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Phosphine-Catalyzed Chemoselective Reduction/Elimination/Wittig Sequence for Synthesis of Functionalized 3-Alkenyl Benzofurans

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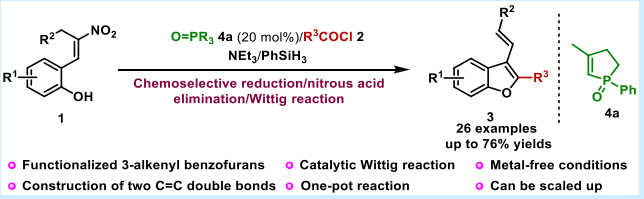
ABSTRACT: An efficient protocol for the construction of functionalized 3-alkenyl benzofurans is demonstrated under metal-free conditions using catalytic amount of phosphine proceeding an intramolecular Wittig reaction. This one-pot reaction initiated by the phospha-Michael addition of phosphine to *O*-acylated nitrostyrene, in which phosphine was in-situ-generated from the chemoselective reduction of phosphine oxide with $PhSiH_3$, would provide the phosphorus ylide to result in the aforementioned multifunctionalized benzofuran via *O*-acylation/nitrous acid elimination/Wittig reaction.

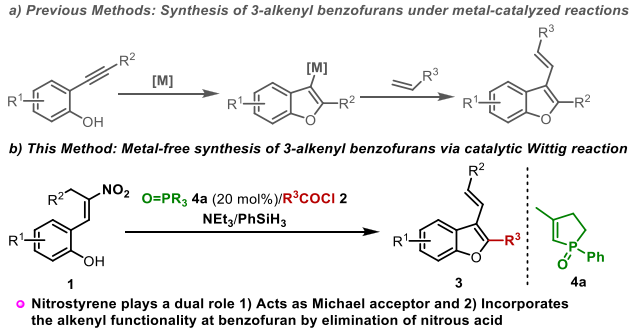


Phosphine-catalyzed reactions of electron-deficient alkenes have emerged as a powerful tool in organic synthesis, because of their potential to construct a variety of natural products and biologically active molecules.[1] Consequently, the conversion of the phosphine-mediated reactions to their catalytic process was achieved by in situ reduction of phosphine oxide using hydrosilane.[2,3] The challenges to be overcome for achieving the chemoselective reduction of phosphine oxide are not affecting the accompanying substrates, reagents, and formed products in a multistep reaction.[2] Remarkably, the development of new methods for the synthesis of multifarious functionalized heteroarenes/heterocycles under phosphine catalysis is of foremost interest.

Benzofuran heterocycles are important synthetic targets, because of their prevalence in bioactive natural products and medicinally valuable compounds.[4] The importance of biological activities of the benzofurans highly relies on their substitution pattern, because their activity is variable, according to the nature of the substituents.[5] Hence, numerous synthetic methods were developed for their production of benzofurans bearing various functional groups.[6] However, a few methods have been reported regarding the synthesis of 3-alkenyl substituted benzofurans, and most of the reactions are *o*-hydroxy-substituted alkynes activated by transition-metal catalysts (Scheme 1a).[7] Therefore, the development of new methods to access functionalized benzofurans has attracted great interest. Besides, starting from more available substrates and the use of metal-free conditions are highly desirable in modern organic chemistry.

Earlier, a novel method for the synthesis of benzofurans from α,β-unsaturated carbonyl compounds via intramolecular Wittig reaction has been demonstrated under catalytic phosphine conditions in this laboratory.[8] To continue our efforts to develop novel methods in the area of organophosphane chemistry,[9] we conceived that *o*-hydroxy substituted nitrostyrene derivatives could be useful synthons to install the extra alkenyl functionality at the heteroaryl ring by in situ removal of nitrous acid.[10] The appropriate design of substrate bearing a nitro group plays a dual role, such as initiation of the phospha-Michael addition, and in situ elimination of nitrous acid to incorporate the additional alkenyl functionality at the desired products. However, the most challenging part is to avoid the polymerization of nitrostyrene under our catalytic Wittig reaction conditions.[11] In this context, we have developed a novel method for the construction of functionalized 3-alkenyl benzofurans from the readily available nitrostyrene derivatives via chemoselective

