

Nickel-Catalyzed Cross-Couplings of Cyclohexenyl Phosphate and Arylboronic Acids

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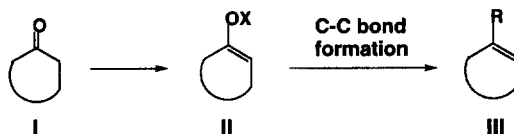
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Abstract: The Nickel-catalyzed cross-coupling reaction of cyclohexenylphosphate with a variety of arylboronic acids is described here for the first time. This methodology opens the door to other palladium or nickel-catalyzed coupling reactions involving vinyl phosphates. © 1999 Elsevier Science Ltd. All rights reserved.

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Recently, the synthetic chemistry community has witnessed significant progress in the development of the Suzuki reaction for cross-coupling of arylboronic acids with aryl chlorides,^[1] bromides, iodides, and triflates.^[2] The functionalization of ketones (I, Figure 1) via their corresponding vinyl derivatives (II) to afford substituted olefin (III) through this reaction has been one of the most useful carbon-carbon bond-forming reactions in organic synthesis. Current methodology for the process involves vinyl triflates (II, X = SO₂CF₃), which suffer from the high expense of the triflating agent (*N*-phenyltrifluoro-methane sulfonimide, 5g/\$ 34.40),^[3] and the difficulty of separating the generated vinyl triflates from the byproduct of the reagent.^[4]

Figure 1. Model of cyclic ketone functionalization.

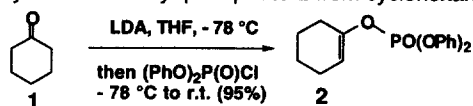


Arylboronic acids are especially valuable as a partner in the cross-coupling reaction due to their ready availability and environmentally friendly features. The recent discoveries that vinyl or ketene acetal phosphates undergo couplings with organo-stannanes,^[5] -aluminum,^[6] -magnesium^[7] and -cuprates^[8], as well as reductive cleavage by Li/NH₃,^[9] prompted us to study the related reaction of arylboronic acids with vinyl phosphates.

Application of the Suzuki reaction for the cross-coupling of vinyl phosphates (II, X = PO(OPh)₂) with arylboronic acid catalyzed by nickel (0) to generate III has to the best of our knowledge not been previously developed. Here we describe the preparation of cyclohexylphosphate 2 (Scheme 1) by treating 1 with the low-cost phosphorylating reagent (diphenyl chlorophosphate, 500g/\$ 63.45, Aldrich)

and its successful reaction with a series of arylboronic acids to prepare a variety of aryl substituted cyclohexenes.

Scheme 1: Synthesis of vinyl phosphate **2** from cyclohexanone **1**.

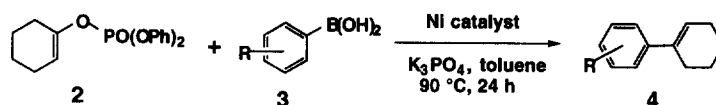


The cyclic vinyl phosphate **2** (Scheme 1) was synthesized in 95% yield from cyclohexanone **1** via its lithium enolate (1.2 equiv of lithium diisopropylamide, LDA) and $(\text{PhO})_2\text{P}(\text{O})\text{Cl}$ (1.2 equiv) in THF at $-78\text{ }^\circ\text{C}$, followed by warm to room temperature. Diphenyl chlorophosphate $[(\text{PhO})_2\text{P}(\text{O})\text{Cl}]$ showed significant advantages over *N*-phenyltrifluoromethane sulfonimide $[\text{PhN}(\text{Tf})_2]$ not only in the high yield obtained, but also in the ease of removal of excess diphenyl chlorophosphate (treatment of the reaction mixture with 5% ammonium hydroxide solution for 20 min at rt). Thus, the pure vinyl phosphate product can be easily obtained by silica gel flash chromatography.

A variety of palladium catalysts were initially used to attempt to promote the cross-coupling between cyclohexenyl phosphate **2** and phenylboronic acid, but at most a trace amount of coupling product was observed. It is possible that the vinyl phosphate **2** is not active enough to oxidatively add vinyl phosphate to the palladium (0) complex.

Recent reports^[10] demonstrated the efficiency of a nickel (0) catalyst for the cross-coupling reaction of less reactive chloroarenes and arenesulfonates with Grignard reagents and arylboronic acids. Thus, by employing the nickel (0) catalyst,^[10a] we successfully generated a variety of aryl-substituted cyclohexenes from cyclohexenyl phosphate **2** and arylboronic acids. Scheme 2 illustrates this general synthetic transformation.

Scheme 2: Synthesis of aryl-substituted cyclohexenes.

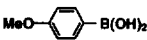
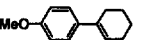

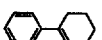

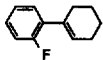
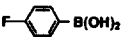
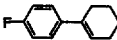
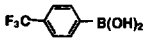
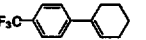
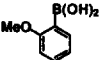
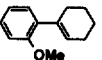
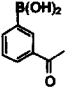
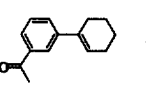

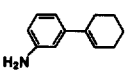

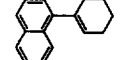

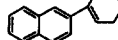


In order to evaluate solvent effects in the cross-coupling reaction, we tested a variety of solvents in the reaction. Dioxane as solvent produces the coupling product in approximately 30% yield; DME and DMF give product yield of 15% and 0%, respectively. Coupling yields of 70-80% have been achieved by carrying out these reactions in toluene at $90\text{ }^\circ\text{C}$ for 24 h. As indicated in Table 1, the reaction is applicable to a wide range of arylboronic acids having an electron-withdrawing or electron-donating group.

The chemistry described above demonstrates the usefulness of vinyl phosphate **2** as a stable and easily accessible substrate, that can undergo the nickel (0) catalyzed cross-coupling with a variety of arylboronic acids to give aryl-substituted cyclohexenes. Further application of this chemistry to the large, medium and small ring systems is currently under way in our laboratory.

The following is a typical experimental procedure for the cross-coupling: A mixture of vinyl phosphate (entry 1, Table 1) (330 mg, 1.5 mmol), K_3PO_4 (637 mg, 3.0 mmol) and dppf [1,1'-bis(diphenylphosphino)ferrocene] (28 mg, 0.05 mmol) was added into pressure tube, capped with a rubber septum. The Ni(0) catalyst^[10a] was made by reducing $NiCl_2(dppf)$ {[1,1'-bis(diphenylphosphino)ferrocene]dichloronickel(II)} (34 mg, 0.05 mmol) in toluene (8 mL) with *n*-BuLi (2.5 M, 120 μ L, 0.3 mmol) at rt for 10 min. The solution was transferred into the pressure tube and the resulting mixture was degassed with argon for 10 min, and then sealed. The reaction mixture was heated with stirring at 90 °C for 24 h. After cooling, the reaction mixture was washed with water (2 x 1.0 mL), brine (1.0 mL) and dried over Na_2SO_4 . The solvent was removed under vacuum and the residue was purified by flash chromatography (hexanes/ethyl acetate = 10/1) to give the product (154 mg, 82%) as a colorless oil.^[11]

Table 1. Nickel catalyzed cross-coupling of vinyl phosphate 2 with arylboronic acids

Entry	Arylboronic acid	Coupling Product ^a	Yield	Entry	Arylboronic acid	Coupling Product ^a	Yield
1			82%	6			71%
2			63%*	7			75%
3			62%	8			77%
4			31%*	9			81%*
5			75%	10			57%

^a isolated yield; * the yields are calculated based on the recovered enol phosphate.

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