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Catalytic Enantioselective Synthesis of Guvacine Derivatives through [4 + 2] Annulations of Imines with α-Methylallenoates

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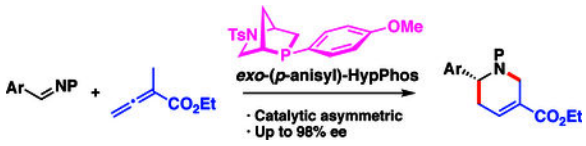
Abstract

P-Chiral [2.2.1] bicyclic phosphines (HypPhos catalysts) have been applied to reactions between α-alkylallenoates and imines, producing guvacine derivatives. These HypPhos catalysts were assembled from *trans*-4-hydroxyproline, with the modular nature of the synthesis allowing variations of the exocyclic P and N substituents. Among them, *exo*-(*p*-anisyl)-HypPhos was most efficacious for [4 + 2] annulations between ethyl α-methylallenoate and imines. Through this method, (*R*)-aplexone was identified as being responsible for the decrease in the cellular levels of cholesterol.

Graphical Abstract



Functionalized tetrahydropyridines and piperidines are common structural motifs in many biologically active natural products[1] and synthetic pharmaceuticals.[2] In fact, piperidine is the most frequently encountered heterocycle in the top-200 drug list.[3] One particular piperidine structure, the guvacine (**1**) moiety (Figure 1), has been identified as the pharmacophore of the γ-aminobutyric acid (GABA) uptake inhibitor.[4–7] GABA is one of the major mammalian inhibitory neurotransmitters, and a number of diseases, including Parkinson's, Huntington's, epilepsy, and schizophrenia, have been linked to the dysfunction of GABAergic synapses.[5] Modification at the C6 position of guvacine (as in compound **2**)

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Supporting Information

Representative experimental procedures and spectral data for all new compounds (PDF). Crystallographic data for compound **7n** (CIF).

The Supporting Information is available free of charge on the ACS Publications website.

can also result in good GABA up-take inhibition.[4c,7] Our recent collaboration with the Chen laboratory has revealed that another guvacine derivative, aplexone (**3**), regulates arteriovenous angiogenesis in zebrafish by acting on the HMG-CoA reductase pathway.[8] In the same zebrafish studies, we found that aplexone lowered the levels of embryonic cholesterol to a degree similar to that of atorvastatin (trade name: Lipitor). Intrigued by the prevalence of 6-substituted tetrahydropyridine motifs in both natural products and active pharmaceutical ingredients (APIs), we wished to develop a simple process for their synthesis.

A survey of the literature revealed a limited number of general methods for the enantioselective synthesis of 6-substituted guvacines.[9] Ramachandran's group was the first to report the preparation of C6-chiral guvacine derivatives. They installed the C6-chiral center through the allylation of imines using (–)-*B*-allyldiisopinocampheylborane, in lengthy syntheses (Scheme 1A).[9a]

Previously, we reported a general method for the synthesis of functionalized tetrahydropyridines through phosphine-catalyzed [4 + 2] annulation of imines with 2-alkyl-2,3-butadienoates.[10,11] A catalytic asymmetric version of this transformation, using a chiral phosphine catalyst, was presented by Fu; while high ee's were obtained in the syntheses of 2,6-disubstituted guvacines, 6-substituted guvacines were formed with only moderate enantioselectivities.[12a] Zhao and colleagues also developed an enantioselective synthesis of 2,6-disubstituted guvacines catalyzed by an amino acid–derived bifunctional phosphine; under their conditions, however, the 6-phenyl guvacine ester could not be obtained (Scheme 1B).[12b] Furthermore, Guo and Sasai both reported catalytic asymmetric [4 + 2] annulations of sulfamate-derived cyclic imines with allenoates; again, they obtained high ee's only for 2,6- or 6,6-disubstituted guvacine derivatives, respectively (Scheme 1C).[12c,d] Seeking to overcome the limitations in preparing 6-substituted guvacine esters, we examined a catalytic asymmetric [4 + 2] annulation of a simple α-methylallenoate.