Scheme 1. Our Approach for the Functionalized 3-Alkenyl Benzofurans



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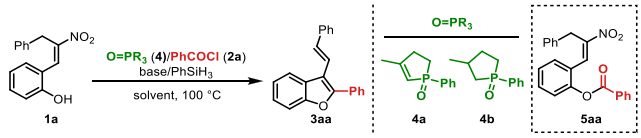
reduction/nitrous acid elimination/Wittig reaction sequence under metal-free conditions. Note that the formation of two C=C conjugated double bonds are achieved by employing the nitrostyrene, acyl chloride in the presence of a limited amount of base under phosphine-catalyzed reaction conditions.

Initially, we have performed the reaction of nitrostyrene derivative **1a** with PhCOCl (**2a**) using a catalytic amount of phosphine oxide **4a** in the presence of Et_3N and $PhSiH_3$ in toluene at 100 °C (Table 1, entry 1). To our delight, the 3-alkenyl benzofuran derivative **3aa** was obtained in 65% yield within 1 h. At an instance, we assumed that the in situ elimination of nitrous acid, along with the Wittig reaction, could be responsible for the generation of the alkenyl functionality on the heteroaryl ring of the benzofuran. These intriguing results of the synthesis of alkenyl-functionalized benzofurans under metal-free conditions encourage us to investigate the reaction conditions (Table 1).

Table 1. Optimization of the Catalytic Intramolecular Wittig Reaction for 3aa[a]



entry	solvent	base	t (h)	3aa/5aa (%)[b]
1	toluene	Et_3N	1	65/–
2	xylenes	Et_3N	5	67/–
3	*o*-xylene	Et_3N	3	67/–
4	*m*-xylene	Et_3N	3	70(69)[c]/–
5	*p*-xylene	Et_3N	3	51/–
6	*m*-xylene	DIPEA	3	70/–
7	*m*-xylene	DABCO	3	49/14
8	*m*-xylene	DMAP	3	54/–
9[d]	*m*-xylene	Et_3N	1	65/–
10[e]	*m*-xylene	Et_3N	5	54/24
11[f]	*m*-xylene	Et_3N	1	61/–
12[g]	*m*-xylene	Et_3N	24	69/–
13[h]	*m*-xylene	Et_3N	3	69/–
14[i]	*m*-xylene	Et_3N	1	70/–
15[j]	*m*-xylene	Et_3N	5	43/36
16[k]	*m*-xylene	Et_3N	5	54/18
17[l]	*m*-xylene	Et_3N	3	60/–

[a]The reactions were performed with nitrostyrene **1a** (0.2 mmol), O=PR_3 **4a** (20 mol %), PhCOCl **2a** (1.1 equiv), base (1.2 equiv), and $PhSiH_3$ (2.0 equiv) sequentially in solvent (1.0 mL) under argon atmosphere at 100 °C. [b]The yield of **3aa** and **5aa** was determined by ^1H NMR analysis of the crude mixture using Ph_3CH as an internal standard. [c]Isolated yield of **3aa**. [d]Reaction at 120 °C. [e]Reaction at 80 °C. [f]30 mol % of **4a** was used. [g]10 mol % of **4a** was used. [h]**4b** was used. [i]3.0 equiv of $PhSiH_3$ was used. [j]1.0 equiv of $PhSiH_3$ was used. [k]2.0 equiv of Ph_2SiH_2 was used. [l]TESCl was used as an additive.

First, various solvents have been screened to find the optimal conditions (Table 1, entries 1–5). After solvent screening, *m*-xylene was found to be the best solvent for the catalytic Wittig reaction (see the Supporting Information (SI) for the detailed optimization). Furthermore, different bases were tested (Table 1, entries 6–8), and Et_3N was found to be a suitable base for synthesis of the 3-alkenyl benzofuran **3aa**. The *O*-acylated nitrostyrene derivative **5aa** was obtained in 14% yield when the reaction was performed using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base. It could be an intermediate for the chemoselective reduction/nitrous acid elimination/Wittig reaction sequence to access the 3-alkenyl benzofuran **3aa**. Further evaluation of other factors, such as utilizing excess amounts of base, different reaction temperatures, and catalyst loading, did not improve the yield of the desired product (Table 1, entries 9–12). When employing the phosphine oxide (**4b**) in the reaction, the desired product was obtained in similar yield within 3 h (Table 1, entry 13). Furthermore, the amount of reducing agent, and the addition of additives, were also tested, but no significant improvement of the yields of the products was observed (Table 1, entries 14–17). Finally, the suitable conditions for synthesis of 3-alkenyl benzofurans are shown in entry 4 in Table 1.

