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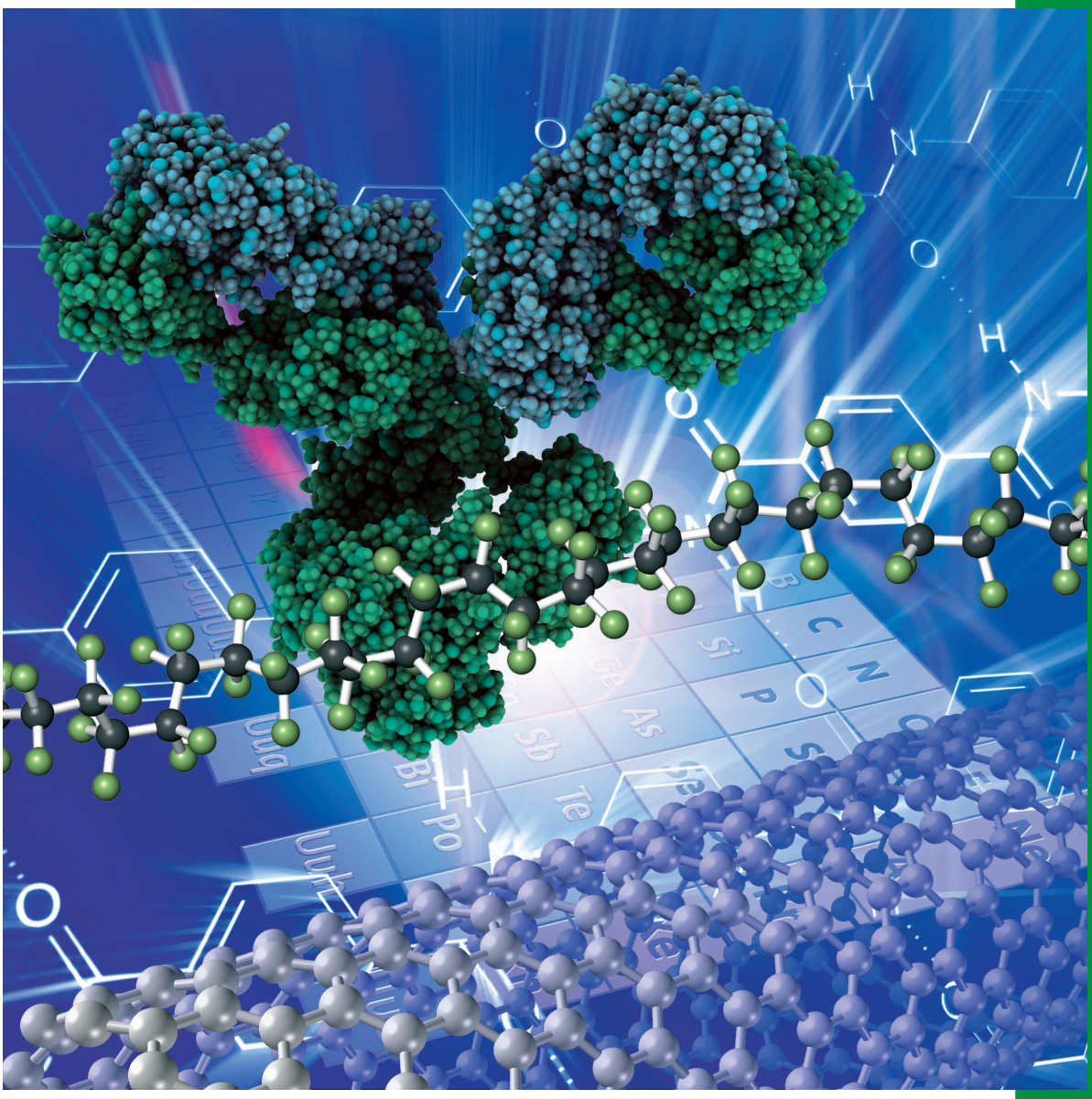

