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Preparation of benziodazole-triflate and its application as both 2-iodobenzamido- and triflate-transfer reagents

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ABSTRACT

Benziodazole-triflate, as a novel heterocyclic hypervalent iodine(III) reagent, was prepared from the reaction of hypervalent chloroiodine(III) with silver triflate under mild conditions. The structure of this new reagent was elucidated by NMR spectroscopy and X-ray crystallography, and its reactions with diverse α-electron withdrawing group substituted carbonyl compounds were investigated. The results implied that benziodazole-triflate could be selectively used as both a 2-iodobenzamido-transfer reagent for the synthesis of oxazole compounds, and a triflate-transfer reagent for the triflation of β-keto-sulfones. Ionic mechanistic pathways, supported by density functional theory (DFT) calculations, were proposed to account for the divergent selectivities of the transformations.

Over the past few decades, hypervalent iodine chemistry has witnessed remarkable progress [1-15], which was partially sustained by the emergence and application of novel hypervalent iodine reagents [16-25]. Among the vast category of these reagents, heterocyclic iodine(III) compounds [26-30], compared to their noncyclic analogues, have demonstrated the merit of higher thermal stability and unique reactivities. Accordingly, a great deal of efforts have been devoted to investigating various heterocyclic iodine(III) reagents bearing versatile ligands including azido [31-35], cyano [36-40], trifluoromethyl [41-48] and triflate groups [49-52]. The most famous and best-investigated heterocyclic iodanes are benziodoxoles, which have achieved significant advances in their preparation, structure determination, and synthetic applications [53-68]. In contrast, benziodazoles, an analogous heterocyclic iodane reagent of benziodoxoles, have received relatively less attention [69-74]. To the best of our knowledge, there was a limited number of benziodazole reagents that have been reported till now (Fig. 1a), and only three known transformation patterns mediated by these existing benziodazole reagents **1a-h** have been established (Fig. 1b). In the majority of these transformations, benziodazoles were employed as ligand- or atom-transfer reagents for various functionalization reactions including azidation [75-78], trifluoromethylthiolation [79,80], aroylation [81], fluorination [82], and alkynylation [83] as shown in Fig. 1b, type 1. As an illustration, Zhang's group reported the design and synthesis of hypervalent fluoroiodane(III) reagent **1e**, which was capable of performing the intramolecular ring expansion/fluorination of unactivated cyclopropanes to afford a diverse array of 4-fully substituted fluoropiperidines [82]. In addition, benziodazoles can also enable the oxidative coupling reactions as solely an oxidant, without incorporating any structural moieties into products (Fig. 1b, type 2). For instance, Wang and coworkers developed a rhenium-catalyzed dehydrogenative olefination of C(sp^3)–H bonds mediated by alanine-derived hypervalent iodine(III) reagents **1g**, which is crucial for oxidizing Re(n) catalyst species from low oxidation states to high ones [84]. Furthermore, benziodazoles may display high electrophilic reactivity and more than one structural moieties can be introduced into the corresponding product (Fig. 1b, type 3). For example, Waser's group demonstrated that both components (alkyne ligand and benziodazole skeleton) of ethynylbenziodazolones (EBZs) **1h** can be found in imidate products, which was produced from the oxyalkynylation of diazo compounds mediated by EBZs **1h** [85].

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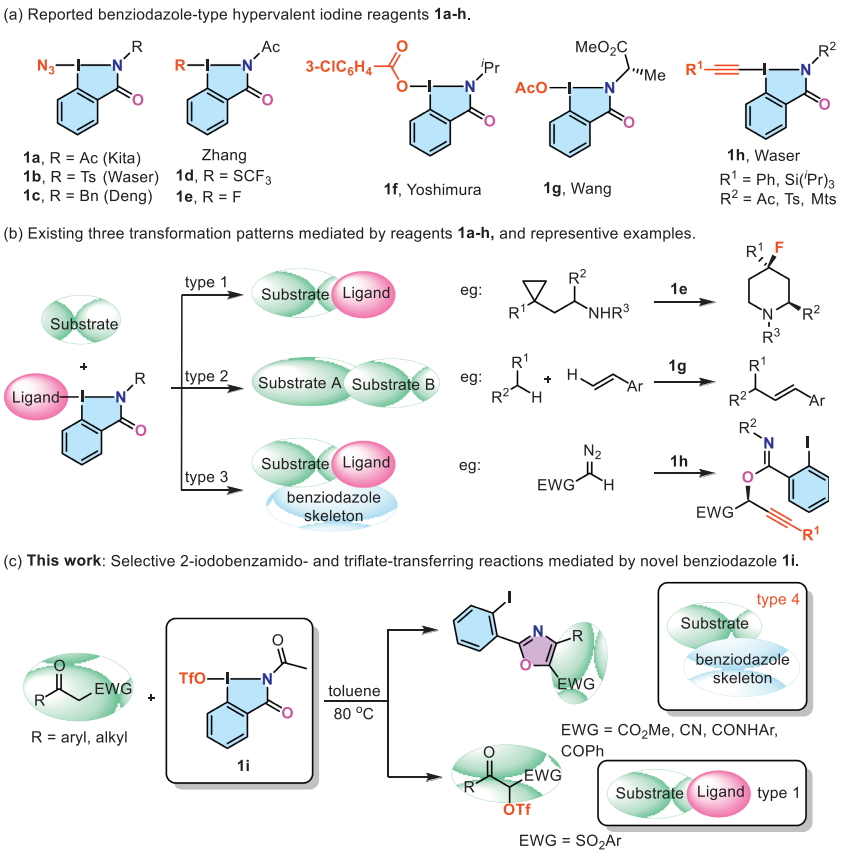
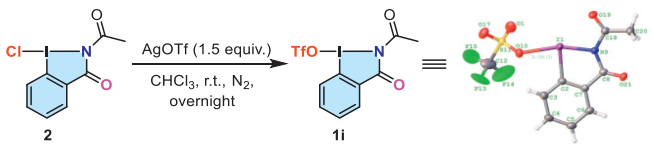


