



Contents

The Broad Scope of Cesium Salts in Organic Chemistry	3
Abstract.	3
Production	3
Making the Difference – the “Cesium Effect”.	4
Advantages of Cesium Compounds in Organic Reactions:	5
C-N bonds	5
C-C bonds	7
C-O bonds	8
C-P bonds	9
C-S bonds	10
Conclusion	11
Cesium compounds available from Acros Organics	11



The Broad Scope of Cesium Salts in Organic Chemistry

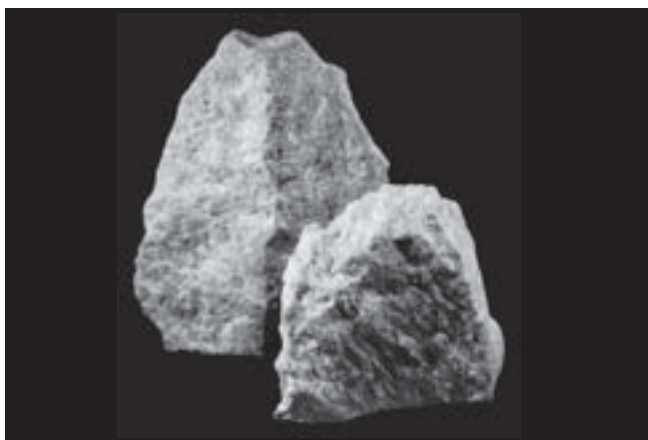
Anja Steinmetz, Chemetall GmbH, Trakehnerstr. 3, 60487 Frankfurt

Abstract

The use of cesium salts in a large variety of synthetic conversions has received increasing interest in the last two decades and today has reached industrial acceptance. Prominent examples for the benefits of cesium salts in organic synthesis are Palladium catalyzed coupling reactions like the Suzuki coupling or the Buchwald amination. However, also straightforward nucleophilic substitution reactions can be improved by substituting standard bases with cesium salts. The unique effect of cesium salts in many reactions emerged empirically and stems from the special properties of the cesium cation: it has a very large ionic radius, a low charge density and a high polarizability.

In practice, cesium carbonate is preferred for sensitive reactions requiring well-balanced base strength. In these reactions bases like sodium tert-butyrate are too strong thus inducing side reactions and bases like potassium carbonate are too weak or not soluble enough to participate in the desired reaction.

The higher cost of cesium is offset by clear advantages such as higher yields, shorter reaction times, smaller amounts of reagents required, milder reaction conditions and easier work-up procedures.



Production

Cesium is the 40th most abundant element within the periodic system. The commercially most important cesium bearing ore is pollucite, a cesium aluminum silicate with the chemical composition $(\text{Cs},\text{Na})_2\text{Al}_2\text{Si}_4\text{O}_{12}\cdot(\text{H}_2\text{O})$. Pollucite is mined in Canada, Africa and at other locations throughout the world, from where it is shipped to Chemetall's factory at Langelsheim, Germany. There it is processed into the full range of cesium containing products. The initial steps are digestion and purification of the ore yielding a cesium hydroxide solution, which is subsequently converted into the desired cesium salts by acid/base chemistry.

Available cesium compounds include carbonate, bicarbonate, hydroxide, acetate, sulfate, nitrate, fluoride, chloride, bromide and iodide. These products are available in solution or in solid form and are sold in laboratory to bulk scale. Purities range from industrial grade to assays of up to 99.999% required for special applications in physics. For organic synthesis, the most frequently used products are cesium carbonate (Cs_2CO_3), cesium fluoride (CsF), cesium acetate (CsOAc) and cesium hydroxide monohydrate ($\text{CsOH}\cdot\text{H}_2\text{O}$).



