SYNTHESIS AND SYNTHETIC APPLICATIONS OF *o*-BENZENEDISULFONIMIDE AND ITS DERIVATIVES

DOI: http://dx.medra.org/10.17374/targets.2020.23.178

Margherita Barbero, Stefano Dughera

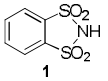
Department of Chemistry, University of Torino, Via P. Giuria 7, 10125 Torino, Italy
(e-mail: margherita.barbero@unito.it; stefano.dughera@unito.it)

Abstract. *The studies dealing with the strong Brønsted acid o-benzenedisulfonimide (OBS) reported in literature in the last ten years are herein summarized. This nearly centenarian simple compound is still receiving attention from the scientific community, due to its easy preparation and safe handling, solubility in organic solvents and water, which permits almost quantitative recovery and recycling. Its chiral derivatives, which can be synthesised in high enantiomeric purity, retain the advantageous characteristics of the parent compound, leading to the asymmetric versions of the reactions previously run in its presence as catalyst. Furthermore, the conjugated base of OBS has been used as stabilizing counter-ion of aryl heteroaryl methylium cations and arenediazonium salts, advantageously employed in gold or palladium catalysed cross-coupling reactions.*

Contents

1. Introduction

o-Benzenedisulfonimide, namely 1,3,2-benzodithiazole-1,1,3,3-tetraoxide (OBS) **1** (Figure 1), was synthesized for the first time as a saccharine-like sweetener by Holleman in 1921,[1] and five years later by Smiles in 1926.[2] Starting from then, **1** and some its derivatives have attracted discontinuous attention from the scientific community.



1

Figure 1. *o*-Benzenedisulfonimide (OBS) **1**.

In 2011 we published a review dealing with the synthesis, synthetic applications and miscellaneous studies of OBS itself and its derivatives, covering the literature until the end of 2009.[3] From then on, the

conjugated base of OBS has been used by us as stabilizing counter-ion of arenediazonium salts and of aryl heteroaryl methylium salts. At the same time, the parent acid and some of its chiral derivatives have been widely used in many common acid-catalysed organic reactions in catalytic amounts, as a safe, nonvolatile and noncorrosive organocatalyst. The main advantages of these protocols were mild and in most cases solvent-free reaction conditions, the easy recovery of this safe, cheap and water-soluble catalyst from aqueous washings and recycling in consecutive runs without significant loss of catalytic activity.

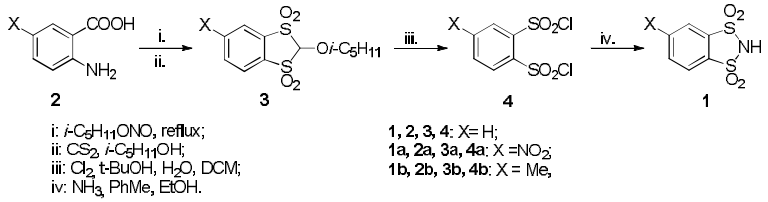
In this contribution, we will report a survey of the literature concerning recent advancements in this field until August 2019, with particular emphasis on synthetic aspects and following a chronological order. Patents were not covered.

2. *o*-Benzenedisulfonimide as Brønsted acid catalyst in acid-catalysed organic reactions

2.1. Theoretical and experimental studies on *o*-benzenedisulfonimide pK_a

Cyclic disulfonimides are well-known strong Brønsted acids. Their acidity, comparable to that of strong mineral acids, is even higher than that of acyclic analogues, due to the acid-strengthening effect of the two sulfonyl groups. Furthermore, this effect is likely enhanced in OBS by the incorporation in the five-membered ring. The high acidity of OBS has been already stated by Hendrickson and co-workers;[4] King and Guo reported a pK_a value of -4.1 as unpublished results,[5] and some years later Blaschette and co-workers reported a calculated value of -1.1.[6] In the light of these findings, we decided to study the acidity of OBS itself and of some its derivatives, for the first time from both an experimental and a theoretical point of view, in order to compare their relative acidity.[7]

Aiming to synthesize disulfonimides more acidic than **1**, theoretical methods were used to calculate a relative scale of pK_a of **1** and of a set of eight selected OBS derivatives; their pK_a values were obtained as differences with respect to the pK_a of picric acids, whose values are available in many solvents. Then, an experimental acidity scale of **1** and two singlet out compounds was determined by potentiometric titrations in butanone as the solvent, using picric acid as the reference. The experimental results confirmed the calculated values: for **1** calculated pKa was 5.9, while the experimental value was 6.09±0.04; for the 4-nitroderivative **1a**, values were respectively 3.8 and 4.3±0.04; and for 4-methylderivative **1b** they were 6.3 and 6.81±0.01. The synthetic sequence for **1a** and **1b** preparation was that adopted for the preparation of **1**, which used as the key intermediate the *o*-benzenedisulfonyl chlorides **4**, prepared from the corresponding anthranilic acids **2** (Scheme 1).[8-10] Then, the 5-nitroderivative **1a**, the more acidic analogue synthesised, was tested as the catalyst in ten reactions, previously successfully performed in the presence of **1**, such as esterification, Hosomi-Sakurai, Friedländer and Ritter reactions. In all of them, **1a** proved to be a more effective catalyst than **1**; the product yields were similar, but reactions took place more quickly and in milder conditions.



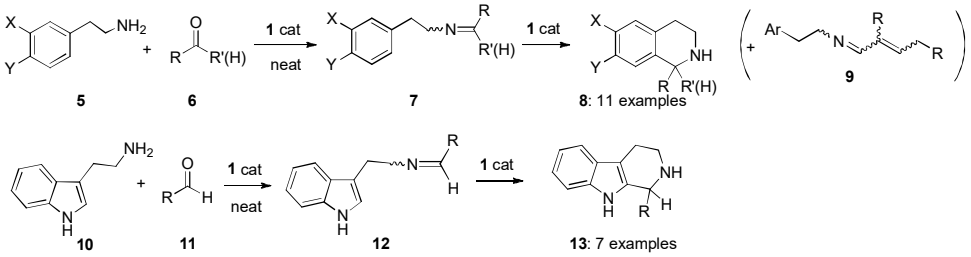
Scheme 1. Synthesis of **1** and singlet out OBS derivatives for acidity scale measurement.

2.2. *o*-Benzenedisulfonimide as catalyst in multicomponent heterocycle syntheses

Starting from 2007,[11] when for the first time *o*-benzenedisulfonimide **1** was reported as a safe, non-volatile, noncorrosive and reusable Brønsted acid catalyst in acid-catalysed organic reactions, many applications of this organocatalyst have been reported by different research groups. The main common advantages are the mild reaction conditions normally required and the easy catalyst recovery and recycling, with economic and ecological advantages. Many organocatalytic applications of **1** deal with the synthesis of heterocycles, therefore we will report them in a chronological order.

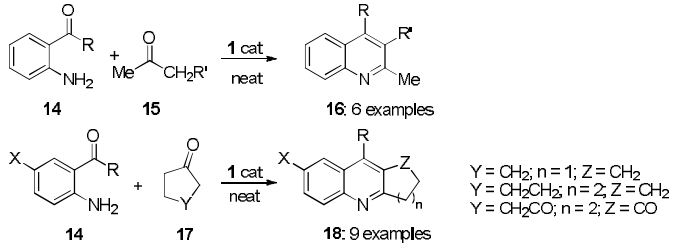
Catalytic amounts of **1** were used by us in the synthesis of heterocyclic compounds, namely tetrahydroisoquinolines and tetrahydro-β-carbolines,[12] quinolines,[13] benzothiazoles, benzoxazoles and benzimidazoles.[14] These widespread heterocyclic scaffolds are endowed with many biological activities, so the interest in new efficient green synthetic procedures is always high. Furthermore, until very recent years Brønsted acids have been used in fewer procedures with respect to Lewis acids.

