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A fast and direct iodide-catalyzed oxidative 2-selenylation of tryptophan†

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A metal-free 2-selenylation of tryptophan derivatives is reported, where the use of iodide as the catalyst and oxone as the oxidant is key to obtain high yields. Various functional groups within the di-seleny and the indole ring are tolerated, and no racemization is generally observed.

L-Tryptophan, which bears an exclusive indole ring, is a unique building block in protein synthesis. Its biotransformation in living organisms contributes either to site-selective bioconjugation with biomacromolecules in cells and tissues while keeping this indole ring or breaking it to generate a variety of bioactive metabolites.[1] 2-Selanyltryptophans are one class of non-ribosomal amino acids that have been found as components of some natural polypeptides, such as the Se-glucosinolate **1** methylselenoneoglucobrassicin (Fig. 1), which is a natural metabolite fraction in black mustard (*Brassica nigra*) seeds grown in seleniferous areas and is believed to have anti-inflammatory activity.[2]

In addition to their natural analogues, synthetic 2-selanyltryptophans also act as precursors of numerous key biologically active integrates (drugs or nutritive additives) for human health. For example, the novel cyclic peptide **2** (Fig. 1, ITFUDLLWYYGKKK) containing a specific selenide bridge was developed as an anti-infective agent for parasiticides and a lead compound for tumor treatment,[3] while the dimeric selenide **3** was able to inhibit tyrosine kinases and the proliferation of Swiss 3T3 Mouse fibroblasts.[4] These compounds should be taken into account in the design of drugs pertaining to tryptophan, as the 2-selanyl substituent may affect the metabolism of such molecules. However, to date only two examples for the synthesis of 2-selanyltryptophan from the amino acid precursor have been reported (Scheme 1). 2-Phenylselanyl product has been prepared by treating tryptophan with moisture sensitive phenylselenenyl bromide.[5] In this case, trimethylamine was used as the quencher to neutralize the generated hydroxyl bromide and the substitution was limited in Ar–Se–X examples (Scheme 1a). Recently, alkane seleninic acids were utilized to react with tryptophan and other electron-rich aromatic rings to deliver the corresponding products in good yields (Scheme 1b).[6] However, the seleninic acids were generally prepared through oxidation of diselenide with dimethyldioxirane, which limited its application in functionality-sensitive substrates. Thus, the development of new synthetic methodologies for the selective 2-selanylation of tryptophan is highly desirable, particularly for the introduction of versatile function moieties. In our continuous effort toward the discovery and development of facile oxidation processes involving bioactive structures,[7] we now present a mild and efficient method for the preparation of the title compounds with easily available diselenides under the catalysis of iodide and promotion of oxone, an eco-friendly and cost-effective oxidant (Scheme 1c). This reaction exhibits exceptional reaction kinetics (accomplishment in minutes) and is able to deliver the designated products in good to excellent yields without any loss of enantioselectivities.

As a starting point, we conducted the reaction of L-methyl acetyl tryptophanate **1a** with dibenzyldiselenide **2a** with our previously developed method (TBAI and H_2O_2), but the desired product **3a** was obtained in 31% yield when CH_3CN was used (Table 1, entry 1). Changing the solvent to others resulted in much lower production (entries 2 and 3) or even totally halted the coupling (entry 4, see the ESI,† for details). Satisfactorily,

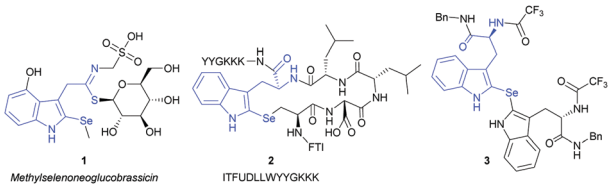

Fig. 1 Represented 2-selanyltryptophan derivatives.

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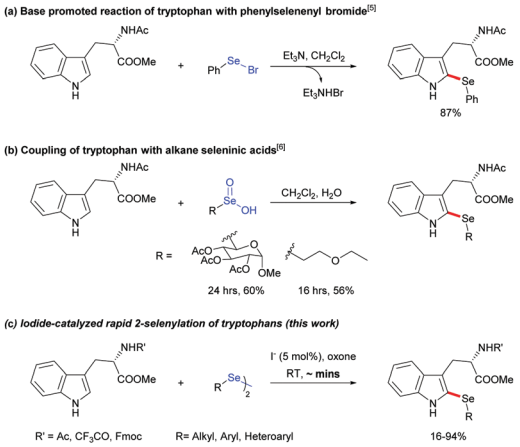
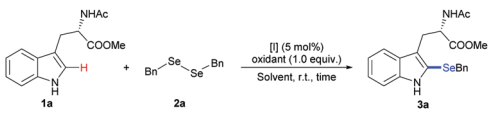


Scheme 1 Traditional (a and b) and currently developed (c) strategies for 2-selenylation of tryptophan.

