Organocatalytic hydrophosphonylation reaction of carbonyl groups

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To Prof. M. Concepción Gimeno (ISQCH-CSIC) for her valuable support of our research.

Abstract: This revision is covering the limited examples reported for a pivotal strategy in the formation of C-P bonds such as the asymmetric organocatalytic hydrophosphonylation of carbonyl groups (Pudovik reaction). The scope and limitations, and the proposed mechanisms for the scarce different possibilities of asymmetric induction are also shown. The recent evolution and future trends of this undeveloped approach are commented.

1. Introduction

The addition of dialkyl- or diphenylphosphites to C=O or C=N bonds (Pudovik reaction)¹ is the most straightforward applied method for the construction of P-C bonds (Scheme 1).² This strategy provides efficient access to chiral α -hydroxy³ or α -amino phosphonates,⁴ as key intermediates in the synthesis of their corresponding phosphonic acids,^{5,6} or other valuable substrates.

Scheme 1. Catalytic Pudovik reaction.

Interestingly, compounds bearing the phosphonate motif have exhibited appealing biological activities and some of them are currently employed as pharmaceutical drugs (Figure 1).⁷ It is well known that the enantiomeric form of many of these compounds could influence their biological role,⁸ and this fact has promoted an increasing interest in the search for new asymmetric syntheses of these scaffolds. Curiously, although many important works have been focused on the preparation of enantioenriched derivatives by mean of diastereoselective approaches,⁹ the asymmetric catalytic version of the Pudovik reaction has not been available for a long time and it still represents a challenging task.

Figure 1. Selected biologically active α -hydroxy- and α -amino phosphonates and their phosphonic acid derivatives.

The lack of background in the catalytic field has promoted an increasing concern for the development of methods allowing the asymmetric preparation of α -amino phosphonates.^{4b,10} However, and strangely, the asymmetric catalytic version for the obtainment of α -hydroxy phosphonates has been shorter studied, overall regarding the organocatalytic approach.¹¹ In some instances, similar approaches have also been used for preparing α -hydroxy phosphonates, and a special remark deserves the first asymmetric organocatalytic Abramov reaction reported just very recently by List and co-workers (2015),¹² in contrast to the first chiral Lewis catalyzed Abramov reaction reported by Nakajima in 2008.¹³ Maybe this is a representative example, in which is possible to compare the rate of evolution of the organocatalysis with that of the metal catalysis.

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Dr. Raquel P. Herrera was born in Alicante (Spain), in 1977. She received her B.S. (1999) and M.S. degrees (2000) at the University of Alicante, and completed her Ph.D. (1999-2003) under the supervision of Prof. Guijarro and Prof. Yus at the same university. She then took up a European postdoctoral contract with Prof. Ricci (Bologna, Italy) until March 2006, at which time she joined Prof. Lassaletta's group at the IIQ-CSIC (Seville, Spain) (until December of 2007). She was appointed as a permanent researcher (ARAID program, as *young research group leader*) at the ISQCH (Instituto de Síntesis Química y Catálisis Homogénea) CSIC-University of Zaragoza in January 2008 and in 2012 she obtained a permanent position as Tenured Scientist of the Spanish High Research Council (CSIC) at the same Institute. Her research interests are focused on asymmetric organocatalysis and its applications. In 2012 she was awarded with the Lilly Prize to the best young scientist less than 40 years, in Spain.

2. Enantioselective organocatalytic addition reaction of phosphites to carbonyl groups

It is worth nothing that although the hydrophosphonylation reaction with aldehydes has been the center of intensive efforts employing chiral organometallic catalysts,¹⁴ the organocatalytic version of this enantioselective approach has been much less explored in the literature.

The first enantioselective organocatalytic example reported in 1983 by Wynberg and co-workers¹⁵ covered a very limited scope of substrates, since only two aldehydes were explored using quinine **3** as catalyst (Scheme 2).¹⁶ Moreover, low enantiomeric excess was obtained in the catalytic process and successive crystallization steps were needed to increase the purity of the enantiomeric mixture. Consequently and unfortunately, the practical usefulness of this method is certainly narrow.

Scheme 2. Enantioselective organocatalytic hydrophosphonylation using quinine **3**.