Recently, we developed a class of *trans*-hydroxy-L-proline (Hyp)–derived chiral phosphines, which we have named "Hyp-Phos" ligands (Figure 2).[13a] These catalysts are readily synthesized on a decagram scale and are also commercially available through Sigma–Aldrich.[14,15] We drew on these unique P-chiral phosphines previously to develop an asymmetric version of Lu's [3 + 2] annulation.[16] Herein, we disclose the asymmetric synthesis of 6-substituted guvacines through the [4 + 2] annulation of imines with ethyl α-methylallenoate (Scheme 1D).

We began our investigation by treating the *N*-(*p*-nitrobenzenesulfonyl) (*p*-Ns) imine **6a** with ethyl α-methylallenoate (**5**) in the presence of the HypPhos catalyst **4a** (Table 1, entry 1). Although we obtained 80% ee, the yield was low despite complete consumption of the imine. One of the byproducts was *p*-nitrobenzenesulfonamide, formed from hydrolysis of the imine. We suspected that beneficial effects would arise if we could inhibit imine hydrolysis using water- or acid-sequestering additives. After testing many inorganic salts, drying agents, and other additives (entries 2–4), we obtained the best results (89% yield, 79% ee; entry 4) after adding 4-Å molecular sieves (MS) at 100 mg/mmol. After vetting several solvents, we found that CH_2Cl_2, the solvent employed in the original 2003 report,[10a]

was most amenable for this annulation.[18] While a *p*-Ns group on the imino nitrogen atom resulted in higher selectivity for the g-adduct, under these conditions a *p*-toluenesulfonyl (*p*-Ts) group provided a similar yield and higher ee (entry 5). The modular synthesis of the HypPhos catalysts **4** allowed straightforward variation of the exocyclic substituents on both the P and N atoms (entries 6–11).[13a] With the exception of **4d**, the *exo*-Hyp-Phos catalysts **4a**–**f** all afforded good yields and enantioselectivities. When using the catalysts **4c** or **4f**, one regioisomer was obtained almost exclusively (entries 7 and 10). The *endo* phenyl-HypPhos **4g**, with the opposite configuration at the P center, rendered the opposite enantioselectivity (as it did also in the allenoate–imine [3 + 2] annulation),[13] but the enantioselectivity was lower (entry 11). Considering the combination of regioselectivity, yield, and ee, we chose *exo*-(*p*-anisyl)-HypPhos **4c** as the catalyst for the enantioselective production of 6-substituted guvacines.

The enantioselectivity decreased slightly in the presence of additives, particularly base (cf. entries 1 and 3). We hypothesized that the higher enantioselectivity in the absence of additives might have been caused by the presence of acidic *p*-nitrobenzenesulfonamide, a byproduct of the hydrolysis of the imine. Bifunctional chiral phosphines containing hydrogen bond donors are ubiquitous in asymmetric phosphine organocatalysis.[19] We have also documented that the presence of a Brϕnsted acid enhanced the reaction rate and enantioselectivity of the allene–imine [3 + 2] annulation employed in our total synthesis of (–)-actinophyllic acid.[16a] From an examination of more than a dozen Brϕnsted acid additives, we found that acetic acid (10 mol%) produced the best enantioselectivity, with a slight decrease in product yield (entry 12).[18] We also tested the effects of other protecting groups on the imino nitrogen atom (entries 13–17). Reasonable yields of the guvacine products were obtained from the imines **6b**–**d** in the presence of both 4-Å MS and acetic acid (entries 13–15). The *p*-bromobenzenesulfonyl imine **6e** and the *o*-nitrobenzenesulfonyl imine **6f** proved to be too labile under these conditions, providing their annulation products in lower yields (entries 16 and 17). Based on the combination of regioselectivity, product yield, enantioselectivity, and ease of removal,[20] we chose the *p*-Ns protecting group for further application.

