ORGANIC LETTERS

2012
Vol. 14, No. 13
3296–3299

Catalytic Asymmetric Synthesis of α,β-Disubstituted α,γ-Diaminophosphonic Acid Precursors by Michael Addition of α-Substituted Nitrophosphonates to Nitroolefins

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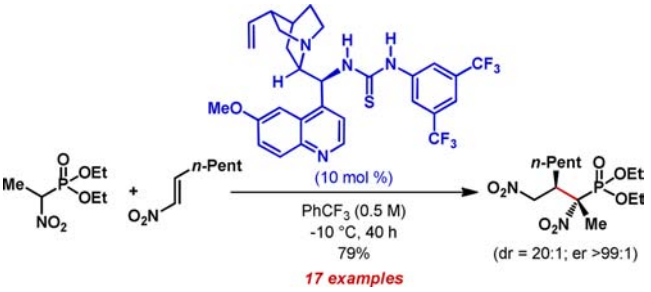
Received May 8, 2012

ABSTRACT



Michael additions of α-substituted nitrophosphonates to various nitroolefins are shown to proceed with high diastereo- and enantioselectivity when catalyzed by a quinine-derived thiourea-tertiary amine bifunctional catalyst and generate α,γ-diaminophosphonic acid precursors with contiguous quaternary and tertiary stereocenters.

Structural resemblance of aminophosphonic acids with a hydrated tetrahedral intermediate of amino acids has established aminophosphonic acids as structural and functional surrogates for amino acids.[1] Consequently, aminophosphonic acids owing to their diverse biological and medicinal applications[2] prompted the development of new methodologies for their asymmetric synthesis. The past decade has witnessed substantial progress in this area in terms of catalytic asymmetric C–H,[3] C–C,[4] C–P,[5] and C–N[6] bond formation.[7]

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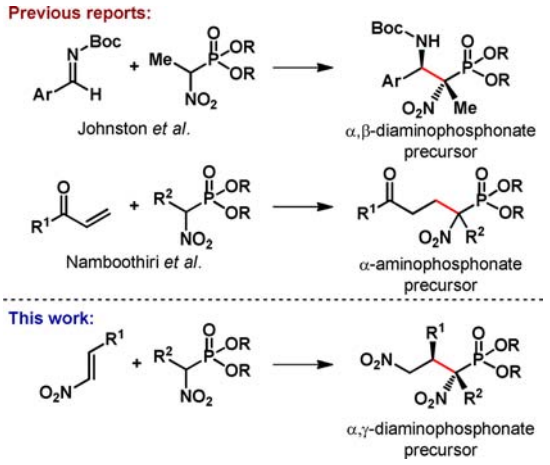
10.1021/ol3012666 © 2012 American Chemical Society
Published on Web 06/15/2012

Scheme 1. Nitrophosphonates in Asymmetric Catalysis



α-Nitrophosphonates can be regarded as immediate precursors of α-aminophosphonic acids, the straightforward synthesis of which can be realized via addition to a potentially wide variety of electrophiles. The use of parent α-nitrophosphonates is complicated by postreaction epimerization of the α-center, but the corresponding α-substituted nitrophosphonates are innocuous in this regard. However the application of substituted α-nitrophosphonates as a nucleophile has remained rather limited. In 2008, Johnston reported a diastereo- and enantioselective Mannich-type reaction of α-methyl-α-nitrophosphonates to imines using a chiral Brønsted acid catalyst (Scheme 1).[8] Very recently, during the course of our investigation, Namboothiri achieved an enantioselective Michael addition of α-substituted-α-nitrophosphonates to vinyl ketones with the help of a bifunctional catalyst (Scheme 1).[9] While the above methods led to the generation of quaternary α,*β*-diaminophosphonic acid and α-aminophosphonic acid precursors, respectively, there is no report for the enantioselective synthesis of the precursor of α-substituted α,*γ*-diaminophosphonic acids.

As part of our research program,[10] we became intrigued by the possibility of accessing such a class of compounds via an asymmetric C−C bond formation. It was reasoned that Michael addition of α-substituted-α-nitrophosphonates to nitroolefins would generate such densely functionalized compounds with an additional *β*-substituent (Scheme 1). Herein, we report the first catalytic asymmetric Michael addition of α-substituted-α-nitrophosphonates to nitroolefins which generates products with contiguous quaternary and tertiary stereocenters.

