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Suzuki–Miyaura cross-coupling of α-phosphoryloxy enol ethers with arylboronic acids

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This Letter is dedicated to Professor Hung-wen Liu on the occasion of his 55th birthday

ABSTRACT

The Suzuki–Miyaura cross-coupling reaction of cyclic ketene acetal phosphates with arylboronic acids was found to be a convenient and highly efficient method for the construction of aryl vinyl ethers. A wide variety of differentially substituted electron-poor and electron-rich arylboronic acids smoothly underwent the coupling process to provide the desired dihydropyrans in moderate to excellent yields.

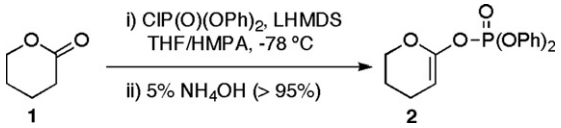
Transition-metal mediated cross-coupling reactions have emerged as powerful synthetic tools for the construction of a myriad of carbon–carbon bonds.[1] Of the various methodologies available, most require the use of alkenyl or aryl halides or trifluoromethanesulfonates as coupling partners. In particular, the functionalization of lactone substrates have relied heavily upon the formation of cyclic ketene acetal triflates for further derivitization. However, these intermediates often exhibit instability upon prolonged storage in addition to suffering from poor yields in their formation and in the subsequent coupling event.[2]

Recently, the development of enol and cyclic ketene acetal phosphates has emerged as attractive and more practical methodologies for the functionalization of lactam and lactone intermediates.[3] Nicolaou has illustrated the synthetic utility of cyclic ketene acetal phosphates in Stille cross-coupling reactions during his elegant synthesis of brevetoxin A,[3e] a causative agent of the red tide phenomena.[4–6] Additionally, Sasaki has demonstrated the efficiency of ketene acetal phosphates as coupling partners in *B*-alkyl Suzuki–Miyaura cross-coupling processes in the total synthesis of polycyclic ether secondary metabolites.[3f,h,j,l–n]

During the course of our research program aimed at the total synthesis and biological evaluation of structurally complex natural products, we required the synthesis of an aryl vinyl ether functionality. While there are methodologies available for the construction of this prevalent architectural motif,[7] we viewed the possibility of performing a Suzuki–Miyaura cross-coupling reaction employing cyclic ketene acetal phosphates with arylboronic acids as a mild and robust method that would also greatly expand the scope of this underutilized synthetic intermediate. To our knowledge, this methodology has not been explored and we now wish to report our early findings regarding this process.

With this in mind, we undertook our exploration into the application of cyclic ketene acetal phosphates in the Suzuki–Miyaura cross-coupling reaction with arylboronic acids by treating δ-valerolactone (**1**) with diphenylphosphoryl chloride followed by the addition of lithium bis(trimethylsilyl)amide (LHMDS) according to the procedure of Occhiato and Prandi as illustrated in Scheme 1.[3i]

Next, to study the feasibility of our proposed methodology, we initially surveyed several palladium catalysts. As can be seen from Table 1 (entries 1–5), we explored the use of $Pd(Ph_3P)_4$, $Cl_2Pd(Ph_3P)_2$, $Cl_2Pd(dppf)\cdot CH_2Cl_2$, $[allylPdCl]_2$, and $Pd_2dba_3\cdot CHCl_3$. Tetrakis(triphenyl)phosphine palladium(0) was clearly the superior catalyst cleanly producing the desired coupled product **4a** in over eighty percent yield without the production of any side products. We then focused our attention on examining the effects of various organic solvents and temperatures (entries 6–8) on the outcome of the reaction. Our findings indicated that both *N*,*N*-dimethylformamide (DMF, entry 1) and 1-methyl-2-pyrrolidinone (NMP, entry 8) were the most efficient at facilitating the Suzuki–Miyaura cross-coupling reaction of ketene acetal phosphate **2** with 3-nitrophenylboronic acid (**3a**). Further investigation (entry 9) aimed at using DMF as our reaction solvent revealed that the product yield could be increased by changing the base to potassium



Scheme 1. Synthesis of cyclic ketene acetal phosphate.

