

Bioorthogonally activatable iminosydnone-caged compounds

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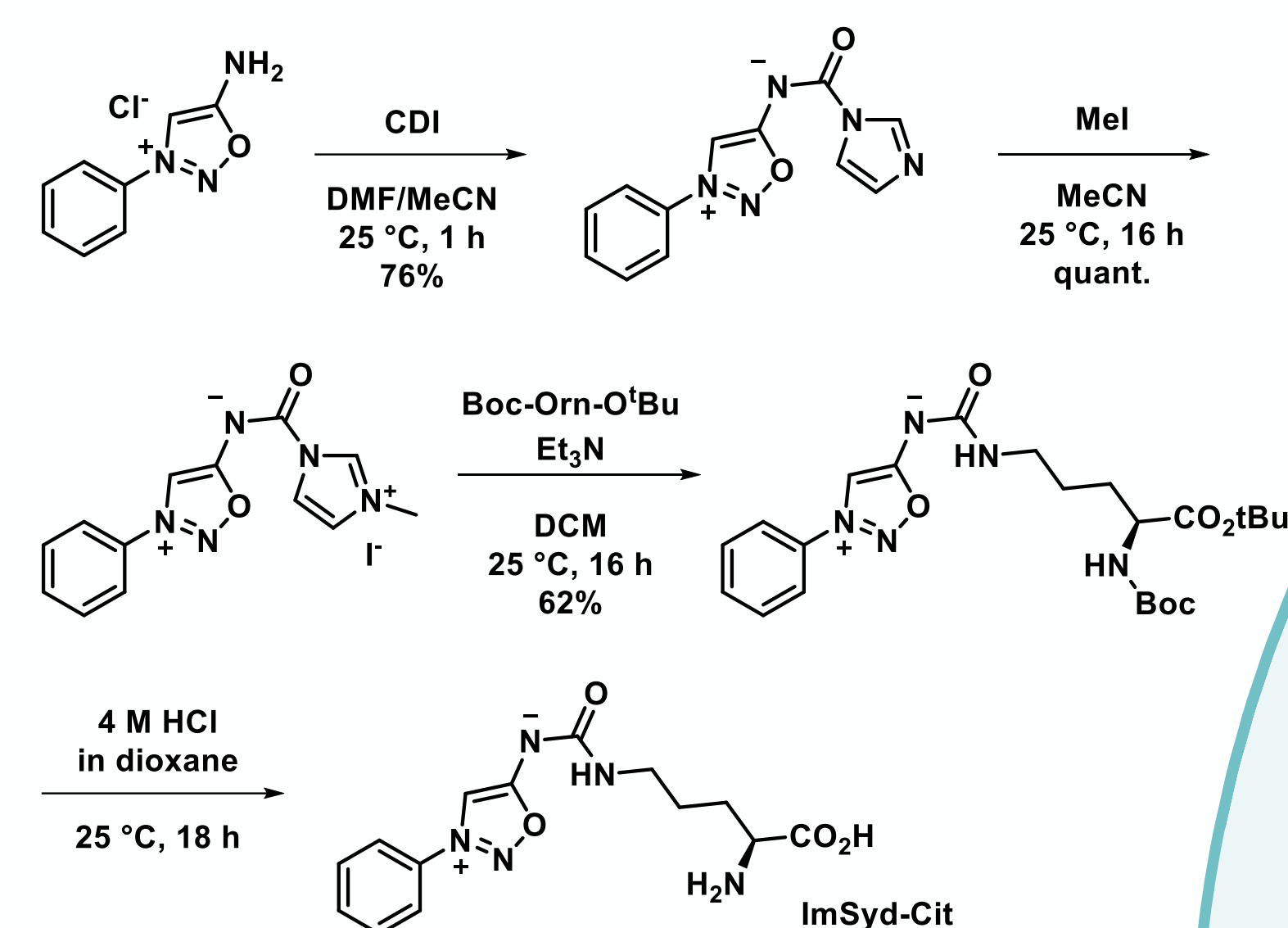
