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Perspectives on Alkyl Carbonates in Organic Synthesis

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1. Overview

Alkyl organic carbonates stand on the verge of becoming an extremely valuable tool to the organic chemist. Industry has used carbonates for many years in numerous applications including medicine and polymer chemistry. However,

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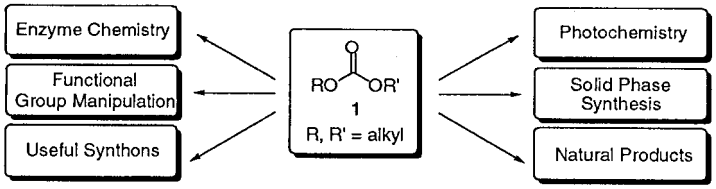


Scheme 1.

carbonates as useful synthetic elements have been widely overlooked, presumably due to a lack of fanfare or unfamiliarity. Sivaram has recently reviewed the carbonate moiety,[1] and discussed in depth the various methods for carbonate preparation. The purpose of this review is to give a general overview regarding carbonate applications in organic synthesis (Scheme 1).

1.1. Physical and chemical properties

Alkyl carbonates are usually clear liquids or oils, and most have been noted as possessing pleasant odors. The simplest of all carbonates, namely dimethyl carbonate (DMC), has a boiling point of 90°C, a density slightly greater than water, and is nearly insoluble in aqueous media. Other dialkyl carbonates show similar properties to DMC. These compounds are known to be extremely flammable and have relatively low flash points (DMC flash point=18°C). Additionally, carbonates are known to be incompatible with oxidizing and reducing agents, as well as strong acids and bases. Furthermore, aliphatic carbonates are vulnerable to hydrolysis while being more resistant to saponification than esters.

1.2. Preparation of alkyl carbonates

The synthesis of alkyl carbonates has been recently reviewed by Sivaram.[1] Therefore, only a brief mention of three crucial classifications will be elaborated upon.

1.2.1. Preparation using carbonyl equivalents. Among the methods for introduction of the carbonate moiety,[2] the reaction of phosgene with diols[3–5] and the coupling of haloformates with isolated alcohols and phenols have been the most common procedures.[6,7] Both methods involve the use of toxic and costly materials, therefore there has been a drive to develop alternative methods. In this regard, the use of urea with an appropriate catalyst has been frequently employed in industrial applications.[8,9] Additionally, the oxidative carbonylation of alcohols from carbon monoxide and a transition metal has also met with much success for carbonate generation.[10–17]

1.2.2. Preparation using CO_2 or MCO_3. Carbon dioxide has been shown to be an excellent alternative to phosgene, due to its high abundance and environmentally benign nature.[18] The use of this reagent in the synthesis of carbonates has been an inviting endeavor for chemists in this field. In addition, metal carbonates have been used as carbon dioxide equivalents.[19–32] A plethora of transformations utilizing alkyl halides and alcohols to synthesize carbonates have been performed using the carbonate and bicarbonate salts of alkali metals and silver.[33–38] Although these methods offer safer alternatives, they usually suffer in practicality since carbonate formation occurs under harsh reaction conditions such as high temperatures.

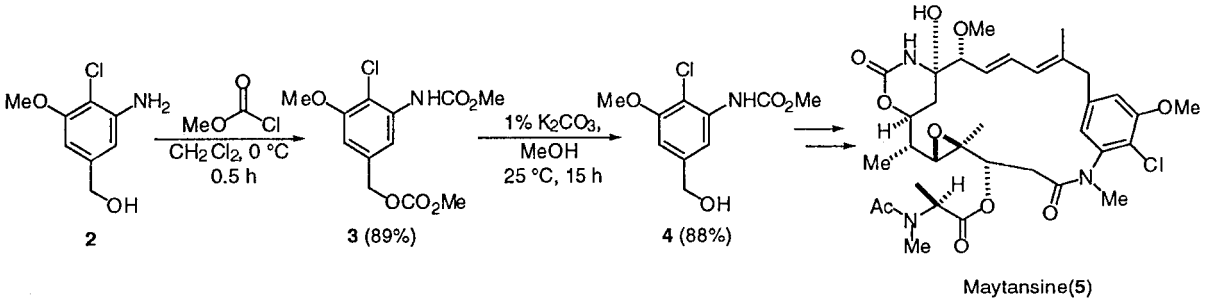
1.2.3. Carbonate exchange. The carbonate exchange reaction is characterized by the nucleophilic attack of carbonates by alkoxides or their equivalents to generate new carbonate structures. A Lewis acid or strong base usually catalyzes this reaction.[39–43] However, the enzymatic exchange of carbonates has also been reported.[44,45]

1.3. Practical applications of alkyl carbonates

1.3.1. Applications in polymer science. In the past, the polymerization reactions of carbonates were classified into three categories: transesterification reactions, the use of phosgene with diols, and interfacial polycondensation.[46] However, more recent advances in the production of polycarbonates have been made, and carbon dioxide can now be inexpensively and safely incorporated in place of phosgene. Darensbourg reported that epoxides reacted well with CO_2 in the presence of a Lewis acid to give high-molecular weight polymers in good yields.[47] Enzymatic polymerizations have become popular alternatives to the known methods. Gross and others have shown that carbonate monomers can be polymerized to give nearly quantitative conversions and products with high molecular weights using biocatalysts.[48,49]

Polycarbonates have found widespread applications in everyday life. For example, polycarbonates have been used as engineering resins for CD's and DVD's. The automotive industry uses polycarbonates for instrument and body panels, and soon hopes to replace glass with this material.[50] Polycarbonates also can be used as abrasion resistant cast films.[51] Polymers derived from cyclic carbonate precursors have been used for electrolyte supports and optical dyes.[52] Electronics continue to be the widest application area, where polycarbonates are used as insulators, housings, starters, and terminals. The lighting industry uses carbonate polymers for their excellent impact resistance.[46] Football and baseball helmets have been constructed from these polymers, taking advantage of the lightweight features associated with the materials.

1.3.2. Practical and industrial applications. Carbonates have been used as fuel additives due to their high oxygen content and reduced emissions,[53] and have been utilized as lubricating oils in refrigerators.[54,55] Cyclic carbonates are useful as photoresistors, and show good profiles in sensitivity and resolution.[56] Carbonates with high dielectric



Scheme 2.

constants have been used for condensers and batteries.[57] Laminates of carbonates and their polymers have been used as packaging materials.[58] Additionally, carbonate linkers have been used in conjunction with other materials as dyes.[59,60] Carbonates have also been used in industry as a solvent for the separation of phenols and cyclohexanones.[61] Sivaram has reviewed this topic and many other applications can be found therein.[1]

1.3.3. Medicinal and biological applications. Due to their interesting physical properties and behaviors, carbonates have contributed a great deal to biology and medicine. For instance, polycarbonates have been used as biodegradable drug delivery systems with potential for application in controlled drug release and as surgical implant substances.[62–66] Several carbonates of 1-substituted-3-dimethylamino-1-propanols have been studied as possible anti-depressant alternatives to the clinical agent imipramine.[67,68] Recently, an orally active prodrug of the antibiotic sanfetrinem was reported which contains a carbonate ester as its hydrolytic side chain.[69] Carbonate containing drugs have also been used to treat lipidemia and as a non-steroidal growth inducer for ruminants.[70,71] During a high throughput screen for candidates that would inhibit tissue factor/factor VIIA complexes, an aryl carbonate linker was used in a combinatorial approach.[72]

2. Applications of Alkyl Carbonates as Protecting Groups

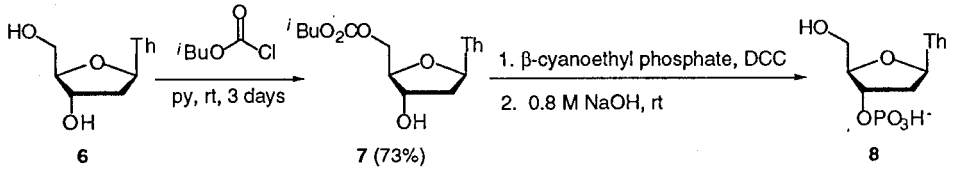
Alkyl carbonates have found the most use in organic synthesis as protecting groups for alcohols, where the protection of amino acids and carbohydrates have been extensively studied.[73] Aliphatic carbonates are introduced via haloformates under Schotten–Bauman conditions,[74] although many other techniques have been employed.[2–45] The carbonate moiety is commonly cleaved under basic hydrolysis, but is typically more resistant to this condition than esters.[73] Other specialized carbonate protecting groups have been developed to be cleaved only under certain situations, so that proper groups may be selected to avoid constant protecting group shufflings. In this context, discussed hereafter is a brief overview of the representative carbonate protecting groups, focusing on the characteristic utilities and selectivities in protection and removal processes.

2.1. Alkyl carbonate protecting groups

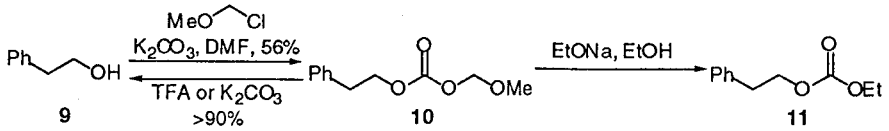
During the synthesis of the anti-tumor agent maytansine **5**, Meyers et al. used alkyl methyl carbonate to protect the benzylic alcohol **2** shown in Scheme 2. The primary alcohol and the aryl amine were both protected, and selective cleavage of the carbonate over the carbamate was subsequently performed using methanolic potassium carbonate to give alcohol **4** in a high yield.[75] It appears that the carbonate is more readily hydrolyzed than the carbamate under mild basic conditions.

Interestingly, carbonates have been utilized in the regioselective mono-protection of diols and polyols, often demonstrating superb selectivity. For example, Letsinger reported the use of the isobutyloxycarbonyl group to exclusively protect the 5′ position of carbohydrates including **6** (Scheme 3).[76] The authors suggested that this masking group was superior to others such as the acetyl moiety because of higher yields, better selectivities, and greater tolerance to aqueous pyridine. The resultant carbonate was stable under phosphorylation conditions and easily removed by treatment with dilute aqueous base to furnish 3′-phosphate **8** smoothly. Other alkyl carbonates encompassing ethyl and *t*-butyl have also been used in a similar fashion as protecting groups in various syntheses.[77,78] Using these alkyl carbonates, the selective masking of alcohols has been feasible, thus providing an efficient method to distinguish primary groups for steric reasons.

A noteworthy feature in carbonate protecting groups is the incorporation of additional functionalities at the α or β positions which allows the chemist options such as chemical modification of the protecting group. For instance, Teranishi



Scheme 3.



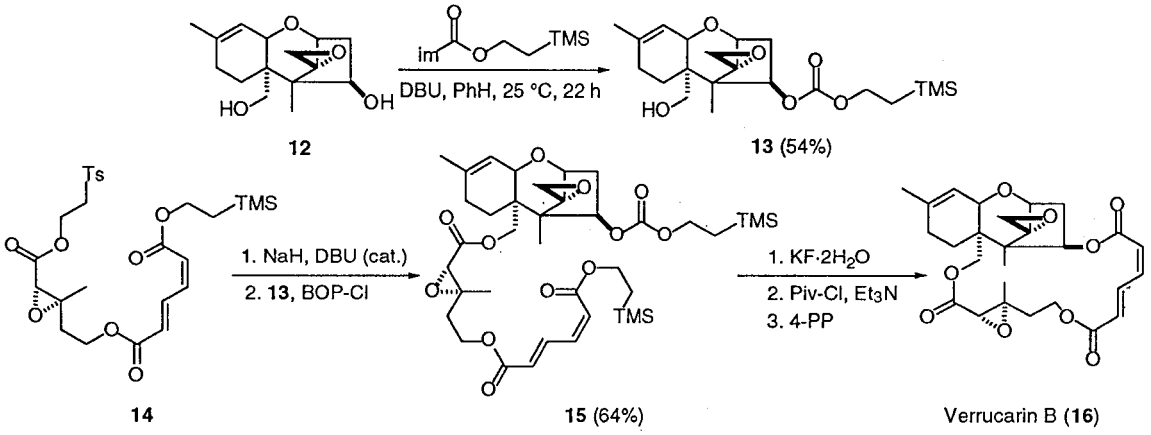
Scheme 4.

employed the alkoxymethyl carbonate group to protect a variety of alcohols as shown in Scheme 4.[79,80] This α-functionalized carbonate (e.g. **10**) was prepared by using MOMCl, which did away with the use of chloroformates, whereas its removal was efficiently carried out both under acidic and basic conditions to return the alcohol **9** in high yield. Thus, this route serves as another option for selective carbonate deprotection, sometimes unavoidable during synthesis. On the other hand, such α-functionalized carbonates can undergo facile alcohol exchange to deliver new carbonates like **11**, which can be further functionalized during ensuing organic synthesis.

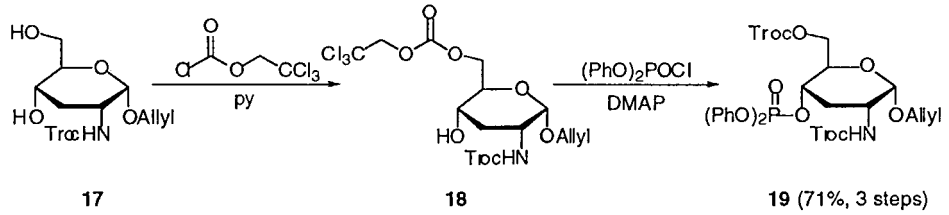
Among various β-substituted carbonates, 2-(trimethylsilyl)-ethyl carbonate (TMSEC) has been widely employed for hydroxyl protection as demonstrated in Roush's synthesis of verrucarin B (**16**, Scheme 5).[81] Treatment of diol **12** with the carbonyl imidazole precursor gave rise to the formation of TMSEC mainly at the secondary carbinol center, to afford alcohol **13** in moderate yield. The subsequent coupling between alcohol **13** and the acid derived from **14** generated compound **15**, possessing two 2-(trimethylsilyl)ethyl groups. Simultaneous deprotection of these TMS ethyl moieties was successful with $KF{\cdot}2H_2O$ without interfering with other functional groups present in this complex molecule. The resulting seco acid was then cyclized to the natural product. Several other fluoride sources and Lewis acids such as TBAF,[82] CF_3CO_2H,[83] and $ZnBr_2$[84] have been used to effect the removal of this β-functionalized carbonate protecting group.

β-Functionalized carbonates are useful because they are often more stable under a variety of conditions, and more importantly cleavage, is highly specific. The 2,2,2-trichloroethoxycarbonyl group (Troc) has been used in this manner for the protection of alcohols. In Shiba's synthesis of bacterial lipopolysaccharides, it was necessary to use a stable and selective protecting group that could be cleaved under mild conditions.[85] As shown in Scheme 6, the Troc group was utilized to protect carbohydrate **17** selectively. This β-substituted group can then be removed via Zn dust in refluxing methanol or under electrolysis conditions after the desired transformations.[86] There are several similar protecting groups such as 2-chloro-,[87] 2-bromo-,[88] 2-iodo-,[89] 2,2,2-tribromo-,[90] and 2-bromo-^{t}butyloxycarbonyl,[91] which all show similar properties to the Troc group in the unmasking procedures.