Our initial focus was to identify the best catalyst and suitable reaction conditions for the aforementioned Michael reaction. The addition of diethyl(1-nitroethyl)-phosphonate **1a** to *ω*-nitrostyrene **2a** served as the model reaction toward this effort (Table 1). Rapid evaluation of the catalyst structure was facilitated by the lack of any measurable background reaction at room temperature (entry 1). The catalysts of interest were confined to thiourea-based bifunctional compounds derived from *trans*-1,2-diaminocyclohexane or cinchona alkaloids, considering their well-established mode of substrate activation.[11] Not surprisingly, the reaction was found to be catalyzed by this type of bifunctional catalysts. In the presence of 10 mol % of Takemoto catalyst[12] **I** in CH_2Cl_2, nearly complete conversion to the desired product **3a** (with modest dr) was observed within 14 h at rt (entry 2). The relative and absolute stereochemistry of the product was determined by X-ray analysis (*vide infra*). Even though **3a** was obtained only with moderate er of 36:64 at rt, lowering the reaction temperature to 0 °C led to substantial improvement of enantioselectivity (entry 3). Replacement of an electron-deficient aryl moiety of the catalyst with cyclohexyl produced a more active catalyst (**II**); however the stereochemical integrity of the resulting product was diminished (entry 4). Catalyst **III** with bulkier ethyl substituents at the Brønsted basic tertiary amine center promoted the reaction with much poorer enantioselectivity (entry 5). Cinchona alkaloid-derived bifunctional compounds **IV**−**VIII** proved to be good catalyst candidates (entries 6−10), particularly the quinine and cinchonine-derived catalysts **IV** and **VII**, respectively.[13] The reaction medium was found to have a dramatic influence on the diastereoselectivity of the reaction (entries 11−16), with trifluorotoluene emerging as the optimum solvent (entry 16). Reversibility of the reaction at 0 °C turned out to be a barrier toward complete conversion as slight erosion of both dr and er was observed during the course of the reaction.[14] Further temperature optimization provided −10 °C as the optimum reaction temperature, and the product with a consistent dr and er was obtained over the complete reaction course (entry 18).[14]

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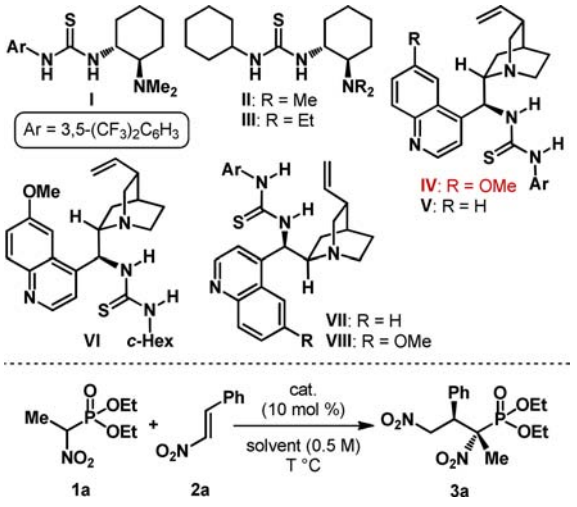
(14) See Supporting Information for details.

Table 1. Catalyst Evaluation and Reaction Conditions Optimization for Asymmetric Michael Addition of Nitrophosphonate **1a** to ω-Nitrostyrene **2a**[a]

