

Selective C-H Chalcogenation of Thiazoles via Thiazol-2-yl-phosphonium Salts

You Zi, Konrad Wagner, Fritz Schömberg, [Ivan Vilotijevic](#)

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Thiazoles and benzothiazoles undergo regioselective C2-H chalcogenation via the sequence of thiazole C2-functionalization with phosphines to produce phosphonium salts which in turn react with S- and Se-centered nucleophiles to give products of C2-H chalcogenation and allow for recovery of the starting phosphine. The atom economical sequence proceeds under mild conditions and features broad scope for both the nucleophiles (electron-rich, electron-poor, sterically hindered thiols) and the various substituted benzothiazoles. The access to the substituted medicinally relevant C2-thio benzothiazoles also enables stereoselectivity improvements in the modified Julia olefinations.

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Selective C-H Chalcogenation of Thiazoles via Thiazol-2-yl-phosphonium Salts

You Zi, Konrad Wagner, Fritz Schömberg and Ivan Vilotijevic*

Institute of Organic Chemistry and Macromolecular Chemistry, Friedrich Schiller University Jena,
Humboldtstr. 10, 07743 Jena, Germany.

E-mail: ivan.vilotijevic@uni-jena.de

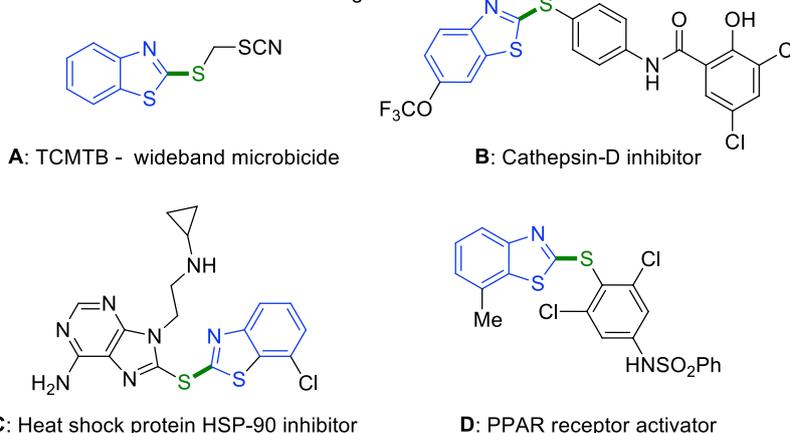
Abstract: Thiazoles and benzothiazoles undergo regioselective C2-H chalcogenation via the sequence of thiazole C2-functionalization with phosphines to produce phosphonium salts which in turn react with S- and Se-centered nucleophiles to give products of C2-H chalcogenation and allow for recovery of the starting phosphine. The atom economical sequence proceeds under mild conditions and features broad scope for both the nucleophiles (electron-rich, electron-poor, sterically hindered thiols) and the various substituted benzothiazoles. The access to the substituted medicinally relevant C2-thio benzothiazoles also enables stereoselectivity improvements in the modified Julia olefinations.

Thiazoles and benzothiazoles are important constituents of electronic materials,¹ common intermediates in organic synthesis,² and a regular occurrence in natural products³ and biologically active molecules.⁴ They are the most common aromatic 5-membered N-heterocycles among FDA approved pharmaceuticals.⁵ Vast majority of these bioactive molecules feature a heteroatom substituent at C2 which highlights the need for methods to introduce such substituents and makes these methods valuable tools in medicinal chemistry.

