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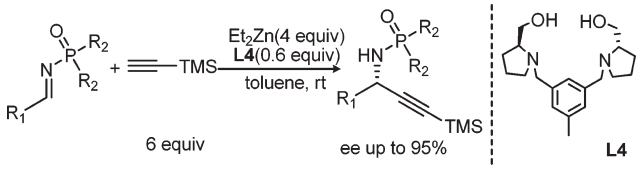
Enantioselective Nucleophilic Addition of Trimethylsilylacetylene to *N*-Phosphinoylimines Promoted by C_2-Symmetric Proline-Derived β-Amino Alcohol

Shaoqun Zhu,[†] Wenjin Yan,[†,‡] Bin Mao,[†] Xianxing Jiang,[†] and Rui Wang*[,†,‡]

[†]*Institute of Biochemistry and Molecular Biology and State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China, and* [‡]*State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, China*

wangrui@lzu.edu.cn

Received July 12, 2009



Both C_2- and C_3-symmetric proline-derived β-amine alcohol ligands were designed, synthesized, and successfully applied to the enantioselective direct addition of trimethylsilylacetylene to *N*-phosphinoylimines. Aromatic, heteroaromatic, and aliphatic *N*-(diphenylphosphinoyl) imines and several *N*-(diethoxyphosphoryl) imines were tested, and optically active propargylic amides in good yields (up to 92%) and excellent enantioselectivities (up to 95%) were obtained by the simple experimental procedure. The convenience, mild conditions, and easy deprotection of the phosphonamide products made the present method very attractive. Furthermore, the Michael-type addition process of C=N alkynylation was studied and proposed on the basis of React ^{31}P NMR investigation.

Introduction

Optically active propargylic amines are synthetically versatile intermediates for a wide range of natural products and pharmaceuticals.[1] Among the several methods that are available for the preparation of these highly functionalized structures, asymmetric addition of alkynylmetallic to imines is one of the most straightforward and convenient methods.[2] In the past few years, significant improvements have been made in this area.[3] Since Li[4] found that tridentate bis(oxazolinyl)pyridine (pybox) in combination with CuOTf could effectively catalyze the direct asymmetric alkynylation of *N*-arylimines, some other nitrogen-containing ligands were subsequently exploited by Chan et al.,[5] Singh,[6] Benaglia,[7] Knochel,[8] Carreira,[9] and Zhao.[10] Other methods,

(1) For selected examples of the use of optically active propargylic amines in synthesis, see: (a) Harvey, D. F.; Sigano, D. M. *J. Org. Chem.* **1996**, *61*, 2268. (b) Arcadi, A.; Cacchi, S.; Cascia, L.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2001**, *3*, 2501. (c) Yamamoto, Y.; Hayashi, H.; Saigoku, T.; Nishiyama, H. *J. Am. Chem. Soc.* **2005**, *127*, 10804. (d) Chen, J.-J.; Swope, D. M. *J. Clin. Pharmacol.* **2005**, *45*, 878. (e) Weiss, J.; Herzog, M.; Konig, S.; Storch, C. H.; Ketabi-Kiyanvash, N.; Haefeli, W. E. *J. Pharmacol. Sci.* **2009**, *109*, 242.

(2) For reviews, see: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Wei, C.; Li, C.-J. *Synlett* **2004**, 1472. (c) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, *20*, 4095. (d) Zhu, H.-J.; Jiang, J.-X.; Ren, J.; Yan, Y.-M.; Pittman, C. U., Jr. *Curr. Org. Synth.* **2005**, *2*, 547. (e) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263. (f) Hatano, M.; Miyamoto, T.; Ishihara, K. *Curr. Org. Chem.* **2007**, *11*, 127. (g) Yamada, K.; Tomioka, K. *Chem. Rev.* **2008**, *108*, 2874. (h) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963.

(3) For examples, see: (a) We, C.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5740. (b) Benaglia, M.; Negri, D.; Dell'Anna, G. *Tetrahedron Lett.* **2004**, *45*, 8705. (c) Dube, H.; Gommermann, N.; Knochel, P. *Synthesis* **2004**, 2015. (d) Ji, J.-X.; Wu, J.; Chan, A. S. C. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 11196. (e) Taylor, A. M.; Schreiber, S. L. *Org. Lett.* **2006**, *8*, 143. (f) Liu, J.; Liu, B.; Jia, X.; Li, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2007**, *18*, 396. (g) Hatano, M.; Asai, T.; Ishihara, K. *Tetrahedron Lett.* **2008**, *49*, 379. (h) Irmak, M.; Boysen, M. M. K. *Adv. Synth. Catal.* **2008**, *350*, 403. (i) Wang, J.; Shao, Z.; Ding, K.; Yu, W.; Chan, A. S. C. *Adv. Synth. Catal.* **2009**, *351*, 1250.

(4) We, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638.

(5) Ji, J.-X.; Wu, J.; Chan, A. S. C. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 11196.

