Highly Regio- and Diastereoselective Tethered *Aza*-Wacker Cyclizations of Alkenyl Phosphoramidates

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ABSTRACT: We present highly diastereoselective tethered *aza*-Wacker cyclization reactions of alkenyl phosphoramidates. "Arming" the phosphoramidate tether with 5-chloro-8-quinolinol was essential to achieving >20:1 diastereoselectivity in these reactions. The substrate scope with respect to alkenyl alcohols and phosphoramidate tether was extensively explored. The scalability of the oxidative cyclization was demonstrated, and the product cyclophosphoramidates were shown to be valuable synthons, including for tether removal. With chiral alkenyl precursors, enantiopure cyclic phosphoramidates were formed.

Introduction

The regioselective functionalization of olefins remains an area of intense research activity.[1-9] While intermolecular olefin functionalization reactions often rely on subtle steric and electronic effects for selectivity, intramolecular reactions are generally much more predictable due to geometric constraints. A particularly powerful class of intramolecular olefin functionalization reactions is the *tethered aza*-Wacker cyclization.[10-17] In such reactions, a nitrogen containing auxiliary ("the tether") is appended to an alkenyl alcohol prior to the cyclization event.

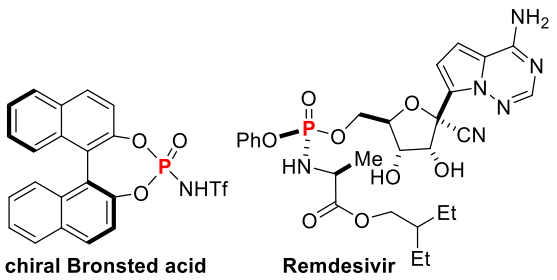
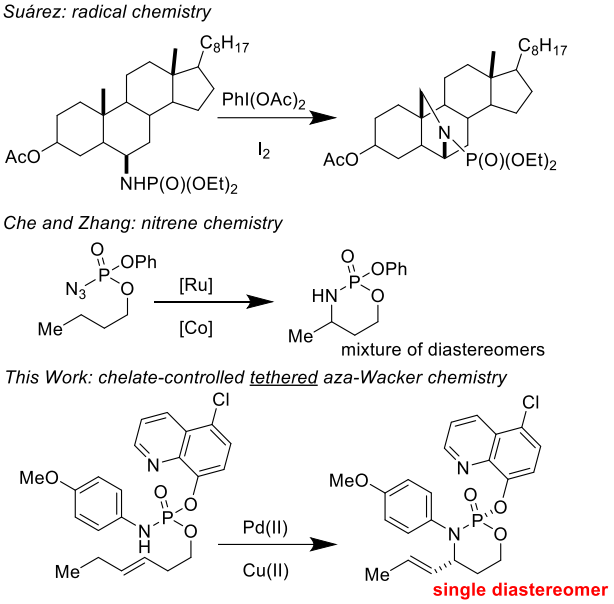


Figure 1. Phosphoramidates are indispensable to catalysis and medicine.

Tethered *aza*-Wacker cyclization reactions are enabling because they free the synthetic practitioner from the constraint of needing a pre-existing C–N bond in order to forge a new one. [18,19]



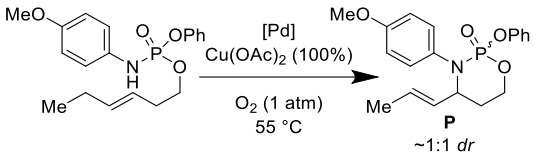
Scheme 1. Oxidative Strategies for Phosphoramidate Construction.

Phosphoramidates are an important class of heteroatom-rich compounds, and its members have found applications in diverse fields, ranging from asymmetric catalysis[20] to medicinal chemistry[21] (**Figure 1**). Cyclic phosphoramidates are traditionally assembled from condensation of amino-alcohols with phosphoryl chlorides, requiring precursor molecules with both amino and alcohol functionalities pre-installed. We envisioned developing a tethered *aza*-Wacker protocol for the synthesis of such heterocycles, allowing for the attachment of a phosphoramidate auxiliary to alkenyl alcohols and subsequent oxidative cyclization. There is sparse precedent for the use of oxidation reactions in cyclo-phosphoramidate construction. To date, such reactions have largely been restricted to phosphoryl azide decomposition with subsequent nitrene insertion[22, 23] and radical Suárez-type oxidations with $Pb(OAc)_4$ or $PhI(OAc)_2/I_2$ (**Scheme 1**).[24-

[27] Diastereocontrol remains a challenge with these reactions, with many of these protocols furnishing mixtures of diastereomers. We have found that "arming" the phosphoramidate tether with an unusual chloroquinolinol auxiliary allows for complete diastereocontrol during the cyclization event. The use of palladium-chelating auxiliaries is well known in the related field of C–H activation,[28-32] and the Engle group has shown that amino-quinolines appended to amides are excellent for regio-control in olefin mono- and di-functionalization reactions.[33-36] To our knowledge, ours is the first example of the use of an auxiliary to control *diastereoselectivity* in an olefin functionalization process.