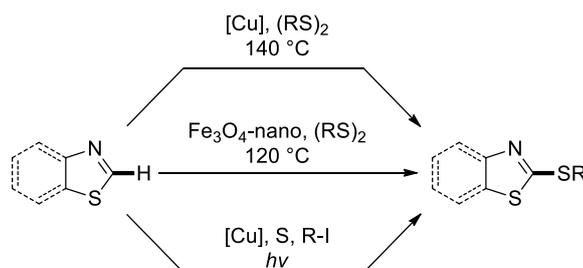
2-thio-substituted (benzo)thiazoles, such as the wideband microbicide TCMTB (**A**),⁶ cathepsin-D inhibitor (**B**),⁷ heat shock protein 90 inhibitor (**C**)⁸ and PPAR receptor activator (**D**),⁹ have attracted attention for their biological activities (Scheme 1a). Other 2-thio-substituted (benzo)thiazoles are common intermediates in organic synthesis where they are used to construct double bonds via Julia olefination¹⁰ or as substrates for transition metal-catalysed coupling reactions.¹¹ While other strategies to prepare 2-thio-substituted thiazoles exist,¹² C2-H thiolation (and chalcogenation) is of particular interest as a method for their direct functionalization. Despite the apparent demand, the methods for C2-H thiolation of thiazoles have thus far been limited to transition metal mediated processes that (i) typically proceed under harsh conditions at temperatures between 120 and 140 °C with long reactions times,¹³⁻¹⁴ (ii) use stoichiometric amounts of transition metal salts and/or (iii) require the use of strong oxidants (Scheme 1b).¹⁴ These features greatly limit the reaction scope and prevent general application of such methods in more complex settings common in medicinal chemistry. A recent report of photochemically promoted Cu-catalyzed chalcogenation of thiazoles which proceeds at room temperature and improves the functional group tolerance is an important improvement in this field but it requires a specific photochemical setup and is limited to synthesis of diaryl sulphides (Scheme 1b).¹⁵ A general method for C2-H thiolation of thiazoles that

proceeds under mild conditions with broad substrates scope, uses readily available starting materials and avoids the use of transition metals would provide a simple way to create the C2-S bond of interest and generate libraries of medicinally relevant C2-thio substituted thiazoles.

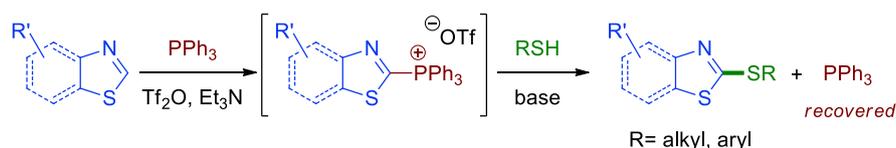
a) Bioactive C2-thio benzothiazole containing molecules



b) Previous work on C2-H functionalization of thiazoles:



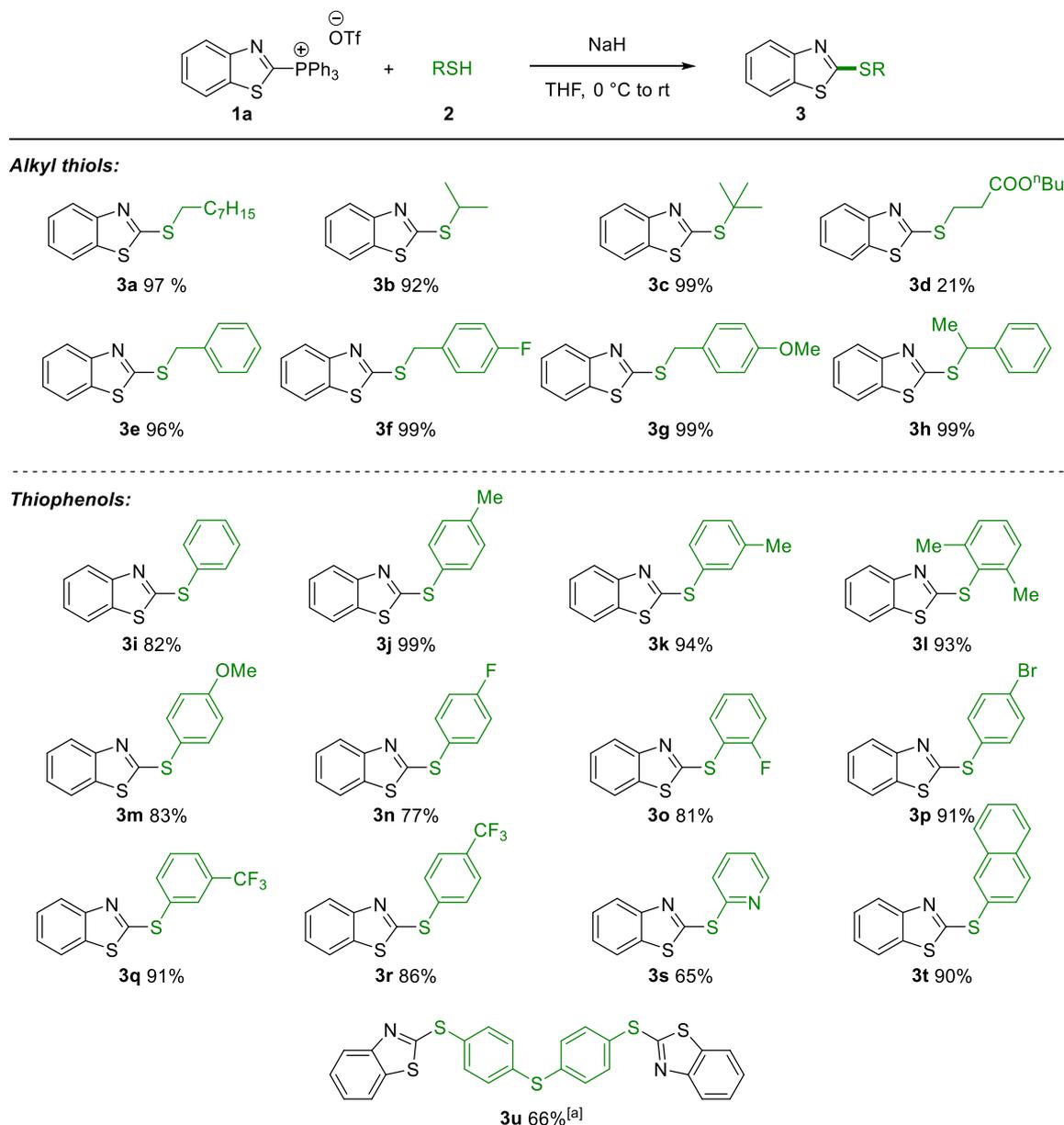
c) **This work:** C2-H thioetherification (and selenation) of thiazoles