(6) Bisai, A.; Singh, V. K. *Org. Lett.* **2006**, *8*, 2405.

(7) (a) Benaglia, M.; Negri, D.; Dell Anna, G. *Tetrahedron Lett.* **2004**, *45*, 8705. (b) Orlandi, S.; Colombo, F.; Benaglia, M. *Synthesis* **2005**, 1689. (c) Colombo, F.; Benaglia, M.; Orlandi, S.; Usuelli, F.; Celentano, G. *J. Org. Chem.* **2006**, *71*, 2064.

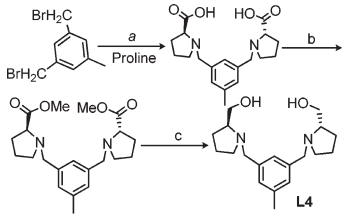
(8) (a) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (b) Gommermann, N.; Knochel, P. *Chem. Commun.* **2004**, 2324. (c) Gommermann, N.; Knochel, P. *Synlett* **2005**, 2799. (d) Gommermann, N.; Knochel, P. *Chem.—Eur. J.* **2006**, *12*, 4380.

(9) (a) Knopfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971. (b) Aschwanden, P.; Stephenson, C. R. J.; Carreira, E. M. *Org. Lett.* **2006**, *8*, 2437.

(10) (a) Dodda, R.; Zhao, C.-G. *Org. Lett.* **2007**, *9*, 165. (b) Dodda, R.; Zhao, C.-G. *Tetrahedron Lett.* **2007**, *48*, 4339.

Published on Web 08/20/2009 DOI: 10.1021/jo901492w

SCHEME 1. Preparation of C_2-Symmetric Proline-Derived β-Amino Alcohol Ligand (L4)[a]



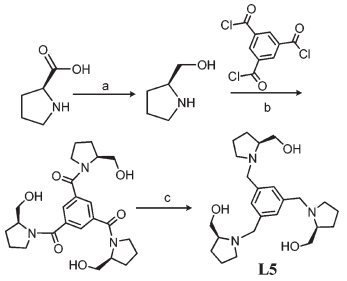
[a]Reagents and conditions: (a) *i*-PrOH, 3.0 equiv of NaOH and 2.0 equiv of proline, 40 °C, overnight, 74%; (b) MeOH, $SOCl_2$, reflux for 6 h, 92%; (c) Et_2O, Ar, 2.2 equiv of $LiAlH_4$, 3 h, 83%.

which did not make use of copper complexes as the catalyst, have also been reported. Hoveyda and co-workers[11] have described the use of a peptide-based ligand and Zr-$(OiPr)_4$·HO*i*Pr to catalyze the addition of trimethylsilylacetylene to *N*-aryl aromatic imines. Jiang and Si have reported the addition of alkynes to a trifluoromethyl activated cyclic imine with a stoichiometric amount of a chiral amino alcohol ligand and $Zn(OTf)_2$ as promoter.[12] Bolm and co-workers used amine alcohol and dimethylzinc to promote the addition of terminal alkynes to *N*-aryl imines.[13] Chong[14] and Soderquist[15] accomplished the alkynylation of *N*-acyl imines by using chiral alkynylboronates or alkynylboranes as nucleophilic reagents, respectively. Rueping[16] achieved good results in the addition of aryl alkynes to α-imino esters by dual catalysis strategy.

While many methods are known to construct optically active propargylic amines effectively, a very limited number of examples about the alkynylation of *N*-activated imines (i.e., imines bearing an electron-withdrawing group on the nitrogen atom) have been reported.[12,14,15,17] Recently, an actual example of alkynylation of *N*-activated imines was reported by Pedro,[18] who described the direct addition of alkynes to *N*-sulfonylimines by the use of dimethylzinc and binol as catalyst.

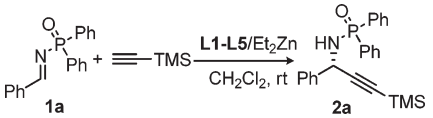
As a synthetic equivalent of acetylene, trimethylsilylacetylene has received great attention in organic synthesis because the $SiMe_3$ unit could be removed easily and the resulting terminal alkyne could be converted to a wide range of other structures (by oxidization, hydrogenation, alkylation, cross-coupling, etc.).[11,19] Unfortunately, only three examples of asymmetric addition of trimethylsilylacetylene to imines have been reported by Hoverda, Knochel, and Carreira, respectively.[8d,9b,11] To the best of our knowledge, systematic study on the addition of trimethylsilylacetylene to *N*-activated imines has not been reported yet.

SCHEME 2. Preparation of C_3-Symmetric Proline-Derived β-Amino Alcohol Ligand (L5)[a]



[a]Reagents and conditions: (a) THF, Ar, 2.5 equiv of $LiAlH_4$, reflux for 3 h, 90%; (b) DCM, TEA, 82%; (c) THF, Ar, 4.0 equiv of $LiAlH_4$, reflux for 48 h, 73%.