Under the optimized conditions, a range of imines could be employed as substrates in the catalytic syntheses of guvacine derivatives, with excellent enantioselectivities (Table 2).[21] Imines derived from benzaldehydes presenting electron-donating substituents reacted with higher yields and stereoselectivities (entries 2–5), while benzaldimines featuring electron-withdrawing substituents produced slightly lower yields and enantioselectivities (entries 6–12). These trends became more prominent for *ortho*-substituted benzaldimines (cf. entries 2 and 6). While the imine **6g** provided the guvacine product **7g** in 81% yield and 95% ee, the imine **6k**, derived from *o*-chlorobenzaldehyde, generated its product **7k** in 29% yield and 74% ee.

On the basis of X-ray diffraction of **7n**, we assigned the absolute configuration of the 6-substituted guvacine esters unambiguously as the *R*-configuration.[22] Strikingly, the C6 phenyl substituent adopts the axial position of the half-chair conformer of the guvacine ester ring, presumably to minimize any steric clash with the adjacent *p*-nitrobenzenesulfonyl group. Heteroaryl imines were also suitable substrates for this annulation (entries 13 and

14). 2-Furyl and 2-thienyl substituents produced their guvacines in 93 and 96% ee, respectively. The 2-*N*-methylpyrrole-imine **6t** produced the corresponding guvacine product **7t** in good yield, albeit with moderate ee (entry 15), presumably because of the proximal *N*-methyl group, similar to the steric effect observed for the reaction of *o*-chlorobenzaldimine in entry 6.

Based on modeling of the transition state of the allene–imine [3 + 2] annulation, we propose the transition state model shown in Figure 3 for the [4 + 2] reaction between the allenoate **5** and the imine **6a**. Two key favorable interactions present in the stereochemistry-determining transition state are a Coulombic interaction between the allenoate C=O oxygen atom and the phosphorus atom of the phosphonium enolate, and hydrogen bonds between the imine *N*-sulfonyl oxygen atom and hydrogen atoms on the carbon atom α to the phosphonium center.[23] The former locks the phosphonium dienolate in place, and the latter allows for a controlled *Re*-face attack of the imine to give the (*R*)-annulation product.

The products of these [4 + 2] reactions can be further transformed into a variety of derivatives. For example, compound **7a** undergoes denosylation[20] to produce ethyl 6-phenylguvacine **8** with no loss of optical purity (Scheme 2A).[24] In this manner, it should be possible to synthesize a variety of optically pure guvacine derivatives.[25] We suspected that we could use this annulation to synthesize other biologically important compounds in an asymmetric fashion. The asymmetric synthesis of APIs has gained considerable attention in recent years.[26] In this vein, we wished to identify the eutomer of aplexone (**3**) in hopes of employing it in future biological studies. Applying the HypPhos catalysts **4c** and **ent-4c**, we obtained both enantiomers of the annulation product **7c** in 56% yield and 98% ee. We then accessed aplexone (**3**) through a high-yielding Tebbe olefination/hydrolysis sequence (Scheme 2B).

Using the approach reported previously, we examined the development of the caudal vein plexus in zebrafish embryos.[8] These initial phenotypic assays revealed that (*R*)-aplexone is the active enantiomer, while (*S*)-aplexone did not affect plexus development at the concentrations tested. Specifically, (±)-aplexone produced a “no plexus” phenotype at a concentration of 10 μM, while (*R*)-aplexone was more potent, producing a “no plexus” phenotype at a concentration of only 5 μM.[27] (*S*)- Aplexone, on the other hand, did not disrupt plexus formation, even at 20 μM. Next, we tested the abilities of (*R*)- and (*S*)-aplexone to decrease the cellular levels of cholesterol in zebrafish embryos (Figure 4). (±)-Aplexone lowered the cholesterol levels to an extent similar to that of atorvastatin (AT). We concluded that (*R*)-aplexone is the active enantiomer: it decreased the cholesterol levels to a greater extent than AT; (*S*)-aplexone had no such activity.