An efficient and solvent-free Pictet-Spengler reaction between 2-arylethanamines **5** and aryl (or heteroaryl) aldehydes (and a ketone) **6** afforded the expected virtually pure tetrahydroisoquinolines **8** in high yields (Scheme 2). Reactions were run without the use of any solvent in any of the steps, in the presence of **1** (20 mol%), which could be recovered almost quantitatively from aqueous washings, and reused as catalyst in two subsequent runs with comparable catalytic activity.[12] The formation of intermediate imine derivatives **7** and their complete conversion to the cyclisation products were observed. In the case of long-chain aliphatic aldehydes or in the absence of electron-donating substituents on the amine aromatic ring, however, the formation of the homo-aldol condensation products **9** or of the imine was detected, as a result of a tautomerism between the imine and the corresponding enamine, which became competitive with the cyclisation step. In the proposed mechanism, the two pathways are both catalysed by the Brønsted acid **1**. The synthetic method was then extended to tryptamine **10** and aryl (or heteroaryl) and alkyl aldehydes **11**: tetrahydro-β-carbolines **13** were obtained in excellent yields from aryl aldehydes, while alkyl aldehydes gave traces of homo-aldol products as above.



Scheme 2. Tetrahydroisoquinoline and tetrahydro-β-carboline Pictet-Spengler synthesis.

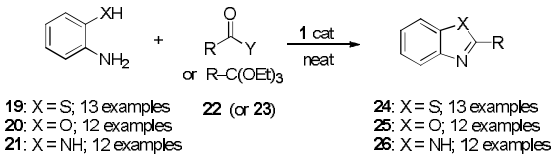
At the same time, we reported an efficient synthesis of quinolines **16** and **18** through a Friedländer annulation by 2-aminobenzophenones and 2-aminoacetophenones **14** with a number of dialkyl or cyclic ketones bearing one activated α-methylene group **15** and **17**, in the presence of **1** (5 mol%) and in solvent-free conditions (Scheme 3).[13] Economic benefits were the avoidance of any solvent along with the virtual purity of the products, the recovery and recycling of the catalyst without loss of catalytic activity.



Scheme 3. Isoquinoline synthesis through Friedländer annulation.

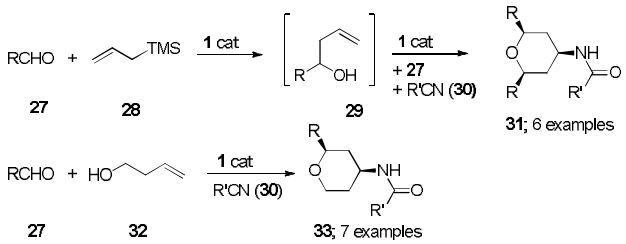
OBS-catalysed reactions of 2-aminothiophenol **19**, 2-aminophenol **20**, *o*-phenylenediamine **21** with various *ortho* esters or aldehydes **22** or **23** (and some other carboxylic acid derivatives, although the *ortho* esters were the best choice) afforded the corresponding benzofused azoles (namely, benzothiazoles **24**, benzoxazoles **25** and benzimidazoles **26**) under neat conditions in excellent yields (Scheme 4). The mild

reaction conditions, the catalytic amounts of **1** (5 mol%), the catalyst recovery and effective recycle were confirmed.[14]



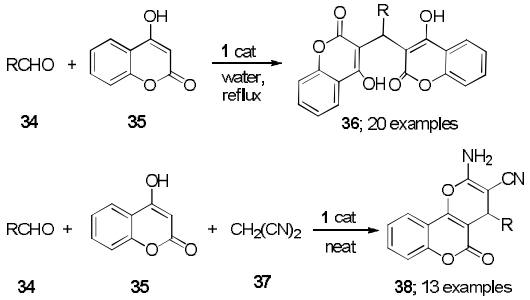
Scheme 4. OBS-catalysed synthesis of benzothiazoles, benzoxazoles and benzimidazoles.

Subba Reddy reported an efficient diastereoselective three-component synthesis of symmetrical 2,6-diaryl (or dialkyl) 4-amidotetrahydropyrans **31** through a sequential Hosomi-Sakurai, Prins-Ritter reaction under mild reaction conditions (Scheme 5). The first allylation step of both aromatic and aliphatic aldehydes **27** catalysed by OBS (10 mol%) furnished in situ the homoallylic alcohol **29** which underwent Prins cyclization with a second equivalent of aldehyde in the presence of nitrile **30** to afford the corresponding 4-amidotetrahydropyrans **31** in good yields and *cis*-selectivity.[15] The simple protocol was extended to the one-pot synthesis of unsymmetrical 4-amidotetrahydropyrans **33** through Prins-Ritter reaction starting from but-3-en-1-ol **32**, in the presence of OBS (10 mol%); results were better than those achievable with other Brønsted acid catalysts.



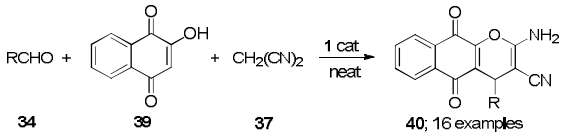
Scheme 5. OBS-catalysed 2,6-disubstituted 4-amidotetrahydropyran synthesis.

In very recent years, Maleki extended the use of OBS as an efficient recyclable organocatalyst in green syntheses of various oxygenated heterocycles and substituted cyclohexanes, through multicomponent reactions (MCRs), under ecofriendly conditions. These synthetic protocols combined the advantages of MCRs with that of a cheap, safe, water-tolerant and recyclable catalyst, with economic and ecological benefits. In the first protocol, biscoumarin **36** were prepared from a variety of aldehydes **34** and 4-hydroxycoumarin **35** in the presence of 50 mol% of **1** in water at reflux; dihydropyrano[3,2-c]chromenes **38** were obtained by an analogous procedure from the same reagents and malononitrile **37** in neat conditions on heating at 130 °C (Scheme 6).[16]



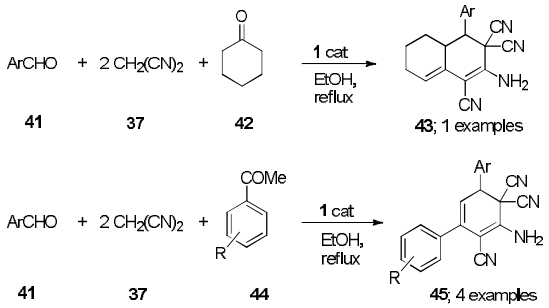
Scheme 6. OBS-catalysed synthesis of bis-coumarin and dihydropyrano[3,2-c]chromene derivatives.

In the second in water one-pot protocol, he reported the synthesis of 2-amino-4*H*-benzo[g]chromene derivatives **40** *via* the three-component reaction reported in Scheme 7, carried out in the presence of OBS as a safe, cheap and reusable catalyst (10 mol%) in solvent-free conditions at 60 °C.[17] The high yields and short reaction times compared with the data observed in recent literature reports clearly showed **1** to be the most efficient catalyst.



Scheme 7. OBS-catalysed synthesis of 2-amino-4H-benzo[g]chromenes.

Finally, in 2017 one-pot syntheses of bicyclic *o*-aminocarbonitrile **43** and of cyclohexa-1,3-dienamine derivatives **45**, interesting as organic intermediates, were achieved by reacting different aromatic aldehydes **41**, cyclohexanone or acetophenones **42** or **44** and malononitrile **37** in the presence of OBS (25 mol%), in ethanol at reflux (Scheme 8). [18] The same reactions were run in ionic liquid triethylammonium acetate at 80 °C, as an environmentally benign catalyst, with comparable results.



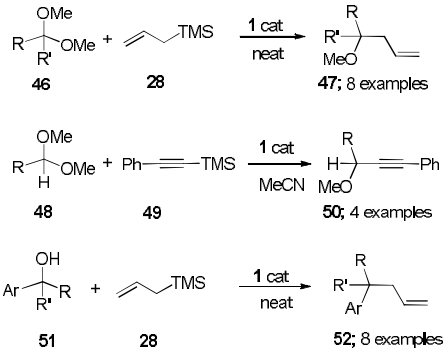
Scheme 8. *o*-Aminocarbonitrile and cyclohexa-1,3-dienamine derivatives synthesis.