Scheme 1 (a) Examples of biologically active C2-thio benzothiazole derivatives; (b) previous work for C2 thiolation of (benzo)thiazoles and (c) our approach.

Early work of Anders demonstrated the ease of synthesis of heteroaryl phosphonium salts by activating the corresponding heterocycle with triflic anhydride and exposing the resulting intermediate to a phosphine nucleophile.¹⁶ In our work on phosphine promoted reactions of Michael acceptors that proceed via vinylphosphonium intermediates,¹⁷ we found out that such intermediates readily undergo reactions with heteroatom-centered nucleophiles which suggested that a two-step sequence where regioselective formation of the phosphonium salt and a subsequent reaction with suitable nucleophile would constitute an efficient and selective C2-H functionalization of (benzo)thiazoles. Recent work on the related reactions with pyridinylphosphonium salts supported the feasibility of this approach.¹⁸ We hypothesized that a range of thiazol-2-yl-phosphonium salts could be accessed starting from various

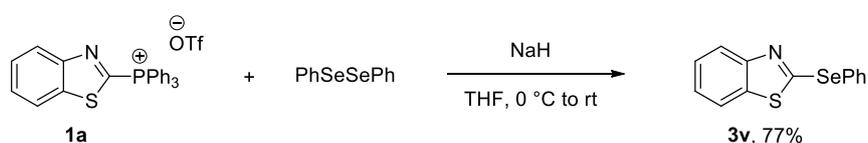
benzothiazoles and thiazoles under the conditions described by Anders. Here we show that such thiazol-2-yl-phosphonium salts undergo highly efficient chalcogenation with a broad range of thiols, thiophenols and a Se-centered nucleophile and produce a variety of C2-chalcogen substituted thiazoles in excellent yields (Scheme 1c).



Scheme 2 Thiolation of benzothiazole with different thiols. Conditions: phosphonium salt (0.2 mmol), pronucleophile (0.3 mmol), NaH (0.3 mmol), THF (2 mL, 0.1 M), at 0 °C to room temperature. [a] Conditions: phosphonium salt (0.2 mmol), pronucleophile (0.15 mmol), NaHMDS (0.3 mmol), THF (2 mL, 0.1 M), at -78 °C to room temperature.