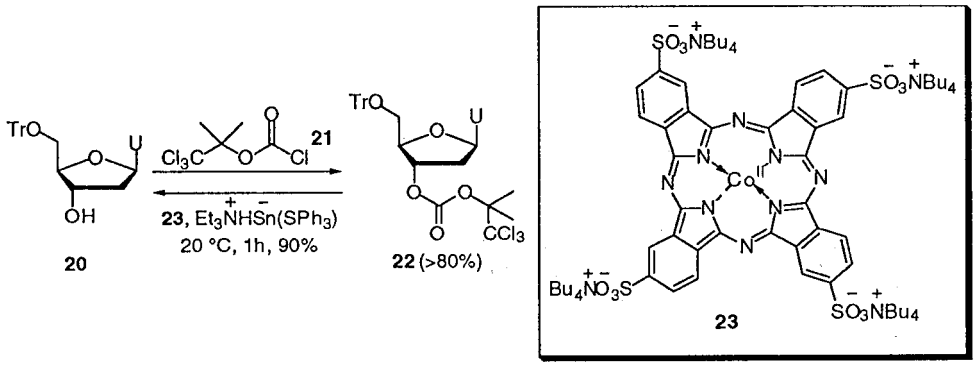
As delineated in Scheme 7, Ugi developed an interesting β-functionalized carbonate, which constituted the 2,2,2-trichloro-^{t}butyloxycarbonyl protecting group within **22** via the corresponding haloformate **21**.[92,93] This functionality was stable to acidic ester hydrolysis and to basic ^{t}butyl ether removal. The deprotection step was achieved



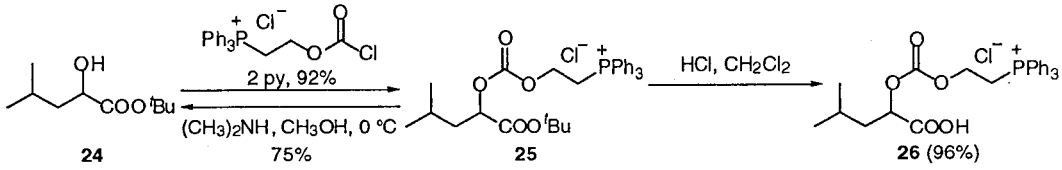
Scheme 5.



Scheme 6.



Scheme 7.



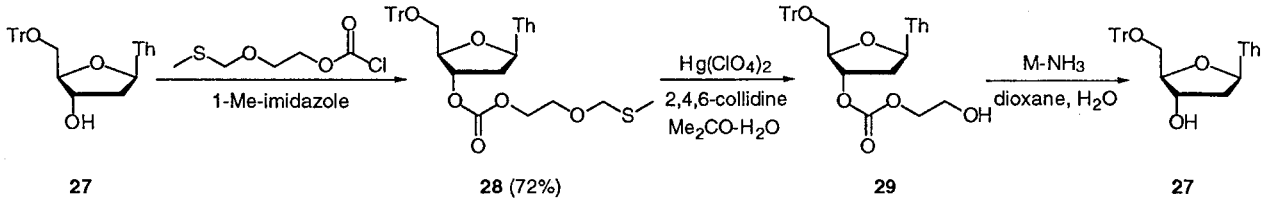
Scheme 8.

smoothly using a supernucleophilic cobalt phthalocyanine reagent **23**, which was exclusive for removal of this group.

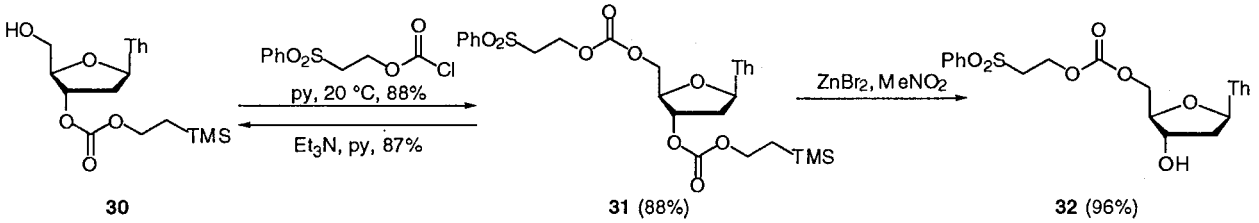
The Peoc, or 2-(triphosphino)ethyl carbonate, protecting group utilizes the reactivity of the phosphino group as its major advantage (Scheme 8).[94] For example, Kunz proved that alcohols such as **24** were protected efficiently as Peoc carbonates to prepare phosphonium salts such as **25** in high yields and that deprotection of Peoc was carried out using mild conditions such as dimethylamine in methanol. Remarkably, this β-functionalized carbonate group was found to be very stable to strong acid hydrolysis conditions, providing acids such as **26** without harming the Peoc group. Thus, the Peoc serves as an excellent masking group, and is an alternative to the existing platforms.

Within the repertoire of β-functionalized carbonate protecting groups, there are two sulfur containing moieties, namely the 2-(methylthiomethoxy)ethyl and 2-(phenylsulfonyl)-ethyl carbonates. These groups are abbreviated MTMEC and PSEC, respectively. The MTMEC protecting group was introduced via the corresponding haloformate and cleaved in a two step sequence (Scheme 9). Mercury promoted hydrolysis of the mixed acetal in **28** furnished the intermediate hydroxyethyl carbonate **29**.[95] Subsequently, subjecting **29** to alkali metal in ammonia provided the starting alcohol **27**.

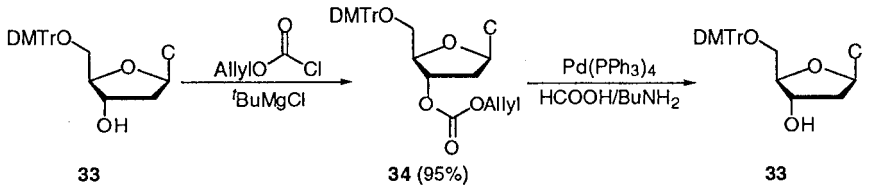
In contrast, the PSEC group can be removed in one step using triethylamine through a β-elimination process (e.g. **31** to **30**, Scheme 10). PSEC can also be used in the presence of other labile protecting groups, making it ideal for use with carbohydrates.[96] During further experiments, the *para* substituents of the phenyl ring were observed to tune the reactivity for removal of the PSEC group. As expected, the electron withdrawing nature of the 4-chloro- (CPSEC)[97]



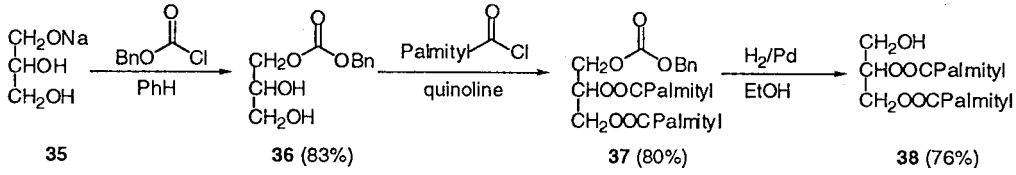
Scheme 9.



Scheme 10.



Scheme 11.



Scheme 12.

and 4-nitro groups makes these versions of the PSEC protecting group more labile to base, whereas the 4-methyl, an electron donating group, decreases this effect.

As addressed in Scheme 10, two distinguishable carbonates can be introduced and then exploited in various syntheses, which allows for specific manipulations of interest. In this regard, alkyl and α- or β-functionalized carbonates can help to facilitate numerous syntheses mainly because these groups can be installed chemo- or regioselectively and can then be removed under specific conditions while preserving other functionalities.

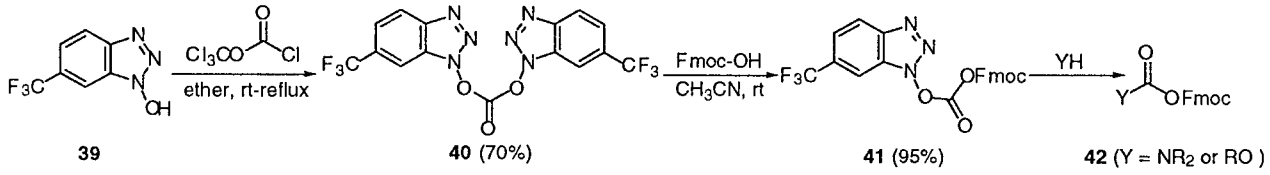
2.2. Allylic and benzylic carbonate protecting groups

The allyl alkyl carbonate has been paramount in palladium catalyzed reactions. This group undergoes a variety of transformations and will be elaborated upon later in this review. The allyl carbonate, or Alloc, protecting group has been used extensively in sugar and peptide chemistry, and for the synthesis of natural products such as the avermectins and acyl glucuronides.[98,99] The advantage of using this protecting group is the fact that it can be removed with simple treatment by transition metal reagents such as palladium, the usual catalyst of choice. Although other metals including nickel catalysts have been used as well, they are unlikely to be utilized commonly due to several factors such as lower efficiency, higher cost, and toxicity (i.e. $Ni(CO)_4$).[100] A typical protection/deprotection sequence is shown in Scheme 11.[101]

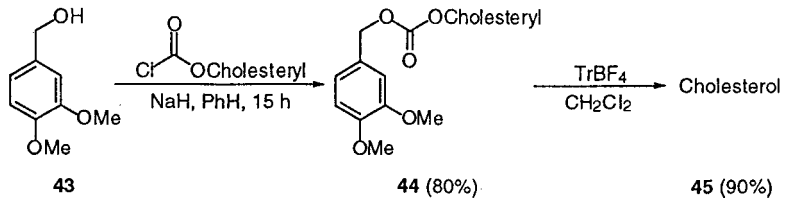
In contrast to allyl carbonates, benzyl carbonates are usually cleaved under mild hydrogenolysis conditions. As depicted in Scheme 12, King used the benzyl alkyl carbonate as a protecting group in the synthesis of α,β-diglycerides derivatives of fatty acids.[102] Thus, the sodium alkoxide **35** was treated with benzyl chloroformate to give monocarbonate **36** in 83% yield. Subsequently, this compound was subjected to esterification with palmityl chloride, then the carbonate was removed via hydrogenolysis to provide alcohol **38**. In this short exhibition, selective mono-protection of a triol was addressed to a reasonable extent. Although the benzyl carbonate group is meritorious, it is not used as frequently as the functionalized benzylic carbonate protecting groups introduced hereafter.

Substituted benzylic carbonates have been used as protecting groups for alcohols and amines. The most widely used is the 9-fluorenylmethyl carbonate group, or Fmoc. This moiety has been extensively employed as an amine protecting reagent in peptide synthesis.[73] Chemical methods for the introduction of Fmoc as a protecting group have been well studied.[103] A variety of methods which avoid the use of toxic haloformates have been developed, namely benzotriazole and succinate derivatives. For instance, Ogura reported the use of 1-(9-fluorenylmethoxy)-[6-(trifluoromethyl)benzotriazolyl] carbonate **41**, derived from active carbonate **40**, to introduce the Fmoc protecting group to alcohols and amines (Scheme 13). This group is traditionally removed under basic hydrolysis conditions using triethylamine or pyridine.[104]

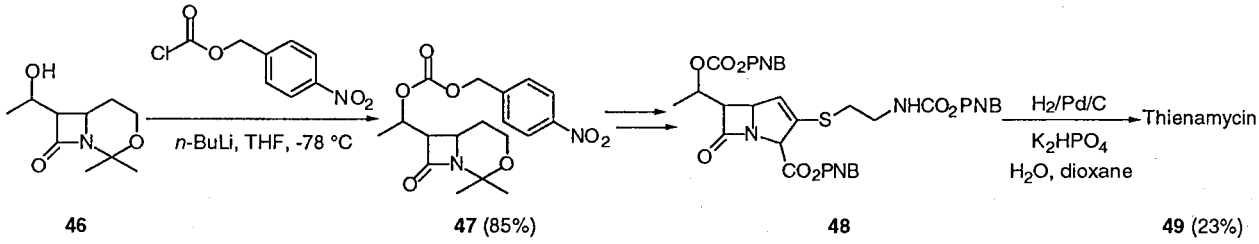
Other substituted benzylic carbonates have thrived containing various substituents on the phenyl moieties. Electron donating and withdrawing groups have been introduced to benzyl carbonates, and these variations have resulted in selective and uniquely differentiated deprotecting strategies. During studies on the synthesis of the antibiotic tetracycline, Barton prepared methoxy benzyl carbonates of cholesterol, including 4-MeO-, 3,4-MeO-, 3,5-MeO-, and 3,4,5-MeO-



Scheme 13.



Scheme 14.



Scheme 15.

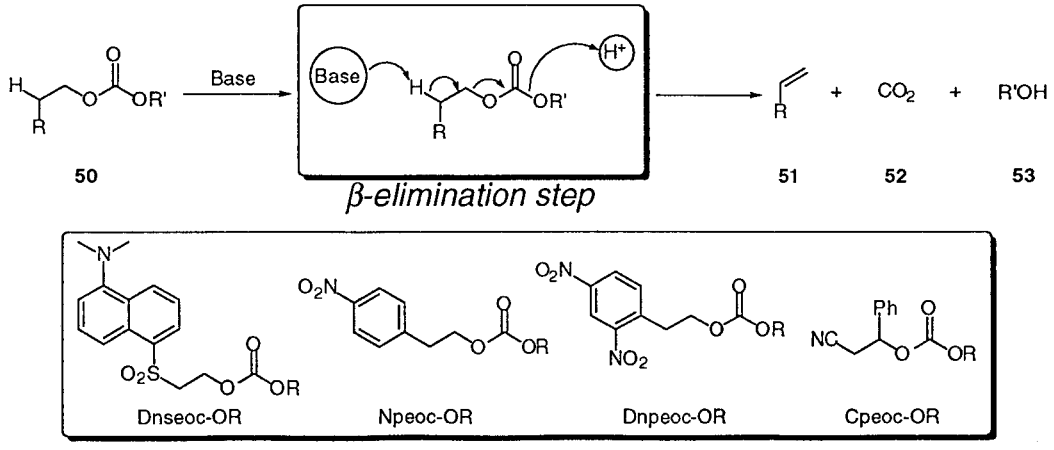
derivatives (Scheme 14).[105] After these model compounds were synthesized, treatment with trityl tetrafluoroborate deprotected the carbonates via a trityl cation. Deprotection steps were generally high yielding (>85%) and unique compared to other carbonates.

Moreover, benzylic carbonates with electron withdrawing groups have paved an alternative avenue in unmasking procedures of related protecting groups. As a representative example, the *o*- and *p*-nitrobenzyl carbonate protecting groups were used in the synthesis of thienamycin antibiotic analogues by Cama.[106,107] The *ortho* derivative was photolabile (c.f. Scheme 77 in Section 5), whereas the *para* derivative was easily removed with hydrogenolysis conditions. As shown in Scheme 15, the *p*-nitrobenzyl carbonate was used in the synthesis of the potent antibiotic thienamycin **49** to protect both an alcohol and an amine, then deprotected via hydrogenolysis.

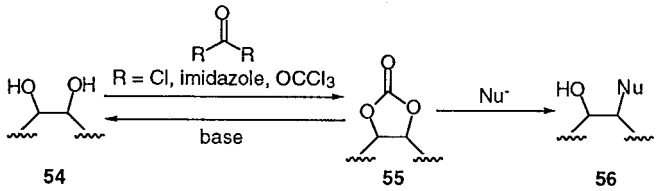
The preparation of allylic and benzylic carbonates as protecting groups is relatively straightforward and the corresponding reagents are commercially available and inexpensive. These carbonate functionalities are usually invulnerable to numerous conditions involved in organic syntheses. The benefit of using these carbonates seem to lie in setting up of versatile choices of deprotecting strategies, which can be summarized by organometallic pathways, hydrogenolysis, mild and selective hydrolysis using specific organic bases, photolysis, and Lewis acid catalysis like trityl cation treatment. Thus, these carbonate structural motifs can serve as excellent protecting groups for alcohols and similar functional groups in a variety of organic syntheses.