In summary, we have demonstrated, for the first time, highly enantioselective [4 + 2] annulations of ethyl α-methylallenoate and imines for the construction of chiral guvacine derivatives. Using HypPhos catalysts, the methodology disclosed herein provides the highest enantioselectivities to date when synthesizing 6-substituted guvacine derivatives. We have also demonstrated that (*R*)-aplexone is the API responsible for the compound’s cholesterol-lowering effects. This methodology is an expedient and economical way of producing (*R*)-aplexone, potentially allowing future studies into its mode of action and medicinal potential.

Further explorations of the catalyst structure, improvements in reaction efficiency, and applications of this methodology to other synthetic endeavors are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

This study was supported by the NIH (R01GM071779) and the NSF (equipment grant CHE-1048804). We are grateful to Boehringer Ingelheim for the generous donation of (2*R*,4*S*)-hydroxyproline and the Scientific Advancement Grant. We thank Dr. Saeed Khan (UCLA) for the crystallographic analyses. Q. X. and N. D. thank Prof. Neil K. Garg, Ben W. Boal, and Lucas Morrill (UCLA) for sharing their SFC instrument.

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(14). See the Supporting Information for the synthetic procedures and characterization data of the HypPhos catalysts 4b–f and ent-4a.

(15). For the Kwon Group Sigma–Aldrich Professor Portal, visit: http://www.sigmaaldrich.com/technical-documents/articles/chemistry/professor-and-product-portal/ohyun-kwon.html.

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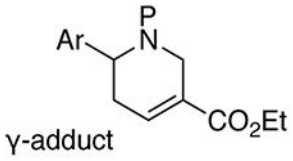
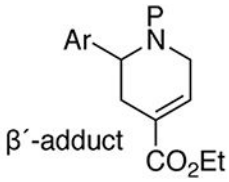
(17). The structures of g- and b´-adducts are provided below.





(18). See the Supporting Information for more details.

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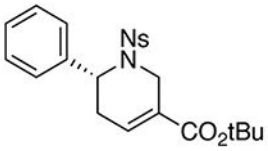
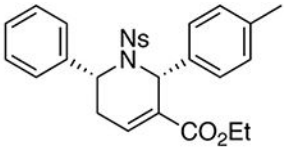
(21). tert-Butyl α-methylallenoate was coupled with the imine 6a to give the annulation product 7u in 85% yield and 74% ee. Ethyl α-(p tolylmethyl)allenoate was coupled with the imine 6a to give the annulation product 7v in 67% yield and 77% ee.



7u
85% yield
74% ee



7v
67% yield
77% ee

(22). CCDC 903385 contains the supplementary crystallographic data for compound 7n. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

(23). The P–O distance was measured at 2.59 Å; the natural bond orbital (NBO) interaction energy (ENBO) was 6.04 kcal/mol in the [3 + 2] annulation.13 Measured distances and NBO interaction energies (ENBO) of these contacts were 2.33 Å (ENBO = 1.88 kcal/mol) and 2.50 Å (ENBO = 1.46 kcal/mol) in the [3 + 2] annulation.

(24). Interestingly, the enantiomer of ethyl 6-phenylguvacine (8) with 88% ee was reported to have a value of [a]D20 of +68° (CHCl3, c = 0.1). See reference (9c) for details.

(25). Attempts to make alkyl-substituted guvacine derivatives akin to the GABA uptake inhibitor 2 led only to hydrolysis of the imine. Withholding the catalytic AcOH did not inhibit hydrolysis of the alkyl imine.

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(27). See the Supporting Information for images of the zebrafish embryo development.

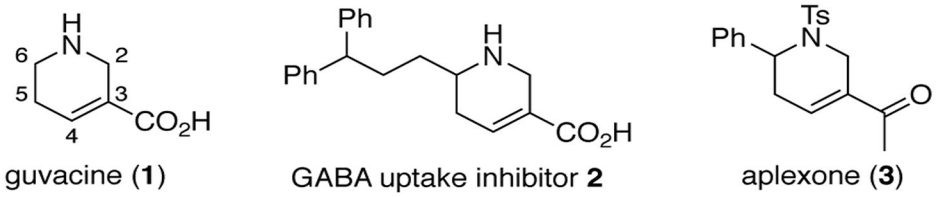


Figure 1.
Guvacine and bioactive guvacine derivatives.