2.3. *o*-Benzenedisulfonimide as catalyst in common acid-catalysed organic syntheses

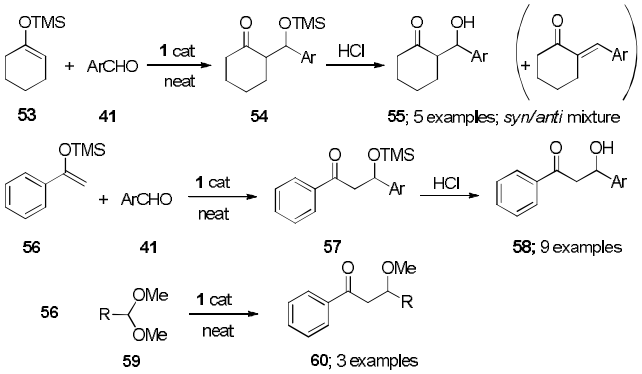
Catalytic amounts of OBS were then used by some research groups and by us in many other well-known synthetic procedures, commonly Brønsted-acid catalysed. The advantages outlined above of using this strong Brønsted acid as catalyst were confirmed in Hosomi-Sakurai, Mukaiyama aldol, hetero-Michael and Friedel-Crafts type reactions.

We found that OBS could catalyse the Hosomi-Sakurai reactions of ketals (or acetals) **46** and **48** and alcohols **51**, as the electrophiles, with silyl derivatives allyl(trimethyl)silane **28** and phenylethinyl(trimethyl)silane **49** (Scheme 9).[19] The catalyst amount varied with respect to the electrophile from 5-10 mol% with the former silane to 20-30 mol% with the latter, or to 5-30 mol% when using alcohols. The reactions were carried out in neat conditions when using **28**, and in acetonitrile when using **49**.

The Mukaiyama aldol reaction of aryl aldehydes **41** with silyl enol ethers **53** and **56** was efficiently catalyzed by the strong Brønsted acid **1** in solvent-free conditions at room temperature.[20] In the case of less reactive aliphatic aldehydes, the corresponding dimethyl acetals **59** were used as more electrophilic reagents. The catalyst amount was very low (1 mol% when using **53**, 2 mol% for **56** and 2-3% when using acetals **59**) (Scheme 10). Mechanistic studies were done in order to distinguish between Brønsted and Lewis acid catalysis, which could derive from the formation in situ of *N*-silylated OBS, as evidenced by List using a binaphthyl-derived chiral disulfonimide as a powerful asymmetric catalyst in an enantioselective Mukaiyama reaction.[21] Our findings, in neat conditions, were in agreement with the involvement of a protic acid catalysis, as reported by Yamamoto and co-workers.[22-23]

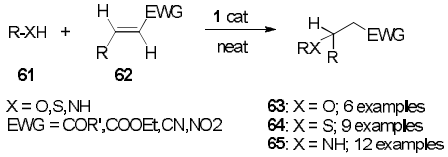


Scheme 9. OBS-catalysed Hosomi-Sakurai reaction.



Scheme 10. OBS-catalysed Mukayiama aldol reaction.

In 2013, we described *o*-benzenedisulfonimide catalysed hetero-Michael reactions of various oxygen, sulfur and nitrogen nucleophiles **61** with different Michael acceptors **62**, in mild solvent-free conditions, to give highly functionalized products **63**, **64** and **65**, useful intermediates in the synthesis of biologically active substances.[24] The catalyst amount was 5 mol% in all examined oxa-, thia- and aza-Michael reactions, and it proved to be advantageous with respect to other acid catalysts previously used (Scheme 11).

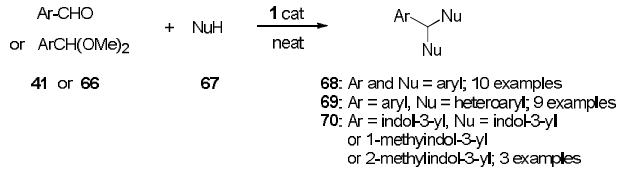


Scheme 11. OBS-catalysed hetero-Michael reactions.

Then, Friedel-Crafts-type reactions were studied between activated arene and heteroarenes **67** and aromatic aldehydes **41** (namely hydroxyalkylation) or acetals **66**, and with benzylic alcohols **71**, actually alkylation *via* a direct S_N1-type nucleophilic substitution, in the presence of OBS as the catalyst (Schemes 12 and 13).

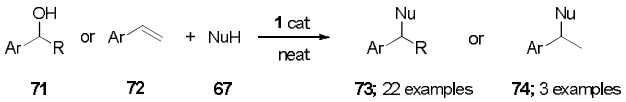
The first study furnished the expected products triaryl, bisindolyl and trisindolylmethanes **68-70** *via* a bisarylation pathway. Despite the high number of protocols reported for their synthesis, the demand for new efficient, metal-free and environmentally benign methods is high. Our procedure was carried out under solvent-free conditions for **68** and **69** or in ethanol for **70**, at room temperature or heating in the presence of

1 (10 mol%) to give very good yields of pure products (Scheme 12).[25] Some reactions were run using OBS adsorbed onto silica gel (10% w/w) as the catalyst: the results were comparable to those obtained with pure OBS; recovery and recycle of the catalyst were improved. Furthermore, to the best of our knowledge, in this work we described for the first time a Friedel-Crafts hydroxylation without catalyst in the case of 4-nitrobenzaldehyde and indoles. The solid-state reaction mechanism was studied by solid-state NMR experiments, and confirmed by DFT calculations.[26]



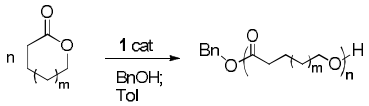
Scheme 12. OBS-catalysed triarylmethane and bisindolylmethane syntheses.

In 2014, the second study developed a simple and efficient alkylation of aromatic and heteroaromatic rings in the presence OBS (10 mol%) under solvent-free conditions at variable temperatures.[27] Benzhydrylic and primary benzylic alcohols **71** and styrenes **72** were reacted with activated arenes and hetereoarenes **67** to give triaryl (or diaryl)methanes **73** and diarylethanes **74**, respectively, in good to high yields (Scheme 13). The plausible proposed mechanism involved alcohol protonation by **1** and the formation of differently stable carbenium ions. The empirical observed scale of reactivity for the different alcohols could be rationalized by referring to electrophilicity and nucleophilicity scales elaborated by Mayr and co-workers.[28-31]



Scheme 13. Arenes and heteroarenes Friedel-Crafts alkylation with alcohols and styrenes.

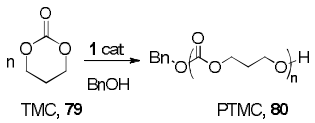
In 2014 and 2015, Guo took advantage of OBS properties in organocatalyzed ring-opening polymerization (ROP) as an attractive and versatile approach for the preparation of polymers in well-controlled polymer weights under mild reaction conditions. Biocompatible and biodegradable poly(δ-valerolactone) (PVL) **76** and poly(ε-caprolactone) (PCL) **78** were prepared by ROP of δ-valerolactone **75** and ε-caprolactone **77** catalyzed by OBS in the presence of benzylic alcohol (initial ratio OBS:BnOH=1:1), in toluene at 30-35 °C (Scheme 14).[32] Besides the safety, recoverability and recyclability of **1**, a further valuable aspect of this organocatalyst was its high solubility in organic solvents and water, which allowed to use water as an initiator in the lactones ROP, a goal unattainable when using previously explored organocatalysts. The mild, clean and economic approach was applied to the synthesis of PVL and PCL and copolymers composed of PVL and PCL with well controlled molecular weights and narrow polydispersities. The authors proposed that the polymerization proceeded through an activated monomer mechanism, where OBS protonated the lactone carbonyl oxygen promoting its attack by the hydroxyl group firstly of the initiator BnOH and then of the propagation polymer chain.



Scheme 14. OBS-catalysed ROP of δ-VL and ε-CL with BnOH as the initiator.

