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Phosphonium Salt Organocatalysis

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Abstract: The field of organocatalysis is growing rapidly and attracts an increasing number of research groups. Most organocatalysts can be classified as Lewis bases, Lewis acids, Brønsted acids and Brønsted bases. However, examples of Lewis acid organocatalysis under homogeneous conditions are comparatively rare. Phosphonium salts are easily accessible and frequently used intermediates in organic synthesis, long known phase-transfer catalysts and potential Lewis acid organocatalysts. This review covers the application of phosphonium salts as Lewis acidic catalysts for a variety of C–C, C–O and C–N bond-forming reactions under homogeneous conditions. Moreover, recent developments are included which show the potential of chiral phosphonium salts as asymmetric (phase-transfer) catalysts.

Keywords: asymmetric catalysis; Lewis acids; organocatalysis; phosphonium salts

1 Introduction

Biological activity often arises through interactions between a chiral organic molecule and an enzyme or receptor. Hence, such molecules play an important part in modern life, especially in the area of pharmaceuticals, agrochemicals and flavours.[1] Asymmetric synthesis is dedicated to the preparation of molecules with defined stereochemistry and is a central field in modern organic chemistry. Nature is in principle the expert in asymmetric catalysis, physiological reactions providing the blueprint for asymmetric metal-based catalysis as well as for organocatalysis.

Over the past four decades asymmetric transition metal-based catalysis underwent remarkable developments. This was reflected in the awarding of the Nobel prize 2001 to Sharpless, Noyori and Knowles for their achievements in asymmetric homogeneous oxidation and hydrogenation reactions, respectively.[2] In the excitement over transition metal-based catalysts the area of asymmetric organocatalysis did not receive the attention it deserved and was only recently recognised as a valuable addition and/or alternative to existing, well established often metal-based methodologies.[3] Nevertheless, this is surprising since organocatalysts often have several advantages over homogeneous metal catalysts and enzymes. They are usually non-toxic, readily available, bench-stable catalysts that are easy to prepare and therefore inexpensive. Reactions can be performed under aerobic conditions and mostly the exclusion of water is not necessary. In addition, the fixation onto a support is relatively easy, there is no risk of metal leakage, and no expensive recovery processes are required for water treatment. Moreover, small organic molecules have been used as catalysts from the early beginnings of synthetic organic chemistry.[4] A milestone in the development of asymmetric organocatalysis was the discovery of the enantioselective intramolecular aldol reaction catalyzed by the natural amino acid proline during the early 1970s.[5] In the following years isolated examples of highly enantioselective organocatalytic processes were reported. The ground-breaking work of List, MacMillan and others on more general and efficient asymmetric organocatalysts and asymmetric organocatalytic reactions in the late 1990s and early 2000s led to a paradigm shift, making organocatalysis a challenging and rapidly growing field of central importance for the asymmetric synthesis of chiral molecules.[6,7] Most organocatalysts can be broadly classified according to their mode of activating a substrate as Lewis acids, Lewis bases, Brønsted acids and Brønsted bases.[7] The vast majority of these catalysts belong to the latter three classes. By contrast, metal-based catalysts are usually Lewis acids. In this context organocatalysis can be regarded as being complementary to metal-based catalysis.

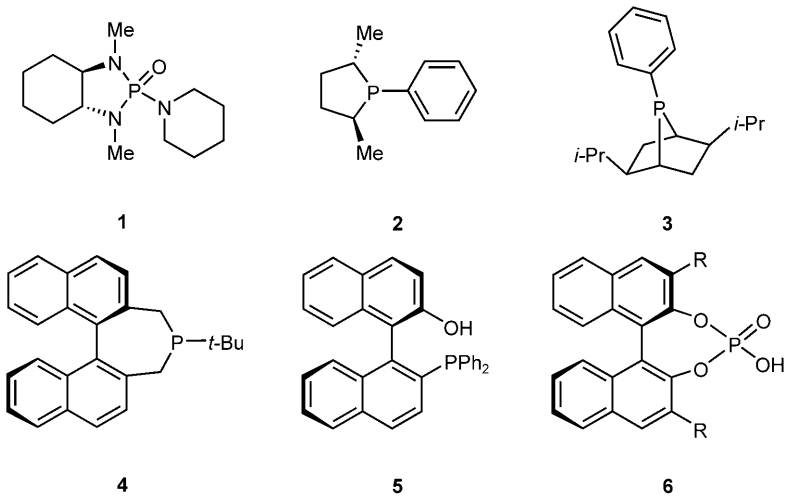
Thomas Werner was born in 1973 in Berlin, Germany. After his apprenticeship as a chemical technical assistant he studied chemistry at the Technische Universität Berlin, Germany, and at the Northumbria University in Newcastle upon Tyne, U.K. After receiving his Diploma from the Technische Universität Berlin in 2001 he moved together with Prof. J. Christoffers to the Universität Stuttgart, Germany, where he worked on cerium-catalyzed transformations of β-dicarbonyl compounds in the presence of molecular oxygen. He completed his Ph.D. in 2004 and joined shortly after the group of Prof. A. G. M. Barrett at Imperial College London, U.K., for postdoctoral work on a biomimetic approach to the antifungal agent 15G256β. In 2006 he joined the Coating and Colorants business unit of Evonik (Degussa) as head of an R&D laboratory. In 2008 he relocated to the Leibniz-Institut für Katalyse e. V. in Rostock, Germany, where he is currently working towards his habilitation in the group of Prof. M. Beller.

Organophosphorus compounds have been extensively utilized in organic synthesis. In the field of organometallic chemistry they are most frequently used as ligands to tune reactivity and selectivity in transition metal complexes for versatile organic transformations.[8] In recent years the use of chiral Lewis basic[9,10] and Brønsted acidic[11] organophosphorus compounds as asymmetric organocatalysts has received considerable interest. Among them, catalysts **1–6** have been extensively investigated as catalysts for a variety of reactions (Scheme 1).

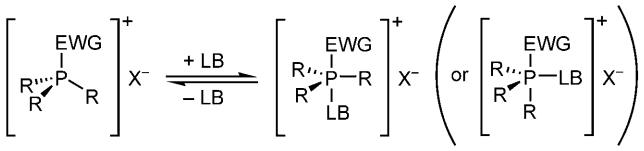
Phosphoramide **1**, for example, has been employed by Denmark et al. as a catalyst for allylation reactions.[12] Vedejs et al. reported on enantioselective acyl-transfer reactions in the presence of **2**[13] and Zhang et al. about [3+2]cycloadditions catalyzed by **3**.[14] Fu et al. performed formal [4+2]cycloadditions with binaphthyl derivative **4** as a catalyst.[15] Bifunctional catalysts based on phosphorus compounds have also been developed. Shi et al. successfully used **5** as a catalyst in the asymmetric aza-Baylis–Hillman reaction.[16] Most recently, BINOL-based chiral Brønsted acid catalysts **6** have been applied by several groups for a variety of asymmetric reactions, e.g., Mannich-type reaction,[17] aza-Diels–Alder reactions,[18] transfer-hydrogenation and Nazarov reactions.[19]

Quaternary phosphonium and ammonium salts can be considered as Lewis acid organocatalysts. The most prominent catalytic application of these compounds is phase-transfer catalysis. However, asymmetric reactions in this field are almost exclusively catalyzed by chiral ammonium salts.[20] Only few examples of the application of Lewis acid organocatalysts, for example, triarylcarbenium,[21] iminium,[22] imidazolinium[23] and imidazolium salts,[24] under homogeneous conditions have been reported.

