JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

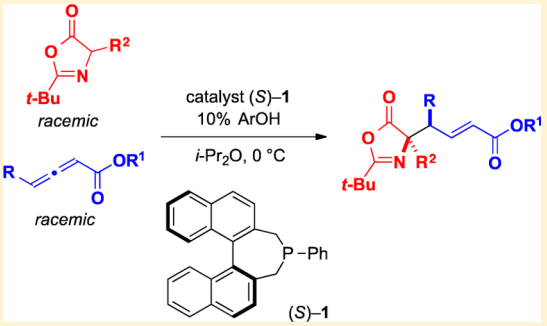
Phosphine-Catalyzed Doubly Stereoconvergent γ-Additions of Racemic Heterocycles to Racemic Allenoates: The Catalytic Enantioselective Synthesis of Protected α,α-Disubstituted α-Amino Acid Derivatives

Marcin Kalek and Gregory C. Fu*

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

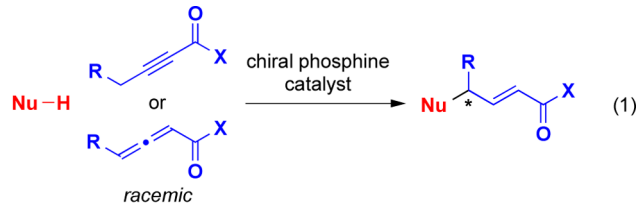
Supporting Information

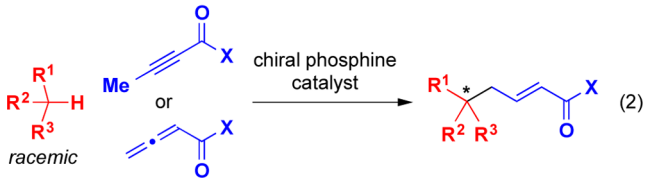
ABSTRACT: Methods have recently been developed for the phosphine-catalyzed asymmetric γ-addition of nucleophiles to readily available allenoates and alkynoates to generate useful α,β-unsaturated carbonyl compounds that bear a stereogenic center in either the γ *or* the δ position (but not both) with high stereoselectivity. The utility of this approach would be enhanced considerably if the stereochemistry at *both* termini of the new bond could be controlled effectively. In this report, we describe the achievement of this objective, specifically, that a chiral phosphepine can catalyze the stereoconvergent γ-addition of a racemic nucleophile to a racemic electrophile; through the choice of an appropriate heterocycle as the nucleophilic partner, this new method enables the synthesis of protected α,α-disubstituted α-amino acid derivatives in good yield, diastereoselectivity, and enantioselectivity.



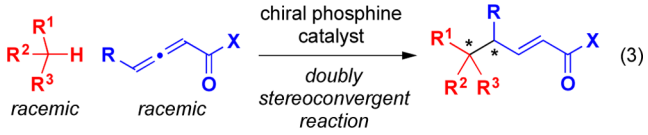
INTRODUCTION

In recent years, nucleophilic catalysis by chiral tertiary phosphines has emerged as a powerful strategy for the enantioselective synthesis of a wide array of useful compounds.[1] Exemplary of this approach is the phosphine-catalyzed addition of nucleophiles to the γ-position of electron-deficient alkynes and allenes,[2] which furnishes α,β-unsaturated carbonyl compounds that are well-suited for further stereoselective functionalizations (eqs 1[3] and 2[4]).[5]





To date, systematic studies of phosphine-catalyzed enantioselective γ-additions have been limited to processes that control a single stereocenter, either in the γ or in the δ position (eqs 1 and 2, respectively).[3,4] We recently decided to attempt to substantially enhance the utility of this strategy by developing a method that would control the stereochemistry at *both* termini of the newly created bond (eq 3). To the best of our