Table 1 Optimization process for the 2-selenylation of tryptophan **1a** with diselenide **2a** under iodide catalysis[a]

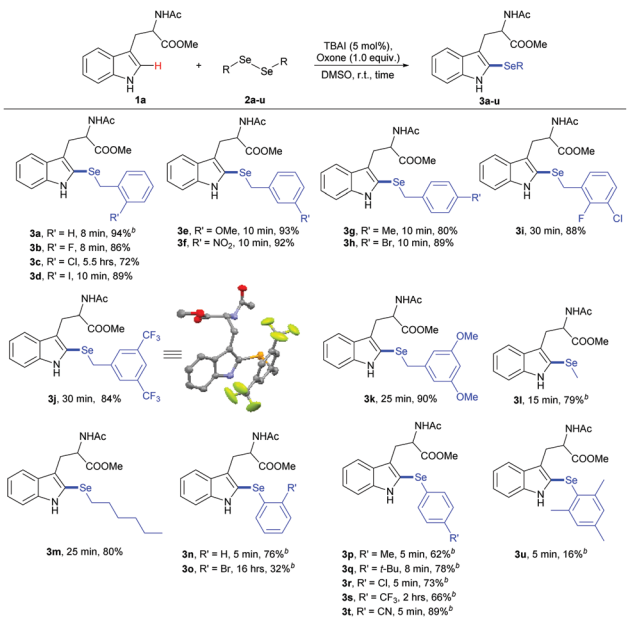


Entry	[I]	[Ox]	Solvent	Rxn time	Yield[b] (%)
1[c]	TBAI	H_2O_2[d]	CH_3CN	24 h	31
2[ce]	TBAI	H_2O_2[d]	THF	24 h	6
3[ce]	TBAI	H_2O_2[d]	MeOH	24 h	21
4[ce]	TBAI	H_2O_2[d]	DMF	24 h	N. R.[f]
5[g]	TBAI	Oxone	CH_3CN	1 h	43
6	NaI	Oxone	CH_3CN[h]	1 h	55
7	KI	Oxone	CH_3CN[h]	1 h	49
8[g]	TBAI	Oxone	MeOH	15 min	31
9[g]	TBAI	Oxone	H_2O	1 h	N. D.
10[g]	TBAI	Oxone	DMF	20 min	69
11[g]	TBAI	Oxone	DMSO	20 min	85
12[gi]	**TBAI**	**Oxone**	**DMSO**	**8 min**	**94**

[a] General conditions: all the reactions were conducted with L-methyl acetyl tryptophanate **1a** (0.1 mmol, 26.0 mg), dibenzyldiselenide **2a** (0.1 mmol, 34.0 mg), catalyst (5 mol%) and oxidant (1.0 equiv.) in selected solvent (1 mL) at room temperature. [b] Isolated yields. [c] 10 mol% of TBAI was used. [d] An aqueous solution of H_2O_2 (35%, m/m) was used. [e] 2 equiv. of H_2O_2 was used. [f] No reaction. [g] Solvent: 0.55 mL. [h] Solvent: CH_3CN (0.5 mL) + H_2O (0.05 mL). [i] Quenched by saturated $Na_2S_2O_3$ solution before purification.

the use of oxone as the oxidant afforded **3a** in 50% yield within just one hour (entry 5). This result encouraged us to optimize the process under the promotion of this oxidant. In this regard, other iodide sources showed comparable catalytic activities (entries 6 and 7, see the ESI,† for details), while the solvent was proven to play an important role in this process (entries 8–11, see the ESI,† for details). The highly polar and water miscible organic liquids DMF and DMSO were identified as efficient solvents for this reaction, affording the product **3a** in 69% and 85% yields, respectively. In both cases, the product **3a** was generated within 20 minutes. Interestingly, the yield would be optimized to 94% when quenching the reaction after 8 minutes before purification, probably excluding further oxidation. It is worth mentioning that this coupling was insensitive to moisture or oxygen. However, it is worth mentioning that oxygen alone was not capable of promoting this reaction (see the ESI,† for details). The present coupling reaction proceeded efficiently using commercial DMSO (without purification) under an open-air condition, which makes a large-scale synthesis possible in the future. On the other hand, this rapid, mild and efficient oxidative coupling has no influence on the chirality. No enantioselectivity loss was observed in this process. Yet the introduction of a C2-selenyl substituent exhibited some restriction on the orientation of the aromatic indole ring with respect to the amino and carboxyl groups[8] as demonstrated by the slight change in circular dichroism spectra (see theESI,† for details).

