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CONCEPT

Selenium(II)-Nitrogen Exchange (SeNEx) Chemistry: A Good Chemistry Suitable for Nanomole-Scale Parallel Synthesis, DNA-encoded Library Synthesis and Bioconjugation

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Abstract: The continuous development of click reactions with new connecting linkage is crucial for advancing the frontiers of click chemistry. Selenium-nitrogen exchange (SeNEx) chemistry, a versatile chemistry in click chemistry, represents an all-encompassing term for nucleophilic substitution events that replace nitrogen at an electrophilic selenium(II) center, enabling the flexible and efficient assembly of linkages around a Se(II) core. Several SeNEx chemistries have been developed inspired by the biochemical reaction between Ebselen and cysteine residue, and demonstrated significant potential in on-plate nanomole-scale parallel synthesis, selenium-containing DNA-encoded library (*Se*DEL) synthesis, as well as peptide and protein bioconjugation. This concept aims to present the origins, advancements, and applications of selenium(II)-nitrogen exchange (SeNEx) chemistry while also outlining the potential directions for future research in this field.

1. Introduction

The chemical properties of Selenium (Se) differ significantly from its congener sulfur (S). For instance, Se exhibits a larger size and higher polarizability ("softness") compared to S, resulting in enhanced nucleophilic power, lipophilicity, and antioxidant properties[1,2]. Consequently, selenocysteine (Sec) is naturally biosynthesized within living organisms and serves as an indispensable component in 25 selenoproteins, thereby facilitating their active involvement in a wide array of physiological processes[3]. Notably, in addition to selenoproteins, the incorporation of Se into small molecules has also been reported to enhance bioactivities *in vitro* and *in vivo*[4–6], including anti-neurodegenerative diseases[7,8], anti-tumor[9,10] and against multi-drug resistance[11,12]. As a consequence, the design and synthesis of organic Se (Org-Se) compounds for disease prevention and treatment has attracted considerable interest in recent years[13–18]. However, the research on Org-Se therapeutic agents is still in its early stage, primarily due to the limited development of the synthetic toolbox for Org-Se compared to their sulfur counterparts[19].

Among a variety of synthetic strategies, click chemistry is very attractive because it consists of a set of highly efficient, selective, and reliable reactions for the rapid preparation of new compounds and combinatorial libraries through a modular connecting approach via carbon-heteroatom bonds (C-X-C)[20,21]. However, the known click chemistry copper-catalyzed azide-alkyne cycloaddition (CuAAC)[22,23], sulfur-fluoride exchange (SuFEx) chemistry[24,25], and phosphorus fluoride exchange (PFEx) chemistry[26] limit to employ carbon, sulfur, and phosphorus as the synthetic connectors (Figure 1A), while there are no reports on click chemistry using Se as the connecting center before. In this context, although full of challenges, the development of new click chemistry with biologically important Se as the connecting center is of significant importance not only for new functional discovery but also for advancing the frontiers of click chemistry. In this concept, we aim to provide an overview of the selenium(II)-nitrogen exchange (SeNEx) chemistry, including its origins,

advancements, and applications, while offering insights into potential future research directions in this field.