2.3. β-Elimination and cyclic carbonate protecting groups

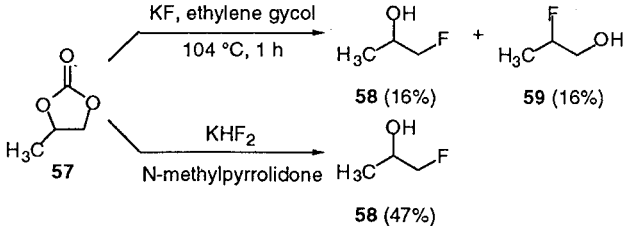
The β-elimination and cyclic carbonates are other structurally interesting protecting groups, and both are extensively used in carbohydrate syntheses. β-Elimination carbonates are defined by their characteristic base mediated elimination processes to bring about the deprotection steps selectively or under mild conditions as illustrated in Scheme 16. Presumably, liberation of carbon dioxide serves as a driving force to give alcohol **53** along with alkenes, which are usually reminiscent of styrene type compounds.



Scheme 16.



Scheme 17.



Scheme 18.

The 2-(4-nitrophenyl)ethoxycarbonyl (Npeoc), 2-(2,4-dinitrophenyl)ethoxycarbonyl (Dnpeoc), and 2-dansylethoxycarbonyl groups (Dnseoc) are the most commonly used β-elimination carbonates, although others have been described.[108–111] Occasional use of the 2-cyano-1-phenylethyl carbonate group (Cpeoc) in carbohydrate chemistry has been reported, although its use is rare. These groups are particularly resistant to mild hydrolytic conditions as well as to phosphate introduction, making them an ideal choice for use in nucleoside syntheses. The β-elimination carbonate protecting groups are usually removed under mild cleavage conditions utilizing DBU or DBN as bases. Such deprotecting techniques have allowed these β-elimination carbonates to be implemented in carbohydrate chemistry.

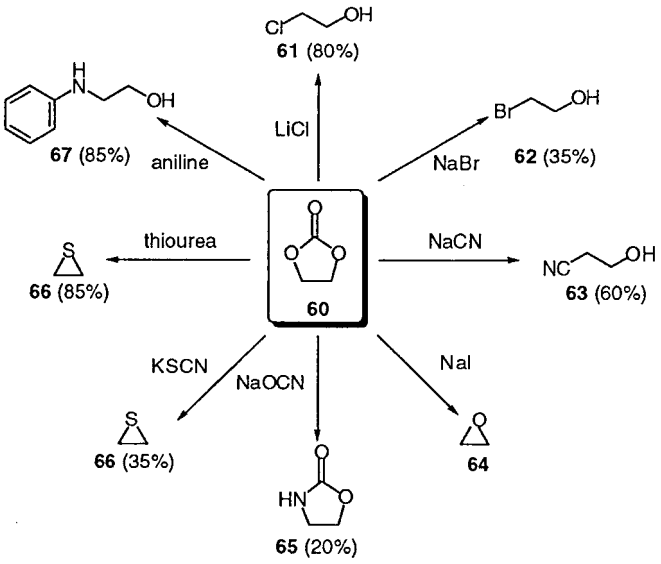
As briefly introduced in Scheme 17, cyclic carbonates have been used as efficient protecting groups for diols, but they are more specifically used in carbohydrate chemistry. This protecting group offers good stability toward acid hydrolysis, and is readily cleaved under basic conditions.[112–115] Alternatively, the cyclic carbonate can undergo ring opening selectively at one position to give a mono-protected diol with the proper selection of reaction conditions.[116–118] Phosgene and carbodiimidazole (CDI) have been the typical reagents of choice for the preparation of the cyclic carbonates,[2–45] although its less toxic analogue, bis(trichloromethyl) carbonate, has become utilized recently.[119] Methodologies employing cyclic carbonates will be further discussed intermittently throughout this report.

3. Applications of Alkyl Carbonates as Useful Synthons

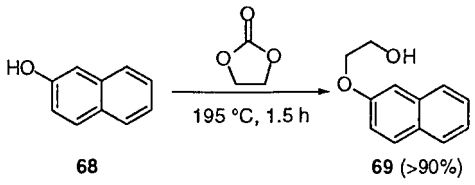
A major thrust in the field of organic synthesis is the development of useful methodologies. These methodologies supplement total syntheses, and produce the necessary intermediates and important classes of compounds needed for the ensuing applications and related fields. Carbonates have been used in this fashion as synthetic precursors to generate a variety of significant materials such as triols, epoxides, functionalized alcohols, and other functionalities. However, these methods have yet to achieve complete acceptance in the synthetic chemist's arsenal, possibly due to lack of exposure or fanfare. Described in this section are selective examples of alkyl carbonates utilized as useful synthetic templates.

3.1. Alkylation of hetero nucleophiles

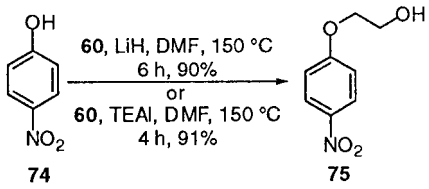
Alkyl carbonates, especially cyclic carbonates, have enjoyed great synthetic utility in the introduction of



Scheme 19.



Scheme 20.



Scheme 22.

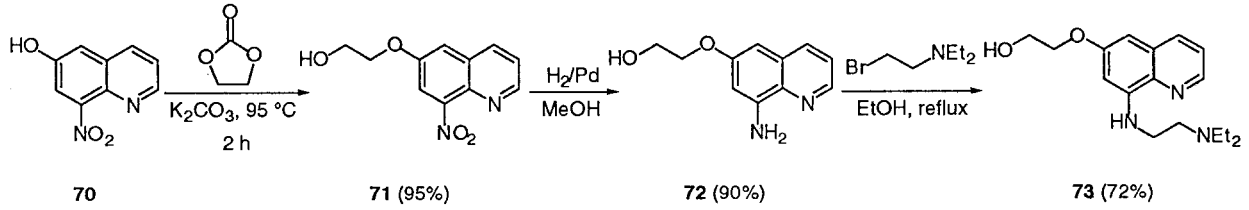
heteroatom functionalities including oxygen and halogen. Generally, cyclic carbonates behave as electrophiles and introduce one hydroxyl to give functionalized alcohols. For example, Bergman demonstrated that the treatment of cyclic carbonates with anhydrous potassium fluoride afforded moderate yields of the β- and γ-fluoroalcohols **58** and **59** as illustrated in Scheme 18.[120] The authors stated that this method was complimentary to known procedures for preparation of these fluorinated alcohols. Other methods for this conversion include the use of the more expensive potassium hydrogen fluoride. However, it was reported that the use of this salt with unsymmetrically substituted ethylene carbonates gave only one of the two possible isomers (**58**), whereas KF furnished both (**58** and **59**).[121]

In addition, ethylene carbonate has been used to prepare a variety of β-functionalized alcohols as delineated in Scheme 19. Treatment of **60** with various nucleophiles gives products **61**–**67** including oxazolidin-2-one (**65**), ethylene sulphide (**66**), and 2-anilinoethanol (**67**). The authors claimed that the method using thiourea was the most facile way to prepare **66** reported to date.[121] As was the case with most halohydrin syntheses, the yields diminished as the halogen ion increased in size, owing to a periodic effect. Iodohydrin, which is unstable and leads to the epoxide **64**, has not been synthesized in this fashion to date. However, it may be possible to intercept the iodohydrin intermediate at low temperatures with an appropriate counterion, which can in effect block the incipient alkoxide ion from undergoing an internal S_N2 type reaction. It appears that nucleophilic substitution reactions at cyclic carbonate centers are feasible with various nucleophiles, which may provide a number of synthetically useful platforms in the future.

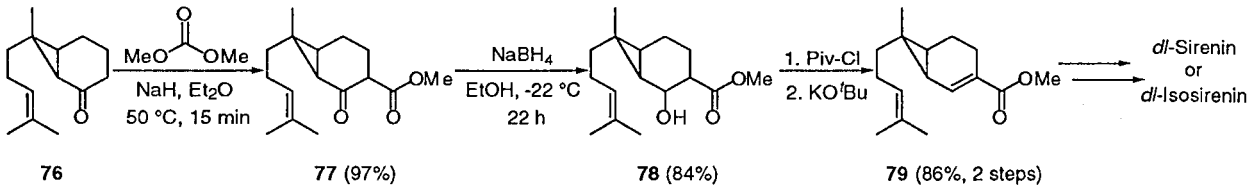
Another important application with cyclic carbonates is cathylation, the process of incorporating a hydroxyethyl moiety into a pre-existing molecule. Carbonates, specifically ethylene carbonates, are well suited for this reaction and have garnered attention in several reports. It was noted that this technology was superior to the existing methods in some syntheses. For example, during the synthesis of phenolic alkaloids, an improved method for the introduction of the hydroxyethyl group was needed.[122] Halohydrins and alkylene oxides proved to be inefficient, offering low yields and complicated reaction mixtures. In other attempts, a two step process was developed using benzyloxyethyl toluenesulfonate to alkylate a phenolic alkoxide, followed by removal of the tosyl group.[123] Compared to these methods, incorporation of ethylene carbonate was efficiently accomplished in a single process. In the synthesis of hydroxyethylapocupreine,[124] Carlson reported the use of ethylene carbonate to cathylate various phenols in greater than 90% yield in one step, avoiding the problems associated with the previous methods (Scheme 20).

While the aforementioned synthesis was undertaken thermally, the presence of a base can facilitate the cathylation as illustrated in Scheme 21. Morgan reported the use of ethylene carbonate with potassium carbonate as the base to give hydroxyethyl quinoline **71** in high yield. Nitro compound **71** was then subjected to hydrogenation and subsequent *N*-alkylation to give **73**. The product is used as a less toxic analog to the antimalarial agent pamaquine.[125] This cathylation approach allowed the conversion to be completed at a lower temperature and efficiently compared to the thermal reaction, likely making it a generally useful synthon preparation.

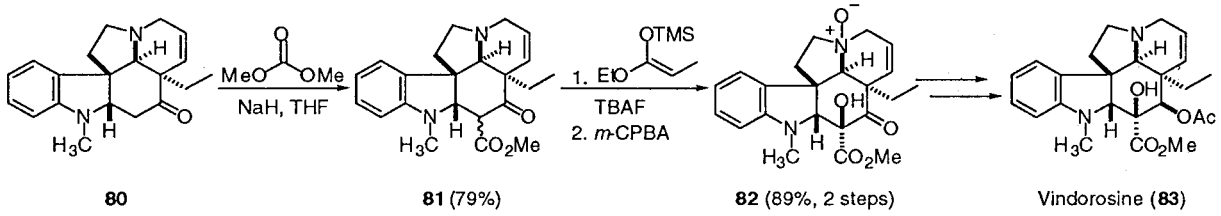
In regards to the bases used in cathylation, Ishido reported interesting results on two different conditions in a condensation reaction with various phenols (Scheme 22).[126] By using LiH, cathylation was possible via S_N2 attack of the nascent phenoxide on the corresponding carbonate. This reaction had the limitation of using a strong and highly reactive base. The authors further reported a neutral cathylation condition using tetraethylammonium iodide (TEAI) as an additive, which offered similar results. These neutral conditions are considered to be mild and compatible with various substrates found in syntheses. The major pitfall of using the cathylation reaction is poor regioselectivity when unsymmetrically substituted ethylene carbonates are employed. Nonetheless, this kind of conversion still can be beneficial to chemists by generating useful functionalities at the β positions, which are ubiquitously found in syntheses.



Scheme 21.



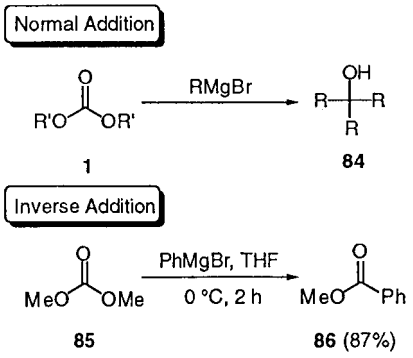
Scheme 23.



Scheme 24.

3.2. Alkylation of carbon nucleophiles

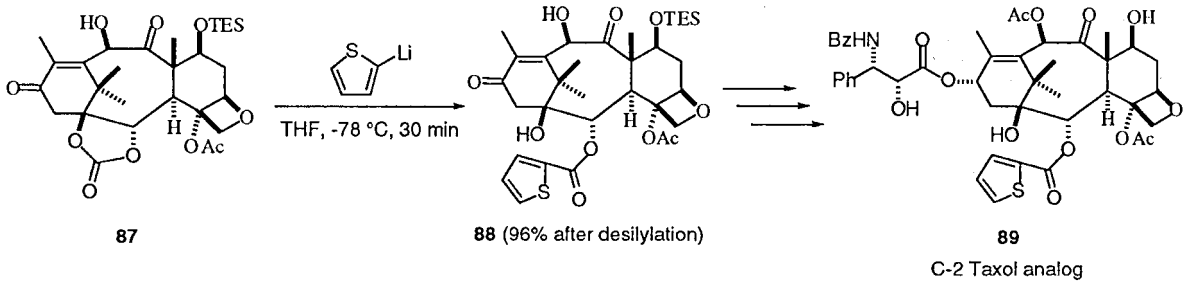
In addition to the numerous reactions in which carbonates are used as synthons, carbonates are polarized and can be attacked by a variety of nucleophiles to effect facile carbon–carbon bond formations. For example, in Rapoport's synthesis of the chemotactic hormone sirenin and isosirenin (Scheme 23), the condensation of ketone **76** with dimethyl carbonate provided the intermediate ester **77** in nearly quantitative yield.[127] The newly formed β-keto ester was then selectively reduced and the corresponding alcohol was eliminated via a pivalate ester to give **79**. In this conversion, the alkyl carbonate served as the source of the ester functionality by efficient C–C bond formation.



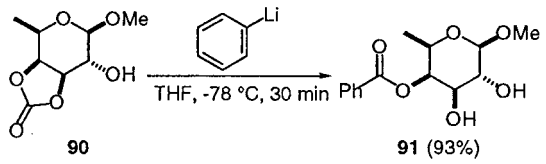
Scheme 25.

The aforementioned methodology leading to the β-keto ester was also implemented in the synthesis of the alkaloids vindorosine **83** and vindoline (Scheme 24). Several reported syntheses of these compounds have used dimethyl carbonate as a carboxylate equivalent as well.[128–131] According to Langlois's report, when **80** was treated with DMC and NaH, compound **81** was prepared in good yield, although the product was isolated as a mixture of the ketone and enol.[128] Compound **81** was α-hydroxylated in a two step sequence. Using the ketene acetal and TBAF, the corresponding TMS enol ether was first prepared, then converted to the desired hydroxyl group upon treatment with *m*-CPBA. Subsequent oxidation of one nitrogen occurred to give *N*-oxide compound **82**.

In the previous C–C bond formation, enolates were utilized as nucleophiles to prepare the corresponding esters. However, when other reactive nucleophiles including Grignard reagents are employed in the C–C bond constructions, carbonates readily react to furnish alcohols exclusively as anticipated. The organomagnesium halide attacks the carbonate to give mainly tertiary alcohols **84** where the three new R groups are all equivalent. Interestingly as depicted in Scheme 25, Sivaram reported the inverse addition of Grignard reagents to dialkyl carbonates for the synthesis of esters, and this reaction turned out to be expeditious and high yielding.[132] Since the current route avoided the two step sequence required for ester synthesis, typically carboxylation followed by esterification, this approach might become a generally applicable technique



Scheme 26.



Scheme 27.

