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Synthesis of 2,2'-Bipyridine Via a Phosphorus Extrusion Reaction

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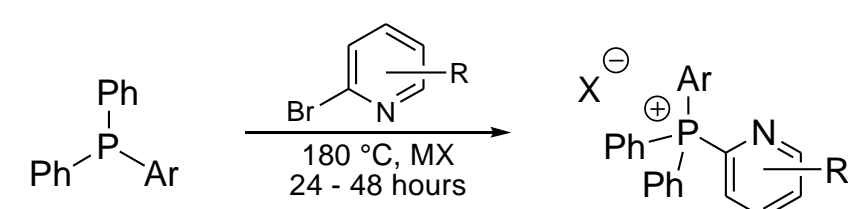


Introduction

The formation of carbon-carbon bonds has long been a synthetic goal for chemists. This has led to the development of many novel and highly synthetically useful reactions. One of the most notable reactions to form $sp^2C - sp^2C$ bonds has been the cross-coupling reaction.¹ Although these transformations have been very well studied and have recently produced a Nobel Prize, these transformations suffer from two drawbacks.¹ First, they often require expensive and exotic transition metal complexes and second, the reaction conditions often require inert or anhydrous conditions.¹ Therefore, any reactions which can substitute these reactions that do not require expensive metals or can be run under less sensitive conditions are in great demand. Our research group in conjunction with the Wicker group at Southeastern Louisiana University has developed a phosphonium species that we are exploring as a novel precursor for the formation of 2,2'-bipyridine and its derivatives. 2,2'-bipyridines and their derivatives are of increasing interest to the chemistry community due to their unique properties as ligands.² However, the majority of syntheses of these species rely on the use of cross coupling reactions to form unsymmetrically substituted bipyridine species. Our protocol, once optimized, will allow us to form these species without the use of cross-coupling reactions.

Synthesis of the Phosphonium Salts

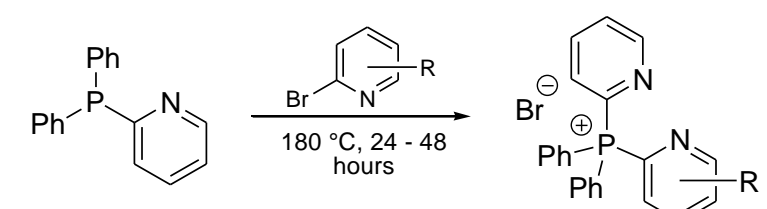
To a thick-walled pressure vessel was added 1.0 equivalents of the desired phosphine species followed by 1.01 equivalents of the desired electrophile, and 2.0 equivalents of the desired anion if different from the electrophile's leaving group. The reaction mixture was sealed and heated with stirring at 180 °C for 24 – 48 hours. The reaction mixture was cooled to room temperature and the reaction mixture was filtered into a round-bottom flask and the solvent was removed *in vacuo*. The resulting material was dissolved in either dichloromethane, methanol, acetone, or acetonitrile and triturated with diethyl ether to yield the desired compound.



Entry	Phosphonium Salt	% Yield	Entry	Phosphonium Salt	% Yield	Entry	Phosphonium Salt	% Yield
1		85%	4		87%	7		77%
2		90%	5		85%	8		80%
3		90%	6		75%	9		85%

Table 1: Synthesis of unsubstituted phosphonium salts. ^a

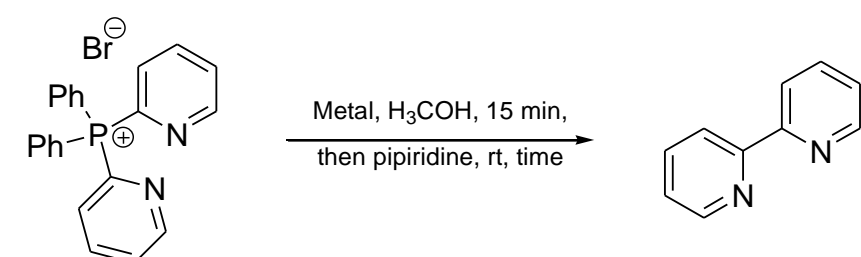
Synthesis of Substituted Phosphonium Salts



Entry	Phosphonium Salt	% Yield	Entry	Phosphonium Salt	% Yield	Entry	Phosphonium Salt	% Yield
1		75%	6		60%	11		55%
2		75%	7		62%	12		60%
3		80%	8		63%	13		70%
4		80%	9		60%	14		60%
5		85%	10		50%	15		75%

Table 2: Synthesis of monosubstituted phosphonium salts.

