



## Cesium carbonate mediated aryl triflate esters' deprotection



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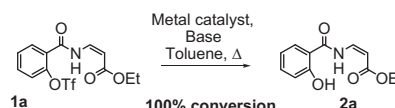
### ABSTRACT

A variety of diversely substituted aryl triflate esters were efficiently deprotected to the parent phenols by exposure to cesium carbonate in toluene. This procedure proved highly compatible with existing functional groups.

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Praised for their oxidoreductive and acidobasic properties, phenols and their derivatives have found use in numerous and multifarious industrial applications, namely dyes, food antioxidants, pharmaceuticals, or polymers. However, synthetic chemistry of phenolic-based compounds usually requires to temporarily shut down their reactivity and to derivatize the hydroxyl moiety with a protecting group. Among the plethora of existing methods,<sup>1a</sup> alkyl/silyl ethers (–OMe, –OMOM, and –OTBDMS) are by far the most represented. Their removal is generally carried out in the presence of a Brønstedt or Lewis acid whereas also commonly used alkyl/aryl esters (–OAc and –OBz) get cleaved in basic media. More seldom, sulfonate esters, and particularly trifluoromethanesulfonates, have been exploited as efficient alternatives to conventional protecting groups for phenols.<sup>1b</sup> Owing to their high stability under a wide range of experimental conditions, they provide ample space for 'extended' chemistry but are not devoid of several drawbacks. Only a few procedures, typically involving strong reductive conditions or the use of hard nucleophiles to effect the S–O bond cleavage, are available in the literature and not always compatible with the presence of other sensitive functional groups.

For example, Katzenellenbogen and co-workers took advantage of the inertness of the estrogen core to cleave an aryl triflate ester under harsh conditions using either a large excess of LiAlH<sub>4</sub> or NaOH.<sup>2</sup> It was also mentioned that partial deprotection could occur in acceptable yields upon exposure to a fluoride anion source as <sup>n</sup>Bu<sub>4</sub>NF.<sup>3</sup> Upon their study of aromatic nucleophilic substitution reactions between aryl triflates and secondary amines, Schio et al. evidenced that aminolysis of aromatic trifluoromethanesulf-



**Scheme 1.** Quantitative cleavage of triflate ester **1a**.

onates was possible with primary amines.<sup>4</sup> More recently, a mild and highly efficient method related to hydrolysis was proposed by Nishiyama and co-workers upon treatment with Et<sub>4</sub>NOH in wet dioxane.<sup>5</sup>

In the course of our investigations aimed at synthesizing highly functionalized isoindolinones, a variety of enamides as exemplified with **1a** were submitted to a set of different metal catalyzed coupling reactions under anhydrous conditions (freshly distilled and degassed solvents, dried reagents). Due to their sluggish reactivity, we were able to notice that whenever cesium carbonate was used as a base, triflates were quantitatively converted to the parent phenol within a few hours (Scheme 1).

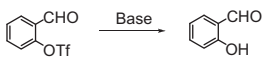
This result prompted us to study the details, scope, and limitations of the reaction with the aim of proposing a new procedure for the mild deprotection of aryl triflate esters.

Salicylaldehyde was initially selected as a model substrate for a short screening of experimental conditions (Table 1). The study confirmed that 3 equiv of Cs<sub>2</sub>CO<sub>3</sub> with heating to 80 °C was required for complete conversion of the starting material in a decent period of time (Table 1). A decrease to a single equivalent (entry 3) resulted in partial reaction within a similar timeframe. Trapping water traces with molecular sieves 4 Å (entry 4) was of no consequence for the conversion. The nature of the base seemed to be

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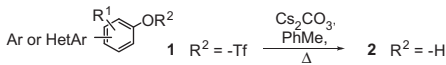
**Table 1**  
Optimization of the reaction conditions on salicylaldehyde

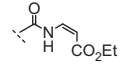




Conditions <sup>a</sup>	Time (h)/(°C)	Conv.	
1	No base	15/80	0
2	Cs <sub>2</sub> CO <sub>3</sub> (3.0 equiv)	4/80	100
3	Cs <sub>2</sub> CO <sub>3</sub> (1.0 equiv)	15/80	33
4	Cs <sub>2</sub> CO <sub>3</sub> (3.0 equiv), mol. sieves (4 Å)	4/80	100
5	Cs <sub>2</sub> CO <sub>3</sub> (3.0 equiv)	120/rt	0
6	Na <sub>2</sub> CO <sub>3</sub> (3.0 equiv)	15/80	0
7	K <sub>2</sub> CO <sub>3</sub> (3.0 equiv)	15/80	0
8	K <sub>3</sub> PO <sub>4</sub> (3.0 equiv)	15/80	37
9	CsF (3.0 equiv)	15/80	22
10	Cs <sub>2</sub> CO <sub>3</sub> , H <sub>2</sub> O (3.0 equiv each)	120/rt	18
11	Cs <sub>2</sub> CO <sub>3</sub> (3.0 equiv), CH <sub>2</sub> Cl <sub>2</sub> (3 mL)	15/80	66
12	Cs <sub>2</sub> CO <sub>3</sub> (3.0 equiv), MeCN (3 mL)	15/80	100
13	Cs <sub>2</sub> CO <sub>3</sub> (3.0 equiv), THF (3 mL)	15/80	100

<sup>a</sup> Reactions set up in a sealed tube on a 0.3 mmol scale. In 3 mL of PhMe for entries 1–10.

