Abramov Reaction

DOI: 10.1002/anie.201409411

The Catalytic Asymmetric Abramov Reaction**

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Abstract: *The first catalytic enantioselective Abramov reaction is described. The process is based on the utilization of a chiral disulfonimide catalyst, which efficiently avoids the difficulties encountered with metal-based catalysts. Several functionalized α-hydroxy phosphonates were synthesized in good yields and with excellent enantiomeric ratios of up to > 99:1. The process was shown to be scalable and up to 1 g of starting material could be employed under mild reaction conditions.*

The hydrophosphonylation of aldehydes with dialkyl phosphites ("Pudovik reaction") is an atom-economic approach toward α-hydroxy phosphonates (Figure 1, top right).[1] In light of the potential of enantiopure α-hydroxy phosphonates with regard to biological activity and synthetic utility,[2] significant efforts have been devoted toward developing asymmetric variants of this reaction.[3] As a result, a number of highly efficient catalytic systems using chiral organic bases[4] or metal-based chiral Lewis acids[5] have been developed. Dialkyl phosphites are in equilibrium with their predominating though unreactive dialkyl phosphonate form, which can in some cases result in sluggish reactivity and the requirement to use base activation to facilitate the reaction.[6] This situation is analogous to the aldol reaction, in which an enol species and not the normally dominant carbonyl tautomer acts as the nucleophile. Here, the preformation of the enol equivalent has proven useful, for example, in the Mukaiyama aldol reaction of enolsilanes. Aldol and Mukaiyama aldol reactions are often complementary and enantioselective variants of both reaction types have been thoroughly studied (Figure 1, left). Interestingly, silyl esters of dialkyl phosphites, which were originally introduced by Abramov,[7] display excellent reactivity in hydrophosphonylation reactions of aldehydes.[8] However, in contrast to the analogous Mukaiyama aldol reactions, enantioselective Abramov reactions of aldehydes are entirely unknown (Figure 1, bottom right).[9] Importantly, after hydrolysis of the silyl ether, the Abramov reaction delivers the same products as the Pudovik reaction. In extending the aldol analogy further, it appeared logical and desirable to develop an asymmetric Abramov reaction, as this would add an additional dimension of possible reaction conditions to the application of hydrophosphonylations in synthesis. Moreover, the initial products of the Abramov reactions are stable α-silyloxy phosphonates, in principle allowing for the direct isolation of protected α-hydroxy phosphonates.[10]

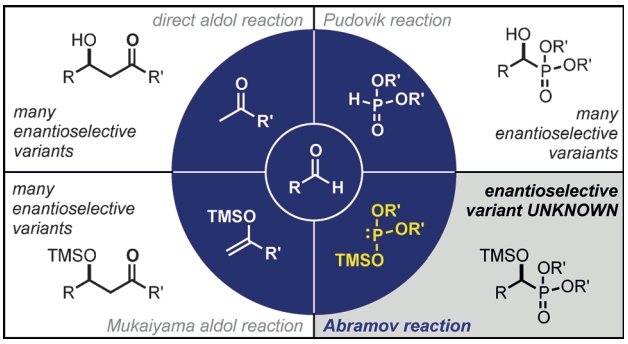

Figure 1. Analogy between the aldol/Mukaiyama aldol reactions and the Pudovik/Abramov reactions, respectively.

We have recently introduced chiral disulfonimides as effective catalysts for the activation of aldehydes in asymmetric Mukaiyama aldolizations.[11] These catalysts achieve enantioinduction based on the concept of asymmetric counteranion-directed catalysis (ACDC).[12] This strategy was shown to offer a general solution to the problem of silylium ion background catalysis,[13] which has likely hampered the development of asymmetric Abramov reactions utilizing chiral metal-based Lewis acids.[14] Encouraged by these considerations, we became interested in applying chiral disulfonimide catalysis to the enantioselective Abramov reaction and report here the successful realization of this concept.