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Catalysis

Convenient Au(III)-Catalysed Synthesis of 1-Alkyl-3-diethoxy-phosphoryl-1,2,3,4-tetrahydroisoquinolines

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We report here convenient approach to the synthesis of 1-alkyl-3-diethoxyphosphoryl-1,2,3,4-tetrahydroisoquinolines through cyclization of alkynylsubstituted α-aminophosphonates in the presence of $AuCl_3$ with following reduction by $NaBH_4$. Starting alkynylsubstituted α-aminophosphonates were easily synthesized by using Sonogashira reaction of diethyl (1-((diphenylmethylene)-amino)-2-(2-iodophenyl)ethyl)phosphonate with series of terminal alkynes. The 1-alkyl-3-diethoxyphosphoryl-1,2,3,4-tetrahydroisoquinolines with different alkyl substituents were obtained as two enantiomers with *cis*-configuration in good yields.

Introduction

α-Aminophosphonates, isosteric analogs of α-amino acids, possess a wide spectrum of biological activity.[1] Over the past decades many synthetic protocols were developed for the synthesis of both acyclic and cyclic α-aminophosphonates, often in optically pure form.[2] Cyclic α-aminophosphonates are of great interest as conformationally restricted analogs of α-aminoacids, such as proline, pipecolic acids and phenylalanine.[3] 3-Phosphorylsubstituted 1,2,3,4-tetrahydroisoquinolines as cyclic analogs of phenylalanine are promising from biomedical point of view due to the availability of 1,2,3,4-tetrahydroisoquinoline moiety in many bioactive compounds.[4] However, the only two examples of 3-phosphorylsubstituted 1,2,3,4-tetrahydroisoquinolines were reported in the literature, and compounds with substituents in position one are still unknown. Previously,[3c] the first synthesis of 3-diethoxyphosphoryl-1,2,3,4-tetrahydroisoquinoline was proposed using alkylation reaction of iminophosphonoglycinate by 1,2-di(bromomethyl)benzene under a phase-transfer catalysis (Figure 1, route a). Another synthetic approach to this compound is Pictet synthesis (Figure 1, route b).[3d] However, it has to be noted that both methods have narrow substrate scope and the introduction of any substituents at position one of the heterocycle is challenging.

The gold catalysis is a powerful tool in modern synthetic chemistry, which widely used in intra- and intermolecular hydroamination or hydroamidation as well as in cyclization of different aminoalkynes.[5] We herein report the novel synthetic strategy for preparation of previously unknown 1-alkyl-3-diethoxyphosphoryl-1,2,3,4-tetrahydroisoquinolines applying gold-catalyzed intramolecular hydroamination of alkynylsubstituted α-aminophosphonates with following reduction (Figure 1).

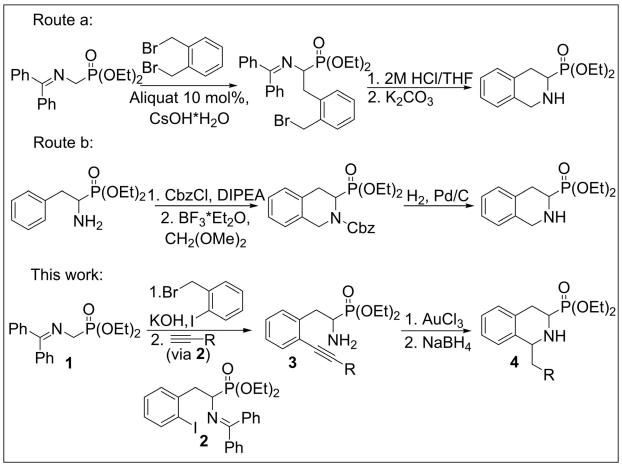

Figure 1. Methods of the synthesis of 3-diethoxyphosphoryl-1,2,3,4-tetrahydroisoquinolines.

