Communication

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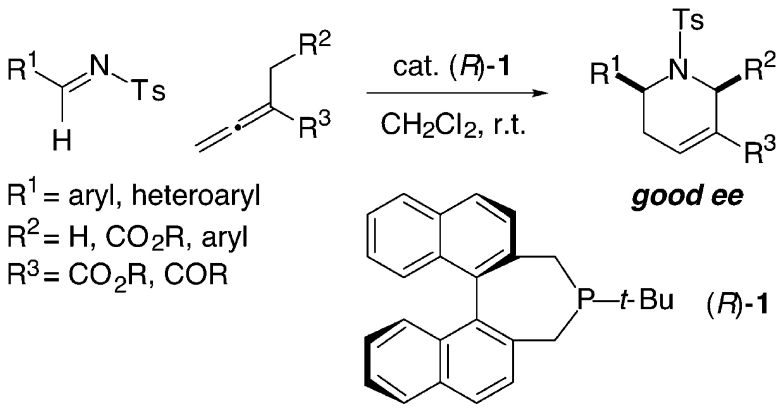

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Catalytic Asymmetric Synthesis of Piperidine Derivatives through the [4 + 2] Annulation of Imines with Allenes

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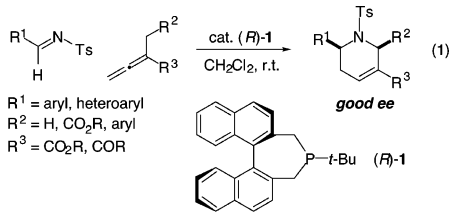
For several years, we have been pursuing the development of enantioselective nucleophile-catalyzed reactions.[1] Until now, our efforts have focused on the use of chiral derivatives of 4-(dimethylamino)pyridine (DMAP), due to the remarkable versatility of DMAP as a catalyst.[2] During the past decade, tertiary phosphines have emerged as effective nucleophilic catalysts for an impressive range of transformations;[3] unfortunately, there has been only very limited progress in achieving high levels of asymmetric induction with *chiral* phosphines.[4] Recognizing this, we recently decided to broaden our program in enantioselective nucleophilic catalysis to include studies of chiral tertiary phosphines.

Due to the bioactivity of many piperidine-containing compounds,[5] the development of efficient methods for the enantioselective synthesis of these six-membered nitrogen heterocycles is an important objective in organic chemistry.[6] Of course, catalytic asymmetric approaches can be particularly attractive from the standpoint of issues such as economy and efficiency.[7]

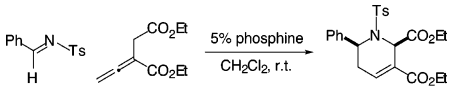
In 2003, Kwon described a novel method for the synthesis of functionalized piperidines via the PBu_3-catalyzed [4 + 2] annulation of imines with allenes.[8,9] As part of her pioneering study, Kwon parenthetically mentioned one example of the use of a chiral phosphine in this process ((*S*,*S*)-DIPAMP: 34% ee). To the best of our knowledge, there have been no subsequent reports of asymmetric catalysis of the Kwon annulation. In this communication, we provide a catalytic enantioselective method that furnishes access to a range of useful piperidine derivatives (eq 1).



Our initial efforts to develop an effective chiral catalyst for the Kwon reaction focused on new chiral tertiary phosphines that we had designed; in addition, we examined the utility of several phosphines that had originally been described by others for use as ligands in enantioselective metal-catalyzed processes. The best of the known phosphines were superior to our own. Thus, for the coupling of the illustrated imine and allene, C_2-symmetric bisphosphines such as Me-BPE (Table 1, entry 1), Et-BPE (entry 2), and TANGPHOS (entry 3) furnish interesting enantioselectivity and excellent yield, but modest diastereoselectivity.

We next turned our attention to binaphthyl-based C_2-symmetric phosphepines (e.g., **1**−**6**). The first phosphine in this class was reported by Gladiali in 1994,[10] and more recently Beller has described the utility of these monodentate phosphines in asymmetric hydrogenation reactions.[11] We have determined that this family of tertiary phosphines serve not only as useful ligands for transition metals but also as effective nucleophilic catalysts (Table 1, entries 4−9). Although phosphepines **2**−**6** provide only low to modest stereoselectivity in the Kwon reaction (entries 4−8), the bulky *tert*-butyl-substituted phosphine (**1**) generates the desired heterocycle with excellent enantioselectivity, diastereoselectivity, and yield (entry 9)! Interestingly, a related bisphosphine, BINAPINE, is ineffective (entry 10).

Table 1. Survey of Chiral Phosphine Catalysts for the [4 + 2] Annulation of Imines with Allenes[a]



entry	phosphine	ee (%)[b]	cis:trans	isolated yield (%)
1	Me-BPE	−72	72:28	94
2	Et-BPE	−87	66:34	99
3	TANGPHOS	−44	34:66	99
4	**2**	−21	74:26	80
5	**3**	−7	75:25	99
6	**4**	−62	72:28	53
7	**5**	0	70:30	46
8	**6**	51	69:31	99
9	**1**	98	91:9	93
10	BINAPINE	−	−	0

[a] All data are the average of two experiments. [b] A negative value for the ee signifies that the illustrated piperidine derivative is the minor, rather than the major, enantiomer. The ee value is for the cis diastereomer.

