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Taking Up the Cudgels for Perchlorates: Uses and Applications in Organic Reactions under Mild Conditions

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Metal perchlorates are compounds of great chemical interest since they possess some unique properties, such as high electronegativity and relatively low charge density, poor complexing ability, high solubility in various organic solvents, and kinetic stability under mild conditions. Besides providing polar media when dissolved in solvents, metal perchlorates have recently found wide employment as Lewis acid promoters in various organic transformations, both in the development of new techniques for known and widely used reactions and in promotion of new kinds of reactivity. This paper presents a general overview of the more recent uses of lithium, magnesium, zinc, and nickel perchlorates, underlining the fact that such perchlorates are quite safe chemical products under mild conditions.

Contents:

1. Introduction

The first perchlorate derivative, potassium perchlorate, was obtained in 1816 by Stadion,[1] while Serullas studied the preparation of other several perchlorates around 1830.[2] By 1860 various papers describing new syntheses of perchlorates and perchloric acid had appeared.[3] The explosive natures of certain perchlorates limited their study and use, however, and only at the end of the 19th century was the first plant for the commercial production of ammonium perchlorate constructed in Sweden, followed by the manufacture of sodium, ammonium, and potassium perchlorates in other countries.[4] The production of perchlorates reached its maximum during the World Wars, and after 1950 it increased again for their use as rocket propellants.[5] However, for a long time, the chemical community has avoided the use of metal perchlorates out of fear that they may act as explosives.[5] Nevertheless, Long[6] recently asserted that the rarity of consideration of perchlorates in commercial processes was due to "the mistaken association of lithium perchlorate with the oxidizing potential of perchloric acid and the pyrotechnic performances of ammonium perchlorate".

Lithium and magnesium perchlorates are dangerous if heated over their decomposition temperatures (300–500 °C)[6,7] in the presence of oxidizable materials or under highly acidic conditions. The National Fire Protection Association (NFPA) ranks magnesium perchlorate as barely hazardous for health and as an oxidizing product, but not as an explosive one, unlike perchloric acid and ammonium perchlorate.[8] Suppliers inform us that common metal perchlorates are stable under ordinary conditions of use and storage, but that contact with heat and reducing agents must be avoided.[9] In conclusion, the infrequent use of perchlorate salts under mild conditions in organic chemistry is mainly due to a bad name rather than a true chemical hazard.

Perchlorates are of great chemical interest and importance, on the other hand, because they possess several unique properties.[10,11] They have large degrees of ionic character; the perchlorate ion in fact has a very high electronegativity, which corresponds to a high solvation energy. This is a major factor in the high solubilities of most of perchlorates in water and in a large number of nonaqueous solvents.[11] Perchlorates generally show inertness toward oxidation or reduction. In fact, perchlorate reduction is extremely slow and can usually be observed only in concentrated strong acid.[10] The perchlorate ion also appears to be kinetically inactive as a chemical oxidizing agent in aqueous solution unless the solution is acidic and hot, and the same chemical stability is usually also observed in nonaqueous solvents.

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The high electronegativity, together with the relatively low charge density, results in poor complexing ability of the perchlorate ion,[12] and it is generally used when a non-complexing anion is required. Metal perchlorates can therefore act as powerful Lewis acids, with this character mainly being exploited to activate bidentate compounds.

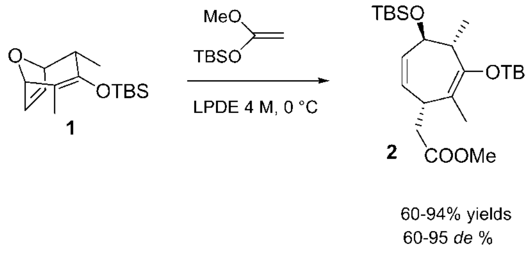
Of the metal perchlorates to have found application in organic chemistry, the most commonly employed are $LiClO_4$, $Mg(ClO_4)_2$, $Zn(ClO_4)_2\cdot 6H_2O$, and $Ni(ClO_4)_2\cdot 6H_2O$. Here we report an overview of recent applications of these salts in various organic transformations.

2. Lithium Perchlorate in Diethyl Ether (LPDE): An Unconventional Solvent

Thanks to its high solubility in organic solvents, lithium perchlorate has been widely employed to obtain polar media that allow many otherwise difficult synthetic transformations, such as pericyclic reactions, Mannich-type reactions, etc., to be carried out under mild conditions.[13]

The most widely used system is a concentrated solution of $LiClO_4$ in diethyl ether. The first successful applications of this unconventional solvent (5.0 M LPDE), by Grieco, date back to the beginning of the 1990s, and significant employment of this medium occurred afterwards. Since two exhaustive reviews have recently appeared in the literature,[13] here we report only a few more recent applications.

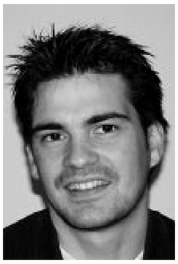
Grieco[14] reported the direct opening of oxabicyclo[3.2.1]octenes **1** (Scheme 1) at the bridgehead on treatment with silyl ketene acetals in LPDE (4.0 M), giving the highly functionalized cycloheptadienes **2**, which can be fur-



Scheme 1.

Giuseppe Bartoli graduated from the University of Bologna in 1967 with a Laurea in Industrial Chemistry. He was Assistant Professor of Organic Chemistry at the University of Bari (Italy) from 1968, moving to the University of Bologna (Italy) as Associate Professor and then to the University of Camerino in 1986 as Full Professor. In 1993 he returned to the University of Bologna, where he is currently Professor of Organic Chemistry. Since 2001 he has held the position of Head of the Department of Organic Chemistry "A. Mangini". His research interests include studies on the reactivity of organometallic compounds with aromatic systems, the use of dianions derived from enamino carbonyl compounds, the stereoselective reduction of various classes of ketones, and the development of new Lewis acid systems.

Manuela Locatelli attended the University of Bologna, where she graduated in Chemistry in 2002 under the supervision of Prof. Pier Giorgio Cozzi. She enrolled in the Science Chemistry doctoral program of Science Chemistry at Bologna, conducted graduate work under the supervision of Prof. Giuseppe Bartoli, and received her Ph.D. in June 2006. Her research activity is focused on organic synthesis, especially in the use of metallic perchlorates as Lewis acid promoters in various organic reactions.

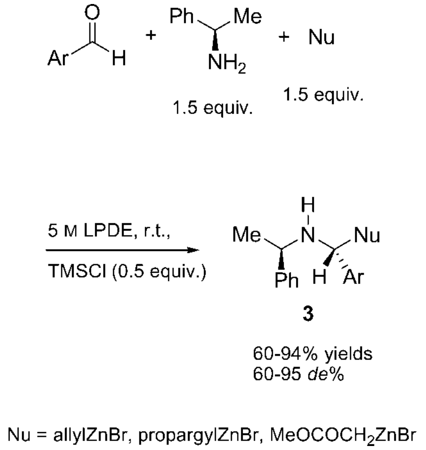


Paolo Melchiorre obtained his B.Sc. degree in Chemistry from Bologna University in 1999. In 2002 he spent eight months in the research group of Prof. K. A. Jørgensen at the "Center for Catalysis", Århus University, Denmark, working on asymmetric organocatalysis. In 2003 he received his Ph.D. under the supervision of Prof. A. Umani–Ronchi, Bologna University. Then he joined the research group of Prof. G. Bartoli at Bologna University. His current scientific interests are focused on the development of new asymmetric organo– and metal-catalyzed processes.

