Tetrahedron: *Asymmetry* 19 (2008) 2335–2338

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Enantioselective conjugate addition of dialkyl phosphites to nitroalkenes

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ARTICLE INFO

Article history:
Received 17 September 2008
Accepted 14 October 2008
Available online 5 November 2008

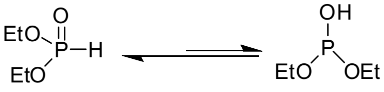
ABSTRACT

The Michael addition of dialkyl phosphites to nitroalkenes in the presence of heterobimetallic (*S*)-(−)-aluminum lithium bis(binaphthoxide), ALB, complex provided β-nitrophosphonates, precursors to β-aminophosphonic acids, in good to excellent enantioselectivities.

1. Introduction

Nitrophosphonates are immediate precursors to aminophosphonic acids, which, in turn, are isosteric analogues of amino acids.[1] β-Aminophosphonic acids, in particular, exhibit antibacterial, enzyme inhibitory, and anti-HIV properties.[2] Although numerous methods are available in the literature for the synthesis of β-nitro/aminophosphonates,[2,3] there are only handful of approaches for the asymmetric synthesis of such compounds.[3,4] This is despite the fact that the introduction of chirality in the flexible aminophosphonic acid chain is likely to enhance its diverse and potent biological properties. The early asymmetric approaches relied primarily on substrate-controlled diastereoselective additions.[3] Recent auxiliary approaches to the synthesis of β-nitrophosphonates include the addition of menthol derived[5] and TADDOL derived[6] phosphites to nitroalkenes. Recent catalytic approaches involved Mannich reactions,[7] aminohydroxylations,[8] aminobrominations,[9] nitroaldol reactions,[10] and phospha-Michael additions.[11] Although the catalytic asymmetric Michael addition of phosphite to nitroalkenes provides a convenient entry into enantioenriched β-nitrophosphonates, it turns out that only diphenyl phosphite has successfully been added.[11] This is presumably due to the drastic variation of pK_a's of various phosphites, viz. dialkyl, diaryl, etc., with change in substituents.[12]

Yet another property of such P-nucleophiles is the tautomerism that exists between phosphite **T1** and phosphonate **T2** (Scheme 1).[4] It has been reported that **T2** is the active nucleophile, while **T1** is the resting species.[13]

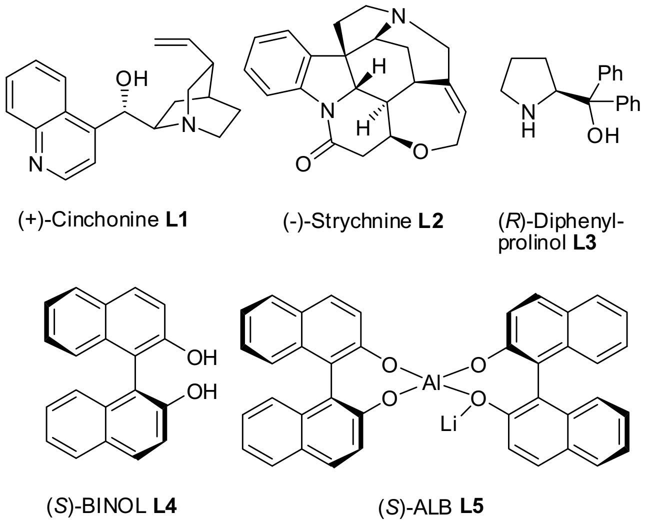


T1 **T2**

Scheme 1. Tautomeric existence of diethyl phosphite **1a**.

2. Results and discussion

At the outset, we have chosen diethyl phosphite **1a** as the model phosphite for our optimization studies. Our initial attempts to carry out the conjugate addition of diethyl phosphite **1a** to nitroalkene **2a** under organocatalytic conditions using chiral Lewis bases such as cinchonine **L1** and strychnine **L2** were unsuccessful (Fig. 1 and Table 1, entries 1 and 2). When these bases and diphenyl prolinol **L3** were employed in conjunction with LDA, that is, as their lithiated complexes, the products were isolated in excellent yields, but with no selectivity (Table 1, entries 3–5).



(+)-Cinchonine **L1** (-)-Strychnine **L2** (*R*)-Diphenyl-prolinol **L3**

(*S*)-BINOL **L4** (*S*)-ALB **L5**

Figure 1. Chiral ligands **L1–L5**.