After optimizing the reaction conditions with 2-naphthaldehyde and commercially available diethyl trimethylsilyl phosphite (**2a**) as model system (see the Supporting Information, SI), we could indeed obtain the hydrophosphonylation product **3** in excellent yield and enantioselectivity using catalyst **1a** (Table 1, entry 1).[15] We also explored several other substituted silylphosphites in this reaction. These reagents were either commercially available or readily synthesized in one step by the silylation of the corresponding phosphonates with TMSCl (trimethylsilyl chloride) in the presence of Et_3N or with TBSCl (*tert*-butyldimethylsilyl chloride) and LDA (lithium diisopropylamide).[10,12a,b,16] Substituents on the phosphite nucleophiles had a significant influence on the reactivity and enantioselectivity. Sterically less demanding dimethyl-substituted silyl phosphite delivered the corresponding product **4** with high enantioselectivity (entry 2). Efficient product formation was also observed by

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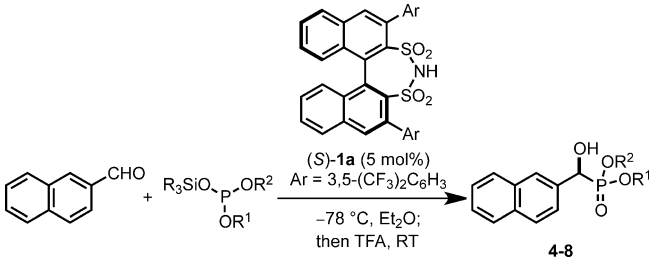
[**] We gratefully acknowledge generous financial support from the Max-Planck-Society, the European Research Council (Advanced grant "*High Performance Lewis Acid Organocatalysis*, HIPOCAT" to BL), and the Alexander von Humboldt Foundation (fellowships for J.G.).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201409411.

Table 1: Phosphite scope of the disulfonimide catalyzed enantioselective Abramov reaction.



Entry[a]	Phosphite	Product	Yield [%]	e.r.[b]
1	TMSO, OEt, OEt **2a**	2-Naph, OH, OEt, OEt **3**	98	98:2
2	TMSO, OMe, OMe **2b**	2-Naph, OH, OMe, OMe **4**	97	96.5:3.5
3	TMSO, O*i*Pr, O*i*Pr **2c**	2-Naph, OH, O*i*Pr, O*i*Pr **5**	96	98.5:1.5
4	TMSO, O*t*Bu, O*t*Bu **2d**	no reaction	–	–
5[c]	TMSO, OPh, OPh **2e**	2-Naph, OH, OPh, OPh **6**	66	80.5:19.5
6	TBSO, O*i*Pr, O*i*Pr **2f**	2-Naph, OH, O*i*Pr, O*i*Pr **5**	70	75:25
7[d]	TMSO, OMe, OEt **2g**	2-Naph, OH, OMe, OEt **7** d.r.[e]=1.25:1	96[f]	96.5:3.5 96.5:3.5
8[d]	TMSO, OMe, O*i*Pr **2h**	2-Naph, OH, OMe, O*i*Pr **8** d.r.[e]=1.5:1	95[f]	96:4 (major) 97:3 (minor)
9	HO, O*i*Pr, O*i*Pr **2i**	no reaction	–	–

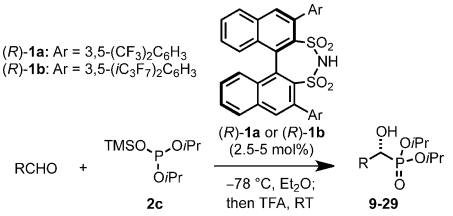
[a] Unless otherwise indicated, all reactions were carried out on a 0.1 mmol scale with 3.0 to 5.0 equiv of phosphite and 5 mol% of catalyst (*S*)-**1a** for 4 d. [b] Determined by HPLC analysis on a chiral stationary phase. [c] At −20°C. [d] Reactions were carried out in 0.125 to 0.2 mmol scale with 3.0 equiv of phosphite and 5 mol% of catalyst (*S*)-**1a** for 4 d. [e] Diastereomeric ratio (d.r.) was determined by ^{1}H and ^{31}P NMR analysis. [f] Combined yield of both diastereoisomers.