TABLE 1. Selected Ligands for the Alkynylation of *N*-(Diphenylphosphinoyl) Imines[a,b]



entry	ligand	*t* (h)	yield (%)	ee[e] (%)
1[c]	L1	NR	NR	NR
2[c]	L2	NR	NR	NR
3[c]	L3	96	58	38
4[d]	L3	72	72	54
5[c]	L4	72	67	58
6[c]	L5	72	67	58

[a]Reactions were carried out under argon on a 0.2 mmol scale. [b]Mole ratio of imine/Et_2Zn/silylacetylene = 1:4:4. [c]Proportion of the ligand is 20 mol %. [d]Proportion of the ligand is 40 mol %. [e]Enantiomeric excess was determined by HPLC analysis on a Chiralcel AD column.

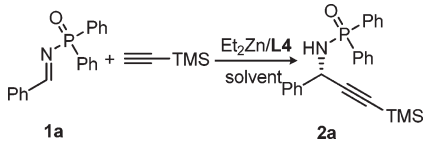
Herein, we report a systematic study on the asymmetric addition of trimethylsilylacetylene to *N*-activated imines. C_2-Symmetric 1,1′-(5-methyl-1,3-phenylene)bis(proline-derived)-β-amino alcohol and C_3-symmetric 1,1′,1″-(benzene-1,3,5-triyltris(methylene))tris(pyrrolidine-2,1-diyl)trimethanol β-amino alcohol were designed and used as promoters. Considering the resulting phosphonamides could be easily deprotected under mild conditions (e.g., HCl/MeOH),[20] *N*-phosphinoylimines were used as substrates. In addition, the Michael-type addition process of C═N alkynylation was studied and proposed on the basis of React ^{31}P NMR investigation.

Results and Discussion

Recently, we have developed the asymmetric addition of terminal alkynes to *N*-(diphenylphosphinoyl) imines by the use of proline-derived β-amino alcohols as ligands. Although trimethylsilylacetylene was tested, only moderate result in 84% ee and 53% yield were obtained after 72 h.[21] We noticed that many C_2- and C_3-symmetric ligands were employed in the nucleophilic addition of alkyl-zinc to aldehydes with

(11) Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 3273.
(12) Jiang, B.; Si, Y.-G. *Angew.Chem., Int. Ed.* **2004**, *43*, 216.
(13) (a) Zani, L.; Eichhorn, T.; Bolm, C. *Chem.—Eur. J.* **2007**, *13*, 2587. (b) Labonne, A.; Zani, L.; Hintermann, L.; Bolm, C. *J. Org. Chem.* **2007**, *72*, 5704.
(14) Wu, T. R.; Chong, J. M. *Org. Lett.* **2006**, *8*, 15.
(15) Gonzalez, A. Z.; Canales, E.; Soderquist, J. A. *Org. Lett.* **2006**, *8*, 3331.
(16) Rueping, M.; Antonchick, A. P.; Brinkmann, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6903.
(17) For selected examples of asymmetric alkynylation of *N*-activated imines, see: (a) Wei, W.-L.; Kobayashi, M.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2006**, *35*, 176. (b) Sun, Z.-K.; Yu, S.-Y.; Ding, Z.-D.; Ma, D.-W. *J. Am. Chem. Soc.* **2007**, *129*, 9300.
(18) Blay, G.; Cardona, L.; Climent, E.; Pedro, J. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 559.
(19) Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319.
(20) For a review, see: Weinreb, S. M.; Orr, R. K. *Synthesis* **2005**, 1205.
(21) Yan, W.-J.; Mao, B.; Zhu, S.-Q.; Jiang, X.-X.; Liu, Z.-L.; Wang, R. *Eur. J. Org. Chem.* **2009**, *19*, 3790.

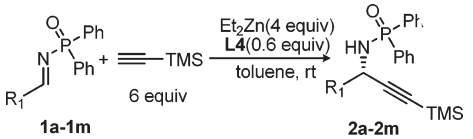
TABLE 2. Selected Screening Results for the Alkynylation of *N*-(Diphenylphosphinoyl) Imines[a]



entry	solvent	ligand (mol %)	*t* (h)	yield (%)	ee[i] (%)
1[b,f]	CH_2Cl_2	20	84	47	58
2[b,f]	Et_2O	20	82	36	57
3[b,f]	THF	20	76	42	0
4[b,f]	hexane	20	NR	NR	NR
5[b,f]	toluene	20	48	48	58
6[b,f]	toluene	30	48	58	61
7[b,f]	toluene	40	48	65	70
8[b,f]	toluene	60	48	73	84
9[c,f]	toluene	60	48	70	88
10[d,f]	toluene	60	48	81	88
11[e,f]	toluene	60	48	83	90
12[e,g]	toluene	60	12	82	78
13[e,h]	toluene	60	72	48	89

[a]Reactions were carried out under argon on a 0.2 mmol scale. [b]Mole ratio of aldimine/Et_2Zn/silylacetylene = 1:4:4. [c]Mole ratio of imine/Et_2Zn/silylacetylene = 1:5:4. [d]Mole ratio of imine/Et_2Zn/silylacetylene = 1:6:4. [e]Mole ratio of imine/Et_2Zn/silylacetylene = 1:4:6. [f]At room temperature. [g]At 40 °C. [h]At 0 °C. [i]Enantiomeric excess was determined by HPLC analysis on a Chiralcel AD column.