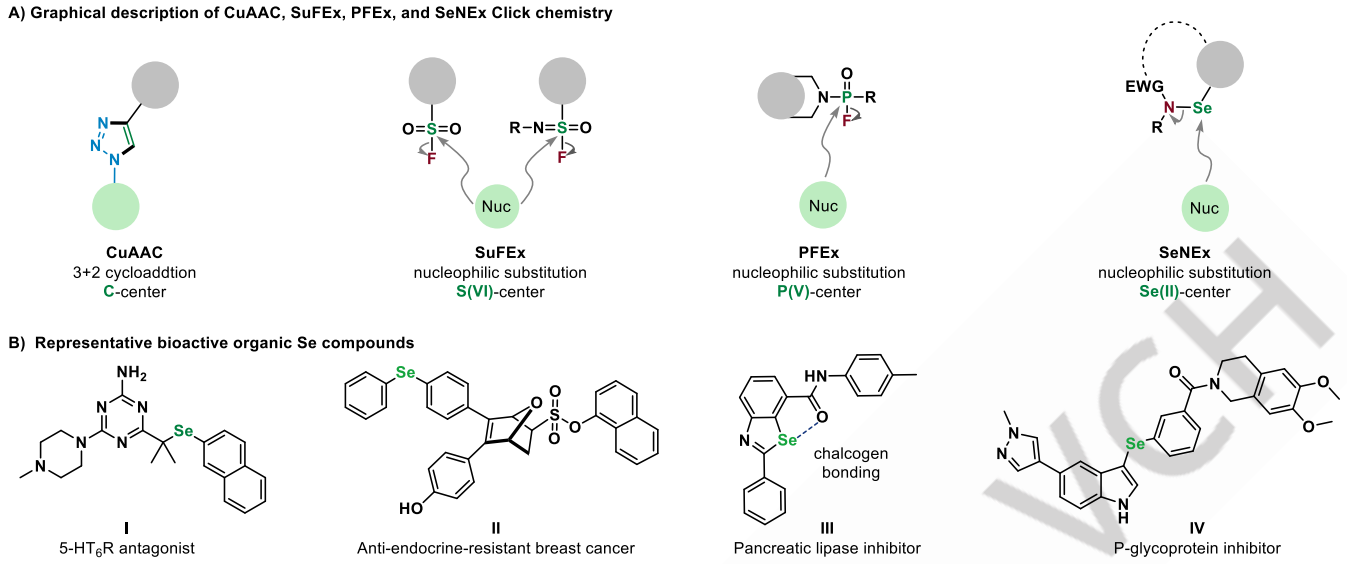

Figure 1. Representative click chemistries and bioactive selenium-containing compounds. A) Graphical description of CuAAC, SuFEx, PFEx, and SeNEx Click chemistries. B) Representative bioactive organic Se compounds.

2. The origins and advancements of selenium(II)-nitrogen exchange click chemistry

Ebselen, an air and water-stable molecule, is a multifunctional drug in active clinical research[27]. Notably, it readily undergoes a Se−N exchange (SeNEx) chemistry to form Se−S adducts via the nucleophilic attack of cellular thiols to its electrophilic Se center[28] (Figure 2A). This biochemical SeNEx chemistry is similar to nature's biosynthesis of amide bonds (proteins) and phosphate diesters (DNA and RNA), both driven by the nucleophilic exchange of the activated acid[29]. It is an important clue for us to design new SeNEx chemistry for four reasons: i) Ebselen and its derivatives are readily available, and are stable to air and a broad of biological nucleophiles, e.g., serine, lysine, and tyrosine; ii) the mild condition of biochemical SeNEx chemistry indicates that new SeNEx reactions can be achieved at mild condition (≤ 37 °C); iii) the amide leaving group is preserved as a pharmacophore in the product molecule, making the new SeNEx reactions with high atomic economy; iv) the N atom in Ebselen can link a broad range of functionalities to achieve sufficient molecular diversity. This, indeed, proved to be the case. We have developed some new SeNEx chemistries by replacing the nucleophilic thiol with carbon nucleophile (Figure 2B).

In 2020, our group first employed benzoselenazolone (BSEA, core structure of Ebselen) as the selenylation reagent for C(sp^2)−H selenylation under rhodium(III)-catalysis. This method shows good functional groups (e.g., amide, -OH, -COOH, ester, pyridine, and pyrimidine) tolerance, and enables the synthesis of selenylation products that contain an adjacent aminoacyl group with high atom economy[30] (Figure 2C). Despite its requirement for elevated temperature and inability to meet the criteria of click chemistry, this study demonstrates that BSEA can indeed serve as a bifunctional selenylation reagent, thereby establishing a solid foundation for the development of SeNEx click chemistry. Soon afterward, based on the lowest unoccupied molecular orbital (LUMO) activation strategy, we further developed the first clickable selenylation reaction between unprotected indole and BSEA by using $B(C_6F_5)_3$ as a Lewis acid catalyst[31] (Figure 2C). This SeNEx chemistry is robust, modular, predictable, highly site-selective, and proceeds in a mild and simple reaction system. In addition to the formation of C(sp^2)-Se bonds, we have recently utilized terminal alkynes as versatile nucleophiles to establish a general and multi-orthogonal SeNEx click chemistry for C(sp)-Se bond formation under Ag(I) or Cu(I) catalysis. This SeNEx click chemistry features modular, robust, mild reaction conditions and excellent functional group compatibility. Notably, the formed selenoalkyne connection can be readily elaborated, thereby endowing this chemistry with multidimensional molecular diversity[32] (Figure 2C). Besides BSEA, we have recently designed benzothiaselenazole-1-oxide (BTSA) as a new Se-N-containing reagent for SeNEx click chemistry development. Firstly, we achieved its racemic and asymmetric synthesis via Rh(III)-catalysis. Then, we discovered that it smoothly undergoes $B(C_6F_5)_3$-catalyzed SeNEx chemistry to yield sulfoximine-containing indole selenides in high yields. Furthermore, BTSA readily reacts with thiols, leading to the identification of a new anti-COVID-19 agent (*R*)-**2e**[33] (Figure 2D).