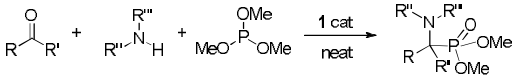
The general feasibility of the procedure was then demonstrated in the controlled/living OBS catalysed ring-opening polymerization of trimethylene carbonate (TMC) **79** (Scheme 15). α,ω-Dihydroxy telechelic

and star-shaped polycarbonates were prepared under similar reaction conditions. Furthermore, branched structures were obtained using polyols.[33] The same OBS-activated monomer mechanism was proposed.



Scheme 15. OBS-catalysed ROP of TMC with BnOH as the initiator.

In 2017, Akbari described a synthesis of α-aminophosphonates **84** in the presence of OBS as the catalyst (5 mol%) with the advantages reported in previous works. The one-pot three-component reaction between many different aldehydes (or ketones) **81**, secondary amines **82** and phosphite **83** was run at room temperature under solvent-free conditions, giving products **95** in high yields (Scheme 16).[34]



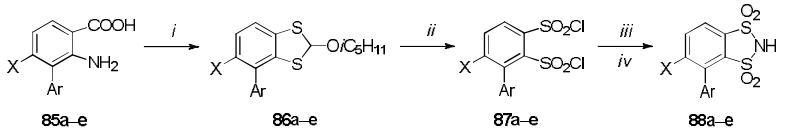
Scheme 16. OBS-catalysed synthesis of α-aminophosphonates.

3. Synthesis and synthetic applications of *o*-benzenedisulfonimide derivatives

3.1. Chiral derivatives of *o*-benzenedisulfonimide

Results and advantages of the use of OBS as Brønsted acid catalyst are very encouraging in view of the application of this catalyst in the field of asymmetric catalysis. In fact, asymmetric catalysis is one of the most significant topics in current organic chemistry and chiral Brønsted organic acid catalysis is an intriguing area since it is a very efficient means for the synthesis of chiral molecules with excellent stereoselectivity. A Brønsted acid should have the following characteristic if it is to be considered a good chiral catalyst: suitable acidity in order to catch up the substrate through hydrogen bonding without loose ion-pair formation, type C2 symmetry, and the presence of bulky substituents closer to the acidic function that enhance the stereochemical communication between catalyst and substrate.

Of course, structural modifications are needed for OBS to become chiral leaving unaffected, however, the acidic function responsible of the catalytic activity. On this ground, we prepared a set of 3-aryl-1,2-benzenedisulfonimides **88** in good overall yields (about 50%) starting from corresponding anthranilic acids **85** (in turn prepared from corresponding isatins; Scheme 17).[35] The possible chirality is due to the hindered rotation of the aryl groups (atropisomerism).



85,86,87,88	Ar	X
a	Ph	H
b	2-MeC$_6$H$_4$	H
c	1-naphthyl	H
d	2-MeC$_6$H$_4$	Me
e	1-naphthyl	Me

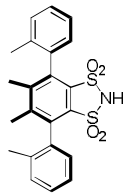
Scheme 17. Synthesis of 3-aryl derivatives of OBS.

The conformational free energy barrier in water at room temperature were calculated for some selected OBS derivatives **88**. The results, collected in Table 1, show that the rotational barrier is high enough to lead to stable atropisomers only for derivatives **88d** and **88e**.

Table 1. Calculated rotational free energy barrier (in kcal mol^{-1}) and life times

Disulfonimides **88**	ΔG‡	Life Time	Optical purity (% after 24 h)
88b	19.4	26 sec	0
88c	21.9	29 min	1
88d	39.5	10^8 year	100
88e	39.6	10^8 year	100

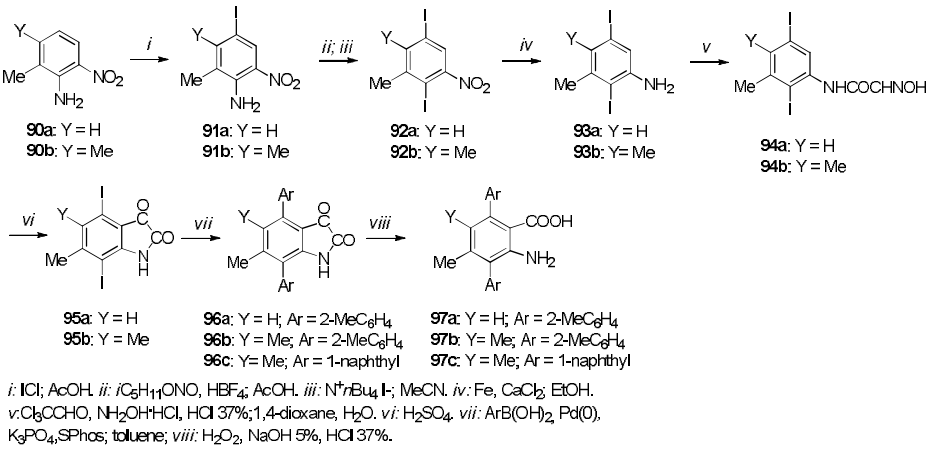
88d Was used as a chiral catalyst in the Strecker reaction but unsatisfactory results were obtained in terms of enantioselectivity.[36] Actually, **88d** cannot be a good chiral catalyst mostly because it does not have C2 symmetry. So, another chiral derivative of OBS, namely (–)-4,5-dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide **89b** (Figure 2), which has two bulky groups in *ortho* positions and *C2* symmetry, was synthesized.[37]



89b

Figure 2. (–)-4,5-Dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide **89b**.

Its precursor was the anthranilic acid **97b** which was obtained from commercially available 2-methyl-6-nitroaniline **90b** as reported in the Scheme 18.[37]



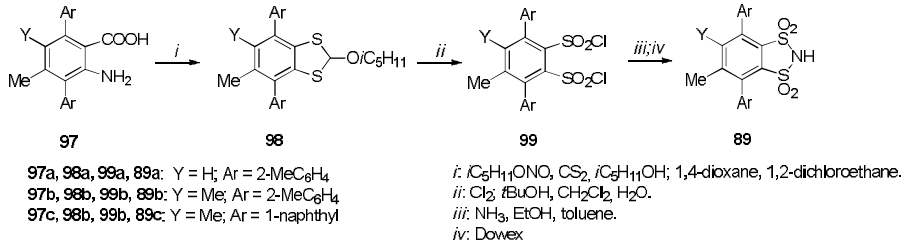
i: ICl; AcOH. *ii:* $iC_5H_{11}ONO$, HBF_4; AcOH. *iii:* $N^+nBu_4I^-$; MeCN. *iv:* Fe, $CaCl_2$; EtOH. *v:* Cl_3CCHO, $NH_2OH^+HCl^-$, HCl 37%;1,4-dioxane, H_2O. *vi:* H_2SO_4. *vii:* $ArB(OH)_2$, Pd(0), K_3PO_4,SPhos; toluene; *viii:* H_2O_2, NaOH 5%, HCl 37%.

Scheme 18. Synthetic protocol for anthranilic acids **97**.

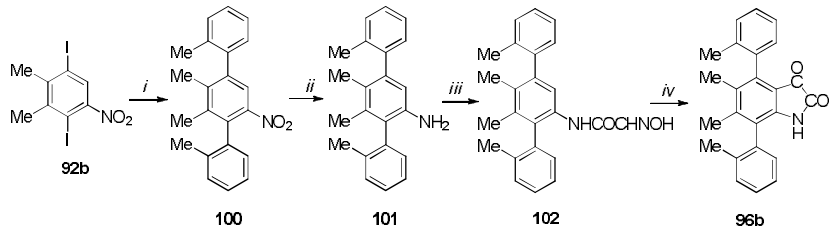
Acid **97b** were then converted into **89b** using the same synthetic protocol employed in the preparation of parent OBS, reported in Scheme 19. However**,** the overall yields of **89b**, calculate starting from **90b**, was very low (about 10%), and the critical step was the conversion of intermediate **94b** into isatin **95b**.