TABLE 3. Addition of Trimethylsilylacetylene to Various *N*-(Diphenylphosphinoyl) Imines[a,b]



entry	R_1	product	*t* (h)	yield (%)	ee[c] (%)
1	Ph	**2a**	48	83	90
2	2-naphthyl	**2b**	27	80	93
3	4-MePh	**2c**	48	91	94
4	2-MeOPh	**2d**	38	89	76
5	4-MeOPh	**2e**	38	75	95
6	4-FPh	**2f**	38	84	88
7	3-ClPh	**2g**	38	71	78
8	4-ClPh	**2h**	38	81	88
9	4-BrPh	**2i**	38	74	86
10	2-furyl	**2j**	64	66	84
11	2-thienyl	**2k**	38	82	90
12	3-thienyl	**2l**	38	86	90
13	*i*-Pr	**2m**	18	92	72

[a]Reactions were carried out under argon on a 0.2 mmol scale. [b]Mole ratio of imine/Et_2Zn/silylacetylene = 1:4:6. [c]Enantiomeric excess was determined by HPLC analysis on a Chiralcel AD or OD column.

good results.[22] Thus, we designed and synthesized C_2- and C_3-symmetric proline-derived β-amino alcohol ligands in order to perfect the addition of trimethylsilylacetylene to *N*-phosphinoylimines (Scheme 1 and 2).

To search for efficient chiral metal complexes, the reaction of trimethylsilylacetylene with *N*-benzylidene-*P*,

(22) For selected examples of C_2- and C_3-symmetric ligands employed in the nucleophilic addition of alkyl-zinc to aldehydes, see: (a) Moberg, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 248. (b) Li, Z.-B.; Liu, T.-D.; Pu, L. *J. Org. Chem.* **2007**, *72*, 4340. (c) Trost, B. M.; Weiss, A. H.; Wangelin, A.; von., J. *J. Am. Chem. Soc.* **2006**, *128*, 8. (d) Lu, G.; Li, X.; Li, Y.-M. F.; Kwong, Y.; Chan, A. S. C. *Adv. Synth. Catal.* **2006**, *348*, 1926.

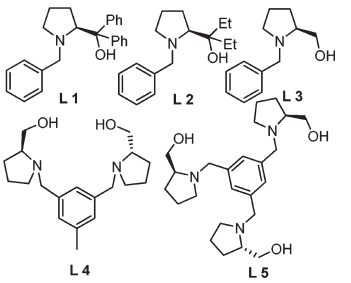
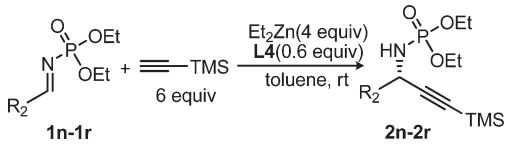


FIGURE 1. Ligands used as catalysts in the alkynylation of *N*-(diphenylphosphinoyl) imines.

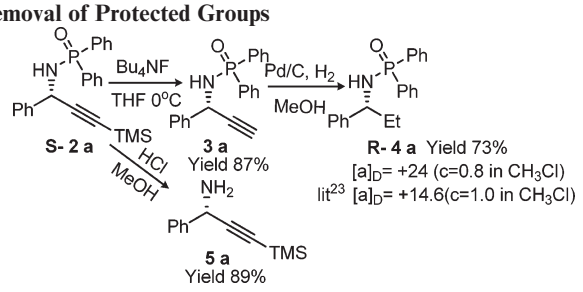
TABLE 4. Addition of Trimethylsilylacetylene to *N*-(Diethoxyphosphoryl) Imines[a,b]



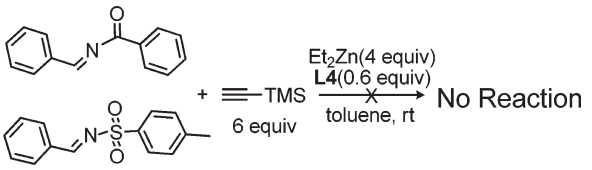
entry	R_2	product	*t* (h)	yield (%)	ee[c] (%)
1	Ph	**2n**	18	71	92
2	4-MePh	**2o**	18	71	93
3	4-MeOPh	**2p**	18	72	92
4	4-FPh	**2q**	18	73	88
5	2-naphthyl	**2r**	18	82	89

[a]Reactions were carried out under argon on a 0.2 mmol scale. [b]Mole ratio of imine/Et_2Zn/silylacetylene = 1:4:6. [c]Enantiomeric excess was determined by HPLC analysis on a Chiralcel AD or OD column.

