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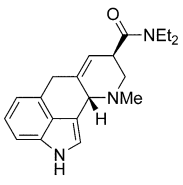
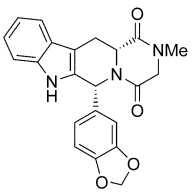
Bifunctional *N*-Acyl-Aminophosphine-Catalyzed Asymmetric [4+2] Cycloadditions of Allenoates and Imines

Hua Xiao,[a] Zhuo Chai,[b] Hai-Feng Wang,[b] Xiao-Wei Wang,[b] Dong-Dong Cao,[a] Wen Liu,[a] Ying-Peng Lu,[b] Ying-Quan Yang,[a] and Gang Zhao*[a, b]

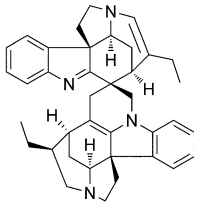
Tetrahydropyridines are important structural motifs present in a huge number of pharmaceutically interesting substances and bioactive natural products. For example, the ergot alkaloid derivative lysergic acid diethylamide (LSD, **1**), a strongly psychedelic agent; tadalafil (**2**), a drug which has been marketed for the treatment of erectile dysfunction and pulmonary hypertension, and the cytotoxic bisindole alkaloid Leucoridine B (**3**) all share the chiral tetrahydropyridine structure.[1] Although many powerful synthetic methods for accessing these nitrogen-containing six-membered heterocycles have been established,[2] the development of catalytic asymmetric approaches allowing for the construction of these structures in optically active forms remains an attractive goal in organic synthesis.[3]



LSD (**1**)



tadalafil (**2**)



Leucoridine B (**3**)

Since the seminal work of Lu and co-workers reported in 1995,[4] the phosphine-catalyzed cycloaddition reactions of allenoates have evolved to be an efficient method for the construction of a variety of synthetically useful carbo- and heterocycles due to intensive research efforts.[4–8] In addition to the initial fruitful use of unsubstituted allenoates as a "C3 synthon" in this type of reaction with various electrophiles, the incorporation of α and/or γ-substituted allenoate into these reactions has greatly expanded the reaction scope.[8] Particularly, in 2003, Kwon pioneered the use of α-substituted allenoates in the annulation reaction with imines, leading to a novel [4+2] cycloaddition reaction in which the allenoates served as novel "C4 synthons".[8a] Such a reaction provides an efficient and atom-economical access to multifunctional tetrahydropyridines. Later, this kind of [4+2] cycloaddition was further successfully extended to electron-deficient alkenes and trifluoromethylketones to give highly functionalized cyclohexenes[8c] and dihydropyrans.[8h]

Despite the above impressive progress achieved in phosphine-catalyzed cycloaddition reactions of allenoates, the development of enantioselective variants remains rather limited and unbalanced. Up to now, most enantioselective annulations in this field were achieved only with non-substituted allenoates and electron-deficient species, namely asymmetric [3+2] cycloadditions.[9,10] To the best of our knowledge, there is only one report on an asymmetric α-substituted allenoate–imine [4+2] cycloaddition catalyzed by a chiral monodentate phosphine developed by Fu in 2005, two years after Kwon's finding of the non-enantioselective reaction.[8d] Therefore, there is still a great potential for asymmetric catalysis to be fulfilled in this field. Inspired by the works from Miller and Jacobsen,[10a–b] our group have recently developed simple bifunctional *N*-acyl aminophosphines derived from amino acids as organocatalysts for highly regio- and enantioselective [3+2] cycloadditions between allenoates and dual-activated olefins.[11] Besides their accessibility and air stability, these bifunctional catalysts could also obviate some demanding reaction conditions such as an inert atmosphere and anhydrous solvents usually required for chiral monodentate phosphine catalysts. As part of our efforts to extend the application of these catalysts in asymmetric synthesis, we describe herein the highly diastereoselective and enantioselective [4+2] cycloadditions between allenoates and tosylaldimines catalyzed by bifunctional *N*-acyl aminophosphines.