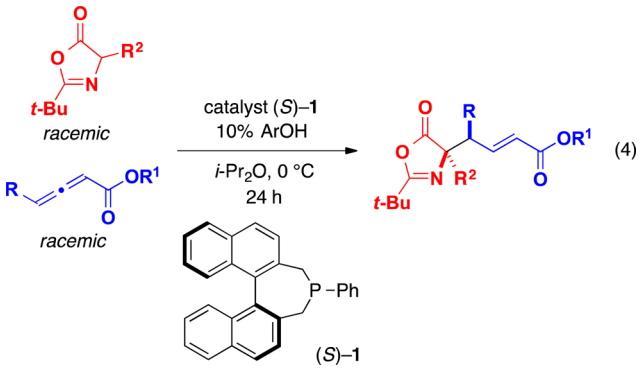


knowledge, there has been only a single isolated example of a phosphine-catalyzed γ-addition between such partners, a coupling that proceeded with modest diastereoselectivity (2.5:1) and good enantiomeric excess (91–92%).[3c]

Although we were concerned that this effort might be stymied by the propensity of the electrophilic allene/alkyne to isomerize to a 1,3-diene[6] rather than form a carbon–carbon bond with a hindered tertiary nucleophile, we were particularly attracted by the potential to generate products that are more stereochemically rich than in previous studies and to achieve a doubly stereoconvergent reaction of two racemic coupling partners, one with a stereogenic center and the other with a stereogenic axis. In this report, we describe the achievement of our objective, specifically, a phosphine-catalyzed γ-addition that furnishes α,α-disubstituted α-amino acid derivatives,[7,8] an important family of target molecules, with very good diastereoselectivity and enantioselectivity (eq 4).

Received: May 28, 2015
Published: July 20, 2015

DOI: 10.1021/jacs.5b05528
J. Am. Chem. Soc. 2015, 137, 9438–9442

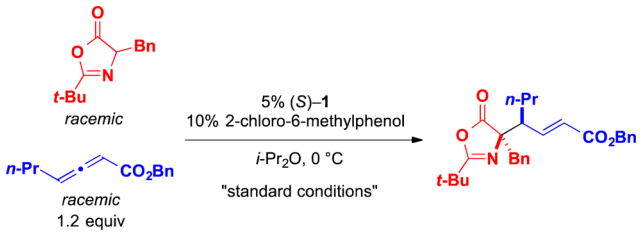


(4)

RESULTS AND DISCUSSION

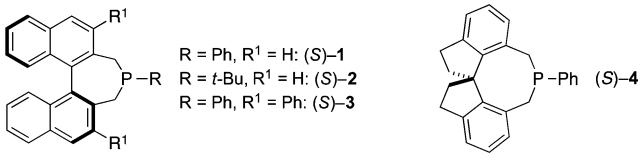
Upon exploring a variety of reaction parameters for a model coupling between a 1,3-oxazol-5(4*H*)-one and an allenoate, we have been able to develop conditions that furnish the desired γ-addition product in good yield, diastereoselectivity, and enantioselectivity in the presence of phosphepine **1**[9] (Table 1, entry 1). No γ-addition is observed in the absence of the

Table 1. Phosphine-Catalyzed Doubly Stereoconvergent γ-Additions: Effect of Reaction Parameters[a]



entry	change from the standard conditions	yield (%)[b,c]	dr[c]	ee (%)[d]
1	none	92	14:1	91
2	no (*S*)–**1**	<1	–	–
3	(*S*)–**2**, instead of (*S*)–**1**	<1	–	–
4	(*S*)–**3**, instead of (*S*)–**1**	25	14:1	78
5	(*S*)–**4**, instead of (*S*)–**1**	11	9:1	–65
6	r.t., instead of 0 °C	90	11:1	88
7	no 2-chloro-6-methylphenol	75	11:1	84

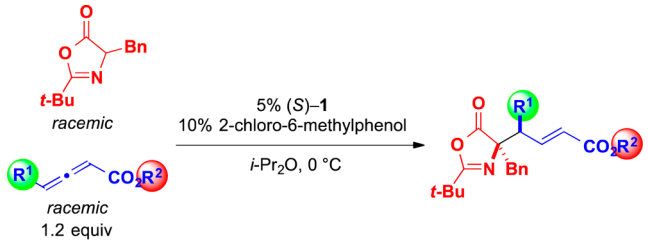
[a]All data are the average of two experiments. [b]Combined yield of the two diastereomers. [c]Determined through analysis by ^{1}H NMR spectroscopy. [d]ee of the major diastereomer. A negative ee value signifies the predominant formation of the enantiomer of the illustrated product.



