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C−H Functionalization of Benzothiazoles via Thiazol-2-yl-phosphonium Intermediates

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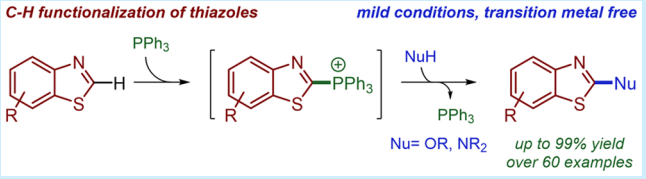
ABSTRACT: Benzothiazoles undergo regioselective C2−H functionalization with triphenylphosphine to form thiazol-2-yl-triphenylphosphonium salts, and these phosphonium salts react with a wide range of O- and N-centered nucleophiles to give the corresponding ethers, amines, and C−N biaryls. The reactions proceed under mild conditions and allow for the recovery of triphenylphosphine at the end of the sequence. In the presence of hydroxide, phosphonium salts undergo disproportionation, resulting in the reduction of the benzothiazole, which is useful for specific C2 deuteration of benzothiazoles.



Phosphonium salts are commonly used in organic synthesis as reagents in Witting-type olefinations,[1] catalysts in phase-transfer catalysis and related transformations,[2] solvents in processes that rely on the use of ionic liquids,[3] and catalytic intermediates in Lewis-base-catalyzed reactions with phosphine catalysts.[4] The breadth of their reactivity and the electrophilic character of the phosphorus atom, in particular, have driven the recent leaps in the development of synthetic methods that feature pentavalent phosphorus intermediates such as biphilic organophosphorus catalysis,[5] contractive C−C coupling via P(V) intermediates,[6] and the redox-neutral organocatalytic Mitsunobu reactions.[7] Our interest in phosphonium ions stems from reactions that use phosphines as Lewis base catalysts with typical Michael acceptors, which, in the presence of water and other protic additives, produce vinylphosphonium intermediates (Scheme 1a).[8] We hypothesized that the distinctly different outcomes these reactions have in the presence of alcohols (oxidation of C3 of the ynone)[9] and water (reduction of C3)[10] are the consequence of the differences in the reactivity of the pentavalent phosphorus intermediates generated in these processes. If this is also reflected in the reactivity of arylphosphonium salts,[11] the easily accessible heteroarylphosphonium salts would become valuable intermediates in the regioselective functionalization of heterocycles.

Thiazoles and benzothiazoles are the most common five-membered aromatic N-heterocycles among the FDA-approved pharmaceuticals,[12] and they are present in numerous biologically active molecules (Scheme 1b),[13] are important components of functional materials,[14] and are common intermediates in organic synthesis.[15] Although they almost always feature a heteroatom substituent at C2 in approved pharmaceuticals, the direct C2−H functionalization of benzothiazoles remains largely limited to metal-catalyzed processes that proceed at elevated temperatures, often as high as 130 °C (Scheme 1c).[16] A metal-free pathway for the C2−H functionalization of benzothiazoles under mild conditions would be a valuable addition to medicinal chemistry toolbox and an enabling factor for rapid access to libraries of small benzothiazole-containing molecules. In his seminal work on the synthesis of benzothiazol-2-yl-triphenylphosphonium triflate, Anders showed that the treatment of benzothiazole with triphenylphosphine in the presence of triflic anhydride and a base provides direct regioselective access to this salt.[11] Here we demonstrate the generality of this process and show that benzothiazol-2-yl-triphenylphosphonium salts react with a wide range of O- and N-nucleophiles under mild conditions and produce C2-substituted benzothiazoles (Scheme 1d). The two-step sequence constitutes an efficient method for the C2−H functionalization of benzothiazoles because the phosphine can be recovered at the end of the sequence.