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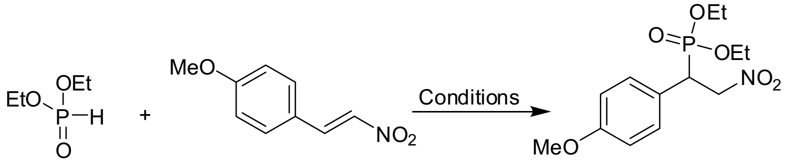
doi:10.1016/j.tetasy.2008.10.010

Table 1
Catalyst screening for the Michael addition of diethyl phosphite **1a** to 4-methoxynitrostyrene **2a**



1a **2a** **3a**

Entry	Conditions	Yield[a] (%)	ee[b] (%)
1	**L1** (10–50 mol %), THF, rt, 10 d	$\leqslant$5	–
2	**L2** (50 mol %), THF, rt, 10 d	<5	–
3	**L1** (10 mol %), LDA (1.2 equiv), THF, −78 °C, 3 h	93	0
4	**L2** (10 mol %), LDA (2 equiv), THF, −78 °C, 3 h	95	0
5	**L3** (10 mol %), LDA (2 equiv), THF, −78 °C, 3 h	94	0
6	**L1**-Ti(*i*-OPr)$_4$ (20 mol %), THF, rt-reflux	48	0
7	**L4**-Ti(*i*-OPr)$_4$ (20 mol %), THF, rt	20	–
8	**L1**-LiAlH$_4$ (20 mol %), toluene, 0 °C–rt, 4 h	58	8
9	**L5** (30 mol %), toluene, rt, 2 d	74	91
10	**L5** (20 mol %), toluene, rt, 2 d	72	87
11	**L5** (15 mol %), toluene, rt, 2 d	74	97[c]
12	**L5** (10 mol %), toluene, rt, 2 d	62	90

[a] Isolated yields.
[b] Determined by HPLC (Chiralcel OD-H column, 5% IPA in *n*-hexane).
[c] THF and THF + toluene were also employed as solvents, but the use of THF for generation of catalyst and toluene for reaction provided the best results.

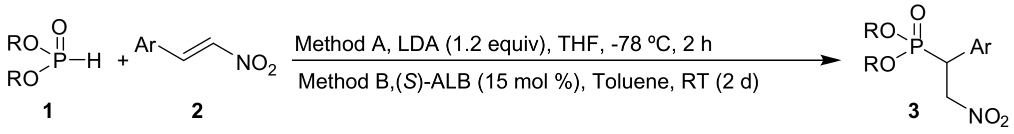
Since the above attempts to activate the diethyl phosphite tautomer **T1** toward the enantioselective Michael addition using chiral bases were unsuccessful, we shifted our focus to utilize the phosphonate tautomer **T2** using chiral Lewis acids.[14] However, Lewis acids, generated by combinations of cinchonine **L1** and (*S*)-BINOL **L4** with Ti(O^{i}Pr)$_4$, provided only poor results (Table 1, entries 6 and 7).

The above observations emphasized the requirement of a bifunctional catalyst possessing, for instance, a Brønsted base moiety and a Lewis acid moiety. Although such a species is presumably formed from **L1** and LiAlH$_4$, the outcome was still unsatisfactory (Table 1, entry 8). This prompted us to resort to a heterobimetallic complex, for example, (*S*)-(−)-aluminum lithium bis(binaphthoxide), ALB **L5**,[15] which is known to induce stereoselectivity in many reactions such as the nitroaldol and hydrophosphonylation of aldehydes, Mannich reaction, and Michael addition through a synergistic cooperation between two different metals (Li and Al) and a chiral template (binaphthol) in a manner analogous to that seen in metal-ion co-catalyzed enzymatic processes.[16] Such a heterobimetallic complex enhances the reactivity of both the reaction partners by orienting them appropriately in the transition state.

Much to our delight, the Michael addition of diethyl phosphite **1a** to nitroalkene **2a** in the presence of 30 mol % of (*S*)-ALB **L5** provided the desired product **3a** in good yield (74%) and high enantioselectivity (91% ee, Table 1, entry 9). Finally, the optimum amount of the catalyst **L5** turned out to be 15 mol %, which provided product **3a** in good yield (74%) and excellent enantioselectivity (97% ee, Table 1, entry 11).