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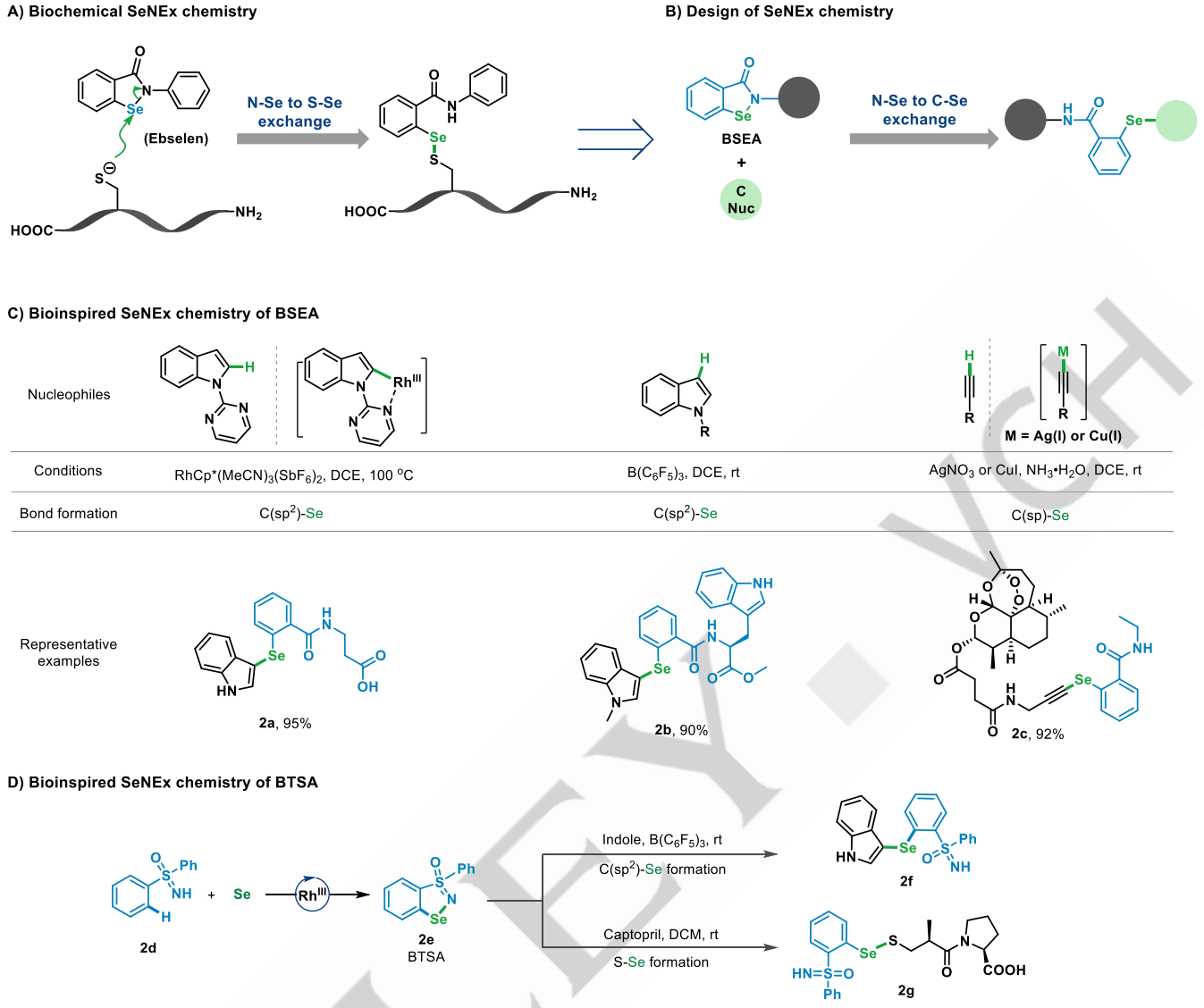