Making the Difference – the “Cesium Effect”

“Cesium effect” is a term widely spread in scientific publications to describe the advantages concerning yield and reaction conditions of cesium assisted reaction protocols as compared to conventional non-cesium routes. The effect is based on observations, it is empirical and quite difficult to pin down and clarify. Attempts at an explanation primarily focus on the status, which the cesium atom has within the periodic system of elements. C. Galli’s critical review on the “cesium effect” ^[1] is a prominent example.

With its large cationic radius, low charge density and its large polarizability it stands out against the other alkali metal ions (see table 1). Two general rules are relevant for the behaviour of cesium salts:

- The smaller an ion, the larger its degree of solvation in a reaction medium
- The smaller the ions, the more pronounced the ion-pairing

As a consequence the ions of a cesium salt have the lowest degree of solvation and ion-pairing compared to the ions of analogous alkali metal salts.

If the appropriate solvent is selected – an aprotic solvent (protic solvents provide a more structured solvation shell) with a large dielectric constant ϵ (high ϵ correlates with low ion-pairing) – the cesium salt ions will be as “naked” as possible. In nucleophilic substitution reactions the naked ion has the highest reactivity.

Cation	Cationic radius r_i for $cn=6$ [Å]	Electronic polarizability α [10^{-24} cm ³]
Li ⁺	7.30	0.029
Na ⁺	32.55	0.179
K ⁺	36.64	0.83
Rb ⁺	38.25	1.40
Cs ⁺	47.24	2.42

Table 1: Cationic radii and polarizabilities of alkali metal ions ^[2]

Solvent	Cs ₂ CO ₃	K ₂ CO ₃
DMF	1.195	0.075
DMSO	3.625	0.470
DMAC	0.490	0.046
sulfolane	3.950	0.160
NMP	7.224	0.237

Table 2: Solubilities of alkali carbonates in g/10 mL, determined at ambient temperatures by flame photometry ^[3]

The “naked” ion is one prerequisite for high reactivity for a lot of reactions, another relevant factor is the solubility. In comparison to potassium carbonate, cesium carbonate has a superior solubility in aprotic solvents (compare table 2). Higher solubility leads to a higher accessibility of the material and thus to a higher reactivity.

For chemical reactions of substances bearing sensitive functional groups, the use of a very strong base is prohibitive. To design a reaction that is both efficient and tolerant to functional groups the choice of a well-balanced base, which is neither too strong nor too weak, is essential. Experiments have shown (e.g. ^[4]) that cesium carbonate or cesium fluoride provide this balance. An investigation of the

strength of some common bases in aprotic solvents supports these findings. A direct comparison of KOtBu, Cs₂CO₃, CsF and K₂CO₃ and KF is given in graphs 1a and 1b ^[5].

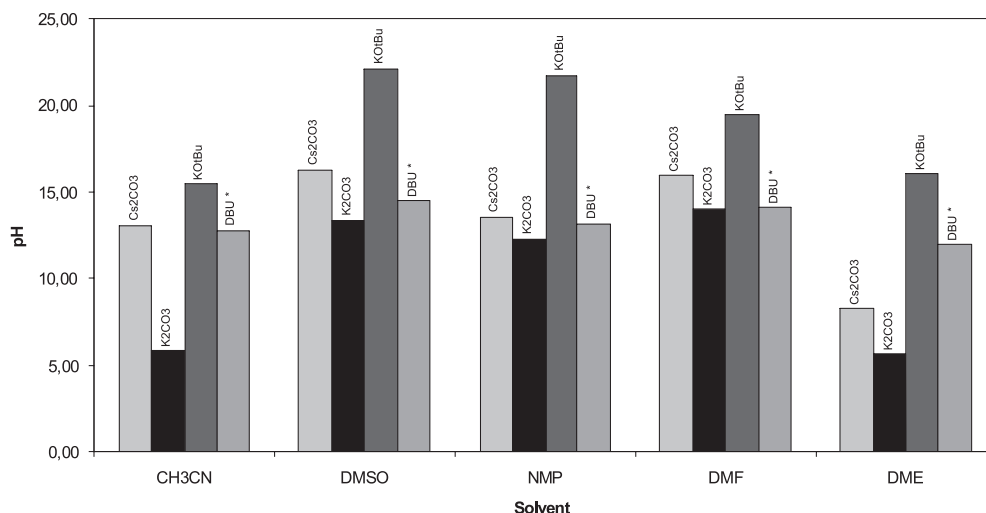
^[1] C. Galli, Org. Prep. Proced. Int. 24 (1992), 287-307.