Letizia Sambri graduated from the University of Bologna in 1993 with a Laurea in Industrial Chemistry and she obtained her Ph.D. degree in 1998 in the group of Professor Bartoli. During her thesis she spent a research period at the University of Nijmegen (NL) in the group of Prof. Zwanenburg. Since 2000 she has been Assistant Professor at the Department of Organic Chemistry, University of Bologna. Her research interests include the application of Lewis acid activators in organic reactions, in particular the development of new methods for the synthesis of useful intermediates.

ther manipulated for use in natural product syntheses. The bridgehead opening reaction has been employed in the construction of the C(19)–C(27) fragment of Rifamycin S.[14]

Saidi[15] described a highly diastereoselective one-pot, three-component method for the preparation of several secondary amines and amino esters. Treatment of aliphatic or aromatic aldehydes with chiral amines and functionalized organozinc reagents in the presence of trimethylsilyl chloride (TMSCl) in LPDE (5 M) produces *N*-alkylamino esters or *N*,*N*-dialkylamines **3** in good yields and with high diastereoselectivities (Scheme 2).



Scheme 2.

In addition, Saidi[16] also developed a new technique for the direct conversion of epoxides **4** into α-hydroxyphosphonates **5** by treatment with a trialkylphosphite in LPDE (5 M) (Scheme 3). The reaction is highly chemoselective and gives excellent yields under mild and neutral conditions.

3. Perchlorate Salts as Lewis Acids

In the past few years, metal perchlorates have been widely exploited as Lewis acid promoters in various organic transformations, such as esterifications, protection/deprotection methods, Michael and ring-opening additions, condensation reactions, α-halogenation of 1,3-dicarbonyl compounds, and synthesis of *tert*-butyl ethers and ethyl carbonates, which is detailed in the microreview. Moreover, because of growing concerns about the effects of organic solvents on the environment, most of these methodologies have been developed for operation under solvent-free conditions (SFCs) and in several cases the catalyst can be recycled, meeting some important challenges of sustainable chemistry.[17]

Perchlorate salts have proven to be very effective Lewis acids and, in particular, they have shown marked ability to activate chelating compounds such as, for instance, 1,3-dicarbonyl systems.[18] They have therefore found considerable application in the development of new reaction methodologies.

Of the perchlorates, the most widely employed has probably been the lithium salt, followed by magnesium, zinc, and nickel perchlorates. Even $Fe(ClO_4)_3$[19] and $Sc(ClO_4)_3$[20] have found some applications, but to lesser extents, probably owing to their higher costs and to difficulties in their preparation.

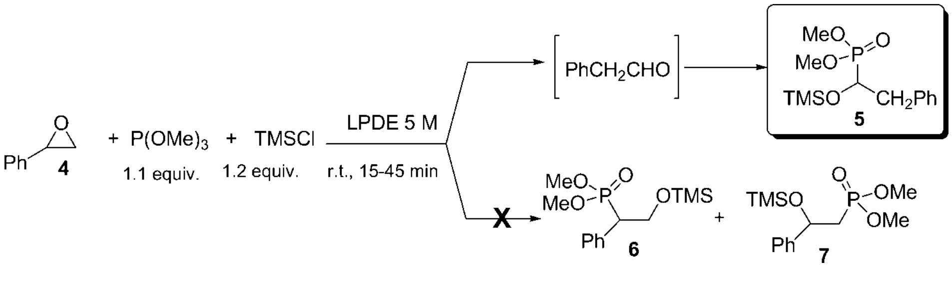
In some cases different perchlorates are able to promote the same kind of reaction: the first applications have usually involved $LiClO_4$ and the activity of other cations has been explored afterwards. We choose to divide this microreview into sections devoted to the individual metal perchlorate rather than to the single kind of transformation, in order better to illustrate the possible applications of each single salt. Moreover, a comparison of the activity of each perchlorate is illustrated along the methodology description.

3.1. Lithium Perchlorate

Besides its use in forming polar solvents, $LiClO_4$ has found exploitation as a co-catalyst in various Friedel–Crafts acylations and also as an efficient Lewis acid.

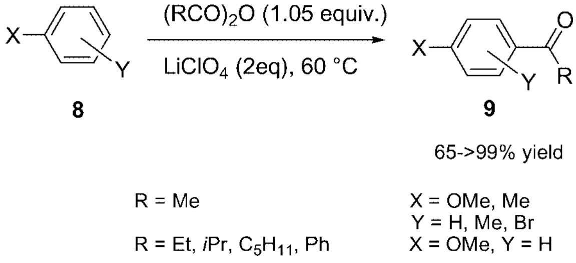
Our first interest in perchlorates just concerned Friedel–Crafts acylation. Subsequently to its classical formulation with $AlCl_3$ as the catalyst, several approaches based on the employment of catalytic amounts of metal triflates have been developed. In many of them the addition of large amounts (2–10 equiv.) of $LiClO_4$ as the promoter accelerates the acylation process and increases the yields. However the action of $LiClO_4$ seems to be limited to enhancing the efficiency of the metal triflate catalyst, and it has in fact been reported that the reaction does not work in the presence of $LiClO_4$ alone.[21]

In contrast, we were able to set up a new methodology for the F.C. acylation of activated substrates in which $LiClO_4$ was itself able to act as an efficient promoter.[22] In fact, on treatment of an activated benzene **8** with an equimolecular amount of anhydride in the presence of



Scheme 3.

2 equiv. of $LiClO_4$ at 60 °C under SFCs, a smooth addition occurs, giving the desired product **9** in good to excellent yields (Scheme 4).



Scheme 4.

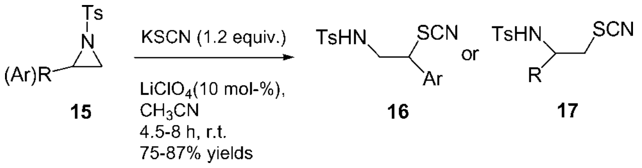
By NMR analysis we observed that $LiClO_4$ strongly coordinates to the anhydride under these conditions, thus promoting the electrophilic attack on the benzene ring. Unfortunately, 2 equiv. of Lewis acid are required, probably since the forming products can compete with $(RCO)_2O$ to coordinate $LiClO_4$. However, it can be recovered by filtration, reactivated, and reused without loss of activity.

The ability of $LiClO_4$ to coordinate chelating compounds was exploited in the almost quantitative acetylation of various alcohols and phenols with an excess of acetic anhydride in the presence of 10 mol-% of $LiClO_4$ as the catalyst.[23] As discussed later on in the text, this kind of reaction can be accomplished more efficiently and with much smaller amounts of catalyst with perchlorates other than lithium.