Figure 2. The origin and development of SeNEx click chemistry. A) Biochemical SeNEx chemistry. B) Design of SeNEx chemistry. C) Bioinspired SeNEx chemistry of BSEA. D) Bioinspired SeNEx chemistry of BTSA.

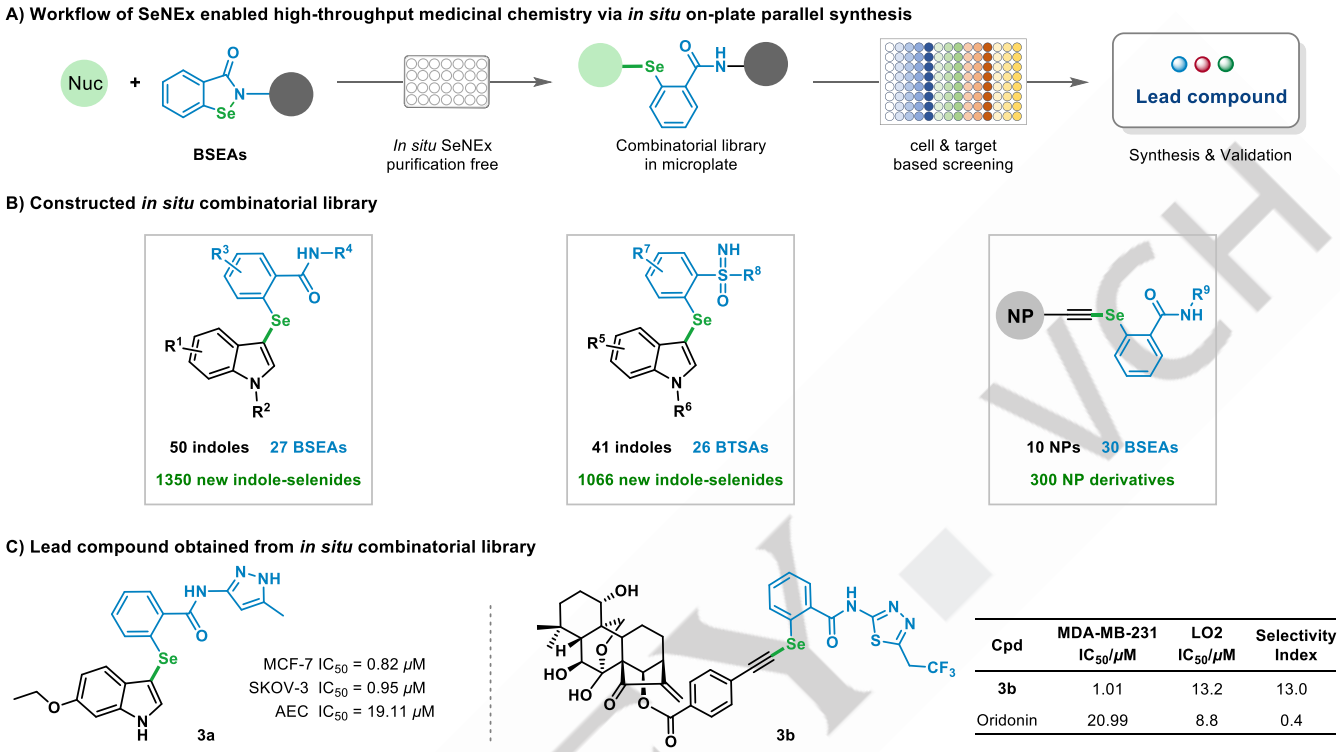
3. Application of SeNEx Click Chemistry in Parallel Synthesis and High-throughput Medicinal Chemistry

Miniaturization of organic reaction to a micromole or even nanomole scale is becoming more and more important for accelerating the discovery of hit or lead compounds because *in situ* combinatorial libraries obtained from on-plate parallel synthesis possess significant advantages over traditional compound libraries including less time and material resources consumption to generate more products and more reaction data, less waste production, and can be used for direct biological screening without purification of the crude products (Figure 3A)[34–36]. However, their effective construction requires reactions to maintain a high yield in a miniaturized scale and behave well at approximately 1:1 reaction partners' ratio under mild and operationally simple reaction conditions[37].