^[2] Handbook of Chemistry and Physics (D.R. Lide, Hrsg.), 83. ed., CRC Press LLC 2002-2003.

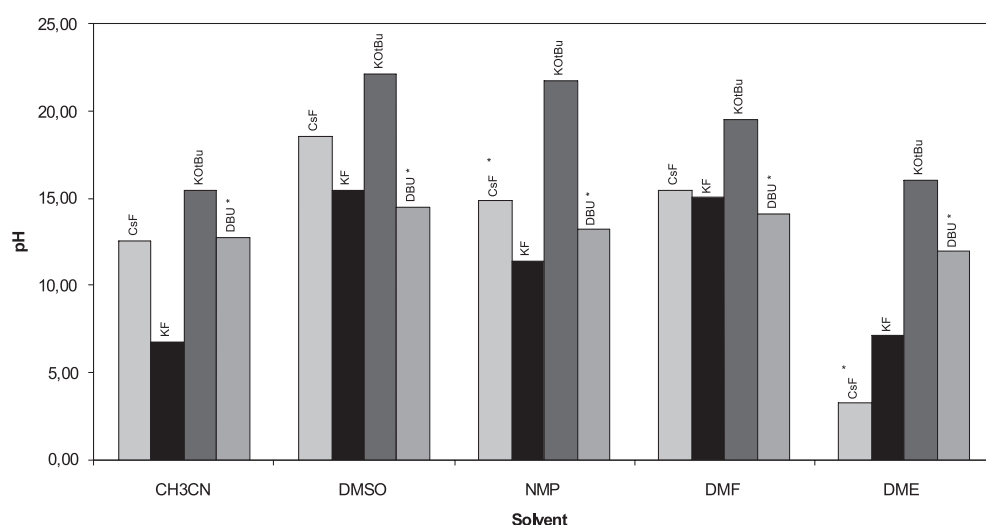
^[3] J. A. Cella and S. W. Bacon, J. Org. Chem. 49 (1984), 1122-1125.

^[4] J. P. Wolfe and S. L. Buchwald, J. Org. Chem. 65 (2000), 1144-1157.

^[5] Adam A., TU Clausthal, private communication (2005).



Graph 1a: Basicities of cesium and potassium carbonates in various aprotic solvents compared to KOtBu and DBU (5 mmol/100mL weight-in quantity, * = complete dissolution)^[5]

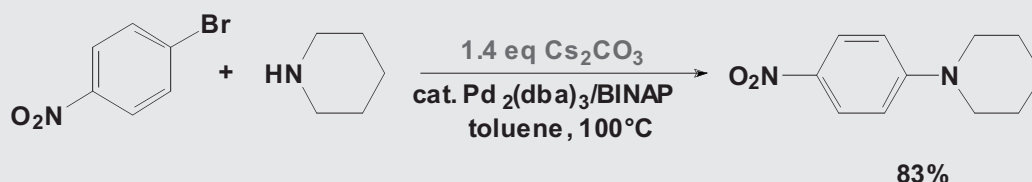


Graph 1b: Basicities of cesium and potassium fluorides in various aprotic solvents compared to KOtBu and DBU (5 mmol/100mL weight-in quantity, * = complete dissolution)^[5]

Advantages of Cesium Compounds in Organic Reactions:

C-N bonds

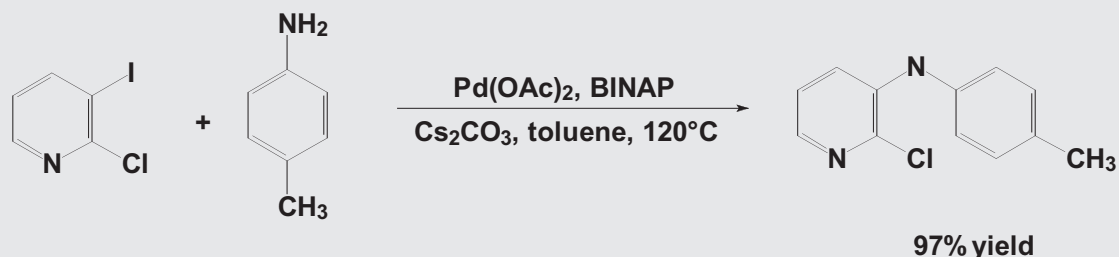
The catalytic amination of aryl halides is a well-known tool in organic synthesis for the formation of aryl-C-N bonds. In the catalytic amination of aryl bromides NaOtBu is frequently used as base as stoichiometric addition is sufficient and the reaction times are the shortest. The mayor drawback of NaOtBu is its enormous base strength rendering it unsuitable for the coupling of reagent with sensitive functional groups such as methyl and ethyl esters, enolizable ketones or nitro groups. The key to perform even such couplings as indicated in scheme 1 is a base with lower basicity. The weak cesium carbonate provides a much higher functional group tolerance. Apart from cesium carbonate, other bases like alkali metal carbonates and phosphates as well as organic bases like DBU or tertiary amines have been screened for their utility, however, in contrast to cesium no generally applicable protocol is available ^[4].



Scheme 1



The catalytic amination of azaheteroaryl iodides proceeds with high yields and selectivities when using cesium carbonate as base. The cross-coupling of p-toluidine with 2-chloro-3-iodopyridine described in scheme 2 selectively provides amination in the 3-position and is significantly faster with cesium carbonate than with potassium carbonate or potassium phosphate. Due to the mildly basic conditions, the scope of the reaction can be extended to base sensitive anilines. An amination of aryl iodides is also possible ^[6].



end of reaction (< 5% starting material left):

K₂CO₃ : 48 h

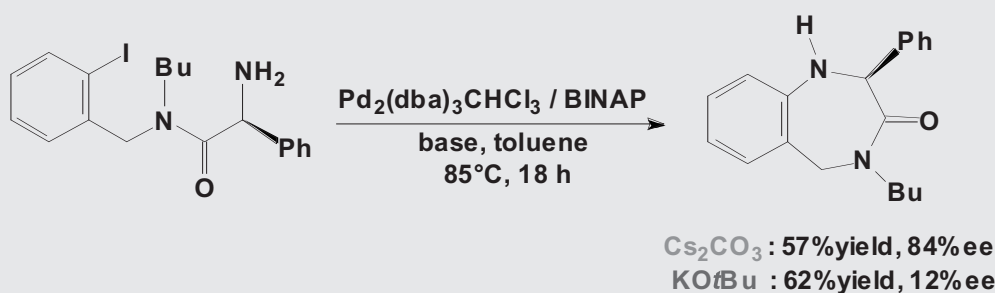
K₃PO₄ : 24 h

Cs₂CO₃ : 8 h

Scheme 2

Another example of an amination reaction is shown in scheme 3. In this intramolecular cyclization the reaction proceeds under retention of the configuration when using cesium carbonate and the product is recovered in good ee's.

The racemisation is a base catalysed step, but cesium carbonate is too weak to induce it. It almost exclusively acts in the amination reaction. KOtBu on the other hand is too strong. With KOtBu both amination and racemisation are promoted and a loss of stereoselectivity is observed ^[7].



