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Hydroxy(tosyloxy)iodobenzene (HTIB) in organic synthesis: Recent advances and applications

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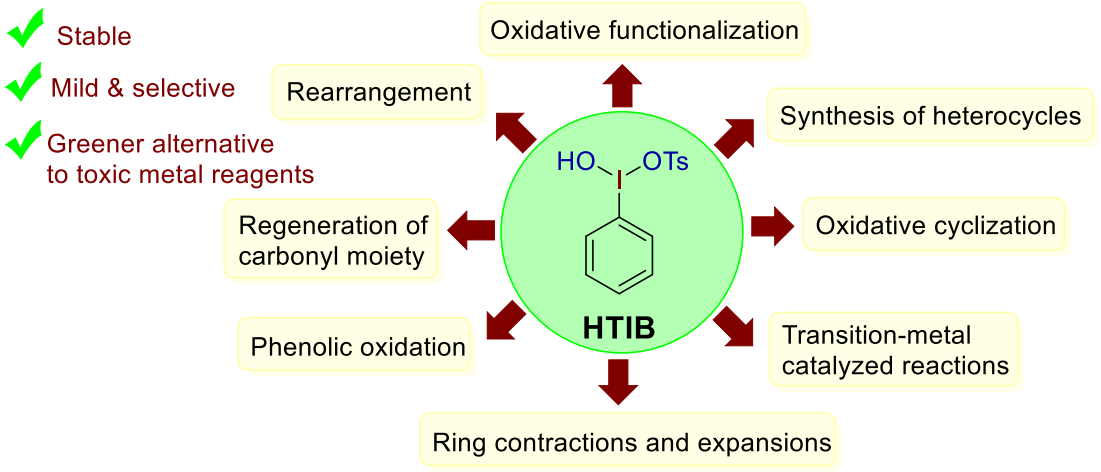
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Abstract

Hydroxy(tosyloxy)iodobenzene (HTIB, Koser's reagent) is a versatile hypervalent iodine(III) reagent with broad utility in organic synthesis. Its distinctive electrophilic and oxidative properties enable diverse transformations under mild conditions, including α-functionalization of carbonyl compounds, oxidative dearomatization, rearrangements, ring contractions and expansions, oxidative functionalization, and heterocycle synthesis. The continued interest in HTIB stems from its operational simplicity, metal-free nature, and ability to facilitate bond-forming and skeletal transformations under relatively mild conditions. This review summarizes advances in the synthetic applications of HTIB from 2019 to the present, with particular emphasis on heterocycle construction and other synthetically important transformations. Recent developments are discussed to highlight the scope, synthetic utility, and emerging role of HTIB in contemporary organic synthesis.



Keywords: Heterocycles; α-tosyloxylation; hypervalent iodine; oxidant; hydroxy(tosyloxy)iodobenzene.

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Introduction

Hypervalent iodine compounds, defined as iodine-containing compounds in oxidation states higher than +1 (predominantly +3 and +5), have emerged as indispensable reagents and catalysts in modern organic synthesis. Since the first reported synthesis of (dichloroiodo)benzene ($PhICl_2$) by Willgerodt in 1886,[1] the chemistry of hypervalent iodine has evolved into a mature and rapidly expanding field, driven by the development of versatile iodine(III) and iodine(V) reagents with broad synthetic utility. Over the past century, these compounds have acted as powerful and environmentally benign tools for a diverse range of organic transformations.[2,3]

Hypervalent iodine compounds have attracted considerable attention as versatile reagents in organic synthesis owing to their unique reactivity and selectivity, low toxicity, excellent functional-group compatibility, high bench stability, moisture tolerance, commercial availability, and relatively low cost. These attributes, along with their ease of handling and straightforward experimental procedures, make them useful alternatives to toxic heavy-metal reagents such as Cr(VI), Hg(II), Tl(III), Pb(IV), and Os(VIII).[4,5] Hypervalent iodine reagents are used primarily for oxidation reactions, C-C and C-heteroatom bond-forming processes,[6] alkene functionalization,[7] oxidative rearrangements,[8] group-transfer reactions,[9] and diverse cyclization reactions.[10,11]

Among the numerous hypervalent iodine reagents developed to date, iodine(III) compounds (λ^3-iodanes) represent the most widely employed class, with representative examples including (diacetoxyiodo)benzene (PIDA or DIB or IBD), [bis(trifluoroacetoxy)iodo]benzene (PIFA), iodosylbenzene (PhIO), and hydroxy(tosyloxy)iodobenzene (HTIB) (Figure 1). These reagents have demonstrated outstanding versatility in both stoichiometric and catalytic oxidative transformations and have become indispensable in the synthesis of structurally complex molecules, natural products and their intermediates, pharmaceuticals, and functional materials.[12,13]

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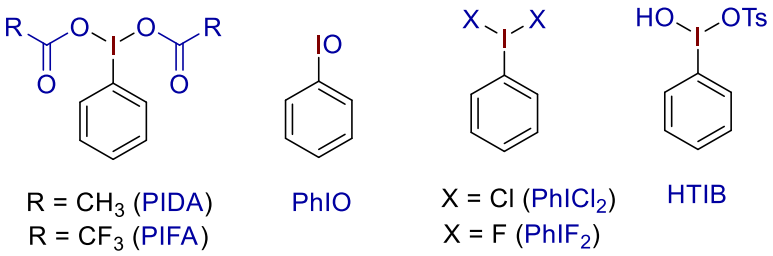


Figure 1. Commonly employed hypervalent iodine(III) (λ^3-iodanes) reagents.

In recent years, hypervalent iodine compounds have found applications as non-toxic oxidants, efficient organocatalysts for oxidative transformations of diverse organic substrates, and catalysts for asymmetric transformations.[14,15] The rapid growth and continuing evolution of this field are reflected in the large number of comprehensive reviews, monographs, and book chapters published over the past several decades, highlighting the broad scope of hypervalent iodine chemistry, its mechanistic diversity, and its expanding synthetic applications.[16,17,18,19,20,21] Continued advances in reagent design, catalytic strategies, and mechanistic understanding are expected to further enhance the utility of hypervalent iodine compounds, consolidating their position as one of the most important classes of environmentally benign reagents in modern organic synthesis.

Hydroxy(tosyloxy)iodobenzene (HTIB), commonly known as Koser's reagent, occupies an eminent position among hypervalent iodine(III) reagents because its reactivity combines the electrophilic character of a λ^3-iodane with the ability to transfer a tosyl- or oxygen-containing functionality to organic substrates.[22] It can be conveniently synthesized by reacting PIDA with *p*-toluenesulfonic acid monohydrate (TsOH·H_2O).[23] Beyond its classical application in the α-tosyloxylation of enolizable ketones, HTIB has emerged as a versatile hypervalent iodine reagent for a broad range of oxidative transformations.[24,25] These include oxidative rearrangements, such as ring contraction and ring expansion; regeneration of carbonyl compounds; Hofmann degradation of carboxamides; α-azidation and α-iodination; oxyfunctionalization and difunctionalization of alkenes; phenol dearomatization; and oxidative cyclization for the synthesis of oxygen- and nitrogen-containing heterocycles.[26,27,28] In this review, we highlight representative applications of Koser's reagent, reported during 2019-2026, in the synthesis and functionalization of heterocycles, natural product synthesis, phenolic dearomatization, oxidative annulation, bifunctionalization, and oxidative rearrangement, while also discussing selected applications of substituted Koser-type reagents and related hydroxy(sulfonyloxy)iodoarenes to illustrate the expanding synthetic versatility of this reagent class.

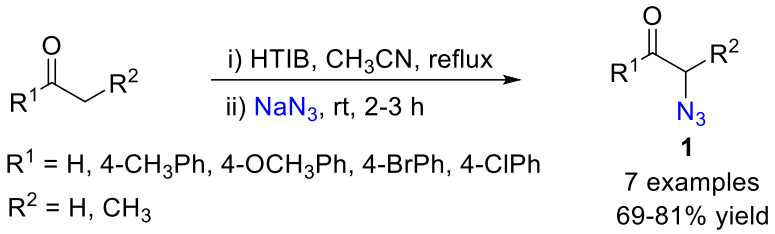
2. Synthetic applications of HTIB

HTIB has found extensive application in organic synthesis, either in stoichiometric or catalytic amounts, for the preparation of synthetically valuable compounds. Its operational simplicity, excellent regio- and chemoselectivity, and reactivity comparable to toxic heavy-metal reagents make HTIB an attractive and reliable oxidant for the synthesis of structurally diverse, biologically significant compounds. Historically, HTIB has been employed in carbonyl and olefin oxidation, skeletal rearrangements, phenol dearomatization, and the synthesis of iodonium salts.[24] Recent studies have expanded the synthetic utility of HTIB to diverse transformations under metal-free, catalytic, electrochemical, and transition-metal-assisted conditions, including C-H functionalization, oxidative dehydrogenation, ring expansion and contraction, oxygen-transfer reactions, and heterocycle synthesis. These developments highlight the versatility of HTIB as an iodine(III) reagent in modern organic synthesis.

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2.1. Oxidative functionalization of carbonyl compounds, enone, aryls and heteroaryls

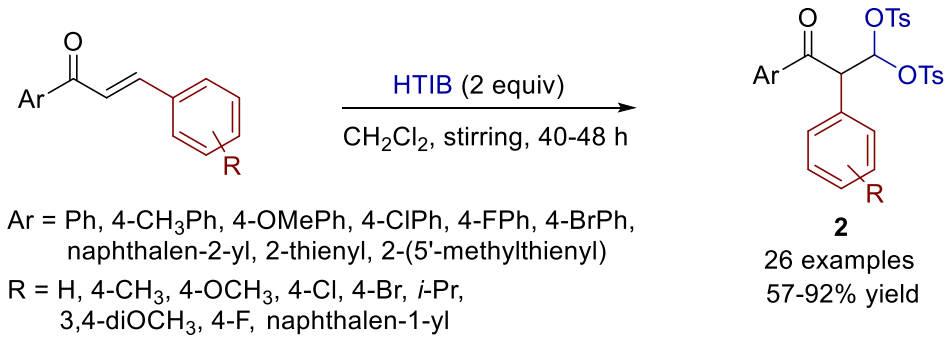
α-Functionalization of carbonyl compounds represents one of the most established applications of Koser's reagent (HTIB).[29] In particular, HTIB-mediated α-tosyloxylation of enolizable ketones was first reported by Koser and coworkers in 1982,[30] who demonstrated that treatment of ketones with HTIB in refluxing acetonitrile afforded the corresponding α-oxytosylated products in moderate to excellent yields. These α-tosyloxy ketones offer synthetically useful alternatives to conventional α-haloketones, which are often highly lachrymatory and unstable.[31] α-Tosyloxy ketones, generated *in situ* from reaction of various enolizable ketones with HTIB, on treatment with sodium azide afforded the corresponding α-azido ketones **1** in high yields in one-pot (Scheme 1).[32]



Scheme 1.

Beyond monotosyloxylation, HTIB can induce further tosyloxylation depending on the substrate and reaction conditions. Sequential functionalization at the same α-carbon affords α,α-ditosyloxy ketones (gem-ditosylates), whereas addition across an enol/enone system can furnish α,β-ditosyloxy ketones (vic-ditosylates).[33] Owing to their two highly competent tosyloxy leaving groups, these ditosylated products serve as versatile bifunctional synthons for subsequent synthetic transformations.

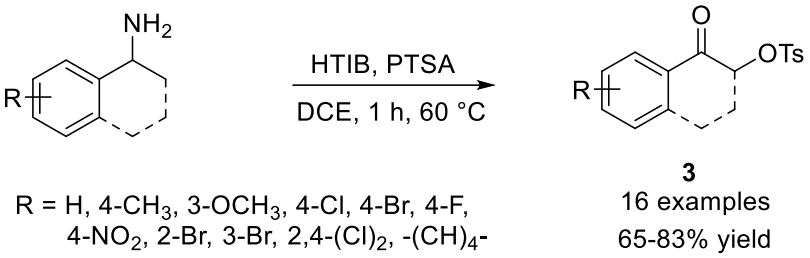
Kumar and coworkers investigated the HTIB-mediated oxidative rearrangement of α,β-unsaturated diaryl ketones in a polar aprotic solvent, leading to the formation of α-aryl-β,β-ditosyloxy ketones **2**, which can serve as potentially useful three-carbon 1,3-dielectrophilic synthons (Scheme 2).[34,35] The structure of the synthesized gem-β,β-ditosyloxy ketone was confirmed by X-ray analysis. This finding differed from earlier reports describing HTIB-mediated ditosyloxylation of unsaturated carbonyl compounds as a route to α,β-ditosyloxy ketones.[36,37] Quantum-chemical calculations further supported the geminal structure for the ditosyloxy ketone as the thermodynamically preferred structure. Mechanistic investigations revealed electrophilic addition followed by an intriguing 1,2-aryl C–C migration, and the influence of electronic effects of electron-donating and electron-withdrawing substituents as well as steric factors was examined across a series of α,β-unsaturated diaryl ketones. Electron-donating groups on the migrating aryl ring favor rearrangement to β,β-ditosyloxy ketones, whereas electron-withdrawing groups result in competing formation of α,β- and β,β-ditosyloxy ketones.[38]



Scheme 2.

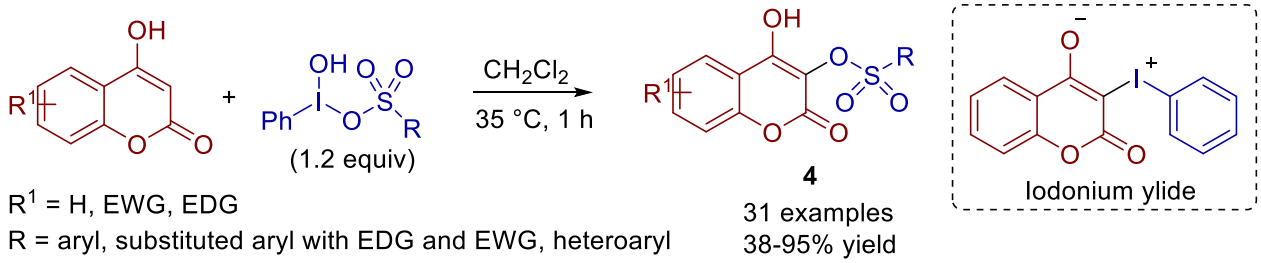
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Rupanawar and coworkers developed an efficient, metal-free protocol for the synthesis of functionalized ketones **3**. This operationally simple protocol involves sequential oxidation of α-alkylbenzylamines, followed by tosylation, to afford α-tosyloxy ketones **3** using HTIB (Scheme 3).[39] The use of readily accessible starting materials, broad substrate compatibility, and short reaction time are notable advantages of this protocol.



Scheme 3.