Results and Discussion

Table 1. Reaction Optimization.

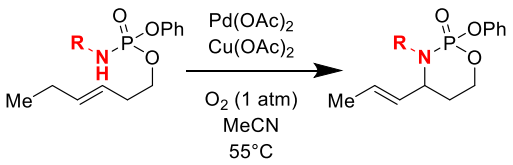


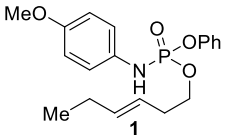
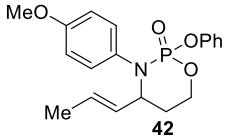
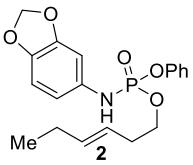
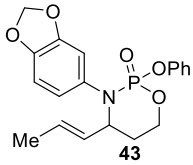
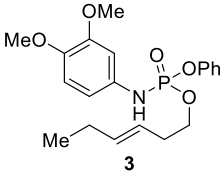
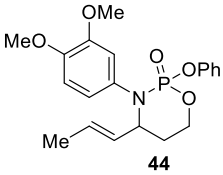
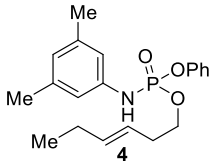
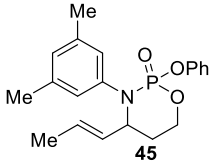
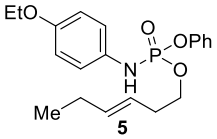
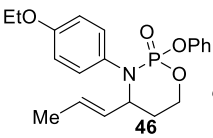
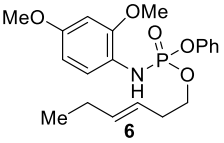
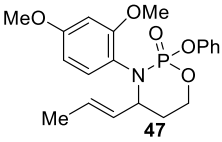
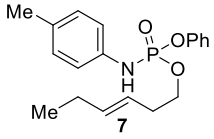
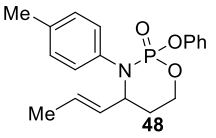
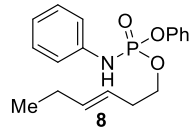
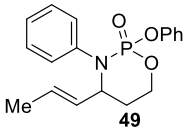
	[Pd] (mol%)	Solvent	Time	P/RSM[a]
1	$PdCl_2$ (20)	MeCN	17h	31/18
2	$Pd(TFA)_2$ (20)	MeCN	17h	36/23
3	$Pd_2(dba)_3$ (15)	MeCN	17h	53/30
4	$Pd_2(dba)_3$ (15)	DCE	17h	26/50
5	$Pd_2(dba)_3$ (15)	DMF	17h	20/80
6	$Pd_2(dba)_3$ (15)	DMSO	17h	30/70
7	$Pd_2(dba)_3$ (15)	EtOAc	17h	11/62
8	$Pd_2(dba)_3$ (10)	MeCN	40h	58/18
9	$Pd_2(dba)_3$ (10)	MeCN	65h	63/14
10	$Pd(OAc)_2$ (20)	MeCN	65h	73/10

[a]Percent product estimated from ^{1}H NMR integration with 1,3,5-trimethoxybenzene as an internal standard.

We began optimizing the reaction with (E)-hex-3-en-1-yl phenyl (4-methoxyphenyl)phosphoramidate, readily prepared from condensation of commercially available *trans*-3-hexen-1-ol and anisidine with phenyl dichlorophosphate. Product formation was observed with 20 mol% $PdCl_2$ in MeCN (**Table 1, Entry 1**), giving us hope that our envisioned oxidative cyclization reaction was viable. We saw little improvement upon switching to $Pd(TFA)_2$ (**Table 1**, **Entry 2**), but product formation did increase with $Pd_2(dba)_3$ (**Table 1**, **Entry 3**). Solvents other than MeCN were invariably deleterious (**Table 1, Entries 4-7**). Increasing the reaction time led to the most marked improvement in performance (**Table 1, Entries 8-10**). Our optimized protocol involved heating substrate, 20 mol% $Pd(OAc)_2$, and 1 equivalent of Cu(OAc) to 55 °C in MeCN for 65 hours (**Table 1, Entry 10**). In all cases, product was furnished as a roughly 1:1 diastereomeric mixture.

Scheme 2. Aniline-reactivity relationship.