Fig. 1. (a) Established benziodazole-type hypervalent iodine reagents **1a-h**. (b) Three transformation patterns mediated by reagents **1a-h** and representative examples. (c) Selective 2-iodobenzamido- and triflate-transfer reactions enabled by benziodazole-triflate reagent **1i**.

However, despite the above advances that have been made in the field of benziodazole-type hypervalent iodine reagents, the development of new-type benziodazole reagents and research on their reactivities are still highly desired. To our knowledge, no former reports have described benziodazole-triflate reagent and investigated its reaction reactivity. In this communication, we reported the first synthesis of benziodazole-type hypervalent triflate-iodine reagent **1i** (Scheme 1) and its unique application as both a 2-iodobenzamido-transfer reagent for the synthesis of polysubstituted oxazoles from diverse α-electron withdrawing group substituted carbonyl compounds and a triflate-transfer reagent for the first access to α-triflate β-keto-sulfones *via* triflation of β-keto-sulfones (Fig. 1c, type 1). Differing from the above benziodazole reagents, this new benziodazole-type reagent **1i** can not only facilitate the ligand-transfer reaction (Fig. 1c, type 1) that well corresponds to the first type of the three known transformation patterns, but also enable a new transformation pattern, namely, incorporating the 2-iodobenzamido moiety of the hypervalent iodine reagent into products (Fig. 1c, type 4).

Oxazole ring, a privileged five-membered heterocyclic motif, is commonly found in a variety of biologically active natural products and pharmaceuticals [86-90], including the anti-diabetic agent



Scheme 1. Preparation of benziodazole-triflate reagent **1i**.

AD-506 [91], the nonsteroidal anti-inflammatory drug oxaprozin [92], the anti-mycobacterial natural product texaline [93], and the anti-pancreatic cancer agent PC-046 [94]. The construction of oxazole skeleton has been continuously studied for decades, leading to numerous significant achievements. Traditional methods for the synthesis of oxazole compounds include the 2-acyl aminoketone Robinson-Gabriel dehydration [95-98] and Cornforth rearrangement [99]. In recent years, more diverse synthetic methods have been reported for the assemblage of oxazole framework [100-107]. As metal or Lewis acid catalysts remain virtually indispensable for these reactions, it should be highly desirable to develop novel additive-free synthetic method for the synthesis of oxazoles. In this research, we demonstrated an alternative straightforward, catalyst-free approach to accessing oxazole derivatives through a benziodazole-triflate-mediated oxidative cyclization of diverse α-electron withdrawing group substituted carbonyl compounds.

The benziodazole-type hypervalent-iodine reagent **1i** could be readily prepared in 85% yield as a white, microcrystalline solid, from the ligand exchange reaction between hypervalent chloro–iodine(III) compound **2** and silver triflate (AgOTf) in chloroform under N_2 atmosphere condition (Scheme 1). It is noteworthy that reagent **1i** can also be accessed on a large-scale of ten grams without significant diminishment of the yield. Furthermore, this new reagent **1i** is bench stable and can be stored in a dry environment at room temperature for months without decomposition.

Benziodazole-triflate reagent **1i** was characterized by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy. The ^{13}C NMR chemical shift of the C–I ipso-carbon (117.4 ppm) had a positive incremental deshielded shift of about 24 ppm from that of iodoarene, which is consistent with the typical characteristics of the reported benziodazole compounds [75-85,108-112]. Thermogravimetry-differential

thermal analysis (TG-DTS) showed that reagent **1i** decomposed at 154 °C to form a brown tar (see Supporting information for details). This reagent exhibited good solubility in common organic solvents including dimethyl sulfoxide, acetonitrile, tetrahydrofuran, chloroform, toluene, *etc.* A single crystal of **1i** (CCDC: 2172493) was grown in the chloroform at room temperature, and X-ray crystallography showed that **1i** has an approximate T-shaped structure (O10—I—N9 bond angle 164.22°) and a I(III)-OTf bond (2.391 Å) [113], indicating the larger bond interactions beyond the ordinary van der Waals attraction.

With reagent **1i** in hand, we initially envisaged that it can be used as a potential triflate-transfer reagent for introduction of the triflate moiety by reacting with an appropriate nucleophile. To our surprise, when reagent **1i** (0.65 mmol, 1.5 equiv.) was treated with the commercially available ethyl benzoylacetate (**3a**, 0.5 mmol, 1.0 equiv.) in acetonitrile at 80 °C, an exclusive oxidative cyclization reaction occurred to give ethyl 2-(2-iodophenyl)—4-phenyloxazole-5-carboxylate **4a** as crystalline solids in 56% yield, rather than the expected triflated product (Table 1, entry 1). The structure of compound **4a** was undoubtedly established by X-ray crystal crystallography (Table 2, **4a**, CCDC: 2207130). This outcome clearly indicated that in this transformation, the benziodazole-type hypervalent-iodine reagent **1i** was used as a 2-iodobenzamido-transfer reagent, rather than the predicted triflate-transfer reagent.

