkylation. Collectively this work demonstrates the broadest prochiral nucleophile scope used in allylic C—H alkylations to date.



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