We next examined the scope of the reaction with a variety of differently diselenides **2**. As shown in Scheme 2, excellent yields were obtained in the reaction of methyl acetyl tryptophanate **1a** with several diselenides. *Ortho*-(**3b–d**), *meta*-(**3e–f**) and *para*-substituted (**3g–h**) benzyl diselenides with either electron-withdrawing or electron-donating substituents were suitable substrates for this transformation. In most cases, the reaction was furnished in 10 minutes, yielding the product **3b–h** in good to excellent amounts (72–94%). Furthermore, hyper-substituted selenyls (**3i–k**) were introduced efficiently within 30 minutes. With respect to the challenging methyl diselenide **2l**, we were able to obtain the 2-methylselenyl tryptophanate **3l** in 79% yield in 15 minutes. A longer alkyl chain was also tolerated (**3m**). Additionally, various aryl diselenides **2n–u** were very suitable for this process, giving the desired products **3n–t** in good to



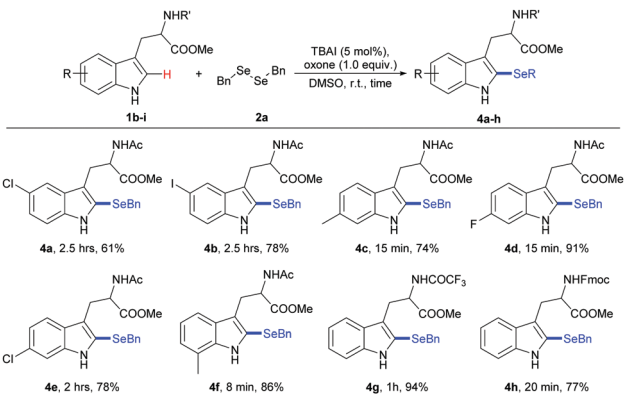
Scheme 2 C-2 Selenylation of methyl acetyl tryptophanate **1a** with various diselenides. [a]Unless noted otherwise, all the reactions were conducted with racemic methyl acetyl-tryptophanate (±)-**1a** (0.1 mmol, 26.0 mg), diselenide (0.1 mmol), TBAI (5 mol%, 0.85 mg), and oxone (0.1 mmol, 61.5 mg) in DMSO (0.55 mL). Isolated yields were given. [b]L-methyl acetyl-tryptophanate **1a** was used as the substrate.

excellent yields (up to 89%). One exception was mesityl substituent **2u**, which reacted slowly due to the steric hindrance. Thus, the mild conditions have enabled us to introduce versatile selenyl functionalities with the preservation of the parent tryptophan, as demonstrated from the single crystal structure analysis of the product **3j**.

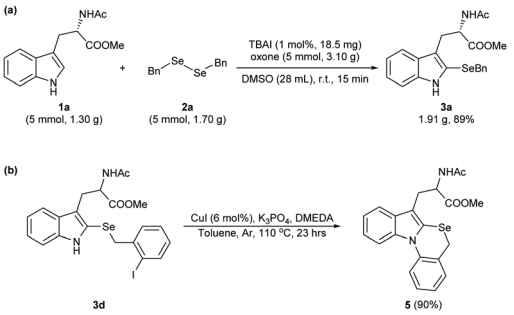
To prove the suitability for other tryptophan derivatives, various substituted tryptophan derivatives **1b–i** were chosen for this coupling (Scheme 3). The direct introduction of the benzylselenyl functionality was very efficient and overcame the electron-donating/withdrawing substituents on the indole ring, furnishing the designated products **4a–f** in good to excellent yields (67–98%). It also allowed the selective preparation of 2-selenyl tryptophanates with CF_3CO (**1h**) and Fmoc (**1i**) Trp-substrates. N-protected derivatives in the products **4g–h** remained untouched under the reaction conditions, indicating that this method could be used directly in a solid-phase peptide synthesis.[9]

The gram-scale synthesis was also demonstrated (Scheme 4a). Product **3a** could be prepared in an excellent yield (89%) with only 1 mol% of a TBAI catalyst in 15 minutes. Besides, the application of this method further proved that it could easily generate the 2*H*-[1,3]selenazino[3,2-*a*]indole derivative **5** *via* an intramolecular Cu^I-catalyzed N-arylation[10] (Scheme 4b). Both of these are great advantages in contrast to other methods that have been reported previously. And also, for the first time, we have developed the highly efficient synthesis of an unprecedented indole-based [1,3]selenazinan compound. Overall, the advantages of this newly developed method include operational simplicity, high kinetics, cost-effectiveness of the transformation, and good functional group compatibility for the synthesis of 2-selenyl tryptophan products, as well as the highly efficient preparation of cyclic selenyl molecules.

