

Cesium Carbonate: A Powerful Inorganic Base in Organic Synthesis

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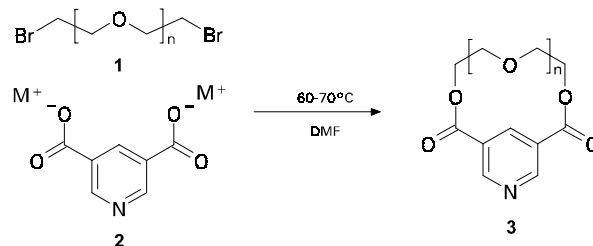
1. Introduction

Alkali metal carbonates represent one of the most important and widely used classes of weak bases in organic synthesis. However, most often Li_2CO_3 , Na_2CO_3 or K_2CO_3 are used to solve synthetic problems. This fact is remarkable since the use of carbonates containing larger alkali metal cations such as Rb^+ and Cs^+ often provides big advantages in terms of obtainable yields or rates. In comparison to Rb_2CO_3 , the cesium salt is less expensive (Rb_2CO_3 : 808.- DM/mol, Cs_2CO_3 : 242.- DM/mol) [1] and represents the carbonate with the larger cation. Therefore Cs_2CO_3 is supposed to be the base of choice, if properties related to large cations are required for a reaction to proceed. In this review several examples are given for the successful application of Cs_2CO_3 to synthetic problems. As far as possible comparisons with other alkali metal carbonates or other bases, which can be substituted by Cs_2CO_3 , are made.

2. Esterification, Macrocyclization, and Alkylation Reactions

The first synthetic advances using Cs_2CO_3 have been made in the early 1970's by Gisin preparing Merrifield-resins [2]. To establish the first amino acid *via* a benzyl ester linkage the reaction of chlormethylated polystyrene resin was carried out with an alkali metal salt of a *N*-Boc-protected amino acid. The author observed a strong dependence of the esterification rate on the alkali metal carbonate used to form the carboxylate. Working in DMF at room temperature gave strong evidence for the presumption that carboxylates with bigger counter-cations are far more dissociated in aprotic solvents and consequently more reactive. In this case the use of the cesium salt resulted in a 10fold higher incorporation of the *N*-Boc-protected amino acid into the resin compared to the lithium salt. In comparison to the potassium salt the incorporation

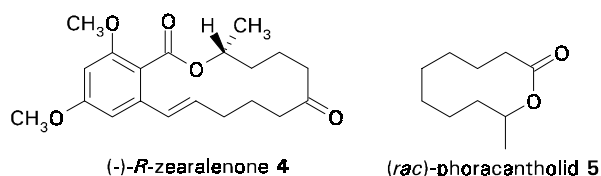
was doubled. In addition to solid-phase synthesis this esterification method was applied to the high yield synthesis of peptide esters [3] or depsipeptides [4] in solution which proceed under mild conditions without racemization. Having these useful results in hand, the method could be expanded to the synthesis of macrocyclic esters. Several examples of macrocyclizations *via* the formation of lactones were described [5]. The first attempts published by Kellogg and coworkers resulted in the formation of pyridine- or benzene-containing crown ethers [5a]. The irreplaceable role of the cesium cation compared to the other alkali metal ions is strongly emphasized by better yields and the fact that the reactions proceed more cleanly. As shown in Scheme 1 the yield of the lactonization step drops dramatically from 75% for the cesium carboxylate to only 15% for the potassium carboxylate.



for $n = 3$
 $M = \text{Cs}$: 85% by nmr; 75% isolated; $M = \text{Rb}$: 45%
 $M = \text{K}$: 15%; $M = \text{Na}$: 5%

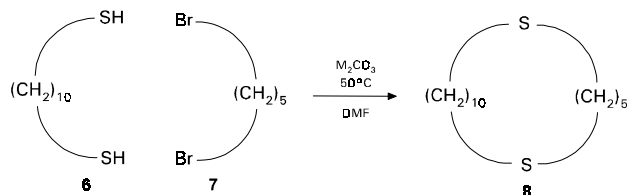
Scheme 1

The first macrocyclic natural product prepared by an analogous cesium-mediated lactone formation was (–)-*R*-zearalenone **4** [5d]. Another example is represented by (*rac*)-phoracantholid **5** (Scheme 2) [6]. In the case of (*rac*)-phoracantholid **5** the use of other bases such as K_2CO_3 for the cyclization step resulted in poor yields of the desired lactone. In the case of (–)-*R*-zearalenone **4** intensive preliminary studies strongly recommended the use of Cs_2CO_3 for the lactonization step.