After this former example, only few works have been reported. Since 1983 and until 2009, and even when this field was still totally unexplored, only Ooi's group published a pivotal work concerning an asymmetric organocatalyzed reaction using aldehydes (Scheme 3).¹⁷ The authors postulated the formation of chiral triaminoiminophosphorane **6a** as the active catalytic species of this process and responsible of the stereochemical course of the reaction. The active species **6a** is assumed to be generated *in situ* from the chiral tetraaminophosphonium salt **8a** with potassium *tert*-butoxide (Scheme 3).¹⁸

Scheme 3. Enantioselective organocatalytic hydrophosphonylation of aldehydes using triaminoiminophosphorane **6a**.

The corresponding α -hydroxy phosphonates **7** with excellent yields (up to 99%) and excellent enantioselectivities (up to 99%) were obtained. The application of the process was successfully demonstrated by using eleven differently substituted aldehydes such as aliphatic, aromatic and heteroaromatic having different electronic properties. Interestingly, the catalyst loading was reduced until 1 mol% without impairing on the enantioselectivity of the process. However, very low temperature is required in this process to achieve good results ($-78\text{ }^\circ\text{C}$ or $-98\text{ }^\circ\text{C}$). Contemporaneously, Feng and co-workers developed the first application of cinchona-derived thiourea organocatalysts **10** and **11**, both pseudo-enantiomers, in the hydrophosphonylation reaction of α -ketoesters **9** (Scheme 4).¹⁹ It is well known that the ketones are less active than the aldehydes, for this reason the authors use in this case highly activated ketones **9** to achieve the final products.

Scheme 4. Enantioselective organocatalytic hydrophosphonylation of α -ketoesters **9** with **2b**.

Under the optimized conditions, after the initial screening, a range of aromatic α -ketoesters **9** differently substituted was explored, and the corresponding (*S*)- and (*R*)- α -hydroxy phosphonates **12** were formed in high yields (up to 95%) and with high enantioselectivities (up to 91%) using both pseudo-enantiomers of the thiourea catalyst (Scheme 4). This contribution represents the first simple and a practical synthetic strategy for the direct addition of dialkylphosphite to activated ketones.

Based on the experimental results and with the absolute configuration of the final products found for each thiourea catalyst (**10,11**), a probable mechanism for this reaction was proposed consistent with a bifunctional mode of action of the catalyst²⁰ (Figure 2).

Figure 2. Proposed mechanism through a bifunctional activation mode.

The thiourea moiety would activate the α -ketoester through a bidentate hydrogen bonding as depicted in Figure 2.²¹ Meanwhile, the basic nitrogen in the quinuclidine scaffold could shift the phosphite-phosphonate equilibrium toward the most reactive phosphite form.²² Therefore, the phosphite would be approached by hydrogen bonding through the interaction between the quinuclidine nitrogen and the acidic hydrogen on the phosphite, affording the observed enantiomer in each case. The theoretical study of this mechanism has been recently investigated by Li and Huang's group.²³

Later, Ooi and co-workers developed the first highly enantioselective hydrophosphonylation of ynones based on their previous work.¹⁷ The authors used their triaminoiminophosphorane derivative prepared *in situ* from chiral aminophosphonium salt **8b** and KOtBu in THF at -78°C , as abovementioned (Table 1).²⁴

Table 1. Scope of the hydrophosphonylation of ynones **13**.

Entry	R	13	Time/h	Yield (%) ^[a]	ee (%) ^[b]	14
1	<i>n</i> Hexyl	13a	19	99	88	14a
2	Ethyl	13b	76	73	90	14b
3	Me(CH ₂) ₈	13c	22	98	88	14c
4	Cyclohexyl	13d	17	96	90	14d
5	Me ₂ CHCH ₂	13e	16	97	79	14e
6	BnOCH ₂	13f	17	97	81	14f
7	<i>t</i> BuMe ₂ SiO(CH ₂) ₂	13g	19	96	87	14g

8	Me ₃ SiO(Me) ₂ C	13h	19	96	88	14h
9	Me ₃ Si	13i	17	96	91	14i

^[a] Isolated yield. ^[b] Enantiomeric excess determined by chiral HPLC.

