Tetrahedron Letters 50 (2009) 6720–6722

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Cu-catalyzed asymmetric conjugate reduction of β-substituted α,β-unsaturated phosphonates: an efficient synthesis of optically active β-stereogenic alkylphosphonates

Zheng-Chao Duan [a,b], Xiang-Ping Hu [a,*], Dao-Yong Wang [a,b], Sai-Bo Yu [a,b], Zhuo Zheng [a,*]

[a] Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, China
[b] Graduate School of Chinese Academy of Sciences, Beijing 100039, China

ARTICLE INFO

Article history:
Received 24 July 2009
Revised 17 September 2009
Accepted 18 September 2009
Available online 24 September 2009

ABSTRACT

A series of chiral alkylphosphonates bearing β-stereogenic center were synthesized in good enantioselectivities (up to 95% ee) via the CuH-catalyzed asymmetric conjugate reduction of β-substituted α,β-unsaturated phosphonates under optimal conditions using $Cu(OAc)_2·H_2O$ as the copper source, (*R*)-SEGPHOS as the ligand, PMHS as the siloxane, and *t*-BuOH as the additive.

Optically active alkylphosphonic acid derivatives have gained much attention in recent decades because of their interesting biological properties as phosphorus analogues of carboxylic acids, as well as their synthetic utility as chiral building blocks.[1] However, the enantioselective synthesis of chiral alkylphosphonates,[2] in particular those bearing β-stereogenic center, remains rarely explored. The first catalytic enantioselective synthesis of chiral β-stereogenic alkylphosphonates, based on the Rh-catalyzed asymmetric 1,4-addition to 1-alkenylphosphonates using arylboroxines as arylating reagents, was reported by Hayashi et al. in 1999,[3] in which a variety of chiral β-arylalkylphosphonates were achieved in good enantioselectivities. Very recently, we have also reported a highly enantioselective synthesis of chiral β-stereogenic alkylphosphonates via the first Rh-catalyzed asymmetric hydrogenation of the corresponding β-substituted α,β-unsaturated phosphonates.[4] However, these methods have the disadvantages of demanding reaction conditions, the use of the expensive Rh catalyst, and high catalyst loadings. These shortcomings prompted us to seek an alternative approach to synthesize chiral β-substituted alkylphosphonates.

In the past decade, copper hydride (Cu-H) with chiral ligands has emerged as a powerful reagent for effecting asymmetric reductions of various α,β-unsaturated compounds,[5] such as enones,[6] α,β-unsaturated esters,[7] nitroalkenes,[8] α,β-unsaturated sulfones,[9] α,β-unsaturated nitriles,[10] and more recently 2-alkenylheteroarenes.[11] Due to the structural similarity between these α,β-unsaturated compounds and β-substituted α,β-unsaturated phosphonates of interest, we envision that an asymmetric 1,4-reduction of β-substituted α,β-unsaturated phosphonates via the copper hydride catalysis is an attractive alternative to prepare chiral β-stereogenic alkylphosphonates. To the best of our knowledge, however, an enantioselective asymmetric conjugate reduction method of α,β-unsaturated phosphonates catalyzed by a copper hydride has not been reported yet. Herein, we report our studies on this new strategy for constructing chiral β-stereogenic alkylphosphonates derivatives.

We started to investigate the asymmetric reductions of diethyl (*E*)-1-(2-phenylpropenyl)phosphonate (**1a**) using 5 mol % of $Cu(OAc)_2·H_2O$ as the catalytic precursor in the presence of excess polymethylhydrosiloxane (PMHS) and *t*-BuOH. Initially, we screened several chiral C_2-symmetrical bisphosphine ligands (Fig. 1). The results in Table 1 disclosed that the catalyst system prepared in situ from $Cu(OAc)_2·H_2O$ and (*S*)-BINAP, (*R*)-MeO-BIPHEP, or (*S*)-SYNPHOS was not effective for the reduction of (*E*)-**1a**, as only low conversions were observed in these cases (entries