SCHEME 3. Determination of Absolute Stereochemistry and Removal of Protected Groups



SCHEME 4. *N*-Tosylimine and *N*-Benzylidenebenzamide Were Tested Using Optimized Conditions



P-diphenylphosphinic amide **1a** was carried out in the ypresence of chiral Lewis acid catalysts generated in situ from $ZnEt_2$ and ligands. The results were shown in Table 1. It was found that C_2-symmetric ligand (**L4**) and C_3-symmetric ligand (**L5**) showed more enantioselectivity than the others (entries 5 and 6, Table 1). In view of the difficulty in the synthesis of **L5**, **L4** was selected as a catalyst to further optimize the conditions. The effect of solvent was briefly examined as shown in Table 2 (entries 1−5), and toluene gave the best result (entry 5, Table 2). Different catalyst loading,

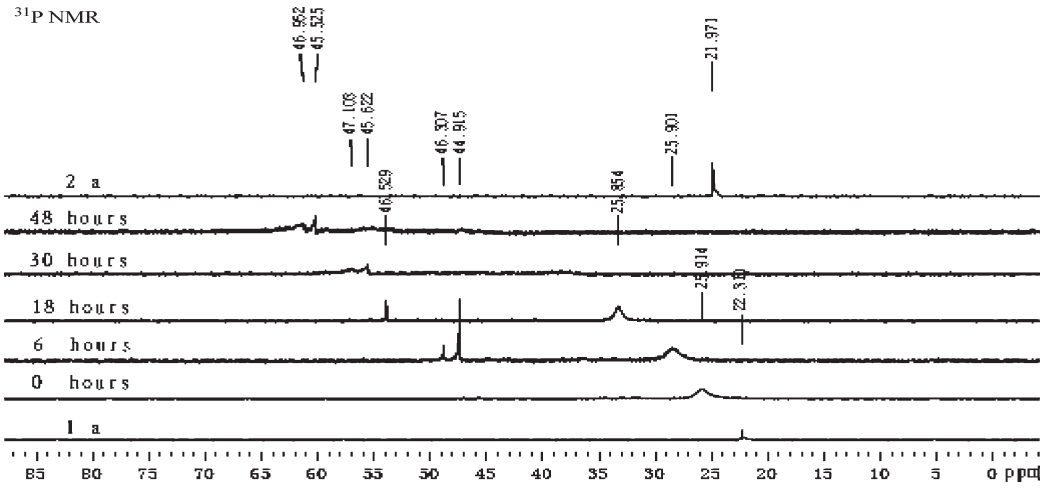


FIGURE 2. ^{31}P NMR (121 MHz) spectra of React ^{31}P NMR investigation.

temperature, and mole ratio of aldimine/Et_2Zn/silylacetylene for the reaction were probed next. The results indicated that a substantial change of the quantity of Et_2Zn did not have significant effect on the enantionselectives (entries 8−10, Table 2), and the catalytic activity of the **L4** appeared to be different at different temperatures (entries 8, 12, and 13, Table 2). Finally, the best result in 83% yield and 90% ee were obtained at 60 mol % catalyst loading with imine/Et_2Zn/silylacetylene = 1:4:6 at room temperature (entry 11, Table 2).

With the optimized conditions in hand, we decided to test a series of aryl, heteroaryl, and alkyl *N*-(diphenylphosphinoyl) imines. Representative results are summarized in Table 3 (entries 1−13). We were delighted to obtain the corresponding propargyl amides for various *N*-(diphenylphosphinoyl) imines in good to excellent enantioselectivities (72−95%) with moderate to good yields (66−92%) at room temperature. It could be obviously found that electronic nature of substituent groups had some influences on the enantionselectivity. *para*-Substitution with an electron-donating group of the aryl *N*-(diphenylphosphinoyl) imines gave excellent enantioselectivities and good yields (entries 3 and 5, Table 3). On the other hand, with -OMe in the *ortho* position of aryl imines, good yield and moderate enantionselectivity was obtained (entry 4, Table 3). Aryl imines with an electron-withdrawing group on the phenyl ring gave lower enantioselectivities (entries 6, 8, and 9, Table 3). It was likely that steric hindrance of *ortho* and *meta* substituents reduced enantioselectivities (entries 4 and 7, Table 3). Heteroarylimines (entries 10−12, Table 3) also showed high reactivity and provided good enantioselectivities (83−90% ee) in moderate to good yields. Aliphatic imine was also employed as substrate, and the expected product in excellent yield and moderate enantionselectivity was obtained (entry 13, Table 3).

The absolute stereochemistry of compound **2a** was determined to be (*S*) by chemical correlation[23] with (*R*)-(+)-*P*,*P*-diphenyl-*N*-(1-phenylpropyl)phosphinic amide **4a** (Scheme 3). The corresponding desilylated product **3a** was obtained in 89% yield by treatment of amide **2a** with Bu_4NF. The deprotection of diphenylphosphinoyl in compound **2a** was achieved by treatment with HCl/MeOH to provide the corresponding free optically active propargylic amine **5a** in 87% yield.