To our delight, the established SeNEx chemistry of indoles and alkynes are all amenable on a miniaturized scale. As delineated in Figure 3B, the on-plate parallel synthesis between 50 indoles and 27 BSEAs[31], 41 indoles and 26 BTSAs[33], 10 alkyne-modified natural products and 30 BSEAs[32] are all performed successfully to afford the corresponding *in situ* combinatorial libraries efficiently. All the compounds in these libraries have not been reported before, thereby they could undoubtedly further enrich the chemical space of selenium medicinal chemistry. Notably, these libraries can be applied *in situ* for the rapid discovery of lead compounds either through target-based or phenotypic-based screening. Impressively, after the phenotypic screening of their antiproliferative activity, we found that indole selenide derivative **3a** could exert nanomolar antiproliferative activities in breast MCF-7 (IC_{50} = 0.82 μM) and ovarian SKOV-3 (IC_{50} = 0.95 μM) cancer cells, but weak cytotoxicity in human normal AEC cells (IC_{50} = 19.11 μM)[31]. Besides, we have also identified alkynyl selenide **3b** as a new lead compound, which

exerts more potent antiproliferative activity (~ 21 times improvement) in breast MBA-MB-231 cancer cells but less potent inhibitory effect on the human normal LO2 cells than the parental Oridonin respectively, implying the improved selectivity index of **3b** (Figure 3C)[32].

Overall, these preliminary rehearsals highlight the great potential of the SeNEx click chemistry in on-plate parallel synthesis and high-throughput medicinal chemistry.



Cpd	MDA-MB-231 $IC_{50}/\mu M$	LO2 $IC_{50}/\mu M$	Selectivity Index
3b	1.01	13.2	13.0
Oridonin	20.99	8.8	0.4

Figure 3. SeNEx chemistry-enabled on-plate parallel synthesis and high-throughput medicinal chemistry. A) Workflow of SeNEx enabled high-throughput medicinal chemistry via *in situ* on-plate parallel synthesis. B) Constructed in situ combinatorial library. C) Lead compound obtained from *in situ* combinatorial library.

4. Application of SeNEx Click Chemistry in Bioconjugation

Chemical modification of nucleic acids has attracted increasing interest because it expands the capacities of natural nucleic acids with many new applications in chemical biology, bioanalysis, and organic catalysis[37]. In particular, DNA-encoded chemical library (DEL), conceptualized by Lerner and Brenner in 1992[38], has emerged as a prevalent technology in current drug discovery for the merits of huge capacity, easy storage, and efficient screening[39–48]. The construction of DEL and its chemical space heavily rely on DNA-compatible reactions[49,50]. As a result, although it is quite challenging due to the highly functionalized and sensitive DNA barcodes, low reaction scale, and highly diluted conditions, developing new DNA-compatible reactions is one of the key tasks in the DEL research field[51–57].

Notably, the mild reaction conditions, robustness to air and water, and excellent functional group tolerance of the SeNEx chemistry have prompted us to convert it into on-DNA synthesis (Figure 4A). In 2020, we successfully developed the first on-DNA C(sp^2)–H selenylation under Rh(III) promotion, thus providing an efficient procedure for the construction of selenium-containing DNA-encoded chemical libraries (*Se*DELs)[30]. After that, we successively achieved to transform our free indole[31] and alkyne[32] based SeNEx chemistry into on-DNA synthesis. Notably, these on-DNA SeNEx reactions exhibit broad substrate scope and excellent DNA compatibility, with 83%-87% remaining amplifiable materials under the established selenylation conditions, which greatly exceeded the required threshold of 30 % in DEL synthesis (Figure 4B).