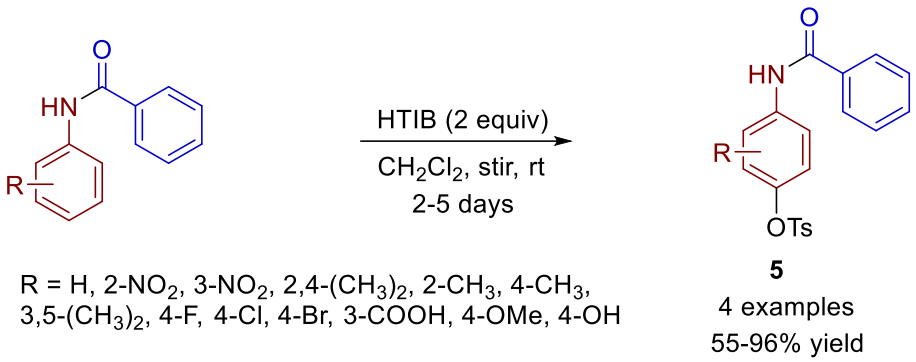
Xu and coworkers developed an efficient approach for the tosyloxylation of 4-hydroxycoumarins using Koser's reagents through sp^2 C-H functionalization, affording 3-tosyloxy-4-hydroxycoumarins **4**, which serve as valuable synthetic building blocks (Scheme 4).[40] The reaction exhibited broad functional-group tolerance toward a variety of Koser's reagents and 4-hydroxycoumarin derivatives under mild reaction conditions and proceeded without the use of a transition-metal catalyst. Koser's reagents bearing electron-donating substituents generally afforded the corresponding tosyloxylated products in higher yields. To gain insight into the reaction mechanism, a low-temperature control experiment was performed, which afforded an iodonium ylide, suggesting its involvement as a reaction intermediate.



Scheme 4.

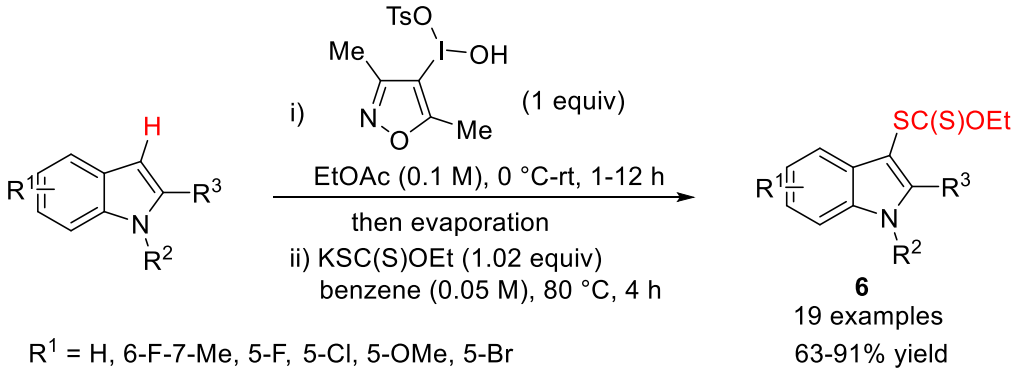
Aneja and coworkers reported a metal-free, *para*-selective tosyloxylation of *N*-arylbenzamides using HTIB in dichloromethane at room temperature (Scheme 5).[22] The protocol afforded *para*-tosyloxylated products **5** with high regioselectivity, avoiding the formation of *ortho*- and *meta*-isomeric products. During reaction optimization, benzanilide remained unreacted when treated with 1.5 equiv of HTIB in the presence of CuCl (1.5 equiv); increasing the HTIB loading to 2.0 equiv afforded product **5** in 58% yield. Notably, removing the CuCl catalyst improved the yield to 61%, whereas further increasing the HTIB loading to 3.0 equiv offered no significant improvement. Accordingly, the substrate scope was investigated under metal-free conditions. The reaction exhibited distinct substrate-dependent selectivity: substrates with an occupied *para*-position failed to undergo tosyloxylation, whereas *meta*-substituted electron-withdrawing groups, such as nitro and carboxyl groups, also suppressed the transformation. In contrast, *ortho*-substitution with either electron-donating or electron-withdrawing groups was generally tolerated, provided that the *para*-position remained accessible. These observations highlight the importance of both electronic effects and *para*-position availability in determining substrate reactivity.

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Scheme 5.

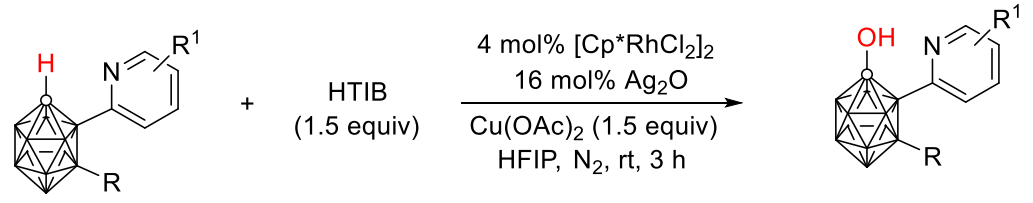
Malashchenko and coworkers reported a metal-free C(3)-H functionalization of indoles using the Koser-type hypervalent iodine(III) reagent, (3,5-dimethylisoxazol-4-yl)–I(OH)OTs. The reaction involves *in situ* generation of highly electrophilic (3,5-dimethylisoxazol-4-yl)(indol-3-yl)iodonium intermediates through chemo- and regioselective functionalization at the C(3) position of indoles. These intermediates readily react with potassium *O*-alkyl xanthates to afford the corresponding *O*-alkyl-*S*-(indol-3-yl) xanthates **6** in good to high yields (Scheme 6).[41] The method exhibited broad functional-group tolerance and was applicable to the late-stage functionalization of structurally complex molecules. Synthetically, this protocol provides convenient access to indol-3-yl xanthates, which serve as useful precursors for the synthesis of C(3)-sulfur-functionalized indole derivatives.



Scheme 6.

The chemistry of Koser's reagent has evolved from classical electrophilic and oxidative transformations toward increasingly sophisticated functional-group-transfer processes. In this context, the recently reported Rh-catalyzed regioselective B(4)-H hydroxylation of pyridyl-*o*-carboranes represents a notable advancement, demonstrating the utility of HTIB in transition-metal-catalyzed B-H functionalization under mild reaction conditions, as well as its potential role as an oxygen source (Scheme 7).[42] Notably, the use of preformed HTIB proved advantageous over an *in situ*-generated iodine(III) system derived from PIDA and *p*-toluenesulfonic acid, which resulted in a significantly lower yield. Furthermore, replacement of the 2-pyridyl directing group with a phenyl substituent completely suppressed the reaction, highlighting the importance of pyridyl coordination in facilitating Rh-catalyzed B-H functionalization. The methodology exhibited a broad substrate scope, accommodating various alkyl-, aryl-, and substituted pyridyl-containing *o*-carboranes, affording the corresponding B(4)-hydroxylated derivatives **7** in moderate to high yields.

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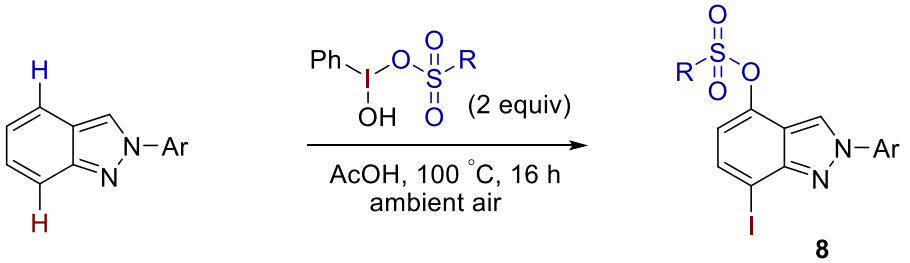
R = H, Me, Et, *n*-Pr, *n*-pentyl, *i*-Pr, cyclohexyl, Ph, 2-MePh, 3-MePh, 4-MePh, 4-OMePh, 4-CF_3Ph, Bn, 4-FBn, 4-ClBn, 4-BrBn, 4-OMeBn, 4-CF_3Bn

R^1 = H, 2-Me, 3-Me, 3-CF_3, 4-CF_3, 5-OMe, 5-Br

24 examples
44-82% yield

Scheme 7.

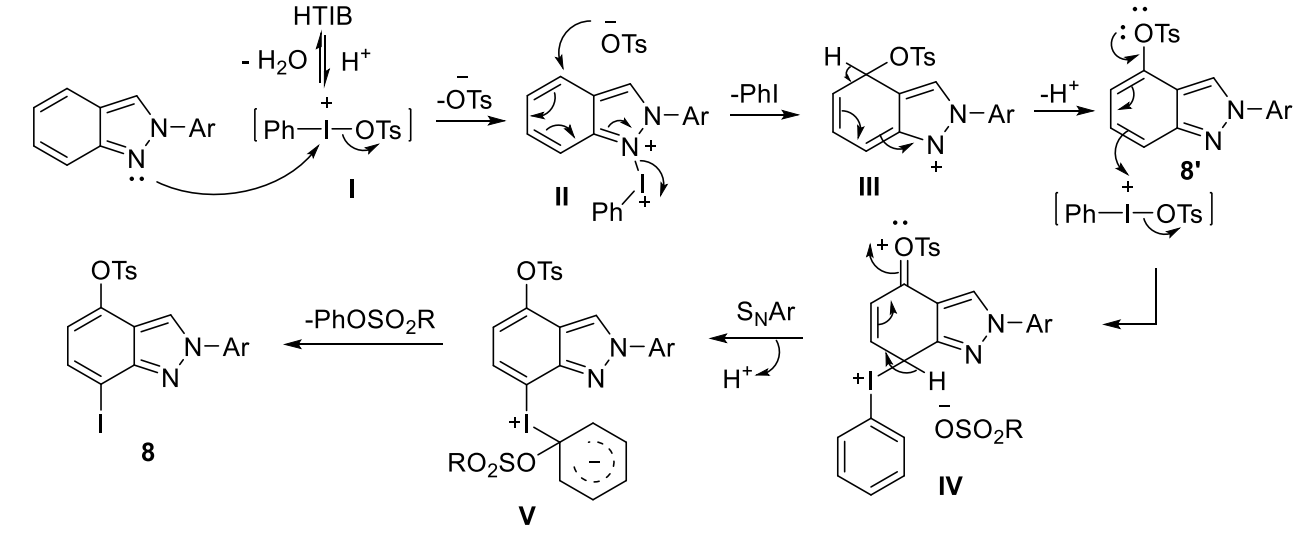
Bhattacharjee and coworkers developed an efficient metal-free protocol for the remote difunctionalization of otherwise inert C-H bonds on the benzene ring of 2*H*-indazoles using Koser's reagents as bifunctional sulfonyloxylating and iodinating reagents under ambient conditions (Scheme 8).[43] The reaction exhibits high regioselectivity, furnishing C-4-sulfonyloxylated and C-7-iodinated 2*H*-indazole derivatives **8** in good to excellent yields. The methodology accommodates a broad range of substrates and functional groups, and variation of the sulfonyloxy group on the iodine(III) reagent provides access to the corresponding derivatives in moderate to high yields. Importantly, the resulting 4,7-disubstituted 2*H*-indazoles **8** serve as versatile synthetic intermediates for the synthesis of structurally diverse C-4- and C-7-functionalized derivatives.



8

Ar = Ph, 4-MePh, 4-OMePh, 4-CO_2MePh, 3-MePh, 2-MePh, etc.
R = *p*-tol, Ph, Me, 4-EtPh, 4-ClPh, naphthalen-2-yl

31 examples
57-89% yield



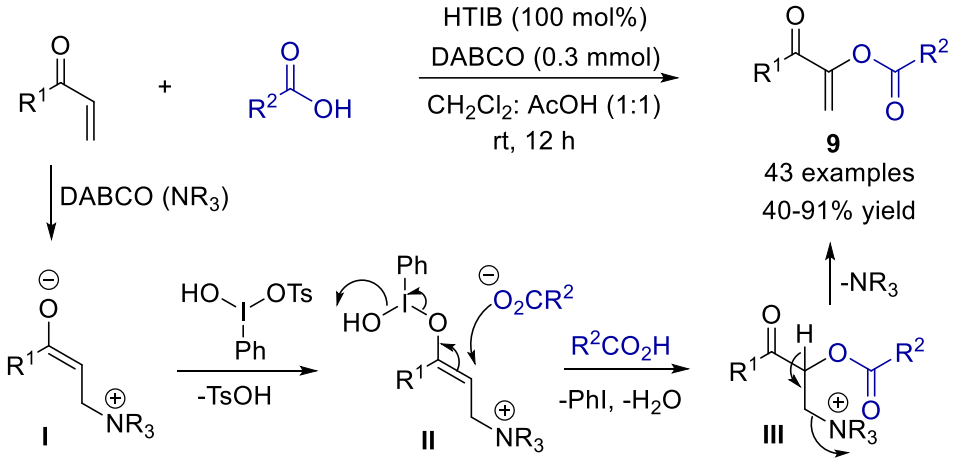
Scheme 8.

Control experiments revealed that the desired product **8** was formed even in the presence of the radical scavenger TEMPO, suggesting an ionic rather than a free-radical pathway. Furthermore, the formation of the

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C-4-tosyloxylated intermediate **8'** using 1 equiv. of HTIB and its subsequent conversion into product **8** upon treatment with an additional equivalent support a stepwise difunctionalization pathway. The authors proposed that the electron-donating effect of the C-4 tosyloxy group facilitates the subsequent remote iodination at C-7, thereby accounting for the observed regioselectivity. On the basis of these observations, the authors proposed an ionic mechanism (Scheme 8). Initially, under acidic conditions, Koser's reagent generates the reactive iodine(III) species **I**, assigned as a phenyl tosyloxyiodonium intermediate. Subsequently, the *N*-1 atom of 2*H*-indazole interacts with the electrophilic iodine center of **I** through its lone pair, generating cationic intermediate **II**. Regioselective nucleophilic attack by the tosylate anion at C-4 gives intermediate **III**, which undergoes deprotonation to restore aromaticity and yield intermediate **8'**. The C-4 tosyloxy group is proposed to facilitate subsequent C-I bond formation *via* electrophilic addition to intermediate **I,** affording intermediate **IV**. Subsequent nucleophilic substitution and proton elimination steps generate intermediate **V** and ultimately furnish the desired C-4-tosyloxylated and C-7-iodinated product **8**.