As an important member of the family of *N*-phosphinoylimines, *N*-(diethoxyphosphoryl) imines also attracted our attention. These imines were synthesized and applied to our system, and the results are summarized in Table 4. Gratifyingly, the corresponding propargyl amides were obtained in good enantioselectivities (89−93%) with moderate to good yields (71−82%). Interestingly, the alkynylation of *N*-(diethoxyphosphoryl) imines was more reactive than the same process with *N*-(diphenylphosphinoyl) imines. We suspected that the electron donor ability of $P(O)(OEt)_2$ may accelerate the alkynylation. To validate our hypothesis, more reactive *N*-activated imines, *N*-tosylimine, and *N*-benzylidenebenzamide were prepared and tested.[24] Unfortunately, the expectant corresponding propargyl amides were not observed in the optimized conditions (Scheme 4).

To better understand the reaction, careful React ^{31}P NMR investigation was undertaken (see Figure 2). First, we obtained the ^{31}P NMR spectra of the *N*-benzylidene-*P*, *P*-diphenylphosphinic amide (substrate, **1a**, +22.31 ppm) and *P*,*P*-diphenyl-*N*-(1-phenyl-3-(trimethylsilyl)prop-2-ynyl)-phosphinic amide (product, **2a**, +21.97 ppm) in toluene. After the mixture of ligands, Et_2Zn, and trimethylsilylacetylene was stirred at room temperature for 7 h, the substrate **1a** was added, and the signal of ^{31}P NMR was found to be +25.91 ppm. After 6 h, ^{31}P NMR of the mixture indicated three signals zat 25.85, 44.92, and 46.31 ppm. After 18 h, ^{31}P NMR of the mixture indicated two signals at 25.85 and 46.53 ppm. After 38 h, ^{31}P NMR of the mixture indicated two signals at 45.62 and 47.10 ppm. After 48 h, ^{31}P NMR of the mixture indicated two signals at 45.53 and 46.96 ppm.

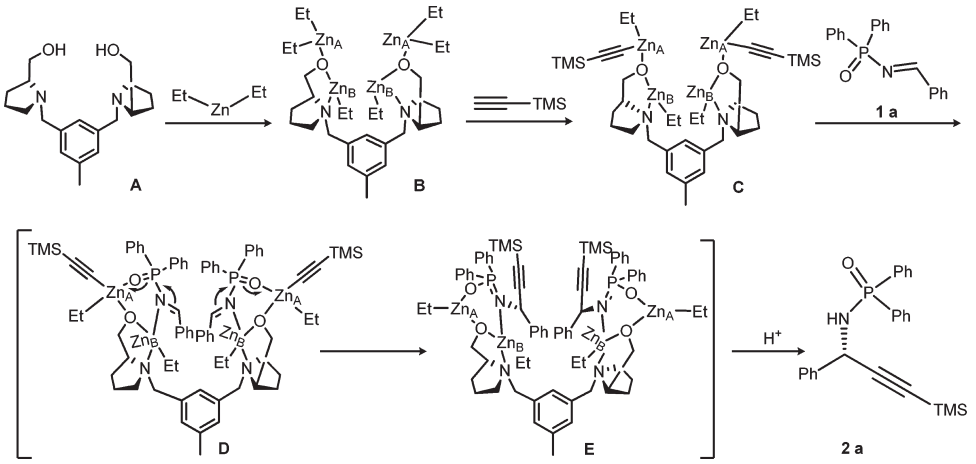
On the basis of the ^{31}P NMR spectra, an addition process of C=N alkynylation was proposed as in Scheme 5. After ligand **A** and Et_2Zn were mixed together, **B** was formed when the pyrrolidine and hydroxyl group reacted with diethylzinc.[25]

(23) Andersson, P. G.; Guijarro, D.; Tanner, D. *J. Org. Chem.* **1997**, *62*, 7364.

(24) A kinetic study of the reactivity order of *N*-actived imines is *N*-acyl > *N*-sulfonyl > *N*-phosphinoyl imines by using 2,4,6,-trichloroaniline as nucleophilic reagent. Drach, B, S.; Popovich, T. P.; Kisilenko, A, A.; Polumbrik, O. M. *J. Org. Chem. USSR* (*Engl. Trans.*) **1979**, *15*, 26.

(25) Similar reports about the same process, see: (a) Frantz, D. E.; Fassler, R.; Tomooka, E. M. *Acc. Chem. Res.* **2000**, *33*, 373. (b) Walsh, P. J. *Acc. Chem. Res.* **2003**, *36*, 739. (c) Lin, L.; Jiang, X.-X.; Liu, W.-X.; Xu, Z.-Q.; Xu, J.-K.; Chan, A. C. S.; Wang, R. *Org. Lett.* **2007**, *12*, 2329.