It must be stressed that with this protocol, other two chiral derivatives of OBS were obtained, namely **89a** and **89c** (overall yields 34 and 10%, respectively). In order to improve the yields of **89b**, the procedure for isatin **96b** (precursor of anthranilic acid **97b**) was modified as reported in Scheme 20. Thanks to this

change, the overall yield (always calculated from **90b**) increased up to 44%.[37] The racemic mixture of atropisomers of disulfonyl chloride **99b**, that have the same chiral structure as **89b**, were resolved by semi-preparative chiral HPLC. One of these separated atropisomers, the (–)-**99b**, was easily transformed into the corresponding (–)-**89b**.

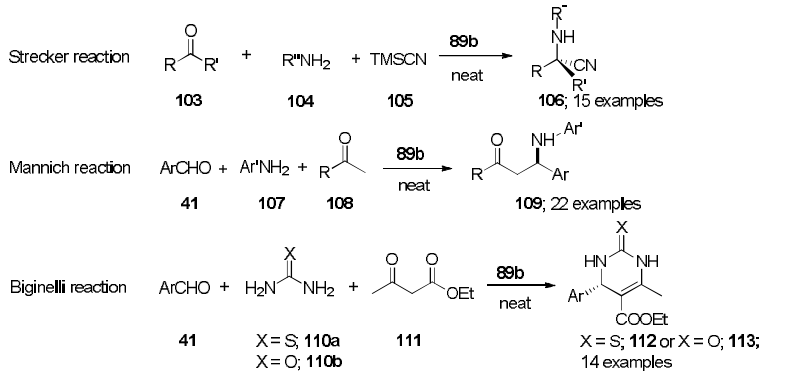


Scheme 19. Synthetic protocol for chiral disulfonimides **89**.



Scheme 20. Improved protocol for isatin **96b**.

One-pot multicomponent reactions, under the appropriate conditions, can be green, sustainable and eco-compatible methodologies, a valid tool to build complex molecules with simplicity and brevity. On this ground, **89b** was used as an efficient and high yields catalyst in three different types of one-pot three component reactions (Scheme 21), namely Strecker (average yield of products **106**: 74%),[37] Mannich (average yield of products **109**: 85%)[38] and Biginelli reactions (average yield of products **112** and **113**: 91%).[39]



Scheme 21. 89b as chiral and green catalyst.

In the first place, **89b** proved to be an efficient chiral catalyst: diastereo- and enantioselectivity (usually up to 90%) were always excellent. Then, it must be stressed that its use allowed to achieve important green benefits. Indeed, the reactions were carried out in neat and mild conditions, the reaction times were relatively short, no chromatographic separations were usually needed, the absence of by-products lead to an atom economy of about 100% and, finally, catalyst **89b** was easily recovered (usually with high yields) and was reused in other consecutive reactions. The yields and the enantioselectivity of the target products were consistently good over the various runs.

From the mechanistic point of view, these chiral Brønsted acid catalysed reactions may be classified as an asymmetric counteranion-directed catalysis (ACDC), according to List classification.

In a project aimed to design and use adducts **114a-c** as chiral catalysts in Mukaiyama aldol reactions (Figure 3), List prepared the OBS derivative 4,7-bis[(3,5-bis(trifluoromethyl)phenylhydroxymethyl]-benzo[d][1,3,2]dithiazole-1,1,3,3-tetraoxide **115** starting from OBS, as shown in Scheme 22. Unfortunately, compound **115** was unstable and spontaneously decomposed into adduct **116**; it was therefore not possible to test it as a catalyst.[40]

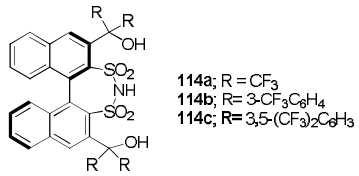
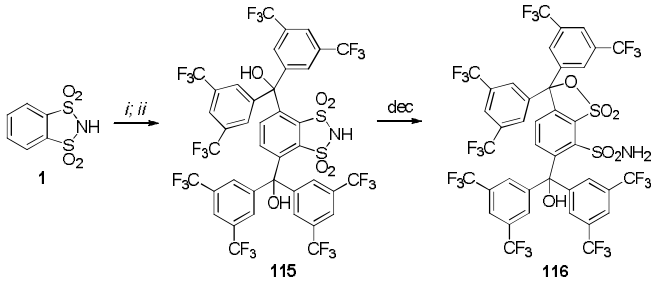


Figure 3. Chiral adducts **114**.



i: TMEDA, secBuLi. *ii:* 3,3',5,5'-tetrakis(trifluoromethyl)benzophenone

Scheme 22. Attempted synthesis of **115** and formation of derivative **116**.

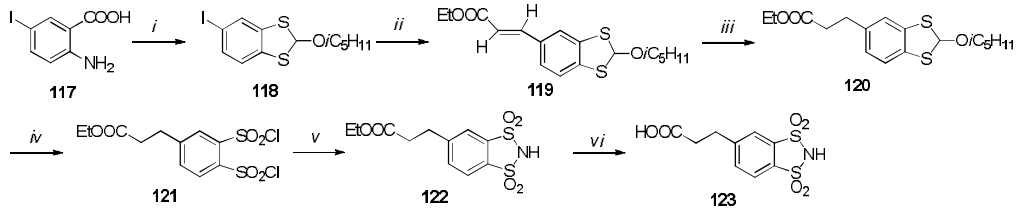
3.2. Silica-supported *o*-benzenedisulfonimide

A braod tendency in catalysis is to convert an optimal homogeneous organocatalyst into a heterogeneous catalytic system. The reasons that make useful the immobilization of an organic catalyst include the easy procurement of the reaction products and the ready and simple recovery of the catalyst from the reaction mixture On this ground, OBS was trasformed into a heterogeneous catalyst by grafting it onto a functionalized silica gel. The presence of an amino group allows a carboxy-functionalised OBS to be linked to silica gel by means of a strong covalent bond, namely an amide bond. Moreover, the connection must be created far from the catalytic active site in order to prevent interactions with the support. In the light of these, 3-(1,2-benzenedisulfonimide-4-yl)propionic acid **123** was prepared in good overall yield (75% from **117**) as shown in Scheme 23.[41]

Then adduct **123** was reacted with 3-aminopropyl functionalized silica **124** (Scheme 24). The condensation reaction between NH_2 and COOH groups was promoted by *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDC) and afforded adduct **125** (91% yield), whose structure was confirmed by IR and NMR analyses.

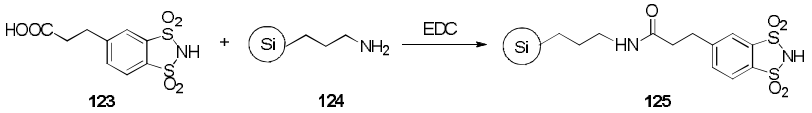
This new heterogeneous catalyst **125** was tested over five different reactions that require acid catalysis and that had advantageously already been catalysed by parent OBS. More precisely catalyst **125** was used in

a Ritter and in a Strecker reactions, a Fischer esterification, a Mannich and a Biginelli reactions (Scheme 25). Results were generally excellent and very similar to those obtained using **1** as catalyst. Furthermore, **125** was easily recovered and reused in ten consecutive runs in a Ritter reaction, without losing catalytic activity.