Motivated by this appealing finding, we then continued our investigation by optimizing the reaction conditions, using ethyl benzoylacetate **3a** as model substrate (Table 1). Solvents screening indicated that aprotic solvents were generally superior to protic solvents, with toluene proved to be the best one in promoting the formation of the poly-substituted oxazole **4a** (entries 1–7). Subsequent temperature testing revealed that either increasing or decreasing temperatures from 80 °C was not beneficial for this transformation (entries 8 and 9). To our delight, increasing the loading of reagent **1i** from 1.5 equiv. to 1.75 equiv. can further improve the yield of product **4a** to 81% (entry 10). Extra attempts to improve the reaction outcome by employing additives including AgOTf, $Cu(OTf)_2$, and $BF_3{\cdot}Et_2O$ turned out to be unfruitful (entries 11–13).

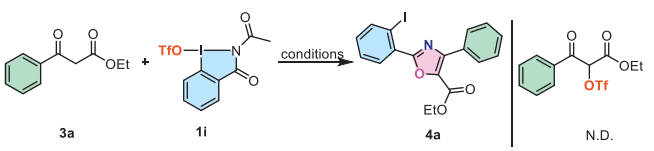
With the optimized conditions established (Table 1, entry 10), we then investigated the generality and scope of this newly established transformation by testing various α-electron withdrawing group- substituted carbonyl compounds (Scheme 2). First, various aryl β-keto esters with electron-rich or electron-poor benzene rings were evaluated, and it was found that they were all successfully converted to corresponding poly-substituted oxazole products **4b-4f** in moderate to good yields. In addition, the incorporation of halogens into the *ortho*-, *meta*- or *para*-positions of the aromatic ring in substrates exhibited good compatibility to this approach, with the corresponding products **4g-4n** obtained in satisfactory yields. Interestingly, the method was equally applicable to substrates bearing heteroaromatic R substituents such as furyl- or thienyl-groups, conveniently affording the desired products **4o** and **4p**, albeit with deteriorated efficiency. Furthermore, the α-aromatic ring in substrates is not indispensable and can be replaced by a methyl or a cyclohexyl group, with the corresponding alkyl-substituted oxazole products **4q** and **4r** achieved in acceptable yields. The substrate scope for this exclusive oxidative cyclization methodology could be further extended to alternative types of carbonyl compounds bearing different α-electron withdrawing groups including cyano, amido, and acyl groups, realizing the access to more abundant substituted oxazoles **4s**-**4z** in acceptable yields. The structure of amide-substituted oxazole product **4w** (CCDC: 2301016) was further corroborated by X-ray crystal analysis. It is worth noting that when the alkyl-substituted carbonyl substrate, *i.e.*, 1-phenyl-2-propanone was subjected to the standard conditions, the reaction did not afford the expected oxazole or triflated product.

Intriguingly, when tosylacetophenone (Scheme 3, **5b**), a carbonyl compound substituted with an α-electron-withdrawing sulfone group was treated with reagent **1i** under the same optimized conditions, a triflation reaction occurred smoothly to provide α-triflate substituted product **6b** in 64% yields, with the isolation of the oxazole product in only trace amount. This exceptional result suggested that reagent **1i** can not only serve as a 2-iodobenzamido-transfer reagent but also as a triflate-transfer reagent, depending on the categories of the substrates being employed.

Motivated by this finding, we then came to investigate the scope and utility of this direct triflation method (Scheme 3). The results manifested that diverse β-keto-sulfones **5** bearing either electron-donating or electron-withdrawing group on the benzene ring were viable substrates for the method, furnishing the corresponding α-triflate-substituted products **6a-6o** in moderate to good yield. The structure of **6b** (CCDC: 2256361) was unambiguously determined by X-ray crystal analysis. Remarkably, this protocol could also be extended to the substrate bearing a thiophene ring, a representative motif of the heteroaryl fragments, delivering the corresponding thienyl-containing product **6p** in acceptable yield. Notably, substrates substituted with a strong electron-withdrawing CF_3 group on either of the two aromatic rings were also converted to the corresponding triflated products **6d** and **6m**, albeit in relatively lower yields.