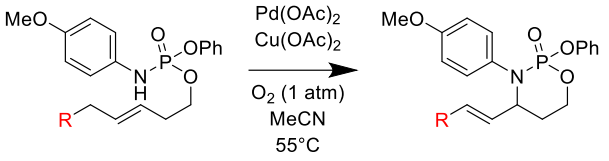
entry	substrate	product	isolated yield
1			73%, *dr* = 1.3:1
2			57%, *dr* = 1.7:1
3			54%, *dr* = 1.2:1
4			37%, *dr* = 1.5:1
5			61%, *dr* = 1.4:1
6			36%, *dr* = 2:1
7			53%, *dr* = 1.4:1
8			29%, *dr* = 1.4:1

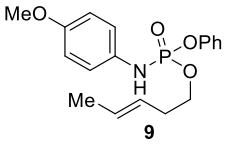
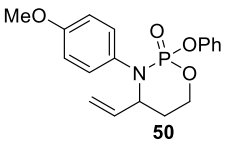
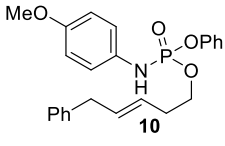
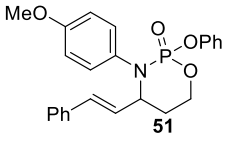
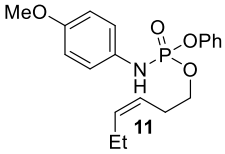
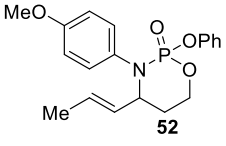
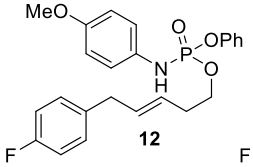
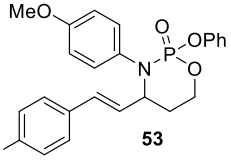
Reaction conditions: $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1 equiv.), O_2 (1 atm), CH_3CN, 55 °C, 65 h

Our optimized protocol was not limited to phosphoramidates containing anisidine (**Scheme 2**). We were pleased to see reasonable yields with phosphoramidates constructed from 3,4-

methylenedioxyaniline (**Scheme 2**, **Entry 2**), 3,4-dimethoxyaniline **(Scheme 2**, **Entry 3**), *p*-ethoxyaniline (**Scheme 2**, **Entry 5**), and toluidine (**Scheme 2**, **Entry 7**). From these structure-reactivity relationship studies, it was clear that electron rich anilines performed much better than electron neutral (**Scheme 2**, **Entry 8**) ones. Steric factors also played an important role, with 2,4-dimethoxyaniline performing poorly (**Scheme 2, Entry 6**). In all cases, diastereoselectivity ranged from ~1:1 to ~2:1.

Scheme 3. Substrate Scope with -OPh containing phosphoramidates.



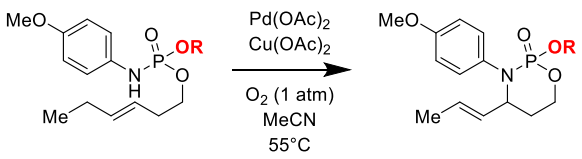
entry	substrate	product	isolated yield
1			**52%** *dr* = 1.3:1
2			**60%** *dr* = 2.2:1
3			**40%** *dr* = 1.3:1
4			**62%** *dr* = 1.1:1

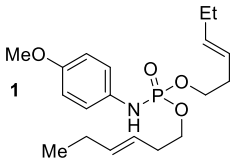
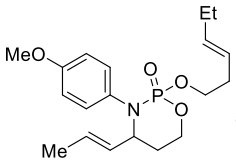
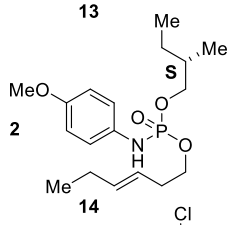
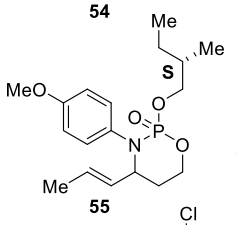
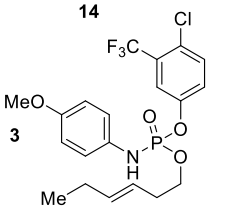
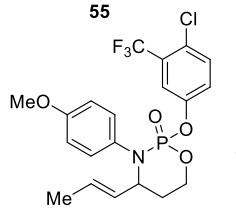
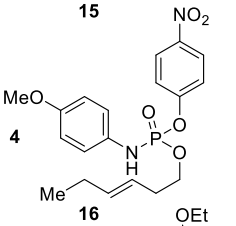
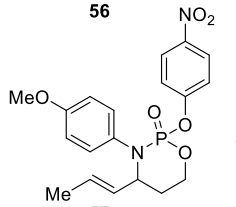
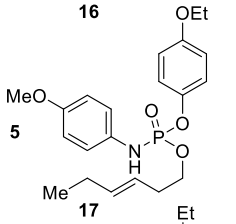
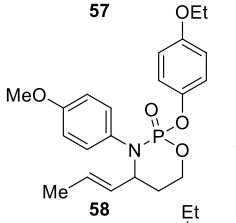
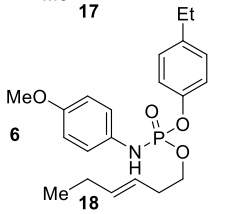
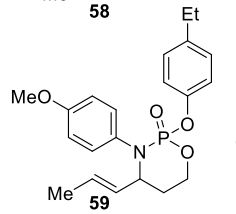
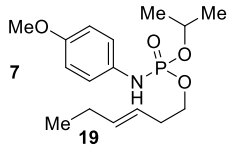
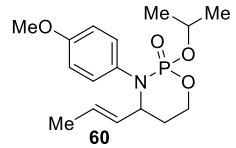
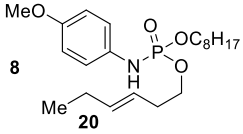
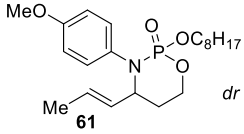
Reaction conditions: $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1 equiv.), O_2 (1 atm), CH_3CN, 55 °C, 65 h

