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Novel chiral 1-phosphono-1,3-butadiene for asymmetric hetero Diels–Alder cycloadditions with nitroso and azodicarboxylate dienophiles

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ABSTRACT

Chiral 1-phosphonodienes bearing a bicyclic (*R*,*R*)-1,3,2-dioxaphospholane or a (*R*,*R*)-1,3,2-diazaphospholidine auxiliary are potent dienes for asymmetric hetero Diels–Alder reactions. Their reactivity towards model nitroso and azodicarboxylate dienophiles has been studied by means of theoretical chemistry at the B3LYP/6-31G** level. This model, taking solvent effects into account, allowed us to identify parameters governing the stereoselectivity of this reaction. Our study emphasizes a synergy effect when increasing the steric hindrance of substituents of both partners. This led us to predict high levels of diastereoselectivity for one diene. Accordingly, we have hereby illustrated a convenient and original synthesis of this diene and its cycloadditions with commercially available nitroso and azodicarboxylate dienophiles.

Aminophosphonic acids and related compounds are recognized as an important class of pharmacologically active molecules.[1] Most of the described synthetic strategies concern α-aminophosphonic compounds, despite the fact that the interest for β-, γ- and δ-homologs is still growing. As a part of a research program[2] dedicated to the synthesis of aminophosphonic compounds, we have studied the hetero Diels–Alder (HDA) cycloadditions of achiral 1-phophonodienes with activated nitrogen-containing dienophiles, namely nitroso and azodicarboxylate compounds.[3] Indeed, the resulting [4+2] cycloadducts can be considered as synthons for the preparation of various aminophosphonic compounds (Fig. 1).

In addition to its versatility, the HDA reaction is also compatible with asymmetric development.[4,5] This led us to consider asymmetric HDA cycloadditions of chiral phosphonodienes and nitrogen-containing dienophiles as an entry towards aminophosphonic chirons. Scarce examples of chiral phosphonodienophiles are illustrated by Wyatt,[6,7] Katagiri[8] and King[9] with chirality either directly surrounding the phosphorus atom itself or being placed elsewhere on the chiral auxiliary. To our knowledge, only one previous report by Wyatt mentioned the use of a chiral 4-phenyl-1-phosphonodiene versus a cyclic azodicarboxylate dienophile (4-phenyl-1,2,4-triazolin-3,5-dione) leading to the corresponding cycloadduct in good yield but with low stereoselectivity.[6]

Two different strategies could be envisaged to build a chiral phosphonodiene: (i) the direct introduction of the chirality on the phosphorus atom[8] (e.g., diene **1g**, Fig. 2); (ii) the introduction of the chirality on an adjacent atom, with a nitrogen relay nearby the phosphorus atom (e.g., diene **1f**, Fig. 2). The first way was abandoned because the synthesis of diene **1g** led to an inseparable mixture of diastereoisomers (see Supplementary data (SD)). For the

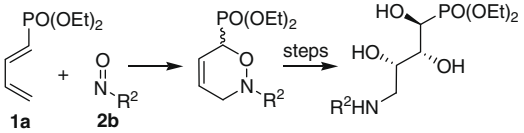

Figure 1. General HDA strategy. See Ref. 3b.

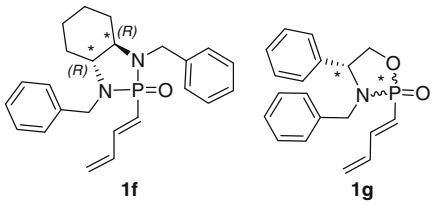

Figure 2. Two examples of chiral phosphonodienes: dienes **1f**–**g**.