In our initial study, benzothiazole was selected as the model system and converted to the corresponding benzo[d]thiazol-2-yltriphenylphosphonium triflate salt (**1a**) which was then used in

reactions with 1-octanethiol. The reactions required nucleophile activation by a base. Sodium hydride proved to be a suitable and atom economical solution for this. With slight excess of the thiol, the reaction between 1-octanethiol and the benzo[d]thiazol-2-yltriphenylphosphonium triflate yielded the product **3a** in excellent yield. The reactions proceeded with high rates at room temperature in THF. The main side product was the triphenylphosphine which could be recovered at the end of the reaction making the entire process atom economical. The ease of preparation of benzo[d]thiazol-2-yltriphenylphosphonium triflate and its favourable solubility profile enabled the two-step sequence to be carried out in one pot with removal of excess ammonium salt by precipitation of the phosphonium salt and decanting between the steps. Although typical reactions used 1.5 equivalents of the thiol and sodium hydride, lower quantities (1.1 equiv.) were often sufficient to achieve good yields for the desired products.



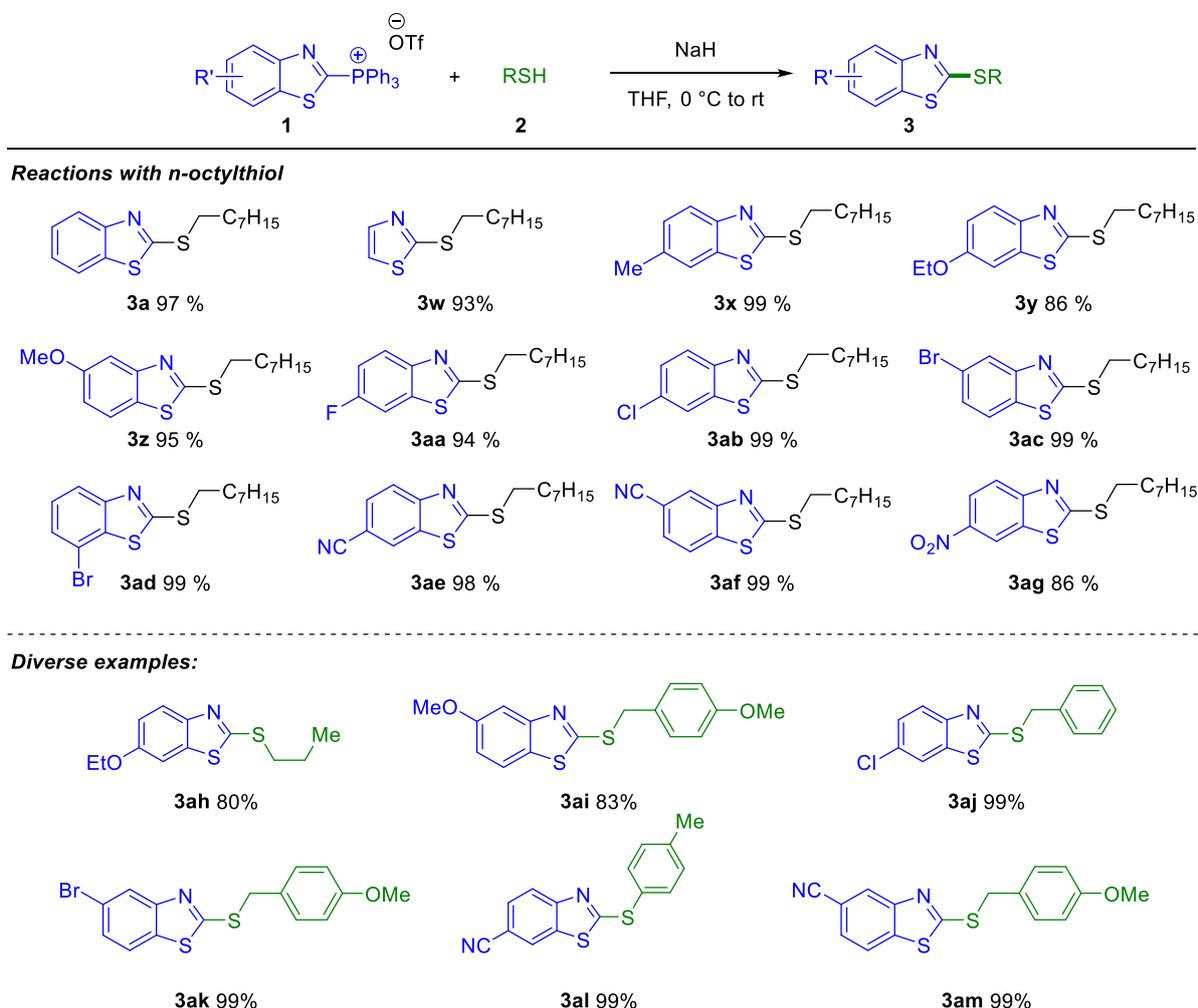
Scheme 3 Synthesis of the diarylselenide **3v** via reaction of phosphonium salt and Se-centered nucleophile. Conditions: phosphonium salt (0.2 mmol), PhSeSePh (0.3 mmol), NaH (0.6 mmol), THF (2 mL, 0.1 M), at 0 °C to room temperature.