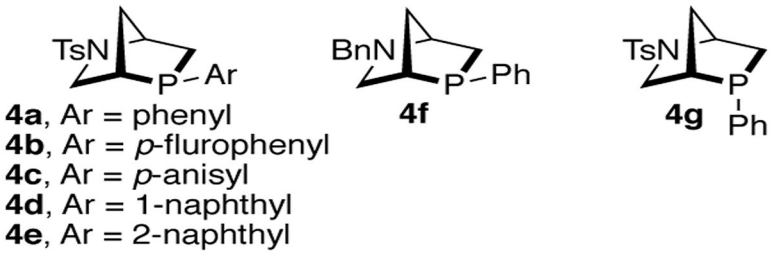


Figure 2.
HypPhos catalysts **4**.

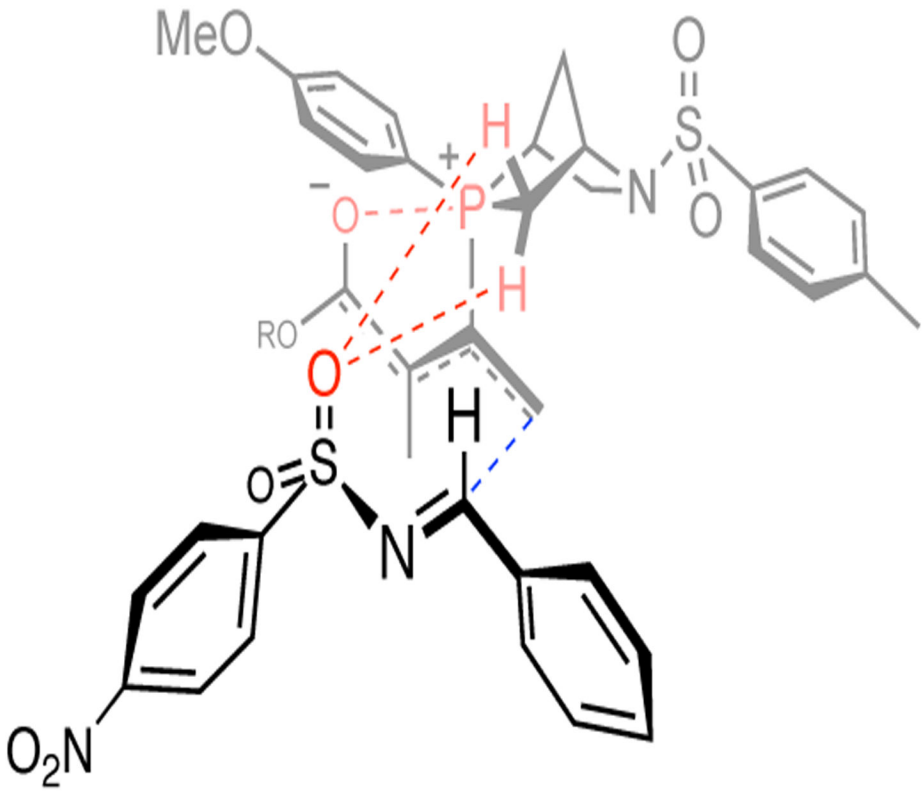


Figure 3.
Proposed transition state for the [4 + 2] annulation of **5** and **6a**.