Pandey and coworkers reported a direct oxidative α-oxyacylation of vinyl ketones using HTIB to furnish α-oxyacylated vinyl ketones **9**, which were subsequently employed as synthetic intermediates for the preparation of densely functionalized chiral δ-lactones and cyclopentenes. The reaction enables the installation of acyloxy groups derived from long-chain aliphatic, (hetero)aromatic, and α,β-unsaturated carboxylic acids at the α-position of vinyl ketones through a mechanistic pathway involving DABCO-mediated umpolung, analogous to the key nucleophilic step of a Morita–Baylis–Hillman reaction (Scheme 9).[44] In the proposed mechanism, conjugate addition of DABCO to the vinyl ketone generates zwitterionic intermediate **I**, which reacts with HTIB to afford intermediate **II**. Subsequent reaction with the carboxylic acid gives intermediate **III**, which undergoes final elimination to furnish the α-oxyacylated product **9** with concomitant regeneration of DABCO. This elimination may be rationalized through enolate formation followed by elimination of the tertiary amine. Among the hypervalent iodine(III) reagents evaluated (PIDA, PIFA, HTIB, *p*-Me-HTIB, and *p*-NO_2-HTIB), HTIB proved to be the most effective for promoting the α-oxyacylation of vinyl ketones. Screening of other bases, including TEA, pyridine, DBU, and pyrrolidine, did not afford the desired product under the investigated conditions. Among the solvent systems examined, CH_2Cl_2/AcOH (1:1) gave the best result. The reaction exhibited broad substrate scope, tolerating mono- and disubstituted aryl vinyl ketones as well as heteroaryl- and aliphatic-substituted vinyl ketones. Notably, the method also displayed good chemoselectivity, as an additional alkene in the substrate remained unaffected under the reaction conditions, with no competing dioxyacylation observed.



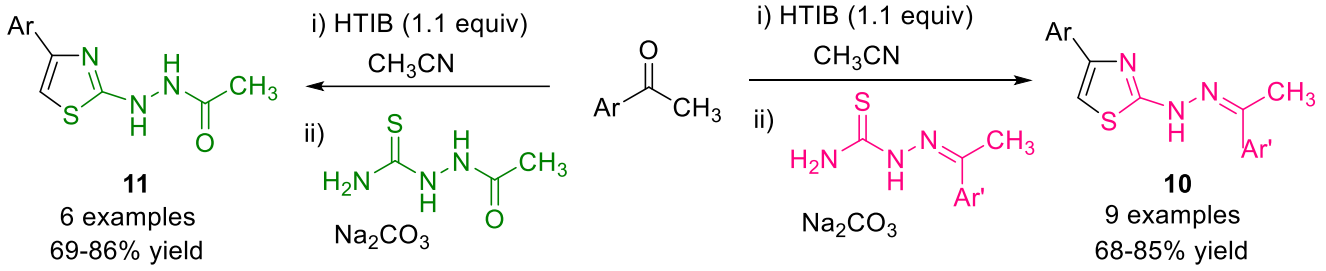
R^1 = R^2 = aryl, heteroaryl, alkyl chain, α,β-unsaturated olefins

Scheme 9.

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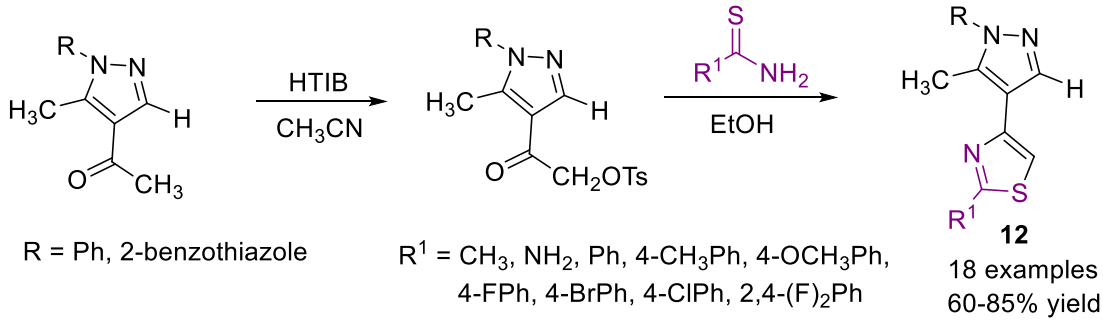
2.2. Synthesis of heterocycles *via* cyclization of tosyloxyketone intermediates

Pundeer and coworkers reported one-pot synthesis of 4-aryl-2-(2-(1-arylethylidene)hydrazinyl)thiazoles **10** and 2-*N*-acetylhydrazino-4-arylthiazoles **11** by treatment of aryl methyl ketones with HTIB followed by reaction with thiosemicarbazones or *N*-acetylthiosemicarbazide, respectively (Scheme 10).[45] The reaction offers a viable method for the construction of the thiazole motif in a single step without the isolation of the intermediate α-tosyloxy carbonyl compound.



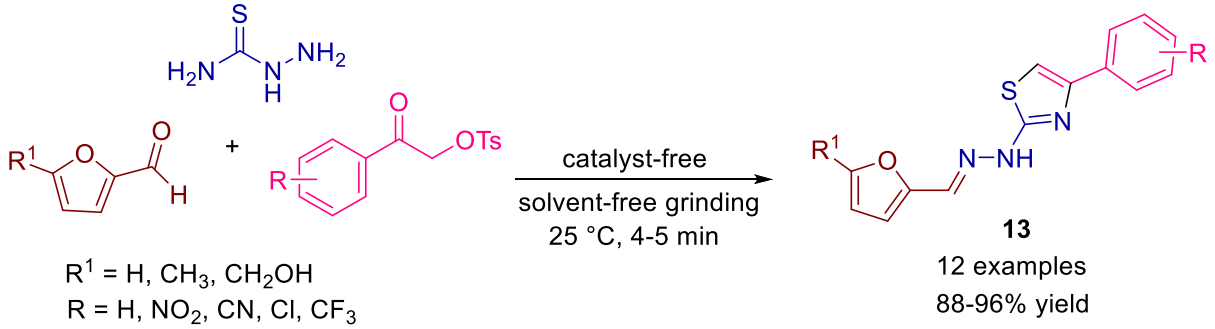
Scheme 10.

Kamra and coworkers accomplished the synthesis of phenyl/benzothiazole linked pyrazolyl-thiazoles **12** from reaction of pyrazolyl ketones with HTIB, followed by treatment with substituted thioamides in refluxing ethanol (Scheme 11).[46] The synthesized pyrazolyl-thiazoles were characterized by spectroscopic studies and evaluated for antimicrobial activity and phytotoxicity.



Scheme 11.

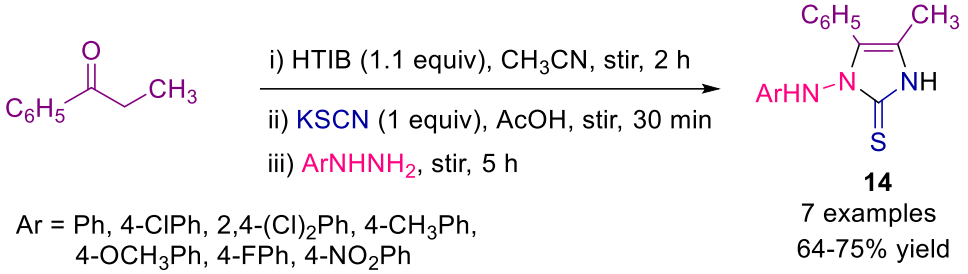
Gurav and coworkers developed a simple, convenient one-pot approach to prepare pharmaceutically valuable hydrazinyl thiazoles **13** using biomass-derived furfurals as key synthons (Scheme 12).[47] The authors employed grindstone chemistry for a three-component reaction between furfural, thiosemicarbazide and non-lachrymatory α-tosyloxy ketones at room temperature. This solvent-free green approach afforded the desired products in good to excellent yields with both electron-donating and electron-withdrawing substituents on the phenacyl tosylate in a short reaction time without a metal catalyst.



Scheme 12.

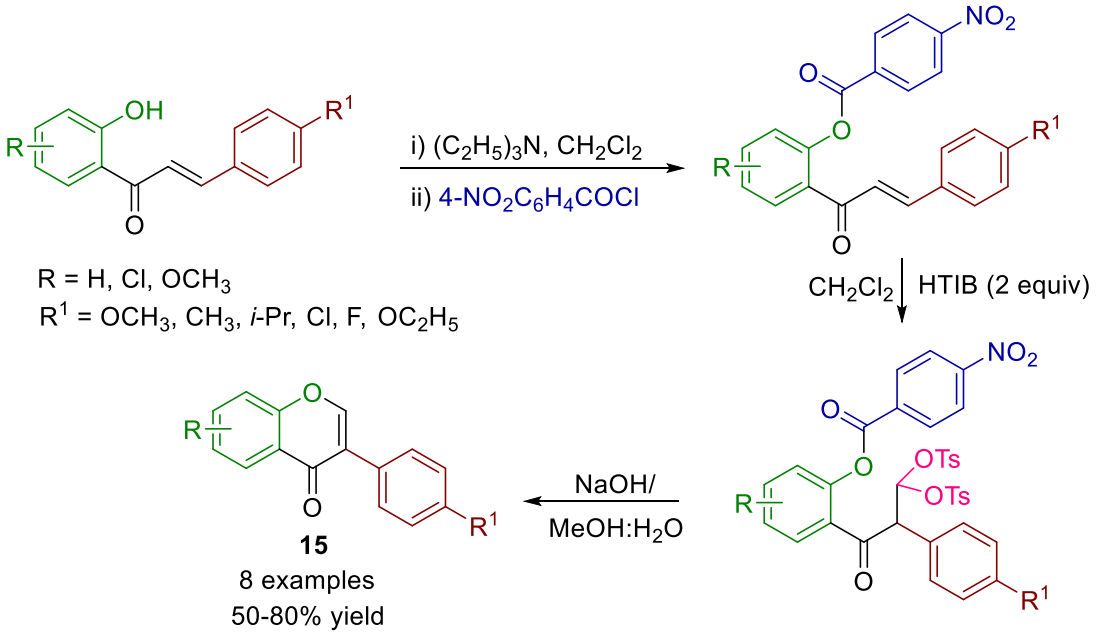
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Pundeer and Chaudhri reported a tandem one-pot protocol for the synthesis of 2,3-dihydro-4-methyl-5-arylamino-1*H*-imidazole-2-thiones **14** from propiophenone. The reaction involves HTIB-mediated α-tosyloxylation of propiophenone, followed by thiocyanation with potassium thiocyanate to generate the corresponding α-thiocyanato ketone and subsequent cyclocondensation with arylhydrazines (Scheme 13).[48] The one-pot sequence afforded the corresponding imidazole-2-thiones **14** in moderate to good yields, providing a concise route to these heterocyclic products from readily accessible ketone precursors.



Scheme 13.

Hypervalent iodine compounds also have applications in the synthesis of flavonoids.[49] Bains and coworkers reported a metal-free and eco-friendly approach for the synthesis of eight isoflavone derivatives **15,** employing α-aryl-β,β-ditosyloxy ketones as key precursors (Scheme 14).[50] The reaction involves the protection of 2'-hydroxy group of the respective chalcone to remove its interference under reaction conditions. The protected chalcones were then transformed to α-aryl-β,β-ditosyloxy ketones in 55–82% yield *via* 1,2-aryl migration on treatment with HTIB in dichloromethane as a non-nucleophilic solvent. These intermediates act as versatile 1,3-dielectrophilic carbon synthons which on subsequent treatment with sodium hydroxide in aqueous methanol afforded the corresponding isoflavones **15** in moderate to good yields.

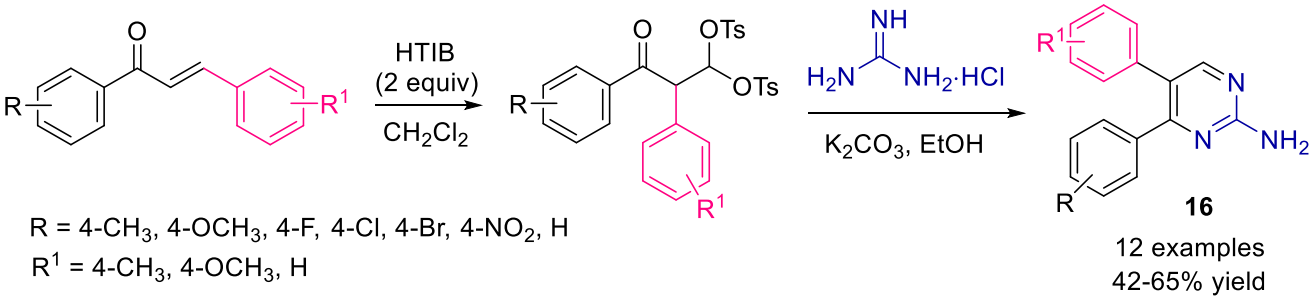


Scheme 14.

Kumar and coworkers developed an efficient and environmentally benign synthesis of a series of 4,5-diphenylpyrimidin-2-amines **16** from readily accessible chalcones *via* HTIB-mediated formation of geminal ditosyloxy ketones through 1,2-aryl migration, followed by base-promoted cyclocondensation with guanidine hydrochloride, affording the products in moderate to good yields (Scheme 15).[51] Attractive features of the synthesis include reduced reaction times, operational simplicity, and high regioselectivity. Furthermore, the

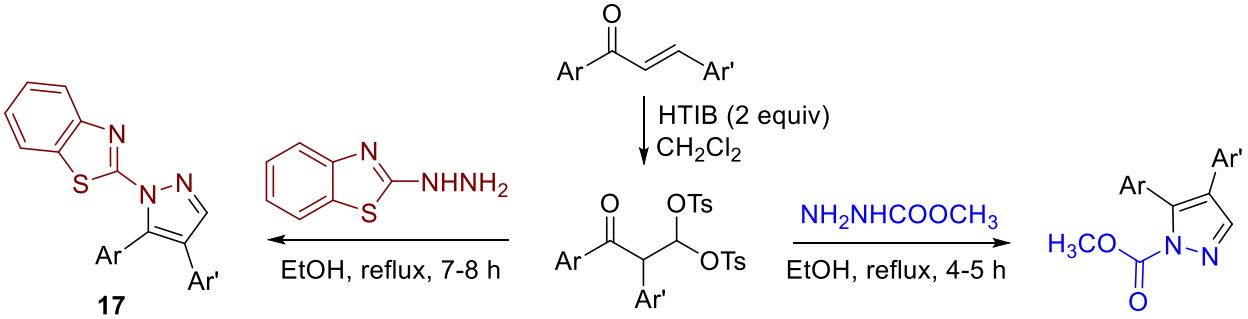
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two tosyloxy (OTs) groups enhance reactivity by acting as excellent leaving groups and strong electron-withdrawing groups, facilitating efficient cyclization under mild conditions.



Scheme 15.