Given the good substrate compatibility and generality, we assumed that these DNA-compatible SeNEx chemistries could be used predictably for the synthesis of *Se*DEL for probing ultra-large Org-Se chemical space, thereby laying the foundation for the development of selenium-containing drugs

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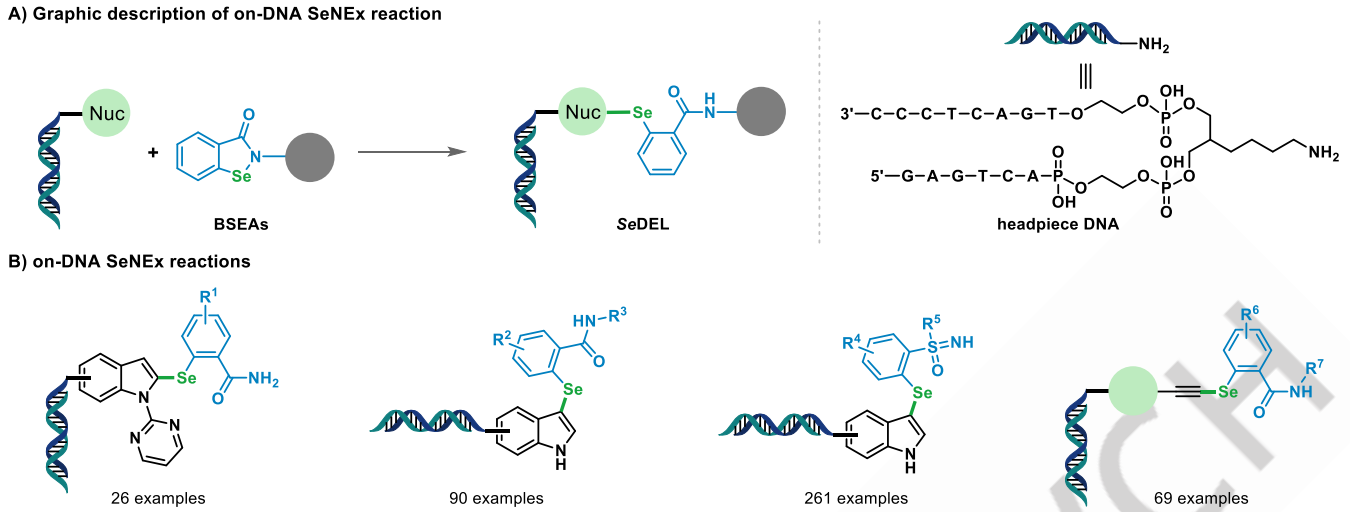

Figure 4. SeNEx chemistry-enabled selenium-containing DNA-encoded library (*Se*DEL) synthesis A) Graphic description of on-DNA SeNEx reaction. B) on-DNA SeNEx reactions.

Late-stage chemical modification of peptide or protein is of great significance in various biological applications, such as modulating the stability and function of protein, probing the dynamic of protein, and synthesis of peptide-drug conjugates (PDC) and antibody-drug conjugates (ADC)[58]. However, chemo-selective modification of peptide and protein poses a significant challenge due to the presence of multiple interfering nucleophilic and electrophilic amino acid residues.

Inspired by the fast kinetics (k_2 ≥ 14.43 $M^{-1}s^{-1}$) and excellent functional group compatibility of the alkyne-based SeNEx click chemistry, we tested its application in peptide and protein modification. As illustrated in Figure 5A, the oxidized *L*-glutathione (GSSG) proceeded with this SeNEx reaction smoothly to generate the title product **5a** in 78% yield. Besides, unprotected alkyne-modified Octreotide also underwent this SeNEx reaction well to deliver the desired derivative **5b** in 88% conversion. Notably, the S-S bonds are completely unaffected in this reaction in these two cases, highlighting the excellent chemo-selectivity on the Se-N motif over the S-S bond. Moreover, two dipeptides containing BSEA (Val-Trp) and ethynyl (Ala-Trp) tags respectively also proceeded with this SeNEx reaction favorably to give the corresponding ligation products **5c** in 68% yield (Figure 5B). Apart from peptide, ethynyl tagged Trastuzumab (**5d**) also performed SeNEx reaction in HEPS buffer to produce FITC-labeled conjugate **5e** efficiently. In addition, a red and a green fluorescent dye dual labeling of the antibody was also achieved to furnish the double-labeled conjugate **5g** via sequential Cys and alkyne-based SeNEx chemistry (Figure 5C). Notably, the binding affinity (K_D) of FITC-labeled conjugate **5e** and Trastuzumab were tested to be 4.83 and 2.93 nM respectively, suggesting the chemical modification showed no obvious negative impact on the binding affinity and highlighting the excellent biocompatibility of this SeNEx click chemistry[32].

