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Communication

Benzene Synthesis

Carbene-Catalyzed Formal [3+3] Cycloaddition Reaction for Access to Substituted 2-Phenylbenzothiazoles

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Abstract: A carbene-catalyzed oxidative cycloaddition reaction is developed for efficient access to multi-functionalized 2-phenylbenzothiazoles. A broad scope of heavily substituted arenes bearing 2-benzothiazole groups have been prepared in good to excellent yields. The remote C(sp^2)–H bond in the substituted arene products can be activated by Pd catalysts in regio-selective fashion with the direction of the 2-benzothiazole groups.

2-Phenylbenzothiazoles are privileged structural units in natural and non-natural functional molecules.[1] For instance, Phortress is an important prodrug for the curation of human mammary tumor *xenografts* and the compound 5F-203 containing a 2-phenylbenzothiazole core is its active moiety.[1a] The multi-conjugated 2-indoline benzothiazole BT-1 and their derivatives are widely used as important indoline dyes.[1b] Benzothiazoles are also widely used as directing groups in the regio-selective C–H activation of arenes (Figure 1a).[2] For example, the *o*-position of the benzene ring attached to a 2-benzothiazole group can be hydroxylated,[2a,2b] allylated,[2c] acylated[2d,2e] and nitrificated[2f] with the catalysis of different transition metal catalysts. Therefore, the construction of functionalized 2-phenylbenzothiazoles has attracted considerable interest.

Substituted 2-phenylbenzothiazoles are traditionally synthesized from 2-aminothiophenols and carbonyl compounds through a condensation/cyclization cascade (Figure 1b, Equ. 1).[3] Phenyl nitriles and thiophenols can also be used as the starting materials for the construction of 2-phenylbenzothiazoles through oxidative cycloaddition process (Figure 1b, Equ. 2).[4] Transition metal-catalyzed C(sp^2)–S and C(sp^2)–C(sp^2) cross coupling reactions have also been developed as effective protocols for the preparations of various substituted 2-phenylbenzothiazoles (Figure 1b, Equs. 3 & 4).[5] Very recently, a copper-catalyzed multi-component cross-coupling reaction of alkyne, sulfur and 2-iodoaniline has been disclosed, with 2-phenylbenzothiazole afforded as the final product through construction of the benzene and thiazole rings (Figure 1b, Equ. 5).[6] To the best of our knowledge, the access to heavily substituted 2-phenylbenzothiazoles through construction of the congested benzene rings via metal-free organocatalytic reactions has not been disclosed.

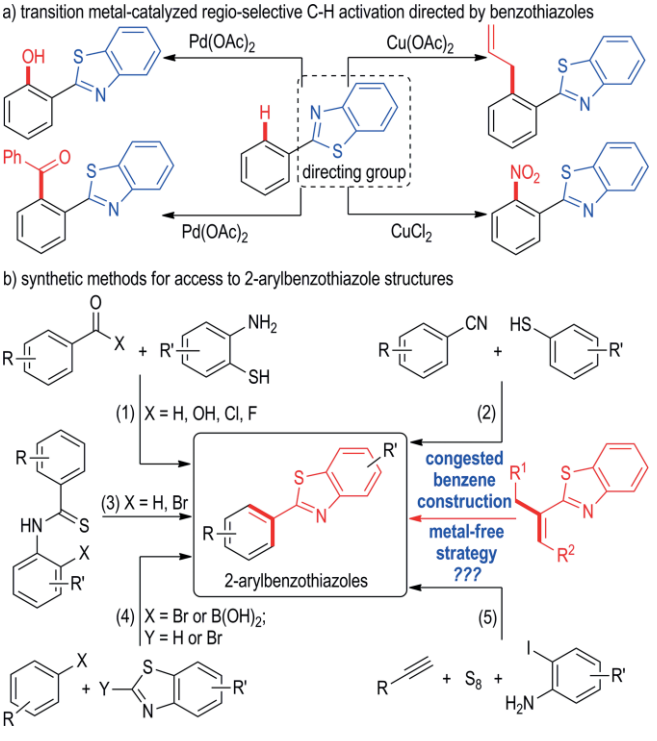

Figure 1. Bioactive and synthetic applications of 2-phenylbenzothiazoles and their preparation.