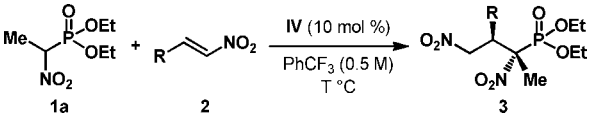


	cat.	solvent	*T*, °C (*t*, h)	conv (%)[b]	dr[b]	er[c]
1	–	CH_2Cl_2	25 (48)	[d]	–	–
2	**I**	CH_2Cl_2	25 (14)	>90	3:1	36:64
3	**I**	CH_2Cl_2	0 (16)	50	4:1	8:92
4	**II**	CH_2Cl_2	0 (16)	72	1.6:1	18:82
5	**III**	CH_2Cl_2	0 (16)	50	1.5:1	33:67
6	**IV**	CH_2Cl_2	0 (16)	40	2:1	95:5
7	**V**	CH_2Cl_2	0 (24)	63	6:1	93:7
8	**VI**	CH_2Cl_2	0 (24)	63	4:1	87:13
9	**VII**	CH_2Cl_2	0 (24)	55	10:1	5:95
10	**VIII**	CH_2Cl_2	0 (24)	50	4:1	9:91
11	**IV**	PhMe	0 (30)	80	7:1	96:4
12	**IV**	$CHCl_3$	0 (30)	94	15:1	94.5:5.5
13	**IV**	THF	0 (30)	80	2:1	96:4
14	**IV**	TBME	0 (30)	90	10:1	95:5
15	**IV**	EtOAc	0 (30)	90	10:1	94:6
16	**IV**	$PhCF_3$	0 (30)	87	12:1	96.5:3.5
17	**VII**	$PhCF_3$	0 (40)	90	7:1	6:94
18	**IV**	$PhCF_3$	−10 (45)	>95	12:1	96.5:3.5

[a] Reactions were carried out using 1.0 equiv of **1a** and 1.5 equiv of **2a**. [b] Conversion and diastereomeric ratio (dr) were determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Enantiomeric ratio (er) determined by HPLC analysis using a stationary phase chiral column (see Supporting Information). [d] No conversion after 48 h. TBME: *tert*-Butyl methyl ether.

The optimized catalyst (**IV**) and reaction conditions (Table 1, entry 18) were then applied for the evaluation of the scope of this reaction. The results are summarized in Table 2. We were pleased to find that a wide range of nitroolefins with a diverse steric and electronic environment reacted smoothly with α-methyl-nitrophosphonate **1a**. Different substituents on aromatic nitroolefins furnished the Michael adducts **3a**–**h** in moderate to good yields with uniform dr and er, regardless of their position and electronic properties (entries 1–8). Heteroaromatic substituted nitroolefins were also tolerated (entries 10–11), although 2-thienylnitroolefin required a somewhat higher temperature and the product was obtained with a slightly diminished dr and er (entry 11). Our reaction conditions are especially suitable for aliphatic nitroolefins as the products were obtained in very good yield with excellent diastereo- and enantioselectivity (entries 13–15). Particularly noteworthy is the high enantioselectivity (er = 97:3) observed for the small methyl substituent (entry 13). The reaction can also be carried out with a lower catalyst loading without much influence on the selectivity, albeit at the expense of the reaction rate.[15]

Table 2. Substrate Scope of the Asymmetric Michael Addition of α-Methyl-nitrophosphonate **1a** to Various Nitroolefins[a]



	R (**2**)	*T*, °C (*t*, h)	**3**	yield (%)[b]	dr[c]	er[d]
1	Ph (**2a**)	−10 (45)	**3a**	75	12:1	96.5:3.5
2	4-ClC_6H_4 (**2b**)	−10 (62)	**3b**	64	10:1	96.5:3.5
3	3-ClC_6H_4 (**2c**)	−10 (26)	**3c**	64	10:1	96:4
4	3-$NO_2C_6H_4$ (**2d**)	−10 (70)	**3d**	64	10:1	94.5:5.5
5	4-$CF_3C_6H_4$ (**2e**)	−10 (36)	**3e**	70	12:1	96:4
6	4-FC_6H_4 (**2f**)	−10 (80)	**3f**	60	10:1	97:3
7	4-$OMeC_6H_4$ (**2g**)	0 (32)	**3g**	65	10:1	96:4
8	4-MeC_6H_4 (**2h**)	−10 (90)	**3h**	82	10:1	96.5:3.5
9	2-Naphthyl (**2i**)	0 (32)	**3i**	38	10:1	93:7
10	2-Furyl (**2j**)	−10 (70)	**3j**	70	11:1	96.5:3.5
11	2-Thienyl (**2k**)	0 (26)	**3k**	76	5:1	94.5:5.5
12	$PhCH{=}CH_2$ (**2l**)	−10 (88)	**3l**	70	6:1	95.5:4.5
13	Me (**2m**)	−10 (60)	**3m**	80	12:1	97:3
14	*n*-Pent (**2n**)	−10 (40)	**3n**	79	20:1	>99:1
15	*i*-Bu (**2o**)	−10 (60)	**3o**	82	13:1	99:1

[a] Reactions were carried out using 1.0 equiv of **1a** and 1.5 equiv of **2**. [b] Isolated yield of the products after column chromatographic purification. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis using a stationary phase chiral column (see Supporting Information).