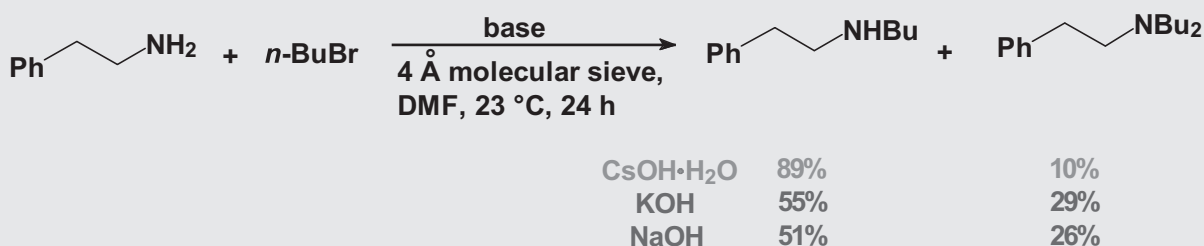
Scheme 3

Cesium assisted C-N bond formation without transition metal catalysis is also well established in practice. The mono-N-alkylation protocol described in scheme 4 is applicable for primary amines, diamines and polyamines. The advantage of cesium hydroxide over other alkali hydroxides is its chemoselectivity as it not only promotes the alkylation reaction but more importantly suppresses an overalkylation ^[8].

^[6] B. U. W. Maes, K. T. J. Loones, T. H. M. Jonckers, G. L. F. Lemi re, R. A. Dommissie and A. Haemers, *Synlett* 12 (2002), 1995-1997.

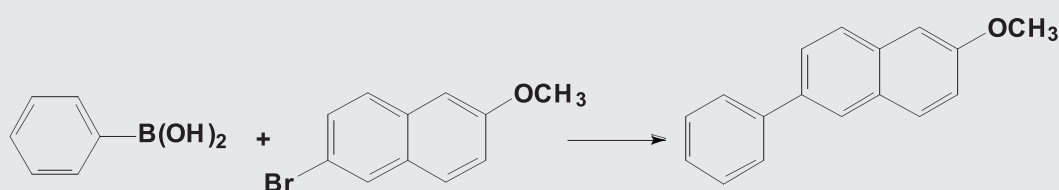
^[7] M. Catellani, C. Catucci, G. Celentano and R. Ferraccioli, *Synlett* 6 (2001), 803-805.

^[8] R. N. Salvatore, A. S. Nagle and K. W. Jung, *J. Org. Chem.* 67 (2002), 674-683.



Scheme 4

C-C bonds



2 eq CsF / Pd(PPh₃)₄ / CH₃CN / 6h \longrightarrow 91% yield

2 eq KF / Pd(PPh₃)₄ / CH₃CN / 18h \longrightarrow 59% yield

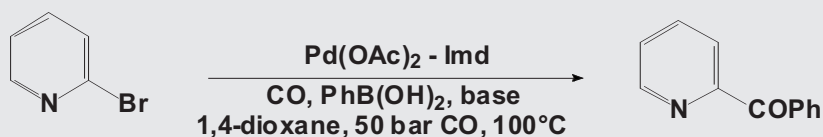
Scheme 5

The above reaction is an example of a generally applicable Suzuki coupling protocol for aryl and vinylboronic acids ^[9]. The protocol is based on a non-aqueous medium making it possible to react substrates with sensitive functional groups. The use of a fluoride anion facilitates a smooth boron to palladium transmetallation. Of all tested fluoride sources, CsF is superior in terms of cost per mole, reaction time, yield, solvent choice and ease of drying. A comparison with the KF example in scheme 5 highlights two ways of economizing reactions with CsF: a) by significantly shortening the reaction time and b) by increasing the yield.