The development of mild and selective methods for the protection of amine groups is important in organic synthesis. In particular, the protection of arylamines as *N*-Boc derivatives is also difficult in the presence of a catalyst, since various side reactions often occur.[24] Basic catalysis has generally been employed and only few methods using a Lewis acid are available.[25,26] As reported below, the first easily available Lewis acid exploited in such a transformation was $Zn(ClO_4)_2{\cdot}6H_2O$ (5 mol-%).[26] Subsequently, a similar procedure involving the use of $LiClO_4$ appeared in the literature. In the presence of $LiClO_4$ (20 mol-%), various functionalized aromatic amines, hydroxylamines, hydrazines, and sulfonamides could be protected as their *N*-Boc derivatives in high yields (74–90%) and relatively short times (5 h, room temp.).[27]

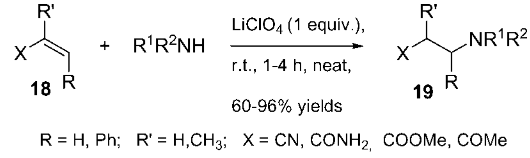
In recent years, Saidi has improved and developed the applications of $LiClO_4$ as a promoter in the epoxide ring-opening reactions that had been partially studied by Crotti and co-workers[28] during the 1990s. In the absence of solvent, $LiClO_4$ (even in its hydrate form) acts as the best perchlorate to catalyze the regioselective ring-opening of epoxides **10** with various nucleophiles such as amines,[29] thiols,[30] and cyanides[31] (Scheme 5). All the procedures work with various substrates under SFCs at room temperature.

Another ring-opening procedure, this time for aziridines, has been developed by Yadav and co-workers.[32] In the presence of $LiClO_4$ (10 mol-%) a regioselective addition of thiocyanate to alkyl and aryl aziridines **15** occurs smoothly at room temp. in CH_3CN (Scheme 6).



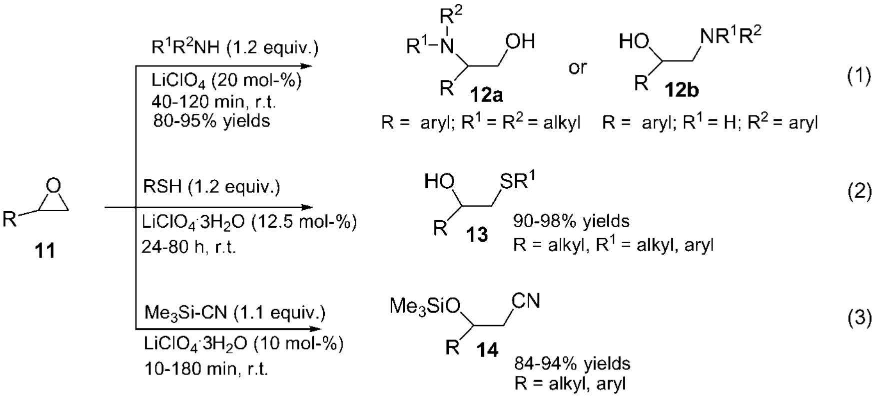
Scheme 6.

$LiClO_4$ also promotes the conjugate addition of several primary and secondary amines to α,β-unsaturated compounds **18** to provide β-amino esters, ketones, amides, and nitriles **19**, which are remarkably interesting products since some of them are precursors of β-amino acids (Scheme 7). The reaction proceeds under SFCs and $LiClO_4$ is required in stoichiometric amount, but it can be easily recovered and reused after reactivation.[33]



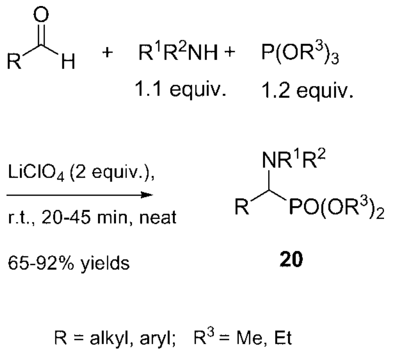
Scheme 7.

Finally, secondary and tertiary α-aminophosphonates **20** were obtained in good yields in three-component couplings of aldehydes with alkyl- (primary and secondary) and arylamines and trialkylphosphites in the presence of solid lith-



Scheme 5.

ium perchlorate under SFCs at room temperature[34] (Scheme 8). Even in this case, $LiClO_4$ can be easily recycled before reactivation.

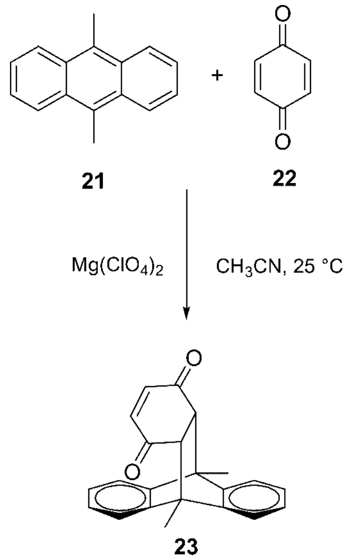


Scheme 8.

3.2. Magnesium Perchlorate

Lithium perchlorate has proven to be an efficient Lewis acid, but the amounts required to achieve high efficiency are often high and in some cases it is necessary to use it in equimolecular amount or even in excess. Other perchlorates, such as $Mg(ClO_4)_2$, have been found to be much more powerful than $LiClO_4$ in various applications.

As well as $LiClO_4$ in diethyl ether,[13] $Mg(ClO_4)_2$ also proved to be a very efficient catalyst in promoting Diels–Alder reactions between the anthracene **21** and *p*-benzoquinone derivatives such as **22** (Scheme 9).[35]

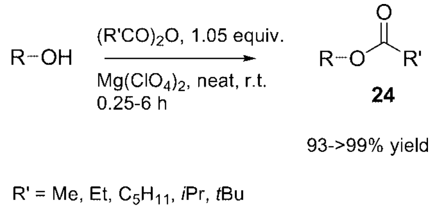


Scheme 9.

Another of the early applications of $Mg(ClO_4)_2$ in organic synthesis was the complexing of flavin analogues to form efficient photocatalysts for the oxidation of *p*-methoxybenzyl alcohol by oxygen under irradiation with visible light.[36]

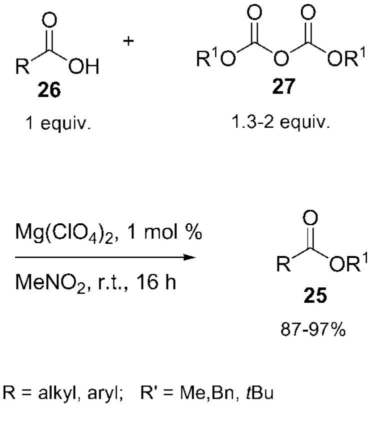
More recently, $Mg(ClO_4)_2$ has found various other applications.

The acylation of alcohols with anhydrides is one of the most routinely used transformations in organic synthesis, and it proceeds under both basic and Lewis acid catalysis. We found that magnesium perchlorate is one of the most active Lewis acids for such transformation: in fact, a trace amount of $Mg(ClO_4)_2$ (0.5–1 mol-%) can function as a powerful activator for acylation of alcohols with various anhydrides[37] as the acylating agent under SFCs, thus providing a simple methodology, which is very efficient in all parameters involved (Scheme 10). The $Mg(ClO_4)_2$-promoted methodology works with primary, secondary, and tertiary alkyl alcohols, and even deactivated substrates such as aromatic, benzylic, and allylic alcohols are converted into the desired esters **24** in very short times.