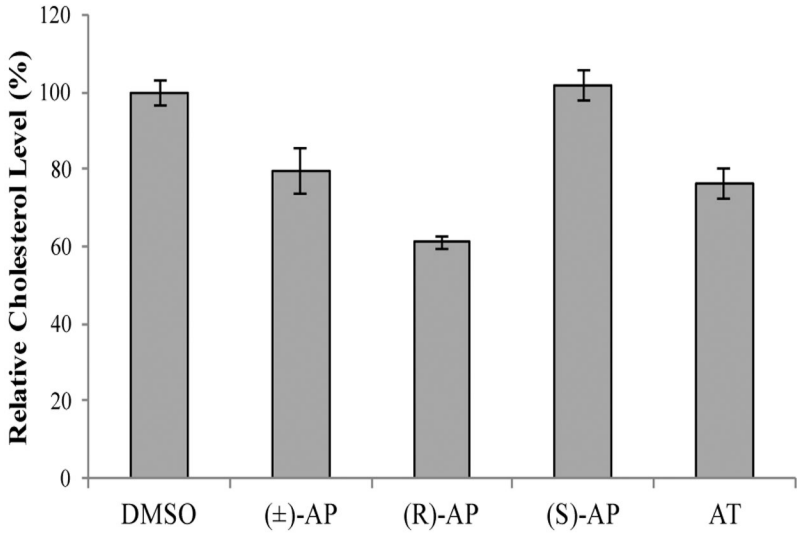
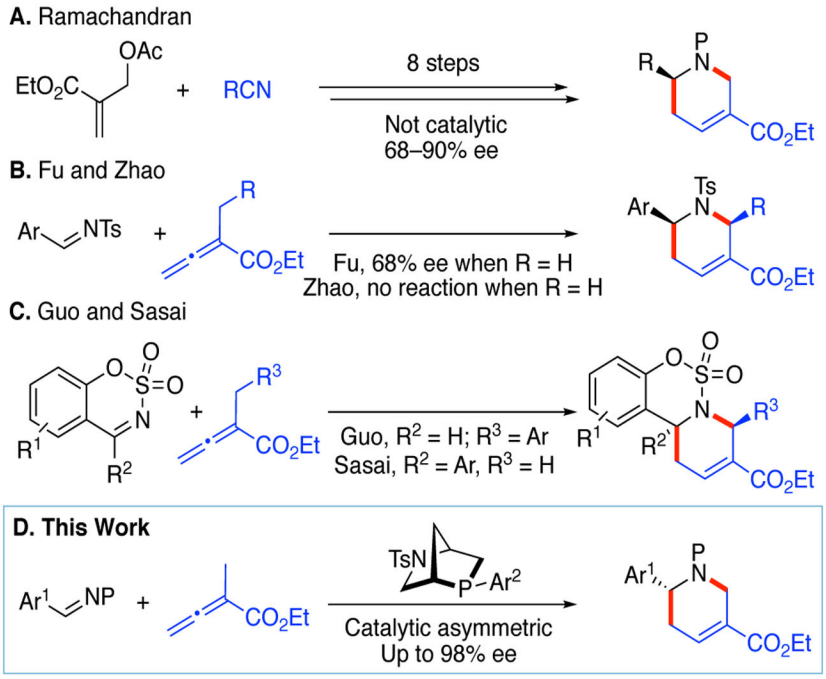
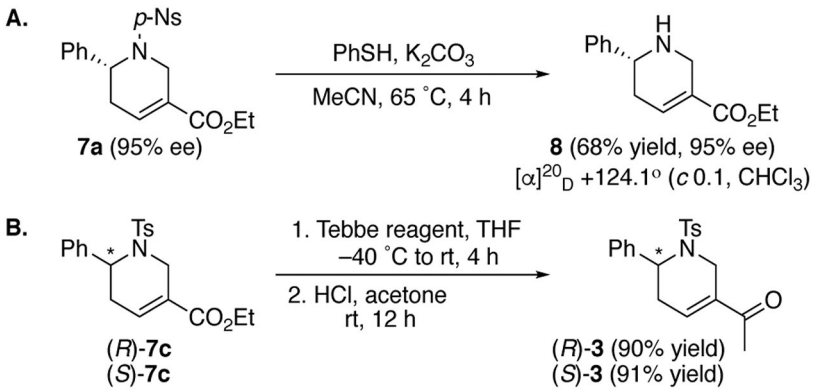


Figure 4.

Relative cellular levels of cholesterol in zebrafish embryos treated with aplexone (AP) and atorvastatin (AT), both at 40 μM; DMSO used as a control.[18]



Scheme 1.
Synthesis of guvacine derivatives.