The key to the successful application of phosphonium salts as Lewis acidic catalysts is the utilization of hypervalent bonding between a Lewis basic substrate and the Lewis acidic catalyst to generate an activated species (Scheme 2).[25,26] The n-σ* interaction between a non-bonding electron pair of the Lewis base and the anti-bonding orbital with σ character of the Lewis acid requires the Lewis acidic acceptor to be able to expand its coordination sphere to attain a hypervalent state.[10,27] The formed hypervalent bond is stabilized when an electron-withdrawing substituent occupies



Scheme 1. Selection of frequently used phosphorus-based organocatalysts.



Scheme 2. Hypervalent interaction between a phosphonium salt and a Lewis base.

the apical position of the trigonal bipyramidal arrangement.[26,28]

This review covers the application of phosphonium salts as Lewis acidic catalysts under homogeneous conditions as well as the use of chiral derivatives as asymmetric (phase-transfer) catalysts.

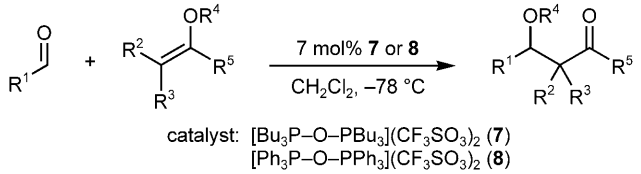
2 C–C Bond Forming Reactions

In the course of their investigations to explore novel metal-free Lewis acidic catalysts Mukaiyama et al. investigated the use of phosphonium salts as catalysts in several carbon-carbon bond forming reactions.[29,30] They successfully employed diphosphonium salts **7** and **8** as a catalyst in Mukaiyama-aldol reactions of aldehydes with silyl enol ethers and ketene silyl acetals (Table 1). In all cases, the reactions proceeded smoothly in CH_2Cl_2 at low temperature and the corresponding aldol products were obtained in fairly good yields. Other solvents such as THF, toluene or acetonitrile gave slightly lower yields. The *syn*-product was preferably formed in moderate selectivity if applicable. Notably, the catalysts were also effective for the reaction of aldehydes containing amino groups, such as *p*-*N*,*N*-dimethylaminobenzaldehyde and indole-3-carboxaldehyde.

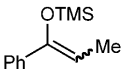
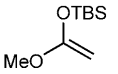
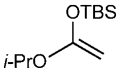
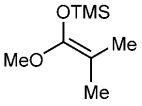
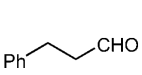
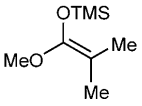
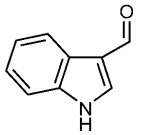
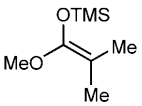
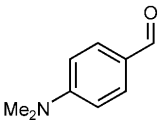
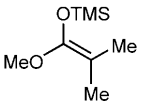
Under the same reaction conditions acetals, synthetic equivalents of aldehydes, were also available in this reaction (Table 2). Other silyl nucleophiles such as allyltrimethylsilane and trimethylsilyl cyanide were smoothly converted to the corresponding aldol-type products.

Moreover, they employed the enol ethers and trimethylallylsilane as nucleophiles in a phosphonium salt-catalyzed Michael reaction. The best result was obtained with trimethylallylsilane as a nucleophile (Scheme 3). Even though yields in this reaction were only moderate the general potential of phosphonium salts as Lewis acidic organocatalysts was demonstrated.

Table 1. Mukaiyama-aldol reaction.[a]

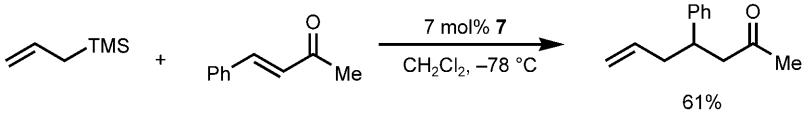


catalyst: $[Bu_3P–O–PBu_3](CF_3SO_3)_2$ (**7**)
$[Ph_3P–O–PPh_3](CF_3SO_3)_2$ (**8**)

Aldehyde	Nucleophile	Cat.	Yield [%]
PhCHO		**8**	98[b]
PhCHO		**7**	76
PhCHO		**7**	67
PhCHO		**7**	54
		**7**	53
		**7**	71[c]
		**8**	70

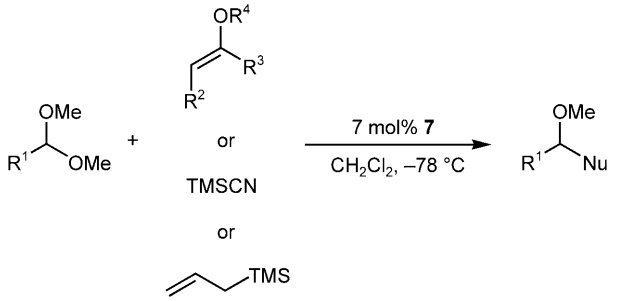
[a] The reaction was carried out in a molar ratio of carbonyl aldehyde:nucleophile = 1:1 in CH_2Cl_2 at −78 °C for 2 h.
[b] The product was obtained in 71:29 *dr* (*syn*:*anti*).
[c] THF was used as solvent.

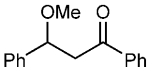
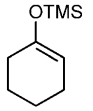
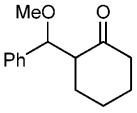
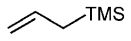
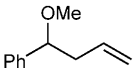
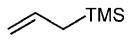
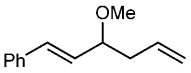
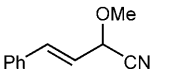
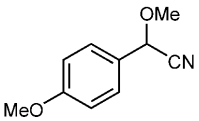
The possibility to convert unprotected indole derivatives in Mukaiyama-aldol-type reactions was utilized by Metz et al. in the synthesis of a potential glycine-site *N*-methyl-D-aspartate receptor antagonist (Scheme 4).[31] The use of substoichiometric amounts of **8** to mediate the reaction between an indole derivative and several ketene silyl acetals gave a mixture of the corresponding alcohols and silyl ethers in low to moderate yields. The relative stereochemistry was not significant, since the mixtures were converted to the corresponding α,β-unsaturated products under acidic conditions.



Scheme 3. Michael reaction catalyzed by diphosphonium salt **7**.

