Tetrahedron Letters 51 (2010) 645–648

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Diastereoselective alkynylation of chiral phosphinoylimines: preparation of optically active propargylamines

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ARTICLE INFO

Article history:
Received 6 October 2009
Revised 17 November 2009
Accepted 20 November 2009
Available online 26 November 2009

Keywords:
Chiral phosphinoylimine
Aluminum reagents
Aluminum acetylides
Propargylamines asymmetric synthesis
Asymmetric induction

ABSTRACT

Chiral phosphinoylimines were prepared from methylphenylphosphonamides and tested as new chiral and activated imines. The addition of aluminum acetylides was proved to be highly diastereoselective while lithium or magnesium acetylides gave poor results. The cleavage of the chiral auxiliary was done under mild conditions and allows the recovery of the starting phosphonamide without loss of optical purity.

1. Introduction

Development of methodologies for the asymmetric synthesis of optically active amines is still a very active area of research due to the general interest of substituted amines. The addition of nucleophiles to imines is a one of the most important reaction used to prepare α-substituted amines.[1] In order to make it a valuable process and to attain optically active amines, the electrophilicity of the imine function must be enhanced and the asymmetry must be introduced in the reaction. Methods have been proposed to simultaneously attain these two goals from which two methods have drawn our attention. The first method is based on the use of a chiral appendage linked to the nitrogen atom by forming a sulfinylimine.[2] The *N*-sulfinylimines are activated chiral imines which have been extensively used by several authors to prepare optically active amines following the pioneering works of Davis et al. (*p*-tolyl-sulfoxide group)[3] and Ellman (*tert*-butyl-sulfoxide).[4] The second method is concerned with the activation of the imine in combination with a chiral catalyst. The use of achiral *N*-diphenyl phosphinoylimines recently emerged as a very attractive activation of the imine function and was developed by several authors[5] showing the broad scope of applications with various nucleophiles and the elaboration of several original catalysts. The method was proved to be highly efficient in terms of activation of the imine: the diphenylphosphynoyl group is as effective as the Boc group while much easier to deprotect.

We recently described the addition of alkynyl dimethyl aluminum compounds onto *N*-*p*-tolylsulfinylimines as a powerful method for the preparation of enantiopure propargylamines.[6] In continuation to this work we wondered if chiral *N*-sulfoxide groups are the only groups able to offer enhanced imine reactivity (through an electron-withdrawing effect) as well as diastereoselective efficiency and easy deprotection. We thus envisaged to study the activation of an imine function with a chiral phosphine oxide and then to prepare chiral phosphinoylimines and to study their reactivity. Phosphorus derivatives have been rarely used as chiral auxiliary and activator of the imine function. We recently reported the use of chiral phosphoryl derivatives as phosphoryliminium equivalents which were found to display good reactivity and fair to good diastereoselectivity.[7] With similar idea, phosphorylimine derivatives were quite recently studied by G. Li[8] who disclosed preliminary results for this chiral auxiliary in the reaction of Darzens and particular enolates showing very interesting stereochemical results. In these cases, a chiral phosphoric acid derivative is used. To the best of our knowledge, there is only one report in the literature dealing with chiral phosphinoylimines used for the preparation of chiral oxaziridines.[9]

As a first attempt and model we have investigated the reaction of *N*-(methylphenylphosphinoyl)-imines with acetylides which could be compared with the alkynylation we described with sulfinylimines.

We will present herein our results related to the preparation of *N*-methylphenylphosphinoylimines followed by diastereoselective addition of acetylides, particularly alkynyl dimethyl aluminum derivatives, to give chiral propargylamines.[5c,d,10]

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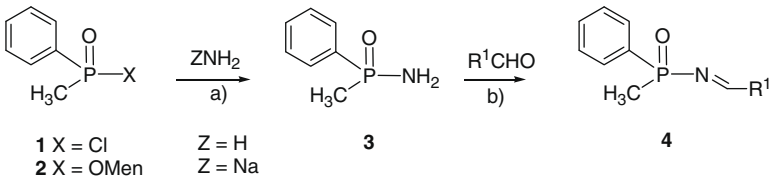
doi:10.1016/j.tetlet.2009.11.091



Scheme 1. Reagents and conditions: (a) from **1**: NH_3, CH_2Cl_2, −78 °C, 15 h. from **2**: $NaNH_2$, THF, −45 °C, 1 h; (b) $TiCl_4$, CH_2Cl_2, 0 °C to rt.