N–Heterocyclic carbene (abbreviated as NHC or carbene) organocatalysis has been developed as one of the robust synthetic methods for organic synthesis.[7] However, the construc-

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tion of benzene rings through NHC organocatalytic strategies has been relatively less developed (Figure 2).[8] In 2014, Chi and co-workers disclosed the formal [3+3] reaction for benzene synthesis with β-methyl cinnamaldehyde and activated enone used as the reaction substrates (Figure 2a, Equ. 1).[8a] They also developed a δ-LUMO activation strategy for the synthesis of multi-substituted benzenes from conjugated dienals and 1,3-diketone substrates (Figure 2a, Equ. 2).[8b] An NHC-promoted intramolecular rearrangement reaction of cinnamic acid ester compounds has been reported by Lupton and co-workers, with heavily substituted benzaldehydes afforded as the final products (Figure 2a, Equ. 3).[8c] In 2016, Ye and Wang's groups independently reported the formation of benzonitriles through addition of the α-cyano-β-methylchalcones to NHC-bound α,β-unsaturated acylazolium intermediates (Figure 2a, Equ. 4).[8d–8f]

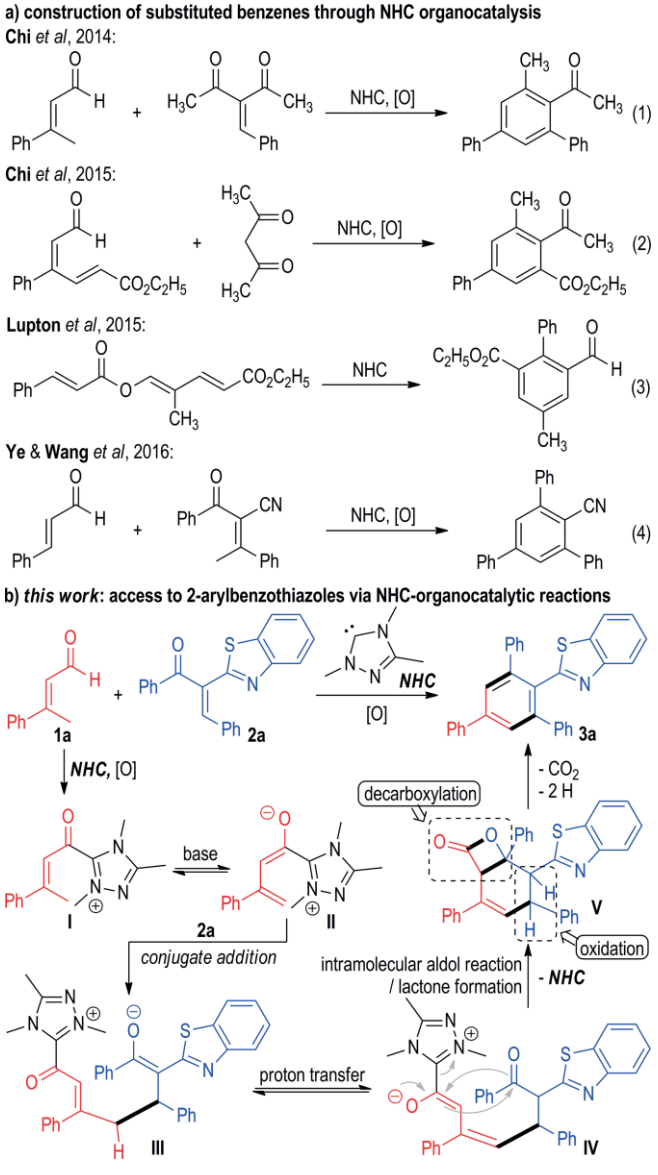
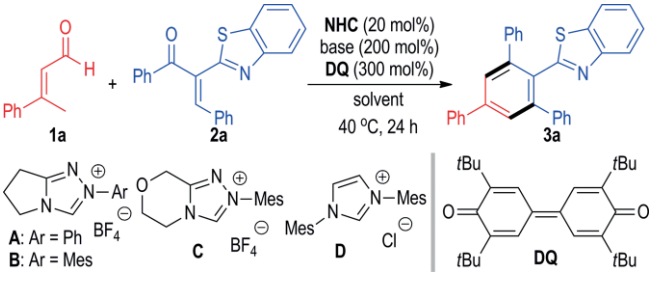


Figure 2. Construction of benzene rings through NHC organocatalytic reactions.

