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Palladium-catalyzed substitution of allylic alcohols with sulfinate salts: A synthesis of bicalutamide

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ABSTRACT

A method is presented for the direct substitution of allylic alcohols with sodium arylsulfinates. The process involves a cooperative action of palladium catalysts, phenylboronic acid and titanium tetraisopropoxide. By taking advantage of this protocol, we achieved a concise synthesis of bicalutamide, an anti-androgen compound for treating prostate cancer.

Sulfones are versatile synthetic intermediates and frequently encountered structural motifs in pharmaceutical agents, agrochemicals and polymer materials [1]. The versatility of a sulfonyl group stems from its transformative ability to masquerade as electrophiles, nucleophiles, or radicals [2]. Moreover, sulfones play a major role in several name reactions (e.g. Julia olefination, Ramberg–Bäcklund reaction, van Leusen reaction, etc.). Given their importance, practical and efficient syntheses of sulfones continue to attract interest from researchers [3] . In particular, extensive efforts have been devoted to the preparation of allylic sulfones as a highly useful building block in various synthetic applications [4].

Trends in green and sustainable chemistry have justified the use of allylic alcohols in allylation chemistry. Despite the fact that the hydroxyl group is intrinsically a modest leaving group in the substitution reactions, chemists have elegantly developed *in situ* activation of unactivated allyl alcohols thus enabling a series of step-economical transformations [5]. For instance, Lewis or Brønsted acid-promoted sulfonylation reactions of allylic alcohols with appropriate sulfur nucleophiles have been reported [6]. But these protocols are mainly applicable to aryl-substituted allyl alcohols that can yield resonance-stabilized carbocationic electrophiles. On the other hand, metal catalysis-enabled approaches hold great promise for attaining satisfactory reaction scope [7]. Chandrasekhar and co-workers described the first palladium-catalyzed conversion of allylic alcohols to the corresponding allyl sulfones by engaging triethylborane as an additive for the hydroxyl group activation [8]. The Tian group subsequently showed a stereospecfic substitution of enantioenriched allylic alcohols with sodium sulfinates by cooperative actions of palladium catalysts and boric acid [9]. More recently, the Loh and Ma groups independently demonstrated dehydrative cross-coupling reactions of sulfinic acids with a range of allylic alcohols under palladium catalysis [10], but the procedures are arguably less straightforward than those employing readily available, bench-stable sulfinate salts as the sulfonyl donor [11]. Nevertheless, these leading reports endorse the continued interest and demand for developing catalytic synthesis of allylic sulfones from alcohol precursors. We have successfully applied the [Pd]/[Ti(IV)] systems [12,13] for the direct nucleophilic substitution of allylic alcohols with sterically demanding secondary nitroalkanes (C-nucleophile) [14], and for a highly N1-selective allylation of indoles (*N*-nucleophile) [15]. These studies showcased unique synthetic potentials of the catalytic system and thereby prompted us to survey the capacity of other heteroatom-based nucleophiles within this context. In the event, sulfinate salts emerged as a competent reaction partner. Here we disclose our pursuit of the palladium-catalyzed sulfination of unactivated allylic alcohols exploiting titanium tetraisopropoxide as an inexpensive and mild additive.

Initially we screened the combination of palladium diacetate and different organophosphorus ligands (SPhos, DavePhos, DPEPhos,

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0040-4039/

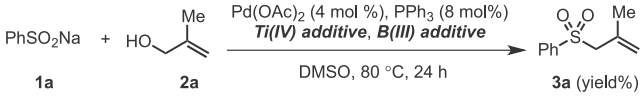
dppe, P(2-furyl)$_3$, and PPh_3) to promote the Ti(IV)-assisted substitution of a model substrate **2a** with sodium benzenesulfinate (Table 1). Triphenylphosphine was proven the most effective among the surveyed monodentate and bidentate ligands (entry 1). The control experiments convincingly indicated that both $Pd(OAc)_2$ and Ti(O*i*-Pr)$_4$ are indispensable to the success of the transformation, thus supporting the synergistic effects posed by the combination (entries 2 and 3). The allylation with tetrakis(triphenylphosphine)palladium in lieu of $Pd(OAc)_2$ and PPh_3 gave a trace amount of the product. Replacing $Pd(OAc)_2$ with $Pd(dba)_2$ under otherwise identical conditions furnished **3a** in only 10% yield. An increase on reaction temperature to 100 °C or a change of solvent to DMF did not provide higher yields of **3a**. Altering the loadings of Ti(O*i*-Pr)$_4$ or replacing Ti(O*i*-Pr)$_4$ with other titanium(IV) alkoxides ($Ti(OMe)_4$, $Ti(OEt)_4$, or Ti(O*t*-Bu)$_4$) failed to offer improved results. After extensive experimentation, we serendipitously found that the addition of phenylboronic acid is beneficial to the allylation of **2a**. The reaction having 150 mol % of phenylboronic acid as the additive was particularly productive (entries 4–6). The experiments conducted in the absence of Ti(O*i*-Pr)$_4$ only furnished a trace amount of **3a** (entry 7), so we confirmed that the titanium(IV) reagent is still primarily responsible for the activation of hydroxyl group even in the presence of phenylboronic acid. We also examined the reactions with boric acid and 4-methoxyphenylboronic acid, and the results showed that these additives are less effective than phenylboronic acid. Regarding to the role of phenylboronic acid, it may serve as a weak acid to quench expelled $(RO)_3TiO^-$ during the formation of palladium π-allyl complex [16]. The allylation using different equivalents of **2a** gave comparable yields (entries 8 and 9).