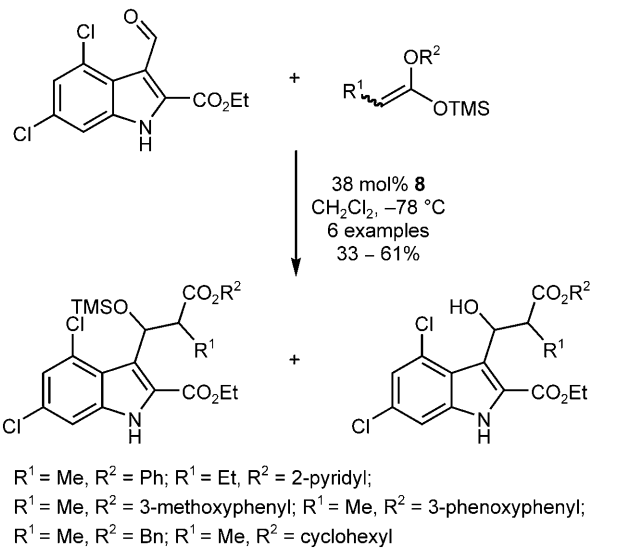
Table 2. Addition of silyl nucleophiles to acetals.[a]



R^1	Nucleophile	Product	Yield [%]
Ph			90
Ph			70[b]
Ph			67
(*E*)-PhCH=CH			80
(*E*)-PhCH=CH	TMSCN		60
p-MeO-C_6H_4	TMSCN		83

[a] The reaction was carried out in a molar ratio of carbonyl compound:nucleophile = 1:1 in CH_2Cl_2 at −78 °C for 2 h.
[b] The product was obtained in 90:10 *dr* (*syn*:*anti*).

A common substructure of several *Stemona* alkaloids is a characteristic pyrrolidinyl-lactone system with a *syn*-relationship of the two vicinal stereocentres.[32] Morimoto et al. reported an efficient stereoselective approach to this substructure (Scheme 5).[33] They investigated the Lewis acid-catalyzed reaction between *N*-Cbz-2-methoxypyrolidine and 3-methyl-2-trimethylsilyloxyfuran under various reaction conditions. Diphosphonium salt **8** proved to be superior to several Lewis acidic metal catalysts such as BF_3•Et_2O, $TiCl_4$, $SnCl_4$ and Et_2AlCl. The desired product was obtained in excellent yield and good selectivity, 89:11 *dr* (*syn*:*anti*), in the presence of catalytic amounts of **8**



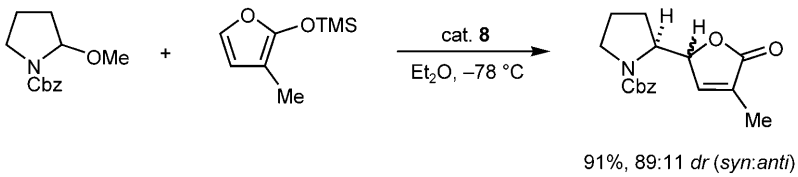
R^1 = Me, R^2 = Ph; R^1 = Et, R^2 = 2-pyridyl;
R^1 = Me, R^2 = 3-methoxyphenyl; R^1 = Me, R^2 = 3-phenoxyphenyl;
R^1 = Me, R^2 = Bn; R^1 = Me, R^2 = cyclohexyl

Scheme 4. Mukaiyama-aldol reaction of an indole derivative with a variety of ketene silyl acetals.

in diethyl ether. Unfortunately, the exact amount of catalyst was not specified. In other solvents such as dichloromethane or THF lower yields and selectivities were obtained.

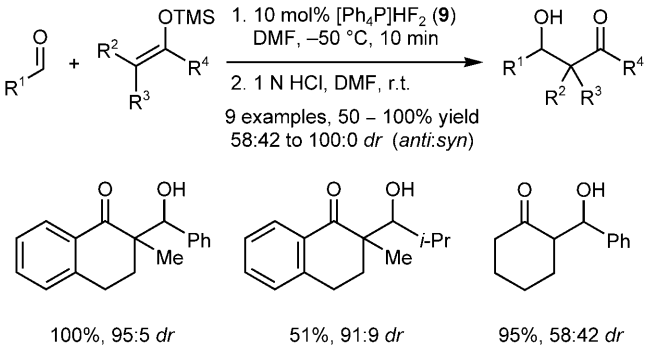
Shioiri et al. used catalytic amounts of tetraphenylphosphonium hydrogen difluoride (**9**) to conduct Mukaiyama-aldol reactions between aldehydes and silyl enol ethers (Scheme 6).[34,35] The reaction proceeded slowly in THF, MeCN and Et_2O at 0 °C. In contrast to the catalysts **7** and **8** no conversion was observed in CH_2Cl_2. However, the use of catalytic amounts of **9** (5–10 mol%) in DMF at lower temperature significantly accelerates the reaction. When the formation of two diastereoisomeric products is possible, in most cases the *syn*-isomer was predominantly formed. Compound **9** is a powerful source of fluoride ions.[36] The authors assumed therefore that the reaction is mediated by fluoride ions but also take in account the possible activation of the carbonyl group by the Lewis acidic phosphonium cation.

Under the same reaction conditions Shioiri et al. performed Grignard-type additions of 1-phenyl-2-trimethylsilylacetylene to the carbonyl group of aldehydes, ketones and α,β-unsaturated carbonyl compounds in the presence of catalyst **9** (Scheme 7).[34,35]

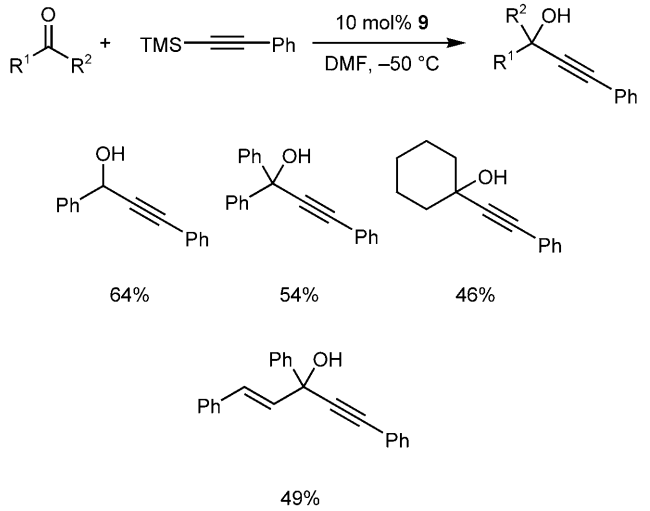


91%, 89:11 *dr* (*syn*:*anti*)

Scheme 5. Efficient access to the pyrrolidinyl-lactone substructure in *Stemona* alkaloids.



Scheme 6. Mukaiyama-aldol reaction catalyzed by **9** and selected examples.