phosphine (entry 2), and related phosphepines (**2** and **3**) as well as spirophosphine **4**[10] do not provide satisfactory results (entries 3–5). A modestly inferior yield, diastereoselectivity, and/or enantioselectivity are obtained at room temperature or in the absence of the phenol (entries 6 and 7).[11]

Having identified effective conditions, we examined the scope of this new method for the catalytic asymmetric synthesis of α,α-disubstituted α-amino acid derivatives. With regard to the allenoate coupling partner (Table 2),[12] the choice of the R^2 group of the ester has only a modest impact on the course of the reaction (entries 1–4). A variety of substituents in the γ-

Table 2. Phosphine-Catalyzed Doubly Stereoconvergent γ-Additions: Scope with Respect to the Allenoate[a]



entry	R^1	R^2	yield (%)[b]	dr[c]	ee (%)[d]
1	*n*-Pr	Bn	90	14:1	92
2	*n*-Pr	Me	81	14:1	92
3	*n*-Pr	$CHPh_2$	83	10:1	89
4[e]	*n*-Pr	*t*-Bu	74	>20:1	82
5	Me	Bn	94	>20:1	96
6	Cy	Bn	86	20:1	90
7	Ph	Bn	95	9:1	89
8	TBSO	Bn	87	17:1	89
9	n-C_8H_{17}	Bn	88	10:1	91
10		Bn	88	15:1	95
11	MeO_2C	Bn	87	14:1	96
12		Bn	88	7:1	89
13	Cl	Bn	86	12:1	95

[a]All data are the average of two experiments. [b]Yield of purified product, isolated as a mixture of diastereomers. [c]Determined through analysis by ^{1}H NMR spectroscopy of the unpurified reaction mixture. [d]ee of the major diastereomer. [e]Catalyst loading: 10%.

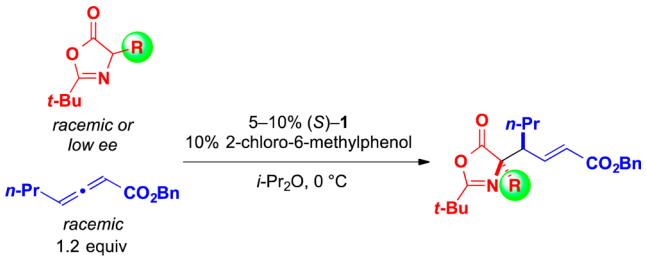
position of the allenoate (R^1) are tolerated, and functional groups such as a silyl ether, a cis alkene, an alkyne, a thiophene, and a primary alkyl chloride are compatible with the reaction conditions (entries 5–13). On a gram scale (1.17 g of product), the catalytic enantioselective γ-addition illustrated in entry 10 proceeds in 90% yield, 15:1 dr, and 94% ee.

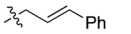
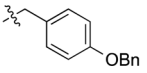
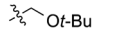
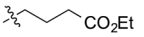
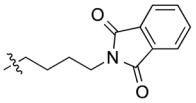
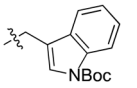
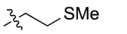
We have also examined the scope with respect to the nucleophilic partner (the 1,3-oxazol-5(4*H*)-one) in the doubly stereoconvergent γ-addition (Table 3).[13] As the substituent R in the 4 position increases in size from Me to *i*-Bu, a small loss in ee is observed, although the yield and the diastereoselectivity remain high (entries 1–3). Functional groups such as an olefin, an ether, an imide, a protected indole, and a sulfide are tolerated. The enantiomeric excess of the product is independent of whether racemic or enantioenriched 1,3-oxazol-5(4*H*)-one is employed as the nucleophile.