Results and Discussion

For the synthesis of 3-diethoxyphosphoryl-1,2,3,4-tetrahydroisoquinolines **4** (Figure 1), we proposed alkynylsubstituted α-aminophosphonates **3** as suitable precursors. It is known, that such type of substrates can easily undergo an intramolecular hydroamination reaction to form a six-membered ring (6-*exo-dig* cyclization) in the presence of catalysts based on transition metals, particularly gold, and resulted cyclic imines can be

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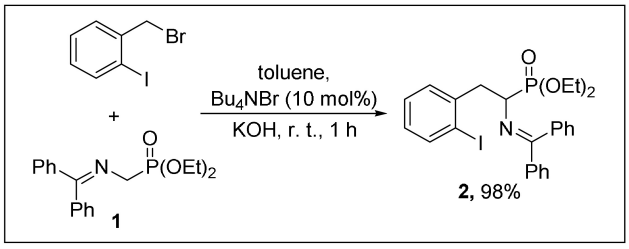
reduced giving 1,2,3,4-tetraisoquinolines.[6] In this context, starting alkynylsubstituted α-aminophosphonates **3** could be obtained by alkynylation of α-aminophosphonate derivative **2** by Sonogashira reaction. Imine **2** could be easily obtained by simple C-alkylation of diethyl (diphenylmethyleneamino)methylphosphonate **1** by 1-(bromomethyl)-2-iodobenzene under phase-transfer catalysis.

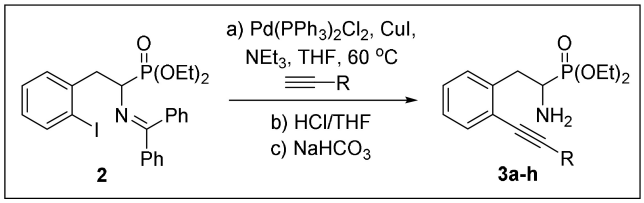
According to this approach we chose diethyl (diphenylmethyleneamino)methylphosphonate **1** as the starting material for the synthesis of target 1,2,3,4-tetrahydroisoquinolines **4**. Diethyl (diphenylmethyleneamino)methylphosphonate **1** was easily prepared by the condensation of diethyl aminomethylphosphonate with diphenylketimine as described previously.[7]

At first we carried out the synthesis of diethyl (1-((diphenylmethylene)amino)-2-(2-iodophenyl)ethyl)phosphonate **2** by using 1-(bromomethyl)-2-iodobenzene. To our delight application of method of C-alkylation developed by Genet[8] leads to the preparation of **2** from **1** with excellent yield of 98%, whereby we use it without further optimization (Scheme 1).



Scheme 1. Synthesis of diethyl (1-((diphenylmethylene)amino)-2-(2-iodophenyl)ethyl)phosphonate **2**.

Next, we introduced compound **2** in the reaction with different aromatic and aliphatic alkynes using 1 mol% $Pd(PPh_3)_2Cl_2$, 2 mol% CuI in triethylamine at room temperature (or at 70 °C for 4-ethynyltoluene and 1-(*tert*-butyl)-4-ethynylbenzene)). The products of Sonogashira reaction were hydrolyzed in acidic conditions (2 M HCl in THF) to form after neutralization by $NaHCO_3$ α-aminophosphonates **3a–h** in good yields (Scheme 2, Table 1).



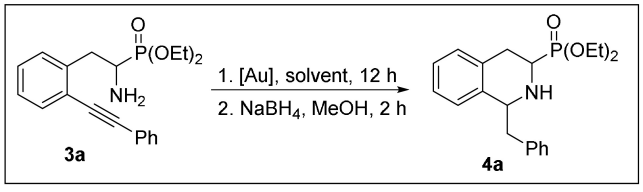
Scheme 2. Preparation of alkynylsubstituted α-aminophosphonates **3a-h**[a].