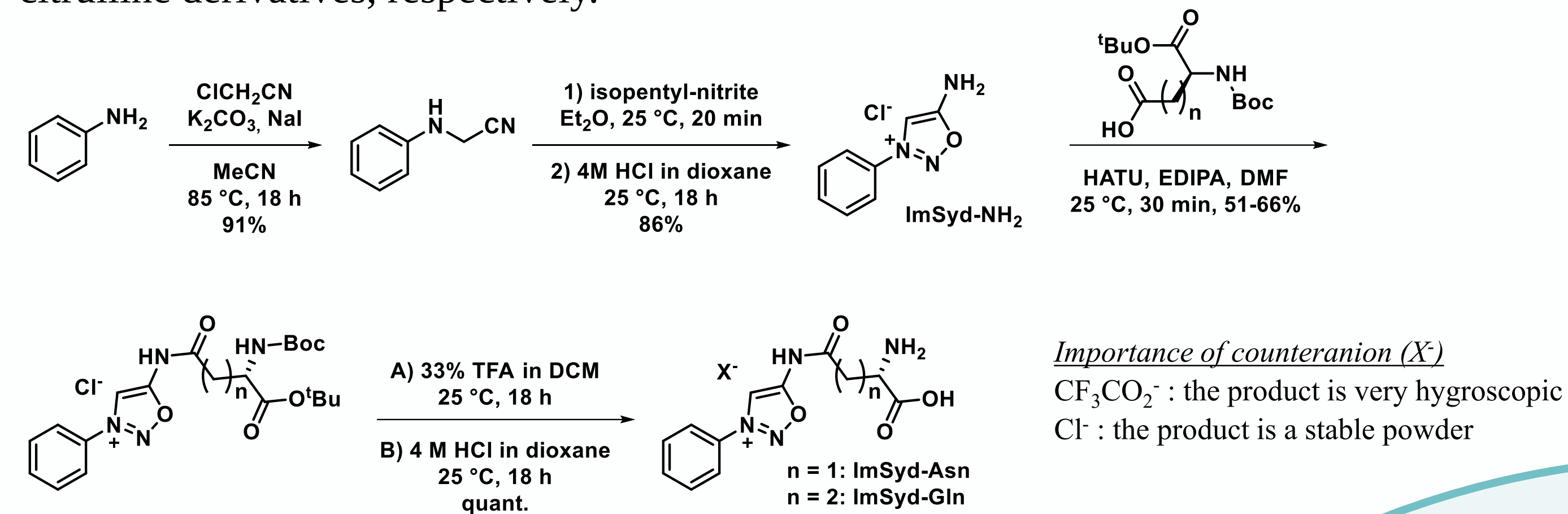
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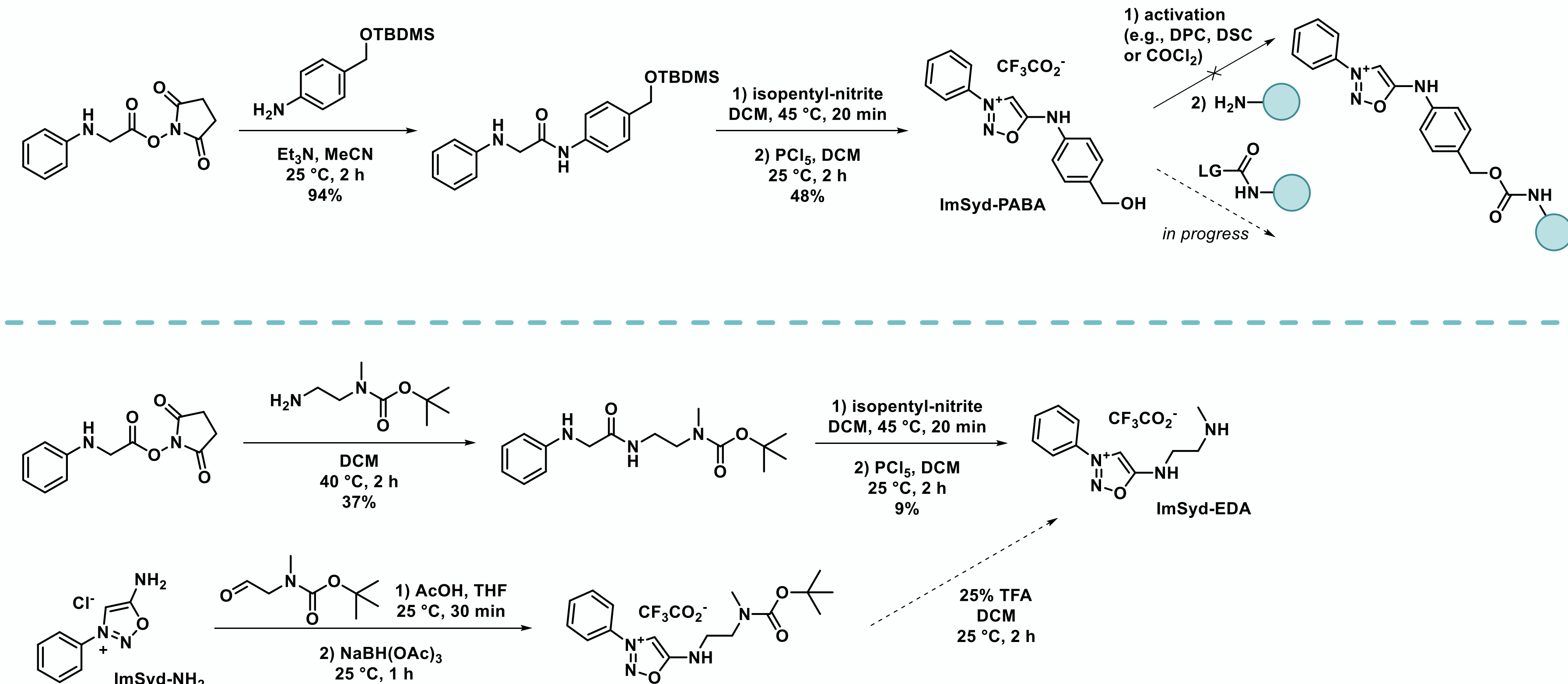
ImSyd-caged amino acids