With fast turnaround in the optimization studies, the attention was focused on exploration of the reaction scope. Primary, secondary, tertiary alkyl and benzylic thiols all produced the desired thioethers in nearly quantitative yields (**3a-3h**, Scheme 2). Thiophenols also gave the desired products in high yields (**3i-3u**) with electron rich and electron poor thiophenols showing comparable efficacy (**3j-3r**). The reactions appeared to be tolerant of steric crowding in the vicinity of the S-centered nucleophile with products **3c** and **3l** derived from *t*-BuSH and 2,6-dimethylphoenylthiol produced in 99% and 93% yields respectively. The double thioetherification to produce **3u** proceeded with satisfactory yield as did the reactions with thiols with extended conjugation and those containing other heterocycles like pyridine (**3s-3t**).

To test the feasibility of the same approach in construction of C-Se bonds, benzo[d]thiazol-2-yltriphenylphosphonium triflate was subjected to reaction with Se-centered nucleophile generated by reduction of diphenyl diselenide with sodium hydride to produce the 2-(phenylselanyl)thiazole **3v** in yield of 77% (Scheme 3).

The scope for the benzothiazol-2-yl-phosphonium triflates has been explored by employing various substituted salts that were available via the method outlined by Anders.¹⁶ Salts derived from substituted thiazoles carrying both electron-donating and electron-withdrawing substituents in positions 5, 6 and 7 have been examined. 1-octanethiol was used as a model nucleophile in these reactions to determine that they all proceed with nearly quantitative yields regardless of the electronic properties of the salt (Scheme 4). Ethers (**3y** and **3z**), aryl halides (**3aa-3ad**), nitriles (**3ae** and **3af**), nitro compounds (**3ag**) were well tolerated in these reactions. In addition to salts derived from

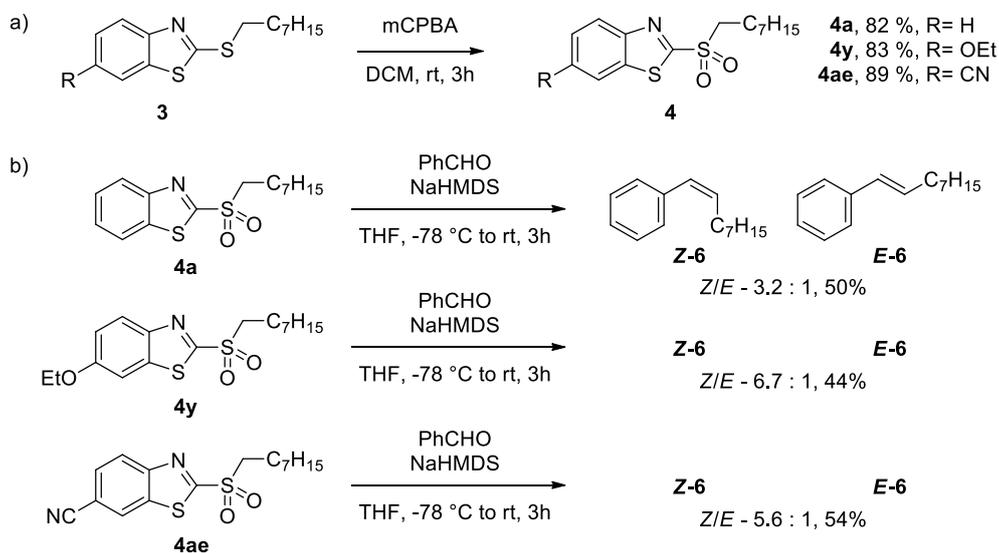
benzothiazoles, those derived from simple thiazoles were also competent substrates in these reactions (**3w**). Finally, a few diverse combinations of phosphonium salts and the thiols showed the generality of the process (**3ah-3am**).