In a modification of the Suzuki reaction, the synthesis of asymmetric biaryl ketones is possible by a three-component coupling under carbonylative conditions. Aryl chlorides usually lack reactivity in such reactions. For heteroaryl chlorides, this problem is solved by selecting the appropriate reaction conditions ^[10]. The low reactivity of aryl chlorides is overcome by using N-heterocyclic carbene ligands. The optimization of the reaction conditions is performed with the more reactive 2-bromopyridine and phenylboronic acid as model system. 1,4-Dioxane is more suitable than DMF, THF or anisole. In a screening of various bases, KF and Mg(OEt)₂ prove to be ineffective, whereas Cs₂CO₃ and K₂CO₃ provide good yields, with cesium carbonate being slightly superior.

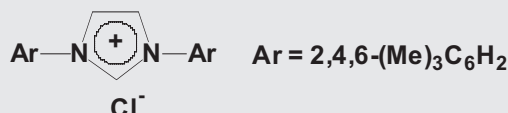
^[9] S. W. Wright, D. L. Hageman and L. D. McClure, J. Org. Chem. 59 (1994), 6095-6097.

^[10] E. Maerten, F. Hassouna, S. Couve-Bonnaire, A. Mortreux, J. - F. Carpentier and Y. Castanet, Synlett 12 (2003), 1874-1876.



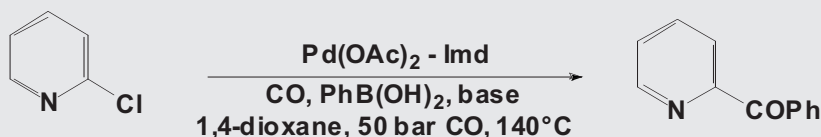
Cs_2CO_3 , 21h - 100% conversion, 95% selectivity
 K_2CO_3 , 22h - 95% conversion, 95% selectivity
 Mg(OEt)_2 , 22h - 7% conversion, 0% selectivity

Imd:



Scheme 6

In scheme 7 the resulting high yield and selectivity of the desired coupling of a heteroaryl chloride with phenylboronic acid using these optimized conditions is depicted:

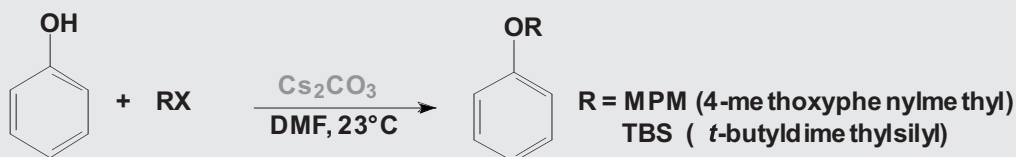


Cs_2CO_3 , 22 h - 88% conversion, 91% selectivity

Scheme 7

C-O bonds

K.W. Jung et al. ^[11] have established a strategy for the alkylation of phenols that allows the use of active (e.g. benzyl halides) as well as unreactive halides like secondary bromides. The reaction is carried out under mild conditions: cesium carbonate is the base and the reaction is run at 23°C. Under these conditions side reactions like decomposition or elimination are not observed. It is thus possible to introduce protection groups like MPM or TBS. Their halides are not stable when subjected to the elevated temperatures of other methodologies:

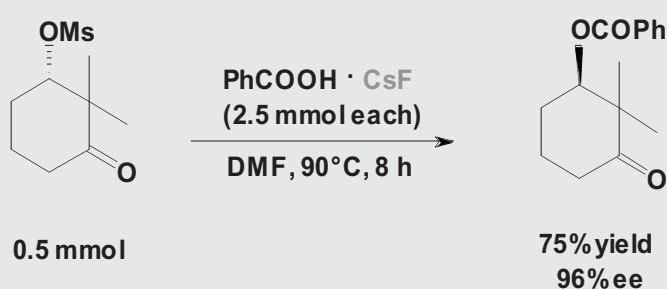


Scheme 8



The selective inversion of the stereochemistry of a secondary alcohol is an important target which needs a generally applicable reaction protocol. A direct inversion of a secondary alcohol is possible with the Mitsunobu reaction. This process, however, requires special reagents and is not successful in the below example of a sterically crowded substrate. Indirect approaches are based on the reaction of the corresponding mesylate with nucleophiles. The classical methods are unfortunately limited to certain classes of nucleophiles.