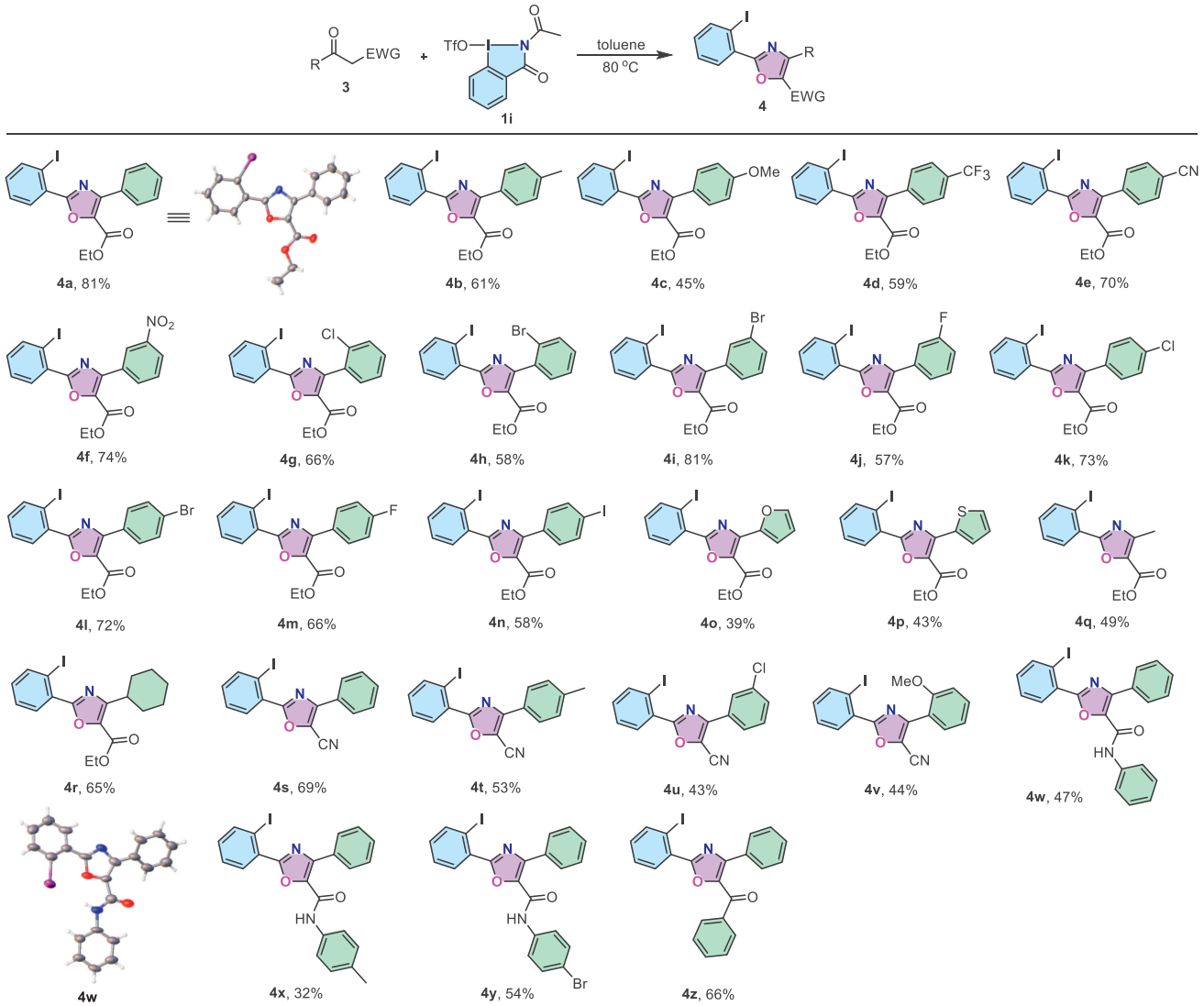
To gain insight into the mechanisms of the exclusive oxidative cyclization and the triflation reaction mediated by reagent **1i**, radical scavenger TEMPO was introduced into the above two reaction systems under standard conditions, respectively (Schemes 4a and b). For the reaction between reagent **1i** and ethyl benzoylacetate **3a**, the formation of desired oxazole product **4a** was fully inhibited with the employment of 2 equiv. of TEMPO (Scheme 4a). Instead, the cross coupling adduct **7a** was separated in 89% yield and the other adduct **8** was detected by high resolution mass spectroscopy (HRMS). Similar outcomes were observed for the reaction between reagent **1i** and tosylacetophenone **5b**, with product **6b** formed in trace amount and the cross-coupling products **9a** and **8** detected by HRMS (Scheme 4b). However, further control experiments indicate that the reaction of substrates **3a** and **5b** with TEMPO in

Table 1
Optimization of the reaction conditions.[a]