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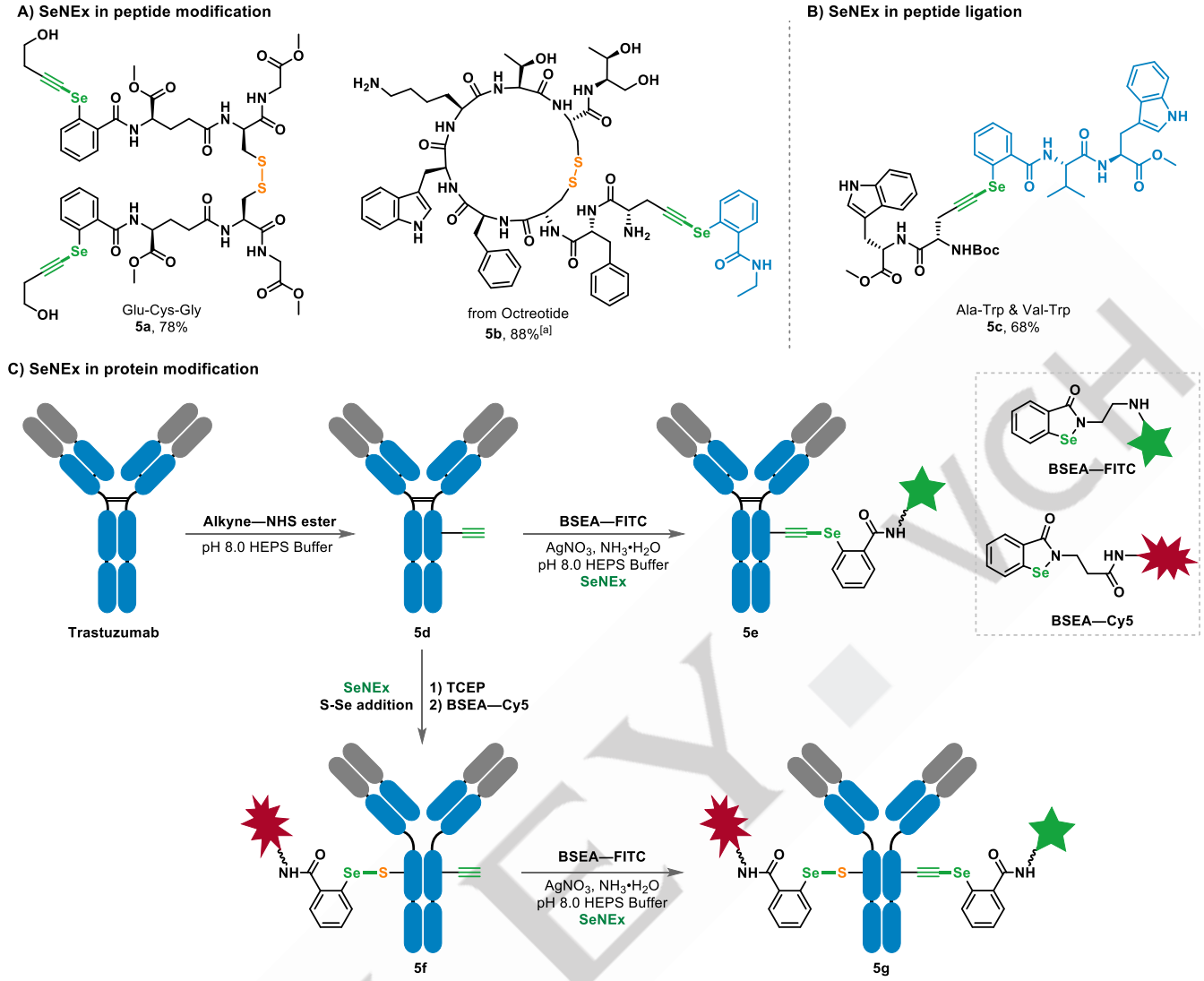

Figure 5. SeNEx-based bioconjugation of peptides and proteins. A) SeNEx in peptide modification. B) SeNEx in peptide ligation. C) SeNEx in protein modification.