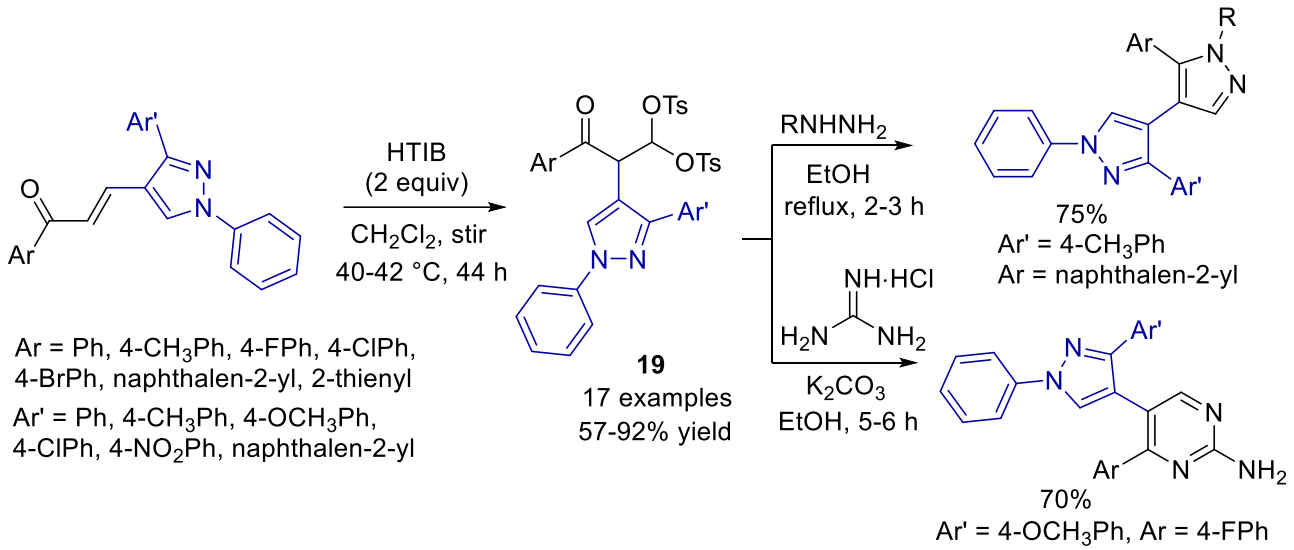
Bains and coworkers reported the regioselective synthesis of eighteen novel pyrazolo-benzothiazole hybrids **17** *via* the reaction of β,β-ditosyloxy ketones with 2-hydrazinobenzothiazole under refluxing conditions in ethanol (Scheme 16).[52] The synthesized derivatives were evaluated for their antiproliferative activity against MCF-7, HeLa, and A549 cancer cell lines. Among the tested compounds, the derivative bearing 4-methoxyphenyl and 4-methylphenyl substituents (Ar = 4-OMePh, Ar′ = 4-MePh) exhibited the highest antiproliferative activity against MCF-7 cells, with an IC_{50} value of 0.051 mM, demonstrating greater potency than the reference drug carboplatin (IC_{50}= 0.439 mM). Kamal and coworkers developed a simple and eco-friendly protocol for the synthesis of a series of 4,5-diarylpyrazole-1-carboxylates **18** *via* condensation of β,β-ditosyloxy ketone with methyl hydrazinecarboxylate in refluxing ethanol (Scheme 16).[53] The authors also studied the effect of substituents on photophysical properties of the synthesized pyrazoles **18**.



Scheme 16.

Extending the HTIB-mediated 1,2-aryl rearrangement to heteroaryl migration, Bains and coworkers reported in 2026 the rearrangement of pyrazolyl chalcones to α-heteroaryl-β,β-ditosyloxy ketones **19** in moderate to excellent yields (Scheme 17).[54] The rearranged products **19** were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and HRMS analyses, with selected compounds further validated by single-crystal XRD and supported by computational investigations. The synthetic utility of β,β-ditosyloxy ketones **19** was demonstrated through regioselective transformations affording bis-pyrazoles and a pyrazolo-pyrimidine hybrid.

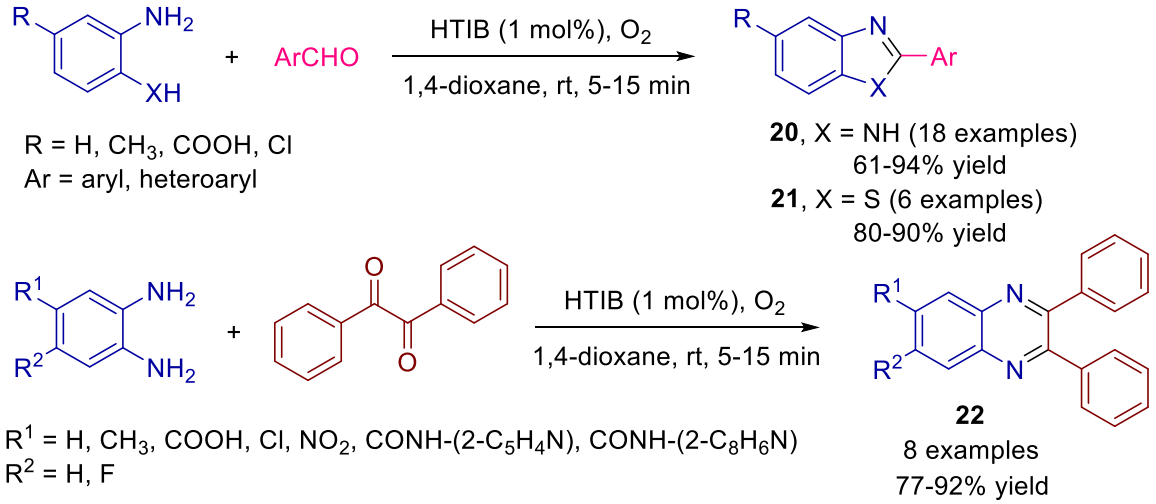
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Scheme 17.

2.3. Synthesis of heterocycles *via* oxidative cyclization

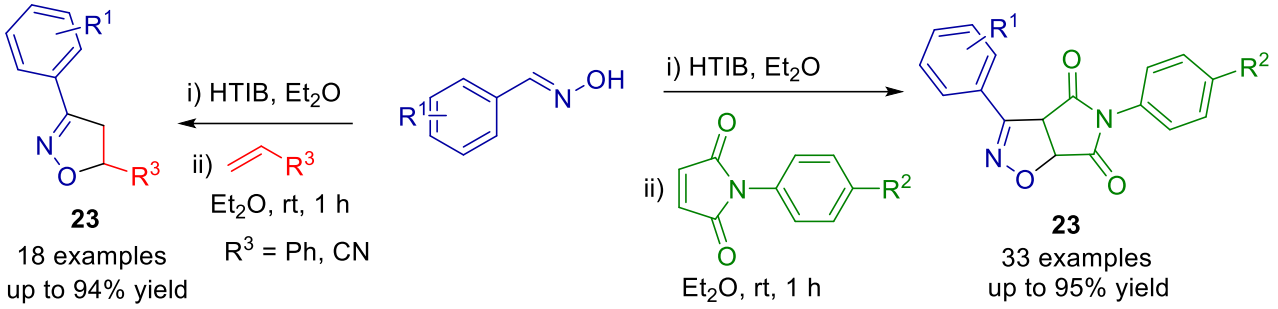
Ramya and coworkers reported a facile and efficient protocol for the synthesis of 2-aryl/heteroaryl-benzimidazoles **20** and 2-aryl-benzothiazoles **21** *via* condensation of *o*-phenylenediamine and 2-aminothiophenol, respectively, with a range of aryl or heteroaryl aldehydes using HTIB as a catalyst under a molecular oxygen atmosphere (Scheme 18).[55] The products were obtained in high yields within short reaction times, and notably, a remarkably low catalytic loading of Koser's reagent (1 mol%) was sufficient to promote the cyclization efficiently. Aromatic aldehydes bearing electron-donating substituents generally afforded slightly higher yields than those containing electron-withdrawing groups. The synthetic utility of this oxidative protocol was further demonstrated by its extension to the synthesis of quinoxaline derivatives **22** *via* HTIB-mediated intermolecular oxidative cyclization of substituted *o*-phenylenediamines with benzil under an oxygen atmosphere, using 1,4-dioxane as the solvent (Scheme 18).



Scheme 18.

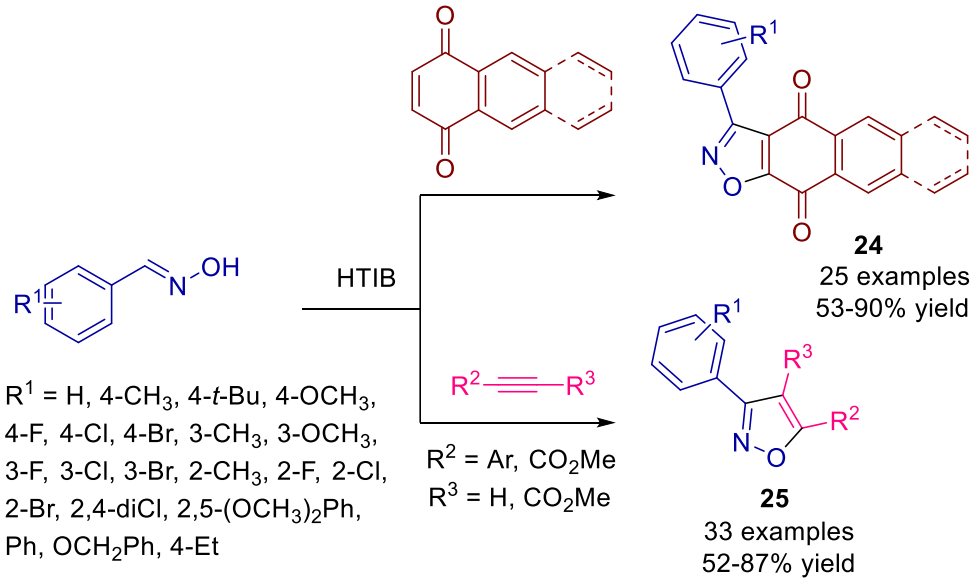
In 2023, Budhwan and coworkers reported a robust and convenient protocol for synthesizing isoxazoline derivatives **23**. The synthesis proceeds *via* a 1,3-dipolar cycloaddition of maleimides, styrene, and acrylonitrile with nitrile oxides generated *in situ* from the corresponding aldoximes using HTIB (Scheme 19).[56] This protocol offers several notable advantages, including operational simplicity, short reaction time, a broad substrate scope, and the absence of any requirement for a base, transition-metal, or additional additives.

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Scheme 19.

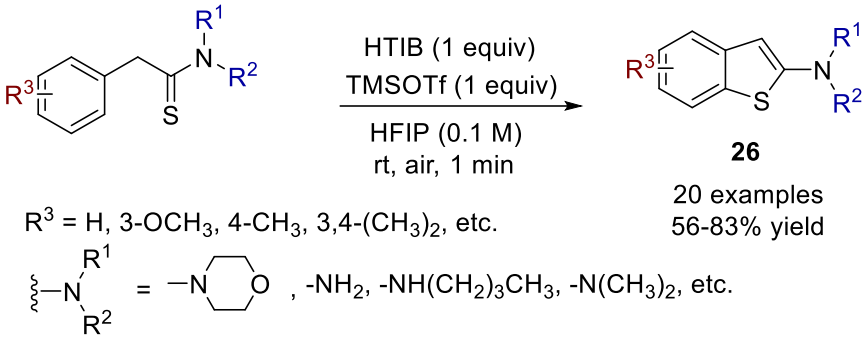
Budhwan and coworkers also recently reported an efficient transition-metal-free protocol for the synthesis of isoxazole-fused polycyclic quinone frameworks **24** in moderate to excellent yields *via* oxidative cyclization of arylaldoximes with 1,4-naphthoquinone or 1,4-anthraquinone under mild ambient conditions using HTIB (Scheme 20).[57] Beyond these substrates, the protocol demonstrates broad applicability in intermolecular (3 + 2) cycloadditions of aldoximes with arylacetylenes and dialkyl acetylenedicarboxylates, affording structurally diverse, functionalized isoxazoles **25** with excellent functional-group tolerance. Its synthetic utility is further established by gram-scale reactions and facile post-synthetic derivatization. Photophysical studies demonstrate pronounced solvent-dependent absorption and emission, with selected derivatives exhibiting strong intramolecular charge-transfer (ICT) characteristics, underscoring their potential for fluorescent and optoelectronic applications.



Scheme 20.

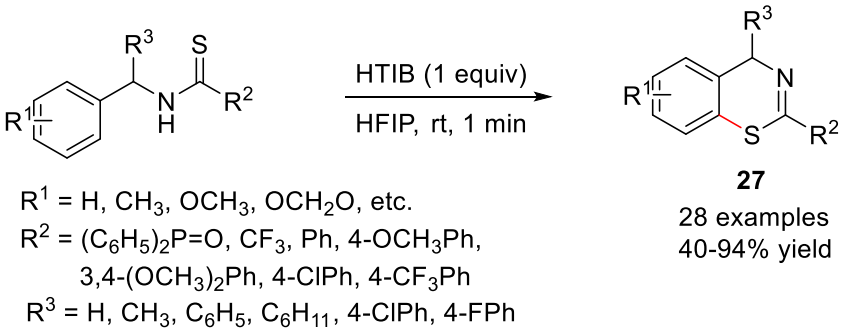
Bugaenko and Karchava accomplished the synthesis of pharmaceutically relevant 2-aminobenzo[*b*]thiophenes **26** *via* HTIB-mediated fast intramolecular cross-dehydrogenative cyclization of substituted thioamides of 2-arylacetic acids (Scheme 21).[58] This metal-free protocol is operationally simple and accommodates readily accessible substrates, diverse substituents on the aromatic ring, particularly electron-donating groups, and various functional groups. Notably, the authors demonstrated the practical utility of the protocol through a multigram-scale synthesis starting from ibuprofen.

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Scheme 21.

Li and coworkers developed a simple and expeditious HTIB-mediated oxidative intramolecular cyclization of thioamides for the synthesis of 1,3-benzothiazine derivatives **27** (Scheme 22).[59] The transformation proceeds through direct intramolecular dehydrogenative C-S bond formation under metal-free conditions, employing hexafluoroisopropanol (HFIP) as the solvent. Notably, the reaction is complete within 1 min at room temperature, affording the corresponding six-membered N, S-containing heterocycles in good yields, and highlighting the mildness and operational efficiency of the protocol. The reaction exhibited a good substrate scope, with 28 benzothiazine derivatives synthesized from a range of thioamides bearing trifluoromethyl groups, different phosphoryl groups, and phenyl rings substituted with electron-donating or electron-withdrawing groups. The reaction was also examined with other hypervalent iodine reagents, including PIDA, PIFA, *p*-F-HTIB, and *p*-Me-HTIB, which afforded lower yields than HTIB under the same conditions, highlighting the superior performance of HTIB. The synthetic utility of the protocol was further demonstrated on a gram scale. Preliminary mechanistic investigations suggested that a spirocyclic intermediate may be involved in the cyclization pathway.