A brief survey of alkenyl alcohols with our optimized protocol (**Scheme 3**) showed that substrates other than those derived from *trans*-hexen-3-ol were fully compatible. Nevertheless, each product was furnished as a mixture of diastereomers. Thus, we concluded that reaction diastereoselectivity was largely insensitive to the nature of the alkenyl alcohol.

We next explored the effect of changing the -OPh arm of the phosphoramidate auxiliary (**Scheme 4**). Product formation was viable with a variety of phenoxides and alkoxides. Electron-deficient phenoxides (**Scheme 4**, **Entries 3-4**) afforded better reactions than

Scheme 4. Changing the alkoxy substituent.



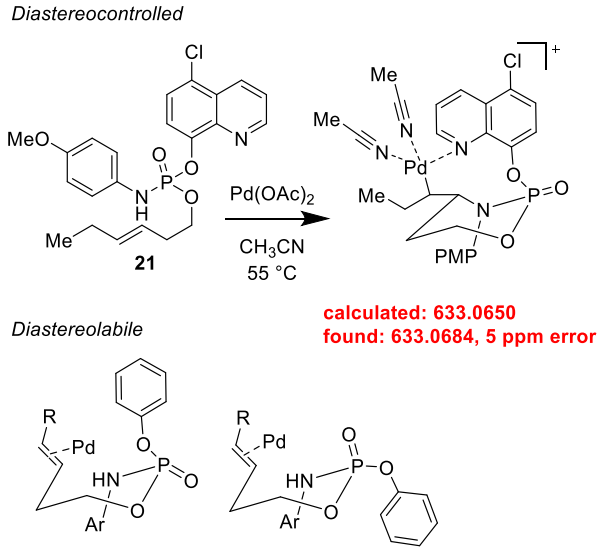
entry	substrate	product	isolated yield
1			**63%** *dr* = 2.4:1
2			**55%** *dr* = 2.4:1
3			**69%** *dr* = 1:1.1
4			**70%** *dr* = 1.1:1
5			**34%** *dr* = 1.4:1
6			**55%** *dr* = 1.4:1
7			**61%** *dr* = 3:1
8			**55%** *dr* = 2.4:1

Reaction conditions: $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1 equiv.), O_2 (1 atm), CH_3CN, 55 °C, 65 h

electron rich ones (**Scheme 4**, **Entries 5-6**). Even

with a chiral auxiliary (**Scheme 4**, **Entry 2)** or with a secondary alkoxide (**Scheme 4**, **Entry 7**), we were unable to break a diastereomeric barrier of ~3:1.

Collectively, these results informed us that we were unlikely to further optimize the diastereoselectivity of this oxidative cyclization by tuning simple steric and electronic factors. Inspired by the use of palladium-chelating auxiliaries in C–H activation and Engle's work on regioselective alkene functionalization with amido-quinolines, we wondered if a chelate approach would resolve the diastereoselectivity problem. We hypothesized that a chelate as depicted in **Scheme 5** would likely transform our diastereolabile reaction into a fully diastereoselective one. We heated one equivalent of $Pd(OAc)_2$ with **21** to 55 °C in acetonitrile and analyzed an aliquot of the reaction mixture by high resolution mass spectrometry. To our delight, we identified the molecular ion corresponding to our proposed chelate.