An attempt to achieve a doubly stereoconvergent γ-addition of a 1,3-oxazol-5(4*H*)-one bearing an *aromatic* substituent in the 4 position furnished essentially none of the desired product (<1% yield). Building on our hypothesis that the greater stability of the conjugate base of this coupling partner might be attenuating its nucleophilicity, we decided to explore the reactivity of a more electron-rich family of heterocycles, specifically, 2-amino-3,5-dihydro-4*H*-imidazol-4-ones. We were pleased to determine that, under related conditions, an array of γ-additions of this family of aryl-substituted nucleophiles can be

DOI: 10.1021/jacs.5b05528
J. Am. Chem. Soc. 2015, 137, 9438–9442

Table 3. Phosphine-Catalyzed Doubly Stereoconvergent γ-Additions: Scope with Respect to the 1,3-Oxazol-5(4*H*)-one[a]

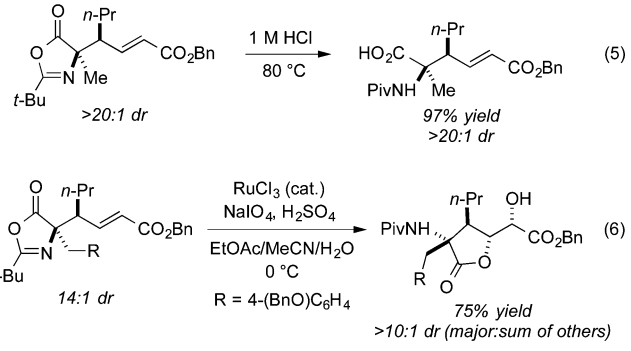


entry	R	yield (%)[b]	dr[c]	ee (%)[d]
1	Me	78	>20:1	91
2	*n*-Pr	84	16:1	91
3	*i*-Bu	84	>20:1	81
4		82	19:1	91
5		85	14:1	90
6[e]		57/17	3:1	89/90
7		74	19:1	88
8		79	17:1	87
9		88	18:1	87
10		82	>20:1	82

[a]All data are the average of two experiments. [b]Yield of purified product, isolated as a mixture of diastereomers. [c]Determined through analysis by ^{1}H NMR spectroscopy of the unpurified reaction mixture. [d]ee of the major diastereomer. [e]The diastereomeric products were isolated separately.

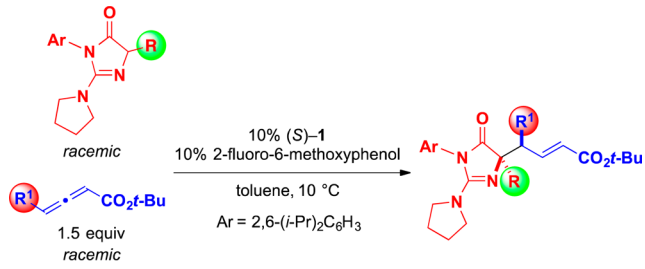
achieved in good yield, diastereoselectivity, and enantioselectivity (Table 4). In addition to serving as protected α,α-disubstituted α-amino acid derivatives, 2-amino-3,5-dihydro-4*H*-imidazol-4-ones are interesting targets in their own right.[14]

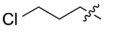
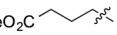
The products of our phosphine-catalyzed stereoconvergent γ-additions can be transformed into other interesting compounds. For instance, selective hydrolytic ring opening of the 1,3-oxazol-5(4*H*)-one reveals an N-protected α,α-disubstituted α-amino acid (eq 5).[7] Furthermore, ruthenium-catalyzed



dihydroxylation, followed by in situ lactonization, proceeds with high diastereoselectivity to afford a product that bears four

Table 4. Phosphine-Catalyzed Doubly Stereoconvergent γ-Additions: 2-Amino-3,5-dihydro-4*H*-imidazol-4-ones as Nucleophiles[a]



entry	R	R[1]	yield (%)[b]	dr[c]	ee (%)[d]
1	Ph	*n*-Pr	77	>20:1	91
2	4-(OMe)C$_6$H$_4$	*n*-Pr	59	7:1	92
3	Ph		91	14:1	92
4	Ph		72	18:1	95

[a]All data are the average of two experiments. [b]Yield of purified product, isolated as a mixture of diastereomers. [c]Determined through analysis by ^{1}H NMR spectroscopy of the unpurified reaction mixture. [d]ee of the major diastereomer.

consecutive stereocenters wherein the newly introduced oxygens are differentiated (eq 6).