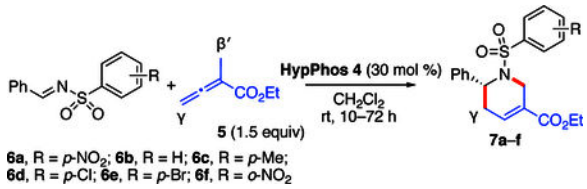


Scheme 2.

Transformations of **7a** and **7c**.

Table 1.

Asymmetric allenoate–imine [4 + 2] annulations.



entry	6	4	additive	ratio[a]	yield (%)[b]	ee (%)[c,d]
1	**6a**	**4a**	none	1:0.03	36	80
2	**6a**	**4a**	$MgSO_4$	1:0.03	42	77
3	**6a**	**4a**	Na_2CO_3	1:0.03	54	75
4	**6a**	**4a**	4 Å MS	1:0.03	89	79
5	**6c**	**4a**	4 Å MS	1:0.22	78	89
6	**6a**	**4b**	4 Å MS	1:0.02	71	77
7	**6a**	**4c**	4 Å MS	>1:0.01	89	77
8	**6a**	**4d**	4 Å MS	1:0.08	54	79
9	**6a**	**4e**	4 Å MS	1:0.03	81	81
10	**6a**	**4f**	4 Å MS	>1:0.01	84	73
11	**6a**	**4g**	4 Å MS	1:0.01	82	−48
12[e]	**6a**	**4c**	4 Å MS	1:0.01	70	95
13[e]	**6b**	**4c**	4 Å MS	1:0.04	50	97
14[e]	**6c**	**4c**	4 Å MS	1:0.05	56	98
15[e]	**6d**	**4c**	4 Å MS	1:0.14	67	91
16[e]	**6e**	**4c**	4 Å MS	1:0.02	46	94
17[e]	**6f**	**4c**	4 Å MS	1:0.05	29	97

[a] Regioisomeric ratio of γ:β′ adducts, determined from the ^{1}H NMR spectrum of the crude reaction product.[17]

[b] Isolated yield after column chromatography.

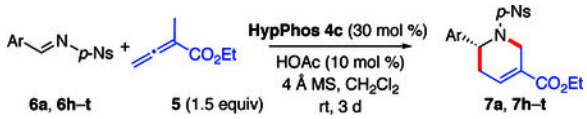
[c] Determined through supercritical fluid chromatography (SFC) using an AS or OJ-H column.

[d] The ee of the major product.

[e] AcOH (10 mol %) was added.

Table 2.

Substrate scope for asymmetric [4 + 2] annulations.



entry	6 (Ar)	product	ratio[a]	yield (%)[b]	ee (%)[c]
1	**6a**, Ph	**7a**	1:0.01	70	95
2	**6g**, *o*-$MeOC_6H_4$	**7g**	>1:0.01	81	95
3	**6h**, *m*-MeOC6H4	**7h**	1:0.01	66	97
4	**6i**, *p*-$MeOC_6H_4$	**7i**	1:0.04	63	96
5	**6j**, *p*-MeC_6H_4	**7j**	1:0.01	64	98
6	**6k**, *o*-ClC6H4	**7k**	>1:0.01	29	74
7	**6l**, *m*-ClC6H4	**7l**	>1:0.01	50	94
8	**6m**, *p*-ClC6H4	**7m**	1:0.01	53	97
9	**6n**, *p*-BrC_6H_4	**7n**	1:0.01	51	97
10	**6o**, *p*-FC_6H_4	**7o**	1:0.02	64	96
11	**6p**, *P*-NCC6H4	**7p**	>1:0.01	51	90
12	**6q**, *P*-O2NC6H4	**7q**	>1:0.01	52	96
13	**6r**, 2-furyl	**7r**	>1:0.01	63	93
14	**6s**, 2-thienyl	**7s**	>1:0.01	59	96
15	**6t**, 2-*N*-methylpyrrolyl	**7t**	1:0.45	73	59

[a] Regioisomeric ratio of g:b´ adducts determined from ^{1}H NMR spectrum of crude reaction product.[17]

[b] Isolated yield after column chromatography.

[c] Determined through SFC using an AS or OJ-H column.