Encouraged by the early observations of Anders and the later work of McNally on similar functionalization of pyridines,[6,11] our optimization studies focused on the reactions of benzo[*d*]thiazol-2-yltriphenylphosphonium triflate salt **2a** with benzyl alcohol. Activation of the nucleophile with a suitable base was required. Strong bases like sodium hydride and alkali hexamethyldisilazide (HMDS) amides performed well, providing yields of up to 82%. (For details of the optimization studies, see the SI.) The outcome depended on the quality of the base used, and some reactions benefited from increasing the amount of the nucleophile to 1.5 equiv, although a further

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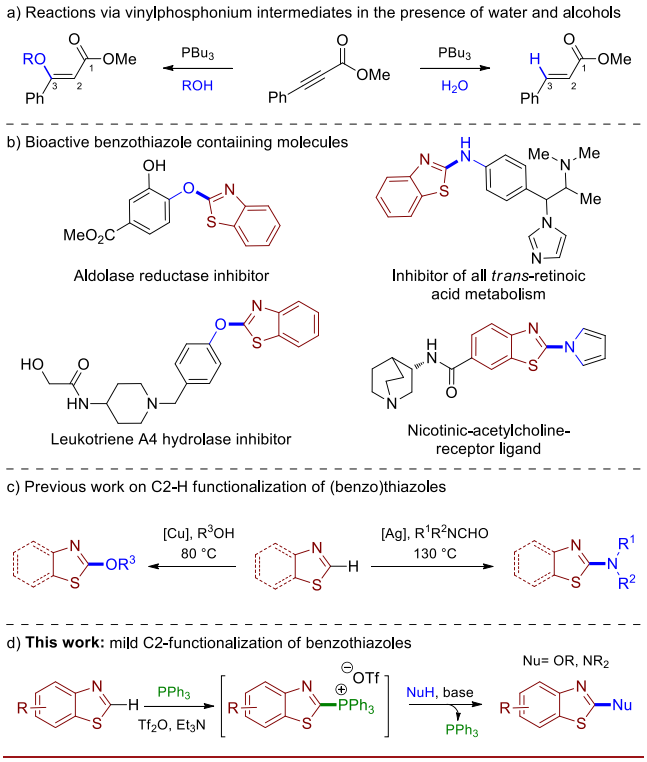
Scheme 1. Bioactive C2-Substituted Benzothiazoles, Previous Work on C2−H Functionalization of Benzothiazoles, and Our Approach Using Phosphonium Ions