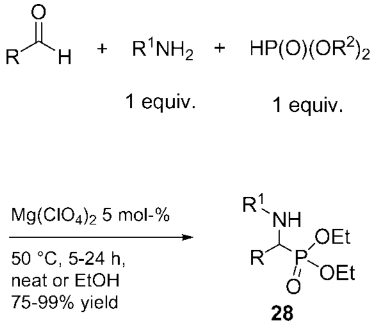
Scheme 10.

Various esters **25** have been obtained by Gooßen[38] through a decarboxylative esterification of alkyl and aryl carboxylic acids **26** with commercially available dialkyl pyrocarbonates **27** at room temperature in the presence of 1 mol% of $Mg(ClO_4)_2$ (Scheme 11). In most cases only volatile by-products are released, so the purification of the products becomes particularly easy. The authors claim that many sensitive functionalities are tolerated, even including phenol esters or free hydroxy and *N*-Boc groups.



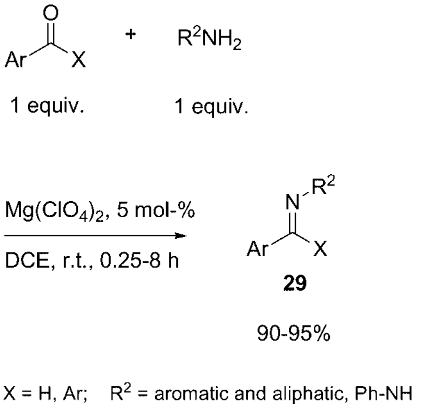
Scheme 11.

Magnesium perchlorate is also an efficient catalyst in various condensation reactions. Wu,[39] for instance, recently reported its application as a catalyst for the efficient synthesis of α-amino phosphonate **28** in three-component reactions involving aldehydes, amines, and diethyl phosphite under mild conditions (Scheme 12). α-Amino phosphonic acids, their phosphonate esters, and short peptides incorporating this unit are excellent inhibitors of a wide range of proteolytic enzymes. In addition, α-amino phosphonate derivatives have broad applications due to their antibacterial and antifungal activities, and also as inhibitors of phosphatase activity.[39]



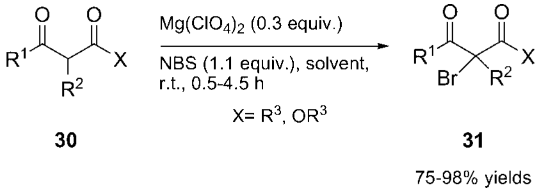
Scheme 12.

Magnesium perchlorate has been found to be an efficient catalyst in the synthesis of imines and phenylhydrazones **29** by condensation of carbonyl compounds with amines and phenylhydrazine, promoting high-yielding reactions at room temperature and in short times (Scheme 13).[40] The procedure is much better than the previously reported ones, and $Mg(ClO_4)_2$ is the most effective among various magnesium salts, with the condensation of poorly electrophilic carbonyl compounds with poorly nucleophilic amines affording imines in excellent yields.



Scheme 13.

The abilities of perchlorates to coordinate 1,3-dicarbonyl compounds have been exploited by Yang[41] for a mild and fast α-bromination of β-diketones and β-keto esters **30** with NBS (Scheme 14). The method was also extended to the α-chlorination and -iodination of 1,3-dicarbonyl compounds with NCS and NIS, respectively. This procedure allows convenient access to a variety of α-halogenated 1,3-dicarbonyl compounds, which are important intermediates in organic transformations.



Scheme 14.

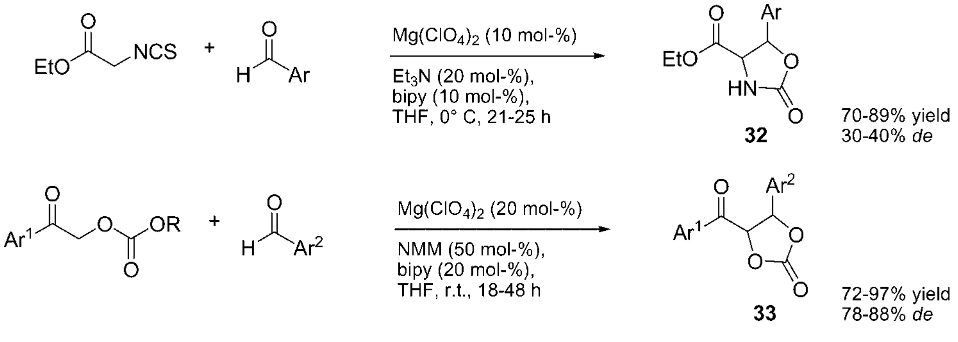
A few years ago, Willis and co-workers reported that $Mg(ClO_4)_2$, in combination with bipyridine and an amine, generates an effective catalyst for direct aldol additions of bidentate functionalized esters and ketones to aromatic aldehydes to give synthetically valuable products such as the protected β-hydroxy α-amino acids **32**[42] and the protected α,β-dihydroxy ketones **33**,[43] respectively (Scheme 15). More recently the same authors have proposed an enantioselective version of the first approach, as reported later on in the text.

In addition, $Mg(ClO_4)_2$ has been employed as a very efficient catalyst to achieve some unusual protection and deprotection reactions.

$Mg(ClO_4)_2$ in organic solvents acts as an extremely mild reagent for highly efficient repetitive Bpoc/Ddz removal during solid-phase peptide synthesis, even in the presence of the acid-labile thioxo amide moiety.[44] Bpoc removal from thioxo peptides with $Mg(ClO_4)_2$ in MeCN at 50 °C is fully compatible with the side-chain Boc protection.

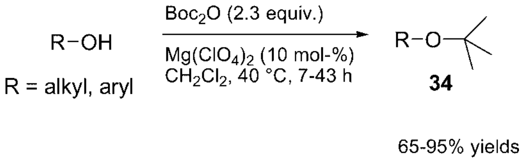
Finally, $Mg(ClO_4)_2$ promotes reactions between alcohols and dicarbonates.

Very recently we reported an unusual reaction through which to obtain aromatic and aliphatic *tert*-butyl ethers **34** by simple treatment of an alcohol with Boc_2O in the presence of a catalytic amount of $Mg(ClO_4)_2$ (Scheme 16).[45] This is a very important result since it represents the first general and simple methodology to afford *tert*-butyl ethers. The *tert*-butyl ether group is "one of the most underused alcohol protecting groups," although it is one of the few ethers stable under strongly basic conditions.[46] Its infre-



Scheme 15.

quent employment in organic synthesis is probably due to the conditions required for its introduction. Most of the known methodologies in fact require harsh conditions based on the reaction between an alcohol and isobutylene in the presence of a strong acidic catalyst. Moreover, the reaction involves the formation of a *tert*-butyl carbocation, thus precluding the application of these methodologies to the protection of aromatic alcohols, which predominantly undergo Friedel–Crafts alkylation.



