

Phosphine-Catalyzed Enantioselective Intramolecular [3+2] Annulations To Generate Fused Ring Systems

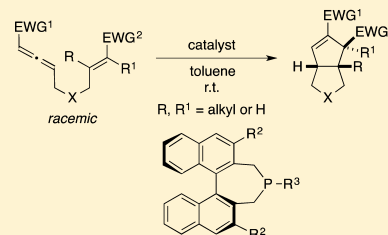
Sarah Yunmi Lee,^{†,‡} Yuji Fujiwara,[‡] Atsuko Nishiguchi,^{†,‡} Marcin Kalek,[†] and Gregory C. Fu^{*,†,‡}

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

[‡]Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

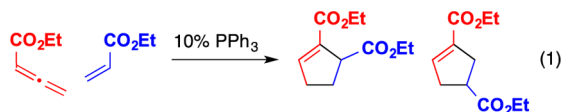
S Supporting Information

ABSTRACT: Substantial progress has been described in the development of asymmetric variants of the phosphine-catalyzed intermolecular [3+2] annulation of allenes with alkenes; however, there have not been corresponding advances for the intramolecular process, which can generate a higher level of complexity (an additional ring and stereocenter(s)). In this study, we describe the application of chiral phosphine catalysts to address this challenge, thereby providing access to useful scaffolds that are found in bioactive compounds, including diquinane and quinolin-2-one derivatives, with very good stereoselectivity. The products of the [3+2] annulation can be readily transformed into structures that are even more stereochemically rich. Mechanistic studies are consistent with β addition of the phosphine to the allene being the turnover-limiting step of the catalytic cycle, followed by a concerted [3+2] cycloaddition to the pendant olefin.



INTRODUCTION

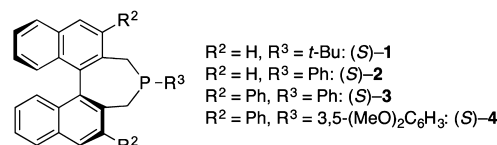
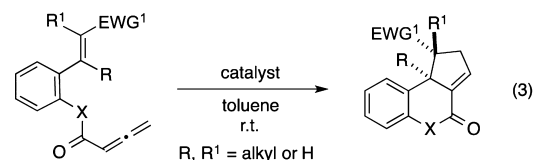
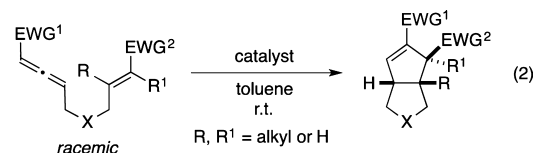
During the past decade, the use of chiral tertiary phosphines as enantioselective nucleophilic catalysts has expanded rapidly.¹ The phosphine-catalyzed [3+2] annulation of electron-poor allenes (or alkynes) with olefins, originally described by Lu,² represents a powerful approach to the synthesis of functionalized cyclopentenes (eq 1).³ Zhang reported the first example of an asymmetric variant of this method,⁴ and we⁵ and others⁶ have since enlarged the scope of such processes.⁷



Krische⁸ and Kwon⁹ have established that the intramolecular version of the Lu [3+2] annulation can circumvent the formation of isomeric products and generate an array of useful, stereochemically rich fused ring systems, including diquinane and coumarin derivatives.^{10,11} To date, despite the considerable progress that has been described for asymmetric catalysis of the intermolecular Lu annulation,^{4–6} there has been no corresponding success with intramolecular reactions, wherein the conformation of the stereochemistry-determining transition state is relatively constrained. In this Article, we establish that such catalytic enantioselective intramolecular [3+2] annulations can indeed be achieved, thereby affording functionalized, fused bicyclic ring systems that bear multiple contiguous stereocenters (eqs 2 and 3).

RESULTS AND DISCUSSION

In our initial studies, we chose to focus on the enantioselective synthesis of diquinanes, which Krische has established can be

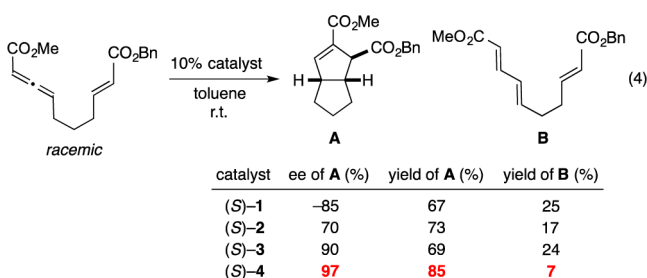


generated effectively in racemic form with $\text{P}(n\text{-Bu})_3$ as the catalyst.⁸ We have reported earlier that phosphinines can serve as useful chiral nucleophilic catalysts,^{12,13} and we have now determined that previously described phosphines 1–3 do indeed furnish promising results in the target annulation (eq 4). Furthermore, new chiral phosphine 4,¹⁴ which bears a 3,5-dimethoxyphenyl group on phosphorus, catalyzes the formation of the desired diquinane in excellent ee and high yield (eq 4; single diastereomer).^{15,16}