2. Results and discussion

2.1. Preparation of *N*-(*P*-methyl *P*-phenylphosphinoyl)imines

Racemic methylphenylphosphinamide (±)-**3** can be easilly prepared as reported[11] in large scale from the corresponding and commercially available phosphinyl chloride **1** while the preparation of (*S*)-**3** was obtained from menthyl methylphenyl phosphinate **2** using a known procedure.[11] The synthesis of different phosphinoylimines **4** has been obtained through the methodology described for the preparation of *N*-diphenylphosphinoylimines by condensation of methylphenylphosphinamide with an aldehyde catalyzed by $TiCl_4/Et_3N$ (Scheme 1).[12]

It is worth noting that this method has been found to be the only one giving rise to the formation of aldimine in a reasonable yield. The methods using *p*-tolylsulfinic acid described by A. Charette[13] or using activation with imidazole introduced by Kresze[14] which give good results with *N*-diphenylphosphinamide were checked but failed to give the reaction when applied to methylphenylphosphinamide. An apparent and unexpected lowered nucleophily of methylphenylphosphinamide compared with diphenylphosphinamide should be invoked.

2.2. Diastereoselective alkynylation of racemic methylphenylphosphinoylimines

The reaction of methylphenylphosphinoylimines with acetylides and more particularly dimethyl aluminum acetylide[15] was investigated. This very first study was done with racemic material, the results are reported in Table 1.

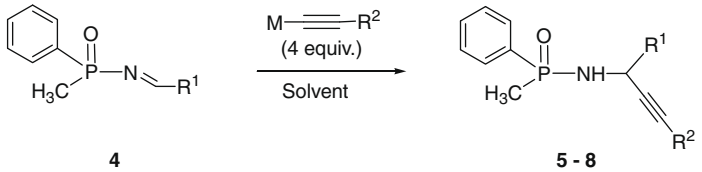
We focused on the reaction of aluminum derivatives which we found to be highly valuable nucleophiles on the addition to sulfinylimines.[6] As for the reaction of these aluminum derivatives onto sulfinylimines it was noticed that the reaction necessitated the use of 4 equiv of organometallic reagent to reach completion in acceptable time. The reaction was first conducted in CH_2Cl_2 at rt with phenyl acetylide and phosphinoylimine derived from benzaldehyde (Table 1, entry 1). The reaction was rather rapid and went to completion within 2-3 h at rt. A 88:12 diastereomeric ratio was obtained for an acceptable 55% isolated yield. The results were found to be better with a 70% isolated yield and a 90:10 dr when the reaction was conducted in toluene. The reaction was also observed at lower temperature (0 °C) but the diastereoselectivity was not improved while the reaction was very slowed and not complete after 20 h (entry 3). By the use of these aluminum derivatives no reaction was obtained in diethyl ether or THF as the solvent from 0 °C to rt. As a matter of comparison, the reaction of lithium acetylide was checked but no reaction occurred. With magnesium acetylide the reaction went to completion within 2 h at rt but without any diastereoselectivity (entry 6). The addition of phenylacetylides was investigated when R^1 = *p*-tolyl. Once again the best conditions were the use of dimethylaluminum derivatives in toluene. While magnesium acetylide showed no selectivity (entry 9), the diastereoselectivity was raised to 95:5 dr with dimethylaluminum acetylide in toluene (entry 8).

Whereas occurring with lowered diastereoselectivity, the use of aliphatic aluminum acetylide derivatives was proved to be possible and interesting results were obtained with functionalized chains (entries 10 and 11)

2.3. Alkynylation of optically active methylphenylphosphinoylimines

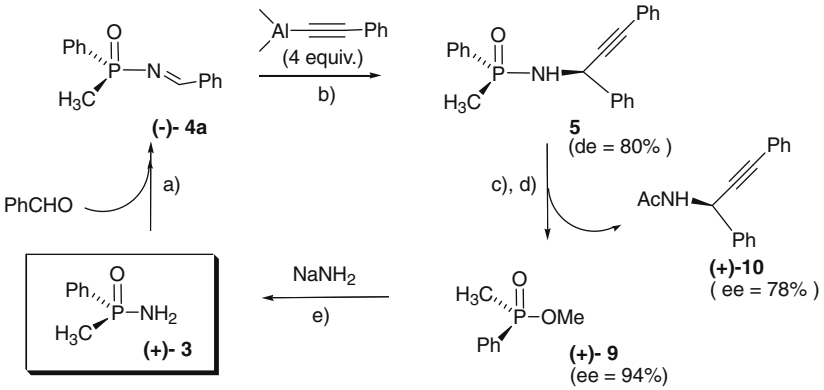
Optically active (*S*)-methylphenylphosphinoylimine (**4a**),[16] was obtained from (*S*)-methylphenylphosphinamide (+)-**3**[17] and