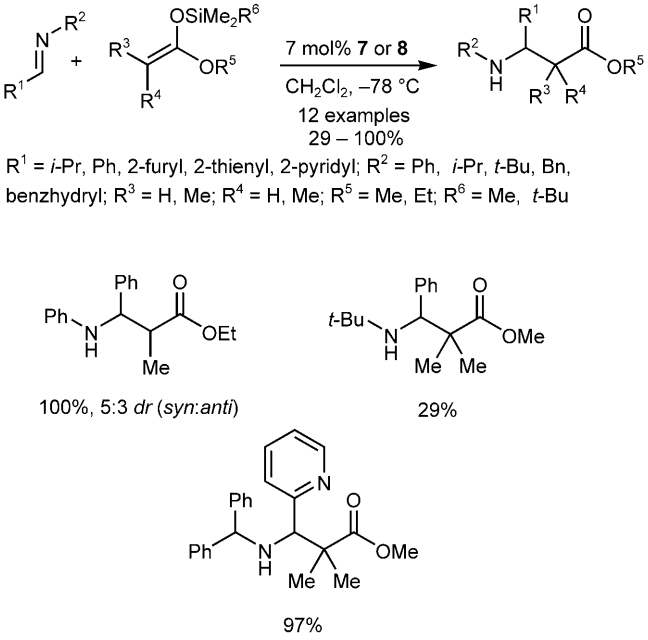
Scheme 7. Grignard-type addition catalyzed by **9**.

The reaction conditions for this transformation were not further optimized.

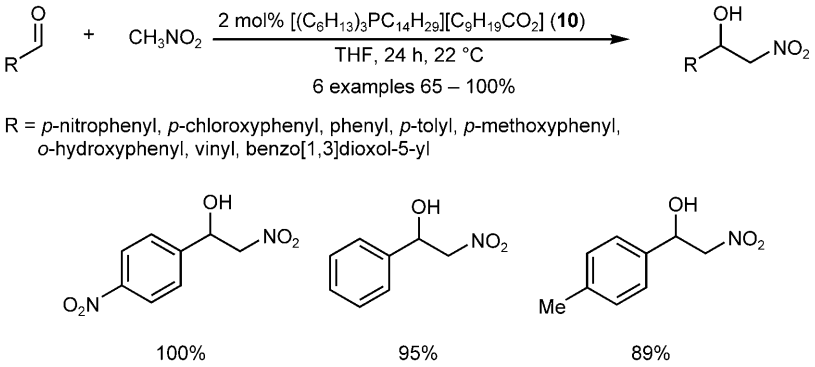
An important class of ionic liquids is based on quaternary phosphonium salts.[37] McNulty et al. investigated the potential of these compounds as mild Lewis acidic catalysts for the Henry reaction.[25] Phosphonium salt **10** proved to be an effective catalyst for the reaction between aromatic aldehydes and nitromethane under very mild conditions (Scheme 8). The conversion of several aldehydes in the presence of 2 mol% of **10** gave the desired products in moderate to excellent yields. However, the reaction did not proceed when a free phenolic hydroxy group was present on the aromatic ring. The authors postulated the activation of the carbonyl function *via* the complexation of the carbonyl compound to the phosphonium salt.

The synthesis of β-amino esters has gained considerable attention due to their occurrence in natural products, pharmaceutically important compounds and as potential precursors for β-lactams.[38]

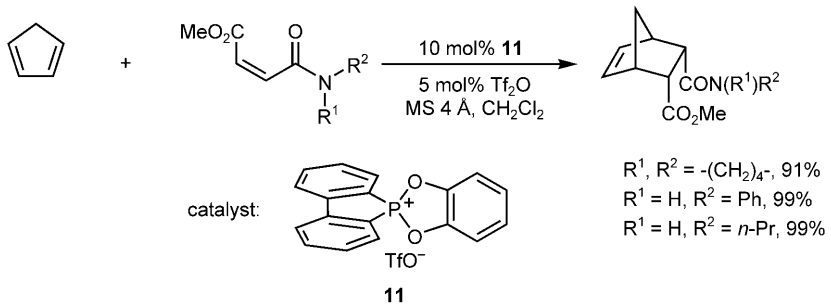
Mukaiyama et al. employed diphosphonium salts **7** and **8** as catalysts for the reaction of various imines with ketene silyl acetals to afford the corresponding β-amino esters (Scheme 9).[29] The reactivity and yield



Scheme 9. Mannich-type reaction catalyzed by **7** or **8** and selected examples.



Scheme 8. Henry reaction catalyzed by **10** and selected examples.



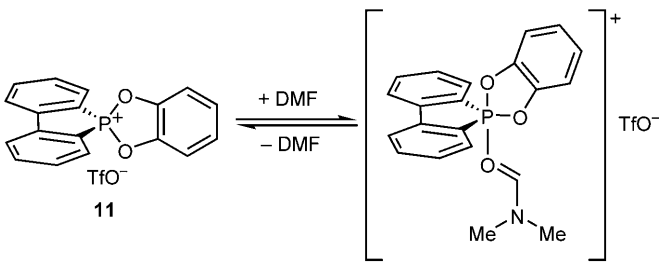
Scheme 10. Diels–Alder reaction catalyzed by **11**.

decreased with increasing steric demand of the substituent R^2 at the nitrogen and R^6 at the silicon, respectively. However, in most cases the desired product was obtained in good to excellent yields but low diastereoselectivity. Higher reaction temperatures and lower catalyst loading (2.5 mol%) had only a marginal influence on the yield. The authors proposed that the reaction proceeds *via* the activation of the Lewis basic imines by the coordination to the Lewis acidic diphosphonium salt.

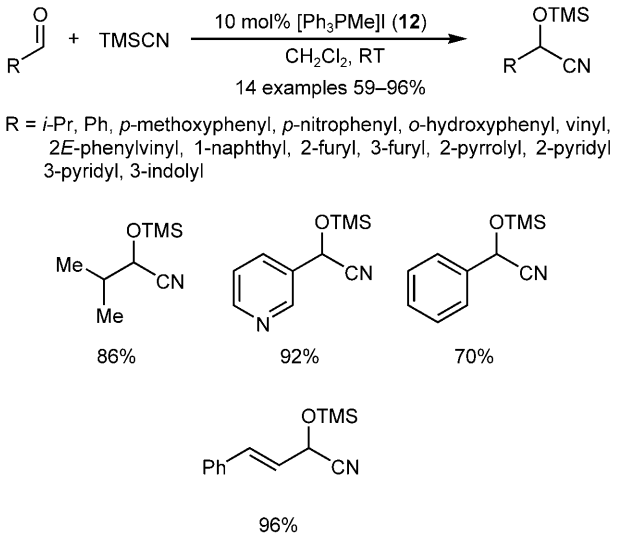
Recently Terada et al. reported about another fundamental carbon-carbon bond forming reaction that can be catalyzed by phosphonium salts. They investigated the Diels–Alder reaction of α,β-unsaturated amides and cyclopentadiene catalyzed by various phosphonium salts (Scheme 10).[26] The addition of Tf_2O increased the yield significantly. It was confirmed by control experiments that Tf_2O alone did not catalyze the reaction at all. In the presence of catalyst **11**, *Z*-configurated dienophiles gave the corresponding Diels–Alder product in excellent yields and high *endo*-selectivity (>97%). In contrast, *E*-configurated amide dienophiles showed lower yields and a preference to form the *exo*-products.