With the optimal conditions in hand, the scope of the substrates was investigated (Scheme 2). At first, substrate **1**, bearing different R^1 and R^2 substituents, were tested with PhCOCl (**2a**). The substrates with electron-donating groups (R^1) worked more efficiently than those with the electron-withdrawing groups, furnishing the desired products **3ba–3ga** in moderate to good yields, regardless of the position of the substituent. The substrates with various R^2 substituents afforded the corresponding 3-alkenyl benzofurans **3ha–3ka** in good yields, irrespective of the electronic and steric nature of the substituent. Delightfully, the substrate containing the heteroaryl (2-furyl) group was also well-tolerated to provide the desired product **3la** in 58% yield. Notably, the substrates with aliphatic methyl and hydrogen as R^2 substituents also participated in the reaction, albeit providing the corresponding products **3ma** and **3na** in lower yields. Interestingly, when the vinyl group bearing substrate **1o** was subjected to **2a**, the doubly conjugated benzofuran **3oa** was obtained in 65% yield without any difficulties. We have noticed that the substrates bearing the aryl or vinyl group as the R^2 substituent were well-participated to furnish the desired 3-alkenyl benzofuran derivatives in good yields, when compared with substrates with less-reactive aliphatic R^2 substituents (**1m** and **1n**).

Furthermore, various acyl chlorides were tested under standard reaction conditions with **1a** to prepare a series of 3-alkenyl benzofuran derivatives **3**. The acyl chlorides with electron-donating groups and electron-withdrawing groups at the *para*-position provided the desired products **3ab–3ae** in yields up to 69%. The *meta*- and *ortho*-chloro-substituted aroyl chlorides also reacted with **1a** smoothly to afford the corresponding products **3af** and **3ag** in 65% and 57% yields, respectively. Delightfully, 1-naphthoyl and heteroaroyl (2-furyl and 2-thienyl) chlorides furnished the desired products **3ah–3aj** in yields of 60%–68% within 4 h. Interestingly, aliphatic acyl chlorides **2k** and **2l** were also well-tolerated to provide the corresponding benzofuran derivatives **3ak** and **3al** in yields up to 67%. In addition, to test the preparative utility of our catalytic protocol, we have performed a gram-scale reaction of **1a** with **2a** under the standard conditions. The 3-alkenyl benzofuran **3aa** was obtained in 69% yield with substantial quantities within 3 h.

Furthermore, a reaction of **1a** and PhCOCl in the presence of Et_3N was examined by employing the stoichiometric amount of PBu_3 in toluene at 30 °C. The desired 3-alkenyl benzofuran derivative **3aa** was obtained in only 50% yield in 3 h. To investigate the mechanism, the *O*-acylated nitrostyrene derivative **5aa** was also prepared (quantitative yields, 30 °C, 15 min.) from the substrate **1a**, PhCOCl, and Et_3N in CH_2Cl_2. The intermediate **5aa** was tested in the reaction with **4a** (20 mol %) and $PhSiH_3$ in the absence of Et_3N in toluene at 100