The incorporation of noncanonical amino acids (nCAAs) into proteins via genetic code expansion (GCE) provides a powerful tool for manipulating and studying cellular processes. Chemically or light-activatable nCAAs enable the conditional control of protein function, and a number of amino acids – including lysine, tyrosine, cysteine, serine, histidine, glutamate, and aspartate – have already been rendered activatable through caging strategies.² The ImSyd-based C2R reaction offers a means to efficiently cage and subsequently release amides and carbamides, potentially enabling the development of activatable asparagine, glutamine, and citrulline derivatives, respectively.



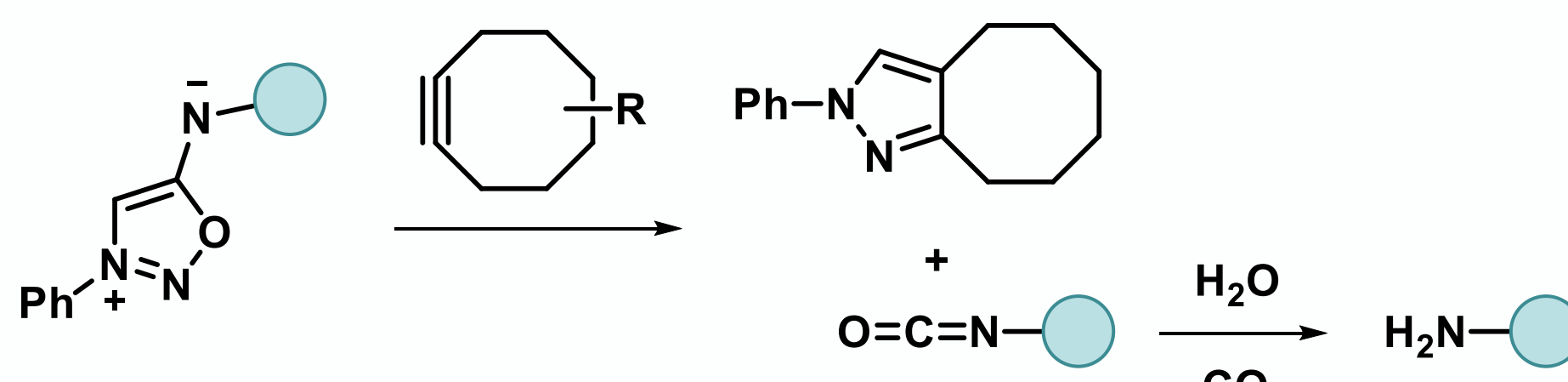
Self-immolative linkers

Although the versatility of ImSyd-based C2R chemistry has been demonstrated through the cyclooctyne-triggered release of amine-type fluorogenic payloads and drugs such as apixaban, carbamazepine, and paroxetine, these studies indicate that the method is particularly well suited for caging sulfonamides, amides, and carbamates, while remaining limited in its ability to cage amines and incapable of masking hydroxyl-containing drugs (e.g., potent chemotherapeutics such as combretastatin, CA-4 or SN38) in its current form.⁵ In addition, caging often requires early-stage incorporation of the bioactive compound, significantly restricting the range of applicable drugs.