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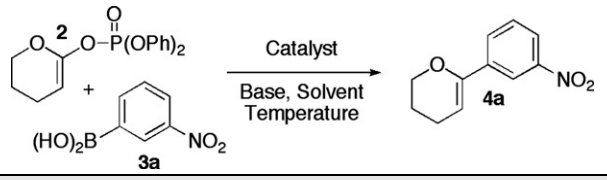
Table 1
Optimization of Suzuki–Miyaura cross-coupling reaction between cyclic ketene acetal phosphate 2 with 3-nitrophenylboronic acid (**3a**)



Entry[a]	Catalyst	Solvent	*T* (°C)	Yield (%)
1	$Pd(Ph_3P)_4$	DMF	**50**	82
2	$Cl_2Pd(Ph_3P)_2$			33
3	$Cl_2Pd(dppf)\cdot CH_2Cl_2$			27
4	$[allylPdCl]_2$			<5
5	$Pd_2dba_3\cdot CHCl_3$			No Rxn
6	$Pd(Ph_3P)_4$	THF	**65**	75
7		1,4-Dioxane	100	74
8		NMP	50	84
9[b]		DMF	50	88

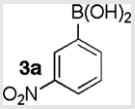
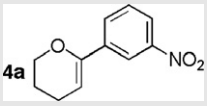
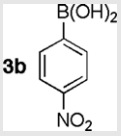
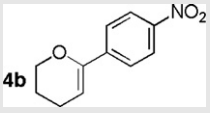
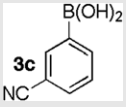
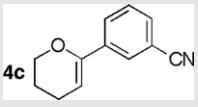
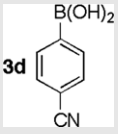
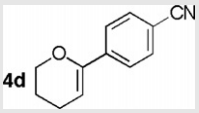
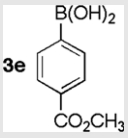
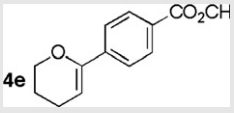
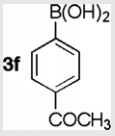
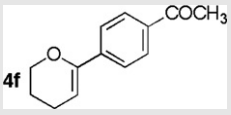
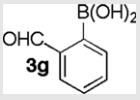
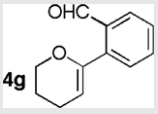
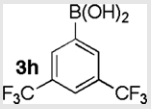
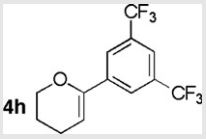
[a] All reactions were performed with 10 mol % of illustrated Pd source, 2.0 equiv of ketene acetal phosphate, 2.0 equiv of triethylamine, and 2.0 equiv of Na_2CO_3 (2.0 M) in the indicated solvent at the temperature listed.
[b] $Pd(Ph_3P)_4$ loading was reduced to 5 mol %. K_3PO_4 was used as base.

phosphate (K_3PO_4) from sodium carbonate (Na_2CO_3). Furthermore, reducing the catalyst loading from ten to five mole percent had negligible impact on the overall efficiency of the coupling process.

Having established the optimal reaction conditions, we embarked on a systematic study regarding the substrate scope. We were interested in exploring the functional group compatibility as well as the positioning of both electron-withdrawing (EWG) and electron-donating (EDG) groups on the arylboronic acid coupling partners. As illustrated in Table 2, the reaction is tolerant of a wide range of EWG's including nitro (NO_2, entries 1 and 2), cyano (CN, entries 3 and 4), ester (CO_2CH_3, entry 5), ketone (CH_3CO, entry 6), aldehyde (CHO, entry 7), and trifluoromethyl (CF_3, entry 8) functional groups. Furthermore, both *meta*- and *para*-substituted electron-withdrawing groups performed well under the reaction conditions affording the desired dihydropyrans in excellent yields. However, the use of *ortho*-substituted electron-withdrawing groups proved somewhat problematic. While 2-formylphenylboronic acid (**3g**) furnished the desired dihydropyran **4g** in a moderate, yet synthetically viable yield (Table 2, entry 7), the use of alternative arylboronic acids bearing *ortho*-EWG's such as NO_2, CN, CO_2CH_3, and CF_3 failed to produce any of the anticipated products. A possible explanation for the poor reactivity of *ortho*-EWG's in the cross-coupling reaction could be chelation of the Lewis basic heteroatoms to the palladium intermediate. This chelation may be retarding the rate of the subsequent reductive elimination step to the point that alternative reaction pathways are occurring leading to decomposition of the starting material.[8] It is worth mentioning that we were unable to find a solitary report in the chemical literature detailing the Suzuki–Miyaura cross-coupling reaction of cyclic ketene acetal phosphates or the structurally analogous α-phosphoryloxy enecarbamates with electron-poor arylboronic acid coupling partners.[9] Taking this into account, our methodology has significantly expanded the scope of this process and should allow for the incorporation of a wide-range of arylboronic acids in various medicinal chemistry applications involving the preparation of aryl vinyl ethers.