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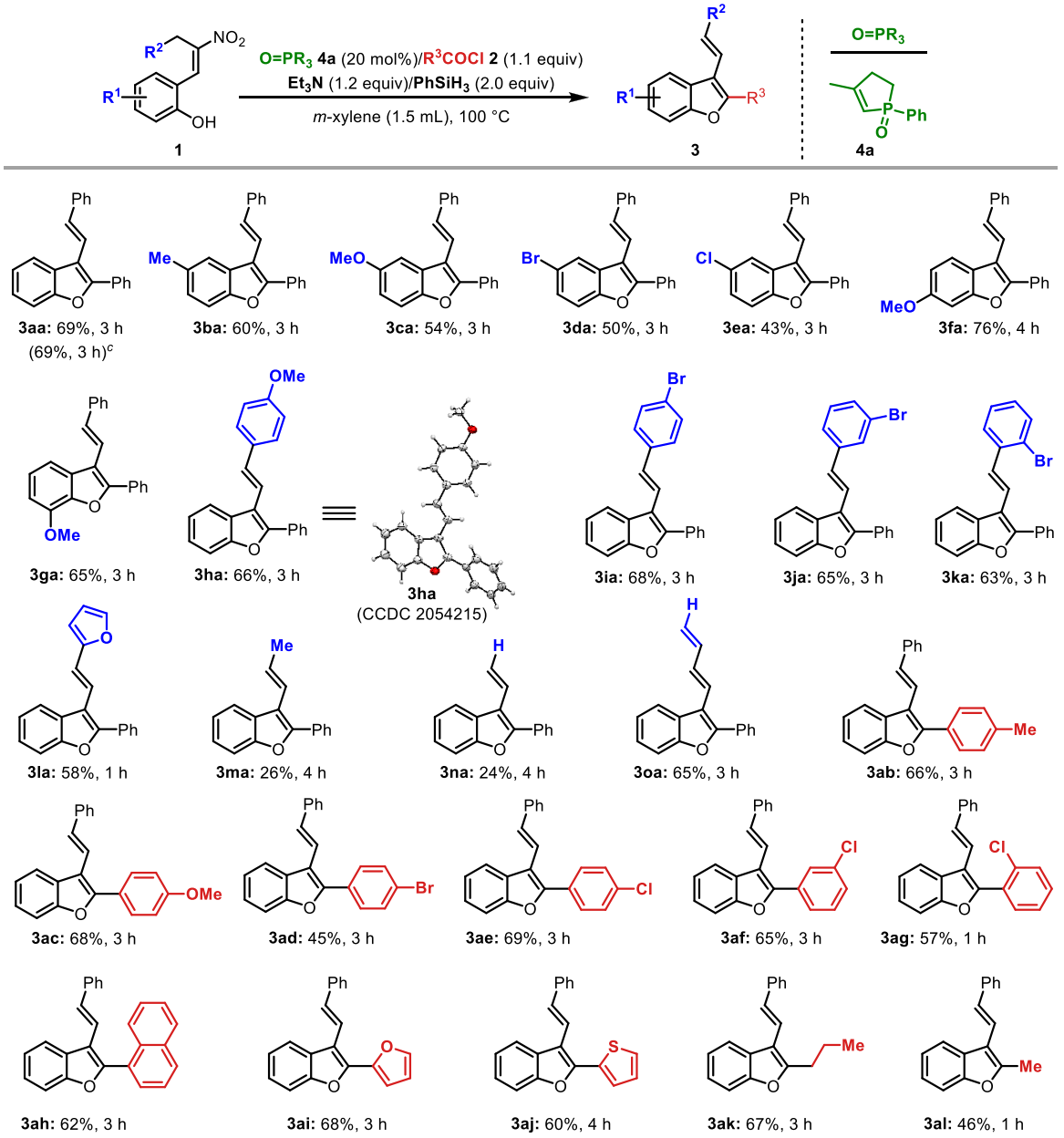
Scheme 2. Substrate Scope of 3-Alkenyl Benzofurans[a,b]

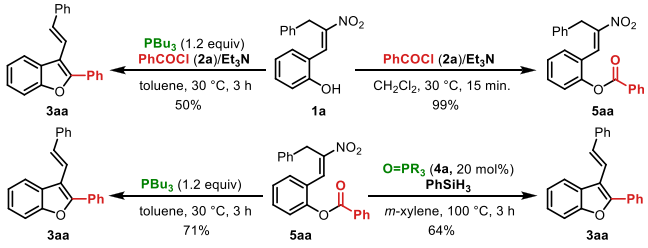


[a]The reactions were performed with nitrostyrene **1a** (0.3 mmol), O=PR_3 **4a** (20 mol %), PhCOCl **2a** (1.1 equiv), Et_3N (1.2 equiv), and $PhSiH_3$ (2.0 equiv) sequentially in *m*-xylene (1.5 mL) under argon atmosphere at 100 °C. [b]Isolated yield of **3**. [c]Performed a gram-scale reaction (**1a**: 4 mmol, 1.0 g).