If the conversion of a secondary mesylate and a nucleophile is carried out in the presence of cesium fluoride, the reaction proceeds highly selectively without formation of elimination products^[12]. The CsF-protocol is applicable to a large variety of nucleophiles and is furthermore attractive in its simplicity and its easy work-up (scheme 9).

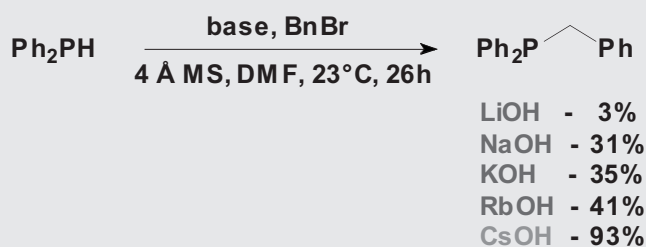


Scheme 9

C-P bonds

The formation of C-P bonds is a fundamental step in the synthesis of tertiary phosphines which serve as ligands in transition metal catalyzed reactions. The direct coupling of a secondary phosphine with an alkyl halide is a mild and general method which relies on cesium hydroxide monohydrate as base. Conventional methods for the preparation of tertiary phosphines suffer from several drawbacks such as the oxidation of the phosphine, harsh reaction conditions or poor yields. The CsOH involving protocol, however, does not encounter these problems. It is even suitable for the preparation of phosphines with chiral centers at the phosphorous atom: owing to the mild conditions, racemization and E2 elimination do not occur.

The screening of a series of alkali hydroxides underscores the importance of cesium in the protocol as the other alkali hydroxides provide significantly inferior results^[13].



Scheme 10

^[12] T. Sato and J. Otera, *Synlett* 4 (1995), 336-338.

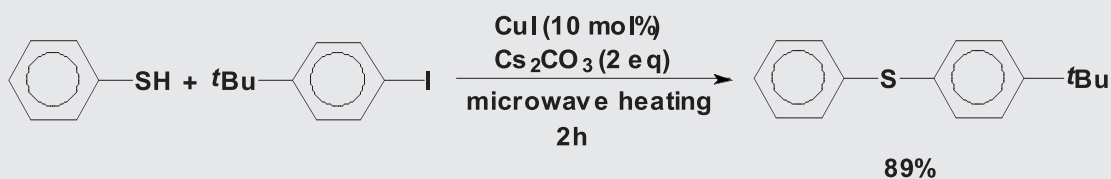
^[13] M. T. Honaker, J. Sandefur, J. L. Hargett, A. L. McDaniel and R. N. Salvatore, *Tetrahedron Lett.* 44 (2003), 8373-8377.

^[14] Y. - J. Wu and H. He, *Synlett* 12 (2003), 1789-1790.