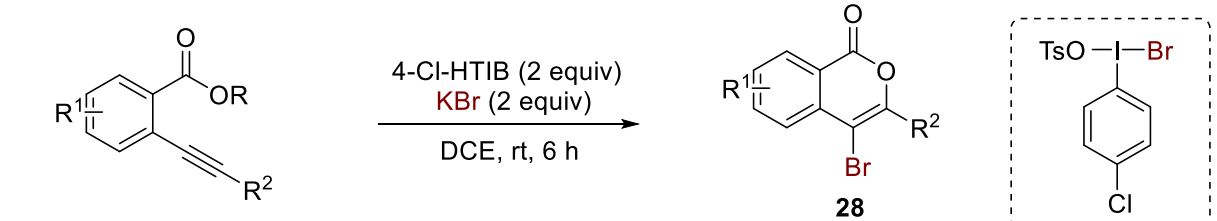


Scheme 22.

Sodoor and Selvakumar reported a metal-free protocol for the synthesis of 4-bromoisocoumarins **28** *via* the brominative annulation of 2-alkynylaryloate esters using an *in situ* generated transient bromoiodane (Scheme 23).[60] Initial optimization using 2 equivalents each of PIDA and KBr in acetonitrile at room temperature failed to afford the desired product. In contrast, PIFA enabled the reaction, albeit with moderate efficiency. Notably, replacing PIFA with HTIB improved product formation. Subsequent solvent screening and modification of the electronic properties of the aryl group attached to iodine identified 4-chloro-substituted HTIB (4-Cl-HTIB) as the most effective reagent, further enhancing the reaction efficiency. Under the optimized conditions, 4-Cl-HTIB served as an oxidant, while potassium bromide acted as the bromine source. The protocol exhibited a broad substrate scope, affording various 4-bromoisocoumarins **28** in excellent yields under ambient-temperature conditions. However, substrates bearing certain electron-withdrawing substituents, such as 4-nitro, 4-cyano, and 4-carbomethoxy groups on the phenyl ring at the R^2 position, failed to undergo the desired transformation, indicating a limitation in the substrate scope. The synthetic utility of

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this methodology was further demonstrated through gram-scale synthesis and subsequent functionalization of the resulting 4-bromoisocoumarins to access structurally diverse compounds.

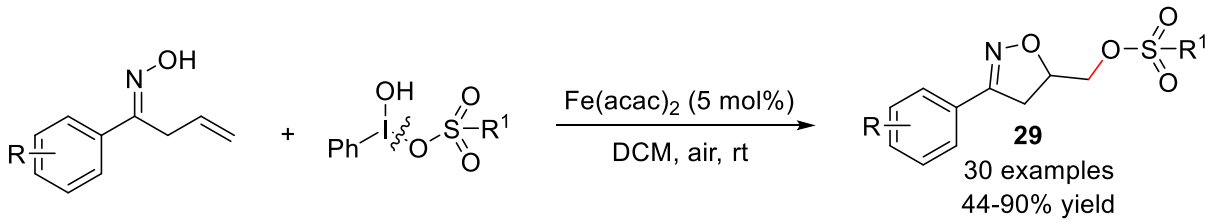


R = CH_3, Et, *i*-Pr, *t*-Bu, Ph, Bn
R^1 = H, CH_3, F, Cl, Br
R^2 = H, Ph, 2-CH_3Ph, 3-CH_3Ph, 4-CH_3Ph, 4-EtPh, 4-*t*-BuPh, 3-OCH_3Ph, 3-FPh, 4-FPh, 4-ClPh, 4-C_6H_4Ph, naphthalen-2-yl, naphthalen-1-yl, 4-CF_3Ph, 5-Br-thiophen-2-yl, cyclopropyl

Scheme 23.

2.4 Transition-metal catalyzed HTIB mediated reactions

The integration of hypervalent iodine reagents with transition-metal catalysis has emerged as a versatile approach for developing efficient and selective synthetic transformations in organic chemistry.[61] Yang and coworkers disclosed that the reaction of unsaturated oximes with Koser's hypervalent iodine reagents at room temperature in the presence of an iron(II) catalyst afforded isoxazoline scaffolds **29** *via* a radical cyclization pathway (Scheme 24).[62] The reaction is proposed to proceed through the selective cleavage of the I–O bond of the hypervalent iodine reagent mediated by the iron(II) catalyst. Other hypervalent iodine reagents, such as PIDA and Togni's reagent, showed no appreciable reactivity under the optimized conditions, highlighting the distinctive reactivity of Koser's reagent. Notably, the resulting isoxazolines **29** bearing a readily transformable *p*-toluenesulfonyloxy group could be further converted into diverse functionalized isoxazolines through nucleophilic substitution with PhONa, PhSNa, KSCN, NaBr, and NaI in acetone at 80 °C.



R = H, 4-CH_3, 4-Et, 4-*i*-Pr, 4-*t*-Bu, 4-OCH_3, 4-Cl, 4-Br, 4-CN, 3-CH_3, 3-OCH_3, 3-F, 3-Cl, 3-Br, 2-OCH_3, 3,4-$(Cl)_2$, 3,4-$(CH_3)_2$, 3,5-$(Cl)_2$, 3,5-$(OCH_3)_2$
R^1 = Ph, 4-CH_3Ph, 4-ClPh, 3-NO_2Ph, 2,4-$(CH_3)_2$Ph, 2,5-$(CH_3)_2$Ph, CH_3

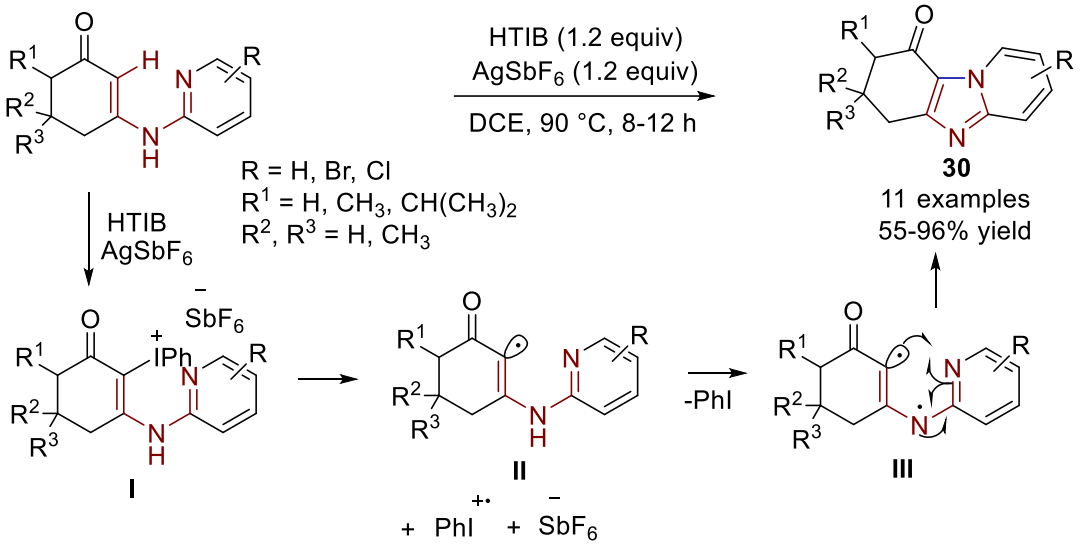
Nu = N_3, OPh, SPh, SCN, Br, I

Scheme 24.

Bhattacherjee and coworkers reported the HTIB/$AgSbF_6$-mediated intramolecular annulation of exocyclic β-enaminones containing a 2-aminopyridine moiety to furnish a range of substituted imidazo[1,2-*a*]pyridines **30** (Scheme 25).[63] The reaction proceeded with high selectivity toward C-N bond formation and afforded the corresponding imidazo[1,2-*a*]pyridines **30** in good to excellent yields. The cooperative action of HTIB and $AgSbF_6$ is crucial for the annulation, with the hexafluoroantimonate counteranion directing the reaction toward the C-N bond-forming pathway. Mechanistically, the authors proposed that the resulting iodonium species **I** generates radical intermediate **II** through a radical-cation pathway, which subsequently undergoes intramolecular annulation *via* intermediate **III** to furnish imidazo[1,2-*a*]pyridines **30**. Overall, this

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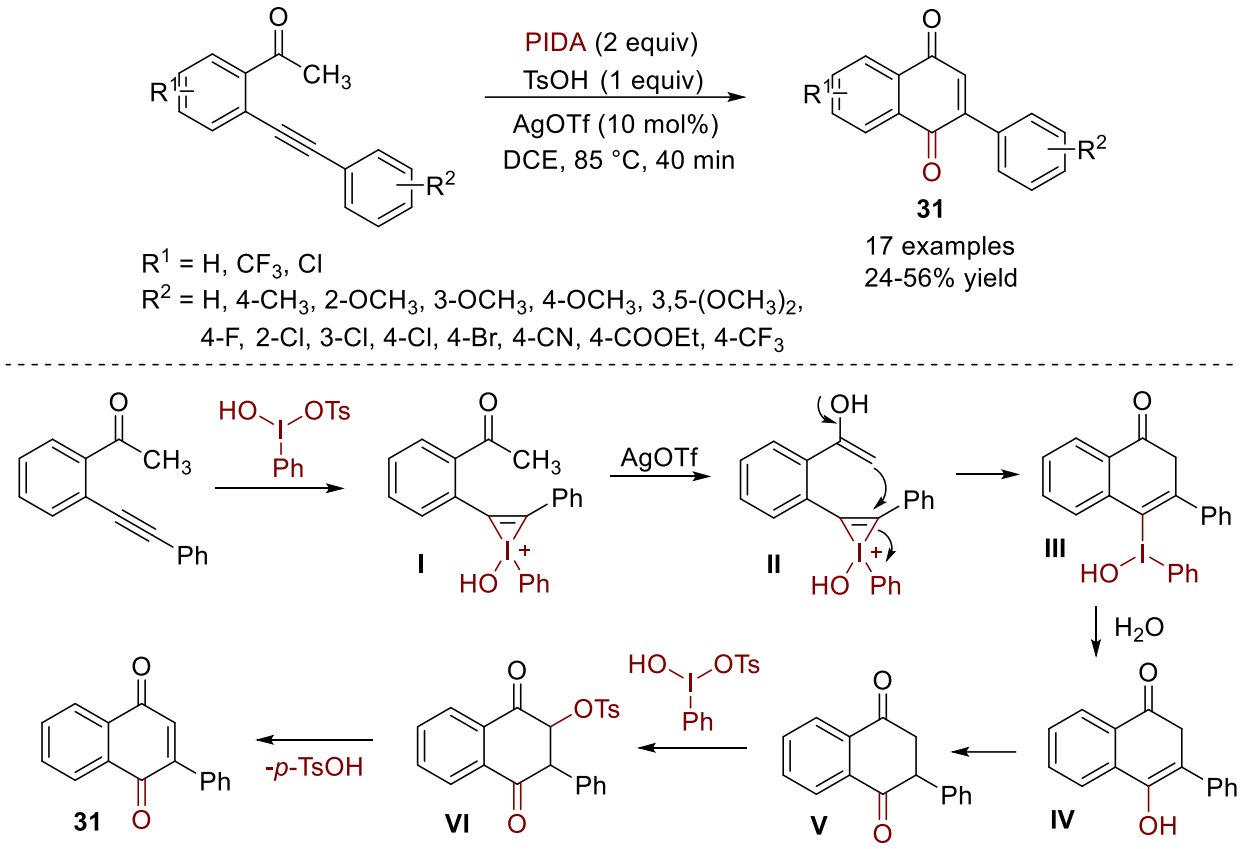
protocol highlights the synthetic utility of the HTIB/$AgSbF_6$ reagent system for C-N and C-C bond-forming annulations and provides an alternative to conventional Pd- and Cu-catalyzed approaches.



Scheme 25.

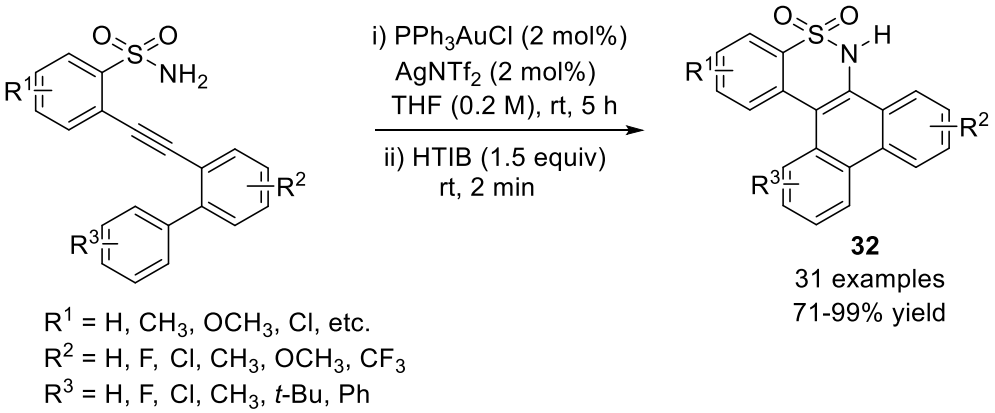
1,4-Naphthoquinones are important motifs in medicinal and synthetic chemistry. Yongpanich and coworkers reported an unexpected oxidative cyclization of (*ortho*-alkynyl)aryl ketones to afford 1,4-naphthoquinone derivatives **31** *via in situ* generation of hydroxyl(arenesulfonyl)- and hydroxyl(alkanesulfonyl)iodobenzene species [PhI(OH)(OSO_2R)] in the presence of AgOTf. Treatment of (*ortho*-alkynyl)aryl ketones with 2.0 equiv of PIDA and 1.0 equiv of TsOH in 1,2-dichloroethane at 85 °C for 40 min afforded the desired product **31** in 24–56% yield (Scheme 26).[64] The authors proposed that AgOTf enhances the electrophilicity of the alkyne, thereby facilitating nucleophilic attack, whereas higher amounts of AgOTf adversely affected the product yield. Mechanistically, activation of the alkyne by the iodine(III) species (HTIB) generates intermediate **I**, which subsequently interacts with AgOTf to form enol intermediate **II**. Intramolecular cyclization then affords intermediate **III**, followed by hydrolysis and tautomerization to intermediate **V**. Subsequent reaction with the HTIB generates intermediate **VI**, which undergoes elimination to furnish product **31**.

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Scheme 26.

Zhang and Song described a facile, efficient one-pot strategy for the construction of polycyclic sultams **32**, valuable building blocks in organic synthesis. The transformation proceeds through gold-catalyzed intramolecular hydroamination of *o*-alkynylbenzenesulfonamides, followed by HTIB-mediated counteranion-assisted intramolecular annulations (Scheme 27).[65] The transformation exhibits broad functional-group tolerance, affording highly functionalized and valuable polycyclic sultam frameworks in moderate to excellent yields.



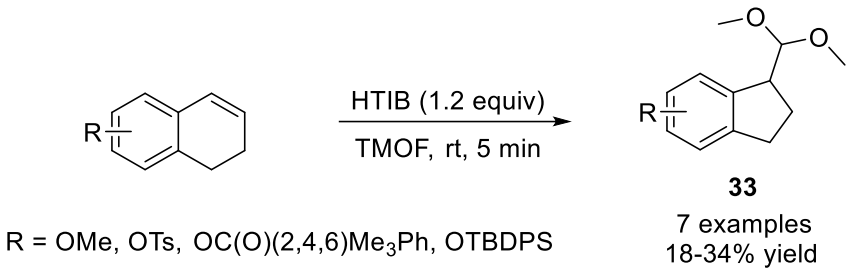
Scheme 27.