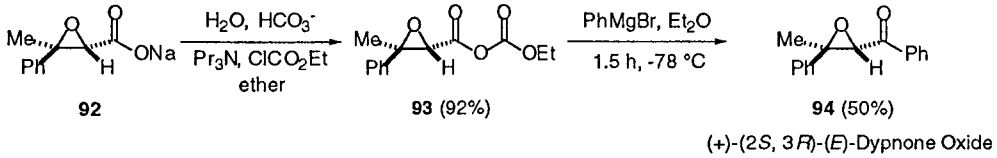
in organic synthesis. Likewise, aryllithium reagents have also been utilized in carbonate alkylations, giving rise to the exclusive synthesis of the corresponding esters. In the case of unsymmetrical carbonates, the choice of the leaving alkoxides was often selective, to the benefit of the desired synthetic goal. Some examples of this selectivity are further elaborated below.

During the total synthesis of the antitumor compound taxol, Nicolaou observed that a cyclic carbonate intermediate **87** was attacked by PhLi to give a product with the precise control of regiochemistry and in high yield.[116] To further explore this reaction, Nicolaou treated the cyclic carbonate derivative of a taxoid **87** with a variety of nucleophiles. Thus, new C-2 analogues of taxol were prepared in high yields as seen in Scheme 26 after further manipulation of **88**.

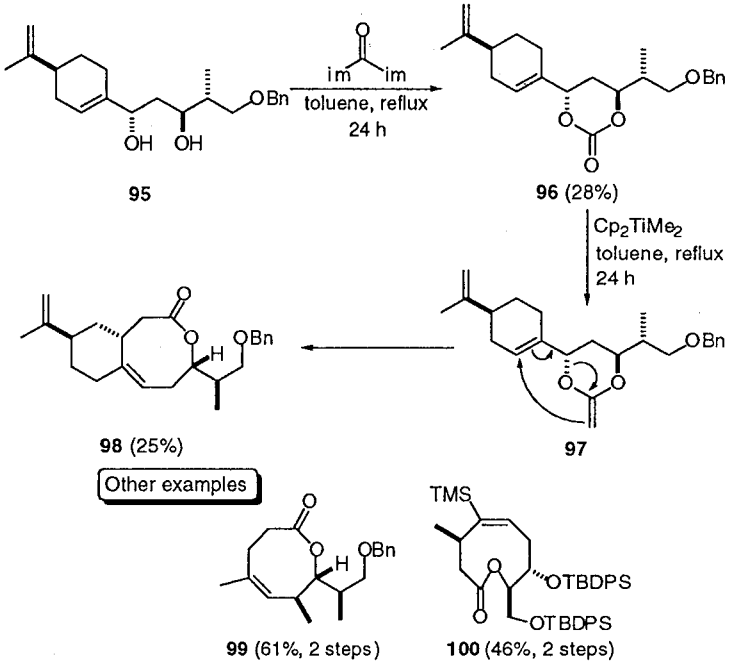
This methodology was then applied to other model systems to give products such as **91** (Scheme 27). The less substituted (or unhindered) ester was usually obtained over the more substituted (or congested) ester. While the diol product was isolated in certain instances, its formation in the above case was not observed. In the carbonate opening, the quaternary alcohol was produced exclusively while making the desired C–C bond formation. The extraordinary feature of this reaction was the chemoselectivity obtained at the carbonate center despite the presence of three other carbonyl groups that are vulnerable to nucleophilic attack. The authors also stated this effect was a result of steric shielding within the taxol molecule.

For the synthesis of optically active glycidic esters such as dypnone oxide (**94**), Bach reported using an activated mixed carbonate **93** as the acceptor for a Grignard alkylation.[133] Scheme 28 demonstrates the reaction of this active species, which, after preparation, is treated with phenyl magnesium bromide to yield ketone **94** in modest yield. The authors reported that the optical purity of the product was 100% as determined by NMR studies. No side products arising from the attack at the carbonate were mentioned in the report, indicating that the carbonate was less reactive than the activated ester group. Hence, the mixed carbonate offers an excellent vehicle to the corresponding ketone.

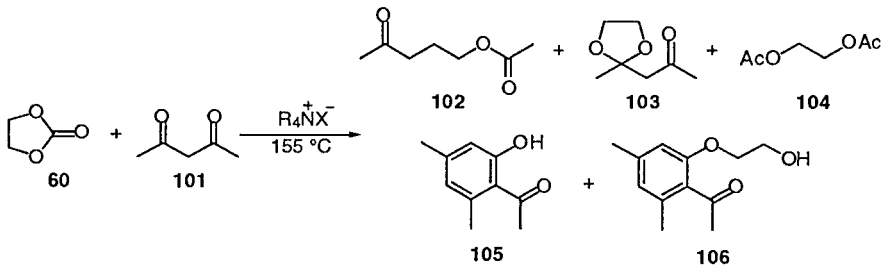
Another noteworthy transformation is methylenation that gives rise to the formation of dialkyl ketene acetals, which seems to bear much promise in further applications. Recently, Holmes reported the synthesis of 8- and 9-membered rings using a tandem methylenation and



Scheme 28.



Scheme 29.



Scheme 30.

Claisen rearrangement of cyclic carbonates.[134] As shown in Scheme 29, methylene insertion occurs at the carbonate carbonyl position via the Petasis reagent (Cp_2TiMe_2) to give compound **97**. The Claisen rearrangement took place immediately to give 8-membered ring **98**. This methodology was then applied to the synthesis of a variety of structures including **99** and **100** and suggested a unique method for entry into medium sized ring templates. Although the yield was moderate to low, the conversion was facile and stereoselective.

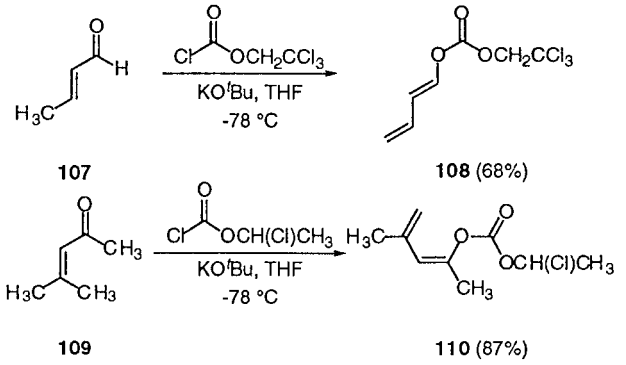
Several papers have been published describing the pyrolytic behavior of carbonates and exhibiting interesting aspects of alkylations using carbonate electrophiles. Ishido reported that ethylene carbonate in the presence of quaternary ammonium or alkali metal halides and active methylene compounds led to a mixture of products.[135] As shown in Scheme 30, when **60** and **101** were heated in the presence of a salt, products **102**–**106** were isolated. The results varied depending upon the salt used; however the major product was either **102** or **103** in all cases. Mechanistically, the reaction was initiated by the nucleophilic attack of the halide on the methylene carbon of **60**, generating a 2-halogenoethanol intermediate. *C*-Alkylation of **101** with the intermediate, followed by hemiacetal formation and ring opening gave **102**. **103** was the product of *O*-alkylation with the enol form of **101** and 2-halogenoethanol, followed by Michael addition. The aromatic system **105** was formed via the acid catalyzed self-condensation of **101** followed by aromatization from loss of water. **105** could then be *O*-alkylated by the 2-halogenoethanol intermediate to give **106**.

3.3. Carbonate enol ether formation

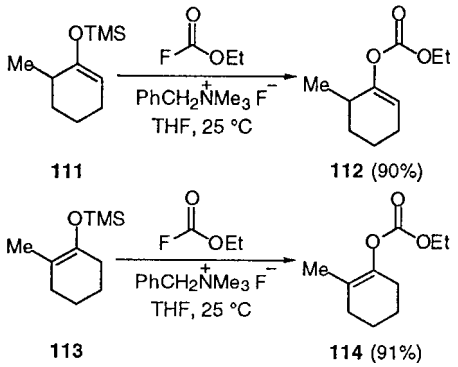
The *O*-alkoxycarbonylation of enolates by chloroformates has been studied extensively since the resultant enol carbonate is an important moiety from both synthetic and industrial standpoints.[136] The major disadvantage of this reaction is competitive *C*-alkylation of the enolate anion, and much effort has been expended attempting to enhance ratios of *O*-versus *C*-alkylation through the modification of reaction conditions. Carbonate enol ethers have been frequently used in aldol type condensations and in Diels–Alder reactions.[137] Enol carbonates have also been used as protecting groups, as they diminish the reactivity of the attached enol olefin. Representative examples including their preparations and applications are elaborated upon hereafter.

Olofson has reported the synthesis of several alkyl dienyl carbonates from their corresponding α,β-unsaturated aldehydes.[138] Using potassium alkoxide bases, the synthesis of 1-(1,3-butadienyl) carbonates like **108** and **110** was performed in high yields using a variety of substrates (Scheme 31). The stereochemical outcome of these reactions can be rationalized based on the fact that **108** prefers the *s-trans* conformation, whereas **110** prefers the *s-cis*. Thus, the reaction proceeded selectively to secure the more thermodynamically stable isomers. These conjugated systems can be further used in polymer chemistry as monomers.[139]

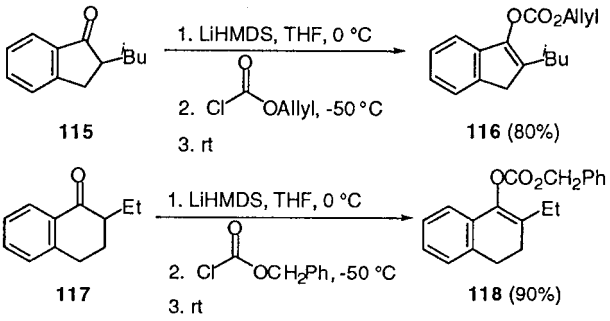
For the synthesis of enol ethers, it is often advantageous to predict the control of the regio- and stereochemical outcomes. Olofson and Cuomo have reported the use of pre-formed silyl enol ethers and fluoroformates as substrates for enol carbonate formation (Scheme 32).[140] Addition of a tetraalkylammonium fluoride generated a hypervalent silicon that favored *O*-over *C*-alkylation. No equilibration in the enol forms were detected. The reaction conditions were mild and applicable to a variety of substrates, offering products in regioisomerically pure form.



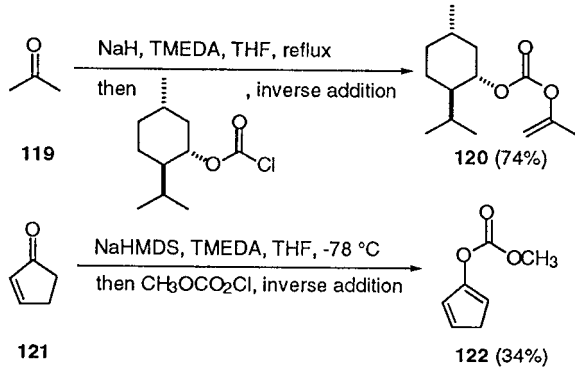
Scheme 31.



Scheme 32.



Scheme 33.



Scheme 34.

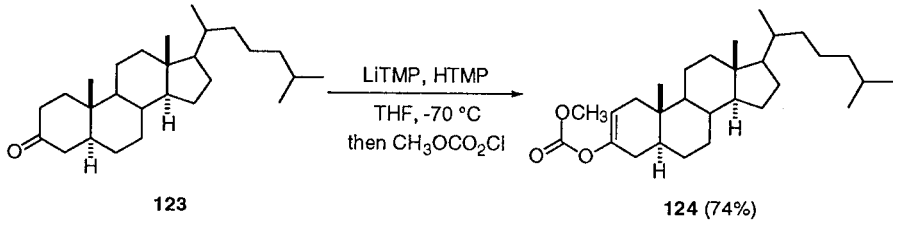
During the synthesis of optically active 2-methyl-1-indanones, Henin reported a method for preparation of enol carbonates without concomitant formation of the *C*-alkylation products (Scheme 33).[141] Thus, when the lithium enolate of **115** or **117** was treated with allyl or benzyl chloroformates, compounds **116** and **118** arose in good to excellent yields. The authors noted that formation of isomeric β-ketoesters, the *C*-alkylation product, was not observed.

Harwood showed that addition of TMEDA during formation of enolates effected exclusive *O*-alkylation after treatment with the desired chloroformates (Scheme 34).[143] Depending upon the nature of the groups on the starting ketones and chloroformates, the desired carbonate enol ethers were exclusively obtained in reasonable yields. Compound **122** is used as a flavorant-release agent in the tobacco industry.[144]

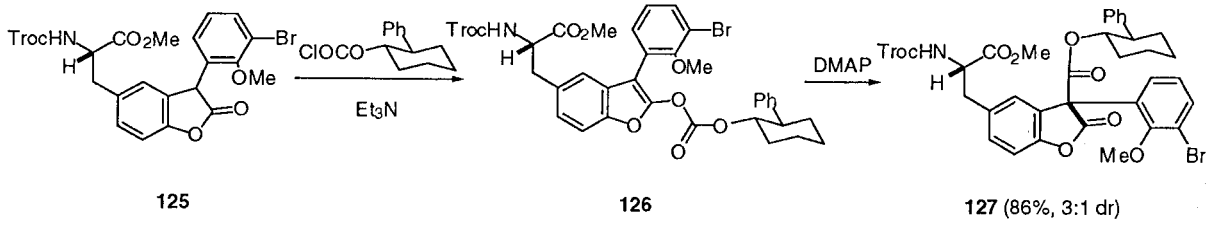
Knowing that high chemoselectivity can be obtained to favor *O*-alkylation, efforts have been made to achieve high regioselectivities in enol carbonate formation. For instance, Olofson prepared enolates encompassing **124** regioselectively using LiTMP as the base and trapped as the alkyl carbonates (Scheme 35).[142] Enol carbonates were synthesized in good yields at low temperatures, and as anticipated, no *C*-alkylation products were detected.

As described above, carbonates can trap enolates in a chemoselective, stereoselective, and regioselective fashion, which is an attractive feature to synthetic applications. Recently, Vedejs used enol carbonates in the synthesis of the potent antitumor agent diazonamide A not only as an enol trapping agent but also as a one carbon homologating source (Scheme 36).[145] Using Black's method,[146] the authors treated compound **126** with DMAP to afford chiral ester **127** in 86% yield and 3:1 diastereoselectivity. The DMAP was presumed to attack the carbonyl of the carbonate, thus acylating the DMAP in the process. The resultant enolate might then undergo *C*-alkylation to attack the active acylated species.

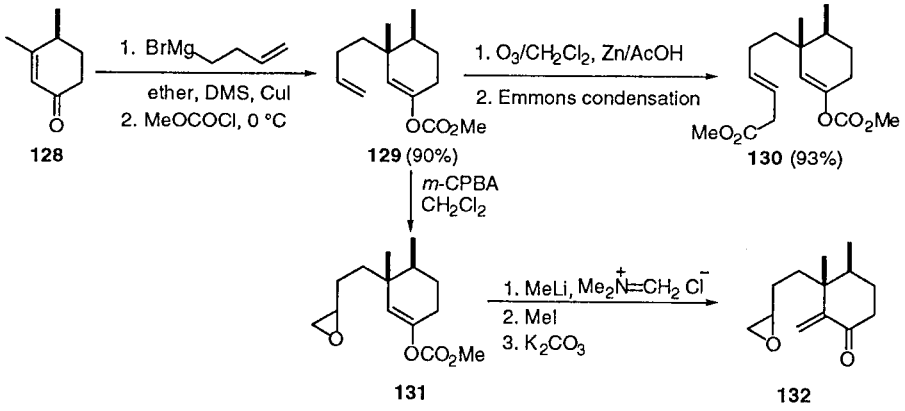
The enol carbonate can also be used as a protecting group and has demonstrated reduced reactivity of the attached olefin. During the total synthesis of the indolic terpenoid aflavanine, Danishefsky reported the synthesis of enol carbonate **129** and its reactions under various conditions.[147] As shown in Scheme 37, selective ozonolysis of **129** followed by an Emmons condensation gave **130** in high yield with the enol carbonate intact. In contrast, treatment of **129** with *m*-CPBA offered the epoxide **131** exclusively at the terminal olefin, and successive alkylation and elimination afforded ketone **132**.