Scheme 16.

The etherification process worked well with primary, secondary, benzylic, allylic, and homoallylic alcohols, many functional groups survived the protection process, and neither isomerization of the substrate nor racemization were observed. Notably, the reaction gave excellent results with a large variety of aromatic alcohols. Moreover, all side products of the reaction are volatile compounds, so that the purification step is very simple and convenient.

Therefore, and in view of the fact that an efficient procedure to cleave *tert*-butyl ethers has recently been reported,[47] a new route to the introduction of the *tert*-butyl ether moiety as a valuable alcohol protecting group is now available, providing simple means both for their formation and for their removal.

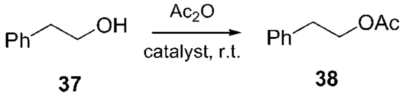
The reaction mechanism that affords *tert*-butyl ethers instead of the expected *tert*-butyl carbonate is still not completely clarified.[48] On the other hand, this anomalous reactivity is restricted to di-*tert*-butyl dicarbonate: reactions between alcohols and diethyl dicarbonate in the presence of catalytic amount of $Mg(ClO_4)_2$ in fact give the expected ethyl carbonate. The remarkable importance of organic carbonates in various chemical fields is well documented by the presence of a large number of patents and papers appearing in the literature. Organic carbonates indeed find employment as fuel additives, lubricating oils, herbicides, pesticides, plastics, solvents, and for medicinal and biological applications.[49] Moreover they can act as useful protecting groups for alcohols and phenols since they are more stable than the corresponding esters under basic conditions, so a very efficient methodology for the synthesis of aryl and alkyl ethyl carbonates **35** and **36** has been established (Scheme 17).[50] The method works at low temperature and under SFCs.

3.3. Zinc Perchlorate Hexahydrate

In the previously reported procedures, both $LiClO_4$ and $Mg(ClO_4)_2$ generally work better when completely anhydrous. However, the continuous demand for powerful Lewis acids efficient even in the presence of water prompted us to compare the activities of hydrate perchlorates with those of anhydrous lithium and magnesium perchlorate in various routinely used organic transformations.

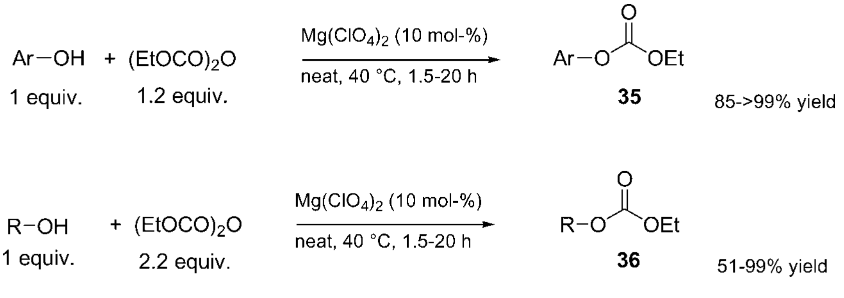
With regard to the acylation of alcohols, we found[51] $Zn(ClO_4)_2{\cdot}6H_2O$ to be much more powerful than $Mg(ClO_4)_2$ and $Bi(OTf)_3$, the most active of the metal triflates.[52] Table 1 gives a comparison of the activities of these catalysts in the acetylation of 2-phenylethanol (**37**): $Zn(ClO_4)_2{\cdot}6H_2O$ is at least ten times more powerful than either $Mg(ClO_4)_2$ or $Bi(OTf)_3$.

Table 1. Acetylation of 2-phenylethanol promoted by different catalysts.



Entry	Ac_2O (equiv.)	Catalyst/mol-%	Time/min	% Yield
1	1.05	$Mg(ClO_4)_2$/0.1	160	>99
2	1.05	$Zn(ClO_4)_2{\cdot}6H_2O$/0.1	10	>99
3	1.05	$Zn(ClO_4)_2{\cdot}6H_2O$/0.01	140	>99
4	10	$Bi(OTf)_3$/0.005	150	99
5	10	$Zn(ClO_4)_2{\cdot}6H_2O$/0.005	10	>99

On the basis of these preliminary results we developed a method for the acylation of alcohols promoted by trace amounts of $Zn(ClO_4)_2{\cdot}6H_2O$ (0.1–1 mol-%). The methodology is general and works with a large variety of substrates and anhydrides. The high efficiency of $Zn(ClO_4)_2{\cdot}6H_2O$ allows reactions between poorly reactive substrates such as sterically hindered tertiary alcohols and aromatic anhydrides to be performed. All the reactions are carried out at a 1:1.05 alcohol/anhydride ratio at temperatures ranging

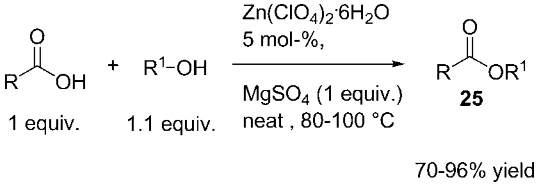


Scheme 17.

from 20 to 70 °C, with yields between 90 and 99% always being attained. These conditions are convenient both from a practical and from an economic point of view, since they avoid waste of reagents and allow a simple workup procedure.

In terms of atom economy, however, this esterification process is still far from perfect. In fact, the reaction between almost equimolecular amounts of a carboxylic acid and an alcohol should be the most straightforward and convenient way to prepare esters.

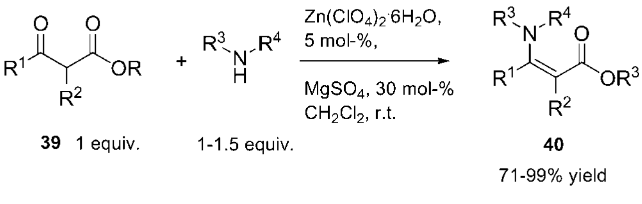
We found[53] that $Zn(ClO_4)_2{\cdot}6H_2O$ efficiently catalyzes esterification between nearly equimolar amounts of carboxylic acids and alcohols when used at 80–100 °C under SFCs in the presence of $MgSO_4$ (Scheme 18). The reaction works without solvent at relatively low temperatures, and the catalyst can be filtered off, regenerated in oven at 60 °C, and reused without loss of activity. Excellent results were obtained with a wide range of substrates, and various functionalities can tolerate the reaction conditions. To evaluate the application of the procedure to large-scale esterification, a reaction was scaled up to 100 mmol, giving almost the same results as the small-scale run (1 mmol).



Scheme 18.

Like the other metal perchlorates, $Zn(ClO_4)_2{\cdot}6H_2O$ can strongly coordinate 1,3-dicarbonyl compounds, so this ability has been widely exploited in the development of various different synthetic procedures.