5. Summary and Outlook

Overall, inspired by the biochemical SeNEx chemistry between Ebselen and thiol (Se−N to Se−S), we have successfully designed and developed a series of efficient, mild, and robust SeNEx chemistry (Se−N to Se−C) between BSEAs or BTSAs and carbon nucleophiles. Some of them meet the requirements of click chemistry and have been applied in on-plate parallel synthesis, DNA-encoded library synthesis, as well as peptide and protein bioconjugation. These successes have led us to propose the concept of selenium-nitrogen exchange (SeNEx) chemistry, an all-encompassing term for nucleophilic substitution events that replace nitrogen at an electrophilic selenium(II) center, enabling the flexible and efficient linkages assembly around a Se(II) core. Notably, compared to the well-known click chemistry CuAAC, SuFEx, and PFEx, SeNEx demonstrates a clear uniqueness. Firstly, the alkyne-based SeNEx yields products with an alkynyl selenide linkage, which can be easily modified, whereas the triazole linkage in CuAAC is hard to modify. Second, although SeNEx, SuFEx, and PFEx are all proceeding with a nucleophilic substitution mechanism, the electrophilic centers in SuFEx and PFEx are both in high valence states (S^{VI} and P^{V}) and employ the F atom as the leaving group. However, the electrophilic center in SeNEx is in a low valence state (Se^{II}) and employs the N atom as the leaving group, thus exhibiting distinct uniqueness. These attributes make SeNEx click chemistry to be a powerful and unique member of the click chemistry family.

The field of SeNEx chemistry is currently in its nascent stages. To propel SeNEx into a transformative platform across multidisciplinary domains, numerous enhancements are required for further advancement.

(i) The established SeNEx chemistries are mainly focused on C(sp^2)-Se and C(sp)-Se bond formation, C(sp^3)-Se and other Se-X bond formation chemistry should be developed.

(ii) The development of metal-free SeNEx chemistry would be highly significant due to its improved biocompatibility. For instance, SeNEx chemistry could find applications in target-templated synthesis through proximity-promoting effects.

(iii) The suitability of SeNEx chemistry in on-plate parallel synthesis makes it an appealing task to apply them in automated synthesis, not only for constructing combinatorial libraries with larger capacity but also because it could generate big reaction data, which has the potential to be leveraged by machine-learning software.

(iv) The compounds synthesized through these SeNEx reactions belong to completely new chemical space, which aids in the discovery of lead compounds with novel structures and mechanisms.

(v) For bioconjugation, SeNEx chemistry has recently been applied in protein modification, its application may be extended to the cell surface, in-cell, and even *in vivo* elaborations.

(vi) In addition to synthesizing small molecules, the use of SeNEx alone or in combination with other reactions (e.g., SuFEx, CuAAC) is also expected to facilitate selenium-containing polymers or oligomers, thereby promoting the discovery of new materials.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Click chemistry • Selenium-nitrogen exchange (SeNEx) • Parallel synthesis • DNA-encoded library • Peptide and protein bioconjugation

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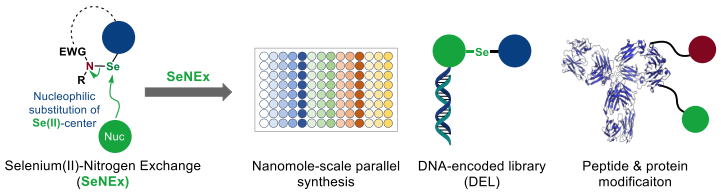

The selenium-nitrogen exchange (SeNEx) click chemistry involves a nucleophilic substitution, in which the nitrogen at the electrophilic selenium(II) center is replaced by a suitable nucleophile, facilitating the flexible and efficient formation of linkages around the Se(II) core.

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