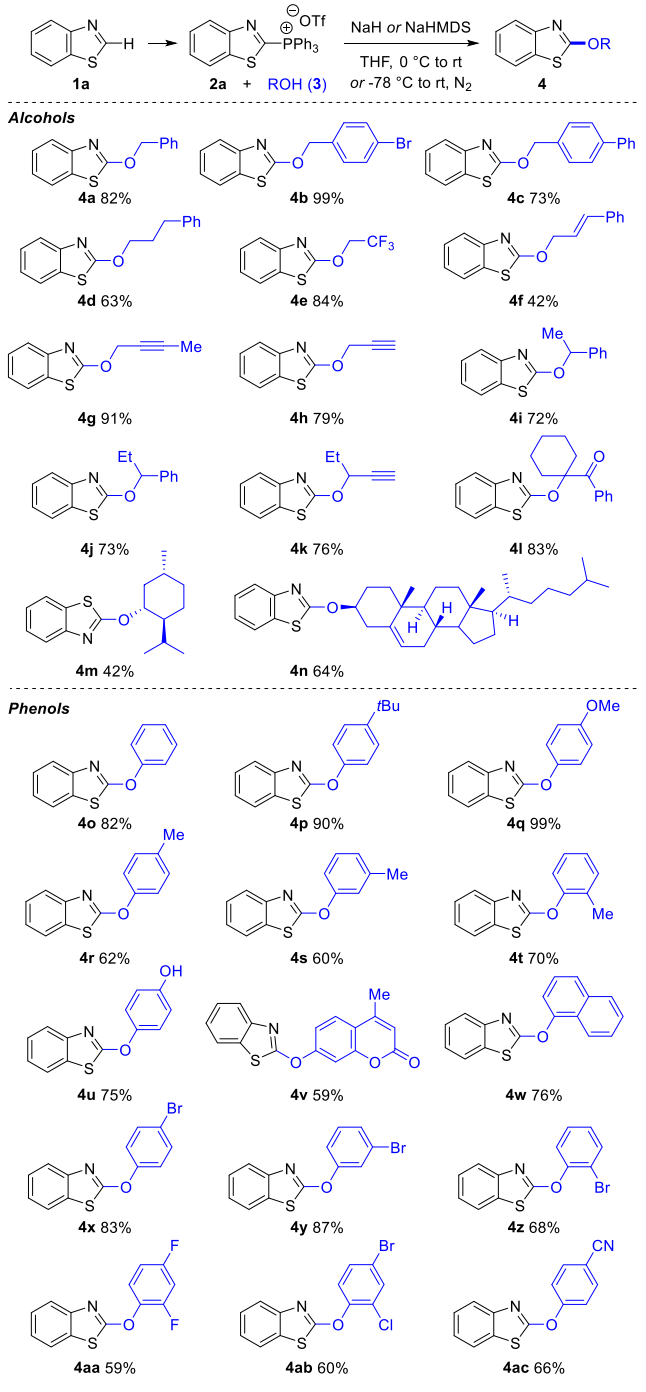


increase had the inverse effect. The reactions proceeded with high rates at room temperature in THF, with deprotonation of alcohol usually performed at a low temperature prior to the addition of the phosphonium triflate.

A range of alcohol nucleophiles were reactive with the benzothiazol-2-yl-phosphonium salt **2a** (Scheme 2). Primary alcohols, including simple alkyl, benzylic, and propargylic alcohols, all gave the desired ethers in a yield range of 42−99% (**4a**−**n**). Even electron-poor alcohol proved efficient in a yield of 84% (**4e**). Secondary (**4i**−**k**) and tertiary aliphatic alcohol (**4l**) gave the desired ethers in 72−83% yields and demonstrated that the reactions tolerate steric hindrance close to the reactive centers. The reactions performed well even in the more complex setting, when menthol and cholesterol were used as the O-nucleophiles (**4m** and **4n**). Electron-rich phenols performed well in a yield range of 60−99% (**4o**−**t**). When hydroquinone was used, the product of monosubstitution was produced in 75% yield (**4u**). Phenols with an extended conjugated system, a coumarin derivative, and naphthalen-1-ol were also suitable reaction partners (**4v** and **4w**). Halogen-substituted phenols were well tolerated in a yield range of 59−87% (**4x**−**ab**). Sterically more demanding and electron-poor substrates gave slightly lower yields between 59 and 66% (**4z**−**ac**). The main side product was triphenylphosphine, which could be recovered during purification.

Encouraged by the good reactivity observed with O-nucleophiles, the focus was shifted to N-nucleophiles (Scheme 3). NaHMDS performs significantly better than NaH with N-nucleophiles. The initial attempts with primary amines and anilines proved futile. Instead of the desired products, the corresponding iminophosphoranes were isolated. Along with

Scheme 2. Scope of the Reaction for O-Nucleophiles



this, secondary amines performed well, with **4ad**−**af** obtained in 61−81% yield. When acetanilide was used, the product of amidation could not be isolated, but the product of amide hydrolysis **4ag** was isolated in yields of 30%. Switching to *N*-methylbenzamide improved the overall yield to 81%, but a 1:2 mixture of the amide **4ah** and the hydrolysis product **4ai** was obtained. A range of N-heterocycles was shown to be reactive under the same conditions, affording good yields observed for pyrroles and indoles regardless of their electronic properties (**4aj**−**ap**, Scheme 3). Imidazoles and benzimidazoles were equally reactive (**4aq** and **4as**), but the yields were lowered by the increasing steric demand of the nucleophile (**4at** and **4au**).