Phosphine 4 serves as an effective catalyst for the highly enantioselective synthesis of an array of diastereomerically pure

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diquinanes (and related structures) from acyclic precursors, generating two rings and three contiguous tertiary stereocenters in the process (Table 1).¹⁷ The electron-withdrawing group of

Table 1. Phosphine-Catalyzed Enantioselective Intramolecular [3+2] Annulations^a

entry	substrate	ee (%)	yield (%) ^b
1		97	83
2		98	86
3		98	84
4		98	90
5		93	88
6		97	75
7 ^c		97	88
8		95	88
9		94	95
10 ^d		86	82

^aAll data are the average of two experiments. ^bYield of purified product; only one diastereomer was observed (analysis of the unpurified mixture by ¹H NMR spectroscopy). ^cReaction temperature: 40 °C. ^dCatalyst (S)-2 (20%) was employed instead of (S)-4.

the allene can be any of an array of esters, and the electron-withdrawing substituent of the alkene can be an ester, thioester, or amide (e.g., entries 1–6).¹⁸ Significantly, good enantioselectivity and yield are observed with a variety of tethers between the allene and the alkene (entries 7–10), thereby furnishing a fused pyrrolidine as well as a benzannulated diquinane. These annulations are stereoconvergent processes wherein both enantiomers of the racemic allene are being converted by the chiral catalyst into the same stereoisomer of the product with good selectivity.

Next, we turned our attention to the challenge of achieving enantioselective intramolecular [3+2] annulations of substrates that include a trisubstituted olefin.¹⁹ We have determined that chiral phosphinines can indeed catalyze the desired annulations with good enantioselectivities and yields, as well as complete diastereoselectivity (Table 2). Any of a variety of linkers between

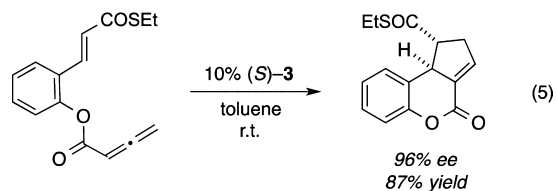
Table 2. Catalytic Enantioselective Intramolecular [3+2] Annulations: Trisubstituted Olefins as a Reaction Partner^a

entry	catalyst	substrate	ee (%)	yield (%) ^b
1 ^c	(S)-1		97	56
2	(R)-4		98	93
3	(S)-1		94	78
4	(R)-2		90	94

^aAll data are the average of two experiments. ^bYield of purified product; only one diastereomer was observed (analysis of the unpurified mixture by ¹H NMR spectroscopy). ^cCatalyst loading: 20%.

the allene and the alkene are tolerated, as are different classes of trisubstituted olefins, thereby affording an array of products that include a quaternary stereocenter.²⁰

We sought to demonstrate that the scope of this new method for catalytic enantioselective intramolecular [3+2] cycloadditions extends beyond the synthesis of diquinane-like structures. Building on Kwon's report of P(*n*-Bu)₃-catalyzed, diastereoselective [3+2] annulations to furnish fused dihydrocoumarins,⁹ we have developed an enantioselective variant of this reaction that proceeds in very good ee and yield (eq 5; a single diastereomer).



Encouraged by this result, we decided to pursue the application of our method to the catalytic asymmetric synthesis of fused quinolin-2-ones, a motif found in an array of bioactive compounds²¹ and which to our knowledge has not previously been generated via such a [3+2] annulation. We have determined

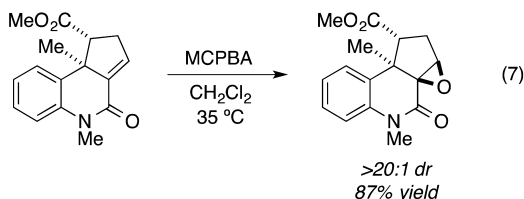
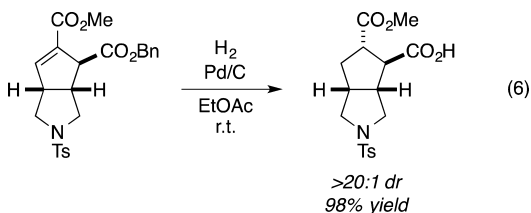
that phosphine **4** does indeed catalyze the desired transformation with moderate-to-good enantioselectivity and in high yield, thereby affording two rings and two adjacent stereocenters (Table 3). The substrates may include either a di- or a trisubstituted olefin.