A possible mechanism for these phosphine-catalyzed γ-additions of heterocycles to allenoates is outlined in Figure 1. In

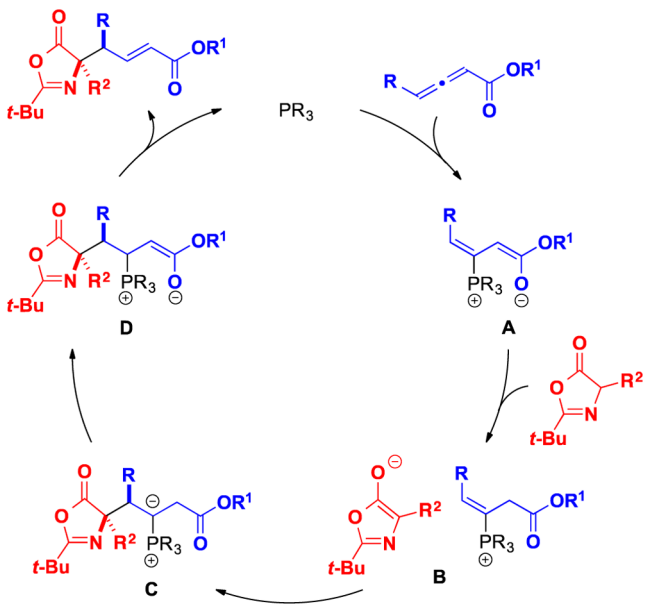


Figure 1. Outline of a possible mechanism for the phosphine-catalyzed γ-addition of 1,3-oxazol-5(4*H*)-ones to allenoates (for the sake of simplicity, all steps are drawn as irreversible, and alkenes are illustrated as single isomers).

the first step of the catalytic cycle, the nucleophilic phosphine catalyst adds to the β position of the allenoate to furnish zwitterion **A**, which upon protonation by the 1,3-oxazol-5(4*H*)-one affords ion pair **B**.[15] Next, the deprotonated heterocycle adds γ to the carbonyl group of the phosphonium salt, generating ylide **C**; if the phosphonium salt (**B**) is instead deprotonated in the δ position, then the undesired diene can be formed.[6a] Tautomerization (**C** → **D**) followed by fragmenta-

DOI: 10.1021/jacs.5b05528
J. Am. Chem. Soc. 2015, 137, 9438–9442

tion yields the desired γ-addition product and regenerates the phosphine catalyst.

By following the progress of a phosphine-catalyzed enantioselective γ-addition over time, we have determined that there is a modest kinetic resolution of the racemic allenoate (selectivity factor ∼4).[16] We have separated the enantiomers of the allenoate, and we have confirmed that they do indeed react at different rates and that they generate the γ-addition product with the same enantiomeric excess, consistent with the mechanism outlined in Figure 1 wherein the original stereochemistry of the allenoate is lost in the formation of intermediate **A**. We have determined that the unreacted 1,3-oxazol-5(4*H*)-one (pK_a ∼19 in DMSO)[17] is essentially racemic throughout the course of the reaction. The ee of the product remains constant during the γ-addition process.