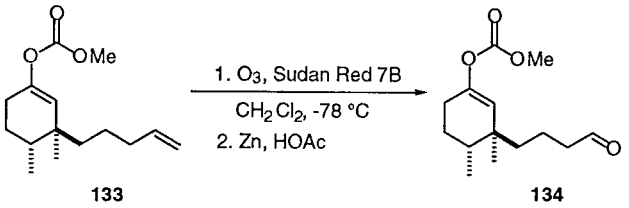
Scheme 35.



Scheme 36.



Scheme 37.



Scheme 38.

Likewise, Silvestri reported selective ozonolysis of dienes containing both an isolated olefin and an enol carbonate (Scheme 38).[148] The reaction occurred exclusively on the isolated olefin, leaving the enol carbonate intact. The authors were unclear as to whether this effect was sterically or electronically driven. However, they postulated that the carbonate underwent a reaction with ozone to give a previously unreported σ-complex, which in turn slows the rate of the carbon-carbon bond cleavage at this position.

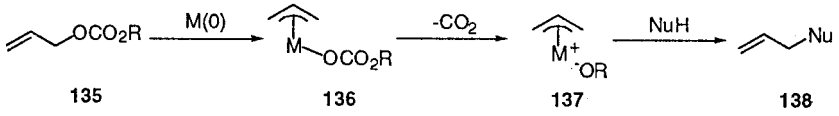
Clearly, carbonate enol ethers have been frequently prepared and utilized in various synthetic projects, often demonstrating superior chemical properties when compared with existing templates. Such beneficial features include outstanding chemoselectivities, which can be summarized by the favorable *O*-alkylation and mitigated reactivity of the resultant enol carbonates. Thus, carbonates facilitate the discovery of solutions to problems that are prevalent in organic syntheses.

4. Functional Group Manipulation through Alkyl Carbonates

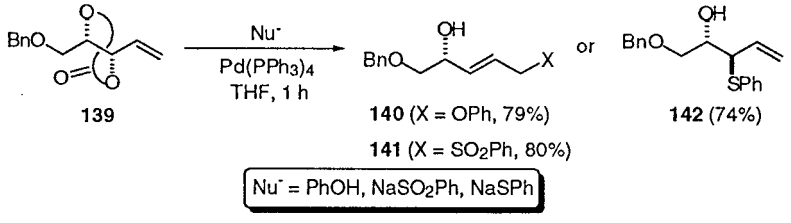
4.1. Organometallic reactions

Carbonates and transition metals have been used together to complete a multitude of reactions, such as oxidations, alkylations, the formation of enones, modification of enol ethers, protecting group removal, including many others. Allylic carbonates are the most commonly used substrates in these reactions because of their high reactivity toward metal catalysts. Typically in these transformations, a π-allyl metal complex **136** is formed first with the loss of CO_2 to give **137**. The complex is then attacked by a nucleophile or eliminates a β-hydrogen as shown in Scheme 39.

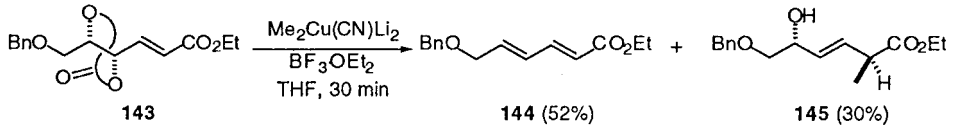
Tsuji published a comprehensive review on palladium catalyzed reactions involving carbonates in 1986,[149] although new reactions have since been reported. Additionally, Dixneuf has authored a review regarding the transformations of cyclic alk-2-ynyl carbonates with transition metals.[150] This section will cover some new methods developed after these reviews were written.



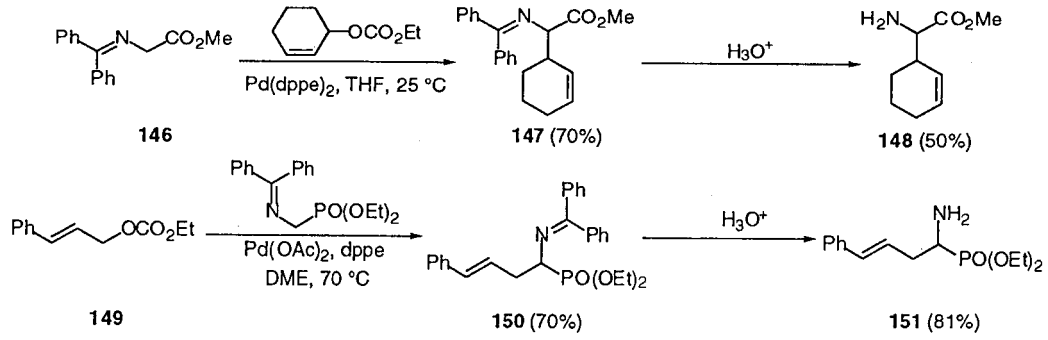
Scheme 39.



Scheme 40.



Scheme 41.



Scheme 42.

4.1.1. Alkylation. Transition metals have been used with carbonates to form new C–C bonds. As described in Tsuji's and Dixneuf's reviews, an assortment of carbonate based alkylation reactions have been performed under catalytic conditions. New methodology is constantly being developed to enhance the known repertoire of techniques.

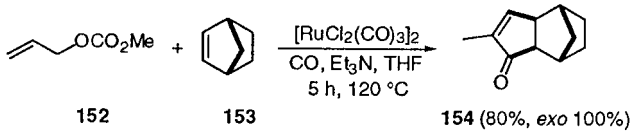
For example, Kang treated allylic and dienylic cyclic carbonates with specific nucleophiles and a palladium catalyst.[151] As shown in Scheme 40, new bonds were formed between the incoming nucleophiles and carbonates in a highly regiospecific manner to give products such as **140**–**142** in good yields. In comparison, this reaction was also performed using a ruthenium catalyst and similar results were obtained.[152] The method was then applied to carbon based nucleophiles including diethyl malonate or phenyl allyl sulfone, and yields were generally high, offering short reaction times.[153]

The addition of organocopper reagents to allylic cyclic carbonates and to carbonates of γ,δ-dihydroxy (*E*)-α,β-enoates has also been reported.[154,155] The products obtained in these reactions are similar to those in Scheme 40, however a competitive reductive elimination occurred in the case of enoates as illustrated in Scheme 41.

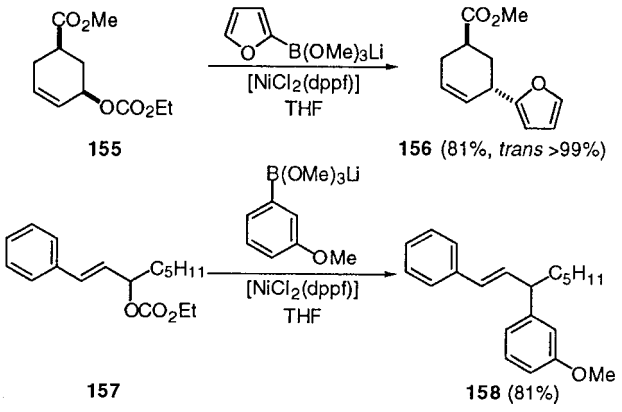
Transition metals have frequently been used to synthesize both α-and β-amino acids.[156] Genet used Schiff bases derived from amino acids as nucleophiles in the alkylation of carbonates.[157] As shown in Scheme 42, **146** was alkylated with an allylic carbonate to give **147** in fairly high yield. The authors stated this technique offered an approach to unsaturated amino acids after hydrolysis of the Schiff base with dilute HCl. Genet has used a similar sequence to synthesize α-aminophosphonic acids such as **151**.[158]

Recently, a highly stereoselective route to cyclopentenones was described by Kondo.[159] In the presence of a ruthenium catalyst, allylic carbonate **152** and alkene **153** were cyclized under carbon monoxide to give product **154** (Scheme 43). Other combinations of allylic carbonates and alkenes provided similar types of adducts. Yields were very high when a triethylamine ligand was employed, and the products were formed in a highly stereoselective fashion, offering the *exo* isomer exclusively. The mechanism of this reaction is described in the report, and is similar in nature to a Pauson–Khand reaction.[160]

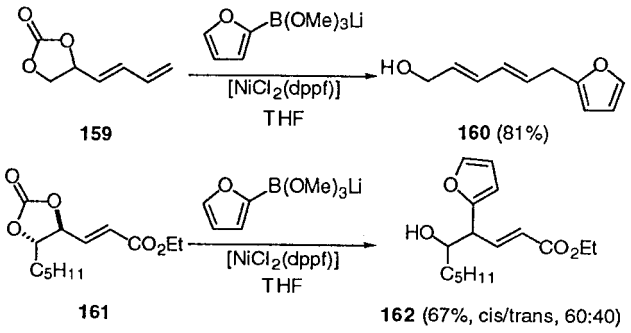
Using the aforementioned approach, Kobayashi demonstrated a nickel catalyzed coupling of aryl- and alkenylborates with allylic carbonates.[161] For example, compounds **156** and **158** were synthesized in good yields upon treatment with appropriate conditions in 12–15 h (Scheme 44). Unlike standard Suzuki reactions, palladium catalysts failed to provide the desired transformations, converting the substrates instead to methyl ethers. When a chiral substrate



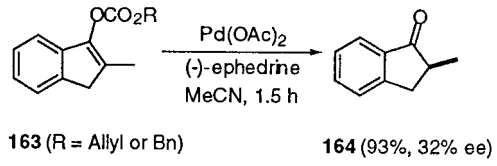
Scheme 43.



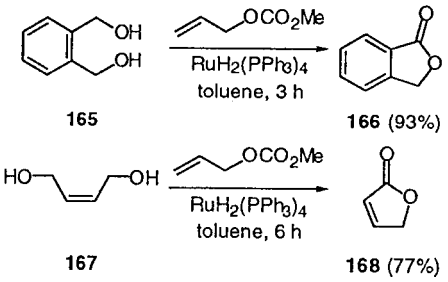
Scheme 44.



Scheme 45.



Scheme 46.



Scheme 47.

like **155** was employed, high diastereoselectivity was obtained >99% *trans*.

Likewise, Kobayashi used similar alkylation conditions with cyclic carbonates to prepare substituted allylic and homoallylic alcohols (Scheme 45).[162] In the case of compound **161**, moderate diastereoselectivity was achieved providing a *cis/trans* ratio of 60:40 in 4 h at 60°C.

Unfortunately, the alkylation using organometallic reagents are currently limited to allylic substrates. However, alkyl carbonates are still invaluable for these transformations since there are numerous available allylic substrates and interesting allylic intermediates during various syntheses. Carbonate routes are anticipated to become employable alternatives to the existing pathways in organometallic alkylations.

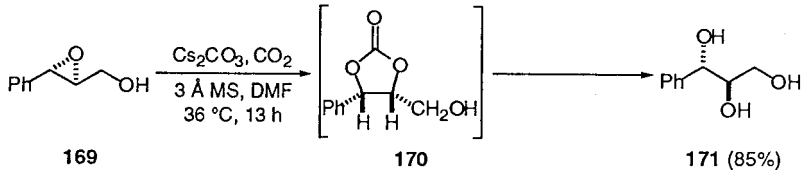
4.1.2. Enol modification. The manipulation of the enol ether or enol carbonate functionalities has been accomplished which allows for several types of organic transformations. Recently, Henin described the palladium-catalyzed formation of optically active ketones from their prochiral enol carbonates.[163] Using a chiral aminoalcohol such as (−)-ephedrine along with a metal catalyst, the authors were able to obtain ketone **164** in high yield and with modest *ee* ratios (Scheme 46).

4.1.3. Oxidation. Mild oxidation of organic materials is one of the most desirable transformations in synthesis. Carbonates have been used to oxidize a variety of functionalities in conjunction with a transition metal catalyst.[164,165] Alcohols have been oxidized from their corresponding allyl carbonates after treatment with palladium or ruthenium catalysts. One-pot oxidations of alcohols by direct treatment with allyl carbonates and an appropriate catalyst is an alternative to this method.

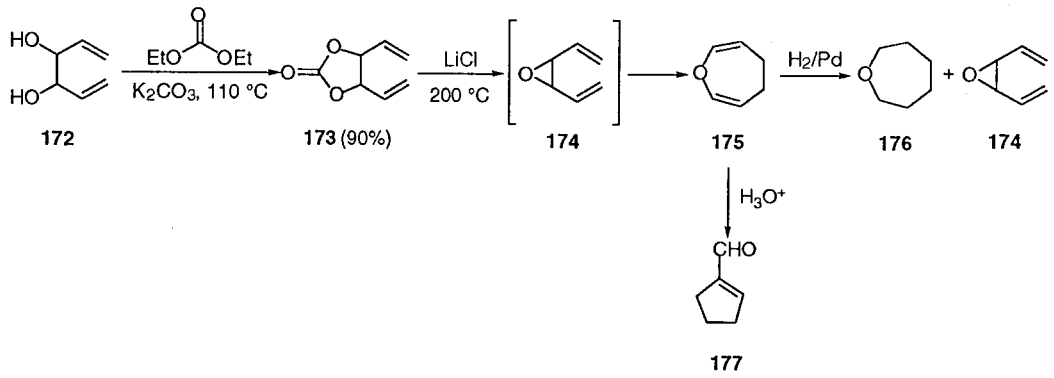
For example, Tsuji reported the oxidation of alcohols to give ketones and 1,4- or 1,5-diols to give the corresponding lactones.[166] As delineated in Scheme 47, when **165** was treated with allyl methyl carbonate and a ruthenium catalyst, **166** was formed in 93% yield and in less than 3 h. Similarly, (*Z*)-2-butene-1,4-diol **167** reacted completely in 6 h to give lactone **168** in 77% yield.

4.2. Oxygen introduction and removal

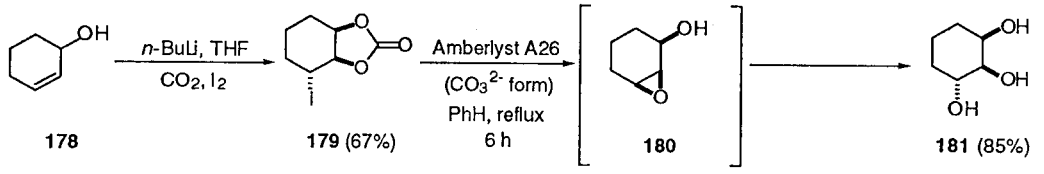
Due to their high oxygen content, alkyl carbonates can become excellent sources of oxygen functionalities such as hydroxyls. Described below are the introduction and removal of those oxygen functional groups. Triol formation in an asymmetric fashion is one of the most useful reactions in this category. As represented in Scheme 48, Myers reported the use of an asymmetric 2,3-epoxy alcohol to give triol **171** under mild conditions. The reaction proceeded through an in situ generated carbonate **170**, offering high yields and excellent ee's in >98%.[167] Cesium bases were used to mildly introduce the carbonate function,[33,34] and in this case facilitated the reaction of the inchoate alkoxide with carbon dioxide. However, the presence of a nucleophilic hydroxyl group in **170** likely rendered the molecule too unstable to be isolated as a carbonate. However, this mild cesium promoted condition may be a valuable tool for conducting Payne-type rearrangements at low temperatures in the absence of undesirable Lewis acids or strong bases.[168]



Scheme 48.