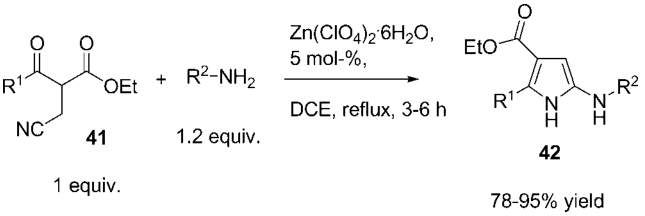
$Zn(ClO_4)_2{\cdot}6H_2O$ proved to be a very powerful catalyst for the condensation of primary and secondary amines with β-keto esters **39** to give *N*-substituted β-enaminoesters **40** (Scheme 19),[54] an important class of functionalized building blocks that can act as valuable intermediates for the synthesis of, for example, biologically active compounds such as α- and β-amino acids, γ-aminols, alkaloids, peptides, and heterocyclic derivatives. Even in this procedure, the addition of 30 mol-% of $MgSO_4$ is required to improve yields.



Scheme 19.

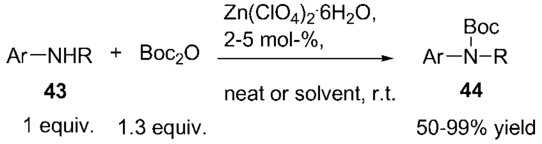
This methodology proved to be very efficient and in some cases superior to those reported previously: it works at room temp., and the catalyst can easily be recovered and recycled. Lhommet and co-workers have recently exploited this technique for the stepwise synthesis of complex chiral piperidines[55] and tetrahydropyridines.[56]

Moreover, a peculiar reactivity pattern was observed when the starting β-keto ester **41** bore a cyanomethyl group in the α-position (Scheme 20). In this particular case the addition of the amine occurs on the CN triple bond rather than on the C=O, and a subsequent annulation reaction gives aminopyrroles **42**.[57]



Scheme 20.

We exploited the high efficiency of $Zn(ClO_4)_2{\cdot}6H_2O$ in the protection of arylamines as *N*-Boc derivatives. Protection of the amino group is often required during the synthesis of peptides, amino acids, and other natural products, so various reagents and methodologies by which to introduce this protection by use of Boc_2O have been developed over the years. Most of them require the presence of a base and work well only with alkylamines; the analogous reactions of primary and secondary arylamines proceed sluggishly, owing to their reduced nucleophilicity, and various side reactions can occur. On the other hand, methods that use a Lewis acid catalyst to perform this protection are still rare. We reported the first example of an efficient protection methodology that employs $Zn(ClO_4)_2{\cdot}6H_2O$, a simple and mild Lewis acid, as the catalyst (Scheme 21).[26]

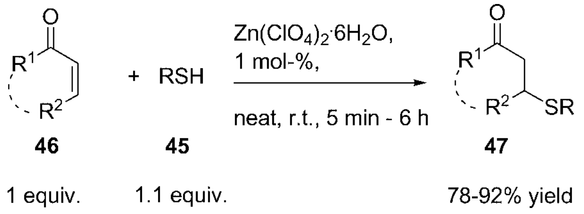


Scheme 21.

The reaction works with primary and secondary aromatic amines under mild conditions and the protecting agent is used only in a small excess. Reaction rates and yields are governed by the nucleophilicities of the amines. In particular, activated anilines give the Boc derivatives **44** in very good yields, while deactivated substrates, on the other hand, give the protected derivatives with acceptable results in view of their low reactivity. The protection reaction is chemoselective: the amine is exclusively protected in the presence of amide, acid, indole, and thiol groups.

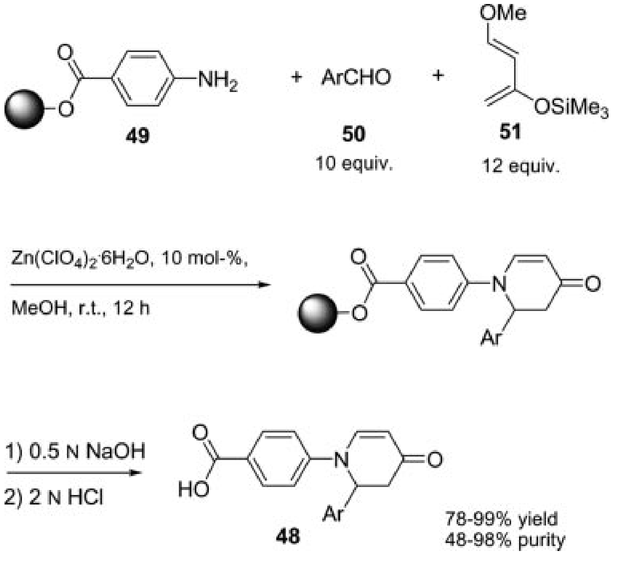
As previously reported in the $LiClO_4$ section, after this work a similar method based on $LiClO_4$ as the promoter was reported.[27]

Zn^{II} perchlorate hexahydrate has been found to be a new and efficient catalyst for conjugate addition of thiols to α,β-unsaturated ketones under solvent-free conditions at room temperature (Scheme 22).[58] Reactions of aryl, aryl-alkyl, and alkyl thiols **45** with cyclic and acyclic α,β-unsaturated ketones **46** take place to afford compounds **47** in good to excellent yields in short times. The rate of thiol addition is dependent on the electronic and steric natures of the enones and the thiols. When a substituent is present at the β-carbon of **46**, longer reaction times are required owing to the steric hindrance met by the conjugate addition. The addition of aryl thiols occurs more rapidly than that of alkyl ones.



Scheme 22.

Finally, $Zn(ClO_4)_2{\cdot}6H_2O$ has been employed to promote a one-pot, three-component reaction for the construction of structurally diverse 2,3-dihydropyridin-4-ones **48** on a soluble polymer support (Scheme 23).[59] The proposed aza Diels–Alder reaction involves either PEG-supported amine **49**, aromatic aldehydes **50**, and Danishefsky's diene (**51**), or PEG-supported aldehyde, aromatic amines, and Danishefsky's diene.

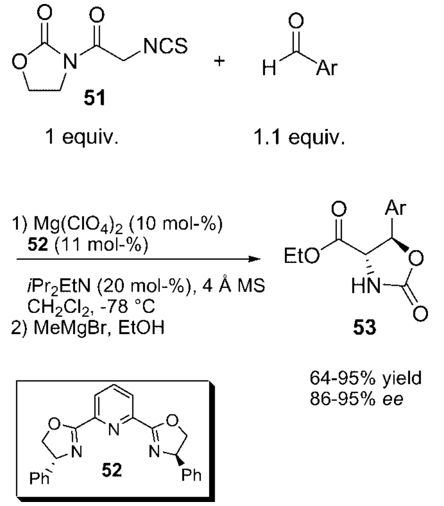


Scheme 23.

4. Perchlorate Salts as Lewis Acids in Enantioselective Syntheses: The Major Role of Nickel Perchlorate

Thanks to their highly ionic characters, perchlorate salts can be employed when a "naked" cation is necessary, and so some perchlorates have been exploited to form, with chiral ligands, chiral catalysts capable of coordinating bidentate substrates, in order to develop new methodologies for enantioselective reactions, such as conjugate additions, radical cyclizations, and 1,3 dipolar cycloadditions.