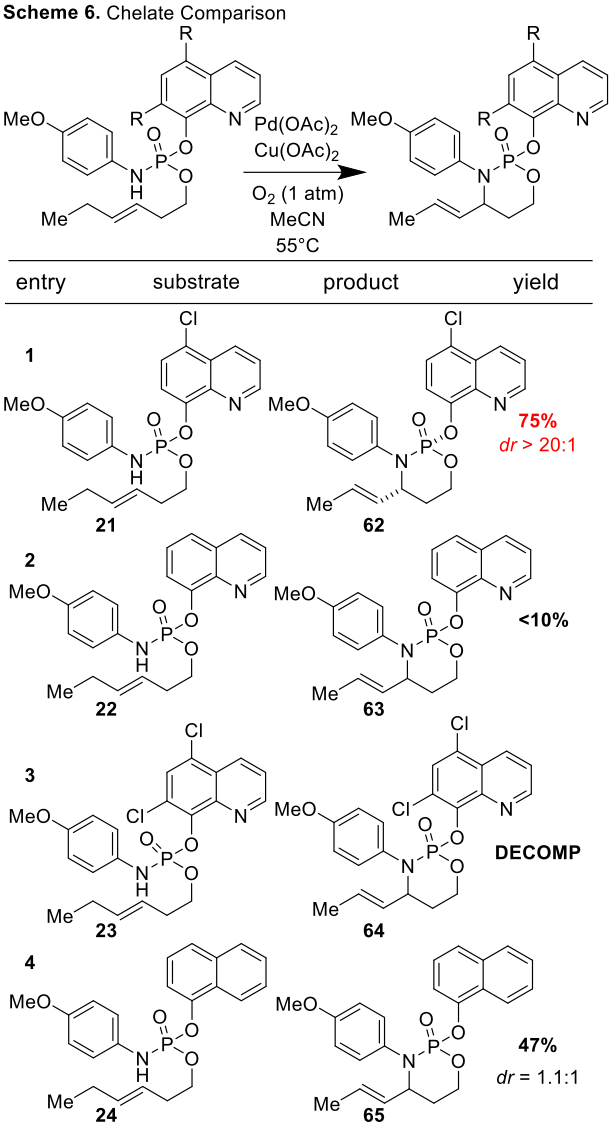


Scheme 5. HRMS analysis identifies a putative chelate for diastereocontrol in the oxidative cyclization.

We thus examined a range of quinolinol auxiliaries (**Scheme 6**). We found that phosphoramidate tethers containing a 5-chloro-8-quinolinoxide arm afforded cyclized product in good yields and, most importantly, *as a single diastereomer* **(Scheme 6**, **Entry 1**). At present, the differential performance of 5-chloro-8-quinolinol relative to other quinolinol auxiliaries (**Scheme 6**, **Entries 2-3**) remains unexplained. The presence of a nitrogen, presumably critical for palladium chelation, was essential for diastereoselectivity. With naphthoxide (**Scheme 6**, **Entry 4**), a 1:1 mixture of diastereomers re-emerged.

The phosphoramidate tether containing a 5-chloro-8-quinolinoxide arm was compatible with a wide range of alkenyl alcohols (**Scheme 7**). Alkenyl alcohols containing aryl rings adorned with $-CF_3$, $-NMe_2$, -OMe groups all reacted smoothly (**Scheme 7, Entry 1**). Heterocycles such as furan and thiophene

Scheme 6. Chelate Comparison

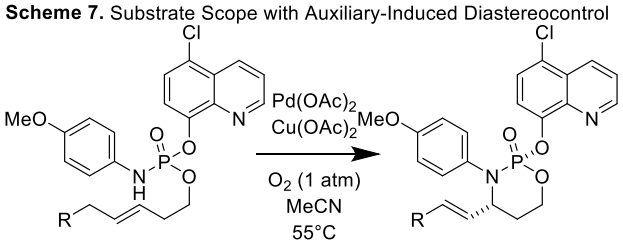


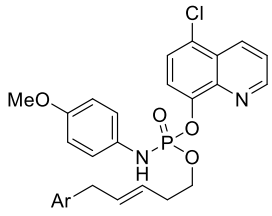
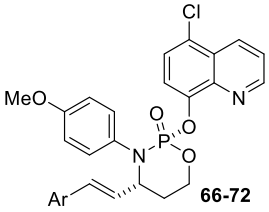
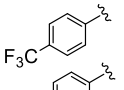
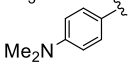
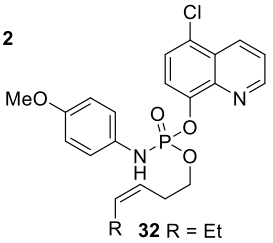
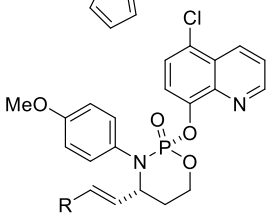
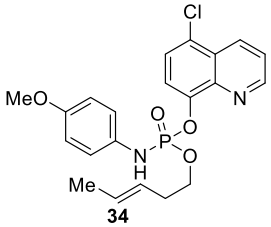
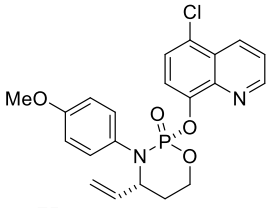
(**Scheme 7, Entry 1**) were also well-tolerated. *Cis*-olefins were compatible (**Scheme 7**, **Entry 2**) but yielded product in slightly lower yields relative to the equivalent *trans*-olefins. *Trans*-olefins containing cyclohexyl, cyclopentyl, and Boc-protected alcohols (**Scheme 7**, **Entry 4**) furnished cyclized products in good yields. The phosphoramidate tether could be appended to phenols (**Scheme 7**, **Entry 5**) as well as to secondary alcohols (**Scheme 7**, **Entry 6**). In all cases, the reactions proceeded with perfect diastereocontrol with respect to the newly formed nitrogen containing stereocenter and the phosphorous stereocenter of the phosphoramidate tether.