Scheme 49.

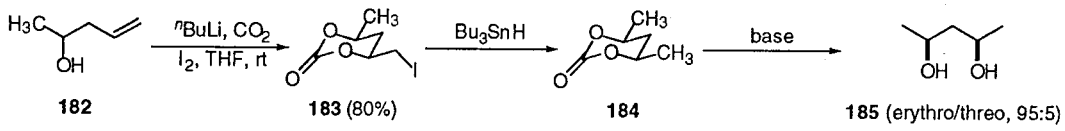


Scheme 50.

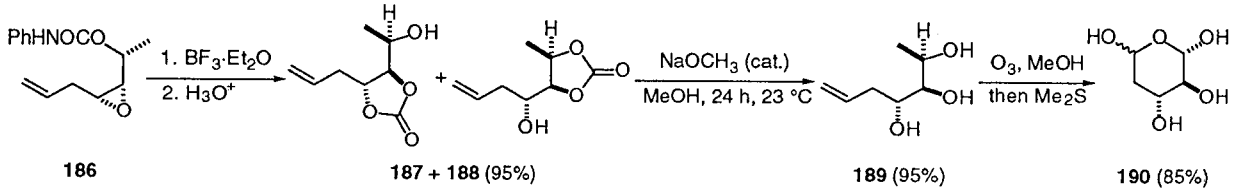
Cyclic carbonates have been used to synthesize several interesting and useful materials. For example, Braun treated **173** with LiCl at 200°C to give 4,5-dihydrooxepine **175** via an epoxy intermediate **174**.[169] This compound was then transformed into **176** under hydrogenolysis, or to **177** by acid hydrolysis (Scheme 49).

Iodo carbonates are also useful synthons and can be utilized for the synthesis of triols as illustrated in Scheme 50. Cardillo employed allyl and homoallyl alcohols to synthesize iodo carbonates. For example, **178** was treated with the appropriate conditions to give **179**, which was then subjected to hydrolysis with the carbonate ion supported on Amberlyst A 26 ion exchange resin.[170] After the reaction had proceeded, the triol product **181** was easily cleaved from the resin with anhydrous methanol, which allowed the highly polar material to be isolated cleanly. The process gave retention of configuration at the initial stereogenic positions found in the starting carbonate **179** (erythro/threo 99:1) via an intermediate epoxide **180**.

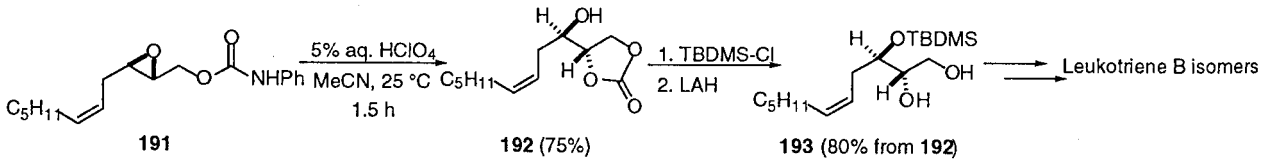
In a similar report (Scheme 51), diols were prepared from homoallylic alcohols via carbonate intermediates.[171] Compound **182** was treated under carbonate forming conditions, then subjected to reduction with tributyltin hydride to



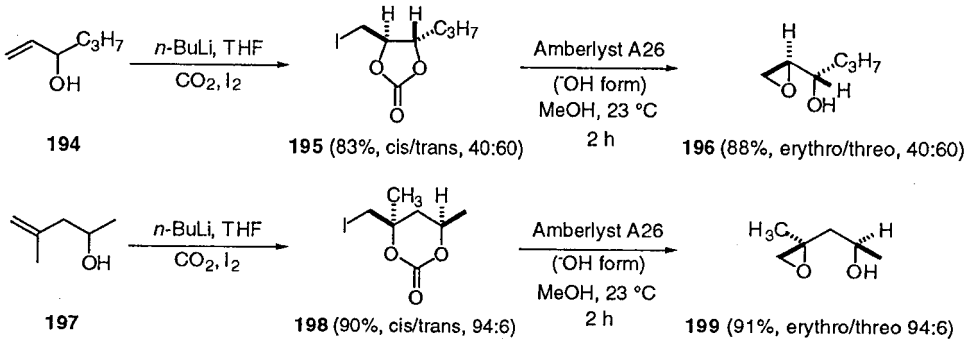
Scheme 51.



Scheme 52.



Scheme 53.



Scheme 54.

give **184**, which after hydrolysis in aqueous base provided the diol **185** stereoselectively.

During the synthesis of olivomycin A, Roush developed a method for the synthesis of carbohydrates (Scheme 52).[172] Carbonates were generated regioselectively from β-epoxy phenylurethanes **186** by treatment with $BF_3{\cdot}Et_2O$.[173,174] The mixture of carbonates **187** and **188** was then subjected to catalytic ring opening conditions to yield triol **189** as a single isomer. Oxidative cleavage of the olefin moiety yielded the desired carbohydrate **190**.

As illustrated in Scheme 53, Corey reported the synthesis of several isomers of leukotriene B using a similar method.[175] Thus, urethane **191** was treated with aqueous acid to give cyclic carbonate **192** stereoselectively, which after silyl protection and LAH reduction furnished diol **193** in high yield.

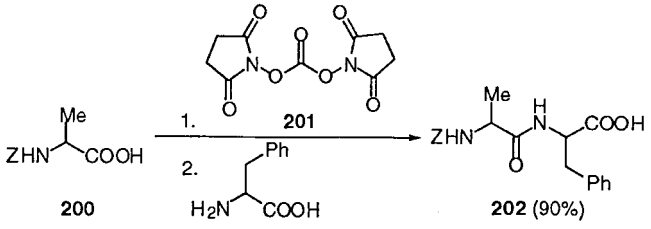
While volumes of work have been done on the synthesis of epoxides from various functionalities, little has been mentioned of carbonates as potential substrates for this conversion. Cardillo reported the transformation of iodo carbonates into epoxides using hydroxide-supported Amberlyst ion exchange resins as shown in Scheme 54. The reaction was quick, mild, and the yields were good depending on the nature of the substituents.[170] As with the synthesis of triols, retention of configuration from the starting carbonate was observed.

In summary, alkyl carbonates have been implemented in numerous syntheses and used to create oxygen functionalities including diols, triols, and epoxy alcohols. Moreover, hydroxyls have also been introduced in a stereoselective manner through cyclic carbonates, which should have merit for various applications in asymmetric synthesis.

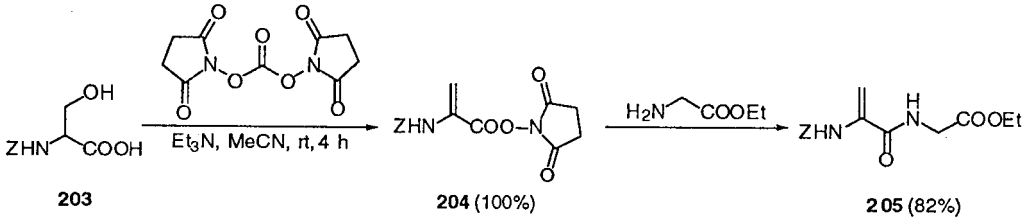
4.3. Activation of functional groups

Disuccinyl carbonate (**201**) has become a very useful reagent for the alteration of organic functionalities. It has been used principally in peptide synthesis, allowing for the conversion of amino acids to active esters, which then undergo the desired coupling reactions. Nonetheless, this carbonate has also found use for the preparation of other important synthons. Ogura has summarized many of the reactions involving this reagent.[176]

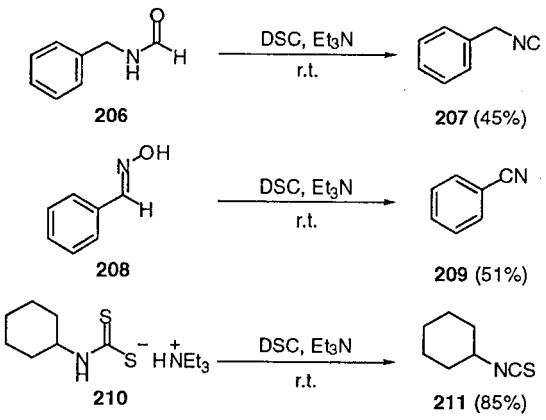
Peptide synthesis has seen many advances throughout the years with the constant development of novel reagents like DCC, EDC, BOP–Cl, etc., which all aid in coupling processes, increase yields, and limit racemization. Disuccinyl carbonate (DSC) has been used in this fashion, and has offered a mild and safe alternative to existing



Scheme 55.



Scheme 56.



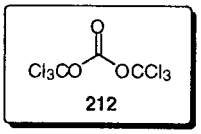
Scheme 57.

agents. In Ogura's paper, the synthesis of active esters via DSC and the ensuing coupling with other amino acids proceeded in excellent yields as illustrated in Scheme 55.

DSC has also been used as a β-elimination reagent with β-hydroxyamino acids.[177] Z-Serine-OH **203** was treated with DSC and triethylamine at room temperature to give the Z-Δ-alanine-OSuc **204** in quantitative yield (Scheme 56). This active ester was then coupled with glycine ethyl ester to yield dehydropeptide **205** in 82% yield. These materials are important precursors for the synthesis of peptide antibiotics.

In addition to the reactions of DSC with amino acids, it has also been used for the synthesis of other important synthons as shown in Scheme 57. Benzyl isocyanide (**207**), benzonitrile (**209**), and cyclohexyl isothiocyanate (**211**) can all be prepared from their respective starting materials via DSC.[176]

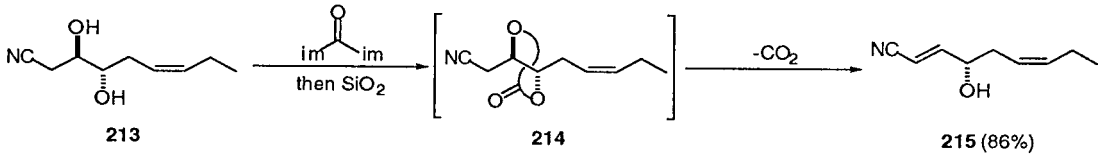
Bis(trichloromethyl) carbonate (**212**) has been used extensively as a phosgene equivalent and was recently reviewed by Cotarca.[119] It offers an alternative to gaseous and highly toxic phosgene. BTC has been used to synthesize isocyanates, heterocycles, acid chlorides, and alkyl chlorides, and is quickly becoming one of the most utilized carbonates in organic synthesis.



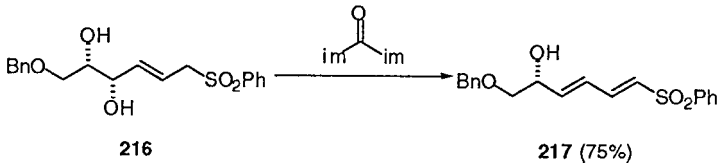
Kang has synthesized chiral (*E*)-γ-hydroxy-α,β-unsaturated nitriles from corresponding diols via an in situ elimination of a cyclic carbonate.[178] The reaction was both mild and rapid, affording the nitriles in 80% yield (Scheme 58). The (*Z*)-isomer was not observed in any case, and the reaction occurred with high enantioselectivity. Additionally, in the case of **215** no isomerization of the preexisting olefin was observed.

This same technique has been applied to dehydration of dihydroxy sulfones.[179] As shown in Scheme 59, the selective elimination of allylic hydroxyl in diol **216** gave **217** in good yield. Mechanistically, this reaction proceeded through an intermediate carbonate like **214**. Elimination of the alcohol provided more extended conjugation in the system, leaving the allylic alcohol intact.

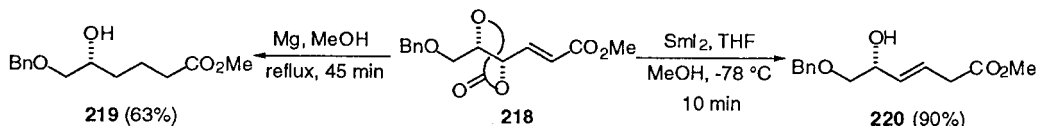
Furthermore, the reductive elimination of cyclic carbonates of unsaturated esters has been reported.[180] By variation in conditions, saturated alcohol **219** or allylic alcohol **220** could be obtained from carbonate **218** (Scheme 60). In a similar report, the authors showed the same reductions occurred with the cyclic carbonates of 1-halo-2,3-alkanediols to yield optically active allylic alcohols.[181] Utilizing these procedures, alcohol synthons can be further manipulated in Sharpless asymmetric epoxidations, transesterification to form cyclic enoates, or in other olefinic transformations.



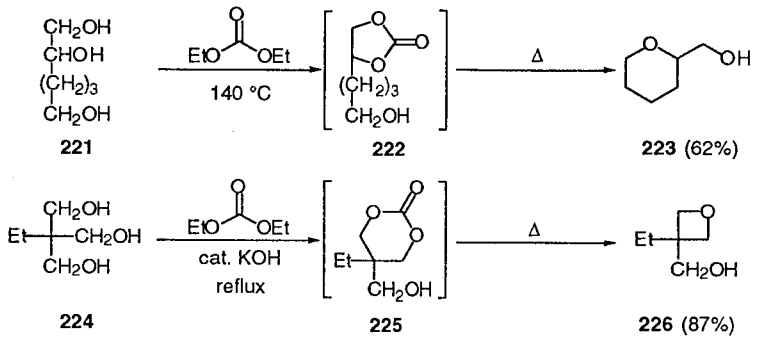
Scheme 58.



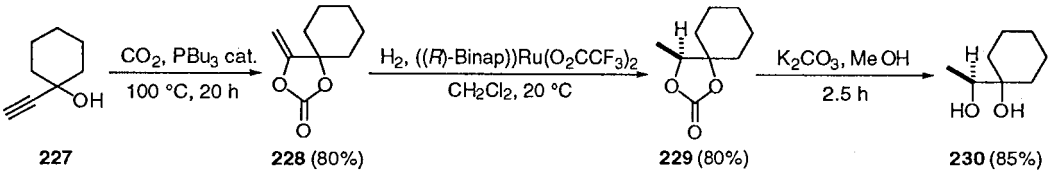
Scheme 59.



Scheme 60.



Scheme 61.



Scheme 62.

While the aforementioned examples showed selective elimination of diols via activated carbonates, the following showcase exhibits the activation of polyols, facilitating the intramolecular cyclization. Pattison described the preparation of cyclic ethers containing a hydroxyl moiety from polyol starting materials.[182] Thus, the pyrolysis of in situ prepared cyclic carbonates such as **222** and **225** afforded various oxygen containing cyclic ethers in good yields (Scheme 61). Oxacycles of different sizes, including 4-, 5-, and 6-membered rings, were synthesized. This method for the activation of polyols avoids phosgene and is safer for industrial purposes.

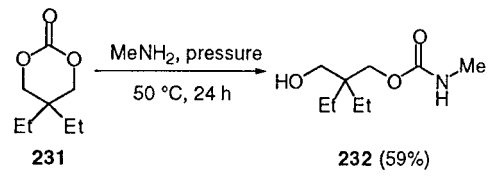
In an asymmetric sense, the synthesis of diols from carbonates has been described.[183] Dixneuf reported that hydrogenation of compounds like **228** with a chiral diphosphine ruthenium catalyst gave carbonates **229** with >90% *ee* (Scheme 62). These molecules were then subjected to hydrolysis with methanolic potassium carbonate to give high yields of optically active diols such as **230**. By choosing the enantiomer of the ruthenium catalyst, the synthesis of the alternative isomer can be performed, consolidating this method into a more general procedure. This remarkable chemistry addressed the regioselective activation of the triple bond, which generated a stable enol carbonate for further operations.