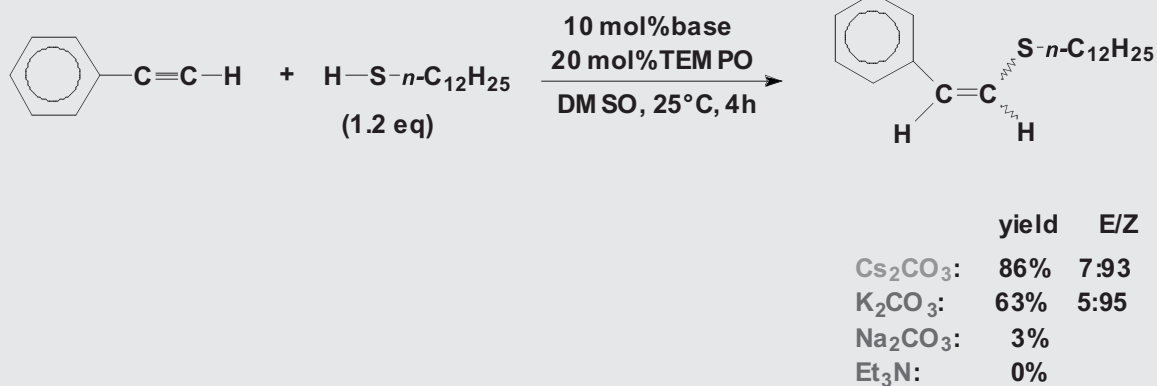
C-S bonds

A simple and efficient method for the preparation of aryl sulfides is based on the Cu(I) catalyzed cross-coupling of aryl bromides or iodides with thiols using cesium carbonate and microwave irradiation ^[14]. Advantages of the protocol given in scheme 11 are that strongly basic conditions are avoided, that unactivated aryl bromides can be employed and that yields are improved by the irradiation technique. A similar protocol of a Cu(I) catalyzed cross-coupling using potassium carbonate does not extend to unactivated bromides ^[14].



Scheme 11

The addition of a thiol to a triple bond provides straightforward access to (Z)-1-alkenyl sulfides ^[15]. Compared to the other bases tested, cesium carbonate furnishes a significantly higher yield and a very good regioselectivity for the anti-Markovnikov adduct. The competing base-free radical addition reduces the regioselectivity but can be entirely suppressed by using TEMPO (2,2,6,6-tetramethylpiperidine-N-oxyl) as radical inhibitor.



Scheme 12

^[15] A. Kondoh, H. Takami, H. Yorimitsu and K. Oshima, J. Org. Chem. 70 (2005), 6468-6473.



Conclusion

Cesium salts are very versatile in their use for organic chemistry and in a lot of cases superior to the analogous potassium compounds regarding e.g. economic factors like yield, reaction time or reaction temperature.

Almost every synthetic target can be handled with a cesium protocol. The reason for its unique success is not entirely clear, but practice proves its applicability. Reactions include C-C, C-O, C-N, C-P and C-S bond formation and also cover the field of ring closure reactions, protection group chemistry, and stereochemical reactions. Cesium salts are easy to handle and readily available in various purities from gram to tonnage quantities. They have long ago left behind the stigma of being an exotic niche product.

Cesium compounds available from Acros Organics

Cesium 99.95+%	21919
Cesium acetate 99%, pure	19104
Cesium azide 80-90%, pure	40435
Cesium bicarbonate 99.9%, pure	20360
Cesium bromide 99.9%, pure	19206
Cesium carbonate	27802
Cesium carbonate 99.5%, for analysis	19204
Cesium chloride 99+%, pure	42285
Cesium chloride 99.99%, optical grade, for spectroscopy	20632
Cesium chloride 99.999%, extra pure	19281
Cesium chloride 99+%, for analysis	18950
Cesium fluoride 99.9%, extra pure	31591
Cesium fluoride 99%, for analysis	18951
Cesium hydroxide monohydrate 99.5%, for analysis	18952
Cesium hydroxide 99%, 50 wt% solution in water, for analysis	21360
Cesium iodide 99.9%, for analysis	19205
Cesium nitrate 99.99%, for analysis	19207
Cesium sulfate 99+%, pure	21870



for Canada and the US

Acros Organics USA

500 American road, Morris Plains, NJ 07950

tel.: 1-800-766-7000

fax: 1-800-926-1166

www.fishersci.com

for Asia, Europe and Latin America

Acros Organics

Geel West Zone 2

Janssen Pharmaceuticaaan 3a, B-2440 Geel

tel.: +32-14-57.52.11

fax: +32-14-59.34.34

www.acros.com

for the UK

Fisher Scientific UK Ltd

Bishop Meadow Road

Loughborough

Leicestershire LE11 5RG

United Kingdom

tel.: (01509) 231166

fax: (01509) 231893

www.fisher.co.uk/acros