Initially, the reaction between 2-(2-ethoxy-2-oxoethyl)-2,3-butadienoate and *N*-tosylbenzaldimine in CH_2Cl_2 was chosen to probe the catalytic efficiency of the bifunctional phosphines (Table 1). Interestingly, the isoleucine-derived catalyst **7f**, the best catalyst identified in our previous asymmetric [3+2] cycloaddition, also proved the best one in this [4+2] cycloaddition, giving the desired cycloadduct **6a** in 85% yield and with 90% enantiomeric excess (*ee*) (Table 1,

[a] H. Xiao, D.-D. Cao, W. Liu, Y.-Q. Yang, Prof. Dr. G. Zhao
Department of Chemistry
University of Science and Technology of China
Hefei, Anhui 230026 (P.R. China)
Fax: (+86) 21-64166128
E-mail: zhaog@mail.sioc.ac.cn

[b] Z. Chai, H.-F. Wang, X.-W. Wang, Y.-P. Lu, Prof. Dr. G. Zhao
Laboratory of modern synthetic chemistry
Shanghai institute of organic chemistry
354 Fenglin Road, Shanghai, 200032
Chinese Academy of Sciences (P.R. China)

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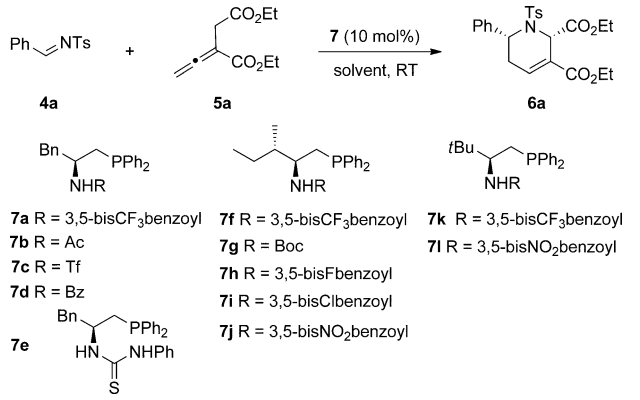
Table 1. Screening of reaction conditions for the asymmetric [4+2] cycloaddition.[a]



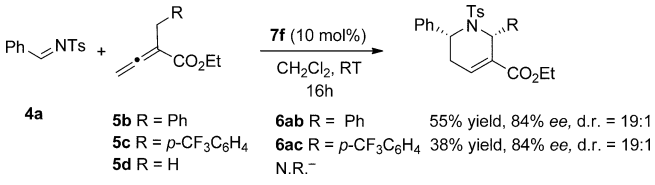
Entry	Catalyst	Solvent	*t* [h]	Yield[b] [%]	d.r.[c]	*ee*[d] [%]
1	**7a**	CH_2Cl_2	24	46	19:1	79
2	**7b**	CH_2Cl_2	48	28	19:1	60
3	**7c**	CH_2Cl_2	24	NR[g]	–	–
4	**7d**	CH_2Cl_2	24	41	19:1	73
5	**7e**	CH_2Cl_2	48	26	19:1	23
6	**7f**	CH_2Cl_2	8	85	19:1	90
7	**7g**	CH_2Cl_2	8	68	14:1	24
8	**7h**	CH_2Cl_2	8	81	19:1	88
9	**7i**	CH_2Cl_2	8	76	19:1	88
10	**7j**	CH_2Cl_2	12	44	19:1	90
11	**7k**	CH_2Cl_2	8	90	17:1	88
12	**7l**	CH_2Cl_2	8	74	19:1	90
13	**7f**	$CHCl_3$	12	61	17:1	91
14	**7f**	CCl_4	12	26	5:1	95
15	**7f**	Et_2O	12	20	9:1	58
16	**7f**	acetone	12	31	9:1	71
17	**7f**	*m*-xylene	12	33	9:1	90
18	**7f**	PhCl	6	68	19:1	96
19	**7f**	$PhCF_3$	6	61	15:1	97
20	**7f**	$CH_2Cl_2/PhCF_3$[e]	12	78	15:1	93
21[f]	**7f**	CH_2Cl_2	8	99	19:1	89
22[f]	**7f**	$PhCF_3$	12	65	15:1	95
23[f]	**7f**	$CH_2Cl_2/PhCF_3$[e]	12	85	15:1	92