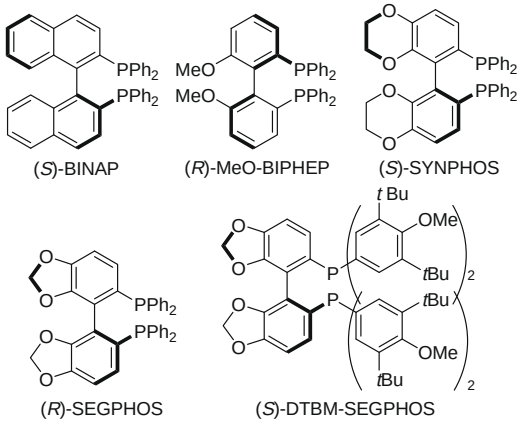
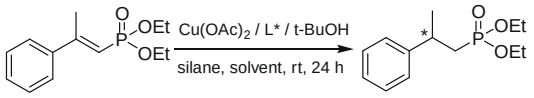


Figure 1. Bisphosphine ligands evaluated in asymmetric reduction.

* Corresponding authors. Tel.: +86 411 84379276; fax: +86 411 84684746.
E-mail addresses: xiangping@dicp.ac.cn (X.-P. Hu), zhengz@dicp.ac.cn (Z. Zheng).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.09.094

Table 1
Cu-catalyzed asymmetric conjugate reduction of (*E*)-(2-phenyl-1-propenyl)phosphonate (**1a**)[a]



1a **2a**

Entry	Ligand	Silane (equiv)	Cu-source	Additive (equiv)	Solvent	Conv.[b] (%)	ee[c] (%)
1	(*S*)-BINAP	PMHS (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	Toluene	34	—[d]
2	(*R*)-MeO-BIPHEP	PMHS (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	Toluene	37	—[d]
3	(*S*)-SYNPHOS	PMHS (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	Toluene	36	—[d]
4	(*R*)-SEGPHOS	PMHS (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	Toluene	85	93
5	(*S*)-DTBM-SEGPHOS	PMHS (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	Toluene	52	90
6	(*R*)-SEGPHOS	PMHS (4)	$Cu(OAc)_2·H_2O$	—	Toluene	36	91
7	(*R*)-SEGPHOS	PMHS (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (2)	Toluene	46	—[d]
8	(*R*)-SEGPHOS	PMHS (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (8)	Toluene	38	—[d]
9	(*R*)-SEGPHOS	PMHS (2)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	Toluene	25	—[d]
10	(*R*)-SEGPHOS	PMHS (8)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	Toluene	62	—[d]
11	(*R*)-SEGPHOS	Et_3SiH (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	Toluene	<10	—[d]
12	(*R*)-SEGPHOS	TMDS (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	Toluene	<10	—[d]
13	(*R*)-SEGPHOS	$PhSiH_3$ (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	Toluene	26	—[d]
14	(*R*)-SEGPHOS	Ph_2SiH_2 (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	Toluene	99	66
15	(*R*)-SEGPHOS	PMHS (4)	CuCl/NaO*t*-Bu	*t*-BuOH (4)	Toluene	55	92
16	(*R*)-SEGPHOS	PMHS (4)	$CuF(PPh_3)_3·MeOH$	*t*-BuOH (4)	Toluene	65	92
17	(*R*)-SEGPHOS	PMHS (4)	$CuF_2·2H_2O$	*t*-BuOH (4)	Toluene	<10	—[d]
18	(*R*)-SEGPHOS	PMHS (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	THF	72	93
19	(*R*)-SEGPHOS	PMHS (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	Et_2O	92	92
20	(*R*)-SEGPHOS	PMHS (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	CH_2Cl_2	15	—[d]
21	(*R*)-SEGPHOS	PMHS (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	Et_2O/toluene	85	94
22	(*R*)-SEGPHOS	PMHS (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	Et_2O/THF (1/1)	81	94
23	(*R*)-SEGPHOS	PMHS (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	Et_2O/THF (2/1)	79	93
24	(*R*)-SEGPHOS	PMHS (4)	$Cu(OAc)_2·H_2O$	*t*-BuOH (4)	Et_2O/THF (4/1)	91	94

[a] All reactions were performed at 5 mol % of catalyst loadings prepared in situ from Cu-precursor and 1.2 equiv of chiral diphosphine ligand with 0.25 mmol of substrate (**1a**) at room temperature in 2 mL of solvent for 24 h.
[b] Degrees of conversion were determined by GC.
[c] The ee values were determined by HPLC on a chiral column.
[d] Not determined.