The ability of the employed phosphonium salts to function as a Lewis acid catalyst in this reaction strongly depended on the structure and the substituents at the phosphorus atom. A five-membered dioxaphosphacycle was thereby crucial for catalytic activity. The performed coordination studies using **11** and DMF as a model system revealed that DMF coordinates to the Lewis acidic organophosphorus compound (Scheme 11). The performed NMR studies suggest that the phosphonium salt arranged in a trigonal bipyramidal configuration upon coordination of the Lewis base DMF. One of the two catechol moiety oxygen atoms and the carbonyl oxygen of DMF occupy the apical positions, thus stabilizing the formed hypervalent bond.

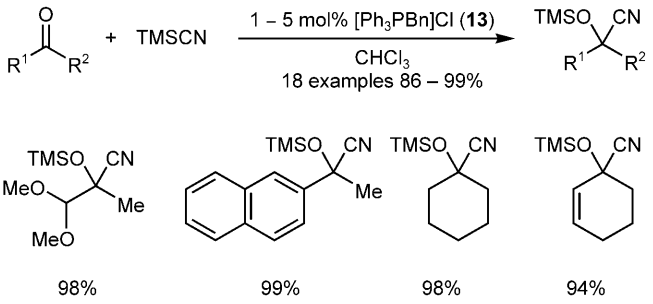
Cyanohydrin trimethylsilyl ethers are versatile intermediates, e.g., for the synthesis of α-hydroxy acids and β-amino alcohols.[39] The cyanosilylation of an acetal as an aldehyde equivalent, namely *E*-cinnamaldehyde dimethyl acetal, catalyzed by **7** was first reported by Mukaiyama et al.[30] Plumet et al. reported the synthesis of cyanohydrin trimethylsilyl ethers from aldehydes and TMSCN catalyzed by the simple and easily accessible phosphonium salt **12** (Scheme 12).[40] Aliphatic, aromatic and heterocyclic aldehydes were converted under very mild conditions yielding the corresponding cyanohydrin trimethylsilyl ethers in good to excellent yields. In the case of α,β-unsaturated aldehydes the exclusive formation of the desired product was observed. If reactants with



Scheme 11. Formation and coordination mode of the DMF/phosphonium salt **11** complex.



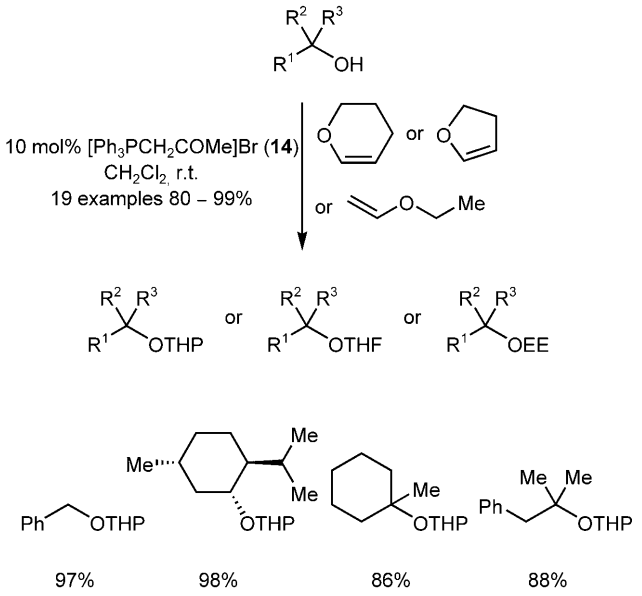
Scheme 12. Cyanosilylation of aldehydes catalyzed by **12** and selected examples.



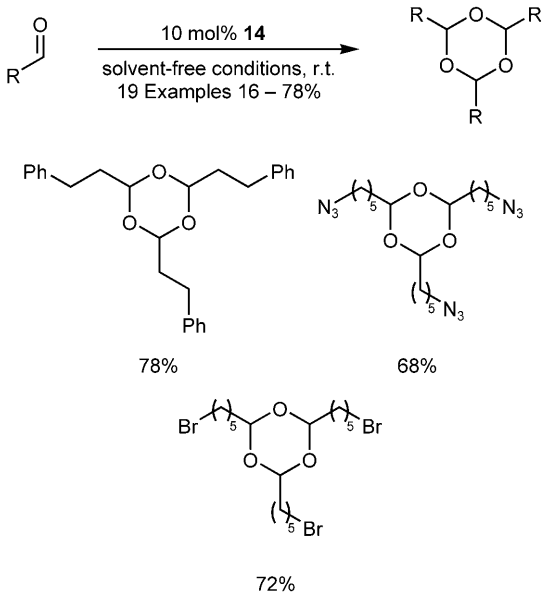
Scheme 13. Cyanosilylation of aldehydes catalyzed by **13** and selected examples.

free hydroxy or amine functions were employed the use of 2 equivalents of TMSCN was required. However, catalyst **12** proved to be inconvenient for the conversion of ketones with TMSCN due to the very long reaction times needed.

Tian et al. tested several readily available phosphonium salts as catalysts for the cyanosilylation of ketones.[41] The catalytic activity of the employed salts was closely associated with the nature of both phosphonium cation and counterion, e.g., the conversion of 2-heptanone with TMSCN in the presence of 5 mol% of either **12** or benzyltriphenylphosphonium bromide gave the corresponding cyanohydrin silyl ether in poor yields ($\leq$5%). However, when benzyltriphenylphosphonium chloride (**13**) was used as a catalyst instead of the bromide the desired product was isolated in 92% yield. Catalyst loadings as low as 1 mol% orf **13** were sufficient to transform a wide range of acyclic and cyclic ketones to the corresponding cyanohydrin silyl ethers in excellent yields (Scheme 13). Remarkably, as for the conversion of α,β-unsaturated aldehydes, only 1,2-addition was observed for unsaturated ketones. The authors suggest a double activation mechanism in which the Lewis acidic phosphonium cation coordinates to the carbonyl group of the ketone and thereby increases its electrophilicity. On the other hand IR spectroscopic experiments imply a Lewis basic activation of TMSCN by the counterion Cl^-.



Scheme 14. Protection of alcohols as THP, THF and EE ethers and selected examples.

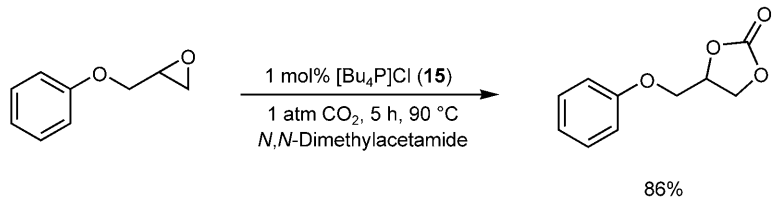


Scheme 15. Cyclotrimerisation of aldehydes catalyzed by **14** and selected examples.