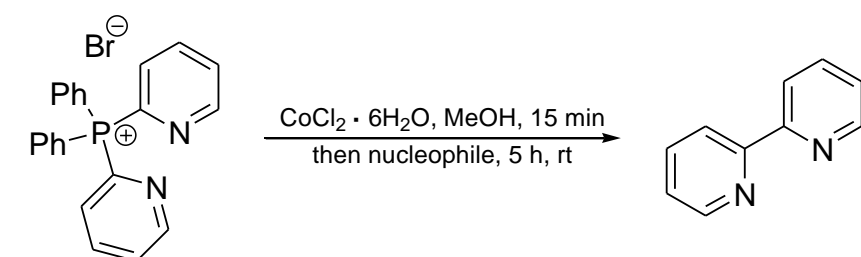
Reaction Optimization: Metal Screen



Entry	Metal	Time	% Yield	Entry	Metal	Time	% Yield
1	CoCl ₂ · 6H ₂ O	5 h	20.8%	9	ZnCl ₂ · 4H ₂ O	1 h	0.0%
2	LiCl	1 h	1.6%	10	MgCl ₂ · 6H ₂ O	1 h	0.6%
3	NaCl	1 h	9.6%	11	CaCl ₂ · 2 H ₂ O	5 h	20%
4	KCl	1 h	5.8%	12	SrCl ₂ · 6 H ₂ O	5 h	15%
5	FeCl ₂ · 4H ₂ O	1 h	15.1%	13	BaCl ₂ · 2 H ₂ O	5 h	10%
6	FeCl ₃ · 6H ₂ O	1 h	0.0%	14	NiCl ₂ · 6H ₂ O	5 h	3.9%
7	CuCl ₂ · 2H ₂ O	1 h	8.3%	15	SnCl ₂ · 2H ₂ O	1 h	0.0%
8	TsOH · 1H ₂ O	5 h	8.1%	16	SnCl ₄ · 5H ₂ O	1 h	0.0%

Table 3: Metal ion screen for the extrusion of 2,2'-bipyridine.