2.5. Ring contractions and expansions

Khan and coworkers reported an HTIB-mediated ring-contraction reaction for the synthesis of indane derivatives **33** from a series of protected 1,2-dihydronaphthalenes using trimethyl orthoformate (TMOF) as the reaction medium (Scheme 28).[66] The authors carried out a comparative study of thallium nitrate trihydrate (TTN·3H$_2$O) and HTIB-mediated ring-contraction reactions for the synthesis of indanes. Their findings

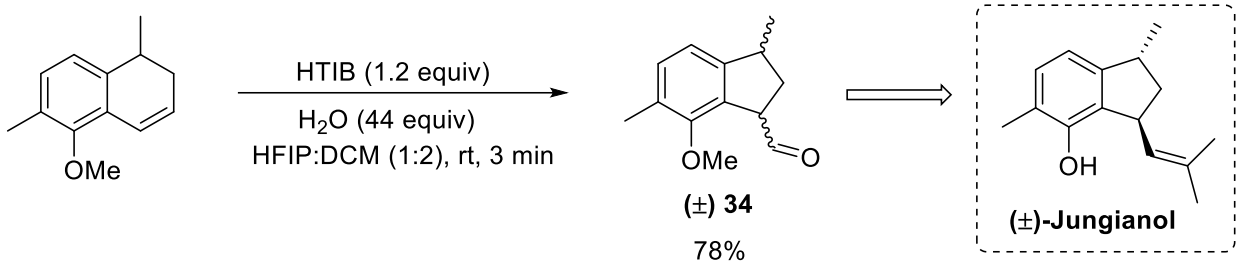
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demonstrated that thallium(III) salt exhibits substantially greater oxidative efficiency than HTIB in this transformation. Substrates bearing various protecting groups were examined to study their tolerance for both oxidizing agents.



Scheme 28.

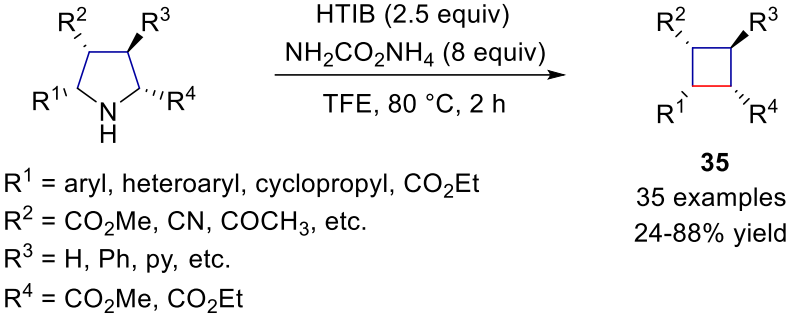
Khan and Rezende explored an HTIB-mediated ring-contraction strategy for constructing a *trans*-1,3-disubstituted indane framework present in the phenolic sesquiterpene (±)-jungianol. In the key transformation, the 1,2-dihydronaphthalene derivative was initially treated with HTIB in different solvents, including MeOH, HFIP, and CH_3CN, however, complex product mixtures were obtained, indicating poor selectivity toward the desired ring-contraction pathway. Optimization using HTIB in HFIP/DCM (1:2) with 44 equiv of H_2O at room temperature afforded the ring-contracted indane **34** in 78% yield (Scheme 29).[67] HFIP provided a highly polar, weakly nucleophilic, and strongly ionizing medium favorable for cationic intermediates, while DCM improved substrate solubility and water enhanced HTIB solubility. Notably, ^{1}H NMR analysis supported the formation of the ring-contracted indane product **34** with a trans-1,3-disubstituted configuration. In contrast, treatment with thallium(III) nitrate (TTN) under the same HFIP/DCM (1:2) solvent conditions afforded the indane product mixture in only 11% yield, highlighting the superior efficiency of HTIB in promoting the ring-contraction pathway leading to the desired trans-1,3-disubstituted indane framework.



Scheme 29.

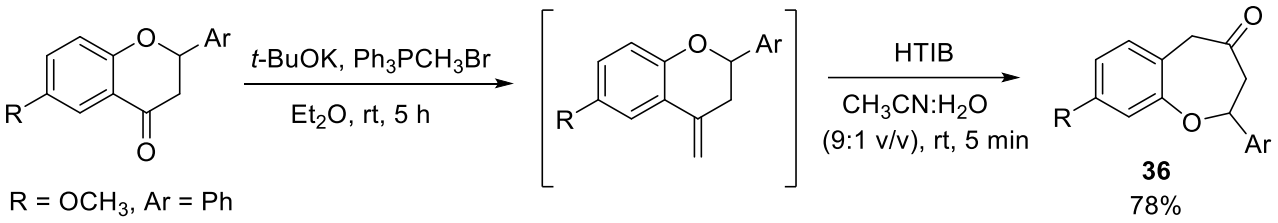
Hui and coworkers developed a novel, highly stereoselective synthesis of multisubstituted cyclobutanes **35** bearing multiple stereocenters from readily accessible pyrrolidines *via in situ* generated iodonitrene species. Using 2.5 equiv of HTIB and 8 equiv of ammonium carbamate as an ammonia surrogate in 2,2,2-trifluoroethanol (TFE), pyrrolidines were transformed into cyclobutanes **35** (Scheme 30).[68] The reaction scope was investigated using pyrrolidines bearing diverse substitution patterns, affording 35 cyclobutane products, including spirocyclobutanes. The stereospecific formation of cyclobutanes was proposed to proceed through nitrogen extrusion *via* a radical pathway, with a 1,4-biradical proposed as a key intermediate**.**

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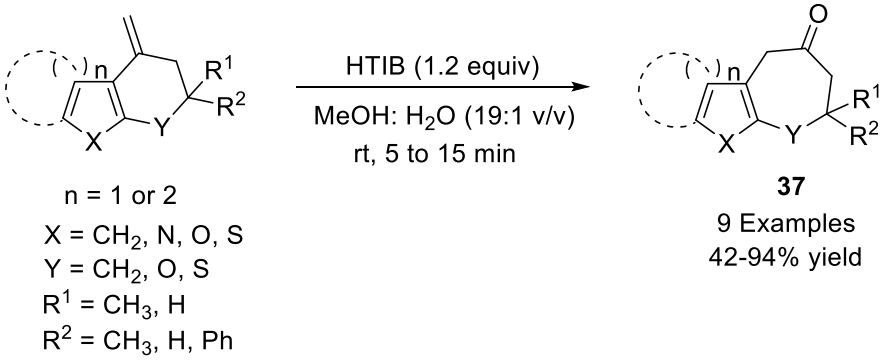
Scheme 30.

Bauhiniastatins are naturally occurring dibenz[*b,f*]oxepins that exhibit significant cytotoxic activity. Given the pharmacological relevance of seven-membered heterocycles, Khan and coworkers reported a metal-free approach to their synthesis through an iodine(III)-mediated ring-expansion strategy using HTIB. The ketone was treated with potassium *tert*-butoxide and methyltriphenylphosphonium bromide (Ph_3PCH_3Br) in diethyl ether to afford the corresponding methylenic chromane intermediate. Subsequent treatment of the chromane with HTIB in aqueous acetonitrile effected ring expansion, furnishing the corresponding seven-membered oxygen-containing heterocycle **36** in good yield (Scheme 31).[69]



Scheme 31.

Lussari and coworkers reported a mild, practical, metal-free strategy for the synthesis of seven-membered fused heterocyclic frameworks incorporating furan, indole, pyrrole, and thiophene motifs **37** *via* HTIB-mediated ring expansion of bicyclic heterocycles bearing exocyclic double bonds (Scheme 32).[70] These structurally diverse and complex scaffolds are of considerable significance as valuable intermediates in the synthesis of biologically active natural products and pharmaceutical agents. To elucidate the underlying reaction mechanism, the authors performed density functional theory (DFT) calculations, which provided mechanistic insights into the HTIB-mediated ring-expansion process in aqueous methanol.



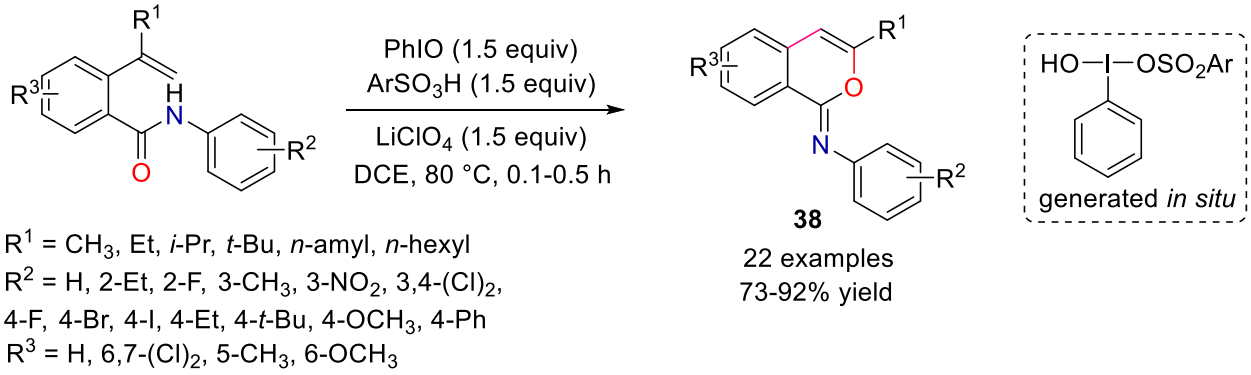
Scheme 32.

2.6. Rearrangement

He and coworkers reported a chemodivergent cycloisomerization approach for the synthesis of iminoisocoumarin derivatives **38** from *o*-alkenylbenzamide derivatives bearing different alkyl substituents at the R_1 position and variously substituted phenyl rings (Scheme 33).[71] The chemoselective transformation

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proceeds through an *O*-cyclization followed by a 1,2-aryl migration/elimination cascade and is enabled by a modified Koser's reagent generated *in situ* from iodosobenzene and 2,4,6-tris-isopropylbenzene sulfonic acid. The addition of lithium perchlorate as an exogenous Lewis acid further promotes the transformation, affording the corresponding iminoisocoumarins **38** in 73-92% yield with exclusive *O*-cyclization selectivity.



38

R^1 = CH_3, Et, *i*-Pr, *t*-Bu, *n*-amyl, *n*-hexyl
R^2 = H, 2-Et, 2-F, 3-CH_3, 3-NO_2, 3,4-$(Cl)_2$, 4-F, 4-Br, 4-I, 4-Et, 4-*t*-Bu, 4-OCH_3, 4-Ph
R^3 = H, 6,7-$(Cl)_2$, 5-CH_3, 6-OCH_3

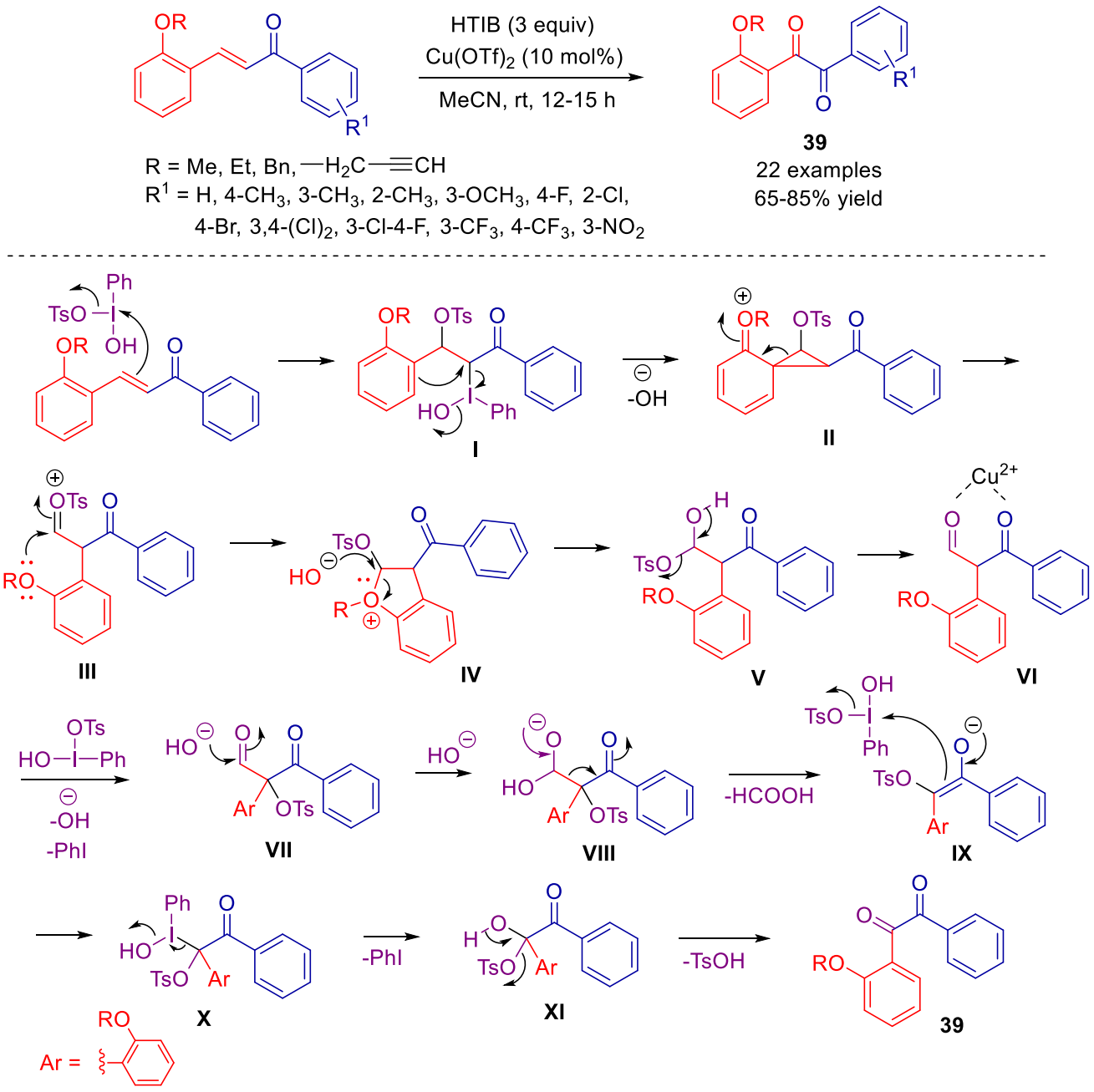
22 examples
73-92% yield

Scheme 33.