Furthermore, the reaction could be scaled greater than ten-fold without much diminishment of product yields; in this larger-scale reaction, product was again furnished as a single diastereomer (**Scheme 8**). With the 5-chloro-8-quinolinoxide auxiliary, we were no longer constrained to just using *p*-anisidine; a

variety of anilines engaged in good yield and with greater than 20:1 diastereoselectivity (**Scheme 9**).

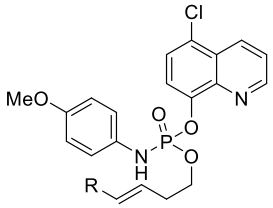
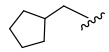
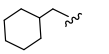
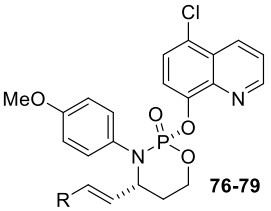
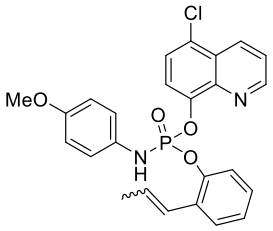
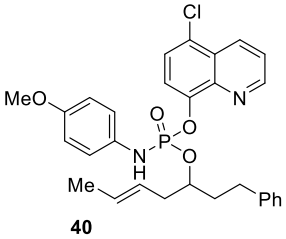
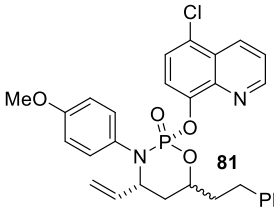
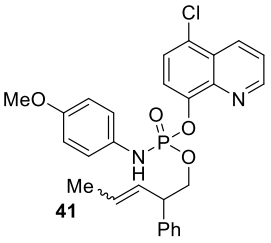
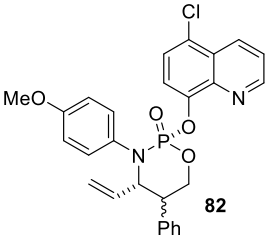
Scheme 7. Substrate Scope with Auxiliary-Induced Diastereocontrol



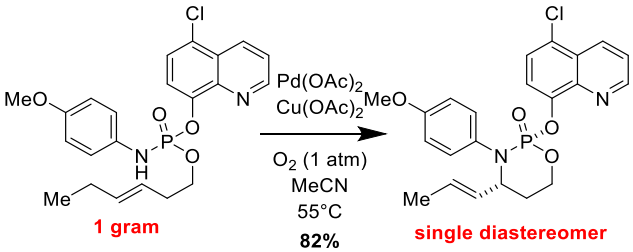
entry	substrate	product	isolated yield
1	 **25-31**	 **66-72**	Ar = Ph **80%** *dr* > 20:1
			**61%** *dr* > 20:1
			**65%** *dr* > 20:1
			**49%** *dr* > 20:1
			**53%** *dr* > 20:1
			**54%** *dr* > 20:1
			**64%** *dr* > 20:1
2	 **32** R = Et **33** R = C_4H_9	 **73** R = Me **57%** *dr* > 20:1 **74** R = C_3H_7 **44%** dr > 20:1	
3	 **34**	 **75**	**77%** *dr* > 20:1

Reaction conditions: $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1 equiv.), O_2 (1 atm), CH_3CN, 55 °C, 65 h

Scheme 7. Continued

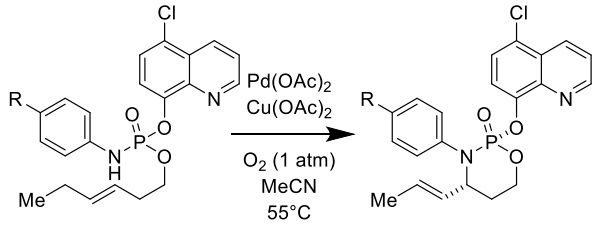
entry	substrate	product	isolated yield
4	 **35** R = C_4H_9 **36** R = $BocOC_2H_4$ **37** R =  **38** R = 	 **76-79**	R = C_3H_7 **66%** *dr* > 20:1 R = $BocOCH_2$ **62%** *dr* > 20:1 R=  **75%** *dr* > 20:1 R=  **65%** *dr* > 20:1
5	 **39**	**80**	**37%** *dr* > 20:1
6	 **40**	 **81**	**65%** 1:1 *cis*/*trans* mixture
7	 **41**	 **82**	**47%** 1:2 *cis*/*trans* mixture