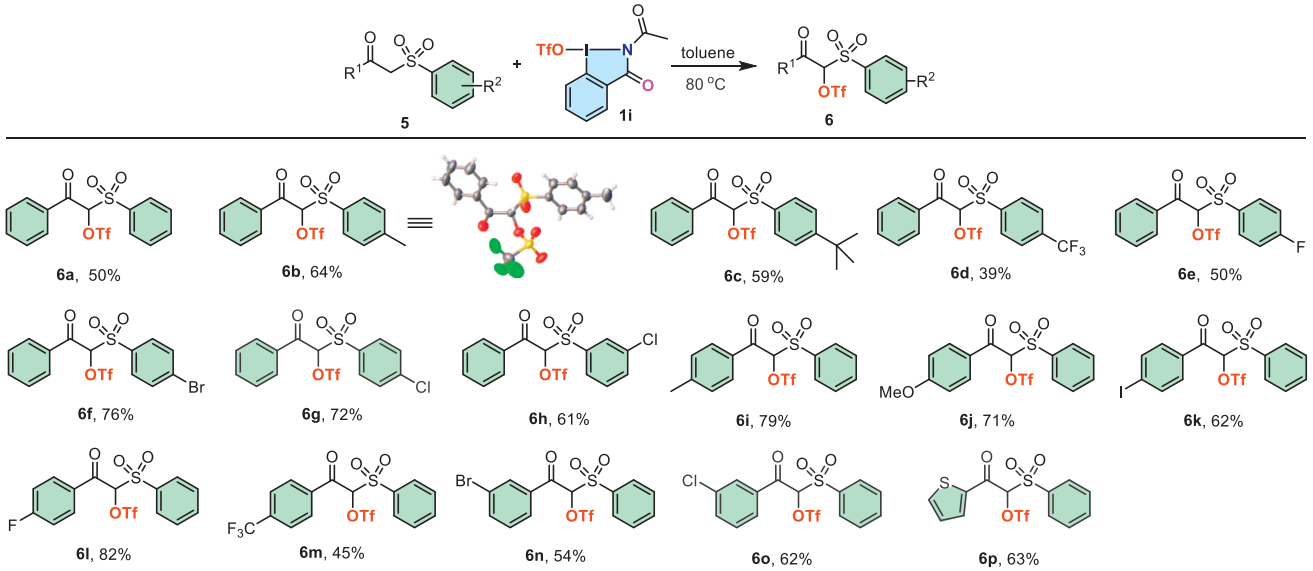


Entry	Oxidant (equiv.)	Solvent	Temp. (°C)	Addtive	Yield (%)[b]
1	**1i** (1.5)	MeCN	80	None	56
2	**1i** (1.5)	DCE	80	None	31
3	**1i** (1.5)	THF	reflux	None	49
4	**1i** (1.5)	DMSO	80	None	64
5	**1i** (1.5)	MeOH	reflux	None	N.D.
6	**1i** (1.5)	AcOH	80	None	N.D.
7	**1i** (1.5)	Toluene	80	None	77
8	**1i** (1.5)	Toluene	50	None	72
9	**1i** (1.5)	Toluene	110	None	70
10	**1i** (1.75)	Toluene	80	None	81
11[c]	**1i** (1.75)	Toluene	80	AgOTf	75
12[c]	**1i** (1.75)	Toluene	80	$Cu(OTf)_2$	72
13[c]	**1i** (1.75)	Toluene	80	$BF_3{\cdot}Et_2O$	70

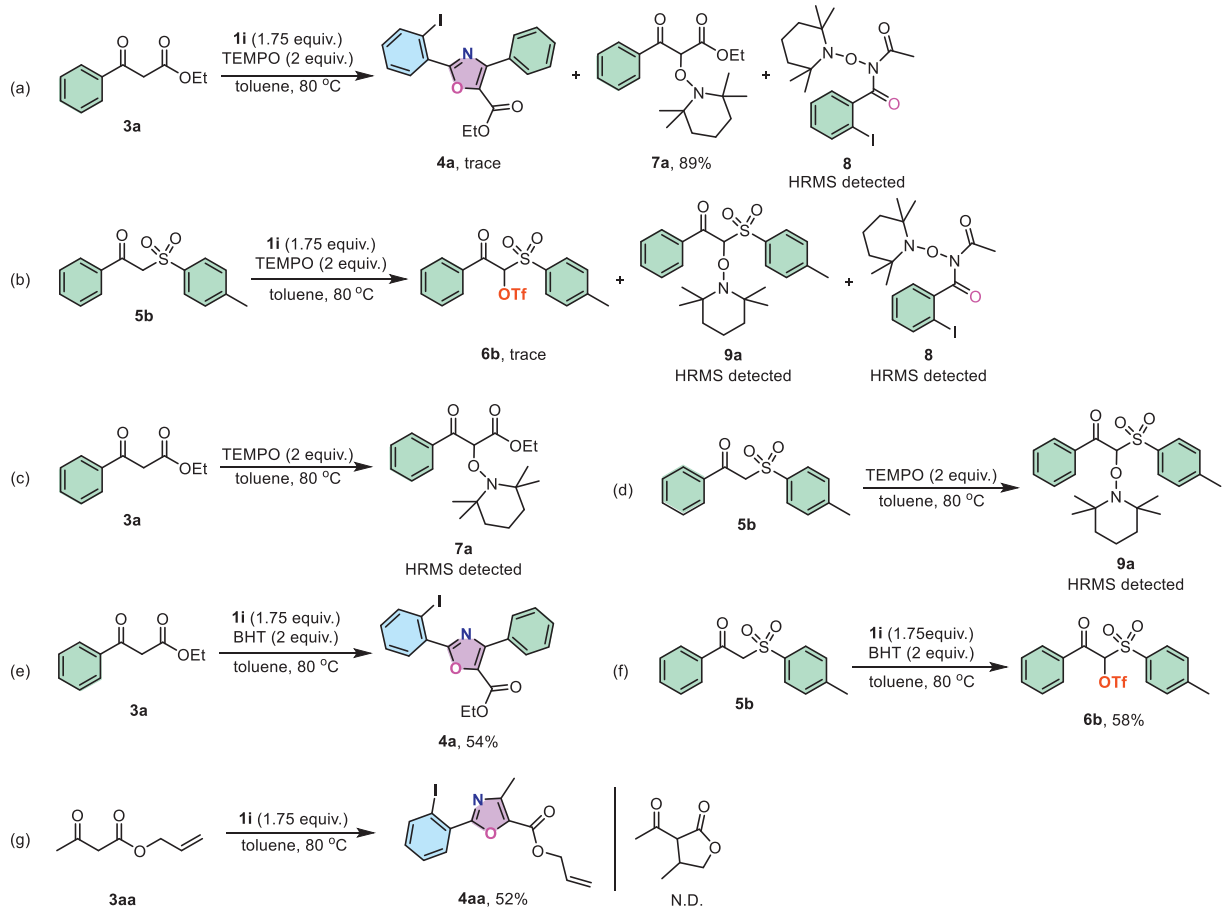
[a] Reaction conditions (unless otherwise specified): **3a** (0.26 mmol), solvent (5 mL), 12 h.
[b] Isolated yield. N.D. = not detected.
[c] 2.0 equiv. of the additive was used.



Scheme 2. Synthesis of poly-substituted oxazoles *via* reagent **1i**-mediated oxidative cyclization. Reaction conditions: substrate **3** (0.5 mmol, 1.0 equiv.), reagent **1i** (0.875 mmol, 1.75 equiv.) in toluene (10 mL) at 80 °C for 12 h.