Table 3. Catalytic Enantioselective Intramolecular [3+2] Annulations To Generate Quinolin-2-one Derivatives^a

entry	substrate	ee (%)	yield (%) ^b
1 ^c		66	91
2 ^d		90	91
3 ^c		82	82

^aAll data are the average of two experiments. ^bYield of purified product; only one diastereomer was observed (analysis of the unpurified mixture by ¹H NMR spectroscopy). ^cCatalyst loading: 20% (S)-**4**. ^dCatalyst loading: 10% (S)-**4**.

Diastereoselective functionalization of the various annulation products can provide additional stereocenters. For example, hydrogenation and epoxidation proceed with high stereoselectivity and yield (eqs 6 and 7).



An outline of a possible mechanism for the phosphine-catalyzed enantioselective intramolecular [3+2] annulation of allenes with alkenes is depicted in Figure 1.⁷ Nucleophilic addition of the phosphine to the β position of the allene

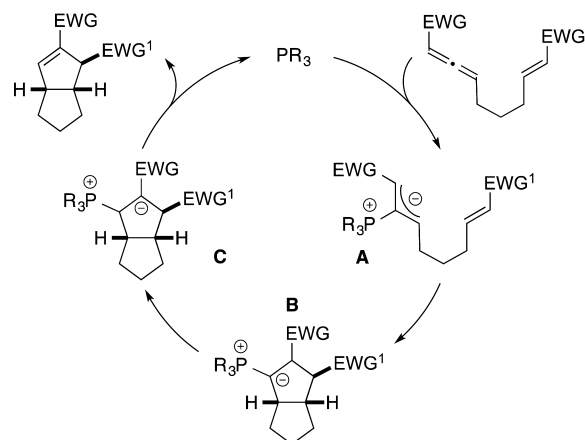
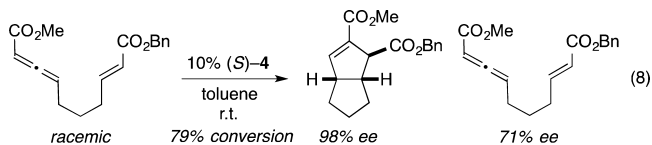


Figure 1. An outline of a possible mechanism for phosphine-catalyzed enantioselective intramolecular [3+2] annulations of allenes with alkenes.

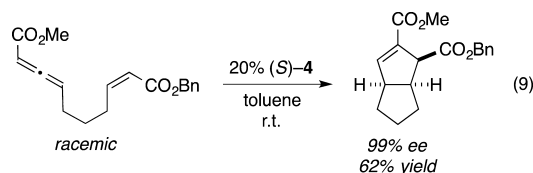
generates zwitterion **A**, which undergoes a cycloaddition with the alkene, furnishing a new zwitterion (**B**), which tautomerizes to **C**. Fragmentation then affords the bicyclic product and regenerates the phosphine catalyst.

When an asymmetric intramolecular [3+2] annulation is stopped at partial conversion, modest enantiomeric enrichment of the unreacted allene is observed (eq 8; $s \sim 2.7$), indicating that



the chiral catalyst can discriminate between the enantiomers of the racemic substrate.^{22,23} Taking into account our observation that the predominant resting state of the catalyst during the reaction is the free phosphine (³¹P NMR spectroscopy), we hypothesize that the first step of the catalytic cycle is likely the turnover-limiting step (Figure 1).