**Table 2**  
Cleavage of the aryltrifluoromethanesulfonates<sup>a</sup>



Entry	R <sup>1</sup>	R <sup>2</sup>	Isol. yields % (conversion %)
1	3-Me	-Tf ( <b>1c</b> ) -H ( <b>2c</b> )	78 (100)
2	2-Br	-Tf ( <b>1d</b> ) -H ( <b>2d</b> )	25 (28 + 72 sm) <sup>b</sup>
3	3-OMe	-Tf ( <b>1e</b> ) -H ( <b>2e</b> )	32 (35 + 65 sm) <sup>b</sup>
4	4-CHO	-Tf ( <b>1f</b> ) -H ( <b>2f</b> )	86 (96)
5	2-CHO	-Tf ( <b>1b</b> ) -H ( <b>2b</b> )	100 (100)
6	3-NO <sub>2</sub>	-Tf ( <b>1g</b> ) -H ( <b>2g</b> )	85 (96)
7	4-CO <sub>2</sub> Me	-Tf ( <b>1h</b> ) -H ( <b>2h</b> )	87 (96)
8	2-NHAc	-Tf ( <b>1i</b> ) -H ( <b>2i</b> )	93 (100)
9		-Tf ( <b>1a</b> ) -H ( <b>2a</b> )	89 (100)
10		-Tf ( <b>1j</b> ) -H ( <b>2j</b> )	92 (100)
11		-Tf ( <b>1k</b> ) -H ( <b>2k</b> )	95 (100)

<sup>a</sup> 0.3 mmol scale of substrate/Cs<sub>2</sub>CO<sub>3</sub> (3.0 equiv)/toluene (5 mL/0.3 mmol of substrate), heating at 80 °C during 15 h unless otherwise specified.

<sup>b</sup> Reactions were conducted at 130 °C (oilbath temp).

crucial as anhydrous Na<sub>2</sub>CO<sub>3</sub> or K<sub>2</sub>CO<sub>3</sub> (entries 6 and 7) was found to be totally ineffective whereas K<sub>3</sub>PO<sub>4</sub> (entry 8) afforded salicylal-

dehyde though in a modest 37% yield. Exposure to nucleophiles such as fluoride or hydroxide anions (entries 9 and 10) partially unveiled the phenols as previously observed by Katzenellenbogen<sup>2,3</sup> or Nishiyama.<sup>5</sup> We finally examined the importance of the solvent. Although THF and MeCN (entries 12 and 13) proved to be appropriate for this reaction, the choice of toluene was mainly driven by the good solubilities of the phenols, ease of purification, and highest boiling point.

As shown in Table 2, our typical procedure<sup>6</sup> could be successfully applied to a set of diversely substituted aryl triflates. Conversions measured by <sup>1</sup>H NMR showed complete consumption of the starting material with the exception of compounds **1d** and **1e** that were partly recovered after work-up. The weak electron-withdrawing character of bromide or the strong electron-donating effect of the methoxy group might account for their low reactivity toward deprotection even after prolonged times of reaction or treatment with larger excesses of base.<sup>7</sup> Our conditions proved however compatible with all other type of substituents. Interestingly, functional groups prone to hydrolysis as esters **1h** and **1a**, N-branched **1i**, or C-branched **1a** amides were spared during the cleavage. 2-Chloropyridine **1k**, an heterocyclic structure known to easily undergo S<sub>N</sub>Ar in the presence of nucleophiles,<sup>8</sup> remained unaffected as well as quinoline **1j**.

In summary, we have developed an efficient protocol for the cleavage of aryl trifluoromethanesulfonates. Neither hard nucleophile nor strong reductive conditions are required thus making our approach mild and chemoselective. Despite existing limitations for some substitution patterns, this work also highlights the importance in the choice of the base for palladium catalyzed cross-coupling reactions with triflates.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2013.10.087>.

## References and notes

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- Typical experimental procedure for deprotection of aryl triflate esters*: To a solution of aryl triflate **1a–k** (0.3 mmol) in toluene (5 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (3 equiv). The suspension was heated at 80 °C (oilbath temp) during 15 h. The crude mixture was quenched with ethyl acetate (~5 mL) and a saturated aqueous solution of ammonium chloride (~10 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL). Organic layers were then combined, dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford the corresponding phenol that was purified by flash chromatography over silica gel.
- To a lesser extent, same tendency was observed by Nishiyama in the presence of <sup>n</sup>Bu<sub>4</sub>NF.
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