Next, we set out to examine the reaction of **2b**-**k** with sulfinate salts **1a**-**d**. Of special interest is to compare reactivity of allylic alcohols of different substitution patterns in the reaction system (Table 2). We found that reactivity of **2b**-**k** is lower than **2a**, and therefore it requires the use of 2 or 6 equivalents of the alcohols for better performance. In general, the arylsulfone group was regioselectively installed at the less hindered terminus of the allyl moiety. The reactions of cinnamyl alcohol (**2b**) and α-vinylbenzyl alcohol (**2c**) gave product **3b** in comparable yields. Other cinnamyl-type substrates **2d** and **2e** bearing a *para*-substituent of different electronic properties were uneventfully converted to the corresponding products **3c** and **3d**. Interestingly, the synthesis of **3e** from prenyl alcohol (**2f**) proceeded with much lower efficiency than that with its congener **2g**. Geraniol (**2h**) and linalool (**2i**) were also subjected to the reaction conditions, delivering product **3f** in moderate yields. For these stericallly more demanding substrates (**2h** and **2i**), the use of 6 equiv of alcohols was critical for achieving the mentioned results. The reaction of **2j** furnished an inseparable *trans*/*cis* mixture of crotyl sulfones (3.5:1), and a similar product distribution was seen with the reaction of **2k**. Since the isomeric alcohols were converted into the same corresponding products (see entries 5–10), we presumed common π-allylpalladium intermediates were involved in these sets of cases. Also, we noted a subtle reactivity difference between these isomeric allylic alcohols (cf. **2f**/**2g**, **2h**/**2i**, and **2j**/**2k**); more specifically, the one bearing a more substituted carbinol group, (i.e. with a less substituted alkenyl moiety) reacts more favorably in the allylation processes. Other arylsulfinate salts **1b**-**d** worked equally well under the conditions (entries 11–14).

There has been a long-standing interest in exploring sulfur(VI)-containing compounds in medicinal chemistry [17]. Being one of sulfone-derived chemotherapeutic agents, racemic bicalutamide (**4**) is the active pharmaceutical ingredient in Casodex [18]. This small molecule drug is a nonsteroidal anti-androgen for the treatment of prostate cancer [19]. Accordingly, the development of an efficient and practical access to **4** is certainly of great significance [20]. Motivated by this concern, we sought to establish a new synthetic route to bicalutamide (**4**) by exploiting compound **3k** accessed by our method (Scheme 1). The alkene within **3k** provides a synthetic handle for the installation of key tertiary alcohol through an oxidation reaction. In the event, compound **5** could be prepared by Upjohn dihydroxylation in good yield [21]. The TEMPO-catalyzed conversion of diol **5** into α-hydroxy acid **6** was achieved in 94% yield [22]. Subsequent to the oxidation was an amide coupling between **6** and 4-amino-2-(trifluoromethyl)benzonitrile, thus completing the synthesis of racemic bicalutamide (**4**) in 84% yield [23]. The spectral data (^1H and ^{13}C NMR) of synthetic **4** are in good agreement with those reported in the literature [20b].

In summary, we present the catalytic approach to a range of allyl aryl sulfones. The palladium catalyst and the titanium reagents act synergistically to generate π-allylpalladium species

Table 1
Evaluation of conditions.

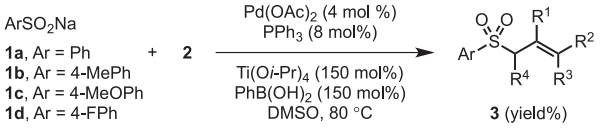


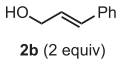
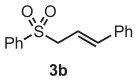
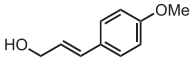
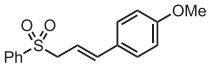
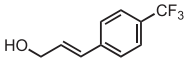
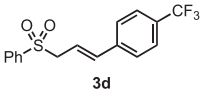
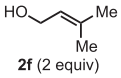
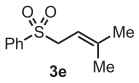
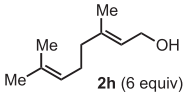
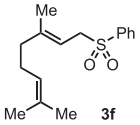
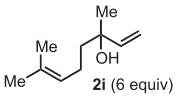
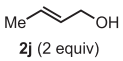
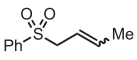
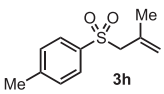
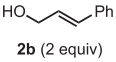
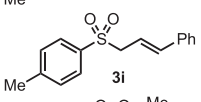
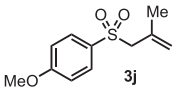
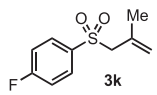
1a **2a** **3a** (yield%)