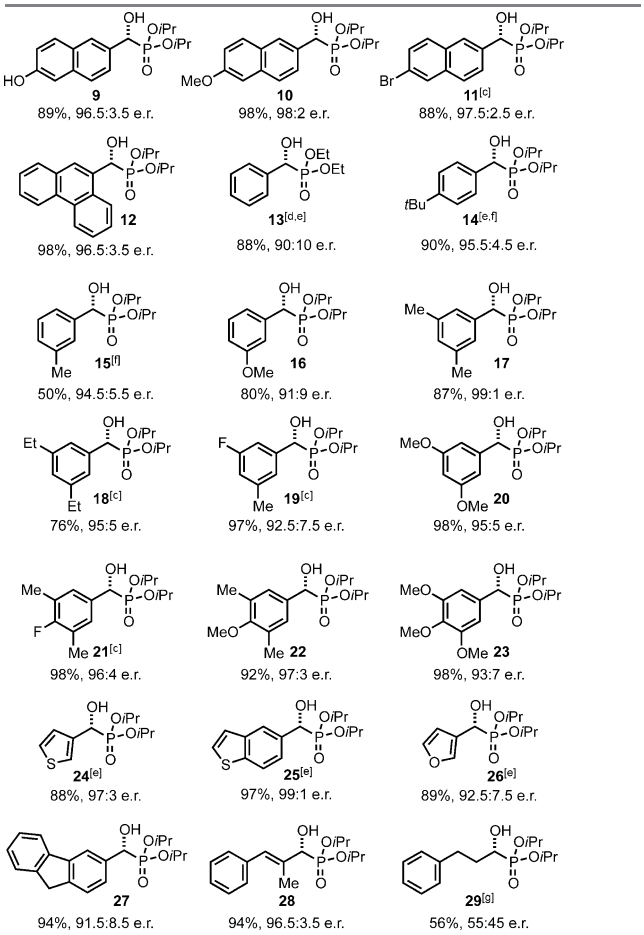
applying sterically demanding diisopropyl(trimethyl)silyl phosphite (**2c**; entry 3), furnishing the corresponding phosphonate **5** in an excellent enantiomeric ratio of 98.5:1.5. However, the even bulkier *tert*-butyl-substituted silyl phosphite **2d** did not give any product (entry 4). Phenyl-substituted phosphite **2e** was found to be only moderately reactive, providing the product at −20°C with moderate enantioselectivity (entry 5). When we employed TBS-substituted phosphite **2f**, a significant lowering of the reaction efficacy was realized (entry 6). Silylphosphites bearing two nonidentical alkoxy substituents were also investigated.

The corresponding α-hydroxy phosphonates with a P-stereogenic center were obtained in good yields and enantioselectivities.[17] However, only poor diastereoselectivity was achieved, even upon introducing sterically more distinguishable substituents (entries 7 and 8). Importantly, control experiments showed that the reaction indeed requires the use of silylated nucleophiles and no reaction was observed when the corresponding dialkyl phosphites were employed as nucleophiles under identical conditions (entry 9).

Having explored the variation of silylphosphites, we next investigated the utility of various aldehydes using phosphite **2c** (Table 2). Substituted 2-naphthaldehydes bearing various

Table 2: Aldehyde scope of the disulfonimide catalyzed enantioselective Abramov reaction.[a,b]



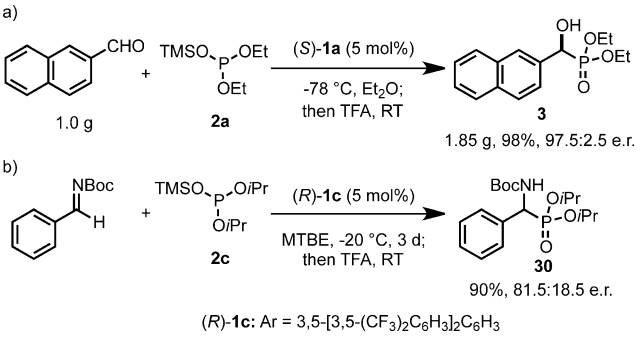


[a] Unless otherwise indicated, all reactions were carried out on a 0.2 mmol scale using 5.0 equiv of phosphite **2c** and 5 mol% of catalyst (*R*)-**1a** for 4 d. [b] Enantiomeric ratios (e.r.) were determined by HPLC analysis on a chiral stationary phase. [c] At −50°C. [d] Phosphite **2a** was used. [e] The reaction was conducted on a 0.125–0.15 mmol scale with 5.0 equiv of phosphite and 2.5 mol% of catalyst (*R*)-**1b** for 4 d. [f] 5 d reaction time. [g] Reaction performed with 10 mol% of catalyst (*R*)-**1a** at −10°C for 10 d.