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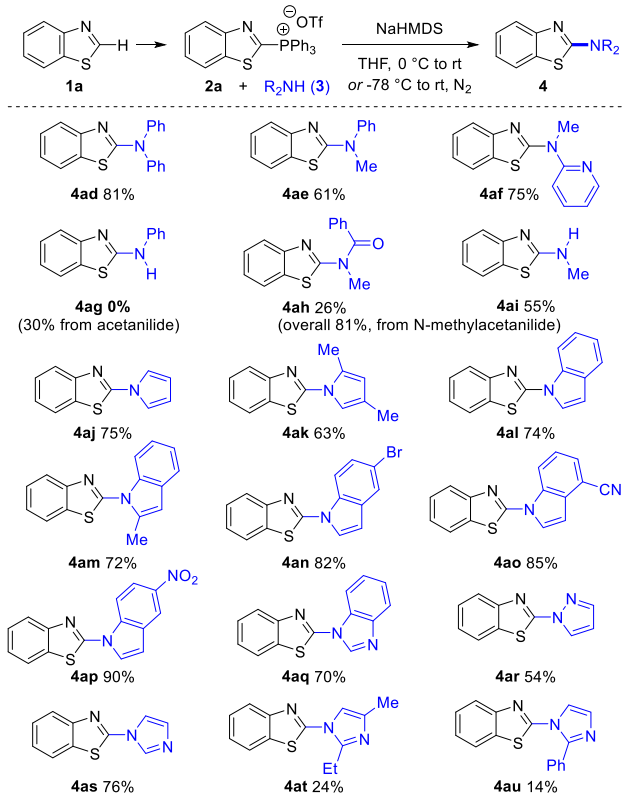
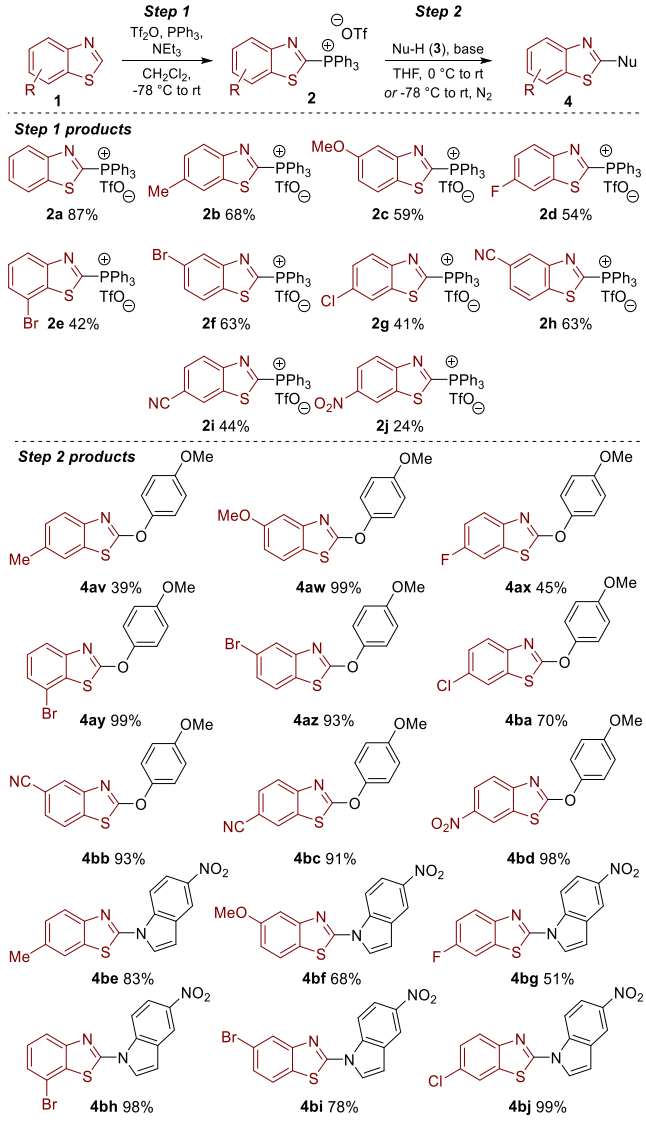
Scheme 3. Scope of the Reaction for N-Nucleophiles



Scheme 4. Reaction Scope for Substituted Benzothiazoles



Using pyrazole as the nucleophile resulted in the formation of biaryl **4ar** in a yield of 54%.

A set of benzothiazol-2-yl-phosphonium triflates carrying both electron-donating and electron-withdrawing substituents in positions five, six, and seven, **2a**–**j** (Scheme 4, Step 1), was prepared in a yield range of 24–87% following the method described by Anders. (The mechanistic proposal for the formation of the phosphonium salts is shown in Scheme 5a.) 4-Methoxyphenol and 5-nitroindole were used to evaluate the reactions with substituted salts. Both electron-rich and electron-poor phosphonium salts performed well, giving the products of etherification (**4av**–**bd**) and amination (**4be**–**bj**) in good yields (Scheme 4, Step 2). No obvious trends for the electronic effect of the substituents on benzothiazole could be observed, suggesting the generality of this method. The studies of scope also established the tolerance for ether, nitro, ester, nitrile, ketone, alkene, alkyne, aryl halides, and other N-heterocyclic substituents.