3 C–O and C–N Bond-Forming Reactions

2-Tetrahydropyranyl (THP) and 2-ethoxyethyl (EE) are two of the most versatile protecting groups for alcohols in organic synthesis. They are inexpensive, easy to introduce, stable to most non-acidic reagents and easy to remove.[42] Hon et al. developed a useful protocol for the protection of alcohols as THP, EE and tetrahydrofuranyl (THF) ethers under very mild conditions (Scheme 14).[43] The reaction of primary, secondary and tertiary alcohols with the corresponding alkyl vinyl ether catalyzed by acetonyltriphenylphosphonium bromide (**14**) gave the protected alcohols in good to excellent yields. The same catalyst can be applied to cleave the THP, THF and EE ethers to the corresponding alcohols in methanol at room temperature with equal efficiency.[43]

Hon et al. also discovered that acetonyltriphenylphosphonium bromide (**14**) is an effective catalyst for the cyclotrimerization of aldehyds bearing a variety of functional groups under solvent-free conditions at room temperature (Scheme 15).[44]

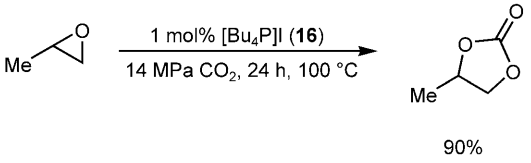


Scheme 16. Addition of CO_2 to 2-phenoxymethyloxirane catalyzed by **15**.

Transformations utilizing carbon dioxide as an easily available and renewable carbon source are receiving increasing attention.[45] The reaction with oxiranes to produce cyclic carbonates as raw materials, e.g., for polycarbonates, is of particular interest.[46] Several reports on the use of phosphonium halides as homogeneous as well as immobilized catalysts for the conversion of oxiranes with carbon dioxide have been published.[47–50] Nishikubo et al. investigated the onium salt-catalyzed conversion of 2-phenoxymethyloxirane with CO_2. Under mild conditions using tetrabutylphosphonium chloride (**15**) as a catalyst they obtained the respective product in 86% yield (Scheme 16).[48] Depending on the degree of introduction and the solvent, the polymer-supported phosphonium salt gave slightly better results.

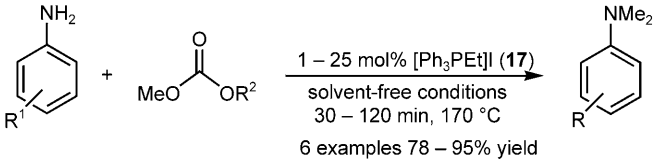
Sakakura et al. reported the phosphonium salt-catalyzed selective conversion of propylene oxide to the corresponding cyclic carbonate under supercritical CO_2 conditions.[50] In the presence of tetrabutylphosphonium iodide (**16**) they obtained the desired product in 90% yield and 99% selectivity (Scheme 17). Polyfluoroalkylphosphonium iodides gave similar yields but provided a more convenient catalyst recycling. However, upon immobilization of **16** onto a silica support, a dramatic enhancement of catalytic activity compared to the simple salt **16** was observed.[49] While in the presence of 1 mol% of **16** the yield of the desired product was 5% after 1 h, it was quantitative after the same period of time using the silica-supported analogue. The observation of this large cooperative effect between the catalyst part and the solid support is remarkable, since usually the catalytic activities of homogeneous catalysts decrease upon immobilization.

Dialkyl and unsymmetrical methyl alkyl carbonates are substitutes for highly noxious alkyl halides, dialkyl



Scheme 17. Addition of CO_2 to propylene oxide catalyzed by **16**.

sulfates and phosgene in a variety of reactions.[51] Selva et al. employed unsymmetrical carbonates as methylating agents of primary aromatic amines in the presence of Lewis acidic ammonium and phosphonium salts, respectively.[52] Ethyltriphenylphosphonium iodide (**17**) proved to be a particularly efficient catalyst for the *N*,*N*-dimethylation of various substituted anilines (Scheme 18). At 170 °C the reaction times

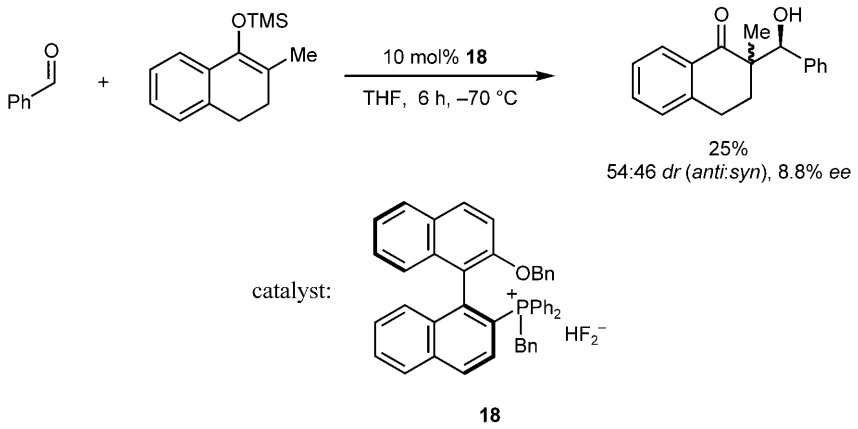


Scheme 18. *N*,*N*-Dimethylation of aniline derivatives catalyzed by **17**.

were short and the desired products were obtained in good to excellent yields and selectivities. Even if most of the results were obtained in the presence of substoichiometric amounts of **17** (25 mol%), the authors showed that quantitative conversions with lower catalyst loadings (10 mol%) are also possible. Performed IR spectroscopic investigations indicated that the aniline derivatives are activated by interactions with the Lewis acidic phosphonium salt.

4 Asymmetric Transformations

Although phosphonium salts catalyze several fundamental reactions in organic synthesis and are well-known phase-transfer catalysts, it is rather curious that only scattered asymmetric transformations using chiral phosphonium salts have been reported so far. Based on their work on aldol reactions catalyzed by the achiral phosphonium salt **9**, Shioiri et al. designed several chiral binaphthyl-based phosphonium hydrogen difluoride catalysts.[35] The chiral phosphonium salts were tested in the model reaction shown in Scheme 19. Under similar reaction conditions (DMF, −50 °C) as previously reported for the reaction catalyzed by **9**, the yields and diastereoselectivities ob-

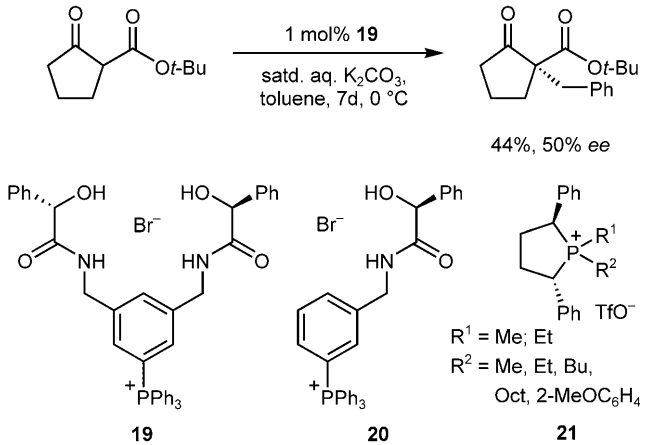


Scheme 19. Asymmetric aldol reaction catalyzed by **18**.