Reaction Optimization: Nucleophile Screen

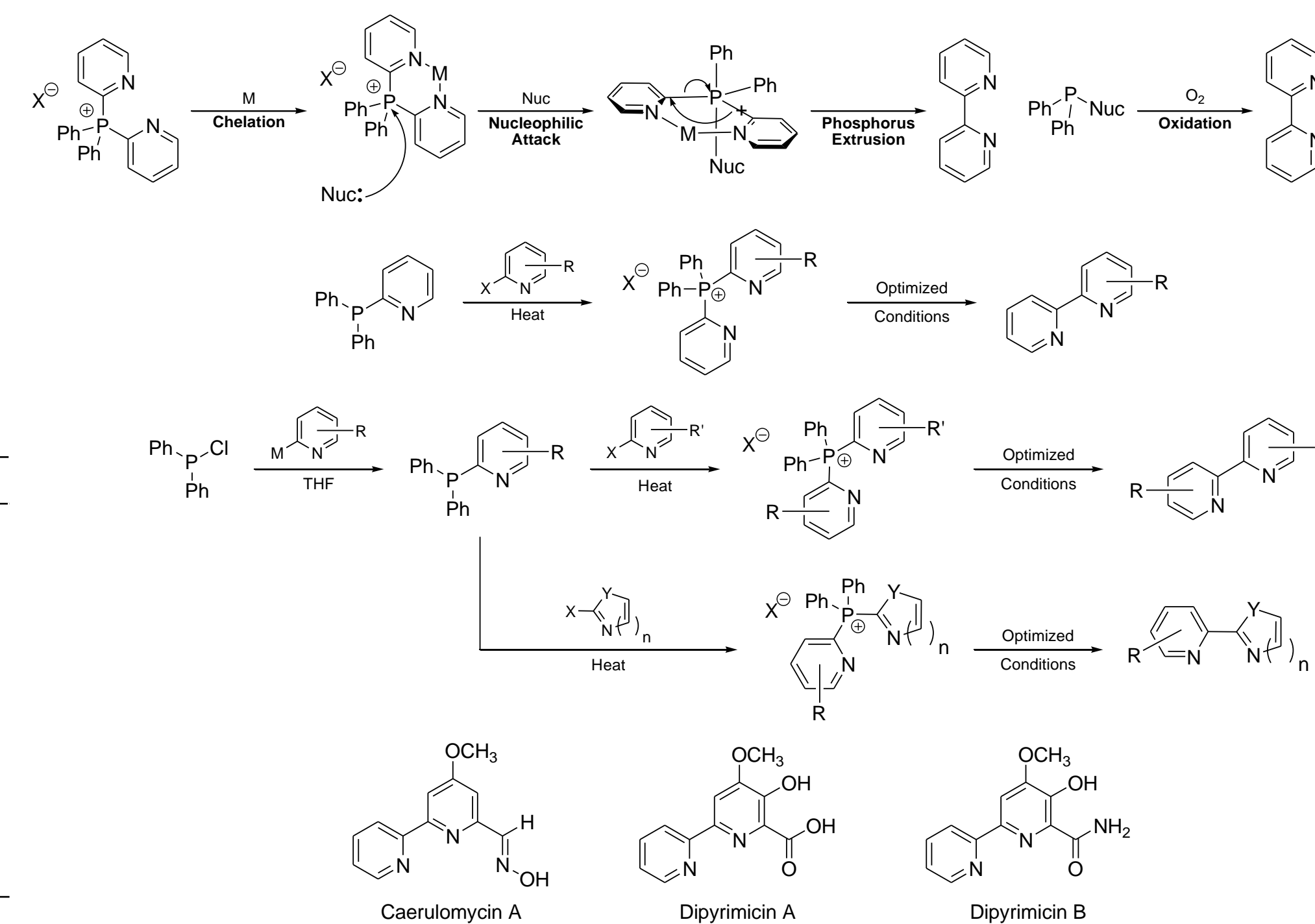


Entry	Nucleophile	% Yield	Entry	Nucleophile	% Yield	Entry	Nucleophile	% Yield
1	piperidine	20.8%	6	DABCO	10%	10	morpholine	35%
2	NaOH	8.1%	7	DBU	10%	11	N-Me-piperazine	35%
3	KSCN	6.2%	8	Et ₂ NH	36%	12	TMP	37%
4	Et ₃ N	35.7%	9	iPr ₂ NH	35%	13	Ph ₃ P	0.0%
5	EDA	11.4%						

Table 4: Nucleophile screen for the extrusion of 2,2'-bipyridine.

Future Work

In conclusion, we have developed a novel phosphorus extrusion method to synthesize 2,2'-bipyridine from phosphonium salts. We have been able to slightly optimize these conditions and have probed the role that the metal salt additives and the nucleophiles play in this reaction. In addition, we have a working hypothesis of the mechanism for the transformation based upon the results we have observed (**Scheme 1**). Currently we are working to further optimize the reaction conditions to produce 2,2'-bipyridine. Once we have fully optimized the reaction conditions, we will begin to explore the scope of the reaction. This will be done by utilizing our substituted phosphonium salts (**Table 2**) to prepare unsymmetrically substituted bipyridines as well as other nitrogen containing heterocycles. Once these goals have been accomplished we will then begin synthesizing a library of phosphine species which incorporate substituted pyridines into the phosphonium precursor to allow for the synthesis of novel polysubstituted bipyridine derivatives as well as other non-ring fused diheterocyclic species. Eventually this work will be utilized to synthesize pharmacologically active species as well as natural products.³



Scheme 1: Proposed mechanism, synthesis of polysubstituted 2,2'-bipyridines, and natural product targets.

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- 5) Department of Chemistry and Physics, SELU

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