The corresponding α -hydroxy phosphonates **14** were obtained in excellent yield and with high enantioselectivity starting from ynones bearing a long linear chain or an α -branched alkyl group. This study provides a new synthetic route to optically active α -tetrasubstituted α -hydroxy phosphonates, demonstrating the potential use of chiral triaminoiminophosphorane species as strong organic base catalysts with hydrogen-bonding donor ability. This is an important work for the first use of less active ketones with very good results.

In this work, a plausible reaction mechanism is proposed. This is based on the generation of the highly reactive catalytic tetraaminophosphonium phosphite species (intermediate A) as a uniquely reactive chiral P-nucleophile (Scheme 5). Hence, the authors hypothesized that the phosphite anion with extremely high nucleophilicity could participate in the activation of less reactive ketones through hydrogen bonds and in a stereoselective way. Then, the fast proton transfer from the aminophosphonium cation to the alkoxide anion intermediate would occur in a pseudo-intramolecular manner (intermediate B) yielding the desired α -tetrasubstituted α -hydroxy phosphonates **14** as the sole products, and avoiding both retro-hydrophosphonylation and phospho-Brook rearrangement.

Scheme 5. Mechanistic proposal.

More recently, based on our own experience in the hydrophosphonylation reaction of imines (Scheme 6, a),²⁵ hydrazones (Scheme 6, b),²⁶ and nitroalkenes (Scheme 6, c),²⁷ all of them important examples in their corresponding areas of research, and the lack of background concerning aldehydes encouraged us to explore the viability to catalyze this process with chiral squaramide **16**, as hydrogen bond donor catalyst.

Scheme 6. Our previous hydrophosphonylation works.

Squaramide catalysts have received special interest in the last years.²⁸ Although in that moment, we used the unique commercially available squaramide catalyst **16**, we have recently developed an interesting one-pot procedure to obtain this and many other promising squaramide catalysts following a very simple strategy.²⁹ In our work, the first asymmetric squaramide-organocatalyzed Pudovik reaction using aldehydes was disclosed (Scheme 7).³⁰

Scheme 7. Scope of the squaramide-catalyzed hydrophosphonylation reaction.

Our methodology covers a broader range of compounds compared with the pioneering protocol described by Wynberg and co-workers.¹⁵ Since it tolerates the use of aromatic aldehydes with different functional groups such as halides, nitro, cyano, and also aliphatic aldehydes through a simple and general approach, with very good results in terms of enantioselectivity and reactivity. Moreover, this is a more straightforward protocol achieving the final goal in a simplest manner, without the necessity of subsequent derivatization or recrystallization in order to obtain high enantioselectivities. Interestingly, using a more available chiral catalyst **16** compared with that used by Ooi and co-workers and the development of the reaction at $-38\text{ }^{\circ}\text{C}$ instead of at $-98\text{ }^{\circ}\text{C}$ ¹⁷ makes this approach an attractive alternative from a practical point of view.

On the base of the experimental results and having in hand the absolute configuration obtained by X-ray diffraction for two final adducts, we proposed the following transition state to explain the role of the catalyst (Figure 3).

Figure 3. Proposed TS for the squaramide catalyzed reaction.

Based on the experimental results and on the absolute configuration observed on final products, we hypothesized that the catalyst acted in a bifunctional fashion.²⁰ Thus, the carbonyl group in the aldehyde would be activated by the squaramide moiety through a bidentate double hydrogen bonding. Simultaneously, the basic nitrogen atom on the piperidine ring would activate the phosphonate form in the tautomeric equilibrium.²² This approach would drive the attack of the phosphite over the *Re* face of the aldehyde. This attack would afford the *R* enantiomer in final products, which was consistent with the observed absolute configuration in the crystal structures of two α -hydroxy phosphonates **17**. Currently, we are developing computational calculations in order to support our mechanism that we will report in due course, but until now, the calculations seem to be in agreement with the bifunctional role of the catalyst shown in this TS.

Additionally, it was the first time that diphenylphosphite **2c** was successfully used in the asymmetric version of this reaction with aldehydes, since until that moment other dialkylphosphites had been employed to perform this reaction. Thus, this work amplified the generality of this asymmetric methodology.