Introduction

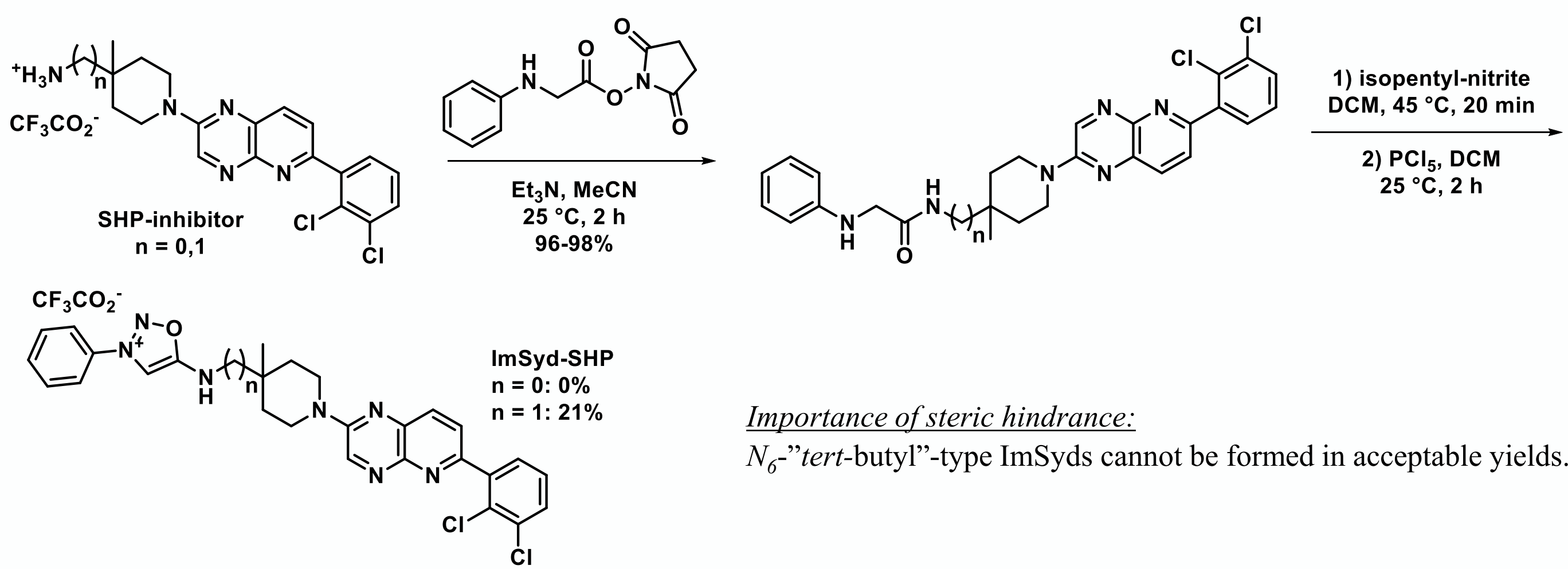
The last decade has seen the reinvention of bioorthogonal chemistry from a biocompatible and efficient bond-forming strategy into a reaction-triggered bond-cleavage platform. Click-to-release (C2R) reactions have evolved into powerful tools in chemical biology and medicinal chemistry, particularly as promising approaches for chemically controlled drug release in living systems.



One of the latest C2R platforms is the [3+2] cycloaddition of iminosydnone (ImSyds)¹ with various cyclooctynes, in which the initially formed bicyclic intermediate rapidly collapses into a pyrazole product with concomitant elimination of an isocyanate derivative. Subsequent rapid hydrolysis and decarboxylation of the isocyanate leads to the release of the final payloads, e.g., amines, carbamates or carbamides.