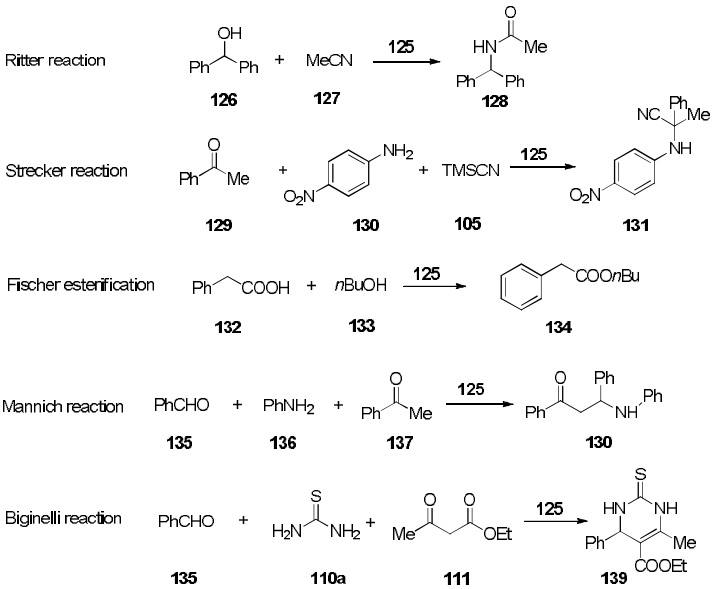


i: $iC_5H_{11}ONO$,CS_2 $iC_5H_{11}OH$; 1,4-dioxane, 1,2-dichloroethane.
ii: H_2C=CH–COOEt, $PdCl_2$·PPh_3, K_3PO_4. *iii*: CuCl, $NaBH_4$.
iv: NCS, HCl 2N. *v*: NH_3, Dowex; *vi*: spontaneous hydrolysis

Scheme 23. Preparation of adduct **123**.



Scheme 24. Immobilization of **123** on silica.



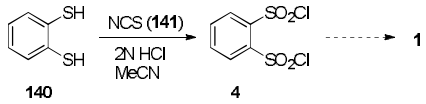
Scheme 25. Selected reactions catalyzed by **125**.

3.3. Miscellaneous studies

The key intermediate for the synthesis of *o*-benzenedisulfonimide **1** and *N*-substituted derivatives is *o*-benzenedisulfonyl chloride **4**, in turn reacted with ammonia or amines.

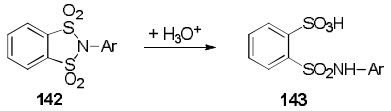
In 2010 we reported a new general procedure for the synthesis of arene mono- and disulfonyl chlorides and a new synthesis of **4**, on a laboratory scale, by treating *o*-benzenedithiol **140** with *N*-chlorosuccinimide **141** in 2N HCl/acetonitrile (1:5) at 0-10°C (Scheme 26).[42] The synthetic strategy was applied also to the

preparation of 2,2'-biphenyl and 2-2'-binaphthyldisulfonyl chlorides, which were converted into the corresponding cyclic imides simply by treatment with ammonia. These imides represent interesting synthetic goals, owing to the fact that they are strongly acidic chiral compounds, successfully explored as Brønsted acids catalysts.[43]



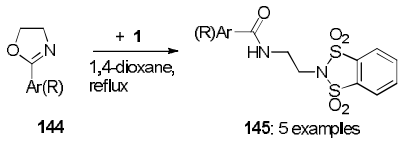
Scheme 26. *o*-Benzenedisulfonyl chloride (**4**) synthesis.

In 2012, Eren reported a systematic study on the acid-catalysed hydrolysis of *N*-(*p*-substituted phenyl)-*o*-benzenedisulfonimides **142**, prepared from **4** and *p*-substituted anilines by a slightly modified procedure (benzene under reflux, in the presence of trimethylamine) (Scheme 27).[44] The mechanism proposed in the studied conditions is an A-1, which first proceeds *via* rapid protonation of the nitrogen atom, and then through S-N bond cleavage in the rate-determining step.



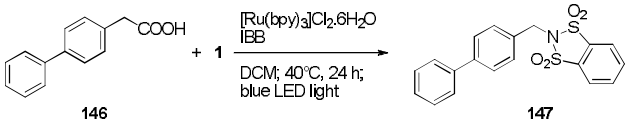
Scheme 27. Acid-catalysed hydrolysis of derivatives **142**.

Although the *o*-benzenedisulfonimide anion is normally considered non-nucleophilic, it has been reported as a nucleophilic agent in the ring-opening of electron-rich 2-substituted 2-oxazolines **144**, along with other acidic sulfonimides, to give sulfonimidation products **145**, in refluxing dioxane, in high yields (Scheme 28).[45] OBS was able to open 2-aryl, 2-alkyl and 2-heteroaryl substituted oxazoline rings. The reaction took place only on electron-rich substrates, which likely favour the protonation of the nitrogen atom and allow the attack of the nucleophilic imide anion.



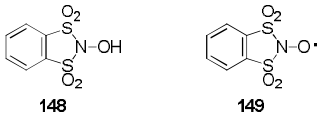
Scheme 28. Sulfonimidation of 2-oxazoline by ring-opening with acidic sulfonimides.

In 2018, Murakami and Itami reported a ruthenium-catalysed photoredox decarboxylative functionalisation of arylacetic acids under blue LED light.[46] New carbon-nitrogen and carbon-oxygen bonds were formed; OBS gave the sulfonimidation product **147** in 45 % yield (Scheme 29).



Scheme 29. Photoredox decarboxylative functionalisation of arylacetic acids.

In a study dealing with stable cyclic bis sulfonyl nitroxide radicals formation, *N*-hydroxy-*o*-benzenedisulfonimide **148** was treated with excess CAN and gave the corresponding nitroxide **149** (Figure 4), whose lifetime was sufficient enough for characterization by EPR.[47]



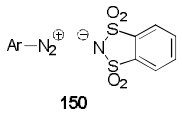
148 149

Figure 4.

4. Synthesis and synthetic applications *o*-benzenedisulfonimide salts

4.1. Arenediazonium *o*-benzenedisulfonimides

Since 1998,[8] a new and large family of arenediazonium salts, the arenediazonium *o*-benzenedisulfonimides. 1**50** (Figure 5) were prepared and successfully used by us in the classical reactions of diazonium salts. These salts are in fact easy to prepare and isolate, very stable and they can be stored for an unlimited time and reacted easily in water but also in organic solvents. Interestingly, an easy recovery and reuse of OBS was always possible.



150

Figure 5. Arenediazonium *o*-benzenedisulfonimides **150**.

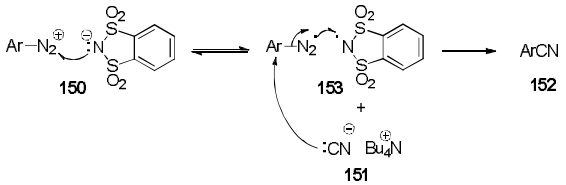
4.1.1. Sandmeyer cyanation

More recently, arene and heteroarenediazonium *o*-benzenedisulfonimides were used as efficient reagents in a copper-free Sandmeyer cyanation under mild conditions and with tetrabutyl ammonium cyanide as a safe cyanide source (Scheme 30). The yield of target products was satisfactory (average yield 75%).[48]

150 151 MeCN 152; 25 examples

Scheme 30. Sandmayer cyanation of arenediazonium *o*-benzenedisulfonimides.

Mechanistic insights suggested that the anion of salts **150** would react as electron donor toward the arenediazonium cation giving rise to the complex **153**, where the partner of aryl diazenyl radical was highly stabilized by resonance. Then, this complex reacted with CN^- provided nitriles **152** (Scheme 31).



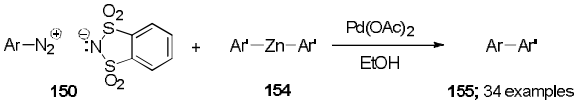
150 153 151 152

Scheme 31. Proposed mechanism of Sandmeyer cyanation.

4.1.2. Palladium catalysed cross-coupling reactions

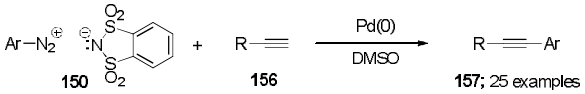
Arenediazonium salts have recently been extensively used as effective aryl halide alternatives in the palladium catalysed C–C bond forming cross-coupling reactions. Indeed, there are many advantages associated with diazonium salts. These include their greater reactivity, due to the fact that the diazonium group is a better nucleofuge than the halide, which allows the use of milder reaction conditions. Moreover, no bases or additional ligands were necessary.