The rate law for the phosphine-catalyzed γ-addition of a 1,3-oxazol-5(4*H*)-one to an allenoate is first-order in the catalyst and in the allenoate, and it is zeroth-order in the nucleophile and in the phenol; moreover, we have established through a ^{31}P NMR spectroscopic study that the resting state of the catalyst is the free phosphine. Taken together, these observations are consistent with a mechanism wherein the first step of the catalytic cycle, the addition of the phosphine catalyst to the allenoate to form zwitterion **A**, is the turnover-limiting step.[18]

CONCLUSIONS

We have developed the first phosphine-catalyzed γ-addition reactions in which two adjacent stereogenic centers are controlled with very good diastereoselectivity and enantioselectivity; this doubly stereoconvergent process employs two racemic coupling partners, one with a stereogenic center and the other with a stereogenic axis. The method provides ready access to an array of protected, unsaturated α,α-disubstituted α-amino acid derivatives, which can undergo selective transformations that further enlarge the diversity of products that can be generated through this method. A mechanistic investigation establishes that, during the course of the γ-addition, there is modest kinetic resolution of the racemic allenoate, whereas the nucleophile remains racemic. The available data are consistent with the addition of the phosphine catalyst to the allenoate being the turnover-limiting step of the catalytic cycle. Further studies of phosphine-catalyzed stereoselective reactions are underway.

EXPERIMENTAL SECTION

General Procedure. An oven-dried 20 mL vial was charged with catalyst **1** (6.8 mg, 0.018 mmol, 5%), 2-chloro-6-methylphenol (4.2 μL, 5.0 mg, 0.035 mmol, 10%), and the 1,3-oxazol-5(4*H*)-one (0.35 mmol). The vial was capped with a PTFE-lined septum cap and evacuated/backfilled with nitrogen (3 cycles). Diisopropyl ether (anhydrous; 3.5 mL) was added via syringe, and then the vial was cooled to 0 °C. Next, the allenoate (0.42 mmol, 1.2 equiv) was added via syringe, and then the reaction mixture was stirred at 0 °C for 24 h. To deactivate the catalyst, a solution of *tert*-butyl hydroperoxide (5.0–6.0 M in decane; 50 μL) was added. The resulting mixture was stirred at 0 °C for 10 min, and then it was allowed to warm to rt. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05528.

AUTHOR INFORMATION

Corresponding Author

*gcfu@caltech.edu

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences: R01-GM57034) and the Swedish Research Council (fellowship for M.K.: Dnr 350-2012-6645). We thank Dr. Nathan D. Schley, Dr. Michael K. Takase (X-ray Crystallography Facility; a Bruker KAPPA APEX II X-ray diffractometer was purchased via NSF CRIF:MU Award CHE-0639094), Dr. David G. VanderVelde (NMR Facility), Dr. Scott C. Virgil (Center for Catalysis and Chemical Synthesis, supported by the Gordon and Betty Moore Foundation), and Dr. Daniel T. Ziegler for assistance.

REFERENCES

(1) For recent reviews and leading references, see: (a) Xiao, Y.; Sun, Z.; Guo, H.; Kwon, O. *Beilstein J. Org. Chem.* **2014**, *10*, 2089–2121. (b) Fan, Y. C.; Kwon, O. In *Science of Synthesis: Asymmetric Organocatalysis*; List, B., Maruoka, K., Eds.; Georg Thieme Verlag: Stuttgart, 2012; Vol. *1*, pp 723–782.

(2) For initial studies of γ-addition processes that generated achiral or racemic products, see: (a) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 3167–3168. (b) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 10819–10820.

(3) For examples of processes that generate a γ stereocenter with good enantiomeric excess, see: (a) Chung, Y. K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2225–2227. (b) Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 14231–14233. (c) Sinisi, R.; Sun, J.; Fu, G. C. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 20652–20654. (d) Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 4568–4569. (e) Fujiwara, Y.; Sun, J.; Fu, G. C. *Chem. Sci.* **2011**, *2*, 2196–2198. (f) Lundgren, R. J.; Wilsily, A.; Marion, N.; Ma, C.; Chung, Y. K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 2525–2528. (g) Fang, Y.-Q.; Tadross, P. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2014**, *136*, 17966–17968.

(4) For examples of processes that generate a δ stereocenter with good enantiomeric excess, see: (a) Chen, Z.; Zhu, G.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 5631–5635. (b) Wang, T.; Yao, W.; Zhong, F.; Pang, G. H.; Lu, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 2964–2968. (c) Chen, J.; Cai, Y.; Zhao, G. *Adv. Synth. Catal.* **2014**, *356*, 359–363.