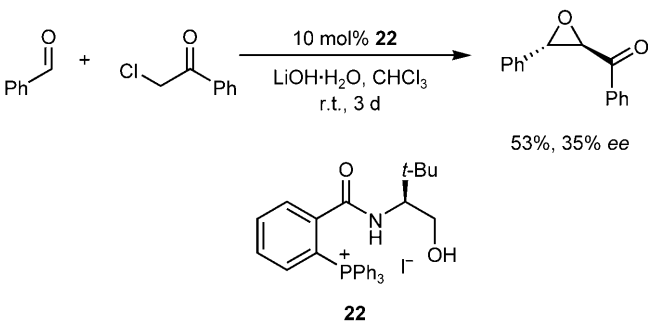
served were lower. Moreover, the enantiomeric efficiency was very poor ($\leq$5% *ee*). Replacement of DMF by THF or diethyl ether resulted in even lower yields and diastereoselectivities, though a slightly better enantioselectivity for the *E*-isomer was observed. The best result in respect to enantioselectivity was obtained with catalyst **18**.

In 1998 Manabe et al. reported the asymmetric phase-transfer benzylation of *tert*-butyl 2-oxocylopentanecarboxylate promoted by phosphonium salt **19** in moderate yield with encouraging levels of enantioselectivity (Scheme 20).[53] A higher reaction temperature (20 °C) leads to a decrease in enantioselectivity (38% *ee*) but improved the yield up to 80%. Comparable selectivity was obtained with a catalyst loading as low as 0.2 mol%. Unfortunately, other alkylating agents or different ester substituents afforded low enantioselectivities. Furthermore, salt **20** afforded the product in almost racemic form. This suggests that two mandelamide units are crucial to create an effective chiral environment for the substrate anion and hence for the selectivity of catalyst **19**. Recently, Toffano et al. reported the synthesis of a variety of chiral enantiopure phospholanium salts **21** and their application as phase-transfer catalyst in the benzylation of *tert*-butyl 2-oxocylopentanecarboxylate as well as the corresponding methyl ester.[54] At room temperature the conversion was quantitative after 2 h in the presence of 4 mol% of catalyst and potassium carbonate as a base. However, the obtained selectivities did not exceed 20% *ee*. It was verified that the presence of potassium carbonate did not modify the phospholane structure and, in particular, epimerization at the benzylic position could be ruled out. Other bases such as potassium or sodium hydroxide led to decomposition of the catalyst.

Bolm et al. employed a variety of chiral phosphonium salts as catalysts for the asymmetric Darzen reaction between benzaldehyde and 2-chloroacetophenone.[55] The best result was achieved with catalyst **22**, yielding 53% of the desired product with 35% *ee* (Scheme 21). The amide function, a bulky substituent in the α-position as well as the absence of a substituent in the β-position were crucial to obtain selectivities >30% *ee*. A further increase of steric demand of the substituent in the α-position, namely the introduction of an adamantyl moity, led to a decrease in



Scheme 20. Asymmetric phase-transfer benzylation.

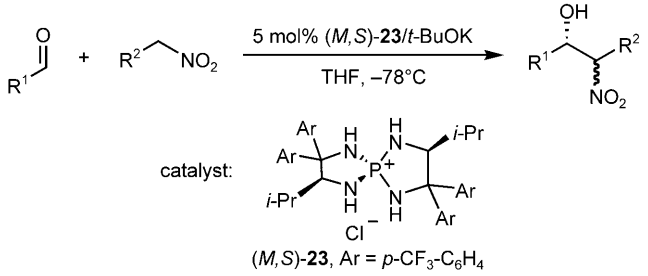


Scheme 21. Asymmetric Darzen reaction.

chemical yield to 13%. However, the influence on the selectivity was only marginal (36% *ee*).

Ooi and co-workers reported a highly selective asymmetric direct Henry reaction catalyzed by chiral *P*-spiro-tetraaminophosphonium salt (*M,S*)-**23** (Table 3).[56] α,β-Unsaturated and aromatic aldehydes were converted with different nitroalkanes in the

Table 3. Asymmetric direct Henry reaction.

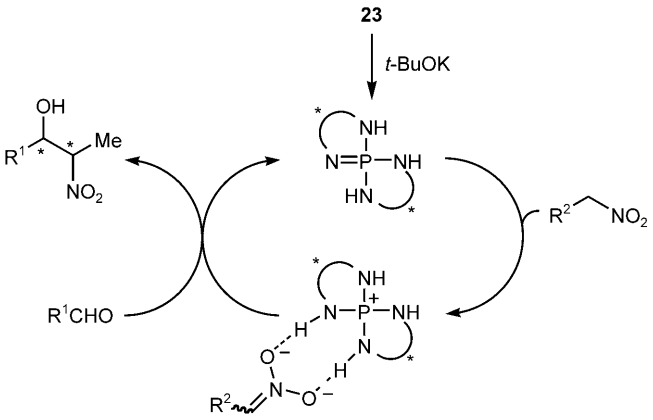


R^1	R^2	Time [h]	Yield [%]	*dr* (*anti*:*syn*)	*ee* [%]
Ph	H	8	90	–	94
Ph	Me	8	93	>19:1	97
Ph	Et	8	78	13:1	96
o-F-C_6H_4	Et	5	94	>19:1	96
p-F-C_6H_4	Et	9	91	>19:1	97
p-Cl-C_6H_4	Et	9	95	>19:1	97
p-Me-C_6H_4	Et	24	90	>19:1	97
1-naphthyl	Et	8	84	>19:1	96
2-furyl	Et	6	96	>19:1	97
(*E*)-PhCH=CH	Et	21	74	>19:1	99
$Ph(CH_2)_2$	Et	24	76	4:1	93
$Me(CH_2)_7$	Et	24	77	4:1	94

presence of catalytic amounts of salt (*M,S*)-**23** to the corresponding nitro alcohols. The products were obtained in very good yields with high diastereo- and excellent enantioselectivities. The catalyst loading could be reduced to 1 mol% without any effect on the selectivity although a longer reaction time was required. Comparable enantioselectivities but lower diastereoselectivites were observed for the conversion of aliphatic aldehydes.