Table 1
Diastereoselective alkynylation of methylphenylphoninoylimines

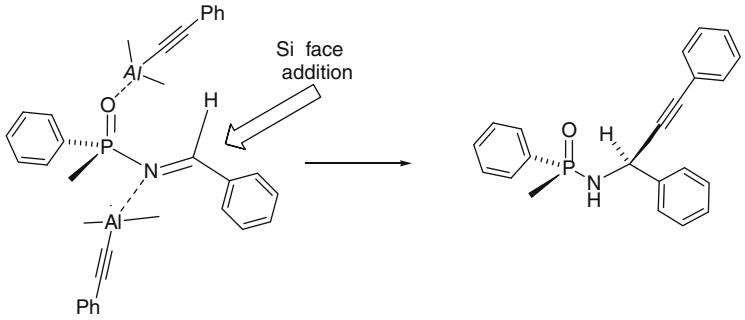


Entry	R^1	Imine	R^2	M	Conditions	Propargyl amine	Yield[a] (%)	dr[b]
1	Ph	**4a**	Ph	Me_2Al	CH_2Cl_2,3 h, rt	5	55	88:12
2	Ph	**4a**	Ph	Me_2Al	Toluene, 1 h, rt	5	70	90:10
3	Ph	**4a**	Ph	Me_2Al	Toluene, 20 h, 0 °C	5	53	85:15
4	Ph	**4a**	Ph	Me_2Al	Ether or THF, rt	5	0	—
5	Ph	**4a**	Ph	Li	Toluene, rt	5	0	—
6	Ph	**4a**	Ph	Mg	Toluene, 1.5 h, rt	5	70	50:50
7	*p*-Tol	**4b**	Ph	Me_2Al	CH_2Cl_2, 1.5 h, rt	6	64	90:10
8	*p*-Tol	**4b**	Ph	Me_2Al	Toluene, 1.5 h, rt	6	69	95:5
9	*p*-Tol	**4b**	Ph	Mg	Toluene, 1.5 h, rt	6	74	50:50
10	Ph	**4a**	$-(CH_2)_2CH_2Cl$	Me_2Al	CH_2Cl_2, 15 h, rt	7	42	75:25
11	Ph	**4a**		Me_2Al	CH_2Cl_2, 15 h, rt	8	50	83:17

[a] Isolated yield.
[b] Determined by integration of the ^{31}P NMR and/or the ^1H NMR signals of the crude reaction mixtures.



Scheme 2. Reagents and conditions: (a) $TiCl_4$, CH_2Cl_2, 0 °C to rt, 1 h; (b) toluene, 0 °C to rt, 1 h; (c) aq 3 M HCl in MeOH (1:5), 0 °C to rt, 1.5 h; (d) Ac_2O, CH_2Cl_2, iPr_2NEt, 0 °C to rt, 1 h; (e) $NaNH_2$, THF, −45 °C, 1 h.



Scheme 3. Proposed model for the alkynylation of phosphinoylimine.

reacted with dimethyl aluminum phenylacetylide[18] to give optically active **5**[19] as a mixture of two diastereomers in a 90:10 ratio (Scheme 2). The separation of the diastereomers was not attempted and the mixture was submitted to the cleavage of the chiral auxiliary. Treatment of **5** with HCl in MeOH, was followed by Ac_2O treatment and allowed the isolation of methylphosphinate (+)-**9**[20] and *N*-acetyl propargylamine (+)-10.[21] The $[\alpha]_D$ value of **10**[21] was consistent with diastereomeric excess (80%) of the alkynylation and the enantiomeric purity of the chiral auxiliary, its sign allowed the determination of the absolute configuration of **10** as *R*.[6] The model we proposed for the alkynylation of *N*-*p*-tolylsulfinylimines can also be applied here.[6] This model (Scheme 3) was based on the necessity to use 4 equiv of organometallic reagent to attain a reasonable reaction time, it was then proposed that two molecules of the organoaluminum are complexed to the imine: one at the nitrogen and the other at the oxygen of the phosphoryl. The antiperiplanar disposition of these groups resulting from these complexations and the addition on the less-hindered face could explain the configuration of the major propargylamide **5**.