functionalities underwent efficient reactions providing the corresponding phosphonates **9**–**11** in good yields (88–98%) and with excellent enantioselectivities (e.r. = 96:4–98:2). Phosphonate **12** was obtained with similar efficiency and selectivity from the corresponding phenanthrene carbaldehyde. Benzaldehyde as well as *para*- and *meta*-substituted benzaldehyde derivatives afforded the corresponding products **13**–**16** in good yields (50–90%) and with good to very good enantioselectivities (e.r. = 90:10–95:5). 3,5-Disubstituted benzaldehydes with electron-neutral, electron-rich, and electron-deficient substituents furnished the corresponding products **17**–**20** in good yields (76–98%) and with good to excellent enantioselectivities (e.r. = 92:8–99:1). Similarly, trisubstituted benzaldehydes could also be employed in our reaction, delivering the corresponding phosphonates **21**–**23** in excellent yields (92–98%) and high enantioselectivities (e.r. = 93:7–97:3). Heteroaromatic aldehydes such as thiophene-3-carbaldehyde, benzo[b]thiophene-5-carbaldehyde, and furan-3-carbaldehydes were efficiently converted into the corresponding phosphonates **24**–**26**. Phosphonylation of 9*H*-fluorene-2-carbaldehyde to product **27** could be achieved in good yield and stereoselectivity. A conjugated aromatic aldehyde was also transformed into the corresponding phosphonate **28** in excellent yield with an enantiomeric ratio of 96:4. Aliphatic aldehydes proved to be challenging substrates for our reaction. Under slightly modified conditions, hydrocinnamaldehyde could be converted into the corresponding phosphonate **29** in moderate yield and with a disappointingly low enantiomeric ratio of 55:45.[18]

Absolute (*R*)-configurations were established for compound **11** by single-crystal X-ray structure analysis and for compounds **13** and **16** by comparing optical rotation values with literature data (see SI).[5c] The absolute configurations of all other compounds were assigned by analogy.

To illustrate the practical synthetic utility of our methodology, a gram scale experiment was performed. Phosphite **2a** was reacted with 1 g of 2-naphthaldehyde, providing 1.85 g of the corresponding phosphonate **3** in 98% yield and an enantiomeric ratio of 2.5:97.5 (a, Scheme 1). Additionally, we envisaged that our protocol for the enantioselective Abramov reaction might be suitable for *N*-Boc imines as substrates, which, due to their sensitivity toward hydrolysis, are incompatible with the reaction conditions of most protocols for the enantioselective Pudovik reaction.[19] Indeed, in a preliminary experiment, the hydrophosphonylation of benzaldehyde-derived *N*-Boc imine could be achieved with high yield and a promising enantioselectivity. Product **30** was isolated with an enantiomeric ratio of 81.5:18.5 (b, Scheme 1). This initial result highlights the value of having enantioselective protocols available for complementary reactions such as the Pudovik and the Abramov reaction.



Scheme 1. a) Application of the enantioselective disulfonimide-catalyzed Abramov reaction on gram scale and b) initial results in the analogous hydrophosphonylation of *N*-Boc imines.

In summary, we have developed the first catalytic enantioselective Abramov reaction. Our approach complements previously established methods for synthesizing enantioenriched α-hydroxy phosphonates including the related Pudovik reaction. The successful realization of our enantioselective methodology relies on our recently introduced chiral disulfonimide silyl–Lewis acid precatalysts, which enabled us to circumvent the difficulties typically faced by metal-based catalyst systems. Different substituted silylphosphites and aromatic aldehydes have been utilized in this study, giving access to functionalized α-hydroxy phosphonates, cleanly, effectively, and in excellent enantioselectivity. Our approach offers a scalable, mild, and base-free protocol for the asymmetric hydrophosphonylation of aldehydes, which may enable its application in cases, in which substrates are incompatible with the reaction conditions required by previous methodologies. In addition, we have shown for the first time that our approach to the asymmetric Abramov reaction can be extended to an asymmetric silyl phosphonylation of *N*-Boc imines. The identification of advanced catalysts for these substrates as well as for challenging aliphatic aldehydes and ketones, and the application of our methodology in the synthesis of bioactive materials are current goals in our group.

Received: September 23, 2014
Published online: November 13, 2014

Keywords: Abramov reaction · disulfonimides · hydrophosphonylations · organocatalysis · α-hydroxy phosphonates

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