The above optimized conditions were employed for the addition of diethyl phosphite **1a** to a variety of nitroalkenes **2a**–**f** and for the addition of dimethyl phosphite **1b** to selected nitroalkenes **2a**, **2c**, and **2d** (Table 2). The racemic products were conveniently gener-

Table 2
Scope of the Michael addition of dialkyl phosphites **1** to nitroalkenes **2**[17]



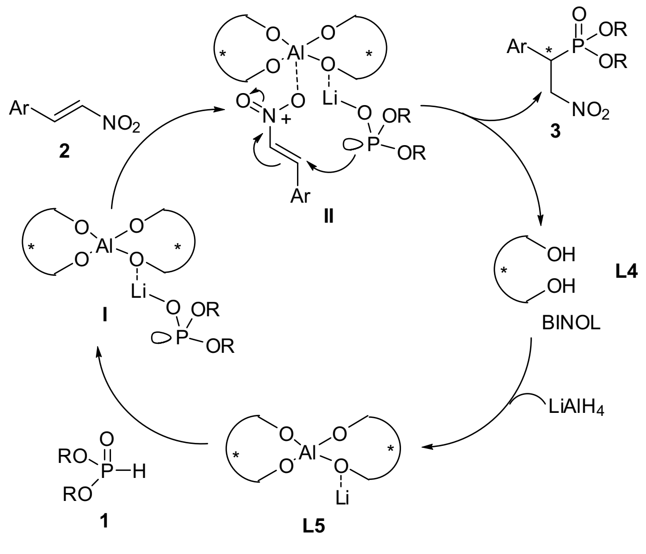
Entry	**2**, Ar	**1**, R	**3**	Yield[a] (%) (method A)[b]	Yield[a,c] (%) (method B)	ee[d] (%) (method B)
1	**2a**, 4-OMePh	**1a**, Et	**3a**	80	74 (08)	97
2	**2b**, 3,4-(OMe)$_2$Ph	**1a**, Et	**3b**	73	54 (16)	84
3	**2c**, Ph	**1a**, Et	**3c**	18	48 (23)	75
4	**2d**, 4-ClPh	**1a**, Et	**3d**	82	52 (24)	>99
5	**2e**, 4-NO$_2$Ph	**1a**, Et	**3e**	28	45 (12)	>99
6	**2f**, 2-Furyl	**1a**, Et	**3f**	25	20 (42)	>99
7	**2a**, 4-OMePh	**1b**, Me	**3g**	84	18 (56)	>99
8	**2c**, Ph	**1b**, Me	**3h**	94	24 (32)	>99
9	**2d**, 4-ClPh	**1b**, Me	**3i**	76	10 (59)	>99
10	**2a**, 4-OMePh	**1c**, Ph	**3j**	96	<5 (78)	2

[a] Isolated yields.
[b] Employed for generating racemic profiles.
[c] Recovered nitroalkene in parentheses.
[d] Determined by HPLC (Chiralcel OD-H/Chiralpak IA column, 5% IPA in *n*-hexane).

ated within 2 h in high yields in most cases via LDA-mediated addition of phosphite **1** to nitroalkene **2**. Low yields of racemic products were obtained only in the case of nitrostyrene **2c** (entry 3), 4-nitronitrostyrene **2e** (entry 5), and 2-furyl nitroethylene **2f** (Table 2, entry 6).

In the enantioselective reactions, the addition of phosphite **1a** to nitrostyrenes possessing electron-donating groups on the aromatic ring **2a** and **2b** provided the Michael adducts **3a** and **3b** respectively, in good yield and selectivity (Table 2, entries 1 and 2). While parent nitrostyrene **2c** provided product **3c** in moderate yield (48%) and selectivity (75% ee, Table 2, entry 3), nitrostyrenes with both weakly and strongly deactivating groups, **2d** and **2e**, respectively, provided adducts **3d** and **3e** in moderate to good yields and excellent selectivities (>99% ee, entries 4 and 5). The addition of diethyl phosphite **1a** to heteroaromatic nitroalkene **2f** (Table 2, entry 6) and the similar addition of dimethyl phosphite **1b** to selected nitroalkenes **2a**, **2c,** and **2d**, although proceeding in low yields (10–24%), provided the desired products **3g–i** in excellent enantioselectivities (>99%, entries 7–9). Finally, these optimized conditions were found not suitable for the addition of diphenyl phosphite **1c** to nitroalkenes **2** (Table 2, entry 10).