1–3). To our delight, we found that with (*R*)-SEGPHOS the reaction proceeded smoothly and yielded the desired product in good conversion (85%) and high enantioselectivity (93% ee) (entry 4).

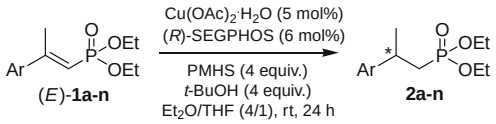
Although high enantioselectivity was obtained in the absence of *t*-BuOH additive, the observable decrease in the reaction rate was observed (entry 6). This result proved that *t*-BuOH additive is very important for this reduction. The amount of *t*-BuOH and PMHS has some influence in the conversions. Both the reduction and the increase in the amount of *t*-BuOH and PMHS led to the decrease in the conversions (entries 7–10). These results are the same as those reported by Buchwald and co-workers in which 4 equiv of PMHS is necessary to reduce α,β-unsaturated esters.[7a] Subsequent experiments in an effort to improve the conversion and enantioselectivity by the variation of the silane reagent proved less fruitful. We found that the use of Et_3SiH, TMDS, and $PhSiH_3$ in the reaction resulted in dramatically decreased conversions (entries 11–13). However, using Ph_2SiH_2 led to higher conversion, but lower enantioselectivity (entry 14). The copper sources also significantly affected this reduction. The reaction with CuCl, $CuF(PPh_3)_3·MeOH$, or $CuF_2·2H_2O$ gave lower conversion than that with $Cu(OAc)_2·H_2O$ (entries 15–17). Solvent-screening experiments revealed that the nature of the solvents had a profound effect on the catalytic reaction. Thus, the reaction performed in Et_2O gave an increased conversion and slightly decreased enantioselectivity (entry 19); while the reaction performed in CH_2Cl_2 showed very low reaction rate (entry 20). Interestingly, a mixed solvent, Et_2O/THF (4/1) was found to favor this reduction. In this case, 91% conversion and 94% ee were achieved (entry 24).

Encouraged by the promising result obtained in the reduction of (*E*)-**1a**, the conjugate reduction of a variety of diethyl 1-(2-arylpropenyl)phosphonates was examined. The reactions were performed at a catalyst loading of 5 mol % prepared in situ from $Cu(OAc)_2·H_2O$ and 1.2 equiv of (*R*)-SEGPHOS in the presence of 4 equiv of PMHS and *t*-BuOH in Et_2O/THF (4/1) at room temperature for 24 h. The results are summarized in Table 2.

The effect of substituent positioning was investigated using methyl- and methoxy-substituted substrates (*E*)-**1b–g** (entries 2–7). The results revealed that the substituent on the *meta*- or *para*-position of phenyl ring of the substrate had no major influence on the enantioselectivity. All of the *meta*- and *para*-methyl or methoxy-substituted substrates gave moderate yields and good enantioselectivities (entries 3, 4, 6, and 7). However, the substrates bearing an *ortho*-substituent were surprisingly not reduced in the present catalytic conditions (entries 2 and 5). The reason is probably due to the steric effect that inhibits the copper hydride coordinating to the C=C bond of substrate and the subsequent hydride transfer onto the β-carbon. The electronic properties of the *para*-substituent on the phenyl ring of the substrate observably impacted the yield of the reduction. The substrates having an electron-withdrawing group on the *para*-position of the phenyl ring were reduced in higher yields than those with an electron-donating group. However, the stereoselectivity of this catalytic reduction was highly tolerant of *para*-substituents on the phenyl ring, regardless of their electronic properties. For example, substrate (*E*)-**1g** with a *para*-methoxy group was reduced in 46% yield and 93% ee (entry 7); while the *para*-CF_3-substituted substrate **1i** gave 96% yield and 94% ee (entry 9). The reduction of thiophene-substituted substrate also gave good enantioselectivity but relatively low yield (entry 14).