Scheme 2

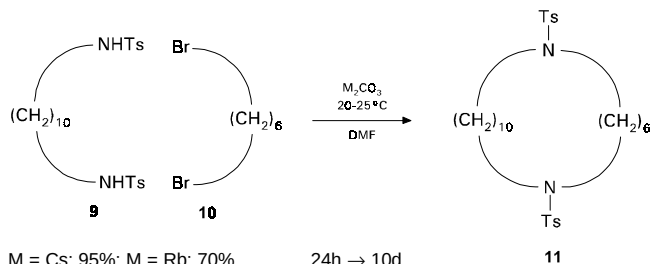
The formation of macrocycles *via* ether, thioether or amine linkages was the next aim envisaged by different authors. The first examples dealt with the construction of oxygen and sulfur containing rings which were interesting for the synthesis of novel ligands and investigations concerning their properties in metal-complex formation [5b, 7]. In the case of thioether formation a very strong dependence on the alkali metal carbonate became evident. The use of Cs_2CO_3 in DMF led to the sulphur-linked product **8** in 90% yield while treatment with Li_2CO_3 did not provide the desired macrocycle at all (Scheme 3).



M = Cs: 90%; M = Rb: 84%
M = K: 48%; M = Na: 33%; M = Li: 0%

Scheme 3

In the formation of aza-containing compounds **11** *via* tosylamides **9** Cs_2CO_3 also became the base of choice [8]. By use of other alkali metal carbonates the yields decreased dramatically and longer reaction times were required (Scheme 4).



M = Cs: 95%; M = Rb: 70% 24h → 10d
M = K: 10%; M = Na: 10%; M = Li: 0%

Scheme 4

During these investigations it was found that the basicity of Cs_2CO_3 is strong enough to deprotonate tosylamides, while carboxamides and urethanes were left unattended.

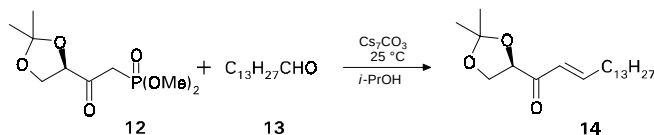
These examples show that Cs_2CO_3 is an efficient macrocyclization reagent for the synthesis of macrocyclic esters, ethers, thioethers and amines (*via* tosylamides). In all these cases Cs_2CO_3 provides consistently higher yields than Li_2CO_3 , Na_2CO_3 , K_2CO_3 and Rb_2CO_3 . Possible explanations for this "cesium effect" have been critically discussed elsewhere [9].

Besides the esterifications mentioned above, alkylations of 1,3-dicarbonyl compounds, Schiff bases of amino acids, phenols and carbohydrates also benefit from the use of Cs_2CO_3 as the employed base. A comparison with K_2CO_3 in the case of phenol alkylations shows that Cs_2CO_3 promotes accelerated reaction rates, generally gives higher product yields, and provides for the introduction of a wider range of

alkyl groups [10]. In the case of alkylations of 1,3-dicarbonyl compounds the use of Cs_2CO_3 compared to K_2CO_3 significantly reduces the amounts of *O*-alkylation and dialkylation [11]. Particularly good results were obtained for Michael additions of Schiff bases of glycine to enones with 10 mol% Cs_2CO_3 in THF. Results obtained under different conditions were less successful [12]. Furthermore carbohydrates can be converted into *O*- α -trichloroacetamides under very mild conditions using 5–10 mol% Cs_2CO_3 . These conditions were shown to have advantages over the standard Schmidt procedure (NaH , CCl_3CN , CH_2Cl_2) in terms of product purity [13].