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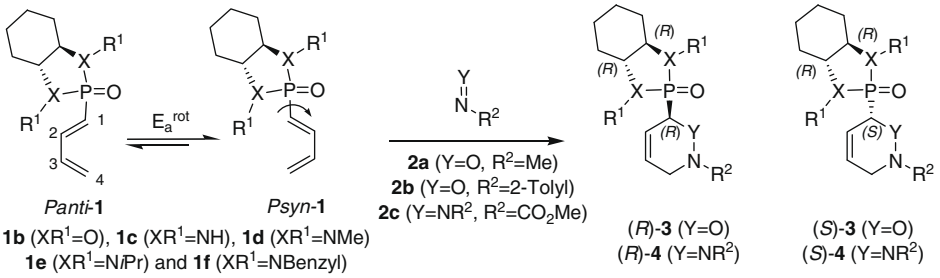


Figure 3. Asymmetric HDA cycloadditions of chiral phosphonodienes (**1b–f**) and nitroso (**2a–b**) or azo (**2c**) dienophiles: partners selected for the theoretical study.

second way, we used C_2-symmetry auxiliaries, namely bicyclic 1,3,2-dioxaphospholane[10] and 1,3,2-diazaphospholidines[11] derived from (*R,R*)-1,2-dihydroxy- and (*R,R*)-1,2-diaminocyclohexane, respectively.

Five different chiral dienes (**1b–f**) have been selected for a theoretical study of their HDA reactions with nitroso (**2a–b**) and azodicarboxylate (**2c**) dienophiles (Fig. 3).The conformational behaviour of the dienes and their respective cycloadditions are discussed at the B3LYP/6-31G** level, including condensed phase calculations.[12] This led to a realistic picture of the incidence of both the XR^1 substituent and dienophile nature on the diastereoselectivity. These theoretical insights have been then applied for the design of a new chiral phosphonodiene **1f**. We propose herein an original and convenient synthesis of (3a*R*,7a*R*)-2-(1-buta-1,3-dienyl)-[3a,4,5,6,7,7a-octahydro-1,3-dibenzyl-1,3,2-benzodiazaphosphole]-2-oxide (**1f**) and the validation of this reagent in asymmetric synthesis using nitroso (**2b**) and azodicarboxylate (**2d–f**) dienophiles.

A local potential energy surface (PES) scan allowed localizing two stationary points for each diene studied, susceptible to undergo a HDA cycloaddition. Both conformers are characterized by a *s-cis* conformation of the butadienyl moiety, but show differences in the O=P–C(1)–C(2) dihedral angles: *Panti* and *Psyn* conformers feature the P=O bond, respectively, in *anti* and *syn* conformations regarding the butadienyl moiety (rotation around the P–C(1) bond, Fig. 3). The *Psyn* conformer is the most stable, whatever the diene studied. The nature of XR^1 has a slight incidence on this energetic discrimination. Nevertheless, the diene **1f** showed the highest level of conformational discrimination (ΔE_{conf}, Table 1) both in gas and condensed phase [tetrahydrofuran (THF), dichloroethane (DCE) and acetonitrile (ACN)].

Concerning the activation barrier for this conformational equilibrium (E_a^{rot}, Fig. 3 and Table 1), the nature of XR^1 has a stronger incidence. An activation barrier of 11.7 kcal mol^{-1} was found for the diene **1f**.

For both conformers of dienes **1c–f** (X = N), the substituents attached to the nitrogen atoms were found in a *pseudo-equatorial* position. In agreement with the previous observations of Bennani and Hanessian,[11] there is a clear differentiation of the preferred orientation of R^1 groups on either size of the chiral auxiliary.