Eventually, it was demonstrated that the chiral auxiliary can be recovered (Scheme 2). Methylphosphinate (+)-**9** was obtained through inversion of configuration at phosphorus from the acidic cleavage of **5**. Furthermore, treatment of (+)-**9** with $NaNH_2$ led to phosphinamide (**+**)-**3**, resulting in a second inversion of configuration, in fair yield (31%) but without loss of enantiomeric purity (ee = 94% from chiral HPLC).

In conclusion, we have shown that chiral phosphinoylimines are good substrates for the addition of aluminum acetylides giving rise to propargylamines in good chemical yields and enantiomeric excesses. The chiral inductor can be recovered without loss of optical purity.

Acknowledgment

The authors would like to thank 'Groupe Saidal' (Alger) for financial support.

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16. *Analytical data for* **4a**: $[\alpha]_D$ −17 (*c* 0.35, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.88 (3Il, d, J = 14.3 Hz), 7.85 (8H, m), 7.93 (4H, m), 9.20 (1H, d, J = 33.6 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ ppm: 34.58 ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 17.1 (d, J_{C-P} = 93.0 Hz); 128.5 (d, J_{C-P} = 12.0 Hz); 128.9; 130.0; 130.9 (d, J_{C-P} = 9.3 Hz); 131.3 (d, J_{C-P} = 10.3 Hz); 131.9 (d, J_{C-P} = 2.7 Hz); 132.8 (d, J_{C-P} = 126.8 Hz); 133.5; 173.2 (d, J_{C-P} = 8.2 Hz).
17. (+)-**3**: ee 94% from HPLC measurement (Chiralpak AD, 250 × 4.6 mm, λ = 210 nm, 1 mL/min, *n*-Hex/*i*-PrOH 82:18); $[\alpha]_D$ 7.3 (*c* 2.2, MeOH), lit.[11] $[\alpha]_D$ 8.3 (*c* 2.2, MeOH).
18. *Experimental procedure*: a 1.45 M toluene solution of dimethylaluminum phenylacetylide[15] (1.64 mmol) was added at 0 °C to *N*-phosphinoylimine **4a** (0.411 mmol) in anhydrous toluene (2 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of 3 ml of a 2 M Rochelle salt solution and the reaction mixture was stirred for 15 min at rt. The aqueous layer was separated and extracted with ethyl acetate. The organic layers were mixed and washed successively with water and brine. After drying, the solvent was evaporated under reduced pressure, and the oily residue was purified by column chromatography on silica gel (ether/*n*-heptane 6/4) to leave **5** as a white solid (56%).
19. *Analytical data for* **5**: (9:1 mixture of isomers). MS: 712.81 g/mol $[MNa]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.69 3Il, d, J = 14.4 Hz), 3.25 (0.1H, t, J = 9.9 Hz), 3.39 (0.9H, t, J = 9.9 Hz), 5.38 (0.9H, t, J = 9.9 Hz), 5.44 (0.1H, t, J = 9.9 Hz), 7.06 (2H, m), 7.28 (4H, m), 7.45 (5H, m), 7.53 (4H, m); ^{31}P NMR (121 MHz, $CDCl_3$) δ ppm): 30.64 ppm (0.1H), 30.65 ppm (0.9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm signals of the major isomers from the mixture: 16.9 (d, J_{C-P} = 90.5 Hz); 46.7 (d, J_{C-P} = 2.9 Hz); 85.4; 88.5 (d, J_{C-P} = 5.6 Hz); 122.5;127.3; 128.2; 128.5 (d, J_{C-P} = 12.0 Hz); 128.8; 131.2, 131.6; 131.7 (d, J_{C-P} = 9.1 Hz);131.9 (d, J_{C-P} = 2.7 Hz); 133.2; 133.7; 140.0.
20. (+)-**9**: $[\alpha]_D$ 42 (*c* 3.7, MeOH), lit.[22] $[\alpha]_D$ 45.2 (*c* 3.7, MeOH).
21. (+)-**10**: $[\alpha]_D$ 28 (*c* 0.8, $CHCl_3$), lit.[6] $[\alpha]_D$ 36.1 (*c* 0.82, $CHCl_3$).
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