(5) For leading references, see: *Catalytic Asymmetric Conjugate Reactions*; Cordova, A., Ed.; Wiley–VCH: Weinheim, 2010.

(6) (a) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933–7935. (b) For a review, see: Kwong, C. K.-W.; Fu, M. Y.; Lam, C. S.-L.; Toy, P. H. *Synthesis* **2008**, *2008*, 2307–2317.

(7) For a brief review with leading references on the synthesis and the significance of α,α-disubstituted α-amino acids, see: Metz, A. E.; Kozlowski, M. C. *J. Org. Chem.* **2015**, *80*, 1–7.

(8) For an example of a bioactive 1,3-oxazol-5(4*H*)-one, see: Pinto, I. L.; West, A.; Debouck, C. M.; DiLella, A. G.; Gorniak, J. G.; O'Donnell, K. C.; O'Shannessy, D. J.; Patel, A.; Jarvest, R. L. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2467–2472.

(9) (a) This family of phosphepines was originally developed to serve as chiral ligands for metal-catalyzed enantioselective processes. For an overview, see: Gladiali, S.; Alberico, E.; Junge, K.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 3744–3763. (b) For the first application of such a phosphepine as a chiral nucleophilic catalyst, see: Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234–12235.

(10) (a) This spirophosphine was originally developed to serve as a chiral ligand for metal-catalyzed enantioselective processes. See: Zhu, S.-F.; Yang, Y.; Wang, L.-X.; Liu, B.; Zhou, Q.-L. *Org. Lett.* **2005**, *7*,

DOI: 10.1021/jacs.5b05528
J. Am. Chem. Soc. 2015, 137, 9438–9442

2333−2335. (b) For the first application of this spirophosphine as a chiral nucleophilic catalyst, see: Reference 3a.
(11) In a preliminary study, the use of TBME as the solvent led to a somewhat lower yield (∼82%) and enantioselectivity (∼88% ee).
(12) In preliminary studies, when the γ-substituent of the allenoate (R^1) was Ph, Bn, or cyclopentylmethyl, unsatisfactory results were obtained.
(13) Under our standard conditions, an attempt to employ a 1,3-oxazol-5(4*H*)-one with R = *i*-Pr led to a low yield of the γ-addition product.
(14) For examples of natural products/bioactive compounds that include a 2-amino-3,5-dihydro-4*H*-imidazol-4-one subunit, see: (a) Gadwood, R. C.; Kamdar, B. V.; Dubray, L. A. C.; Wolfe, M. L.; Smith, M. P.; Watt, W.; Mizsak, S. A.; Groppi, V. E. *J. Med. Chem.* **1993**, *36*, 1480−1487. (b) Tsukamoto, S.; Kato, H.; Hirota, H.; Fusetani, N. *J. Nat. Prod.* **1996**, *59*, 501−503. (c) Edrada, R. A.; Stessman, C. C.; Crews, P. *J. Nat. Prod.* **2003**, *66*, 939−942.
(15) We hypothesize that the phenol may serve as a proton shuttle in this process.
(16) For other phosphine-catalyzed enantioselective γ-additions in which kinetic resolution of the allene has been examined, see: (a) No kinetic resolution: References 3b, d. (b) Kinetic resolution: References 3c, e.
(17) Estimated through computations: B3LYP/6-311+G(2d,2p); DFT-D3; CPCM; gas-phase G correction.
(18) Under the same conditions but in the absence of the 1,3-oxazol-5(4*H*)-one, the allenoate isomerizes to the 1,3-diene (Reference 6) at a rate and with a selectivity factor (kinetic resolution of the allenoate) that are essentially identical to those for the γ-addition reaction, consistent with the two processes sharing the same turnover-limiting step (formation of **A**).

DOI: 10.1021/jacs.5b05528
J. Am. Chem. Soc. 2015, 137, 9438−9442