To expand the scope of this new procedure, some other α,β-unsaturated phosphonates were subjected to the catalytic reduction. As shown in Figure 2, substrate (*E*)-**1o** without an aryl group at the prochiral carbon was also selectively reduced and it behaved

Table 2
Enantioselective conjugate reduction of α,β-unsaturated phosphonates[a]



Entry	Substrate (Ar)	Yield[b] (%)	ee[c] (%)
1	(*E*)-**1a**: Ar = Ph	86	94 (*S*)
2	(*E*)-**1b**: Ar = 2-MeC_6H_4	—[d]	—[d]
3	(*E*)-**1c**: Ar = 3-MeC_6H_4	71	94
4	(*E*)-**1d**: Ar = 4-MeC_6H_4	61	94
5	(*E*)-**1e**: Ar = 2-MeOC_6H_4	—[d]	—[d]
6	(*E*)-**1f**: Ar = 3-MeOC_6H_4	57	95
7	(*E*)-**1g**: Ar = 4-MeOC_6H_4	46	93
8	(*E*)-**1h**: Ar = 3-$CF_3C_6H_4$	92	94
9	(*E*)-**1i**: Ar = 4-$CF_3C_6H_4$	96	94
10	(*E*)-**1j**: Ar = 4-FC_6H_4	80	94
11	(*E*)-**1k**: Ar = 4-ClC_6H_4	95	93
12	(*E*)-**1l**: Ar = 4-BrC_6H_4	79	93
13	(*E*)-**1m**: Ar = 2-naphthyl	77	92
14	(*E*)-**1n**: Ar = 2-thiophenyll	41	90

[a] All reactions were performed at 5 mol % of catalyst loadings prepared in situ from $Cu(OAc)_2·H_2O$ and 1.2 equiv of (*R*)-SEGPHOS with 0.25 mmol of substrate in the presence of 4 equiv of PHMS and 4 equiv of *t*-BuOH in 2 mL of Et_2O/THF (4/1) at room temperature for 24 h.
[b] Isolated yields.
[c] The ee values were determined by HPLC on a chiral column.
[d] Not determined because of low conversion.

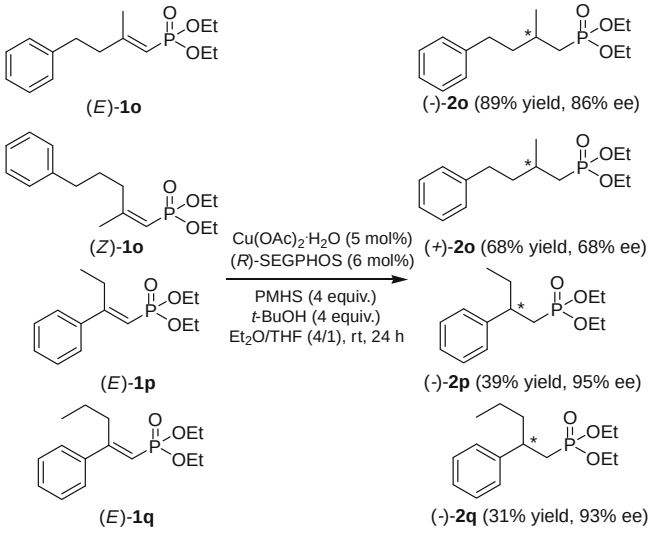


Figure 2. Some other α,β-unsaturated phosphonates evaluated in asymmetric reduction.

similarly to its aryl cohorts. However, (*Z*)-configuration in the substrate seems to be unfavorable to both reactivity and enantioselectivity. Thus, (*Z*)-**1o** was reduced in 68% yield and 68% ee, significantly lower than that obtained with (*E*)-**1o**. The reduction of β-ethyl-β-phenyl-substituted substrate (*E*)-**1p** and β-propyl-β-phenyl-substituted substrate (*E*)-**1q** gave similar enantioselectivities but lower yields in comparison with the result obtained with their methyl analogue (*E*)-**1a**.

In conclusion, we have developed a copper-catalyzed asymmetric conjugate reduction of β-substituted α,β-unsaturated phosphonates that provides ready access to optically active β-stereogenic alkylphosphonates. A wide range of β-substituted α,β-unsaturated phosphonates were reduced with high enantioselectivities (up to 95% ee) under optimal conditions using a $Cu(OAc)_2·H_2O$/(*R*)-SEGPHOS catalytic system in the presence of PMHS and *t*-BuOH. The reduction was sensitive to the substitution pattern and to the electronic properties of the substituent on the phenyl ring of the substrate. Generally, the substrates having an electron-withdrawing group at the *para*-position of the phenyl ring were reduced in higher yields than those with an electron-donating group. Further applications of this methodology are in progress.