Scheme 3. Synthesis of α-triflated β-keto-sulfones *via* reagent **1i**-mediated triflation. Reaction conditions: substrate **5** (0.5 mmol, 1.0 equiv.), reagent **1i** (0.875 mmol, 1.75 equiv.) in toluene (10 mL) at 80 °C for 12 h.



Scheme 4. Control experiments.

the absence of benziodazole-triflate reagent **1i** also afforded the corresponding adduct **7a** and **9a**, respectively (Schemes 4c and d). Thus, the results from the above radical scavenger experiments cannot provide convincing evidence that the reaction undergoes radical pathways. Furthermore, BHT was introduced as an alternative radical scavenger to the corresponding reaction of substrates **3a** and **5b** under standard conditions. It was found that products **4a** and **6b** could be achieved in 54% and 58% yield, respectively (Schemes 4e and f). Additionally, a radical clock experiment was also designed and conducted. When (2-propenyl)-3-oxobutanoate **3aa** was subjected to the standard conditions, it was oxazole product **4aa** rather than any radical cyclized product that was obtained (Scheme 4g). These outcomes might indicate that both reactions did not undergo radical pathway and ionic mechanism is more applicable for the two transformations.

To gain an insight into the mechanism of above reactions, we performed DFT calculations on the reaction of the new hypervalent iodine reagent **1i** and **3a**, as well as the reaction of **1i** and **5a**, and the corresponding calculated Gibbs free energy profiles are depicted in Figs. 2 and 3, respectively.

As to the reaction of **1i** and **3a**, the calculation results show that the reaction is triggered by the coordination of **IM1** with the electrophilic iodine(III) atom of **1i**, where **IM1** is formed by the tautomerization of **3a**. The ligand exchange step needs to overcome an energy barrier of 21.3 kcal/mol, and **IM2** is generated *via* ligand exchange with the OTf anion still remaining around the iodine(III) center. Subsequently, an intramolecular proton shift occurs to give **IM3**, which leads to a decrease in energy of 9.2 kcal/mol. The OTf anion attacks the activated carbon atom bonded to I^{III} to form **IM4,** where the formed imide and α-oxytriflated β-ketone ester are connected through the hydrogen bonding interaction. The Hirshfeld charge analysis of **IM4** shows that the more positive charge (0.16) is concentrated on the carbonyl carbon atom (**C1**) rather than the α-carbon atom (**C2**, 0.05), which indicates that the carbonyl carbon would be more favorable for the nucleophilic attack of the imide nitrogen. The nitrogen atom attacks the carbonyl carbon to form **IM5** *via* **TS3**, which needs to overcome an energy barrier of 18.7 kcal/mol. After that, the oxygen on the benzoyl group attacks the α-carbon atom connecting OTf group to give **IM6** *via* **TS4** with an activation energy of 28.0 kcal/mol relative to **IM4**; this process is the rate-limiting step in the reaction. Then, an addition-elimination step occurs to remove the acetyl group and generate the by-product TfOAc. Finally, the product **4a** is obtained by a dehydration process. The Gibbs free energy profile of the overall reaction shows that the formation of **4a** is highly exergonic by 27.3 kcal/mol.

For another reaction (Fig. 3), it starts with the coordination of $\mathbf{IM1_S}$ to the electrophilic iodine(III) atom of **1i**, with an activation energy of 27.5 kcal/mol, to give $\mathbf{IM2_S}$; this process is the rate-limiting step in the reaction. Subsequently, the OTf anion attacks the activated carbon atom bonded to I^{III} to form $\mathbf{IM4_S}$ with an energy barrier of 23.5 kcal/mol.

To understand the origin of the different chemoselectivity of two reactions, we calculated the energy barrier of the intermolecular cyclization process for $\mathbf{IM4_S}$. The nitrogen atom on the imide attacks the carbonyl group and this step would lead to the formation of $\mathbf{IM5_S}$. Then, the oxygen atom on the benzoyl group of the imide attacks the carbon atom bonded to OTf group