Finally, to gain insight into whether ring formation (**A** \rightarrow **B** in Figure 1) occurs through a concerted or through a stepwise pathway, we have examined the configuration of the product as a function of the configuration of the olefin of the starting material. The stereochemical outcomes for all of the reactions described above are consistent with a concerted mechanism; however, there are no direct comparisons between corresponding *E* and *Z* olefins. We therefore investigated the [3+2] annulation of the *Z* isomer of the substrate depicted in entry 1 of Table 1, and we have determined that it leads to the epimeric diquinane as a single isomer (eq 9), consistent with formation of the five-membered ring via a concerted pathway.²⁴



CONCLUSIONS

We have developed the first phosphine-catalyzed enantioselective intramolecular [3+2] cycloadditions of allenes with olefins, a

process that generates two new rings and multiple stereogenic centers. Thus, an array of diastereomerically pure fused ring systems that are found in bioactive compounds, including diquinane and quinolin-2-one derivatives, are produced in generally good ee and yield with the aid of chiral phosphine catalysts; furthermore, the bicyclic reaction products are well-suited for further diastereoselective functionalizations. Mechanistic studies establish that the chiral catalyst has a modest preference for reaction with one of the enantiomers of the racemic substrate and that the rate-determining step for the overall process is likely the initial addition of the phosphine to the allene; the resulting adduct then undergoes a concerted intramolecular [3+2] cycloaddition with the pendant olefin. Further studies of enantioselective nucleophile-catalyzed processes are underway.

EXPERIMENTAL SECTION

General Procedure. The phosphine catalyst (0.10 equiv) was added to an oven-dried 20 mL vial equipped with a stir bar. This vial was capped with a septum-lined cap, the joint was covered with electrical tape, and then the vial was evacuated and backfilled with nitrogen (three cycles). The substrate (1.00 equiv) was added to a separate vial, which was then capped with a septum-lined cap, the joint was covered with electrical tape, and then the vial was evacuated and backfilled with nitrogen (three cycles). Next, toluene (anhydrous) was added to the vial that contained the substrate. This solution was added via syringe to the vial that contained the catalyst (under a positive pressure of nitrogen). Next, the reaction vial was detached from the nitrogen manifold, and grease was applied to the puncture hole in the septum in order to impede moisture/air from entering the vial. The reaction mixture was stirred at room temperature for 24 h, and then an aqueous solution of hydrogen peroxide (10%; 1.0 mL) was added. The resulting mixture was stirred for 10 min, and then an aqueous solution of Na₂S₂O₃ (saturated; 2.0 mL) was added. The mixture was stirred for 10 min, and then the aqueous layer was extracted with EtOAc (5 mL × 3), and the combined organic layers were dried over MgSO₄ and then concentrated under reduced pressure. The resulting residue was purified by column chromatography.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

*gcfu@caltech.edu

Notes

The authors declare no competing financial interest.

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- (14) As a solid, phosphine **4** is stable to air: after exposure to air for 2 months, no phosphine oxide was detected upon analysis by ³¹P NMR spectroscopy; as a solution in toluene open to air, no phosphine oxide was evident after 12 h.
- (15) For an example of a PPh₃-catalyzed isomerization of an allenolate to an $\alpha,\beta,\gamma,\delta$ -unsaturated ester, see: Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933–7935.
- (16) A negative ee value signifies that the major annulation product is the enantiomer of **A**.
- (17) Notes: (a) For entry 1 of Table 1, the ee of the product is constant throughout the annulation. (b) A preliminary attempt to apply our standard conditions to the corresponding synthesis of a hydrindane was not successful. (c) For the determination of the relative and absolute configuration of the various reaction products, see the Supporting Information.
- (18) In contrast, α,β -unsaturated esters were not suitable reaction partners in Krische’s P(*n*-Bu)₃-catalyzed intramolecular [3+2] annulation (ref 8a).

(19) To the best of our knowledge, there has been only one report of an intramolecular Lu annulation of a substrate wherein the olefin is trisubstituted (ref 8b).

(20) For a discussion of the challenges associated with the enantioselective synthesis of quaternary stereocenters, see: *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: New York, 2005.

(21) Abilify is an example of a bioactive compound that includes a quinolin-2-one subunit.

(22) We are aware of one previous report of kinetic resolution in a Lu [3+2] annulation, an intermolecular coupling with $s \sim 1.3$ (ref 5b).

(23) Notes: (a) The ee of the product is independent of the enantiomeric purity of the allene. (b) The reaction of an enantioenriched allene with an achiral phosphine led to racemic product. (c) We have examined the rate law, employing enantioenriched (the more reactive enantiomer), rather than racemic, starting material, to avoid complications due to the divergent reactivity of the two enantiomers. The rate law is first order in the catalyst and \sim first order in the substrate. No racemization of the enantioenriched substrate is observed during the course of these kinetics studies.

(24) This is consistent with Krische's observations for a $P(n\text{-Bu})_3$ -catalyzed intramolecular cycloaddition (ref 8b) and stands in contrast to the stepwise pathway that has been suggested for intermolecular annulations (ref 7).