We further considered the global electrophilicity (ω) of the selected reagents.[13] The static global properties, namely chemical potential (μ) and chemical hardness (η) as well as the global electrophilicity (ω) are listed in the SD. We found that all selected heterodienophiles are located above the chiral phosphonodienes in the electrophilicity scale (ω = 2.27 eV (**2a**), ω = 2.82 eV (**2b**) and ω = 2.91 eV (**2c**)). Thus, in such HDA reactions they will act as formal electrophiles while the phosphonobutadienes will act as formal nucleophiles. The differences between dienes and dienophiles are between 0.6 and 1.6 eV, suggesting a Polar Diels–Alder reaction (P-DA).[13] The global electrophilicity of the dienes depends on the nature of the chiral auxiliary. Diene **1b** (X = O) is significantly higher in the electrophilicity scale (ω = 1.65 eV) than dienes **1c–f** (X = NR^1): ω = 1.41 eV (**1c**), ω = 1.38 eV (**1d**), ω = 1.31 eV (**1e**) and ω = 1.41 eV (**1f**). But in this series of dienes, the incidence of the N-substitution (R^1) appeared to be quite low.

The transition states (TSs) of the cycloaddition reactions of the selected dienes with some model dienophiles were examined. As the transition states related to the *Panti* (**TSan**) and *Psyn* (**TSsy**) conformers led, respectively, to the (*R*)-P–C(1) and (*S*)-P–C(1) stereoisomers (see Fig. 3 and SD), the subjacent conformational equilibrium may be considered as a key element for stereochemical drifts (i.e., HDA reactions leading to low diastereoselectivities). The energetic differences between **TSan** and **TSsy** will thus give information in terms of stereoselectivities (ΔE_a^{sel}, Table 2). The TSs associated to the *proximal* (nitroso) and *endo* approaches will be the only considered ones for discussion, since the *distal* (nitroso) and *exo* pathways are disfavoured by 4–10 kcal mol^{-1} and 3–6 kcal mol^{-1}, respectively. These TSs are characterized by a highly

Table 1
Energetic discrimination between the *Panti* and *Psyn* conformers

	E_a^{rot}	ΔE_{conf} (kcal mol^{-1})			
	Gas	Gas	THF	DCE	ACN
1b	2.1	0.8	0.5	0.5	0.4
1c	3.8	0.9	0.6	0.6	0.5
1d	4.0	0.9	0.9	0.9	0.8
1e	4.9	1.4	1.2	1.2	0.8
1f	11.7	1.6	1.2	1.2	1.4

Table 2
Selectivities computed for the HDA reactions of dienes **1b–f** and dienophiles **2a–c**

Entry	Dienes	Media	Dienophiles		
			A **2a**	B **2b**	C **2c**
1	**1b**	Gas	1.7	1.7	0.7
2	XR^1 = O	THF	0.7	0.8	0.8
3		DCE	0.6	0.7	0.7
4		ACN	0.3	0.6	0.7
5	**1c**	Gas	1.8	0.9	0.5
6	X = N, R^1 = H	THF	0.6	0.6	1.3
7		DCE	0.4	0.5	1.1
8		ACN	0.4	0.6	1.2
9	**1d**	Gas	2.3	1.8	2.6
10	X = N, R^1 = Me	THF	1.3	0.6	1.4
11		DCE	1.2	0.4	1.3
12		ACN	0.9	0.4	1.4
13	**1e**	Gas	2.9	2.0	3.2
14	X = N, R^1 = *i*Pr	THF	2.3	1.8	1.4
15		DCE	2.2	1.7	1.4
16		ACN	2.0	1.6	1.4
17	**1f**	Gas	3.1	2.8	5.0
18	X = N, R^1 = Bn	THF	3.7	3.1	7.5
19		DCE	3.6	3.0	6.0
20		ACN	3.4	2.7	4.6

ΔE_a^{sel} values are given in kcal mol^{-1}.

asynchronous bond formation, the C(4)–N bond being almost completely formed (1.87–2.06 Å) and the C(1)–Y bond remaining close to the sum of the corresponding van der Waals radii (2.66–2.88 Å). No significant differences are observed between **TSsy** and **TSan** in terms of bond formation (pictures of TSs for the reactions of **1f** with **2a–c** are provided in SD).