Recently, after our work, Miura and co-workers have successfully employed a new family of catalysts to promote this reaction, the novel diaminomethylenemalononitrile (DMM) cinchona catalyst **19**.³¹ This new motif has been envisioned as a promising alternative to thiourea or squaramide catalysts, and it has been applied to some efficient asymmetric organocatalytic reactions by the same group.³² After a preliminary screening and with the optimal conditions in hand, the authors explored the scope and limitations of this methodology using a variety of substituted aldehydes **18** and phosphite **2c** (Table 2).

Table 2. Scope of reaction using diaminomethylenemalononitrile catalyst **19**.

Entry	R	18	Time/h	Yield (%) ^[a]	ee (%) ^[b]	20
1	4-NO ₂ -C ₆ H ₄	18a	16	83	94	20a
2	4-NC-C ₆ H ₄	18b	16	95	96	20b
3	4-Br-C ₆ H ₄	18c	15	96	94	20c
4	4-Cl-C ₆ H ₄	18d	23	98	93	20d
5	3-Cl-C ₆ H ₄	18e	22	94	88	20e
6	2-Cl-C ₆ H ₄	18f	22	61	94	20f
7	C ₆ H ₅	18g	28	97	90	20g
8	1-naphthyl	18h	52	70	93	20h
9 ^[c]	4-Me-C ₆ H ₄	18i	22	80	91	20i
10 ^[c]	4-MeO-C ₆ H ₄	18j	45	53	92	20j
11	Cyclohexyl	18k	18	99	67	20k
12	PhCH ₂ CH ₂	18l	24	94	52	20l

^[a] Isolated yield. ^[b] Enantiomeric excess determined by chiral HPLC. ^[c] Use of 20 mol% of catalyst.

Aldehydes with representative electron-withdrawing groups on the aromatic ring rendered the final adducts in moderate to high yields and with excellent enantioselectivities (entries 1–6). The reactions with benzaldehyde (**18g**) and 1-naphthaldehyde (**18h**) or with electron-donating groups in the aromatic ring (**18i** and **18j**), afforded the corresponding products with excellent stereoselectivities and moderate yields (entries 7–10). In contrast, aliphatic aldehydes (**18k** and **18l**) provided final products in high yields with moderate enantioselectivities (entries 11 and 12). Based on experimental proofs, such as that the bulkier arylmethylene scaffold afforded better stereoselectivities, the addition of diphenyl phosphite **2c** to aldehydes **18** using catalyst **19** was supposed to proceed following the transition state models depicted in Figure 4.

TSa

TSb

Figure 4. Plausible activation modes.

The quinuclidine amine would deprotonate the phosphite form, which is generated by tautomerism from the phosphonate form as explained above. Simultaneously, the DMM motif would successfully interact with the carbonyl group of the aldehyde by a bidentate hydrogen bonding. In this concomitant activation of both reagents, the phosphite would preferably attack on the Si face of the aldehydes (**TSa**, Figure 4) avoiding the steric repulsion caused by the 3,5-di-tert-butyl benzyl group with the R group in the aldehyde (**TSb**, Figure 4). **TSa** affords the observed absolute configuration on final products with excellent enantioselectivity.

3. Conclusions

Since 1983 only a limited number of works have been developed using a chiral organocatalyst in the Pudovik reaction of carbonyl compounds and most of the asymmetric syntheses of α -hydroxy phosphonates have been carried out either through diastereoselective approaches or using chiral metal complexes. The first practical organocatalytic example was developed in 2009 and the subsequent few works have also achieved excellent enantioselectivities and high yields, improving the former one reported in 1983. Of course, these six crucial works cannot mark the end of this field and future development of other asymmetric catalytic approaches with high efficiency and selectivity are still needed for the preparation of such important molecules. It is worth noting that in terms of chiral scaffolds present in the catalysts, the use of chiral organocatalytic bases seems crucial for the success of such a process. Maybe a fast growth in this field is not expectable, since in the last thirty years only 6 new methods have appeared, but the development of new catalysts, or the use of new reagents and reaction conditions could be key for the progress of this field and for

further applications in the preparation of more complex products. Therefore, the very small number of asymmetric variants appeared so far deserves the urgent necessity for further efforts in the progress of this catalytic approach, and it is only a matter of time that new pivotal findings are reached.

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