[a] All reactions were carried out with **4a** (0.1 mmol) and 2-(2-ethoxy-2-oxoethyl)-2, 3-butadienoate **5a** (0.2 mmol) in the presence of **7** (0.01 mmol) in solvent (1.0 mL). [b] Yields of isolated products. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] 1:1 (v/v) co-solvent of CH_2Cl_2 and $PhCF_3$. [f] 20 mg of 4 Å MS was added. [g] NR = no reaction.

entry 6). Compared with catalysts bearing the 3, 5-bistrifluoromethylbenzoyl group, **7b**, **7d** and **7g** with any other groups such as an acyl, benzoyl or *tert*-butoxycarbonyl (Boc) group may be expected to give a slightly weaker acidity on the NH functionality, and these catalysts gave inferior results, whereas the more acidic **7c** was completely ineffective in the reaction, which highlights the importance of the NH functionality in the catalytic process (Table 1, entries 2–7). Moreover, the structure of the chiral backbones of these catalysts seemed highly influential on the catalytic activity; the isoleucine or *tert*-butylleucine-derived catalysts were much better than those derived from phenylalanine. In contrast, the diastereoselectivity of the product **6a** was much less influenced by this kind of catalyst alteration. An examination of the solvent effect revealed that solvents with a hydrogen-bonding acceptor atom (O or N), such as Et_2O and acetone, were not suitable for the reaction (Table 1, entries 15–16). Polar aromatic solvents such as PhCl and $PhCF_3$ were most favorable in terms of the enantioselectivity and reaction time, albeit with diminished yields (Table 1, entries 18–19). As a compromise of both the yield and *ee* value, the reaction could be performed in a co-solvent of CH_2Cl_2 and $PhCF_3$ (v/v = 1:1) to give the product in 78% yield and with 93% *ee* (Table 1, entry 20). The addition of 4 Å molecule sieves, which may minimize the decomposition of the moisture-sensitive Ts-imine, proved to be beneficial to the chemical yield (Table 1, entries 21 and 23).

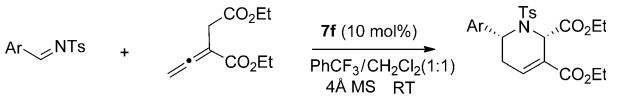
Subsequently, we examined the reactivity of three other allenoates with different substituents (R) on the α carbon atom (Scheme 1). Consistent with the observations from Kwon and Fu, the anion-stabilizing ability of the substituents (R) plays a key role in this reaction; changing the ester group in **5a** to the aryl groups in **5b** and **5c** led to decreased yield and enantioselectivity, but with improved diastereoselectivity, and the simple allene **5d** (R = H) failed to undergo the reaction in our case.

The scope of the asymmetric [4+2] cycloaddition with regard to different aldimines was next investigated (Table 2). In general, all the *N*-tosylaldimines derived from



Scheme 1. Asymmetric [4+2] cycloaddition of *N*-tosylbenzaldimine **4a** and different substituted allenoates.