Acknowledgments

We thank the National Natural Science Foundation of China (20802076, 20873145) and the Knowledge Innovation Program of the Chinese Academy of Sciences (DICP-S200802) for financial support.

References and notes

1. (a) Hilderbrand, R. L. *The Role of Phosphonates in Living Systems*; CRC Press: Boca Raton, 1983; (b) Bellucci, C.; Gualtieri, F.; Scapecchi, S.; Teodori, E.; Budriesi, R.; Chiarini, A. *Farmaco* **1989**, *44*, 1167–1191; (c) Kafarski, P.; Lejczak, B. *Phosphorus Sulfur Relat. Elem.* **1991**, *63*, 193–215; (d) Kelly, S. E.. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 761–773; (e) Jung, K. W.; Janda, K. D.; Sanfilippo, P. J.; Wachter, M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2281–2282; (f) Lo, C.-H. L.; Wentworth, P.; Jung, K. W.; Yoon, J.; Ashley, J. A.; Janda, K. D. *J. Am. Chem. Soc.* **1997**, *119*, 10251–10252; (g) Datta, A.; Wentworth, P.; Shaw, J. P.; Simeonov, A.; Janda, K. D. *J. Am. Chem. Soc.* **1999**, *121*, 10461–10467; Savignac, P.; Iorga, B. *Morden Phosphonate Chemistry*; CRC Press: Boca Raton;, 2003; (i) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **2005**, *16*, 3295–3340.
2. (a) Henry, J.-C.; Lavergne, D.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Beletskaya, I. P.; Dolgina, T. M. *Tetrahedron Lett.* **1998**, *39*, 3473–3476; (b) Goulioukina, N. S.; Dolgina, T. M.; Beletskaya, I. P.; Henry, J.-C.; Lavergne, D.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Tetrahedron: Asymmetry* **2001**, *12*, 319–327; (c) Goulioukina, N. S.; Dolgina, T. M.; Bondarenko, G. N.; Beletskaya, I. P.; Ilyin, M. M.; Davankov, V. A.; Pfaltz, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1397–1401; (d) Wang, D.-Y.; Hu, X.-P.; Deng, J.; Yu, S.-B.; Duan, Z.-C.; Zheng, Z. *J. Org. Chem.* **2009**, *74*, 4408–4410; (e) Cheruku, P.; Paptchikhine, A.; Church, T. L.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8285–8289.
3. Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591–11592.
4. Duan, Z.-C.; Hu, X.-P.; Wang, D.-Y.; Huang, J.-D.; Yu, S.-B.; Deng, J.; Zheng, Z. *Adv. Synth. Catal.* **2008**, *350*, 1979–1983.
5. For a review, see: Rendler, S.; Oestreich, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 498–504.
6. (a) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797–6798; (b) Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892–2893; (c) Lipshutz, B. H.; Servesko, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4789–4792; (d) Lipshutz, B. H.; Servesko, J. M.; Petersen, T. B.; Papa, P. P.; Lover, A. A. *Org. Lett.* **2004**, *6*, 1273–1275; (e) Lipshutz, B. H.; Frieman, B. A.; Tomaso, A. E., Jr. *Angew. Chem., Int. Ed.* **2006**, *45*, 1259–1264.
7. (a) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473–9474; (b) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253–11258; (c) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352–8353; (d) Rainka, M. P.; Aye, Y.; Buchwald, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5821–5823; (e) Rainka, M. P.; Milne, J. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6177–6180; (f) Lipshutz, B. H.; Tanaka, N.; Taft, B. R.; Lee, C.-T. *Org. Lett.* **2006**, *8*, 1963–1966; (g) Deng, J.; Hu, X.-P.; Huang, J.-D.; Yu, S.-B.; Wang, D.-Y.; Duan, Z.-C.; Zheng, Z. *J. Org. Chem.* **2008**, *73*, 6022–6024.
8. (a) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4793–4795; (b) Czekelius, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 4575–4577; (c) Czekelius, C.; Carreira, E. M. *Org. Process Res. Dev.* **2007**, *11*, 633–636.
9. Llamas, T.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3329–3332.
10. (a) Lee, D.; Kim, D.; Yun, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2785–2787; (b) Lee, D.; Yang, Y.; Yun, J. *Org. Lett.* **2007**, *9*, 2749–2751.
11. Rupnicki, L.; Saxena, A.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 10386–10387.