entry	equiv of **2a**	Ti(IV) additive (mol %)	B(III) additive (mol %)	yield (%)[a]
1	1.1	Ti(O*i*-Pr)$_4$ (150)	–	46
2	1.1	–	–	N.R.
3[b]	1.1	Ti(O*i*-Pr)$_4$ (150)	–	N.R.
4	1.1	Ti(O*i*-Pr)$_4$ (150)	$PhB(OH)_2$ (150)	68
5	1.1	Ti(O*i*-Pr)$_4$ (150)	$PhB(OH)_2$ (100)	62
6	1.1	Ti(O*i*-Pr)$_4$ (150)	$PhB(OH)_2$ (50)	37
7	1.1	–	$PhB(OH)_2$ (150)	N.R.
8	2	Ti(O*i*-Pr)$_4$ (150)	$PhB(OH)_2$ (150)	64
9	6	Ti(O*i*-Pr)$_4$ (150)	$PhB(OH)_2$ (150)	66

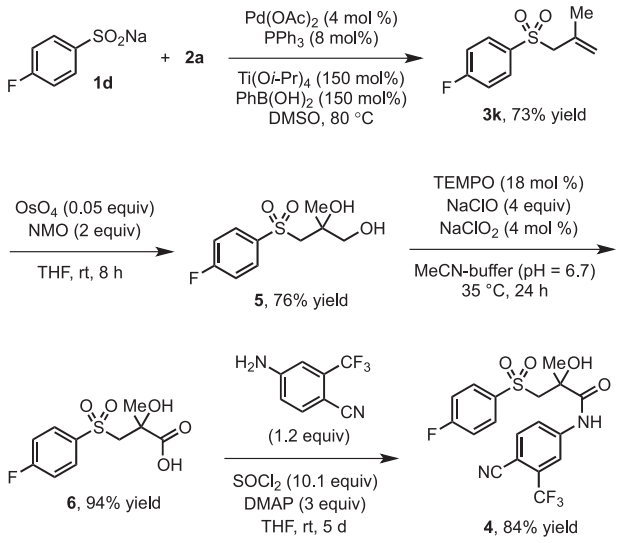
[a] Isolated yield.
[b] Without $Pd(OAc)_2$ and PPh_3. N.R. = no reaction.

Table 2
Reaction scope.



entry	1	allyl alcohol	product(s)	yield (%)[a]
1	**1a**	 **2b** (2 equiv)	 **3b**	75
2	**1a**	 **2c** (2 equiv)		67
3	**1a**	 **2d** (2 equiv)	 **3c**	70
4	**1a**	 **2e** (2 equiv)	 **3d**	54
5	**1a**	 **2f** (2 equiv)	 **3e**	21
6	**1a**	 **2g** (2 equiv)		60
7	**1a**	 **2h** (6 equiv)	 **3f**	35
8	**1a**	 **2i** (6 equiv)		45
9	**1a**	 **2j** (2 equiv)		49[b]
10	**1a**	 **2k** (2 equiv)	**3g** (trans)/**3g'** (cis)	63[b]
11	**1b**	 **2a** (2 equiv)	 **3h**	65
12	**1b**	 **2b** (2 equiv)	 **3i**	72
13	**1c**	 **2a** (1.1 equiv)	 **3j**	57
14	**1d**	 **2a** (2 equiv)	 **3k**	73

[a] Isolated yield.
[b] An inseparable mixture. **3g**:**3g'** = 3.5:1 (determined by NMR analysis).



Scheme 1. Synthesis of Bicalutamide.

for the allylation event. The addition of phenylboronic acid was serendipitously found to enhance the overall efficiency, and we verified by control experiments that titanium reagent is primarily responsible for the activation of hydroxyl moiety. The synthetic capacity of the [Pd]/[Ti(IV)] system is thus expanded enabling the direct allylation of sulfinate nucleophiles. In this S—O bond-forming reaction, all reagents used are commercially available and inexpensive, and the procedure is operationally simple. Of note is that the performances of isomeric allylic alcohols are quite different even though the reactions are presumed to involve a same π-allyl palladium intermediate. A protecting group-free synthesis of bicalutamide was also achieved further highlighting the utility of this method.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153060.

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