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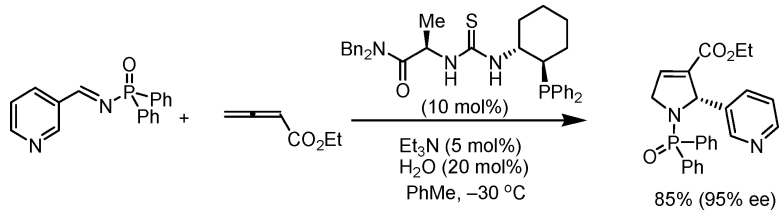
J. Am. Chem. Soc., **2008**, 130 (17), 5660-5661 • DOI: 10.1021/ja801344w • Publication Date (Web): 08 April 2008



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Published on Web 04/08/2008

Cooperative, Highly Enantioselective Phosphinothiourea Catalysis of Imine−Allene [3 + 2] Cycloadditions

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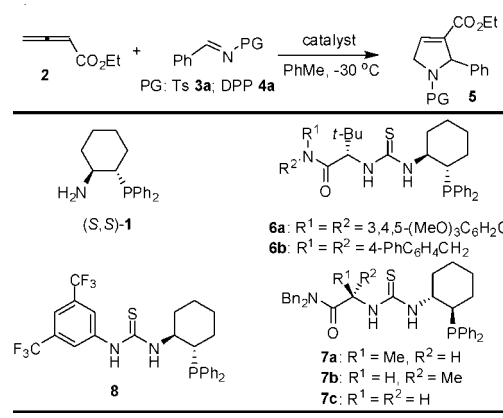
Several classes of polyfunctional small molecule catalysts have been identified capable of inducing enantioselective additions through cooperative activation of nucleophilic and electrophilic reacting partners.[1] Very recently, catalysts bearing hydrogen-bonding motifs in addition to nucleophilic functionality, such as proline and thiourea-based systems, have been utilized successfully in a variety of such transformations.[2] We became interested in the possibility of incorporating reactive phosphine groups into chiral H-bonding catalyst frameworks, with the goal of taking advantage of their high nucleophilicity and low Brønsted basicity in cooperative reaction pathways.[3,4] Among the large number of known, synthetically valuable phosphine-catalyzed reactions, [3 + 2] cycloadditions of electron-deficient allenes with electron-deficient olefins and imines to form cyclopentenes and pyrrolidines are particularly interesting targets for asymmetric catalysis. Zhang and Fu have shown that chiral monodentate phosphines designed originally as ligands for transition metal catalysts effectively promote the enantioselective formation of cyclopentenes.[5] More recently, Miller has demonstrated that α-amino acid-derived phosphines induce analogous allene-alkene cycloadditions with high ee and opposite regioselectivity.[6] In contrast, the enantioselective construction of dihydropyrroles by formal [3 + 2] cycloaddition between allenes and imines has met with very limited success,[7] despite the clear utility that such transformations would hold.[8] Here, we describe the development of a new class of chiral bifunctional thiourea catalysts derived from readily accessible *trans*-2-amino-1-(diphenylphosphino)cyclohexane (**1**),[9] and its application to the highly enantioselective synthesis of a wide range of 2-aryl-2,5-dihydropyrrole derivatives (see Scheme 1).

Exploratory studies on the model reaction between allene **2** and tosyl imine **3a** led to the observation that phosphinothioureas derived from **1** and (L)-*t*-Leu amides displayed promising reactivity and enantioselectivity (**6a**, 68% ee, and **6b**, 62% ee). Variation of the imine *N*-substituent with sterically and electronically modified sulfonyl, phosphinoyl, or carbamate groups revealed that diphenylphosphinoyl (DPP) imine **4a** afforded highest enantioselectivities (93% ee with **6b**). However, the use of DPP imine **4a** led to significantly diminished reactivity (Table 1, entry 1) and variable yields on >0.2 mmol scale. These problems may be attributed in part to the diminished electrophilicity of the DPP imine, and are consistent with Lu's observations in PPh_3-catalyzed imine−allene [3 + 2] cycloaddition reactions.[3b]

Inclusion of a combination of both basic and weakly acidic additives resulted in significant enhancements in reaction rate. The serendipitous observation was made that traces of Et_3N contamination (∼2%) remaining from the synthesis of allene **2**[10] led to improved substrate conversion and cleaner product formation with no detrimental effect on ee. In recent computational and experimental studies, Yu and co-workers identified an important beneficial role for water in phosphine-catalyzed alkene−allene [3 + 2] cycloadditions.[11] This proved to be the case in the present system

Scheme 1



as well, as inclusion of 3Å molecular sieves led to both suppressed rates and formation of a variety of undesired byproduct (Table 1, entry 3). In contrast, addition of 0.2 equiv of H_2O afforded improved reaction rates (Table 1, entries 5 and 6).