Aniline and other primary amines failed to produce any of the desired amination products when used in reactions with thiazol-2-yl-phosphonium salts. Instead, the reduced benzothiazole was isolated alongside the iminophosphorane **5** derived from the amine nucleophile and triphenylphosphine (Scheme 5b). It is reasonable to propose that the N–P bond is formed through direct nucleophilic attack of the anilide anion on the electrophilic phosphonium ion. This would produce the aminophosphonium intermediate ***iv*** via nucleophilic substitution or the pentavalent phosphorus intermediate ***i*** via nucleophilic addition to phosphorus. Under basic conditions, ***i*** would be deprotonated to form ***ii***, which would, in turn, fragment to produce the iminophosphorane **5** and the benzothiazolide anion ***iii***.[11b,17] Because both pathways involve the formation of benzothiazolide ***iii***, we hypothesized that the use of water as the nucleophile (as hydroxide ion) would also result in reduction of the benzothiazole and the formation of phosphine oxide. Experiments using only a slight excess of sodium deuteride demonstrated that this indeed is the case (Scheme 5c). The specific C2 deuterium labeling with 97% yield and >98% deuterium incorporation was observed for **6a**. The process appears general, as benzothiazoles with electron-donating and -withdrawing substituents both undergo efficient C2 labeling (**6b** and **6c**).

The proposed direct nucleophilic attack of the nucleophiles to the phosphorus atom in the phosphonium salt with both primary amines and water suggests that this process could also operate in the reactions that result in C2 functionalization of benzothiazole. If the pentavalent phosphorus intermediate similar to ***i*** is indeed on the reaction path, that would necessitate a contractive C–O or C–N bond formation from the same intermediate akin to reductive elimination. Another possible mechanistic scenario is the simple aromatic nucleophilic substitution reaction that would see nucleophilic attack to the C2 position of the benzothiazole. Our current studies are aiming to decipher the reaction mechanism and determine the chemical competence of the proposed

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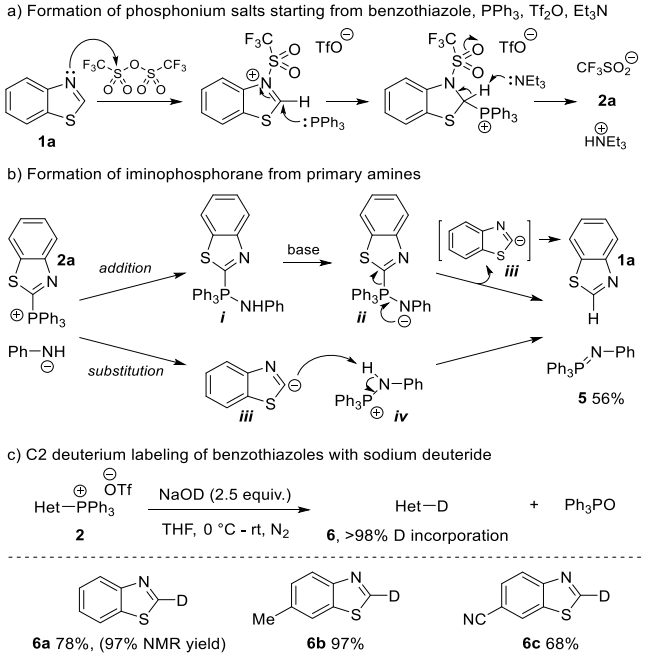
Scheme 5. Formation of Iminophosphoranes and Phosphine Oxides with Primary Amines and Water



pentavalent phosphorus intermediates that have been observed via *in situ* ^{31}P NMR.[18]

In summary, we have developed an effective method for the C2−H functionalization of benzothiazoles via thiazol-2-yl-phosphonium intermediates that readily undergo reactions with O- and N-nucleophiles under mild conditions. Reactions are productive with a range of substituted benzothiazoles and feature an unusually wide scope for nucleophiles including alcohols, phenols, amines, amides, and N-heterocycles. The resulting C2-subsituted benzothiazoles are structurally related to many biologically active molecules, making this method attractive for use in medicinal chemistry development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00882.

Detailed experimental procedures, spectral data for all new compounds, and ^{1}H, ^{13}C, ^{19}F, and ^{31}P spectra (PDF)

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Notes

The authors declare no competing financial interest.

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