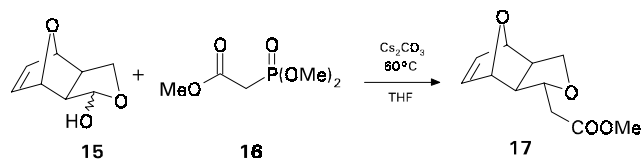
3. Wittig-type Reactions

Another synthetic field was opened by the use of Cs_2CO_3 in Horner-Wittig reactions. Inazu and coworkers showed that phosphonate **12** reacts with aldehyde **13** in the presence of Cs_2CO_3 in isopropanol to give the corresponding unsaturated ketone **14** in 85% yield (Scheme 5). This key step in the synthesis of D-erythro- C_{18} -sphingosine could not be performed successfully using more common bases. When NaH in THF was used, no product was detected at all. The use of triethylamine-LiCl gave the desired olefin in poor yield.



Scheme 5

Cs_2CO_3 is further used with success for Horner-Wittig reactions when the carbonyl compound contains acidic hydrogens which usually causes problems if common bases are employed. Furthermore the methodology could be expanded to tandem Wittig-Michael reaction processes. An impressive example is the conversion of lactol **15** to the tetrahydrofuran derivative **17** which undergoes retro-Diels-Alder reaction at 500 °C to yield an optically active dihydrofuran derivative (Scheme 6) [15]. Again Cs_2CO_3 is used as the base. Unfortunately no comparison with other bases has been made for this reaction.

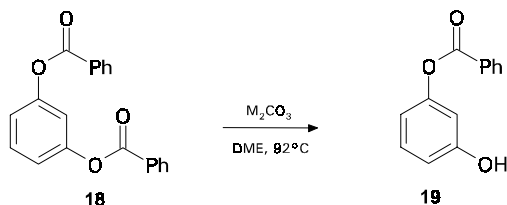


Scheme 6

4. Selective Cleavage of Protecting Groups

Cs_2CO_3 can also be used as a very selective reagent for the cleavage of several protecting groups. Zaugg showed in a detailed study dealing with the ester cleavage of aryl diesters

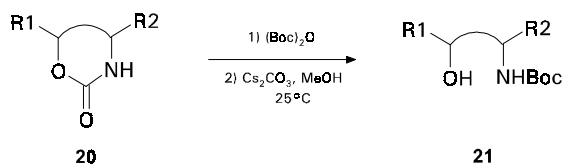
18 that the usage of Cs_2CO_3 leads to a selective mono ester cleavage in high yields [16]. For example the hydrolysis of resorcinol dibenzoate in DME with Cs_2CO_3 produces the corresponding monobenzoate in greater than 95% yield. A comparable reaction using K_2CO_3 leads to desired monobenzoate in only 21% yield (Scheme 7).



M = K (7 equiv): 21%
M = Cs (1.5 equiv): 95%

Scheme 7

There are also useful examples for the application of Cs_2CO_3 in the synthesis of *N*-protected 1,2- and 1,3-amino alcohols by a selective ring cleavage of cyclic carbamates **20** (Scheme 8) [17]. Very often classical methods are too drastic and side reactions such as dehydration and epimerization can not be avoided. Therefore the mild ring-opening of five- and six-membered carbamates using substoichiometric amounts of Cs_2CO_3 (0.2 equiv) in methanol at room temperature represents a method with a lot of advantages. However, a preceding protection of the carbamate-*N*-atom with Boc-anhydride seems to be necessary since other *N*-protecting groups like the benzyloxycarbonyl group are not stable under the reaction conditions.



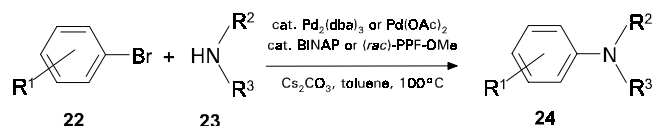
Scheme 8

The only other systems known that are more or less comparable to $\text{Cs}_2\text{CO}_3/\text{MeOH}$ use LiOH or K_2CO_3 in aqueous methanol. But in these cases the base has to be used in stoichiometric or greater quantities.