SCHEME 5. Proposed Process of C=N Alkynylation



It would be transformed to **C** by deprotonation of trimethylsilylacetylene.[26] While substrate **1a** was added, the oxygen atom was coordinated with Zn_A immediately. As the reaction proceeds, the nitrogen of the substrate was coordinated with the Lewis acid (Zn_B, Scheme 5). At the same time, the Michael-type transfer process occurred. When the addition was finished, the −C=N−P=O disappeared and a new −N=P bond formed.[27] As a result of the disappearance of both −C=N and −P=O, the nitrogen atom becomes more electron−rich, and the nitrogen atom of −N=P might coordinate with the Lewis acid (Zn_B, Scheme 5) more strongly. So, it is difficult for the pre-product to disengage from the ligand/Zn species. That would nicely account for why a stoichiometric amount of ligand was employed for this addition.

Conclusion

In conclusion, we have designed and synthesized C_2- and C_3-symmetric chiral proline-derived β-amine alcohol ligands, which have been successfully applied to the enantioselective nucleophilic addition of trimethylsilylacetylene to *N*-phosphinoylimines. Aromatic, heteroaromatic, and aliphatic *N*-(diphenylphosphinoyl) imines and several *N*-(diethoxyphosphoryl) imines were tested and produced the corresponding propargyl amines with good yields (up to 92%) and excellent enantioselectivities (up to 95%) at room temperature. Furthermore, the Michael-type addition process of C=N alkynylation was studied, and a mechanism was proposed on the basis of React ^{31}P NMR investigation.

Experimental Section

Representative Procedure for the Asymmetric Alkynylation of *N*-Benzylidene-*P*,*P*-diphenylphosphinic Amide. Under an argon atmosphere, into an oven−dried Schlenk flask was placed **L4** (34.8 mg, 0.12 mmol), and anhydrous toluene (1 mL) and a solution of diethylzinc in toluene (0.8 mL, 0.8 mmol, 4 equiv) were injected. The mixture was stirred for 30 min, and trimethylsilylacetylene (148 μL, 1.2 mmol, 6 equiv) was added. After an additional 7 h of stirring, the substrate was added into the flask at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL) after stirring for 48 h. The combined organic layers were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvents, the crude residue was purified by flash chromatography (silica gel, hexane/ethyl acetate), giving the corresponding product.

***P*,*P*-Diphenyl-*N*-(1-phenyl-3-(trimethylsilyl)prop-2-ynyl)phosphinic Amide, 2a.** White solid, mp = 141−143 °C, 72% yield. 90% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/isopropyl alcohol 95:5, 1.0 mL/min). Retention time: t_{major} = 13.21 and t_{minor} = 12.24 min. $[\alpha]^{20}_D$ = −21.5 (*c* 5.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09−8.02 (m, 2H), 7.83−7.77 (m, 2H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.55−7.43 (m, 4H), 7.40−7.27 (m, 5H), 5.19 (t, *J* = 10.2 Hz, 1H), 3.54 (t, *J* = 9.6 Hz, 1H), 0.20 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.0 (d, *J*(c-p) = 3.8 Hz), 133.5, 132.8 (d, *J*(c-p) = 9.8 Hz), 132.6, 132.0 (d, *J*(c-p) = 3 Hz), 131.9 (d, *J*(c-p) = 2.3 Hz), 131.7 (d, *J*(c-p) = 6 Hz), 131.6, 130.9, 128.5, 128.3, 127.8, 127.3, 104.9 (d, *J*(c-p) = 6 Hz), 90.1, 47.0. IR (KBr): ν 3394, 3062, 2961, 2252, 1439, 1250, 1195, 1125, 908, 734 cm^{-1}. HRMS calcd for $C_{24}H_{26}NOPSi + H^+$: 404.1594; found 404.1592.

Representative Procedure for the Deprotection of Trimethylsilyl of *P*,*P*-Diphenyl-*N*-(1-phenyl-3-(trimethylsilyl)prop-2-ynyl)-phosphinic Amide. *P*,*P*-Diphenyl-*N*-(1-phenyl-3-(trimethylsilyl)prop-2-ynyl) phosphinic amide (40.3 mg, 0.1 mmol) was dissolved in dry THF (0.5 mL) and cooled to 0 °C, and Bu_4NF (0.03 mL, 0.03 mmol, 1 M in THF) was added dropwise. The mixture was stirred at 0 °C for 15 min. Water (2 mL) was added and extracted with diethyl ether (3 × 2.5 mL). The combined organic fraction was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

***P*,*P*-Diphenyl-*N*-(1-phenylprop-2-ynyl)phosphinic Amide, 3a.** White solid, mp = 152−155 °C, 87% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07−8.00 (m, 2H), 7.90−7.83 (m, 3H), 7.63 (s, 1H), 7.60 (s, 1H), 7.55−7.26 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.6 (d, *J*(c-p) = 9.8 Hz), 132.1 (d, *J*(c-p) = 7.5 Hz), 128.7 (d, *J*(c-p) = 3.5 Hz), 128.5, 128.1, 127.1, 73.7, 46.5. IR (KBr): ν 3372, 3296, 2923, 2979, 2854, 1956, 1734, 1654, 1439, 1383, 1189, 1118, 1066, 1028, 697, 546 cm^{-1}. HRMS calcd for $C_{21}H_{18}NOP + H^+$: 332.1199; found 332.1193.