Table 2. Enantioselective [4+2] cycloadditions of allenoate **5a** with *N*-tosylaldimines **4** catalyzed by **7f**.[a]

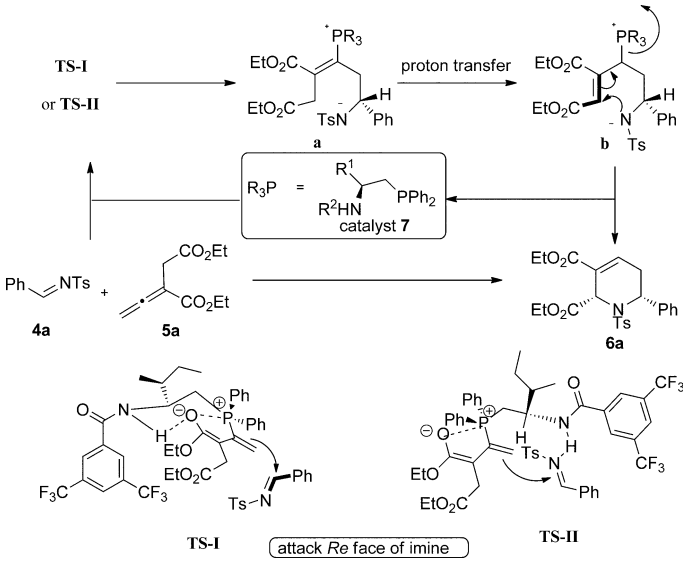


Entry	4	Ar	Product	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**4a**	Ph	**6a**	85	15:1	92
2	**4b**	4-$MeOC_6H_4$	**6b**	94	15:1	90
3[e]	**4c**	2-ClC_6H_4	**6c**	88	4:1	96
4[e]	**4d**	2-FC_6H_4	**6d**	80	6:1	95
5	**4e**	4-ClC_6H_4	**6e**	67 (78)[f]	16:1	96 (93)[f]
6	**4f**	3-BrC_6H_4	**6f**	66 (73)[f]	7:1	96 (94)[f]
7	**4g**	2-naphthyl	**6g**	66 (76)[f]	9:1	90 (87)[f]
8	**4h**	4-MeC_6H_4	**6h**	80	15:1	92
9	**4i**	4-PhC_6H_4	**6i**	72	11:1	91
10	**4j**	3-FC_6H_4	**6j**	81	12:1	95
11	**4k**	2-furyl	**6k**	72	11:1	89
12	**4l**	2-thienyl	**6l**	98	12:1	82

[a] All reactions were carried out with **4** (0.1 mmol) and **5a** (0.2 mmol) in solvent (1.0 mL) at RT for 12 h. [b] Yields of isolated products. [c] Determined by ^{1}H NMR spectroscopy unless otherwise noted. [d] Determined by chiral HPLC analysis. [e] Determined by the isolated product yields of each of the two isomers. [f] Data in the parenthesis refer to reactions run in CH_2Cl_2 without adding 4 Å MS.

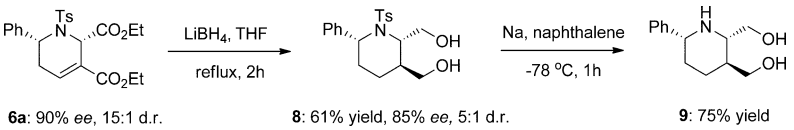
aromatic aldehydes worked well in the reaction,[12] providing a series of chiral tetrahydropyridine derivatives in good yields and diastereoselectivities, and with good to excellent enantioselectivities. Substrates with electron-withdrawing substituents on the arene rings in general gave higher *ee* values than those with electron-donating ones. Similar to the observations in Fu's monodentate phosphine system,[8d] a remarkable drop in diastereoselectivity was also observed for orthosubstituted imines in this system (Table 2, entries 3 and 4). Pleasingly, some imines that did not work well in Fu's system gave somewhat improved results here: the electron-rich 4-anisyl imine **4b**, a sluggish coupling partner, which in that system that gave a rather low yield (42%), worked well in our system to give an excellent yield of 94%, albeit with a decrease in *ee* value (98%→90%; Table 2, entry 2). The result of 2-chlorobenzene aldimine **4c** was also considerably improved from 75% yield, 60% *ee* to 88% yield and 96% *ee* (Table 2, entry 3). These complementary results from the two catalyst systems would be valuable for the practical synthetic application of this asymmetric annulation. In addition, for substrates **4e**–**4g** with modest yields in the co-solvent used, performing the reaction in CH_2Cl_2 alone could improve the yield appreciably with slightly reduced enantioselectivity (Table 2, entries 5–7). Heteroaryl imines were also tolerated in the reaction, albeit with somewhat diminished *ee* values (Table 2, entries 11–12). The absolute configurations of the products were assigned by comparison of the optical rotation values with literature values[8d] (for known compounds) and by analogy (for new compounds).