4.4. Carbonate exchange reactions and subsequent modifications

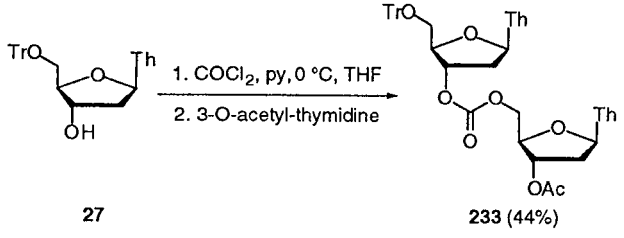
The carbonate exchange reaction is typically categorized by nucleophilic attack on carbonates by alcohols and amines to generate new carbonate equivalent structures. Using such an exchange-type reaction, several anticonvulsant agents have been developed.[184] Starting from a cyclic carbonate percursor **231**, Piech synthesized 2,2-disubstituted-1,3-propanediol carbamate **232** upon treatment of **231** with the appropriate amine (Scheme 63).

Utilizing exchange reactions, carbonates have been applied quite extensively within the field of carbohydrates. In addition to being the source for selective protection/deprotection strategies, the carbonate functionality has been exploited as a tool for oligonucleoside assembly as well as carbohydrate manipulation. In the application to oligonucleoside synthesis, the carbonate scaffold has been used to replace or mask the phosphate region,[185] which was first attempted to overcome cellular permeability and later to serve as a selective enzyme inhibitor.[186] The synthesis of these compounds usually starts with an active carbonate ester attached to a sugar moiety, followed by coupling with a free hydroxyl on another nucleoside via a carbonate exchange reaction.

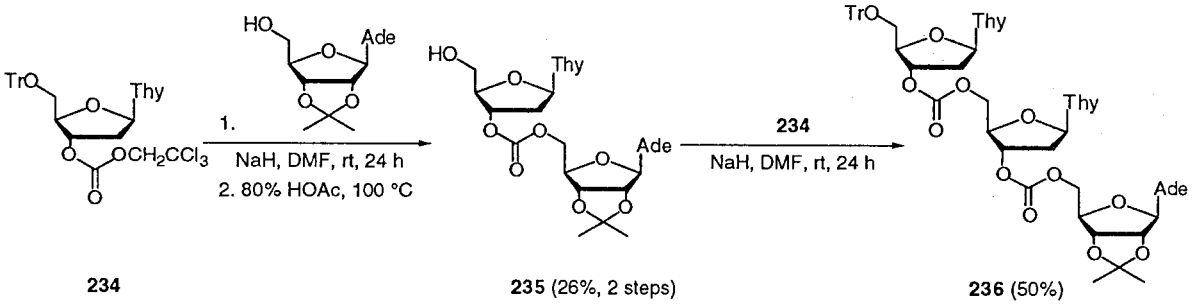
In this regard, in situ formation of nucleoside carbonates has been well studied. Coats passed phosgene into a THF solution containing 5′-tritylthymidine **27** and pyridine to generate a chloroformate intermediate.[187] The solution was then added to an appropriate OH acceptor to form compound **233** in modest yields (Scheme 64). Although



Scheme 63.



Scheme 64.



Scheme 65.

this reaction lacks in yield, the benefit lies in the efficiency. The chloroformate formation is quick and simple, and avoids the need to isolate the active carbonate.

Tittensor reported the use of 5′-*O*-protected deoxyribonucleoside 3′-*O*-carbonate active esters for the synthesis of dinucleoside carbonates.[188] The carbonate **234** was prepared and subjected to further transformations (Scheme 65). Thus, pyrimidine and purine di- and trinucleoside carbonates were synthesized in moderate yields. These compounds serve as growth inhibitors that have increased cellular permeability due to the nonionic carbonate linkage.

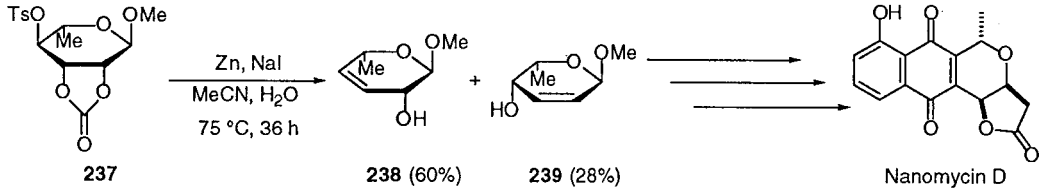
Carbonates have also been used in organic synthesis to modify or transform carbohydrates into new synthons. In the total syntheses of the antibiotics nanaomycin D and kalafungin, 2,3-di-*O*-carbonyl-6-deoxy-4-*O*-tosyl-α-L-mannoside (**237**) was used as a building block for a key intermediate.[189] Thus, when cyclic carbonate **237** was treated with Zn and NaI, unsaturated alcohols **238** and **239** were generated as shown in Scheme 66. The authors stated that this reaction likely proceeded via a 3,4-epoxide intermediate.

In analyzing reactions of polyhydroxy compounds with ethylene carbonate, an unexpected result was obtained with uridine **240** as shown in Scheme 67.[190] Compound **242** was synthesized in good yield via a cyclic carbonate intermediate **241**. Various carbonate exchange reactions and similar conversions have been observed in numerous carbohydrate syntheses because of their versatile utility.

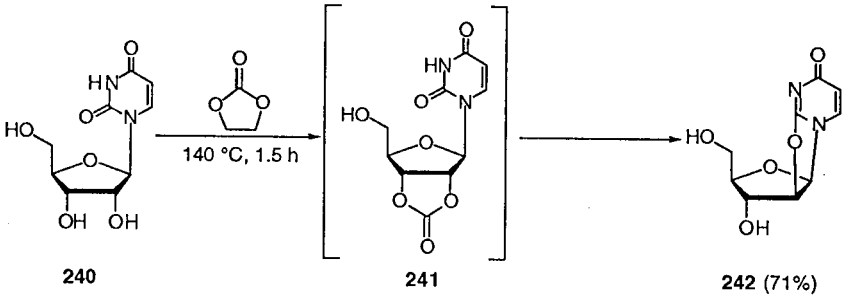
4.5. Promotion of glycosylation

Glycosylation is another important transformation where carbonates have been effectively utilized. Ikegami reported an intramolecular decarboxylative glycosylation using carbonates as the activating group.[191] As shown in Scheme 68, protected carbohydrate **244** was synthesized, then treated with an appropriate Lewis acid like TMSOTf, to affect the decarboxylation. When the carbonate donor group contains a carbohydrate, a new sugar linkage was formed as in the case of **245**. When a non-polar solvent such as toluene was used, the ratio of β to α stereoselectivity became as high as 5.25 to 1. However, the authors did not provide a rationale for this observed solvent effect.

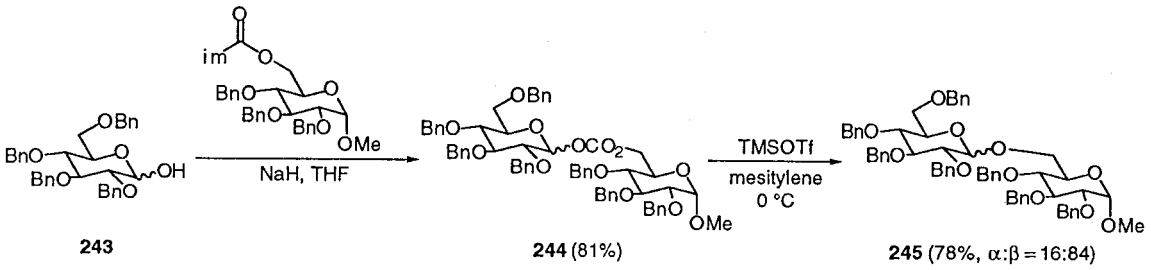
Ishido reported the pyrolytic behavior of D-glucopyranose 1-carbonate derivatives.[192] When compound **246** was heated to 190°C for 4 h, a mixture of products **247**–**250** was observed as shown in Scheme 69. Although this reaction failed to provide good selectivity, the anomeric center was



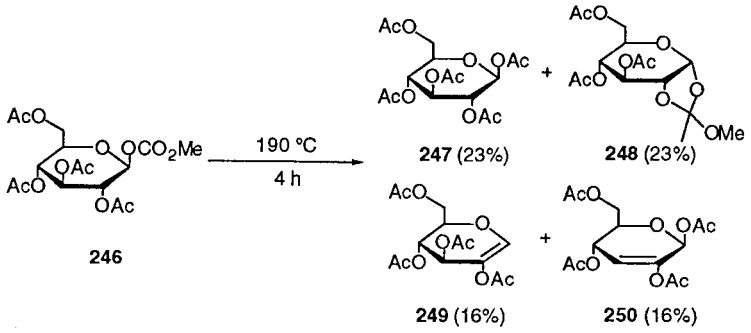
Scheme 66.



Scheme 67.



Scheme 68.



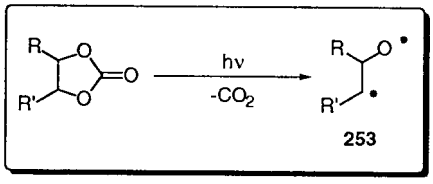
Scheme 69.

functionalized efficiently. The mechanism for the formation of all isolated products was proposed in the paper.

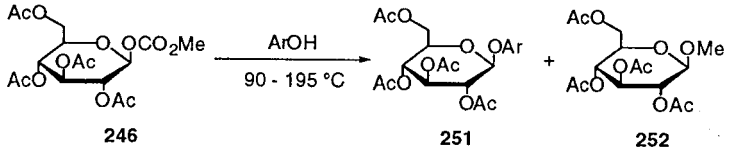
Also described in Ishido's paper was the pyrolysis of carbonates in the presence of various phenols. As depicted in Scheme 70, varying yields of **251** and **252** were obtained depending on the phenols used. Since Knorr type glycosylations involve the use of silver ions, this pyrolysis technique of carbonates can be an inexpensive alternative. The use of nitrophenol was compatible with this methodology.

5. Photochemistry of Carbonates

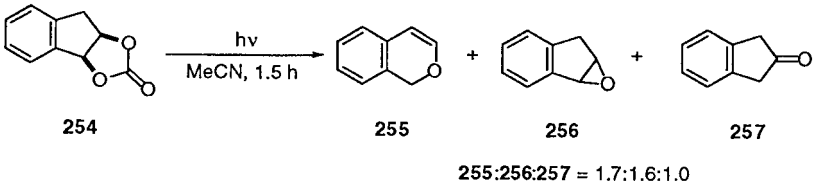
Carbonates have been employed in several types of photo-induced reactions. Cyclic carbonates have been the most widely studied, where the intermediates typically exist as carbenes or diradicals. The most popular proposed mechanism involves the evolution of CO_2 via a singlet state system to give diradical intermediate **253**. This intermediate can then undergo many different reactions depending on solvent choice, conditions, or substitutions at the R and R′ positions. However, other studies have suggested that a carbene type intermediate is involved in the transition state.



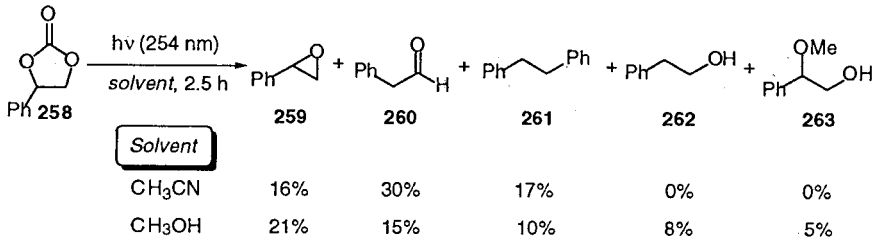
White has shown that the photolysis of **254** afforded isochromene **255**, indene oxide **256**, and 2-indanone **257** in a ratio of 1.7:1.6:1 (Scheme 71).[193] The proposed intermediate in this reaction is a diradical similar to **253**, which can undergo ring closure to give **256** or, after a hydrogen migration, to **257**. Compound **255** is thought to proceed via



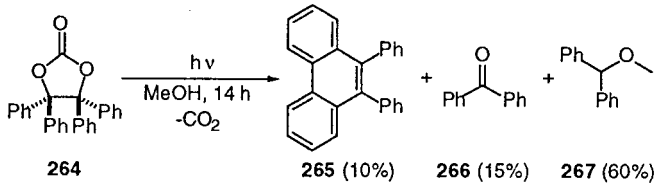
Scheme 70.



Scheme 71.



Scheme 72.



Scheme 73.

a Grob type fragmentation of the proposed intermediate, which then can isomerize to give the isochromene.

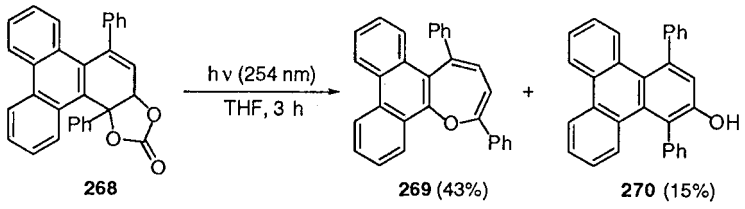
In another study, White demonstrated that the solvent played a role in the photolysis of carbonate systems.[194] When **258** was irradiated at 254 nm in acetonitrile, oxirane **259**, aldehyde **260**, and bibenzyl **261** were obtained after 2.5 h (Scheme 72). However, when the same reaction was run in methanol, a multitude of products **259**–**263** was obtained. Products **262** and **263** were seemingly obtained in an acid catalyzed ring opening of **259**.

Griffin has reported that photocycloelimination reactions of cyclic alkyl carbonates such as **264** proceed through a carbene intermediate.[195] Thus, compound **267** was formed as the major product in 60% yield from the reaction of diphenylcarbene with methanol. Additionally, benzophenone **266** and secondary photoproduct **265** were formed in 15 and 10% yield, respectively, as well as the release of CO_2 (Scheme 73).

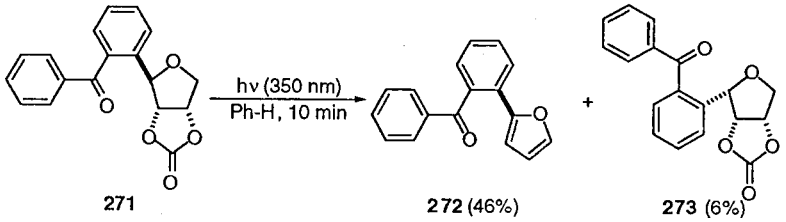
The photolysis of carbonates has also been used to create interesting new heterocycles.[196] Harrison has shown that when **268** was irradiated at 254 nm, two products were obtained which included the 7-membered ring oxacycle **269**, as well as phenol **270**, respectively (Scheme 74).

As a model system for the enzymatic reduction of 2′-ribonucleotides to 2′-deoxyribonucleotides, Berkessel prepared cyclic carbonate **271** and subjected it to photolysis to induce aromatization of the tetrahydrofuran ring.[197] As shown in Scheme 75, furan **272** was prepared in 46% along with a minor amount of its epimer **273**.