A mechanistic rationale provided in Scheme 2 suggests that the lithium naphthoxide moiety, that is, the Brønsted base part of (*S*)-ALB **L5**, could activate dialkyl phosphite **1** to give complex **I**. Further co-ordination of the Lewis acidic Al center with the oxygen atoms of the nitro group in **2** would furnish complex **II**. Such double co-ordination of the catalyst **L5** with both the reactants, nitroalkene **2** and dialkyl phosphite **1**, orientates the latter in a manner that leads to a face selective reaction in a chiral environment (see Scheme 2).



Scheme 2. Proposed mechanism.

Our preliminary DFT calculations to determine the relative stabilities of tautomers **T1** and **T2** of diethyl phosphite confirmed that **T1** was more stable by ~6 kcal mol^{-1} than **T2**. Further, ^{31}P NMR investigations show that the **T1**–**T2** equilibrium is different in the presence of LDA and (*S*)-ALB **L5**. For instance, addition of ALB to diethyl phosphite (δ 6.65, dq, $J = 696.1$, 9.2 Hz) has not changed the ^{31}P NMR pattern of diethyl phosphite (δ 6.85, dq, $J = 696.1$, 9.2 Hz) to any significant extent suggesting the overwhelming predominance of the 'resting' pentavalent species **T1** in the equilibrium mixture. This is also reflected in the rate of ALB-catalyzed reactions (see Table 2). On the other hand, the addition of LDA leads to disappearance of this peak and appearance of two new broad peaks (δ 38.5 and 143.4) in a 35:65 ratio, which is presumably due to the formation of lithiated species comprising both trivalent and pentavalent tautomers in equilibrium.

3. Conclusions

In conclusion, the stereoselective conjugate addition of dialkyl phosphites to nitroalkenes has been successfully carried out for the first time. Compound (*S*)-ALB was found to catalyze the reaction to provide the adducts in moderate to good yields and good to excellent enantioselectivities. The transformation of the enantiopure β-nitrophosphonates to β-aminophosphonic acids and the biological evaluation of the latter are currently being investigated in our laboratory.

Acknowledgments

The authors thank DST, India for financial assistance and SAIF, IIT Bombay for selected NMR data and Mr Narasimhan Ayyagari for additional experimental support. V.R. thanks CSIR, India for a research fellowship.