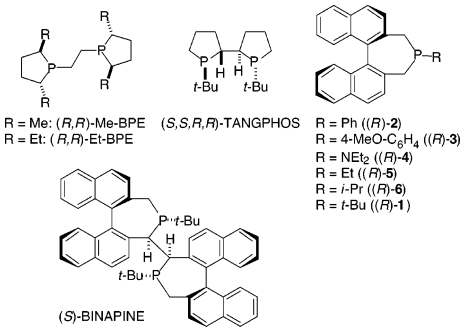
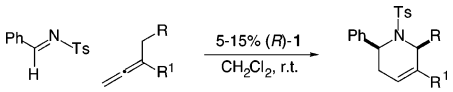


Table 2. Catalytic Asymmetric Synthesis of Piperidines: Scope with Respect to the Allene[a]



entry	R	R^1	ee (%)[b]	cis:trans	isolated yield (%)
1	CO_2Et	CO_2Et	98	91:9	93
2	Ph	CO_2Et	87	99:1	78
3	4-$(CF_3)C_6H_4$	CO_2Et	88	99:1	81
4	H	CO_2Et	68	−	72
5	H	COPh	76	−	97

[a] All data are the average of two experiments. Entry 1: 5% catalyst; entries 2−5: 15% catalyst. [b] The ee value is for the cis diastereomer.

As illustrated in Table 2, this catalytic asymmetric [4 + 2] annulation of imines with allenes proceeds best if the allene bears an R group that can stabilize an anion (e.g., carbonyl or aryl; entries

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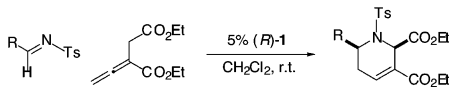
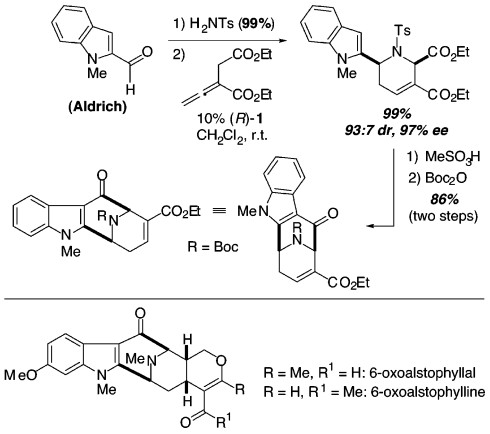
Table 3. Catalytic Asymmetric Synthesis of Piperidines: Scope with Respect to the Imine[a]



entry	R	ee (%)[b]	cis:trans	isolated yield (%)
1	Ph	98	91:9	93
2	3-MeC_6H_4	98	93:7	98
3	3,4,5-$(MeO)_3C_6H_2$	96	96:4	86
4	4-$(MeO)C_6H_4$	98	93:7	42
5	4-ClC_6H_4	96	91:9	99
6	3-BrC_6H_4	99	89:11	98
7	2-$(NO_2)C_6H_4$	68	96:4	98
8	2-ClC_6H_4	60	79:21	75
9	2-naphthyl	99	93:7	96
10	2-furyl	97	87:13	98
11	3-pyridyl	97	91:9	76

[a] All data are the average of two experiments. [b] The ee value is for the cis diastereomer.

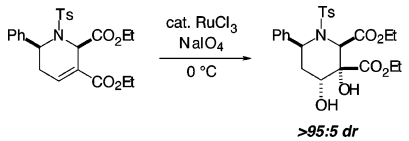
Scheme 1



1−3). In contrast, for an unsubstituted allene (R = H), moderate enantioselectivity is observed (entries 4−5).[12]

A range of imines can be employed as substrates in this catalytic enantioselective synthesis of piperidine derivatives (Table 3). Thus, the imine can bear an electron-rich (entries 3−4), electron-poor (entries 5−8), or ortho-substituted (entries 7−8) aromatic group, although it is worth noting that the electron-rich 4-anisyl imine is a reluctant coupling partner (entry 4) and that ortho-substituted, electron-poor imines react with lower stereoselectivity (entries 7 and 8). Heteroaryl imines are suitable substrates for this annulation process (entries 10 and 11).[13−15]

The products of these [4 + 2] reactions can be transformed into a variety of useful derivatives. For example, the olefin can be dihydroxylated with excellent diastereoselectivity (eq 2).[16] Alternatively, transannular cyclization affords ready access to a framework common to an array of important natural products (Scheme 1).[17,18]



(2)

In summary, we have demonstrated that a chiral phosphepine can catalyze the Kwon [4 + 2] annulation of imines with allenes, providing six-membered nitrogen heterocycles with excellent diastereo- and enantioselectivity. Additional synthetic and mechanistic investigations of asymmetric nucleophile-catalyzed processes are underway.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). X-ray crystallographic file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) If R is an electron-rich aromatic group, the annulation proceeds sluggishly (but with high stereoselectivity).
(13) Notes: (a) Kwon reported that, with PBu_3 as the catalyst, enolizable imines are not suitable substrates for the annulation reaction (ref 8). Under our standard conditions, catalyst **1** is also ineffective for this family of compounds. (b) The phosphine oxide of **1** does not catalyze the Kwon annulation. (c) 1,2-Dichloroethane is also a suitable solvent. Reactions conducted in toluene, acetone, and THF proceed very slowly. (d) If the Ts group is replaced with $P(=O)Ph_2$ or Ms, the annulation proceeds in lower yield and ee.
(14) Like many trialkylphosphines, catalyst **1** is susceptible to oxidation. The corresponding air-stable phosphonium salt can be prepared via protonation with HBF_4 (for a discussion of this general strategy, see: Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295−4298), and, in the presence of K_2CO_3, it furnishes stereoselectivity identical to that of **1** for the annulation illustrated in entry 1 of Table 3 (74% yield).
(15) According to ^{31}P NMR spectroscopy, the resting state of **1** during the reaction is the free catalyst.
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