Narnawre and coworkers reported a mild and efficient oxidative transformation of 2-alkoxychalcones into unsymmetrical 1,2-diaryl diketones **39** using HTIB in the presence of catalytic copper(II) triflate [$Cu(OTf)_2$] in acetonitrile at room temperature (Scheme 34).[72] The transformation involves a tandem oxidative rearrangement and C-C bond cleavage sequence, affording the corresponding diketones in good to excellent yields. During optimization, various oxidants (PIDA, HTIB, and I_2) and solvents (acetonitrile, methanol, and DMSO) were investigated in the presence and absence of a catalyst. HTIB exhibited superior performance over PIDA, providing the desired diketones in higher yields and shorter reaction times. The protocol features a broad substrate scope and good functional-group tolerance, with the *ortho*-alkoxy substituent playing a crucial role in the transformation. Furthermore, the synthetic utility of the resulting 1,2-diketones **39** was demonstrated by their conversion into densely substituted imidazole and quinoxaline derivatives. The authors proposed a plausible mechanism involving hypervalent iodine-mediated substrate activation followed by copper-assisted oxidation.

The proposed mechanism for the oxidative transformation of 2-alkoxychalcones to 1,2-diketones **39** begins with the electrophilic addition of HTIB across the electron-rich C=C bond of the 2-alkoxychalcone, generating a trivalent iodine intermediate **I** (Scheme 34). Subsequent reductive elimination of iodobenzene from the hypervalent iodine intermediate facilitates a 1,2-anionotropic migration of the electron-rich ortho-alkoxy aryl group, affording intermediate **II**, which undergoes further rearrangement to generate intermediate **III**. Intramolecular nucleophilic attack by *ortho*-alkoxy oxygen on the adjacent carbonyl group then leads to the formation of a five-membered cyclic intermediate **IV**. Subsequent interception by a hydroxyl nucleophile affords intermediate **V**, which undergoes elimination of the tosylate group to furnish a 1,3-dicarbonyl intermediate **VI**. This intermediate is proposed to be stabilized through chelation with Cu^{2+} ions. Subsequently, α-tosyloxylation of the 1,3-dicarbonyl system by a second equivalent of HTIB generates intermediate **VII**, which undergoes nucleophilic attack by a hydroxide ion to afford intermediate **VIII**. Further degradation of **VIII**, accompanied by the loss of formic acid, produces an enolate-type intermediate **IX**. Reaction of **IX** with a third equivalent of HTIB affords intermediate **X**, which undergoes reductive elimination of iodobenzene to generate intermediate **XI**. Finally, the elimination of the tosylate group furnishes the desired unsymmetrical 1,2-diketone **39**.

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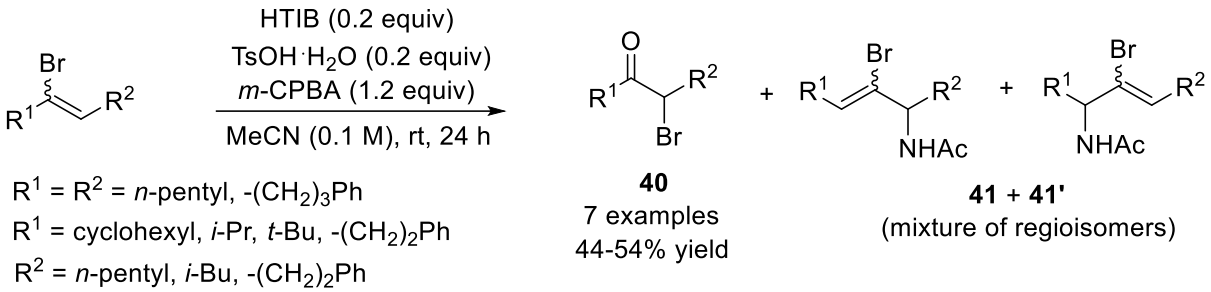


Scheme 34.

Jadhav and Legault reported an operationally simple hypervalent iodine-mediated oxidative hydrolysis of dialkyl bromoalkenes to afford dialkyl α-bromoketones **40**, valuable building blocks for heterocycle synthesis (Scheme 35).[73] Initial investigations using (*E*/*Z*)-1,8-diphenyl-4-bromooct-4-ene and stoichiometric amounts of iodine(III) reagents, including HTIB, mesityl-derived Koser's reagent, PIDA, and *p*-OMe-PIDA, in the presence of various acid additives (TsOH·H_2O, MsOH, or $HNTf_2$) in acetonitrile afforded the desired α-bromoketone **40** along with a regioisomeric mixture of Ritter-type side products **41** and **41'**. Subsequent optimization studies led to the development of a catalytic protocol employing HTIB (0.2 equiv) and TsOH·H_2O (0.2 equiv), with *m*-CPBA (1.2 equiv) serving as the terminal oxidant. Under the optimized conditions, the desired α-bromoketone was obtained in 59% NMR yield. A control experiment conducted in the absence of the hypervalent iodine reagent resulted in a substantial decrease in product yield, highlighting the important role of the iodine(III) species in promoting the oxidative hydrolysis. The developed protocol accommodates both symmetrical and unsymmetrical dialkyl bromoalkenes, furnishing the corresponding α-bromoketones **40**

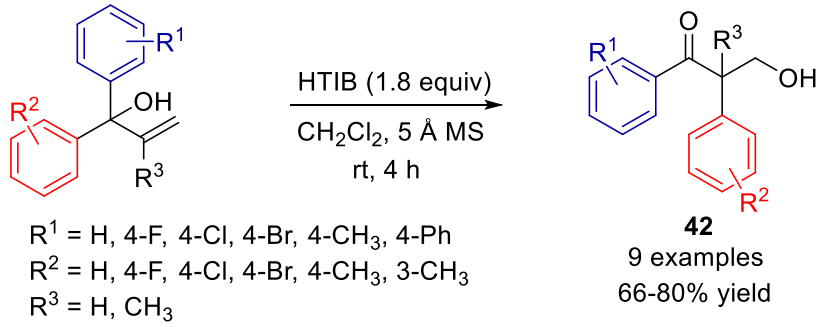
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in moderate yields. Notably, bromoalkenes bearing sterically demanding cyclohexyl and isopropyl substituents were also successfully transformed into the corresponding α-bromoketones **40**, demonstrating the applicability of this methodology to sterically hindered substrates.



Scheme 35.

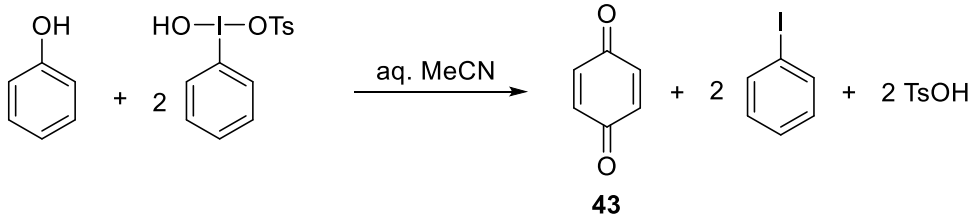
Hu and coworkers reported an HTIB-mediated oxidative hydroxylation of α,α-diaryl allylic alcohols, providing direct access to β-hydroxy ketones **42** *via* a 1,2-aryl migration pathway (Scheme 36).[74] Screening of various hypervalent iodine reagents and solvents identified HTIB (1.8 equiv) in dichloromethane as the optimal reaction system. The addition of 5 Å molecular sieves (15 mg) further improved the reaction outcome. In this transformation, HTIB serves as both the oxidant and the reagent responsible for introducing the hydroxyl functionality. Under the optimized conditions, a range of α,α-diaryl allylic alcohols underwent oxidative rearrangement to afford the corresponding β-hydroxy ketones **42** in yields of up to 80%.



Scheme 36.

2.7. Phenolic oxidation

Bennett and coworkers examined the oxidative potential of HTIB toward simple phenolic substrates using electrochemical and spectroscopic techniques (Scheme 37).[75] Under aqueous conditions, HTIB mediated the oxidation of phenol and the three benzenediol isomers-hydroquinone, catechol, and resorcinol. Hydroquinone and catechol underwent oxidation to form benzoquinone and *o*-quinone, respectively, with complete conversion achieved using 2 equiv of HTIB. In contrast, phenol and resorcinol required a higher oxidant loading of 6 equiv for complete chemical oxidation and exhibited more complex redox behavior. Electrochemical analysis indicated preferential formation of benzoquinone **43** from phenol, with possible concomitant formation of *o*-quinone, whereas the oxidation product resulting from resorcinol did not undergo electrochemical reduction under the conditions investigated.

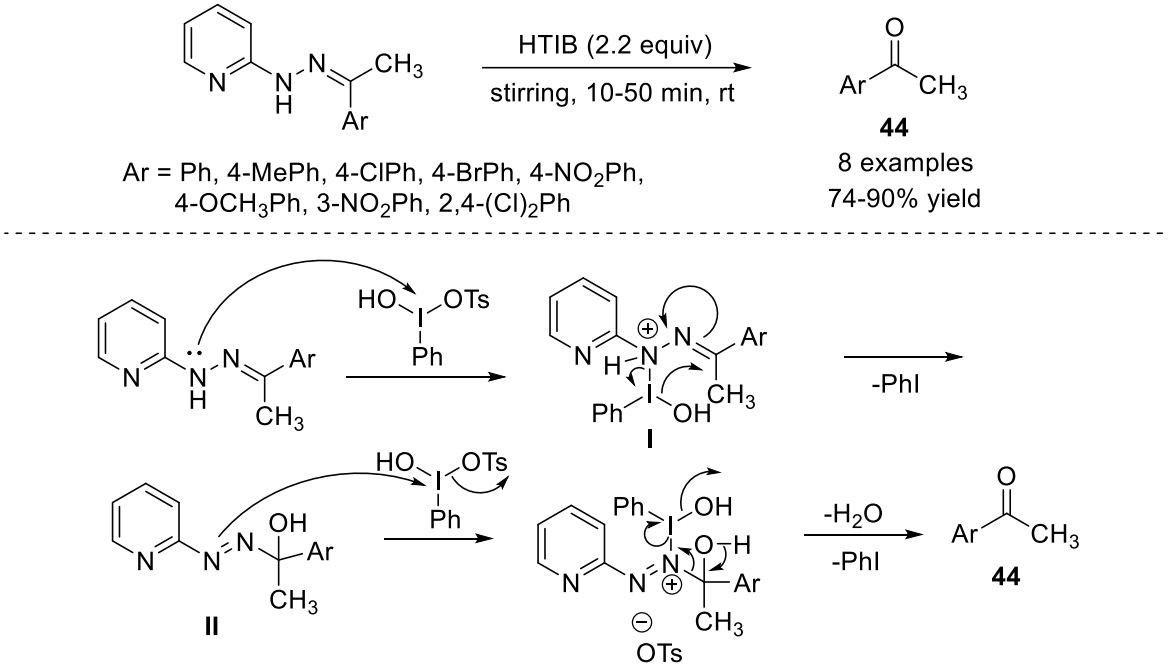


Scheme 37.

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2.8 Regeneration of carbonyl moiety

Protecting groups play an important role in site-selective transformations. Hydrazones are useful protecting groups for carbonyl compounds because they can be readily formed from carbonyl compounds and subsequently hydrolyzed under suitable conditions to regenerate the corresponding carbonyl functionality. HTIB has been reported to facilitate the regeneration of carbonyl compounds through oxidative cleavage of hydrazones derived from nitrogen-containing heterocycles. Sihag and coworkers reported an efficient HTIB-mediated oxidative cleavage of pyridyl hydrazones to regenerate the corresponding aryl ketones **44**. The reaction is performed by stirring the hydrazone with 2.2 equivalents of HTIB in dichloromethane at room temperature (Scheme 38).[76] The proposed mechanism involves interaction of the hydrazone nitrogen with the electrophilic iodine(III) center of HTIB, generating intermediate **I**. Subsequent rearrangement affords intermediate **II**, which undergoes further oxidative transformation with a second equivalent of HTIB to furnish the corresponding carbonyl compound.

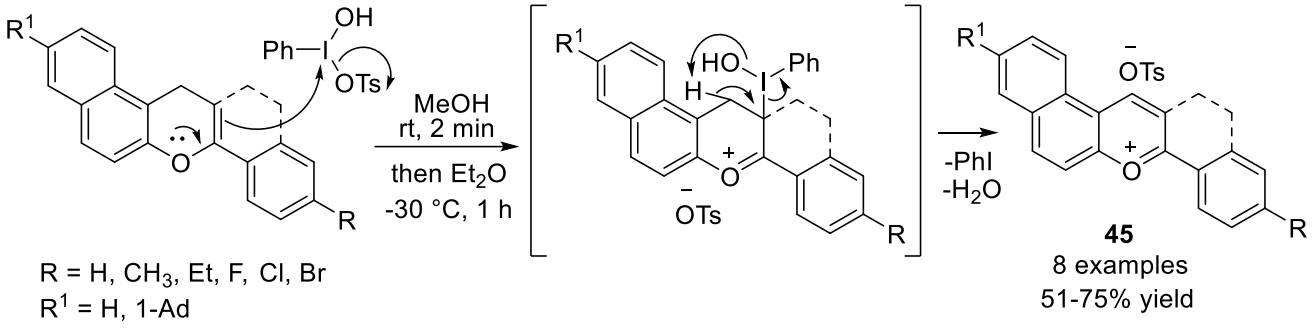


Scheme 38.

2.9 Miscellaneous

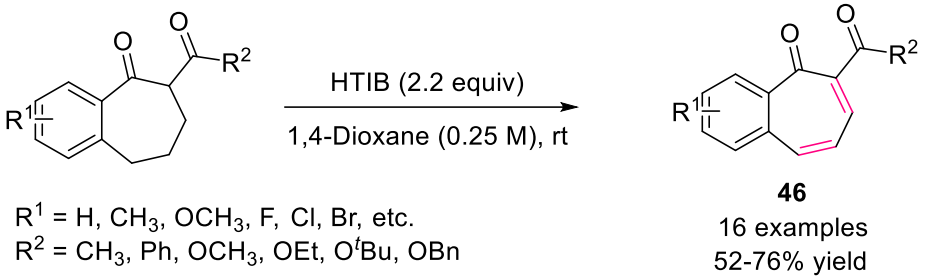
Osyanin and coworkers reported the synthesis of a series of benzoflavylium tosylates **45** through the oxidation of 3-aryl-1*H*-benzo[*f*]chromenes with Koser's reagent in methanol (Scheme 39).[77] Mechanistically, the reaction involves electrophilic addition of iodine(III) at the electron-enriched double bond of the vinyl ether part of benzochromene with concurrent elimination of the tosylate anion, followed by intramolecular syn elimination. Notably, the authors described this transformation as the first example of the synthesis of arene-fused pyrylium salts through the hypervalent iodine-mediated oxidation of 3-aryl-1*H*-benzo[*f*]chromenes.