Scheme 4 Reaction scope for substituted thiazoles. Conditions: phosphonium salt (0.2 mmol), pronucleophile (0.3 mmol), NaH (0.3 mmol), THF (2 mL, 0.1 M), at 0 °C to room temperature.

Having access to a variety of electronically different C2-thio substituted benzothiazoles, piqued our curiosity about the possibility of exploiting electronic effects of these substituents to address selectivity issues in modified Julia olefination reactions that otherwise proceed with lower selectivity. We hypothesized that electronic effects of the substituents may change the selectivity of the reactions by changing the nature of transition states in the selectivity determining addition of the sulfone stabilized anion to the aldehyde or by changing the kinetics of individual elementary steps during the olefination reactions that may ultimately enable different equilibria to be established.¹⁰ With this in mind, for our model study we selected the typical modified Julia olefination substrate (**3a**) and the two substituted starting materials, one featuring an electron donating (**3y**) and the other featuring electron withdrawing group (**3ae**) (Scheme 5). The three sulfones were easily accessed from the

corresponding sulfides by *m*CPBA oxidation. Applying the typical conditions for modified Julia olefination with **4a** resulted in a 3.2:1 mixture of **Z-6** and **E-6** favouring the *Z* product. Under the same conditions, both **4y** and **4ae** gave the products **6** with higher selectivity (6.7:1 and 5.6:1, respectively) while maintaining similar efficacy. Future studies will be directed towards understanding and further establishing the substituent effect in these reactions.



Scheme 5 Modified Julia olefination using differently substituted sulfones.

In conclusion, the regioselective C2-H functionalization of thiazoles with phosphines followed by the highly efficient base promoted reaction with S-centered nucleophiles is an effective way to produce C2-thio thiazole derivatives. The reactions proceed under mild conditions, use simple starting materials and feature broad scope that includes both alkyl thiols and thiophenols. Electronic and steric factor do not significantly change the high efficacy of reactions of phosphonium salts with S- and Se-nucleophiles. The substituted C2-thio benzothiazoles can be of use in organic synthesis to improve the selectivity of the modified Julia olefination reactions. Applications of this methodology to rapidly generate targeted libraries of compounds for medicinal chemistry are envisioned.

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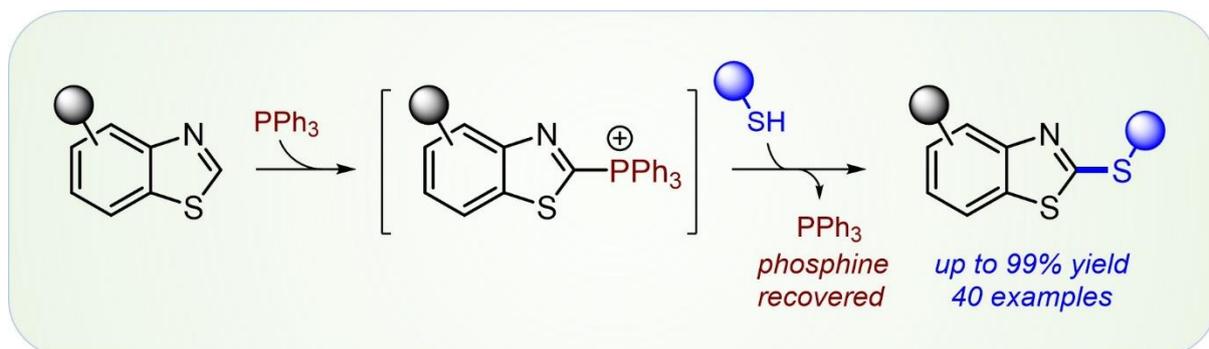
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