Herein, we report the construction of heavily substituted 2-phenylbenzothiazoles through construction of the benzene rings via an NHC organocatalytic protocol (Figure 2b). Mechanistically, addition of the NHC catalyst to the β-methyl enal **1a** under oxidative conditions gives the acylazolium intermediate **I**,[9] which can be easily deprotonated to give intermediate **II** bearing a nucleophilic-carbon.[10] Conjugate addition of **II** to enone **2a** affords adduct **III**, which leads to intermediate **IV** through an intramolecular proton transfer process. An intramolecular aldol reaction/lactone formation process in **IV** gives the fused bicyclic intermediate **V** and releases the free NHC catalyst for additional catalytic cycles. Intermediate **V** is not stable under the catalytic conditions and tends to undergo a decarboxylation/oxidative aromatization process to give the 2-phenylbenzothiazole **3a** as the final product. Our method uses chiral organic NHCs as the reaction catalyst and can avoid heavy-metal contaminations caused by transition metal catalysts.

Different NHC organic catalysts were initially examined for the formal [3+3] reaction between β-methyl enal **1a** and the activated enone **2a** in the presence of the **DQ** oxidant (Table 1, entries 1 to 4). NHC catalysts bearing *N*-mesityl substituents were found effective for this transformation (entries 2 to 3), while no product was observed with NHCs bearing N-Ph groups (e.g., entry 1). Gratifyingly, the IMes NHC catalyst **D** could give the desired 2-phenylbenzothiazole **3a** in 72 % yield (entry 4). Various organic or inorganic bases could be used for this process, although the products were generally afforded in lower yields (e.g., entries 5 to 6). The reactions also went on smoothly in a variety of organic solvents (e.g., entry 7), but only trace product could be observed when carrying out the reaction in high-polar solvents (e.g., entry 8).

Table 1. Condition optimization.[a]

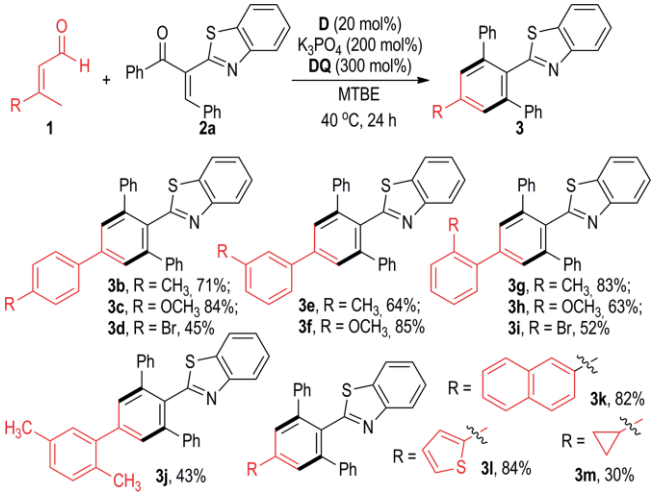


Entry	NHC	Base	Solvent	Yield [%][b]
1	**A**	K_3PO_4	MTBE	0
2	**B**	K_3PO_4	MTBE	10
3	**C**	K_3PO_4	MTBE	14
4	**D**	K_3PO_4	MTBE	72
5	**D**	Cs_2CO_3	MTBE	59
6	**D**	DBU	MTBE	32
7	**D**	K_3PO_4	THF	68
8	**D**	K_3PO_4	DMF	< 5

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.10 mmol), base (0.20 mmol), **DQ** (0.30 mmol), solvent (1.5 mL), 40 °C, 24 h. [b] Isolated yields of **3a**.

Having identified an optimal reaction condition for this formal [3+3] cyclization reaction (Table 1, entry 4), we next ex-