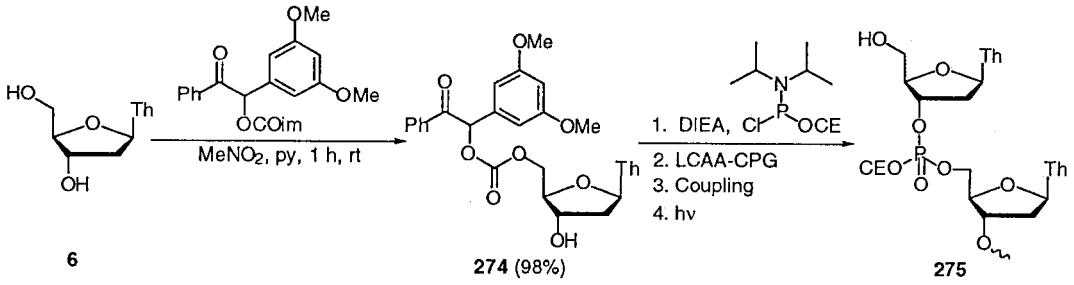
Also, the 3,5-dimethoxybenzoin carbonate has been used as a photolabile alcohol protecting group in the synthesis of phosphoramidite-based DNA.[198,199] The alcohol was first converted to the carbonate, phosphorylated, coupled, then removed selectively by irradiation at 350 nm to offer **275** in high yield after 1 h (Scheme 76).



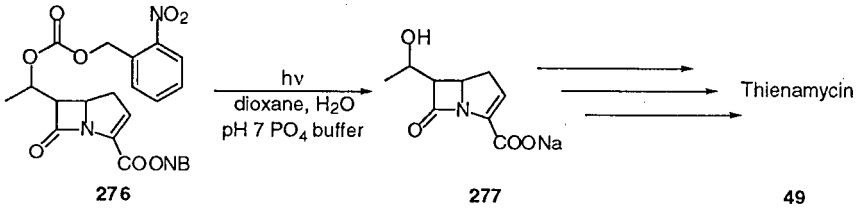
Scheme 74.



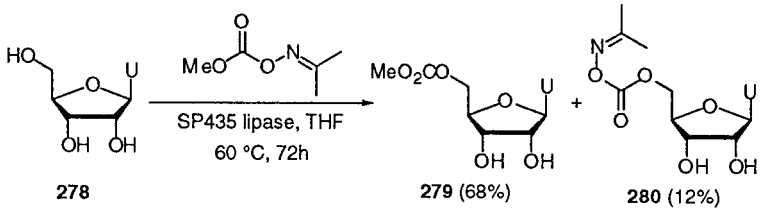
Scheme 75.



Scheme 76.

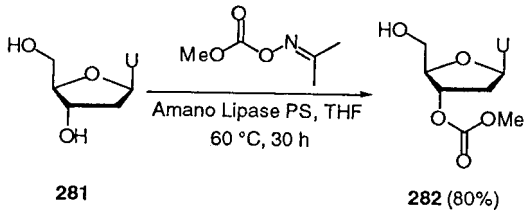


Scheme 77.



Scheme 78.

As summarized in the preceeding section, photolytic techniques have been applied to carbonate moieties for the preparation of new structural motifs and mild cleavage of protecting groups and linkers. Another example of this is in the total synthesis of the potent antibiotic thienamycin (**49**), wherein the *o*-nitrobenzyl carbonate protecting group was used to mask a hydroxyl group.[107] The removal of this group by irradation proved to be a mild, non-destructive protection method (Scheme 77).

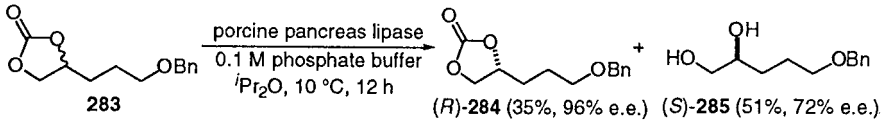


Scheme 79.

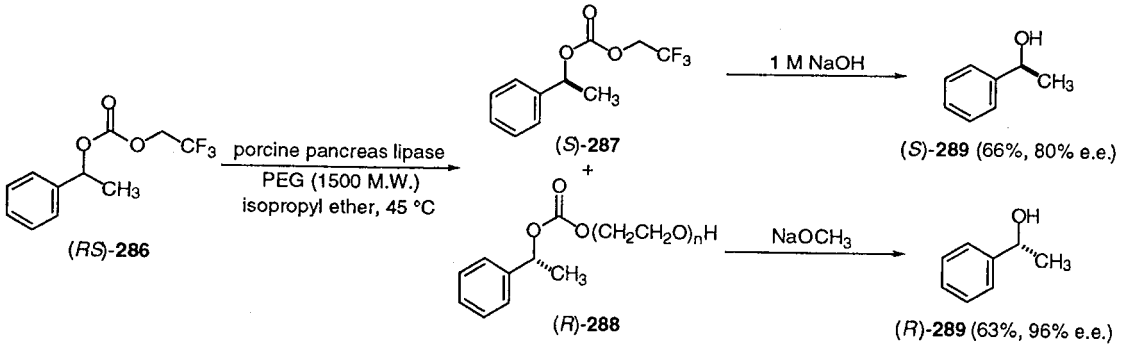
6. Enzymatic Reactions of Carbonates

The major drawback of using the carbonate protecting group is its introduction via haloformates. These materials, as stated previously, are typically generated from phosgene, which is a toxic and costly method. There have been several reports of 'green' alternatives that avoid the use of haloformates and limit the safety hazards. For instance, Gotor introduced a methyl carbonate to the 5′ primary alcohol of a carbohydrate selectively via an enzymatic alkoxycarbonylation in good yield (Scheme 78).[200,201] However, this technique is currently plagued by long reaction times and lower yields when compared to standard methods via haloformates.

In contrast, the 3′-OH group can be protected selectively by varying the enzyme used in the reaction as shown in Scheme 79. In this case, no side products were detected, the reaction time was shorter, and the yield was higher. The authors noted that this method can also be used to introduce allyl, benzyl, and vinyl carbonate groups to the 3′-OH position.[202]



Scheme 80.



Scheme 81.

Carbonates have been used in conjunction with enzymes to resolve racemic alcohols. For example, Matsumoto prepared optically active 1,2- and 1,3-diols via an enzymatic hydrolysis of the starting racemic carbonates.[203] As shown in Scheme 80, resolution of **283** with porcine pancreas lipase (PPL) gave carbonate **284** and diol **285**. The authors screened numerous lipases and found that only PPL had any hydrolytic activity in these type of transformations.

Morrow has shown the resolution of carbonate **286** using a lipase catalyzed transesterification reaction with poly-(ethylene glycol).[204] Thus, the (*R*)-enantiomer was converted selectively by PPL to compound **288**, leaving the (*S*)-enantiomer unchanged (Scheme 81). After basic hydrolysis of the corresponding carbonates, both enantiomers of alcohol **289** were obtained in good yields. Studies on enzymatic chiral resolution of carbonates have been rather rare although the previous results have demonstrated possible future applications.

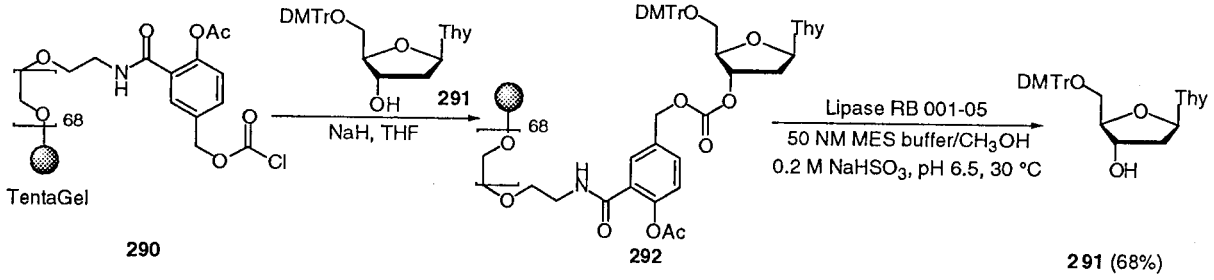
7. Carbonates in Solid Phase Synthesis

Carbonates have seen extensive use in the field of solid phase chemistry as linkers and tagging moieties. Waldmann has shown that alcohols can be placed on an enzyme labile solid phase support containing a carbonate linker (Scheme 82).[205] The acetate of carbonate **292** is an enzyme labile functionality that when subjected to lipase RB 001-05, initiates a cleavage of the carbonate through a quinone intermediate to provide the alcohol **291** in good yield.

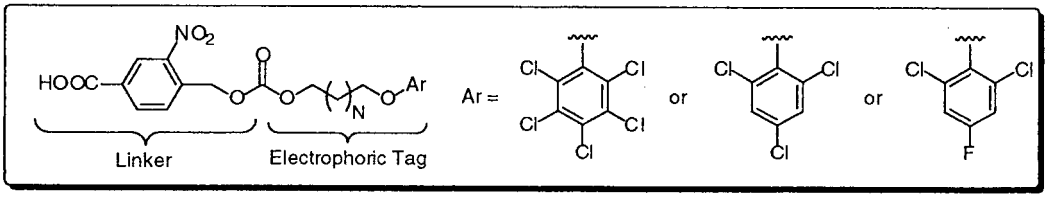
Still has provided the well known molecular tag shown in Scheme 83 for the synthesis of chemical libraries via combinatorial chemistry.[206] These tags allow the user to record reactions that have taken place using a binary coding system. The 'reading' of the code is performed via gas chromatography thus allowing the elucidation of structure for a molecule on a single solid phase bead.

Recently, Greenburg described the synthesis of a palladium labile solid phase support for the synthesis of oligonucleotides (Scheme 84).[207] Thus, when **293** was treated with Pd(0), the support was released, yielding oligonucleotides that have 3′-alkyl carboxylic acids or 3′-hydroxy groups in high yields.

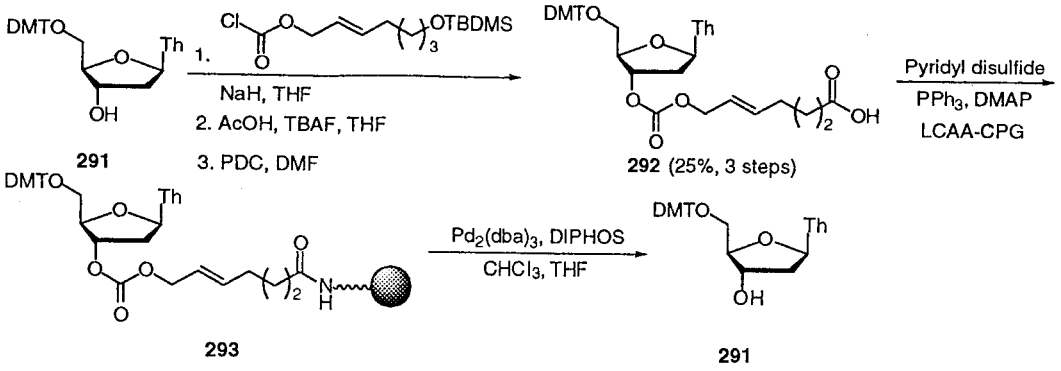
Several photolabile protecting groups for use with alcohols and amines have been developed with the carbonate backbone. The function of an alkyl carbonate as a photolabile support was reported in the synthesis of oligonucleotides with 3′-OH terminals (Scheme 85).[208] This group utilizes



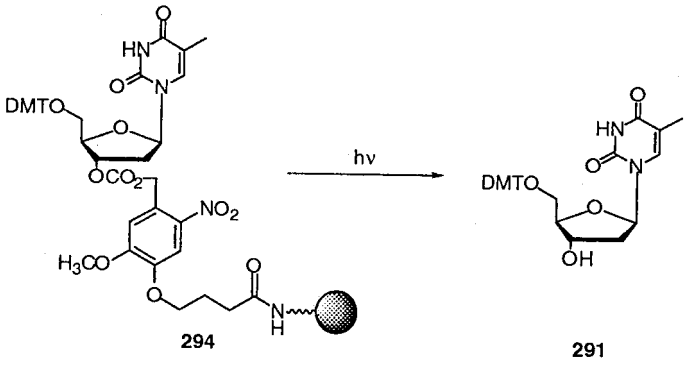
Scheme 82.



Scheme 83.



Scheme 84.

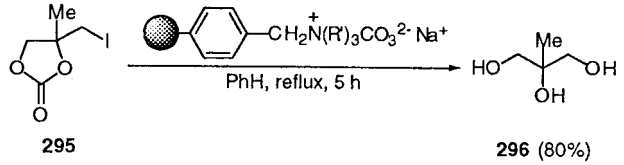


Scheme 85.

the *o*-nitrobenzyl group, which is quite prevalent in photochemistry.

Polymeric bound carbonate salts have been used to perform a variety of transformations. For example, iodo carbonates can also be converted to triols mildly as described in Scheme 86. Thus, treatment of **295** with a carbonate ion-infused polymeric support reagent led to triol **296** after 5 h in refluxing benzene. The intermediate was an epoxide that could be isolated under appropriate conditions.[209] The resin could then be recovered and reused, reducing the amount of by-products. This process would be feasible for the low-cost industrial production of triols.

Cardillo showed that the carbonate ion resin hydrolyzed primary alkyl, allyl, and benzyl halides in 85–95% yield.[209] The propensity for hydrolysis followed the periodic trend of I>Br>Cl (Scheme 87). When secondary halides **299** were employed, elimination was the major process. Although aromatic carbonates have been commonly utilized in solid phase syntheses, aliphatic carbonates have not been well utilized in this field. However, the pioneering examples shown here are anticipated to guarantee wide applications in solid phase synthesis, facilitating the recently emerged combinatorial chemistry.

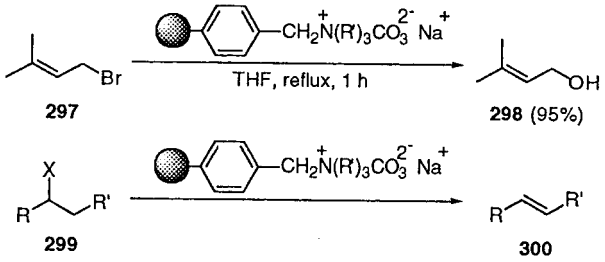


Scheme 86.

8. Conclusion

This review has given a comprehensive survey regarding the synthesis of alkyl carbonates, as well as elaborating upon a variety of their uses and applications. Dialkyl carbonates have clearly been demonstrated to be extremely useful and stable reagents, exhibiting unique physical and chemical properties. Furthermore, in organic synthesis, alkyl carbonates have shown to be a powerful arsenal serving mainly as protecting groups for alcohols and amines, as well as in usage as synthons for other functional group manipulations.

Alkyl carbonates have become excellent templates for the formation of carbon–carbon and carbon–heteroatom bonds. Carbonates have also been utilized in the introduction of



Scheme 87.

oxygen moieties as well as the activation of various functional groups, which allow for a plethora of other applications. Outstanding regioselectivity and chemoselectivity have been noted in numerous examples, and such differentiation in multifunctional groups is presumed to be a salient feature in organic synthesis. Due to these versatilities, aliphatic carbonates have been frequently employed in the organic syntheses of a variety of targets including carbohydrates, nucleosides, natural products, and pharmaceutical substances.

In addition, organic carbonates have made a great impact in the fields of polymer science, biology, and medicine. Organic carbonates have been utilized in industry as well, and have made their way into everyday life. This important functional group class, although often overlooked, holds great potential and no doubt will offer new and exciting chemistry in the future upon further exploration.

Acknowledgements

This review article is dedicated to Professor Leon Mandell on the occasion of his retirement from 45 years of excellence in teaching, research, and academic services.

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