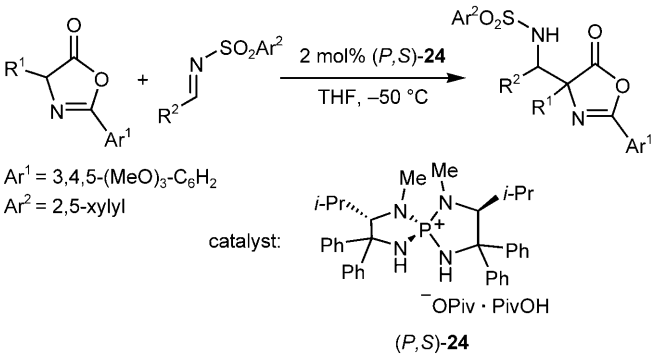
The authors postulate the deprotonation of the nitroalkane by the triaminoiminophosphorane generated from (*M,S*)-**23** and *t*-BuOK (Scheme 22). Since nitronate anions are bidentate hydrogen-bonding acceptors, the formation of a structured ion-pair is proposed allowing the highly stereoselective addition to aldehydes. This hypothesis was partially supported by NMR studies.

The same group employed the chiral tetraaminophosphonium carboxylate (*P,S*)-**24** as the catalyst in direct Mannich-type reactions (Table 4).[57] The conversion of a variety of azlactones with sulfonyl imines gave the corresponding Mannich adducts in excellent



Scheme 22. Postulated mechanism for the asymmetric direct Henry reaction catalyzed by **23**.

Table 4. Asymmetric direct Mannich-type reaction of azlactones.



R^1	R^2	Time [h]	Yield [%]	*dr* (*anti*:*syn*)	*ee*[a] [%]
$PhCH_2$	Me	12	91	4.5:1	92
$PhCH_2$	$CH_3(CH_2)_7$	20	92	6.6:1	96
$PhCH_2$	CH_2=$CH(CH_2)_8$	21	99	7.6:1	96
$PhCH_2$	$PhCH_2OCH_2$	14	98	5.3:1	95
$PhCH_2$	$PhCO_2CH_2$	24	88	12:1	93
$PhCH_2$	$(CH_3)_2CHCH_2$	17	94	4.4:1	95
$PhCH_2$	*c*-Hex	37	98	2.3:1	90
$(CH_3)_2CH_2$	$PhCH_2CH_2$	15	99	7.8	96
CH_3OCH_2	$PhCH_2CH_2$	14	97	3.1	90

[a] Enantiomeric excess for the *syn*-isomers.

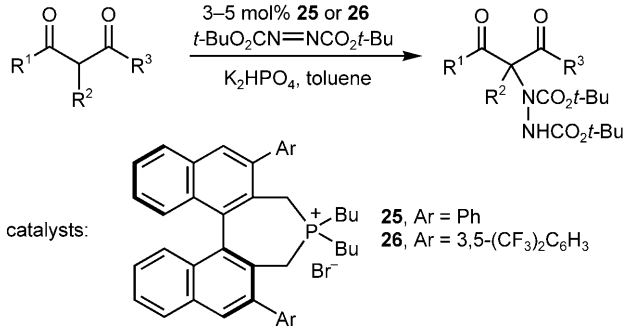
yields, moderate diastereoselectivities and excellent enantioselectivities for the *syn*-isomers. The enantioselectivity strongly depends on the *P*-spiro chirality and the aryl substituents. The diastereomerically pure *syn*-adducts can easily be converted into the corresponding α,β-diamino acids in very good yields and without the loss of enantiopurity.

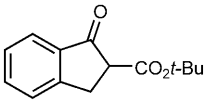
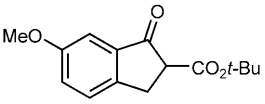
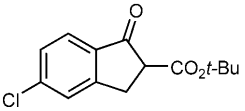
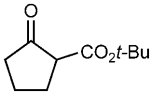
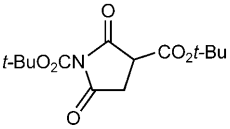
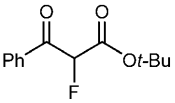
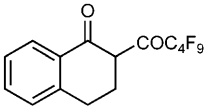
In the proposed working hypothesis the carboxylate anion acts as a base and deprotonates the azlactone in the initial step of the catalytic cycle. The thus formed anion subsequently coordinates to the chiral

tetraaminophosphonium cation which acts as a bidentate hydrogen-bonding donor followed by the addition to the imine. The formed phosphonium sulfonamide could be protonated by carboxylic acid to regenerate the catalyst.

Recently Maruoka et al. employed binaphthyl-modified quaternary phosphonium salts **25** and **26** as catalysts for the asymmetric amination of β-keto esters (Table 5).[58] They obtained the desired products in excellent yields and enantioselectivity. For the first time high levels of asymmetric induction were achieved when using simple chiral tetraalkylphosphonium salts as catalysts. In general, the use of K_2CO_3 or lower catalyst loadings results in a decrease of enantioselectivity. The use of an excess amount of base or azodicarboxylate increases the reaction rate and yield, respectively, with only a marginal influence on the selectivity. The best results were obtained with five-membered cyclic β-keto esters. Under modified reaction conditions the conversions of an acyclic β-keto ester and a six-membered cyclic β-diketone were possible. However, the desired products were obtained in lower yield and/or selectivity even after long reaction times (up to 4 d).

Table 5. Asymmetric amination of β-dicarbonyl compounds.[a]



Substrate	Conditions [°C, h]	Yield [%]	*ee* [%]
	−20, 14	99	91
	−40, 70[b]	97	90
	−20, 22	99	89
	−40, 16[b]	99	95
	−20, 40[c]	99	92
	−40, 84[b,d]	99	73
	−40, 96[b,c]	75	88

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv. of di-*tert*-butyl azodicarboxylate in the presence of 3 mol% of **25** and 1 equiv. of K_2HPO_4 in toluene under the given reaction conditions.
[b] 5 equiv. of K_2HPO_4 were used.
[c] 5 mol% of **26** and 10 equiv. of azodicarboxylate were used.
[d] 5 equiv. of azodicarboxylate were used.

5 Conclusion

This review has shown that catalytic amounts of phosphonium salts can catalyze a variety of important organic reactions. Even if there is a lack of information on the mechanism for most of the described reactions, it is very likely that the activation of the substrates can be attributed to the Lewis acidic nature of the phosphonium salt catalysts. Hence, they are potential substitutes for many Lewis acidic metal catalysts. Recent examples also showed promising results in asymmetric transformations mediated by chiral phosphonium salts. The simple accessibility and the vast range of possibilities to introduce chirality (e.g., by using chiral phosphine ligands as precursors) allow a considerable latitude in designing chiral phosphonium salt catalysts. The scope of these catalysts is by far not fully evaluated yet. Future studies will undoubtedly expand the scope and utility of phosphonium salts as catalysts in organic synthesis.

Acknowledgements

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