References

1. For our recent reports on the asymmetric synthesis of γ-nitrophosphonates via Michael addition of phosphonates to nitroalkenes in the presence of Li-cinchonine complex: (a) Rai, V.; Mobin, S. M.; Namboothiri, I. N. N. *Tetrahedron: Asymmetry* **2007**, *18*, 2719; (b) Rai, V.; Namboothiri, I. N. N. *Tetrahedron: Asymmetry* **2008**, *19*, 767.
2. For a review: Palacios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899 and the references cited therein.
3. For reviews: (a) Enders, D.; Saint-Dizier, A.; Lannou, M.-I.; Lenzen, A. *Eur. J. Org. Chem.* **2006**, 29; (b) Mikołajczyk, M. *J. Organomet. Chem.* **2005**, *690*, 2488.
4. For a review: Ma, J.-A. *Chem. Soc. Rev.* **2006**, *35*, 630.
5. Kolodiazhnyi, O. I.; Sheiko, S.; Grishkun, E. V. *Heteroatom Chem.* **2000**, *11*, 138.
6. (a) Enders, D.; Tedeschi, L.; Bats, J. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 4605; (b) Enders, D.; Tedeschi, L.; Förster, D. *Synthesis* **2006**, 1447.
7. Kjaersgaard, A.; Jorgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 804.
8. (a) Cravotto, G.; Giovenzana, G. B.; Pagliarin, R.; Palmisano, G.; Sisti, M. *Tetrahedron: Asymmetry* **1998**, *9*, 745; (b) Thomas, A. A.; Sharpless, K. B. *J. Org. Chem.* **1999**, *64*, 8379.
9. Qi, X.; Lee, S.-H.; Kwon, J. Y.; Kim, Y.; Kim, S.-J.; Lee, Y.-S.; Yoon, J. *J. Org. Chem.* **2003**, *68*, 9140.
10. Mandal, T.; Samanta, S.; Zhao, C. G. *Org. Lett.* **2007**, *9*, 943.
11. (a) Wang, J.; Heikkinen, L. D.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 1052; (b) Terada, M.; Ikehara, T.; Ube, H. *J. Am. Chem. Soc.* **2007**, *129*, 14112.
12. For instance, the pK_a values in DMSO calculated for dimethyl phosphite is 18.4 whereas for diphenyl phosphite it is 9.0, see: Li, J.-N.; Liu, L.; Fu, Y.; Guo, Q.-X. *Tetrahedron* **2006**, *62*, 4453.
13. (a) Mastrykukova, T. A.; Aladzheva, I. M.; Lemont'eva, I. V.; Petrovski, P. V.; Fedin, E. I.; Kabachnik, M. I. *Pure Appl. Chem.* **1980**, *52*, 945; (b) Kosolapoff, G. M.; Maier, L. *Organic Phosphorus Compounds*; John Wiley and Sons: New York, 1973; vol. 5.
14. For reports on the utilization of phosphonate tautomer **T2** by using chiral Lewis acids in the hydrophosphonylation of aldehydes, aldimines, and cyclic imines, see: (a) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1779; (b) Saito, B.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 1978; (c) Groger, H.; Saida, Y.; Arai, S.; Martens, J.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 9291.
15. Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 104.
16. For reviews: (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 1237; (b) Shibasaki, M.; Kanai, M. *Chem. Pharm. Bull.* **2001**, *49*, 511.
17. *General procedure for the (S)-ALB-catalyzed conjugate addition of dialkyl phosphites to nitroalkenes*: To a solution of lithium aluminium hydride (6 mg, 0.15 mmol) in THF (0.5 ml) was added dropwise a solution of (*S*)-BINOL **L4** (86 mg, 0.3 mmol) in THF (1.0 ml) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was concentrated in vacuo to afford a colorless powder of (*S*)-ALB **L5** (90 mg, 0.15 mmol). Next, under a nitrogen atmosphere, toluene (2 ml) was added followed by dialkyl phosphite (1 mmol). After stirring the reaction mixture for 15 min, nitroalkene **2** (1.2 mmol) in toluene (1 ml) was added to the reaction mixture, which was further stirred for 2 d. The reaction mixture was quenched with 1 M HCl solution (2 ml), further saturated with NaCl, and extracted with ethyl acetate (3 × 10 ml). The combined organic layers were washed with brine (5 ml), dried (anhyd Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/pet ether, 0–80%, gradient elution). The solid compounds were further purified by recrystallization (CH_2Cl_2/pet ether ~10:1). Representative experimental

data: Diethyl 1-(4-methoxyphenyl)-2-nitroethylphosphonate **3a**. Yellowish white solid; yield 74%; R_f 0.36 (EtOAc/pet ether 1:1); mp 56–57 °C; IR (film, cm^{-1}) 2985 (w), 2910 (w), 1612 (m), 1558 (s), 1515 (s), 1442 (w), 1376 (m), 1254 (s), 1183 (m), 1048 (s), 1024 (s), 971 (m); ^1H NMR ($CDCl_3$) δ 1.14 (t, J = 7.0 Hz, 3H), 1.32 (t, J = 7.0 Hz, 3H), 3.74–3.82 (m, 1H), 3.80 (s, 3H), 3.92–4.02 (m, 2H), 4.06–4.13 (m, 2H), 4.89–4.94 (m, 2H), 6.89 (d, J = 8.8 Hz, 2H), 7.30 (dd, J = 8.8, 2.2 Hz, 2H), Multiplicities and J values indicated are both for H–H and P–H coupling; ^{31}P NMR ($CDCl_3$) δ 25.57; ^{13}C NMR ($CDCl_3$) δ 15.9 (d, J = 4.6 Hz), 16.1 (d, J = 6.1 Hz), 42.0 (d, J = 139.6 Hz), 54.9, 62.5 (d, J = 7.7 Hz), 63.3 (d, J = 6.1 Hz), 75.2 (d, J = 6.1 Hz), 114.3 (d, J = 2.2 Hz), 123.0 (d, J = 7.7 Hz), 129.7 (d, J = 6.1 Hz), 159.3 (d, J = 3.1 Hz), multiplicities and J values indicated are only for C–P coupling; MS (TOF ES+) *m*/*e* (relative intensity) 340 (MNa^+, 75), 318 (MH^+, 100), 271 (20); HRMS calcd for $C_{13}H_{21}NO_6P$ (MH^+) 318.1107, found 318.1102.