Thiourea catalysts derived from *tert*-leucine have proven optimal in a wide range of enantioselective reactions,[12] and this was the impetus for selecting this amino acid for the construction of catalyst **6**. However, we were intrigued by the observation that the relative stereochemistry in **6** leading to highest product ee values in the [3 + 2] cycloadditions was opposite from that of all diaminocyclohexane/*t*-Leu-derived thiourea catalysts identified to date. This led us to investigate whether the *t*-Leu component in **6** is in fact optimal or even necessary in the phosphinothiourea catalysts. Indeed, variation of the α-amino acid as its dibenzyl amide in thioureas derived from **1** revealed that the simplified Ala-derived catalyst **7a** afforded markedly improved enantioselectivity (98% ee, Table 1, entry 7). Interestingly, use of the diastereomeric Ala-derived catalyst **7b** or Gly-derived **7c** resulted in slightly diminished ee values (87−88%), but significantly poorer reactivity (Table 1, entries 8−9). Thus, the amino amide plays a secondary role relative to the aminophosphine component of the catalyst with respect to enantioinduction, but is nonetheless important for catalyst activity. Consistent with this notion, 3,5-bistrifluoromethylphenyl thiourea catalyst **8** displayed very poor reactivity (Table 1, entry 10), despite the fact that analogous arylthiourea derivatives are effective catalysts in a wide range of other applications.

Under the optimized conditions and in the presence of catalyst **7a**, the [3 + 2] cycloaddition of allene **2** with DPP imines displays broad scope (Table 2). Excellent enantioselectivities were obtained for a variety of aryl and heteroaryl imines.[13] Electron-rich imines exhibited low reactivity and required the use of higher catalyst loadings (20 mol %) to achieve complete conversion within 48 h (entries 3, 6). Substantially higher catalytic activity was observed with electron-deficient DPP

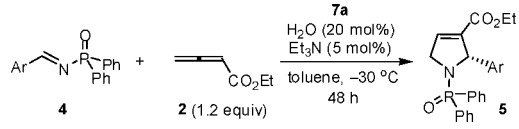
10.1021/ja801344w CCC: $40.75

Table 1. Additive Effects in the [3 + 2] Cycloaddition of **2** and **4a**[a]

entry	catalyst	additives: Et_3N (mol%)	additives: H_2O (mol%)	time (h)	conversion (%)[b]	ee (%)
1	**6b**			48	45	93 (*R*)
2	**6b**	2		48	70	n.d.[c]
3	**6b**	5	[d]	48	70[e]	n.d.[c]
4	**6b**	5		24	70	n.d.
5	**6b**		20	24	86[f]	n.d.
6	**6b**	5	20	24	88[g]	93 (*R*)
7	**7a**	5	20	48	100	98 (*S*)
8	**7b**	5	20	48	17	87 (*S*)
9	**7c**	5	20	48	23	88 (*S*)
10	**8**	5	20	48	5	42 (*S*)

[a] Reaction conditions: **4a** (0.1 mmol), **2** (0.12 mmol), catalyst (0.01 mmol), in toluene (0.1 M) at −30 °C. [b] Determined by ^{1}H NMR using *p*-xylene as an internal standard. [c] Not determined. [d] Reaction run with the addition of 3Å molecular sieves (20 mg). [e] Complex mixture, desired product <20%. [f] Yield of **5**: 70%. [g] Yield of **5**: 76%.

Table 2. Imine−Allene [3 + 2] Cycloadditions Catalyzed by **7a**



entry	Ar	**7a** (mol %)	isolated yield (%)	ee (%)[a]
1	Ph (**4a**)	10	84	98
2	*p*-FC_6H_4 (**4b**)	10	72	95
3	*p*-$MeOC_6H_4$ (**4c**)	20	80	97
4	*p*-PhC_6H_4 (**4d**)	10	81	96
5	*m*-$NO_2C_6H_4$ (**4e**)	10	70	95
6	3,4,5-$(MeO)_3C_6H_2$ (**4f**)	20	70	95
7	*o*-BrC_6H_4 (**4g**)	10	90	95
8	*o*-BrC_6H_4 (**4g**)	2.5	77	95
9	3-pyridyl (**4h**)	10	85	95
10	4-pyridyl (**4i**)	10	70	94
11	2-furyl (**4j**)	20	79	94
12	3-furyl (**4k**)	20	68	94
13	2-thienyl (**4l**)	20	77	97

[a] The absolute configuration of the product derived from **4f** was established by X-ray crystallography. All other products are assigned by analogy.