5. Transition Metal Catalyzed Reactions

In the field of transition metal catalyzed reactions the recently developed palladium catalyzed coupling of amines **23** with aryl halides **22** or triflates forming substituted anilines **24** [18] represents an impressive example for the extraordinary role of Cs_2CO_3 as a base. This coupling reaction which is performed using a palladium catalyst, formed *in situ* from $\text{Pd}(\text{OAc})_2$ or $\text{Pd}_2(\text{dba})_3$ and a chelating bis-phosphine ligand, in toluene at 80 – 100°C requires the stoichiometric addition of a base. This base secures the deprotonation of the amine during the catalytic cycle which is essential for the reaction to

proceed. No reaction takes place without this base. Intensive investigations were made in order to optimize the nature of the employed base. First it was shown, that sodium *t*-butoxide is the most general and effective base. No other base including potassium *t*-butoxide gave rise to the desired products in comparable yields (except LiHMDS, which was used in Hartwig's group for certain reactions [19]). However, due to the strong basicity of sodium *t*-butoxide base labile functional groups were not tolerated. During a study to circumvent this problem Buchwald and coworkers found that Cs_2CO_3 is the base of choice for their amination protocol, if base sensitive substrates are used. It further turned out that Cs_2CO_3 is a very general and effective base for the palladium-catalyzed amination of a wide variety of aryl halides if (*rac*)-1-[2-(diphenylphosphino)ferrocenyl]ethyl methyl ether ((*rac*)-PPF-OMe) is employed as a ligand [20] (Scheme 9). Other carbonates such as K_2CO_3 , Na_2CO_3 , Li_2CO_3 do not represent effective bases under similar reaction conditions.

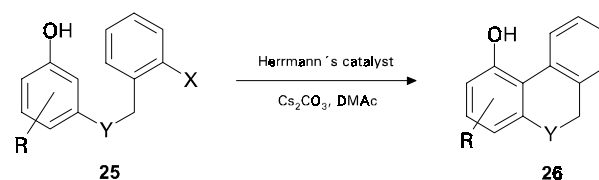


R^1 – alkyl, CN, CO_2Me , COMe, CHO, NO_2 , OMe, Cl
 R^2 , R^3 – alkyl, aryl, H

Scheme 9

Therefore at the moment Cs_2CO_3 is the only weak base which can be used for this very interesting new transformation giving access to the desired aniline derivatives in high yields. It seems that the basicity of Cs_2CO_3 is strong enough to deprotonate the reacting amine during the catalytic cycle and simultaneously weak enough to tolerate base sensitive functional groups such as methyl and ethyl esters, enolizable ketones, aldehydes, and nitro groups, which are incompatible with reaction conditions which employ sodium *t*-butoxide as the stoichiometric base.

Another palladium-catalyzed reaction which is strongly influenced by the nature of the employed base is the intramolecular coupling of phenols with aryl halides (reaction **25** → **26**) building up an aryl–aryl linkage recently published by Rawal and coworkers (Scheme 10) [21].



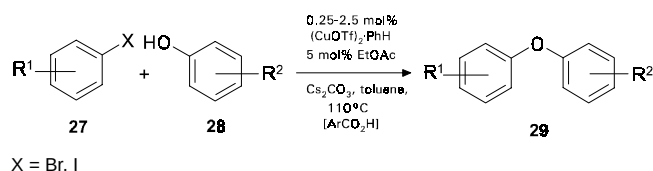
X = Br, I
Y = CH_2 , O, NCO_2Me
R = Me, OH

Scheme 10

First experiments were performed using potassium *t*-butoxide as the base and $\text{Pd}(\text{PPh}_3)_4$ as palladium catalyst in dimethylacetamide (DMAc) as solvent. However, an optimization of this process lead to the conclusion that a discrete

palladacycle (Herrmann's catalyst) [22] in combination with Cs_2CO_3 gives better results in terms of catalyst loading and rate. During this optimization the authors found that the reaction was faster with Cs_2CO_3 than with K_2CO_3 as the base. Little or no cyclization product was observed with Na_2CO_3 or Li_2CO_3 . It was suggested that the larger cations are better solvated, resulting in a more nucleophilic, "naked" phenolate anion which is responsible for the accelerated reaction rate. Unfortunately, a direct comparison between Cs_2CO_3 and KOt-Bu can not be made from the data delivered in this publication. Nevertheless, it was shown again that the weak base Cs_2CO_3 can substitute the stronger base KOt-Bu and therefore can increase the functional group tolerance of the reaction.