Based on Kwon's mechanistic proposal for the reaction[8a] and previously proposed acting models of bifunctional phosphine catalysts in related reactions,[10a,b] a possible mechanism was proposed for the reaction (Scheme 2). After the initial formation of the phosphadienolate structure, two possible transition states TS-I and TS-II, through either of which the catalyst may function, could be proposed based on the observed stereochemical results. As proposed by Marinetti,[9g] the arrangement of the phosphorus center in the two transition states may be square-pyramidal (trigonal-bypyramidal is also possible). Similar to the transition state drawn by Miller for their multifunctional phosphine catalysts,[10a] TS-I involves the formation of a zwitterion between the catalyst and the allenoate **5a**, which is possibly assisted by a hydrogen bonding interaction and a P–O interaction;[10k] the dienolate might approach the *Re* face of the imine to minimize the steric repulsion between the catalyst backbone and the Ts group of the imine. TS-II was drawn with reference to the transition states proposed by Lu[10h] and Jacobsen;[10b] the hydrogen-bonding interaction and P–O interaction might adapt the flexible chiral bone of the catalyst to adopt a conformation favoring the *Re*-face attack of the imine. The firstly formed chiral center (*R* configuration) would direct the formation of the second one.



Scheme 2. A possible reaction mechanism.

To demonstrate the potential utility of the present [4+2] cycloaddition reaction, the cycloadduct **6a** was converted to diol **8**[13] in moderate diastereoselectivty by reduction with $LiBH_4$. Subsequent detosylation of **8** under Na/naphthalene conditions gave a highly functionalized chiral piperidine product **9** (Scheme 3), which may allow easy transformations to more complex N-containing compounds with pharmaceutical interests.[14]



Scheme 3. Useful conversion of the cycloadduct **6a**.

In conclusion, we have successfully extended the applications of our previously developed bifunctional *N*-acyl aminophosphine catalysts to an efficient asymmetric organocatalytic [4+2] cycloaddition between α-substituted allenoates and tosylaldimines, which provides facile accesses to optically active tetrahydropyridines. In addition to the ready catalyst availability and simple manipulation, some substrates, which gave not-so-satisfactory results with the chiral monophophine catalysts, could also give improved results in this system. Endeavors toward the application of these *N*-acyl aminophosphine catalysts in other related reactions are currently underway in our laboratories.

Experimental Section

Typical procedure: 4 Å molecular sieves (20 mg) were added to a stirred solution of *N*-tosylaldimines **4** (0.1 mmol) and catalyst **7** (0.01 mmol) in a 1:1 (v/v) co-solvent of $PhCF_3$ and CH_2Cl_2 (1 mL) at room temperature. The reaction mixture was stirred for 10 min before α-substituted 2, 3-bu-

tadienoate **5a** (0.2 mmol) was added in one portion using a micro-syringe, followed by vigorously stirring at RT. After the reaction was complete (monitored by TLC), the mixture was directly purified by column chromatography on silica gel (petroleum ether/ethyl acetate 5:1, v/v) to give the corresponding product.

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Keywords: aminophosphines · asymmetric catalysis · bifunctional catalyst · cycloaddition · organocatalysis

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[12] Similar to previous reports (refs. [8a] and [8d]), *N*-tosylaldimines derived from aliphatic aldehydes and *N*-Boc protected imines all proved unreactive in this system.

[13] The structure of compound **8** was confirmed by X-ray crystallographic analysis (see the Supporting Information for details).

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