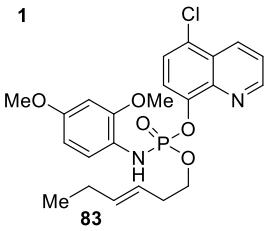
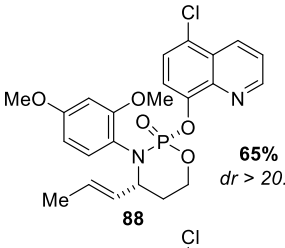
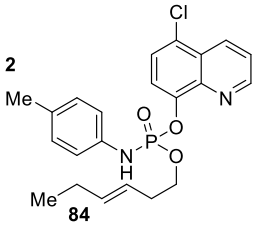
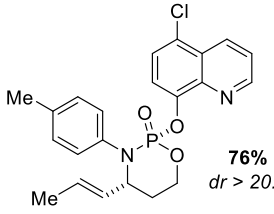
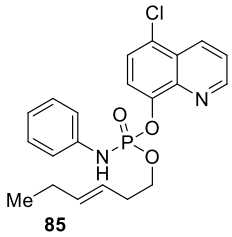
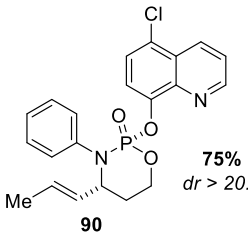
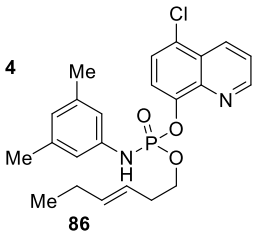
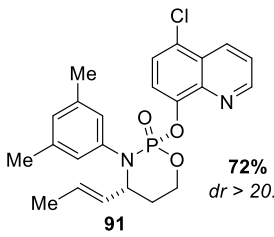
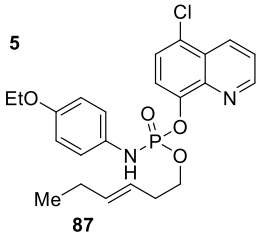
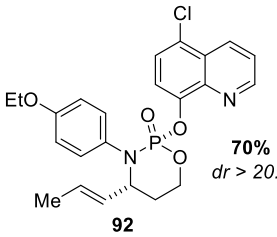
Reaction conditions: $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1 equiv.), O_2 (1 atm), CH_3CN, 55 °C, 65 h



Scheme 8. Oxidative cyclization scales successfully.

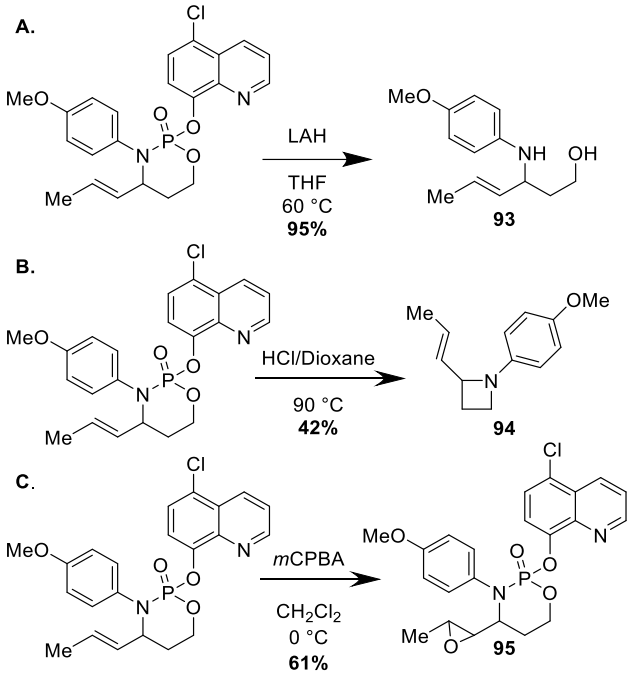
Scheme 9. Aniline Scope with Auxiliary-Induced Diastereocontrol.



entry	substrate	product	yield
1			65% *dr > 20:1*
2			76% *dr > 20:1*
3			75% *dr > 20:1*
4			72% *dr > 20:1*
5			70% *dr > 20:1*

Reaction conditions: $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1 equiv.), O_2 (1 atm), CH_3CN, 55 °C, 65 h

The product cyclophosphoramidates were quite versatile. The phosphorous auxiliary could be removed by reduction with lithium aluminum hydride (**Scheme 10A**). Upon heating with HCl in dioxane, alkenyl azetidine product formed in reasonable yield (**Scheme 10B**). Finally, epoxidation of the pendant alkene proceeded smoothly with *m*CPBA (**Scheme 10C**).