Having aminophosphonates **3a–h** in hands we investigated their cyclization into cyclic derivatives **4a–h** under gold catalysis. Aminophosphonate **3a** was chosen as model compound for the optimization of the reaction conditions. Reactions were conducted in the presence of 5 mol% of gold precatalyst at room temperature. After 12 h of stirring the reaction mixture was filtered, evaporated and MeOH and $NaBH_4$ (2 equiv.) were added to reduce intermediate cyclic imine. Different gold complexes and salts were tested in the cyclization reaction and its catalytic activity was compared in THF and MeCN, which are known appropriate solvents for such type of reactions.[9] In most cases THF showed better results than acetonitrile. Phosphine Au complexes led to the formation of products with only moderate yield (Scheme 3, Table 2, entry 1–4). Better result was obtained with IPrAuCl and AgOTf in THF (entry 7, 72%). $AuCl_3$ was the most effective catalyst in THF (entry 8, 77%) and toluene (entry 9, 80%). Note, that in all these cases full conversion of starting aminophosphonate wasn't observed probably due to deactivation of catalysts and precipitation of metallic gold. However, replacement solvent with DCE resulted to the full conversion of **3a** with 87% ^{31}P NMR and 66% isolated yields of **4a** (entry 10). Sometimes[6e] addition of Brønsted acids increase rate of the hydroamination reaction and yields of products, but in our case addition of 5 equiv. of EtOH didn't influence on the yield of **4a** (entry 11, 80%). Other metal salts such as CuI and AgOTf were inefficient in this reaction (entries 12,13).

Table 1. Preparation of alkynylsubstituted α-aminophosphonates **3a-h**[a].

Entry	R	Yield, %[b]
3a	C_6H_5	86
3b	4-MeC_6H_4	71
3c	4-*t*-BuC_6H_4	84
3d	4-$MeOOCC_6H_4$	80
3e	4-$CF_3C_6H_4$	73
3f	H	78
3g	*n*-Hexyl	86
3h	Cyclohexyl	85

[a] Isolated yields, calculated on the starting **2**.



Scheme 3. Optimization of reaction conditions of cyclization of **3a**.

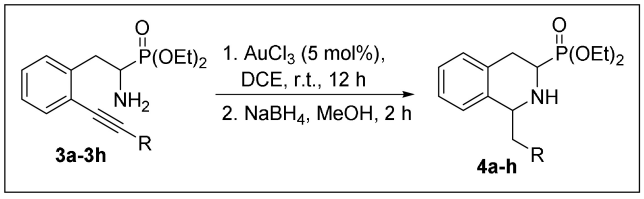
After optimization of the reaction conditions, we carried out cyclization of substrates **3b-h** (Scheme 4, Table 3).

Compounds **4b-e** were prepared with good yields (61-83%). Surprisingly, α-aminophosphonates with alkyl substituents **4f–h** gave almost quantitative yields, determined by ^{31}P NMR, however in the case of **4g** and **4h** yields of isolated products were lower because of losses during isolation (62 and 63%, respectively, Table 3).

Table 2. Optimization of reaction conditions of cyclization of **3a**[a].

Entry	Catalyst, %	Solvent	Yield, %[b]
1	PPh_3AuNTf_2 (5)	THF	6
2	PPh_3AuNTf_2 (5)	MeCN	18
3	$(C_6F_5)_3PAuNTf_2$ (5)	THF	64
4	$(C_6F_5)_3PAuNTf_2$ (5)	MeCN	27
5	$NaAuCl_4{\cdot}2H_2O$ (5)	THF	61
6	$NaAuCl_4{\cdot}2H_2O$ (5)	MeCN	52
7	IPrAuCl (5) + AgOTf (5)	THF	72
8	$AuCl_3$ (5)	THF	77
9	$AuCl_3$ (5)	toluene	80
10	$AuCl_3$ (5)	DCE	87 (66)
11	$AuCl_3$ (5)	DCE	80
12	CuI	THF	0
13	AgOTf	THF	0

[a] Reaction conditions: **3a** (0.28 mmol), Au precatalyst (0.014 mmol, 5 mol%) and solvent (1.5 mL) were stirred at r. t. for 12 h under Ar and then reduced by $NaBH_4$ in MeOH. [b] The yield was determined by ^{31}P NMR spectroscopy of the crude product, isolated yields in the brackets. [c] The reaction was performed in the presence of 5 equiv. of EtOH.