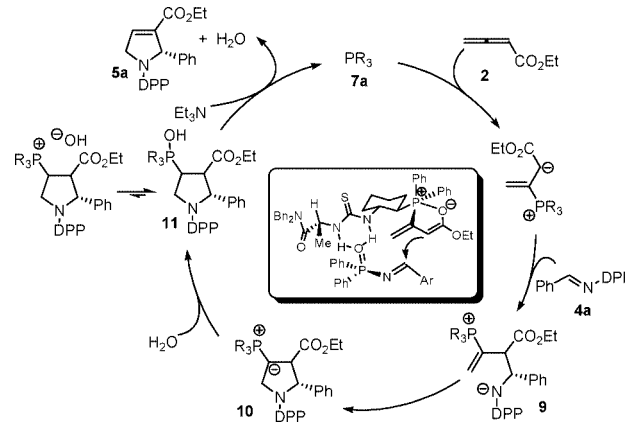
imines (e.g., TON of >30 for *o*-bromophenyl imine **4g**, entry 9). Aliphatic imines proved to be unsuitable substrates, undergoing decomposition under these conditions.

The beneficial effect of Et_3N and H_2O on the rate of the cycloaddition reaction is accompanied by negligible effects on enantioselectivity, suggesting that these additives are not involved in the ee-determining step(s). Consistent with the stepwise [3 + 2] cycloaddition mechanism proposed by Lu and others,[3b,11] it is likely that H_2O effects protonation of the basic ylide intermediate **10** to form a pentavalent hydroxyphosphorane intermediate **11** (Scheme 2). The role of Et_3N is most likely to promote elimination and liberation of the phosphine catalyst via either E_2 or E_1cb mechanisms.

We propose that the thiourea binds and activates the imine by association to the oxygen atom of the phosphinoyl group.[14] The DPP imine has a strong preference for adopting an *s*-cis conformation (dihedral angle C−N−P−O = 0°),[15] and the observed preferential attack at the imine *Re* face with **7a** is consistent with intramolecular delivery of the phosphonium ion enolate (Scheme 2). Secondary interactions ($\pi-\pi$ stacking or C═O···Ar)[16] between the amide portion of the catalyst and the diphenyl portion of the imine may also provide additional selective stabilization of the lowest energy transition state.

In summary, we have developed a new family of phosphinothiourea derivatives for the highly enantioselective synthesis of substituted 2-aryl-2,5-dihydropyrroles via imine-allene [3 + 2] cycloaddition. The fact that enantiopure aminophosphine **1** is prepared readily by classical resolution with tartaric acid and that alanine is the optimal amino acid component enables straightforward access to both catalyst enantiomers. Mechanistic investigation and application of this class of catalysts toward new transformations are currently underway.

Scheme 2



Acknowledgment. This work was supported by the NIH (Grants GM-43214 and GM-69721). Y.-Q. F. thanks the NSERC for postdoctoral fellowship support. Dr. Jingwei Huang and Dr. Richard Staples are acknowledged for crystal structure determination.

Supporting Information Available: Catalyst and substrate optimization studies, calculated energy profile of **4a**, complete experimental procedures, characterization data, ee determinations, and crystallographic data for (*R*)-**5f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) *N*-Deprotection of product **5a** was accomplished with HCl (1.5 equiv) in EtOH at room temp for 24 h (52% unoptimized yield) without detectable racemizaton.
(14) H-bonding of *N,N*′-dimethylthioure to a simple, dimethylphosphinoyl imine was modeled using DFT (B3LYP at the 6-31G(d,p) level). Interaction with the oxygen was found to be favored by ca. 6 kcal/mol over bonding to the nitrogen.
(15) The *s*-cis conformer of **4a** is computed to be 9.1 kcal/mol more stable than the *s*-trans conformer (see Supporting Information).
(16) For a discussion of lone-pair-aromatic interactions, see: Egli, M.; Sarkhel, S. *Acc. Chem. Res.* **2007**, *40*, 197.

JA801344W