

# Synthesis of 4-substituted tetrahydropyridines by cross-coupling of enol phosphates

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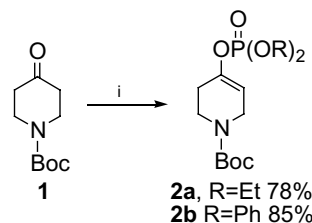
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**Abstract**—Enol phosphates, synthesized from 4-piperidone, react by palladium catalyzed cross-coupling with arylboronic acids and by iron and palladium catalyzed cross-coupling with Grignard reagents to give 4-substituted tetrahydropyridines.  
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Enol phosphates have, in a few cases, proved to work better in cross-coupling reactions than their triflate counterparts due to higher stability, higher yield and easier work up.<sup>1</sup> Enol phosphates have been used in Suzuki,<sup>2</sup> Stille,<sup>2f,3</sup> Negishi<sup>4</sup> and Kumada-Tamao<sup>5</sup> cross-coupling reactions, and have been applied in total synthesis.<sup>6</sup> However, apart from a single exception,<sup>2a</sup> only activated (electron poor) enol phosphates have been used in Suzuki cross-coupling reactions. Unfavourable oxidative addition to the catalyst probably explains the limited application of enol phosphates. Considering the continuous development of phosphine ligands increasing the reactivity of aryl chlorides in cross-coupling synthesis,<sup>7</sup> we found it interesting to determine whether these ligands could enlarge the scope of enol phosphates in cross-coupling synthesis as well.

We now report the first Suzuki cross-coupling reactions of enol phosphates, which take advantage of a highly activated palladium catalyst designed for cross-coupling of deactivated aryl chlorides. In addition, we report iron and palladium catalyzed cross-coupling among enol phosphates and Grignard reagents. The cross-coupling reactions provide 4-substituted tetrahydropyridines.

The enol phosphates **2a** and **2b** were prepared in 78% and 85% yields from the potassium enolates of *N*-Boc-4-piperidone (**1**) (Scheme 1).



**Scheme 1.** Reagents and conditions: (i) **1**, CIP(O)(OR)<sub>2</sub> (1.2 equiv), HMPA (1.4 equiv), KHMDS (1.3 equiv), THF, −78 °C, 2 h.

Palladium tetrakis(triphenylphosphine) usually serves well as a catalyst in cross-coupling reactions between boronic acids and enol phosphates but did not work in the present case. Pd(OAc)<sub>2</sub>/BINAP, Pd(PPh)<sub>3</sub>Cl<sub>2</sub> and Pd(OAc)<sub>2</sub>/tri-*tert*-butylphosphine<sup>8</sup> failed to promote the cross-coupling as well. However, Pd(OAc)<sub>2</sub>/2-(di-*tert*-butylphosphino)biphenyl<sup>9</sup> (Buchwald's ligand) effected cross-coupling using diphenyl phosphate **2b** as the starting material affording *N*-Boc-4-aryl-1,2,3,6-tetrahydropyridine (**3**) (Table 1) in moderate yields. Optimized conditions were found to entail microwave assisted heating at 150 °C for 5 min with 5 mol% of catalyst and KF as base in a 1:1 solution of DME:water (Table 1).

The conditions were quite critical. The reaction only proceeded when boronic acids were applied as starting materials, while boronic esters failed to react. Diethyl phosphate **2a** gave only traces of cross-coupling products. The use of other solvents like toluene, THF,

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**Table 1.** Synthesis of 4-aryl tetrahydropyridines

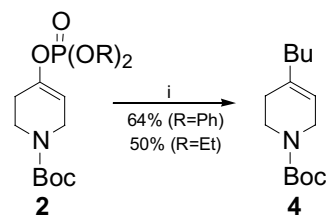
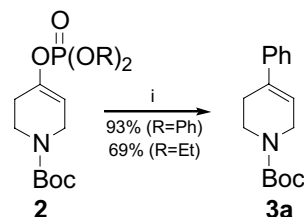
Entry	Ar	Product	Yield (%)
1		<b>3a</b>	48
2		<b>3b</b>	46
3		<b>3c</b>	49
4		<b>3d</b>	45
5		<b>3e</b>	0
6		<b>3f</b>	29
7		<b>3g</b>	25
8		<b>3h</b>	28

Reagents and conditions: (i) **2b**, ArB(OH)<sub>2</sub> (1.2 equiv) KF (3.8 equiv), 2-(di-*tert*-butylphosphino)biphenyl (6 mol%), Pd(OAc)<sub>2</sub> (5 mol%), H<sub>2</sub>O/DME, 150 °C, 5 min.

dioxane and EtOH or other bases such as Na<sub>2</sub>CO<sub>3</sub>, NaOH and Et<sub>3</sub>N resulted in lower yields. Yields also dropped significantly at temperatures below 120 °C or above 160 °C. The yields were influenced both by steric and electronic effects. Thus a substituent at the 2-position of the arylboronic acids impeded cross-coupling (Table 1, entry 5). Electron attracting substituents led to lower cross-coupling yields (Table 1, entries 6–8), while electron donating substituents at C-3 and C-4 did not influence the yield (Table 1, entries 2–4).

Grignard reagents have been subjected to cross-coupling reactions with enol phosphates using nickel, palladium and iron catalysis.<sup>10</sup> In this particular case, the enol phosphates **2a** and **2b** did not react with butyl magnesium bromide under Pd-catalysis, while Fe(III)acac catalysis afforded *N*-Boc-4-butyl-1,2,3,6-tetrahydropyridine **4** (Scheme 2).

Under similar conditions, reaction of **2a** and **2b** with phenyl magnesium bromide gave only traces of cross-coupling products, while Pd-catalysis gave good yields of *N*-Boc-4-phenyl-1,2,3,6-tetrahydropyridine **3a** (Scheme 3). Complete consumption of starting material required addition of TMEDA. It is believed that TMEDA, by complexation of the Mg-ions formed during the reaction, enhance the process. NMP, which reportedly

**Scheme 2.** Reagents and conditions: (i) **2**, BuMgCl (2.0 equiv), TMEDA (2.0 equiv), Fe(acac)<sub>3</sub> (6 mol%), THF, -10 °C → 0 °C, 1 h.**Scheme 3.** Reagents and conditions: (i) **2**, PhMgCl (2.0 equiv), TMEDA (2.0 equiv), Pd(PPh<sub>3</sub>)Cl<sub>2</sub> (3 mol%), THF, 40 °C, 1 h.

has been used for this purpose,<sup>11</sup> did not improve our yields. The phenyl phosphate **2b**, which has to be stored cold and under argon, gave better cross-coupling yields than the corresponding shelf stable ethyl phosphate **2a** (Schemes 2 and 3).

Enol phosphates derived from 4-piperidones are easy to prepare. They are versatile starting materials in efficient palladium or iron catalyzed cross-coupling reactions giving access to a range of 4-substituted tetrahydropyridines. The highly activated catalyst Pd(OAc)<sub>2</sub>/2-(di-*tert*-butylphosphino)biphenyl has been used for the first time to promote Suzuki cross-coupling reactions with non-activated enol phosphate which otherwise fail to react.

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### Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2005.03.203](https://doi.org/10.1016/j.tetlet.2005.03.203).

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