Moreover, asymmetric versions of previously reported reactions have also been achieved. This is the case in the direct synthesis of protected β-hydroxy α-amino acids starting from the oxazolidinone **51** as a glycine equivalent, proposed by Willis (Scheme 24).[60] The bipyridine employed in the achiral version[42] was exchanged with an appropriate enantiopure bidentate ligand, and the best results were obtained with the pyridine bis(oxazoline) (pybox) **52** and $Mg(ClO_4)_2$. The presence of iPr$_2$EtN as the base efficiently generates a chiral glycine enolate of **51**, which undergoes enantioselective addition to a range of aryl aldehydes to provide protected aryl β-hydroxy-α-amino acids **53** in good yields and with high enantioselectivities. Importantly, all of the catalyst components are commercially available and the reactions are simple to perform.

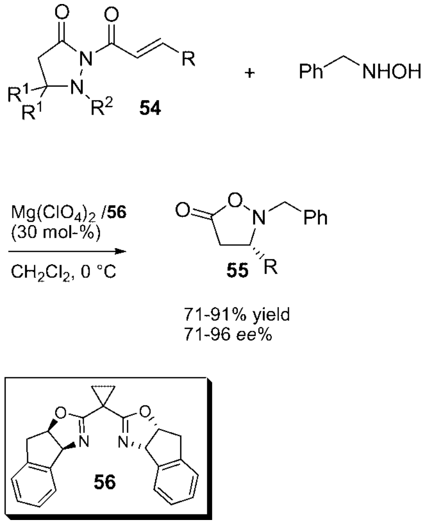


Scheme 24.

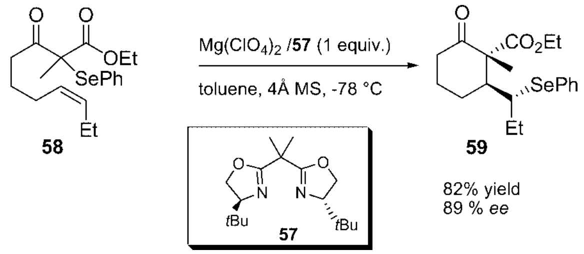
$Mg(ClO_4)_2$ was again the best choice to form a chiral Lewis acid to perform an enantioselective conjugate addition of hydroxylamine to pyrazolidinone acrylamides **54** for the synthesis of β-amino acid derivatives **55**. In this case the most suitable ligand proved to be the bisoxazoline **56** (Scheme 25).[61]

In a series of papers, Yang and co-workers found that $Mg(ClO_4)_2$ was the most suitable Lewis acid with which to form, with bisoxazoline **57**, a catalyst able to promote atom-transfer tandem radical cyclization reactions. A more recent example[62] involves the transfer of the PhSe group in a radical cyclization to construct a variety of monocyclic and bicyclic compounds with high yields and good enantioselectivities. An example is shown in Scheme 26.

In recent years, De Simoni and co-workers have studied the use of Ph-bisoxazolines **60** as chiral ligands for several perchlorates. In their more recent work[63] they found optimum conditions to obtain each of the four possible stereo-



Scheme 25.

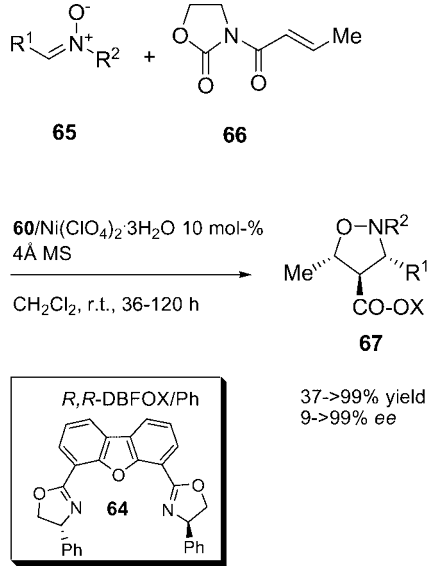


Scheme 26.

isomers of 3,4-disubstituted isoxazolidines **61** with good selectivity, through 1,3-cycloadditions between acryloyloxazolidinone **62** and diphenylnitrone **63** (Scheme 27).

A few years ago, Kanemasa and co-workers proposed the complex derived from the (*R*,*R*)-4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) (*R*,*R*-DBFOX-Ph) ligand (**64**) and Ni(ClO$_4$)$_2$·6 H$_2$O as an excellent chiral Lewis acid catalyst in various 1,3-dipolar cycloadditions and conjugate additions.

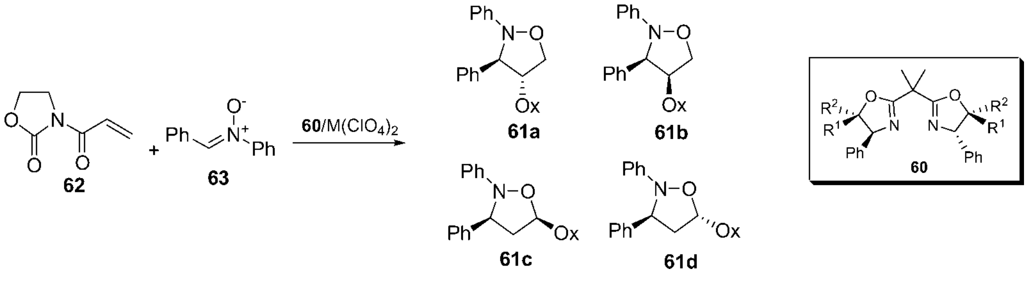
In the presence of the complex **64**/Ni(ClO$_4$)$_2$·3 H$_2$O (10 mol-%), for instance, 1,3-dipolar cycloadditions between nitrones **65** and 3-(alk-2-enoyl)-2-oxazolidinones **66** occur with high diastero- and enantioselectivities to give *trans*-3,4-isoxazolidines **67** in high yields (Scheme 28).[64]



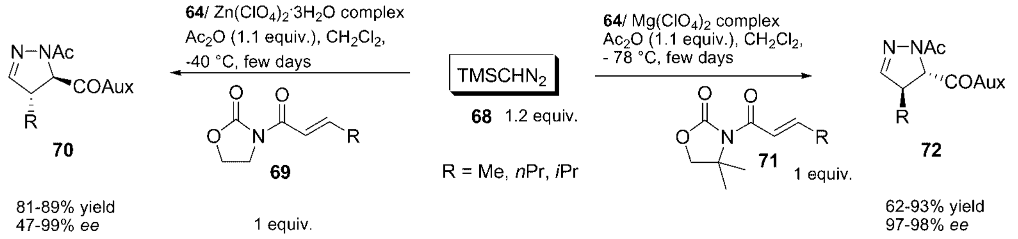
Scheme 28.