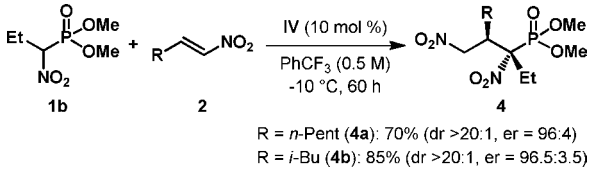
To check the viability of a larger α-substitution on nitrophosphonate, we applied α-ethyl-dimethylphosponate **1b**, with aliphatic nitroolefins **2n**–**o** under our standard reaction conditions (Scheme 2). The corresponding Michael adducts **4a**–**b** were obtained as a single diastereomer in good yield with high enantioselectivity.

The relative and absolute configuration of the Michael adduct **3o** was determined by X-ray structure analysis and found to be (2*S*, 3*R*) (Figure 1). It is expected that the absolute configuration for the remaining examples can be assigned by analogy as the same.

The synthetic potential of the Michael adduct was demonstrated by the reduction of **3a** (Scheme 3). When treated with $NaBH_4$ and $NiCl_2$ for 30 min at −35 to 0 °C, the product pyrazolidinyl phosphonate **5**, generated via reductive N–N bond formation, was obtained in

(15) Using 5 mol % of **IV**, the Michael adduct **3c** was obtained in 59% yield with dr 10:1 and er = 95.5:4.5 after 48 h at −10 °C.

Scheme 2. Substrate Scope with Respect to α-Ethyl-nitrophosphonate **1b**



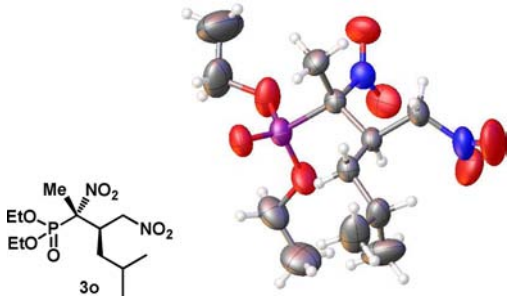


Figure 1. Relative and absolute configuration of **3o** and its X-ray structure.

60% yield. Aminophosphonates and aminophosphonic acids of this type have already been tested as potential organocatalysts for asymmetric aldol and Michael reactions.[16]

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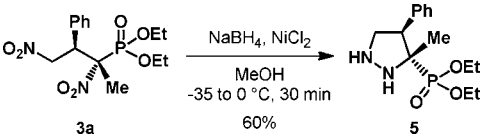
Scheme 3. Synthetic Utility of Michael Adduct **3a**



In summary, we have developed a highly diastereo- and enantioselective catalytic Michael addition of α-substituted nitrophosphonates to nitroolefins using a quinine-derived bifunctional catalyst. The products of this reaction, consisting of adjacent quaternary and tertiary stereocenters, were obtained in good to high yields and represent immediate precursors of α,*β*-disubstituted α,*γ*-diaminophosphonic acids.

Acknowledgment. A generous start-up grant from Indian Institute of Science, Bangalore, is gratefully acknowledged. This work is supported by DST, New Delhi (Grant No. SR/FT/CS-90/2010) and CSIR, New Delhi (Grant No. 01(2505)/11/EMR-II). We thank Prof. T. N. Guru Row and Mr. Pavan M.S. (Solid State and Structural Chemistry Unit, IISc, Bangalore) for their help with the X-ray diffraction analysis. C.B.T. and S.V.K. acknowledge CSIR and IISc, respectively for doctoral fellowships.

Supporting Information Available. Detailed experimental procedures, spectral and analysis data for all new compounds together with HPLC chromatograms of the relevant compounds (PDF), and X-ray data of **3o** (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.