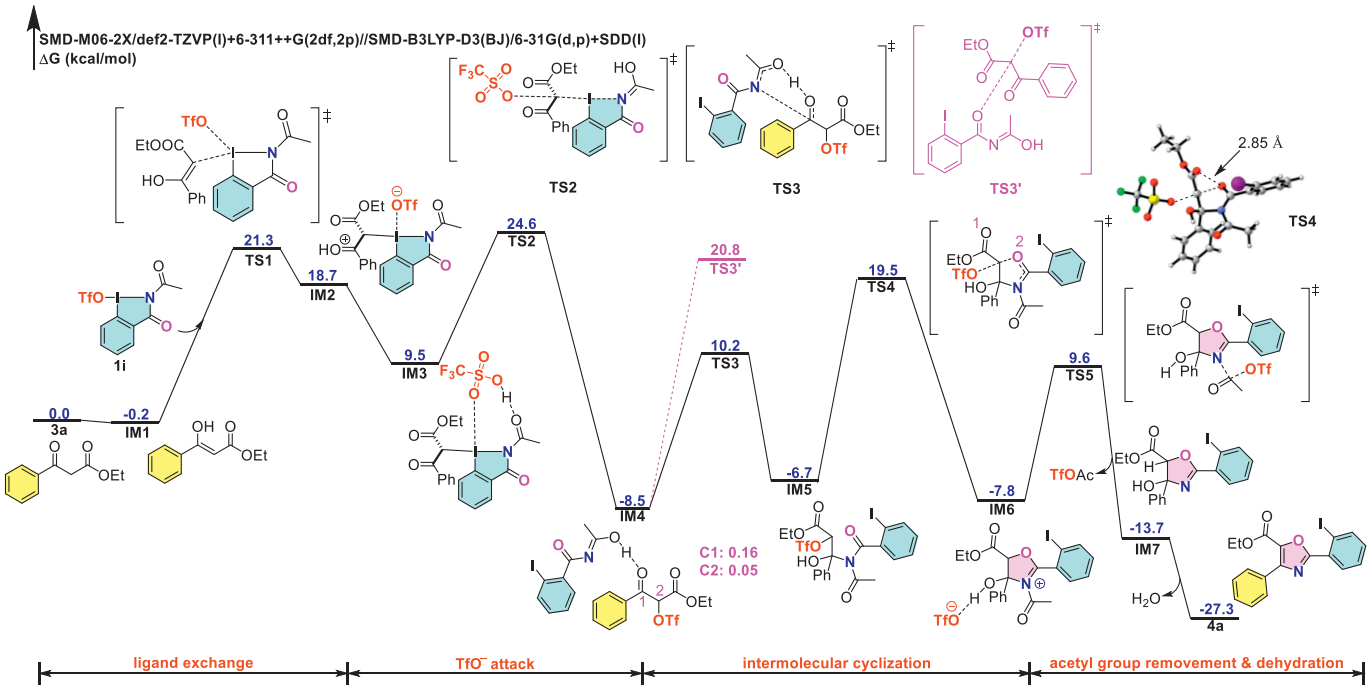


Fig. 2. DFT-computed potential energy profile of the reaction of **3a** and **1i**. The results of Hirshfeld charges analysis are shown (standard state: 25 °C, 1 mol/L).

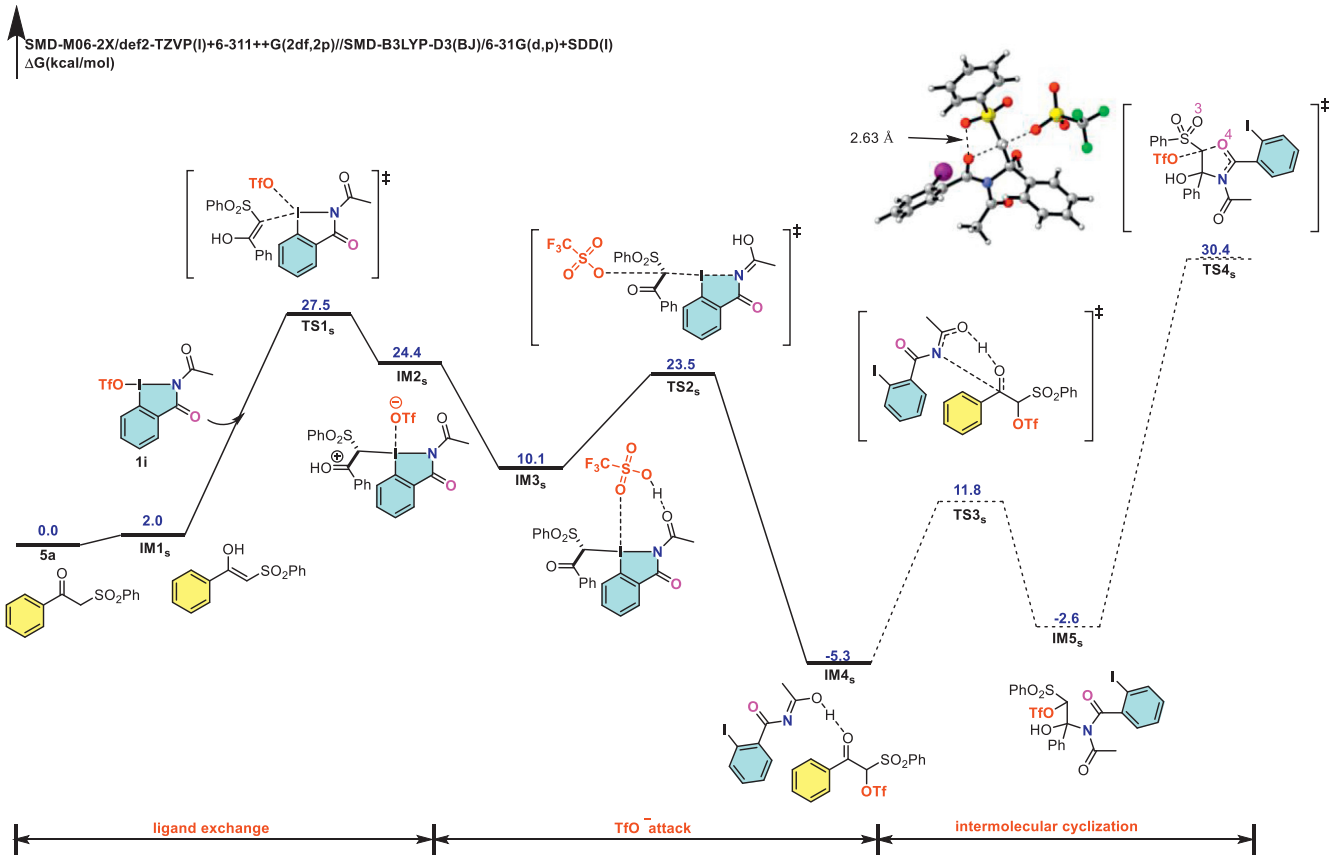
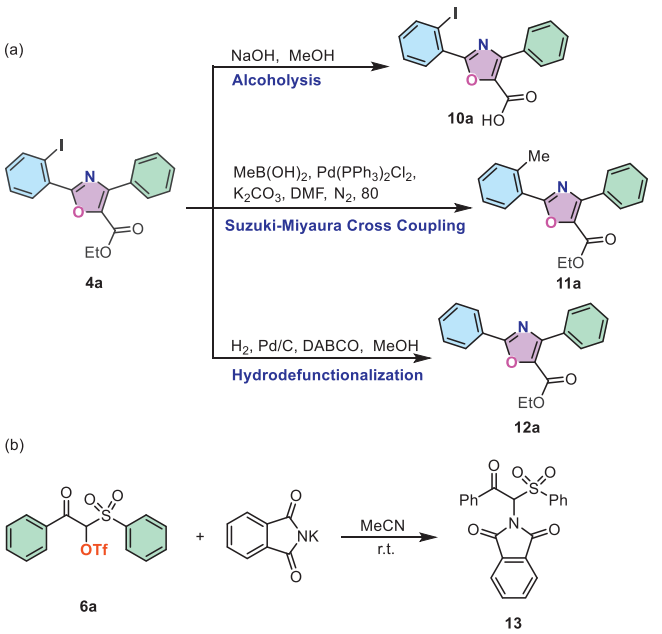