Although nickel perchlorate proved to be the best choice in various reactions, other perchlorates such as Mg(ClO$_4$)$_2$ and Zn(ClO$_4$)$_2$·6 H$_2$O can also form very efficient chiral catalysts with **64**. In fact, the first effective enantioselective 1,3-dipolar cycloaddition reactions between trimethylsilyldiazomethane (**68**) and alkenes were achieved in the presence of these chiral complexes (Scheme 29).[65] The reaction of 3-crotonoyloxazolidin-2-one **69** catalyzed by **64**/Zn(ClO$_4$)$_2$·3 H$_2$O at –40 °C produces (4*S*,5*R*)-1-acetyl-5-(2-oxo-3-oxazolidinylcarbonyl)-2-pyrazoline **70** in 99% *ee*, while the reaction of 3-crotonoyl-4,4-dimethyl-2-oxazolidinone **71** catalyzed by **64**/Mg(ClO$_4$)$_2$ at –78 °C gives (4*R*,5*S*)-1-acetyl-5-(4,4-dimethyl-2-oxo-3-oxazolidinylcarbonyl)-2-pyrazoline **72** in 97% *ee*. An almost complete switch of enantioselectivity has thus been achieved simply by the addition of substituents to the same achiral chelating auxiliary. Diazoalkane cycloadditions to alkenes produce 1-pyrazolines as the initial cycloadducts, and these, not usually being very stable, undergo spontaneous 1,3-proton migration to afford thermodynamically more stable 2-pyrazoline derivatives.

The chiral catalyst **64**/Ni(ClO$_4$)$_2$·3 H$_2$O was also employed by Kanemasa and co-workers to carry out various asymmetric conjugate additions of nucleophiles to α,β-un-

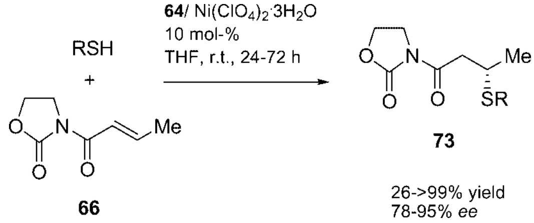


Scheme 27.



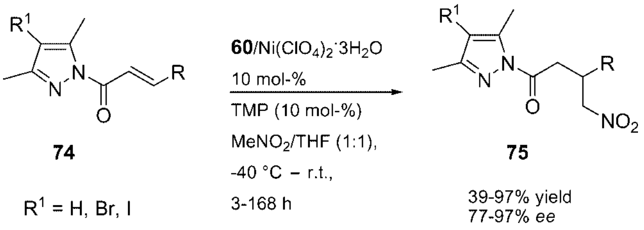
Scheme 29.

saturated carbonyl acceptors. They described the first examples of enantioselective thiol conjugate additions to 3-(alk-2-enoyl)-2-oxazolidinone **66** catalyzed by a chiral Lewis acid.[66] Among a variety of DBFOX/Ph complexes examined as chiral catalysts, the **64**/$Ni(ClO_4)_2$·3 H_2O complex was exceptionally effective (Scheme 30). Although the magnesium and zinc complexes prepared from DBFOX/Ph ligand by treatment with $Mg(ClO_4)_2$, $Zn(ClO_4)_2$·6 H_2O, $Zn(OTf)_2$, or ZnI_2 showed satisfactory catalytic activity, the enantioselectivities observed in the catalyzed thiol conjugate additions were relatively poor. On the other hand, metal complexes prepared from the perchlorates of copper(II), iron(II), and manganese(II) ions showed only a low catalytic activity.



Scheme 30.

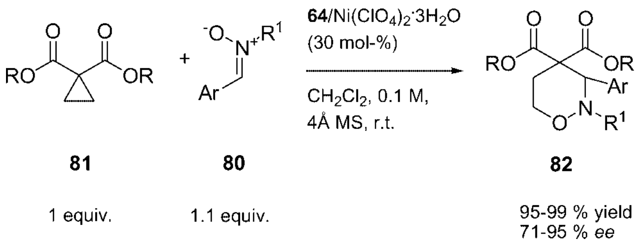
The same system was exploited for catalytic enantioselective Michael addition reactions of nitromethane to 1-crotonoyl-3,5-dimethylpyrazoles **74** (Scheme 31). In this procedure, both α,β-unsaturated carbonyl acceptors as the electrophiles and nitromethane as the nucleophile are activated by catalytic amounts of chiral Lewis acid and amine catalysts, respectively.[67] The nitro adducts **75** were generally obtained in very satisfactory yields and enantioselectivities, showing that the combined use of Lewis acid and amine catalysts works in a highly effective manner to accelerate Michael addition reactions with nitromethane.



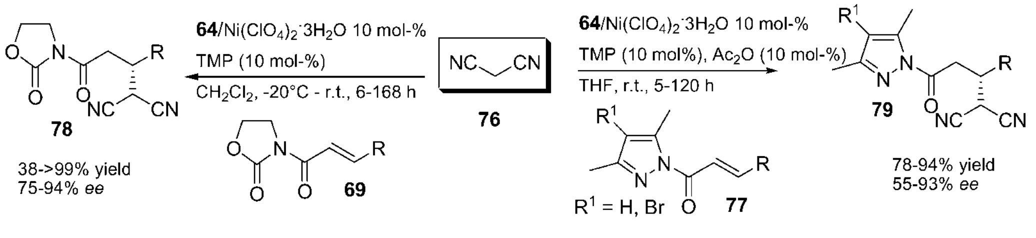
Scheme 31.

Analogously,[68] treatment of malononitrile (**76**) with 3-(2-alkenoyl)-2-oxazolidinones **69** or 1-(alk-2-enoyl)-4-bromo-3,5-dimethylpyrazoles **77** can be doubly activated by the use of catalytic amounts (10 mol-% each) of both **64**/$Ni(ClO_4)_2$·3 H_2O and an amine to give the Michael adducts **78** and **79** in high chemical yields and with satisfactory enantioselectivities (Scheme 32).

Recently, Sibi[69] employed the Kanemasa **64**/$Ni(ClO_4)_2$·3 H_2O complex to obtain the first example of enantioselective addition of nitrones **80** to activated cyclopropanes **81**, which undergo nucleophilic addition, resulting in the for-



Scheme 33.



Scheme 32.

mation of tetrahydro-1,2-oxazines **82** with very high enantioselectivities (Scheme 33). This chiral Lewis acid proved to be very effective, with the reactions proceeding in high yields at room temp. in CH_2Cl_2 in the presence of molecular sieves.

Conclusions

General use of perchlorates had for a long time been avoided, owing to the fear they could act as powerful oxidizers and explosives. Recently, however, these salts have undergone a sort of rehabilitation, since it has been established that the really dangerous compounds are perchloric acid and ammonium perchlorates, and so some metal perchlorates have been extensively employed in the field of organic synthesis during the last years.

Metal perchlorates have in fact showed a wide range of applications, both in providing new methodologies for well known and widely employed reactions and in promoting new ones. In our own experience, we have never had any safety problem with the use of various perchlorate salts, when performing the reactions under mild and almost neutral conditions and working at relatively low temperatures, even in the presence of oxidizable materials such as amines.

The unique properties of perchlorates make them powerful Lewis acids, capable of strongly coordinating electron donors, especially chelating compounds such as 1,3-dicarbonyl substrates and bidentate ligands. They are powerful and selective catalysts that can usually be employed under mild reaction conditions, at relatively low temperatures, and several functional groups are well tolerated.

In several cases perchlorates proved to be much more active than other commonly used Lewis acids, such as triflates, while at the same time being much less expensive. Moreover, they are stable to air and water, so that some of them can be employed in the hydrate form. Therefore they can frequently be recovered and reused without loss of activity.

Since it is only few years that metal perchlorates have been routinely employed in organic chemistry, we believe that they could find increasing use in the future.

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