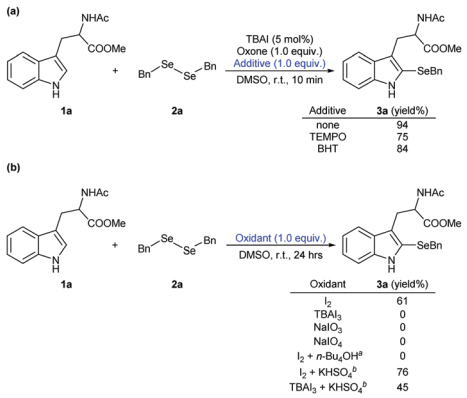
Finally, the mechanism responsible for the efficient selenylation was preliminary investigated (Scheme 5). Comparable yields of the product **3a** were observed when radical quencher TEMPO or BHT was used as the additive (Scheme 5a), demonstrating that the selenylated product may be generated *via* a radical-independent pathway. However, by changing the oxidant to other iodine species, a dramatic difference was



Scheme 3 C-2 Selenylation of tryptophanates with dibenzyl diselenide.



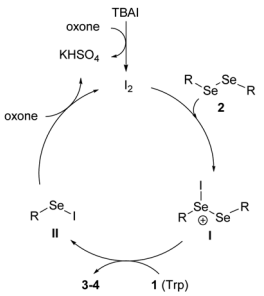
Scheme 4 Gram-scale synthesis of the product **3a** (a) and the cyclization of product **3d** (b).



Scheme 5 Preliminary mechanism studies for this C-2 selenylation. [a]2 equiv. of *n*-Bu_4OH was used. [b]2 equiv. of $KHSO_4$ was used.

observed (Scheme 5b). While elemental iodine I_2 promoted the coupling in an inferior efficiency (61%), no product was formed under $TBAI_3$, $NaIO_3$ or $NaIO_4$. It has been proposed that $TBAI_3$ is in an equilibrium with I_2 and TBAI in CH_3CN,[11] however, its incapability in promoting this reaction, as well as the performance with hypervalent iodines, suggested that iodine was one of the key intermediates in the catalytic cycle.[12] Interestingly, when the corresponding base of TBAI, tetrabutylammonium hydroxide, was used in the combination of iodine, the coupling reaction was completely repressed, indicating that an acidic environment was essential for this reaction. Indeed, by adding $KHSO_4$, the by-product generated from oxone decomposition, a comparable yield of the product **3a** was observed (76%). A re-examination of $TBAI_3$ in the presence of $KHSO_4$ also showed the importance of an acid.

Although the exact mechanism behind these experiments is not fully understood, we proposed that elemental iodine I_2 was first generated from peroxymonosulfate with the assistance of acid (Scheme 6).[13] It then reacted quickly with diselenide to generate a highly electrophilic selenium cation intermediate **I**,[14] which was attacked by the nucleophile tryptophan to afford the 2-selenyl product while releasing the selenenyl iodide **II**. We speculated that I_2 would be generated from acid-facilitated oxidation of **II** with peroxymonosulfate and then finished the catalytic cycle. We also prepared a selenenyl iodide **II** (R═Ph)



Scheme 6 Proposed mechanism for the C-2 selenylation.

by *in situ* condensation of diphenyldiselenide with iodine, which was then reacted with tryptophanate **1a** but only afforded the product **3n** in 28% yield. Although the significant decrease of coupling efficiency did not rule out the possibility that selenenyl iodide may be involved in the coupling, it clearly indicated that it was not likely one of the key coupling partners in this transformation (see the ESI,† for details).

In summary, we have developed a novel methodology for the synthesis of valuable 2-selenylated tryptophan derivatives from diselenide under the catalysis of iodide. In this method, no additional metal[15] was required and no precautions to water or oxygen were needed. Diverse substitution patterns on the diselenides or tryptophans were tolerated under the mild conditions, which highlighted the synthetic potential of this approach. In addition, this reaction represents an efficient and rapid approach to access the title compounds in gram-scale and thus avoids practical complications in the pharmaceutical industry. Furthermore, a precise manipulation of the product to afford 2*H*-[1,3]selenazino[3,2-*a*]indole compound increased the value of this method. Further insightful studies will be required, however, to fully elucidate the reaction mechanism. Overall, this procedure benefits from mild reaction conditions and will open up new areas in the preparation of selenyl containing proteins.

L. C. and L. L. conceived of the presented idea. Y. T. G. and S. D. L. carried out the experiments. L. C. and L. L. wrote the manuscript with input from all authors.

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Conflicts of interest

There are no conflicts to declare.

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