A related example is the well known Ullmann diaryl ether synthesis. This copper mediated reaction, converting aryl halides and phenols into diaryl ethers (reaction **27** + **28** → **29**), is usually characterized by harsh reaction conditions (125–220 °C in neat phenol or solvents such as pyridine, collidine, or DMF), the usual requirement for stoichiometric (or greater) quantities of a copper compound and the fact that unactivated aryl halides usually react in low yields. These facts have limited the utility of this reaction. During a study directed toward finding new catalytic methods for the preparation of diaryl ethers, Buchwald and coworkers discovered that Cs_2CO_3 is particularly effective as a base in Ullmann coupling procedures. They reported a general procedure for the copper catalyzed (0.25 to 2.5 mol% Cu) formation of diaryl ethers from the reaction of aryl bromides and iodides with a variety of phenols using Cs_2CO_3 as a base employing a nonpolar solvent (toluene) under mild conditions (110 °C) [23]. Furthermore, the use of a stoichiometric additive (1-Naphthoic acid/ molecular sieves) promoted the reaction of less reactive phenols which allowed for the first time the successful Ullmann coupling of unactivated aryl halides and less reactive phenols, such as phenol and chlorophenol (Scheme 11).

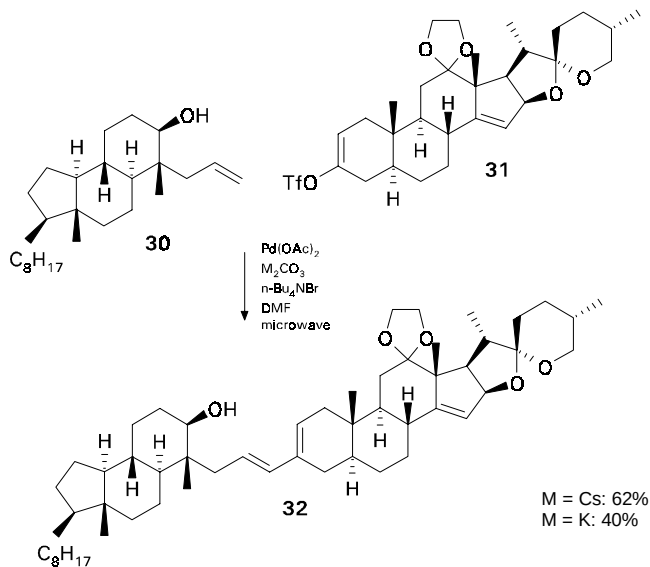


Scheme 11

A survey of reactions with a number of other bases (Et_3N , DIPEA, DBU, 1,2,2,6,6-pentamethylpiperidine, dicyclohexylamine), including other carbonates, such as K_2CO_3 , Na_2CO_3 , Li_2CO_3 , BaCO_3 , confirmed that Cs_2CO_3 is the key element responsible for the improved reaction conditions. Under comparable conditions no or little conversion was observed using these bases.

Finally, we would like to present an example of the microwave induced Heck-reaction between the steroidal vinyl triflate **31** and the tricyclic alkene **30** (Scheme 12) [24].

Using Cs_2CO_3 as the base the yield could be increased up to 62% compared to the use of K_2CO_3 (40%). Additionally, less by-products have been observed, so that the complex diene **32** could be isolated with higher purity.



Scheme 12

6. Conclusion

As seen from the examples mentioned above, the use of Cs_2CO_3 as a base often results in impressive and sometimes surprising improvements in terms of reaction conditions as well as isolated yields. In several examples it also further expands the utility of processes to different substrate classes. At the moment the reasons for this superior behaviour are almost unknown. The higher solubility of Cs_2CO_3 or *in situ* formed cesium salts in organic solvents (Cs_2CO_3 is at least ten times more soluble in aprotic organic solvents than K_2CO_3 [25]), and the fact that these salts are far more dissociated than the corresponding lithium, sodium or potassium salts are often mentioned to explain the outstanding properties of Cs_2CO_3 as a base. However, little work has been done to confirm these theories. Nevertheless every chemist should always consider Cs_2CO_3 as an alternative base while developing a reaction or process which requires the use of a base.

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