Representative Procedure for the Hydrogenation of *P*,*P*-Diphenyl-*N*-(1-phenylprop-2-ynyl)phosphinic Amide. *P*,*P*-Diphenyl-*N*-(1-phenylprop-2-ynyl)phosphinic amide (33.1 mg,

(26) *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995.

(27) For similar reports about the Michael addition process, see: (a) Michael, A. J. *J. Prakt. Chem.* **1987**, *35*, 349. (b) Hunt, D. A. *Org, Prep. Proced. Int.* **1989**, *21*, 705. (c) Hoz, S. *Acc. Chem. Res.* **1993**, *26*, 69. (c) Ihara, M.; Fukumoto, K. *Angew. Chem., Int. Ed.* **1993**, *32*, 1010. (d) Itoh, T.; Shiramaki, S. *Heterocycles* **2001**, *55*, 37. (e) Cai, C.; Soloshonok, V. A.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1339. (f) Bolm, C.; Kanyan, A.; Heider, P.; Saladin, S.; Drauz, K.; Gunther, K.; Wagner, C. *Org. Lett.* **2002**, *4*, 2265.

0.1 mmol) was charged in a 25-mL round-bottomed flask, dissolved in 10 mL of methanol, and palladium on carbon (10% by wt, dry, 0.10 g) was added under argon. The reaction flask was purged with H_2 and kept under a balloon of H_2 for 16 h, the mixture was filtered through Celite, and the methanol was removed under reduced pressure to give a white solid, which was then purified by flash chromatography on silica and gave the corresponding compound.

***P*,*P*-Diphenyl-*N*-(1-phenylpropyl)phosphinic Amide, 4a.** Colorless oil, 73% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89−7.82 (m, 2H), 7.78−7.71 (m, 2H), 7.47−7.37 (m, 4H), 7.34−7.22 (m, 4H), 7.16−7.14 (t, J = 6.0 Hz, 2H), 4.11−4.06 (m, 1H), 3.34−3.29 (t, J = 9.7 Hz, 1H), 2.05−1.96 (m, 1H), 1.87−1.78 (m, 1H), 0.81−0.76 (t, J = 7.5, Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5 (d, J(c-p) = 5.6 Hz), 132.9, 132.6, 132.4, 128.5 (d, J(c-p) = 3.4 Hz), 128.3 (d, J(c-p) = 13.5 Hz), 57.1, 32.4 (d, J(c-p) = 3.3 Hz), 10.5. IR (neat): ν 3150, 3054, 2963, 2927, 2862, 1591, 1454, 1433, 1182, 1109, 1054, 1013, 901, 751, 697, 534 cm^{-1}. HRMS calcd for $C_{21}H_{22}NOP + H^+$: 336.1512; found 336.1517.

Representative Procedure for the Deprotection of Diphenylphosphinoyl of *P*,*P*-Diphenyl-*N*-(1-phenylprop-2-ynyl)phosphinic Amide. *P*,*P*-Diphenyl-*N*-(1-phenylprop-2-ynyl)phosphinic amide (33.1 mg, 0.1 mmol) was added to a 25-mL round-bottomed flask. A mixture of methanol (3 mL) and concentrated aqueous HCl (1 mL) was added. The mixture solvent was stirred at room temperature for 2 h. Then the reaction mixture was concentrated by rotary evaporation and dissolved in 1 M aqueous HCl (2 mL), and the precipitate was removed by filtration. Then it was basified (pH >12) by adding 2 M NaOH, and the result mixture was extracted with dichloromethane (4 × 10 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvents, the crude residue was purified by flash chromatography on silica, giving the corresponding compound.

1-Phenyl-3-(trimethylsilyl)prop-2-yn-1-amine,[8b] 5a. Colorless oil, 89% yield. $[\alpha]^{20}_D$ = −22 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55−7.52 (m, 2H), 7.39−7.29 (m, 3H), 4.78 (s, 1H), 1.77 (s, 1H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.2, 131.7 (d, J(c-p) = 9.8 Hz), 128.5 (d, J(c-p) = 6.0 Hz), 127.7, 126.8, 126.7, 88.5, 48.1. IR (neat): ν 3374, 3300, 2959, 2926, 2170, 1659, 1451, 1367, 1250, 1012, 844, 760, 699, 666 cm^{-1}.

Acknowledgment. We are grateful for grants from the National Natural Science Foundation of China (nos. 20525206, 20772052, 90813012, and 20621091), the National S & T Major Project of China (2009ZX09503-017), and the Chang Jiang Program of the Ministry of Education of China for financial support

Supporting Information Available: Experimental details and spectral and analytical data for all ligands and reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.