For each case in Table 2, the **TSsy** was lower in energy than the corresponding **TSan**. Generally, the introduction of a solvent reduces the difference between the two diastereogenic TSs, except for the cycloaddition **1c**+**2c**[14] and for diene **1f**. These results showed a slight incidence of the solvent polarity. Comparing the different dienes, it appeared that the nature of the heteroatom (O, N) has a weak incidence on the selectivities (entries 1A–C and 5A–C). For diene **1b**, cycloadditions with both nitrosomethane (**2a**) and 2-nitrosotoluene (**2b**) proceed with a selectivity of 1.7 kcal mol^{-1} (entries 1A–B). The diastereoselectivity drops to 0.7 kcal mol^{-1} with dienophile **2c** (entry 1C). Considering the diazaphospholidino dienes (**1c–f**), the selectivity obtained with **2a** is higher than that for **2b** (entries 5A–B, 9A–B, 13A–B and 17A–B). By increasing the steric hindrance of the diene R^1 groups, a slight increase in selectivity is observed: for the dienophile **2a** the selectivity increases twice when going from diene **1c** to diene **1f** (entries 5A, 9A, 13A and 17A), while for dienophile **2b** the increase in selectivity is more pronounced passing from diene **1c** to diene **1f** (entries 5B, 9B, 13B and 17B). The cycloadditions of dienophile **2c** with dienes **1b–f** clearly showed a synergy effect due to the steric hindrance of both the R^1 and R^2 substituents (entries 5C, 9C, 13C and 17C). The highest level of stereoselectivity was obtained with diene **1f**.

The same trends were observed in solvent (entries 18C, 19C and 20C). It may be also expected that working with sterically more hindered azodicarboxylates **2d–f** (R^2 = Et, *i*Pr, *t*Bu) will increase the diastereoselectivity of the reaction. This prediction has been experimentally confirmed.

We have synthesized the chiral diene **1f** in two steps from **1a** in 62% overall yield (Scheme 1 and SD for experimental details). Its structure was confirmed by X-ray diffraction analysis (see SD). Under classical thermal conditions, the reaction of diene **1f** with 2-nitrosotoluene (**2b**) led quantitatively to the corresponding cylcoadduct **3b**, after 12 h in refluxing DCE (Scheme 1, see SD for experimental details).

The selectivity was not influenced by the solvent polarity. Thermal instability of diene **1f** prevents GC determination of the selectivity, but ^{31}P NMR is helpful. Indeed, the two diastereoisomers (*R*)-**3b** and (*S*)-**3b** clearly show different ^{31}P NMR shifts (33.2 and 34.6 ppm). In all cases (Table 3, entries 1–3), we recovered a 1:1 diastereomeric mixture of **3b** cycloadducts, as expected from the low selectivity level computed. Microwave (MW) heating was also investigated in the view of increasing the diastereoselectivity, but without success. HPLC analytical separation of the diastereoisomers could be realized using a CHIRACEL OD-H column (see SD).

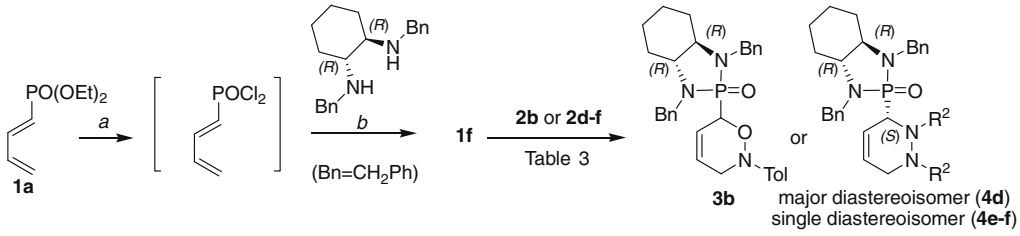
Table 3
Experimental conditions of HDA cycloadditions (Scheme 1)