In particular, arenediazonium *o*-benzenedisulfonimides were used as efficient electrophilic partner in Negishi coupling (Scheme 32). The synthetic protocol was general, easy and gave biaryls in satisfactory yields (average yield 67%). It must be stressed that no other examples of arenediazonium salts in Negishi coupling are known.[49]



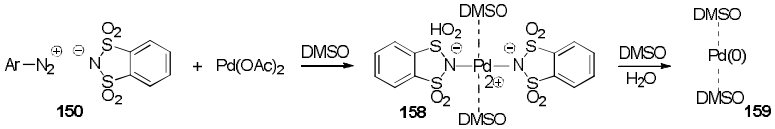
Scheme 32. Negishi coupling of arenediazonium *o*-benzenedisulfonimides.

Moreover, arenediazonium *o*-benzenedisulfonimides were also advantageously employed in Sonogashira coupling. The reactions were carried out in DMSO in very mild conditions (without copper and phosphanes) and gave rise to arylated alkynes in good yields (average yield 83%; Scheme 33).[50]



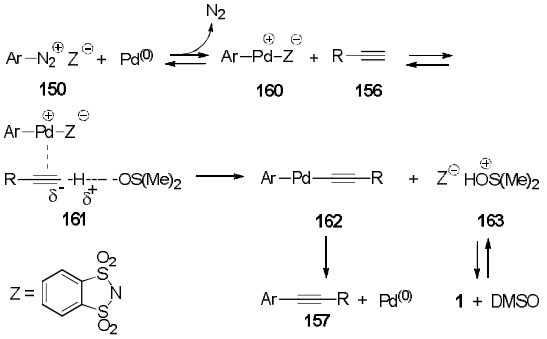
Scheme 33. Sonogashira coupling of arenediazonium *o*-benzenedisulfonimides.

Mechanistic insights highlighted the fundamental role both of DMSO and of the *o*-benzenedisulfonimide anion in the formation of the Pd(0) catalyst and the importance of the first in the catalytic cycle. In the first place, it was hypothesized that the effective Pd(0) catalyst complex **159** resulted from complex **158**, as represented in Scheme 34.



Scheme 34. Formation of palladium catalyst for Sonogashira coupling.

Then, a possible mechanism, showed in Scheme 35, was presented. In the key step, the formation of a hydrogen bond between **161** and DMSO weakens the alkynyl C-H bond and makes the carbon nucleophilic enough to form a new C-Pd bond. The formation of this bond may be also favoured by the fact that Pd-N is an ionic bond, the very weak base Z^- is a good leaving group and DMSO is poor at solvating anions. In this way, it was explained why the reaction proceeded *only* in DMSO; other solvents are not able to sufficiently weaken the alkynyl C-H bond.

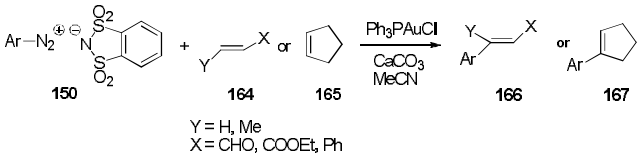


Scheme 35. Mechanism of Sonogashira coupling.

4.1.3. Gold catalysed cross-coupling reactions

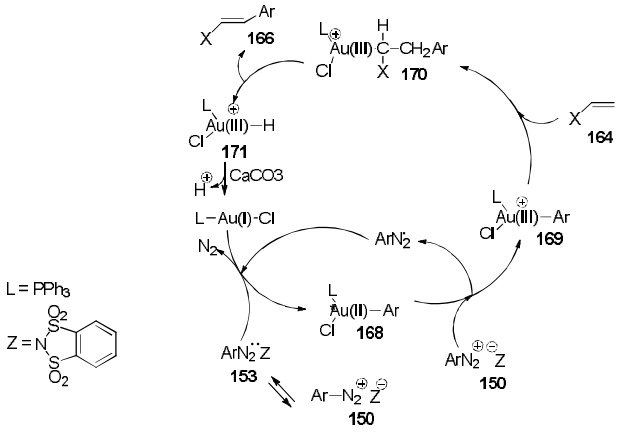
Since Au(I) has the same d^{10} configuration as Pd(0) and Cu(I), it is able to catalyse reactions typically promoted by Pd(0), including cross-coupling reactions. Arenediazonium salts have been recently used as electrophilic reactants in gold catalysed cross-coupling reactions usually under photoredox conditions. In fact, as a result of their capability to be subjected to a single-electron reduction under visible light and in the presence of photosensitizers, they provide aryl radicals, that give sequential oxidative additions onto Au(I) species. The subsequent reductive elimination from the resulting Au(III) complexes produces the desired coupling adducts regenerating the Au(I) catalyst.

In particular, arenediazonium *o*-benzenedisulfonimides have been used by us for the first time as efficient partners in gold-catalysed Heck-coupling reactions. The synthetic protocol was general, easy and gave the target products in satisfactory yields (23 examples; average yield 73%) (Scheme 36).[51]



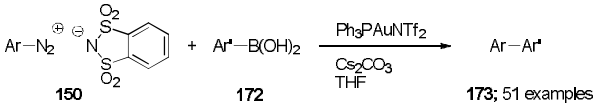
Scheme 36. Gold catalysed Heck reaction.

It is noteworthy the interesting role that the anion of *o*-benzenedisulfonimide plays as an electron transfer agent, allowing a radical pathway (Scheme 37) which does not require the presence of photocatalysts or external oxidants.



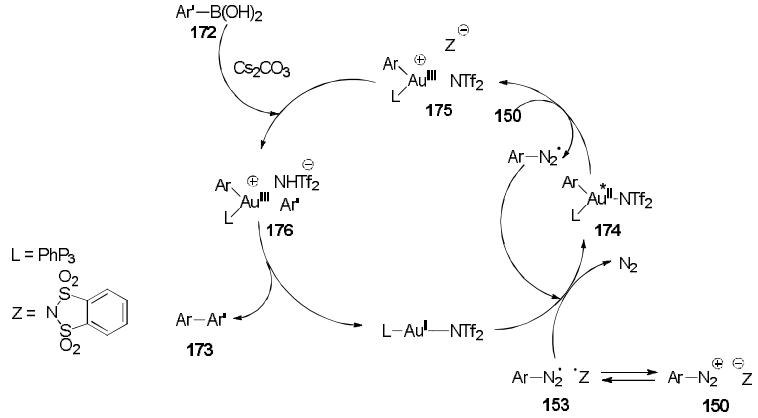
Scheme 37. Mechanism of gold catalysed Heck reaction.

Very recently, arenediazonium *o*-benzenedisulfonimides have been proven to be efficient reagents in Au(I) catalysed Suzuki coupling reactions.[52] The synthetic protocol was general, easy and produced either biaryls or heteroaryl arenes **173** in good yields (Scheme 38; average yield 80%).



Scheme 38. Gold catalysed Suzuki reaction.

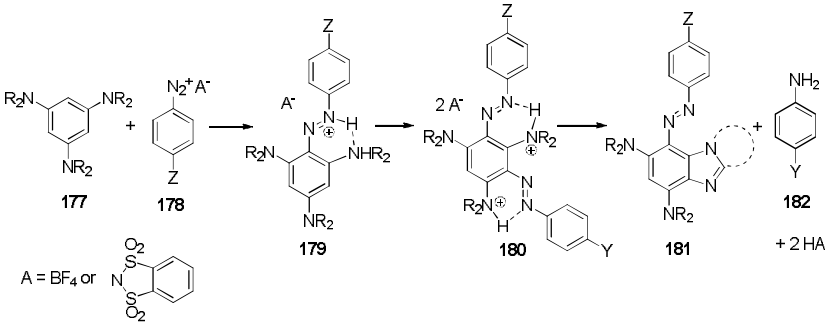
Also in this case, the *o*-benzenedisulfonimide anion acts as an electron transfer agent and promotes a catalytic cycle which does not require the presence of photocatalysts or external oxidants. The proposed catalytic cycle is reported in Scheme 39.



Scheme 39. Mechanism of gold catalyzed Suzuki reaction.