Next, we turned our attention toward defining the substrate scope for arylboronic acids bearing electron-donating groups. As outlined in Table 3, electron-rich arylboronic acids generally fared well furnishing the desired coupled products in modest to excellent yields depending on the nature of the functional group employed. The reaction is tolerant of ethers (OCH_3, entries 1–4),

Table 2
Coupling reaction of cyclic ketene acetal phosphate 2 with electron-poor arylboronic acids **3a–h**

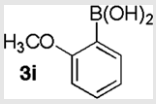
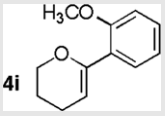
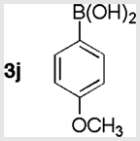
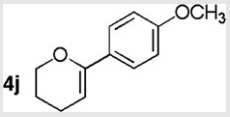
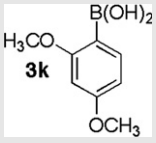
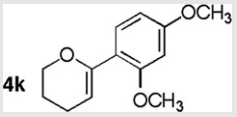
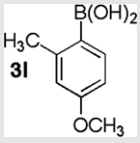
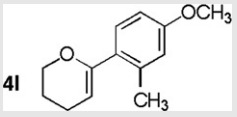
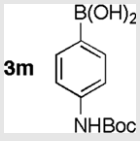
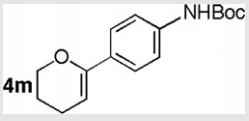
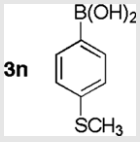
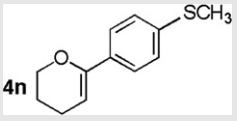
Entry[a]	Boronic acid	Product	Yield (%)
1			88
2			80
3			70
4			81
5			83
6			79[b]
7			58
8			67

[a] All reactions were performed with 5 mol % of $Pd(Ph_3P)_4$, 2.0 equiv of ketene acetal phosphate, 2.0 equiv of triethylamine, and 3.0 equiv of K_3PO_4 (3.0 M) in DMF at 50 °C.
[b] Na_2CO_3 was used as base.

alkyl groups (CH_3, entry 4), as well as protected aniline (NHBoc, entry 5) and thio (SCH_3, entry 6) substituents. In addition, extremely electron-rich arylboronic acids such as 2,4-dimethoxyphenylboronic acid (**3k**), substrates that oftentimes require elevated temperatures and result in poor conversions in palladium-mediated cross-coupling processes, also afforded the desired substituted dihydropyran **4k** in 88% yield, a demonstration of the overall robustness of this process. Interestingly, we found that the inclusion of triethylamine (Et_3N) in the reaction mixture was crucial to obtain high yields for electron-rich arylboronic acids. When reactions were conducted in the absence of triethylamine, product yields were approximately 20% lower compared to those with triethylamine. Our belief is that the presence of Et_3N in the reaction mixture is sequestering adventitious acid that may have resulted in protodeborylation of the arylboronic acid starting material.[10]

In summary, we have developed a mild and efficient methodology for the construction of aryl vinyl ethers employing the Suzuki–

Table 3
Coupling reaction of cyclic ketene acetal phosphate 2 with electron-rich arylboronic acids **3i–n**

Entry[a]	Boronic acid	Product	Yield (%)
1			74
2			86
3			88
4			80
5			64
6			60

[a] All reactions were performed with 5 mol % of $Pd(Ph_3P)_4$, 2.0 equiv of ketene acetal phosphate, 2.0 equiv of triethylamine, and 3.0 equiv of K_3PO_4 (3.0 M) in DMF at 50 °C.

Miyaura cross-coupling reaction between cyclic ketene acetal phosphates with arylboronic acids. The reaction is tolerant of both electron-poor and electron-rich arylboronic acids as well as a variety of aromatic substitution patterns. We believe that this methodology will find broad use in the design and development of natural and unnatural compounds requiring this structural feature. Our own application of this methodology within the context of complex natural products synthesis will be presented in due course.

Acknowledgments

Generous financial support from The Colorado College and the American Philosophical Society is gratefully acknowledged. L.P. is the recipient of a Student-Faculty Collaborative Venture Grant administered by The Colorado College. I.W.V. thanks the donors of the Frank H.J. Figge Memorial Endowment Fund for a summer undergraduate research stipend. High-resolution mass spectrometry analyses were performed by Dr. Shane E. Tichy of the Laboratory for Biological Mass Spectrometry at Texas A and M University.

Supplementary data

Experimental procedures and compound characterization for compounds **4a–4n**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.116.

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