Scheme 4. Synthesis of 3-diethoxyphosphoryl-1,2,3,4-tetrahydroisoquinolines **4a-h**.

Table 3. Synthesis of 3-diethoxyphosphoryl-1,2,3,4-tetrahydroisoquinolines **4a-h**[a].

Entry	R	Yield, %[b]
4a	C_6H_5	66
4b	4-MeC_6H_4	83
4c	4-*t*-BuC_6H_4	72
4d	4-$MeOOCC_6H_4$	77
4e	4-$CF_3C_6H_4$	61
4f	H	87
4g	*n*-Hexyl	62
4h	Cyclohexyl	63

[a] Reaction conditions: **3** (0.28 mmol), $AuCl_3$ (0.014 mmol, 4.2 mg, 5 mol%) and DCE (1.5 mL) were stirred at r. t. for 12 h under Ar and then reduced by $NaBH_4$ in MeOH. [b] The isolated yields.

All compounds were characterized by means of NMR (^1H, ^{13}C, ^{31}P) spectroscopy, elemental analysis. In principle, another isomer of cyclization product could be formed due to the 7-*endo-dig* cyclization of **3**.[10] To prove the formation of 6-membered cyclic products in our case, we investigated its structure on the example of compound **4d** by different NMR techniques (double resonance ^1H-^{31}P, HSQC, HMBC, NOESY-1D) and single-crystal X-ray diffraction. X-ray and NMR data confirm the proposed structure of **4d**, which contains 1,2,3,4-tetrahydroisoquinoline core (Figure 2, Supporting Information).

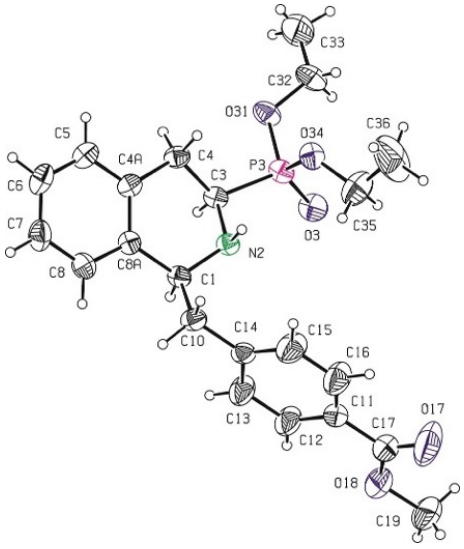


Figure 2. ORTEP view of **4d**. Displacement ellipsoids are drawn at 50% probability. Hydrogen atoms are presented as small rinds of arbitrary radius

Interestingly, after reduction with $NaBH_4$ of corresponding cyclic imines products **4a-h** were formed only as two *cis*-isomers. This phenomenon was observed previously for the cyclic iminophosphonates when reducing by H_2 on the PtO_2 and the observed *cis*-geometry is expected because H_2 adds from the least hindered direction.[11]

Conclusions

In conclusion, we have successfully developed convenient approach to the synthesis of series of 1-alkyl-3-diethoxyphosphoryl-1,2,3,4-tetrahydroisoquinolines using gold(III)-catalyzed intramolecular hydroamination/reduction protocol. Starting alkynylsubstituted α-aminophosphonates were easily prepared from available diethyl (diphenyl-methyleneamino)methylphosphonate using consecutive alkylation under phase-transfer conditions and Sonogashira reaction with different alkynes. A highly diastereoselective reduction of cyclic imines by $NaBH_4$ was observed leading to enantiomers with *cis*-configuration.

Supporting Information Summary

Detailed experimental procedures, ^1H, ^{13}C, ^{31}P NMR, ESI-MS, X-ray single-crystal diffraction data, copies of ^1H, ^{13}C and ^{31}P spectra of all new compounds are available online as Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: gold catalysis · cyclic α-aminophosphonates · cyclization · intramolecular hydroamination · tetrahydroisoquinolines

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