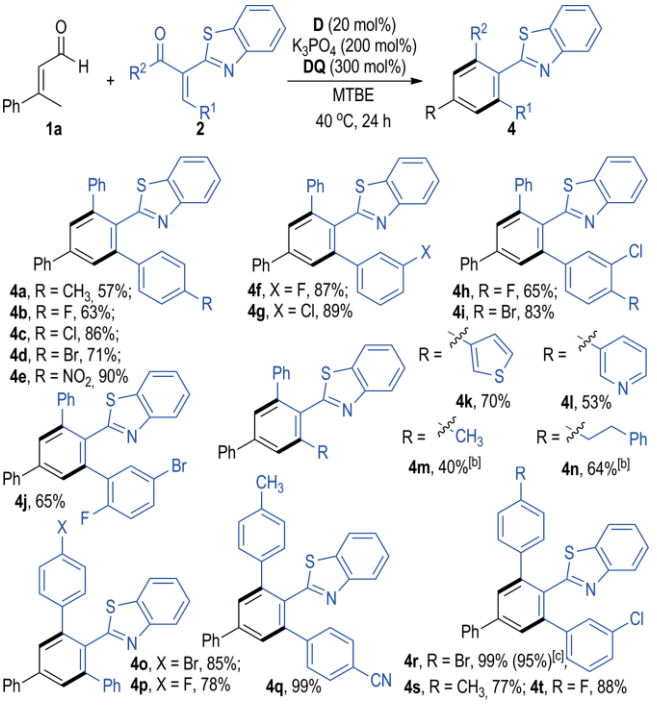
plored the scope of the β-methyl-α,β-unsaturated aldehyde substrates (Scheme 1). Electron-donating substituents were well tolerated on each position of the β-benzene group of the enal substrate **1a**, with the desired products afforded in good yields (**3a** to **3c**, **3e** to **3h**). Electron-withdrawing groups on the β-benzene ring of **1a** led to drops on the product yields (**3d**, **3i**). Multi-substituted benzene groups on the β-position of the enal substrate give the products in lower yields (e.g., **3j**). The β-benzene group of the enal **1a** could also be switched to a naphthalene group or a thiophenyl group without erosion on the product yield (**3k**, **3l**). However, replacing the β-benzene group of the enal **1a** with an aliphatic group led to drops on the product yield (**3m**).



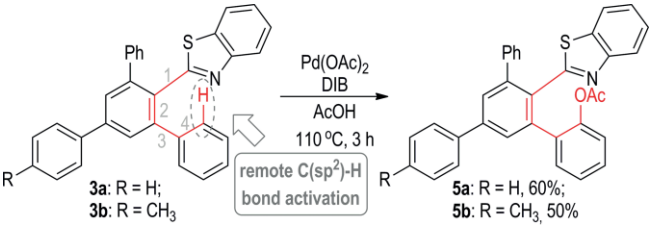
Scheme 1. Scope of enals **1**. Reactions were carried out under condition as in Table 1, entry 4. Yields were isolated yields.

Enone substrates **2** bearing different substituents or substitution patterns were also examined (Scheme 2). Both electron-donating and electron-withdrawing groups could be installed on the β-benzene rings (R^1) of the enone substrates **2**, with the corresponding products afforded in moderate to excellent yields (**4a** to **4j**). Similarly, the β-benzene rings of the enone substrates **2** could also be switched to heteroaromatic groups without much erosion on the product yields (**4k** & **4l**). β-Alkyl-substituted enones could also serve as suitable substrates for this transformation, with the desired products afforded in moderate yields under slightly varied reaction conditions (**4m** & **4n**). The aromatic R^2 group on the enone substrate **2** could also be various substituted benzene rings, with all the products given in good to excellent yields (**4o** to **4t**).[11]

The C(sp^2)–H bonds of the multi-substituted aromatic products (**3**) can be activated by Pd catalysts in regio-selective fashion (Scheme 3). Benzothiazole groups have been extensively explored as directing groups to help activate the *ortho*-C(sp^2)–H bonds on the adjacent aromatic rings. In our cases, a remote C(sp^2)–H bond that is four C-C bonds away from the directing group can be selectively activated with the acyloxylated products **5** given in moderate yields (**5a** & **5b**).[12]



Scheme 2. Scope of enones **2**. Reactions were carried out under condition as in Table 1, entry 4. Yields were isolated yields. [b] K_2CO_3 (200 mol-%) was used instead of K_3PO_4, and the reaction was stirred for 48 h. [c] The reaction was carried out at 1.0 mmol scale.



Scheme 3. Benzothiazole-directed C(sp^2)–H activation of **3**. The structures of the products **5** were assigned via X-ray analysis on the single crystals of **5a** (CCDC 1960046).

Conclusions

In summary, we have developed an NHC-catalyzed oxidative cycloaddition reaction for quick access to 2-phenylbenzothiazoles. A broad scope of heavily substituted benezene products bearing 2-benzothiazole groups can be obtained in moderate to excellent yields. The remote C(sp^2)–H bonds on the substituted benzene rings can be activated by Pd catalysts in a regio-selective fashion with the direction of the benzothiazole units. Further applications of NHC organocatalytic methods in the construction of biologically and synthetically valuable molecules are in progress in our laboratory.

CCDC 1960045 (for **4e**) and 1960046 (for **5a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Conflict of Interest

There is no conflict of interest to declare.

Acknowledgments

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Keywords: 2-Phenylbenzothiazoles · N-heterocyclic carbene · Benzene construction · Remote C(sp2–H) activation · Directing groups

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