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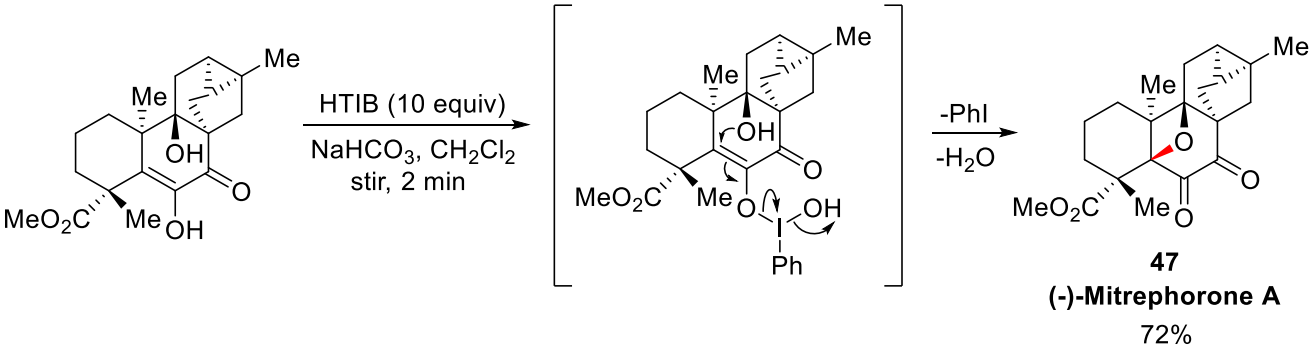
Scheme 39.

Liu and coworkers reported a mild and efficient HTIB-mediated oxidative double dehydrogenation of a range of carbocyclic β-dicarbonyl compounds to afford the corresponding dehydrogenated products **46** (Scheme 40).[78] The reaction exhibited a broad substrate scope, with substrates bearing electron-donating substituents, such as methyl, methoxy, and dimethyl groups, as well as electron-withdrawing substituents, including fluoro, chloro, and bromo groups, on the phenyl ring undergoing smooth dehydrogenation.



Scheme 40.

The enantioselective total synthesis of (−)-mitrephorone A (**47**), a trachylobane diterpenoid exhibiting cytotoxic and antimicrobial activities, was reported by Carreira and coworkers in 2020.[79] A key step in the synthesis involves the late-stage construction of the oxetane ring through Koser's reagent-mediated oxidative cyclization of a suitably functionalized hydroxy-diosphenol precursor. This transformation furnishes the characteristic oxetane moiety and completes the total synthesis of (−)-mitrephorone A (**47**) (Scheme 41).

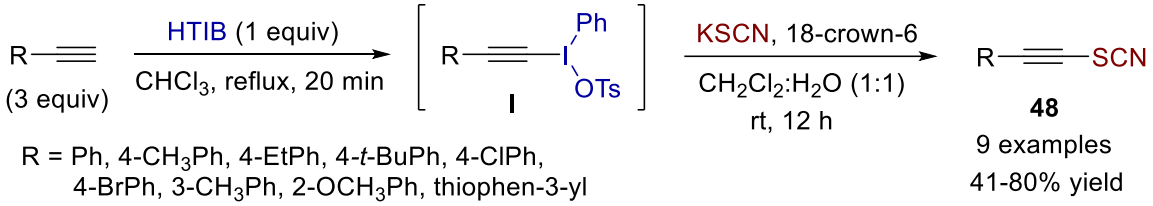


Scheme 41.

Song and co-workers reported a one-pot synthesis of alkynylthiocyanates **48** from terminal alkynes, HTIB, and potassium thiocyanate using 18-crown-6 as a phase-transfer reagent under transition-metal-free conditions (Scheme 42).[80] The reaction proceeds through a hypervalent alkynyl(phenyl)iodonium intermediate **I**, which subsequently undergoes nucleophilic substitution by the thiocyanate anion. The addition of 18-crown-6 facilitates the reaction by complexing K^+ ions, thereby enhancing the nucleophilic reactivity of SCN^-. The substrate scope encompassed electron-rich and electron-deficient aryl-substituted terminal alkynes, as well as the heteroaryl-substituted alkyne 3-ethynylthiophene. In general, *para*-substituted phenylethynes gave the corresponding alkynylthiocyanates in good yields, which varied depending on the electronic nature of the

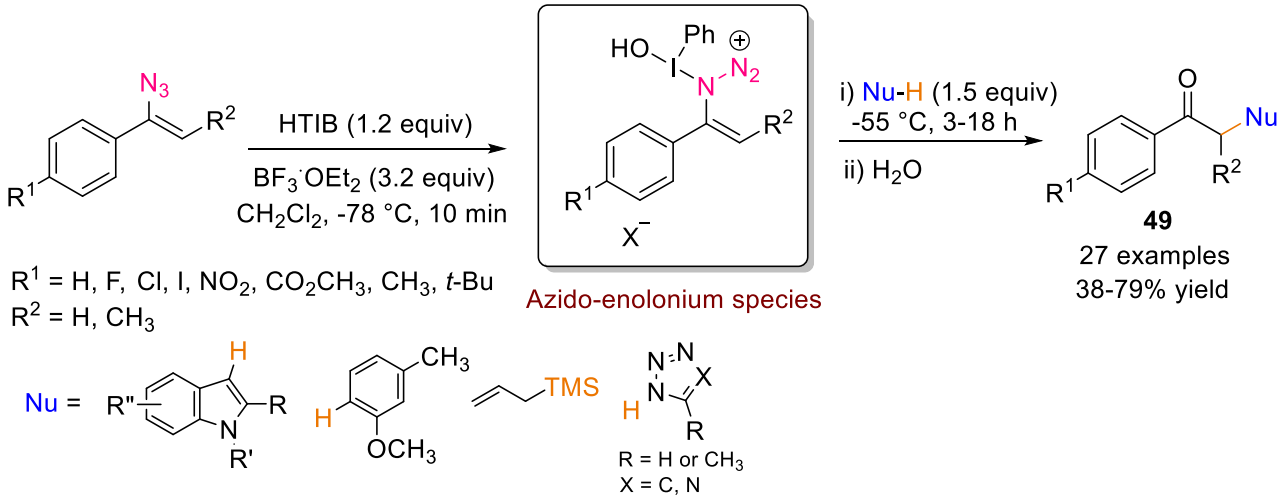
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substituents. Specifically, electron-donating substituents, such as methyl, ethyl, and *tert*-butyl groups, afforded higher yields than electron-withdrawing substituents, such as chloro and bromo groups. However, the *ortho*-methoxy-substituted phenylethyne afforded the product in a comparatively lower yield, which the authors attributed to steric hindrance. In contrast, the reaction was unsuccessful with the sole alkyl-substituted terminal alkyne examined (R = *t*-Bu), possibly owing to the combined effects of unfavorable electronic and steric factors. The synthetic utility of the resulting alkynylthiocyanates was further demonstrated through their conversion into valuable compounds, including 5-thiocyanato-1,2,3-triazoles *via* ruthenium-catalyzed azide–alkyne cycloaddition and (Z)-α-thiocyanato-vinyl trifluoromethanesulfonate *via* a stereoselective transformation.



Scheme 42.

More and coworkers reported the reaction of previously unknown azido-enolonium species, generated from the reaction between vinyl azides and HTIB, with a range of aromatic compounds, allyltrimethylsilane, and azoles. In the presence of boron trifluoride etherate, HTIB facilitates the generation of the corresponding azido-enolonium intermediates, which undergo arylation, allylation, or *N*-heteroarylation to afford the corresponding α-functionalized ketones **49** following hydrolysis during aqueous workup (Scheme 43).[81] The transformation displays a broad substrate scope with respect to both the vinyl azide and the coupling partner and proceeds without a transition-metal catalyst, thereby providing a metal-free approach to the construction of C-C and C-N bonds. The proposed intermediacy of the azido-enolonium species was further supported by IR spectroscopic analysis of the reaction mixture.

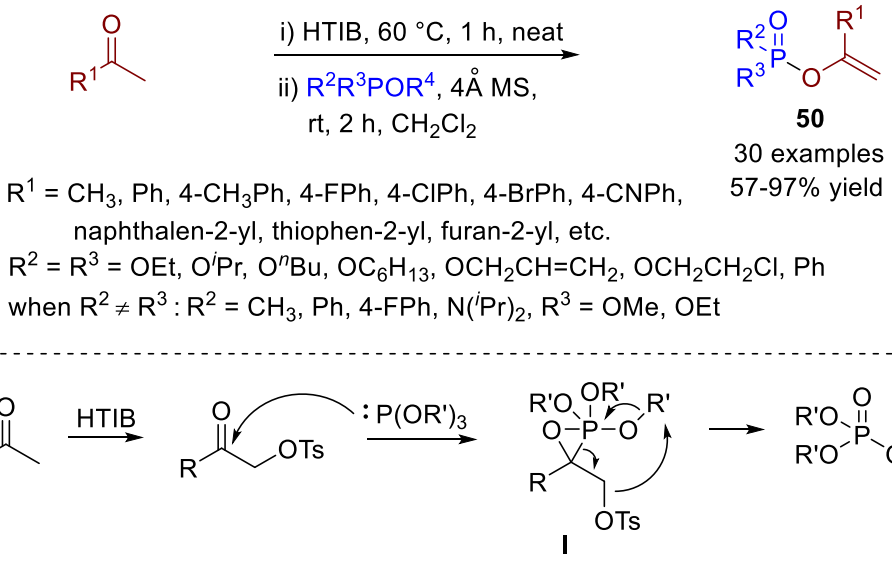


Scheme 43.

Enol phosphates are valuable phosphorus-containing compounds that occur in biologically important intermediates, such as phosphoenolpyruvate, which plays a vital role in cellular energy metabolism and ATP generation. Owing to their versatile reactivity, enol phosphates serve as useful synthetic intermediates in various organic transformations, including cross-coupling, olefination, epoxidation, carbonylation, and cycloaddition reactions. Conventionally, they are synthesized through the Perkow reaction of phosphites with α-haloketones;[82] however, the applicability of this approach is constrained by the toxicity and lachrymatory nature of α-haloketones, as well as challenges associated with substrate availability and regio- and

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stereocontrol. To overcome these limitations, Guo and coworkers reported a modified one-pot Perkow approach for synthesizing diverse enol phosphates, along with enol phosphonates, enol phosphinates, and enol phosphoramidates **50**, directly from readily available ketones using HTIB (Scheme 44).[83] Following extensive optimization, the authors established the optimal conditions involving the treatment of a ketone (1.1 equiv) with HTIB (1 equiv) at 60 °C for 1 h, followed by the addition of phosphite (1 equiv) and 4 Å molecular sieves (1 equiv) in dichloromethane at room temperature for 2 h. Notably, solvent-free α-tosyloxylation of ketones with HTIB offers a significant improvement over conventional solvent-mediated protocols, reducing reaction times from approximately 12 h to 3 h at 60 °C, and to less than 1 h for aromatic ketones. Mechanistically, the authors proposed that the nucleophilic P(III) atom of the phosphite attacks the carbonyl carbon of the *in situ* generated α-tosyloxy ketone, leading to a three-membered heterocyclic intermediate **I**. Subsequent ring cleavage affords a phosphonium salt, which undergoes *O*-dealkylation to furnish the corresponding enol phosphate.

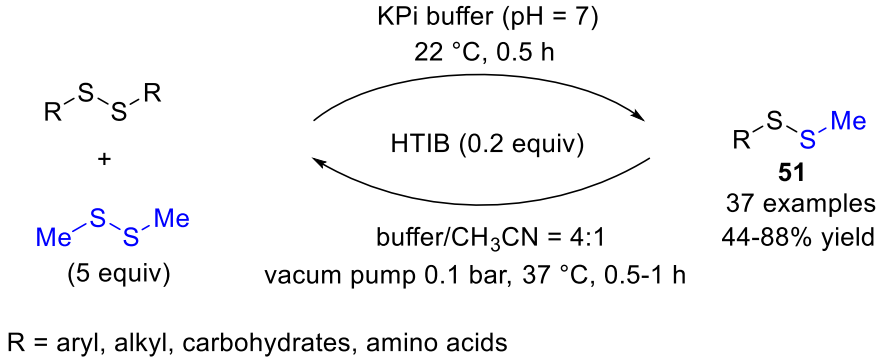


Scheme 44.

Li and coworkers reported an innovative strategy for bidirectional disulfide bond metathesis using HTIB (20 mol%) as a radical initiator under mild and biocompatible conditions (Scheme 45).[84] The reaction proceeded efficiently at 22 °C in potassium phosphate buffer, highlighting the compatibility of this hypervalent iodine reagent with aqueous reaction media. This methodology enabled reversible disulfide bond exchange in both forward and reverse directions, thereby extending the synthetic applications of HTIB to sulfur chemistry and biomolecular modification. A broad range of symmetrical disulfides, encompassing aromatic, aliphatic, and heterocyclic substrates, underwent metathesis with dimethyl disulfide to afford the corresponding unsymmetrical disulfides **51**. Notably, the methodology was successfully applied to the late-stage modification of protected amino acids, carbohydrates, drug molecules, and peptides, including cyclic peptides such as oxytocin, lanreotide, octreotide, and somatostatin. Furthermore, selective disulfide modification of human insulin and bovine serum albumin demonstrated the potential of this approach for protein functionalization. The formation of unsymmetrical disulfides **51** was achieved by employing an excess of one disulfide partner to favour the forward exchange reaction. Conversely, the reverse metathesis was promoted by removing the volatile dimethyl disulphide, thereby shifting the reaction equilibrium towards the corresponding symmetrical disulphides (Scheme 45). Mechanistic investigations involving radical-trapping experiments and EPR spectroscopy supported the involvement of radical intermediates in this transformation. In particular, the detection of a TEMPO-trapped species by LC-MS analysis and a characteristic quadruple peak in EPR signal

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assigned to a hydroxy-containing radical species using DMPO as the spin-trapping agent supported a radical-mediated reaction pathway.



Scheme 45.

Conclusions

In this review, we have highlighted recent applications of HTIB in organic synthesis reported during 2019-2026, encompassing its diverse roles in oxidative functionalization, α-oxyacylation, oxidative cyclization, rearrangement, ring expansion or contraction, regeneration of the carbonyl moiety, oxidative double dehydrogenation, and the construction of complex heterocyclic and carbocyclic frameworks. The growing emphasis on green and sustainable chemistry has further increased interest in HTIB as a readily available, versatile, and environmentally benign hypervalent iodine reagent. Its mild reaction conditions, operational simplicity, ease of handling, and broad functional-group compatibility make HTIB an attractive alternative to conventional heavy-metal-based oxidants and reagents. Recent developments indicate that HTIB can mediate a wide range of synthetically valuable transformations with good efficiency and selectivity while minimizing the reliance on toxic and environmentally persistent metal-based reagents. Nevertheless, further efforts toward catalytic applications, improved atom economy, solvent-free or aqueous protocols, and scalable processes will be important for maximizing the sustainability of HTIB-mediated synthesis. Overall, the advances discussed in this review establish HTIB as a versatile and promising reagent for synthetic organic chemistry.

Acknowledgements

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