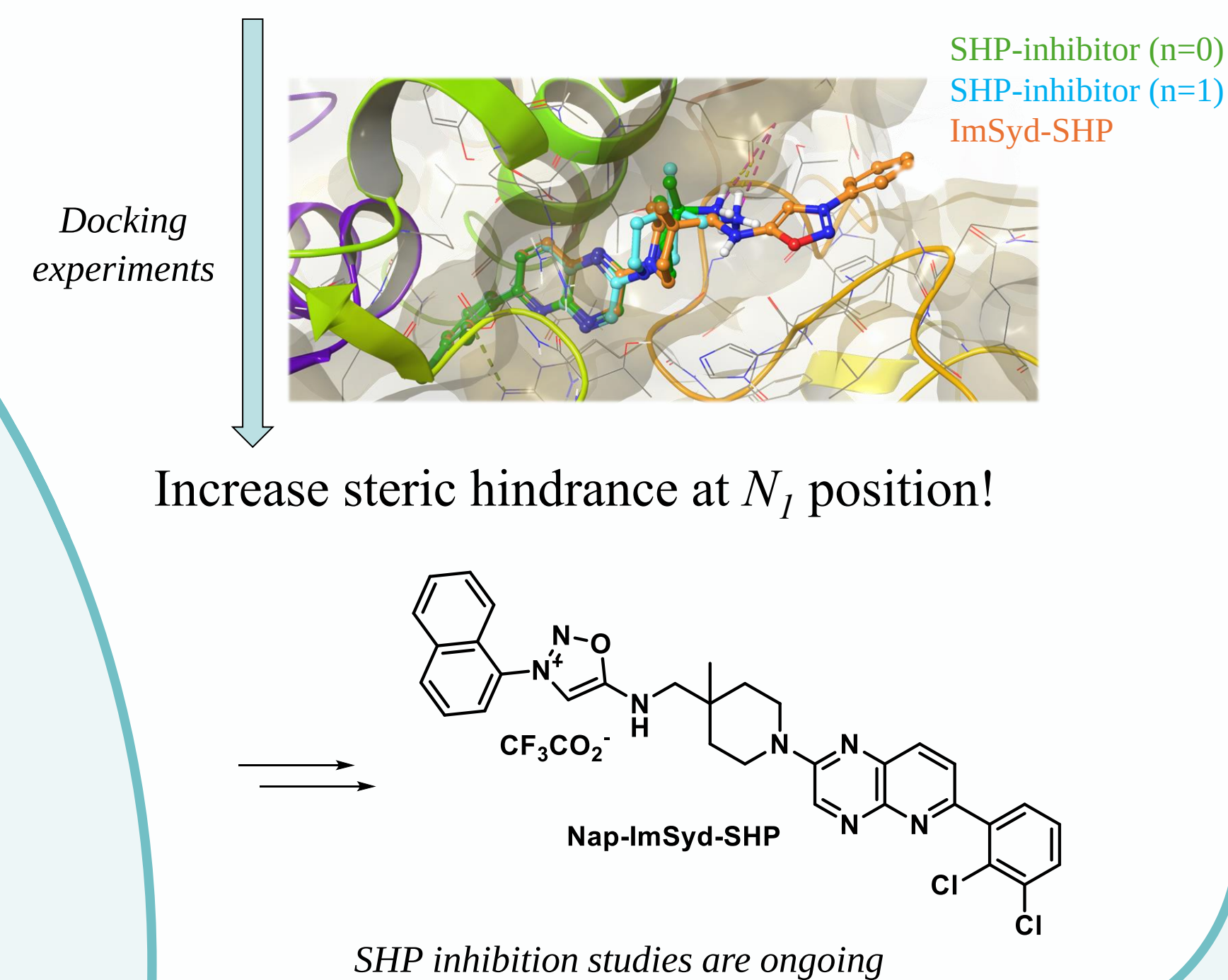
ImSyd-caged SHP inhibitor

SHP2 is an attractive therapeutic target in oncology and immunology-related disorders,³ as it acts as a key regulator of RTK–RAS–MAPK signaling. A recently identified allosteric SHP2 inhibitor scaffold⁴ contains a key aliphatic amine moiety, providing an opportunity for iminosydnone-based caging and site-specific release of the active inhibitor. Based on synthetic considerations, a methylene-extended inhibitor analogue was also synthesized.



Relative SHP inhibition potency:

IC_{50} (ImSyd-SHP) / IC_{50} (SHP-inhibitor) ~ 7.2



Therefore, we aimed to broaden the scope of cageable amine-based compounds and establish a strategy for caging hydroxyl-functionalized drugs. Amine-derived self-immolative linkers are valuable tools because they enable functional group transformation and often allow payload installation at later synthetic stages. We designed ImSyd derivatives incorporating *p*-aminobenzyl alcohol (PABA), ethylene-diamine (EDA), or 3-aminomethyl-2-aminopyridine (AMAP) self-immolative linkers suitable for the caging and release of esters, alcohols, and amines. Notably, these units also enable further modification with photolabile protecting groups for enhanced spatiotemporal control.

References

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Acknowledgements

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