°C. The 3-alkenyl benzofuran derivative **3aa** was obtained in 64% yield in 3 h. Similar results were also found by employing stoichiometric amount of PBu_3 and **5aa** in toluene at 30 °C (Scheme 3). It clearly indicates that the Wittig reaction demonstrated in our protocol is a base-free Wittig reaction, and only 1.2 equiv of base was required for the initial *O*-acylation of **1a** to generate *O*-acylated derivative **5aa**.

Based on the results and the control experiments, a plausible mechanism is depicted in Scheme 4. Initially, the *O*-acylation occurred to generate the intermediate **5** from substrate **1** and acyl chloride **2** in the presence of Et_3N. The phospha-Michael addition reaction of phosphine to **5**, in which phosphine was *in-situ*-generated from the chemoselective reduction of **4a** with $PhSiH_3$, would provide the phosphonium species **Ia**. The

Scheme 3. Control Experiments for the Base-Free Wittig Reaction



subsequent H-shift of **Ia** would generate the phosphorus ylide **Ib**. The crucial conjugated ylide **III** was generated either from the cleavage of C−NO_2 bond of ylide **Ib**, and further

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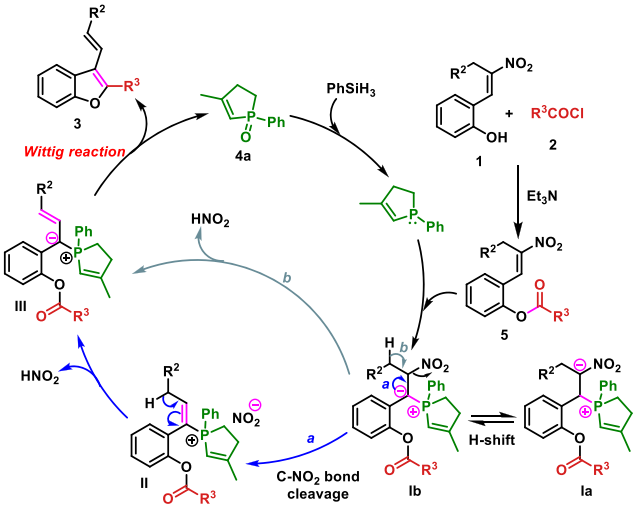
Scheme 4. Plausible Mechanism for the Synthesis of 3-Alkenyl Benzofuran 3



elimination of nitrous acid from the phosphonium salt **II** (Path a), or the direct eviction of HNO_2 from the ylide **Ib** (Path b). Note that the phosphonium salt **II** was found in ESI-HRMS analysis when the reaction was performed with substrate **1n** and acyl chloride **2a** in the presence of **4a** (50 mol %) under the standard conditions.[12] Finally, the intramolecular Wittig reaction of ylide **III** proceeded to result in the desired 3-alkenyl benzofurans **3**.

In summary, we have demonstrated a novel catalytic Wittig protocol for synthesis of 3-alkenyl benzofurans in moderate to good yields under metal-free conditions. The highly functionalized 3-alkenyl benzofurans were provided by in situ elimination of HNO_2 along with the Wittig reaction under our reaction conditions. The highly chemoselective reduction of phosphine oxide has been achieved by using $PhSiH_3$ without affecting of electron-deficient olefins and acyl chlorides in our protocol. This methodology could be scaled-up for the preparation of substantial quantitative of 3-alkenyl benzofuran derivatives. Further exploration of this protocol for synthesis of other multifunctional heteroarenes is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00737.

Optimization data, control experiments, experimental procedures, characterization data and spectra of all compounds (PDF)

Accession Codes

CCDC 2054215 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(12) The reaction of substrate **1n** and acyl chloride **2a** has been examined in the presence of **4a** (50 mol %) under the standard conditions. After 1 h, the reaction mixture was monitored by the ESI-HRMS analysis. The phosphonium salt **II** was found in ESI-HRMS analysis (see the Supporting Information for the experimental details). It indicated that path a is more likely to happen than path b for formation of **III**.

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