Fig. 3. DFT-computed potential energy profile of the reaction of **5a** and **1i** (standard state: 25 °C, 1 mol/L).

through **TS4$_S$**, which has to overcome an activation energy barrier of 35.7 kcal/mol relative to **IM4$_S$**. It is a too high barrier to climb under the used reaction conditions. We think that the high energy barrier of **TS4$_S$** is caused by the steric hindrance of the sulfonyl group adjacent to the α-carbon linking the OTf group. In **TS4$_S$**, the O3-O4 bond length is 2.63 Å, which is shorter than the O1-O2 bond length (2.85 Å) in **TS4**. It illustrates that compared to **TS4**, the nucleophilic attack of oxygen atom at the carbon atom bonded to OTf in **TS4$_S$** requires overcoming greater steric hindrance.

In order to demonstrate the synthetic utility of the obtained oxazole products and α-triflate β-keto-sulfones, **4a** and **6a** were cho-



Scheme 5. (a) Derivatization of the obtained poly-substituted oxazole **4a**. (b) Derivatization of the obtained α-triflate β-keto-sulfone compound **6a**.

sen as representative compounds to perform some further derivatization reactions (Schemes 5a and b). By reacting with sodium hydroxide in methanol, the ester-substituted oxazole **4a** could undergo alcoholysis give to the corresponding carboxylic acid **10a** in 94% yield [114]. In addition, as an organic halide, iodine-containing **4a** is also a suitable precursor for further transition metal-catalyzed cross-coupling reactions. Specifically, treating **4a** with methylboronic acid and potassium carbonate in the presence of bis(triphenylphosphine)palladium(II) chloride smoothly initiated a Suzuki-Miyaura cross-coupling reaction, providing product **11a** in 80% yields [115]. Moreover, Pd/C mediated hydrodefunctionalization of **4a** in hydrogen atmosphere with the catalysis of DABCO could reductively remove the iodine atom on the benzene ring in the substrate, affording deiodinated product **12a** in 75% yields [116]. This final transformation clearly indicated that the iodine atom in all products could be readily removed by hydrogenative reduction, thus addressing the concern that the iodine atom in the products might be a redundant substituent. Furthermore, when **6a** was treated with potassium phtalimide, resulting in the substitution of the triflate group with a phthalimide group, this transformation could achieve the formation of 2-(2-oxo-2-phenyl-1-(phenylsulfonyl)ethyl)isoindoline-1,3–dione **13** in 48% yield.

In conclusion, we realized the preparation of a novel benziodazole-triflate reagent **1i** and had its typical λ^3-iodane T-shaped structure confirmed by X-ray crystallography. The feature of this new reagent was that it can be used as both a 2-iodobenzamido- and a triflate-transfer reagent, reacting with diverse α-electron withdrawing group substituted carbonyl compounds to produce a series of poly-substituted oxazoles or α-triflate β-keto-sulfones. The ionic mechanisms with selectivity were proposed and testified by both control experiments and DFT calculations. This work not only supplements the type of hypervalent iodine reagents, but also represents an exclusive transformation pattern mediated by benziodazole-type hypervalent iodine reagents. Further studies on the application of this reagent **1i** as well as the mechanism on its divergent reactivities are still in progress in our labs.

Declaration of competing interest

We herein declare that all authors (Yadong Li, Feng-Huan Du, Junjie Li, Jun Xu, Zhifang Yang, Shanshan Li, Chi Zhang and Yunfei Du) have seen and approved the submission of this manuscript and there is no interest conflicts between/among all authors.

CRediT authorship contribution statement

Yadong Li: Writing – original draft, Methodology, Formal analysis, Data curation. **Feng-Huan Du:** Writing – original draft, Software, Methodology, Formal analysis, Data curation. **Junjie Li:** Writing – original draft, Software, Methodology, Formal analysis, Data curation. **Jun Xu:** Software, Formal analysis, Data curation. **Zhifang Yang:** Formal analysis, Data curation. **Shanshan Li:** Formal analysis, Data curation. **Chi Zhang:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition. **Yunfei Du:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.110338.

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