Entry	React.	*T*	Solv.	Time (h)	Conv. (%)	dr (^{31}P)	Product
1	**1f+2b**	90 °C	DMF	12	99	1:1	**3b**
2	**1f+2b**	Δ	DCE	12	99	1:1	**3b**
3	**1f+2b**	MW[a]		1	99	1:1	**3b**
4	**1f+2d**	Δ	DCE	5 d	/	/	/
5	**1f+2d**	MW[b]		1	35	1:0.6	**4d** (R^2 = Et)
6	**1f+2e**	MW[b]		3	27	1:0	**4e** (R^2 = *i*Pr)
7	**1f+2f**	MW[b]		5	30	1:0	**4f** (R^2 = *t*Bu)

[a] In DCE, 100 °C, 500 W.
[b] In toluene/DMF 30:1, 120 °C, 750 W.

We next considered the cycloadditions of diene **1f** and azodicarboxylate dienophiles (R^2 = Et, **2d**; R^2 = *i*Pr, **2e** and R^2 = *t*Bu, **2f**). In DCE under thermal conditions, no reaction was observed, even under prolonged heating (degradation of the chiral diene). Nevertheless, under MW heating, the desired cycloadditions occurred (Table 3, entries 4–7) and the heterocycles **4d–f** were isolated in modest yields (Scheme 1 and SD for experimental details). This experimental result is in agreement with the larger charge transfer for the HDA of (**1f**+**2b**) than for (**1f**+**2d–f**), favoring the (**1f**+**2b**) P-DA reaction.[13,15] ^{13}C NMR spectra (benzene-d_6) of cycloadducts **4d–f** showed typical features of the 1-phosphono-3,6-dihydro-1,2-hydrazine pattern (C(6)–P at 55.91 ppm with $^1J_{C-P}$ = 128.4 Hz) and ^{31}P NMR data provided unambiguously the stereochemical information. Raising the size of the azodicarboxylate substituents led to an increase in the selectivity. Indeed, the ^{31}P NMR spectrum of the crude mixture **4d** revealed two signals (36.3 and 35.2 ppm) while the ^{31}P NMR spectra of **4e–f** contained only one signal (38.8 and 38.1 ppm, respectively). By comparison with the previous observations in the 1,2-oxazine and 1,2-pyridazine series, both ^{13}C and ^{31}P NMR values are consistent with the formation of single diastereoisomers, namely cycloadducts (*S*)-**4e** and (*S*)-**4f** (see SD).

In conclusion, this work describes the first computational study of chiral bicyclic 1,3,2-dioxaphospholane-(**1b**) 1,3,2-diazaphospholidine (**1c–f**) dienes and their asymmetric HDA cycloadditions with nitroso and azodicarboxylate dienophiles. Among the series of dienes, diene **1f** showed the highest computed stereoselectivities. However, experimentally, the reaction **1f**+**2b** led to a 1:1 mixture of separable diastereomers **3b**. This can be attributed to (i) a low energetic discrimination between the *Panti* and the *Psyn* conformers of chiral diene **1f**; (ii) the high asynchronicity of bond formation with the nitroso-partner. Our theoretical model showed a synergy effect when increasing the steric hindrance of both the XR^1 and R^2 substituents. The computed high level of stereoselectivity for the reaction **1f**+**2c** prompted us to consider the reactions of diene **1f** with commercially available azodicarboxylates **2d–f**. The cycloadditions with *i*-propyl and *t*-butyl azodicarboxylates **2e** and **2f** led to the formation of single diastereoisomers, cycloadducts (*S*)-**4e** and (*S*)-**4f**, respectively.



Scheme 1. Synthesis and cycloadditions of diene **1f**. Reagents and conditions: (a) TMSBr, DCM, rt; $(COCl)_2$, DMF_{cat}, THF, 0 °C; (b) (*R,R*)-*N,N*-dibenzyl-1,2-diaminocyclohexane, pyridine, THF, 0 °C to rt, 15 h (62%).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.063.

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