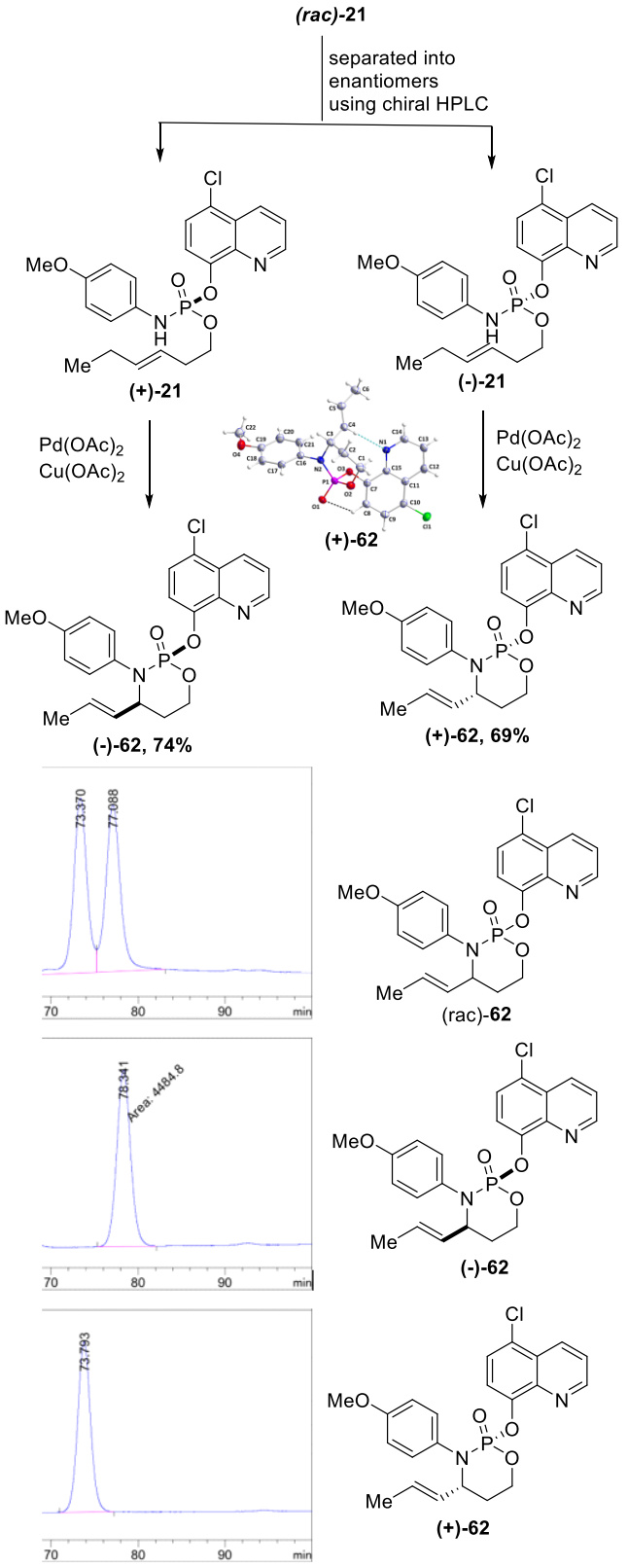
Scheme 10. A. Removal of the phosphorous tether using LAH reduction. **B.** Treatment with HCl/Dioxane led to azetidine formation. **C.** Epoxidation proceeded smoothly with *m*CPBA.

The power of a highly diastereoselective oxidative cyclization reaction is further illustrated in **Scheme 11**. Phosphoramidate **21** was separated into enantiomers using chiral reversed-phase HPLC. Subjecting each to our optimized $Pd(OAc)_2/Cu(OAc)_2$ protocol afforded enantiopure cyclic phosphoramidate products. The absolute structure and conformation of (+)-**62** were determined by x-ray crystallography (CCDC: 2061647). As tether removal is possible with LAH (**Scheme 10A**), this allows for the synthesis of *chiral amino alcohols* from readily available acyclic precursors.

Conclusion

In summary, we present a protocol for highly diastereoselective tethered *aza*-Wacker cyclization reactions of alkenyl phosphoramidates. We found that phosphoramidate tethers containing a 5-chloro-8-quinolinoxide "arm" were essential for diastereoselective cyclizations. We hypothesize that such diastereoselectivity arises from a palladium chelation, and we have identified the molecular ion of a putative chelate using high resolution electrospray ionization mass spectrometry. The substrate scope with respect to the alkenyl alcohol and the phosphoramidate tether was extensively explored. In addition, the scalablility of the cyclization reaction was demonstrated, and the product cyclophosphoramidates were shown to be valuable synthons for

a variety of further transformations, including tether removal. With chiral alkenyl precursors, enantiopure cyclic phosphoramidates were formed.



Scheme 11. Chiral resolution and highly diastereoselective oxidative cyclization reactions afford enantiopure cyclic phosphoramidates. Note: CCDC 2061647

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization of substrates and products, and spectra. "This material is available free of charge via the Internet at http://pubs.acs.org."

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Author Contributions

†Anand H. Shinde and Annu Anna Thomas contributed equally.

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