4.1.4. Azo-coupling reactions

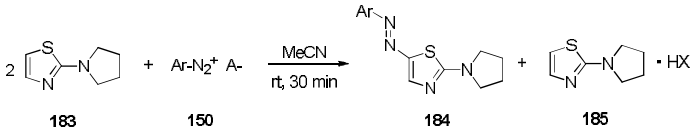
Boga and co-workers have published many works dealing with the chemical reactivity of electron-rich benzene rings substituted in 1,3,5-positions with symmetrical cyclic amino groups **177**. These compounds are defined as "carbon supernucleophiles" and allow, by reaction with electrophilic benzenediazonium cations, the isolation and spectroscopic characterization of reactive intermediate, such as Wheland σ-complexes and zwitterionic Wheland-Meisenheimer complexes. In the former case, the authors used some arenediazonium as *o*-benzenedisulfonimide salts.[53] Successively, they reported the reaction of selected arenediazonium tetrafluoroborates (and *o*-benzenedisulfonimides) **178** with the above anilines **177** giving azocoupling products **179**. These compounds, by a second reaction with salt **178**, afforded bis(azocoupling) dicationic intermediates **180**, which undergo an unprecedented ring closure to tricyclic benzimidazoles **181** containing the *N*-piperidinyl or *N*-morpholinyl moiety as fused ring, accompanied by the loss of one aniline molecule **182** (Scheme 40).[54] The presence of electron-withdrawing groups is crucial for the reaction. The 4-cyano- and 4-trifluoromethylbenzenediazonium cations were used as OBS salts in the reaction with 1,3,5-tris(*N*-morpholinyl)benzene.



Scheme 40. Tricyclic benzimidazoles **181** formation from bis(azocoupling) dicationic intermediates **180**.

The 4-cyano- and 4-chlorobenzenediazonium *o*-benzenedisulfonimides were then used along a wide range of arenediazonium tetrafluoroborates in the synthesis of 5-azoderivatives of

2-(*N*-pyrrolidinyl)thiazoles **185** (Scheme 41). NMR and computational studies showed an unexpected substituent effect on the restricted rotation around the C2-N bond.[55]



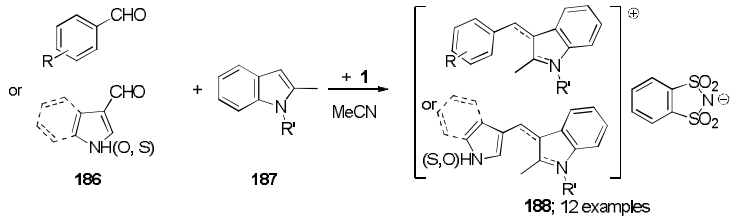
Scheme 41. 5-Areneazo-2-(*N*-pyrrolidinyl)thiazoles.

4.2. Aryl (or heteroaryl) indol-3-ylmethylium *o*-benzenedisulfonimides

The potential of the *o*-benzenedisulfonimide conjugated base was tested as stabilizing non-nucleophilic counter-ion of benzhydrylium carbocations, which are reactive intermediates in many organic reactions. Diarylmethylium ions are often generated *in situ* before their immediate reaction with nucleophiles, and only occasionally they have been isolated, normally as tetrafluoroborates or hexafluorophosphates. In recent years, however, a wide number of benzhydrylium ions have been prepared and used as reference electrophiles in stability and reactivity studies with π-, n-, and σ-nucleophiles by Mayr and co-workers.[31]

Among them, indol-3-ylmethylium ions are highly versatile intermediates in organic synthesis. We were interested in the Friedel-Crafts hydroxyalkylation mechanism involved in the above mentioned preparation of triarylmethane,[25] so we tried to isolate the carbocation intermediate as *o*-benzenedisulfonimide salt, a counter-anion with a well-known stabilizing ability.

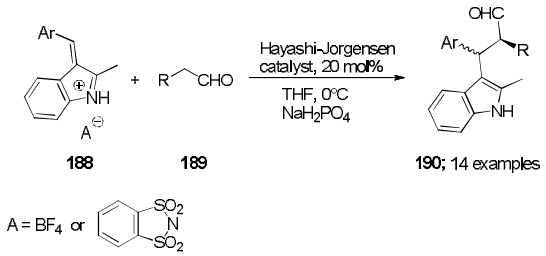
These carbenium ions, never previously isolated in the solid state, were obtained as insoluble salts by direct coupling between aryl (or heteroaryl) aldehydes (**186**, activated or not) and 2-methylindoles **187** in the presence of *o*-benzenedisulfonimide. The reaction was run with nearly equimolar amounts of reagents (*i.e.* **186**:**187**:**1**=1:1.2:1.2 molar ratio) in anhydrous acetonitrile under stirring for a few minutes; the products **188** separated spontaneously from the reaction mixture in excellent yields (Scheme 42). The salts proved to have long shelf-lives, to be storable for long times and ready-to-use reactants.[56] Unfortunately, attempts to substitute the indole nucleus with other aromatic rings as nucleophiles in these reaction conditions were unsuccessful. The indole stabilization effect was confirmed by the X-ray analysis of the 4-methoxyphenyl(indol-3-yl)methylium *o*-benzenedisulfonimide, which supported the highly stable azafulvenium resonance structure of the cation.



Scheme 42. Synthesis of aryl (or heteroaryl)(indol-3-yl)methylium *o*-benzenedisulfonimides **188**.

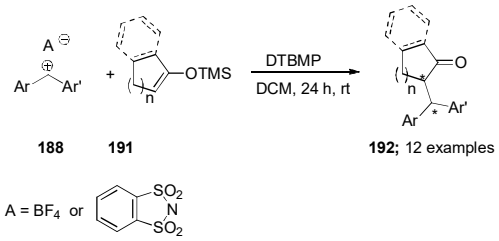
Some of these stable salts were then used in a direct stereoselective alkylation of aldehydes.[57] The reaction gave expected products **190** in a good diastereoselectivity (*anti* favoured adduct) and enantiomeric excess, in the presence of Hayashi-Jørgensen catalyst (Scheme 43). Furthermore, results obtained from the corresponding three-component reaction, in the presence of different organocatalysts, were inferior with respect to those obtained starting from the isolated salts.

In the above work, two carbocations were used as tetrafluoroborates salts.[58] In fact, the synthetic methodology was improved by using a tetrafluoroboric acid/diethyl ether complex as an advantageous alternative to the *o*-benzenedisulfonimide. Furthermore, azole moieties other than indole were found successful for the stabilization of the carbocations positive charge.



Scheme 43. Organocatalytic stereoselective alkylation of aldehydes.

These aryl (or heteroaryl)indol-3-ylmethylium ions **188** (whether as *o*-benzenedisulfonimides or tetrafluoroborates) were reacted with various cyclic silyl enol ethers **191**, in the presence of 2,6-di-*t*-butyl-4-methylpyridine (DTBMP, to prevent acidic hydrolysis of the latter reagents), in a molar ratio 1:1.5:1 (Scheme 44). The alkylated ketones **192** were obtained in a prevalent diastereoselectivity which is independent on the salt counter-anion, the salt substitution and the enol ether ring size. X-Ray analyses were performed on two purified diastereomers; DFT calculations confirmed and explained the observed diastereoselectivity.[59]



Scheme 44. Stereoselective alkylation of cyclic silyl enol ethers.

4.3. *o*-Benzenedisulfonimide-based ionic liquids

Due to the non-basic and non-nucleophilic character of its conjugate base, *o*-benzenedisulfonimide has been used in the preparation of room temperature ionic liquids.

In particular, hydrophobic ionic liquids based on stable anions have been studied with regard to radiation stability, in applications as diluents for liquid-liquid metal ion extraction from spent nuclear fuels and as protecting agents of extracting solvents itself.[60] Although the radiation stability of the cation can scarcely be improved, its fragmentation reactions do not damage the solvents; instead, the anion fragmentation leads to unstable neutral radicals. Hence the authors searched to identify an anion stable to high level of radioactivity. In these studies, four imide-based anions were considered: *o*-saccharinate **194** and *o*-benzenedisulfonimide **195** anions proven to be more stable to radiolytically-induced fragmentation than phthalimide **193** and acesulfame **196** analogues (Figure 6).

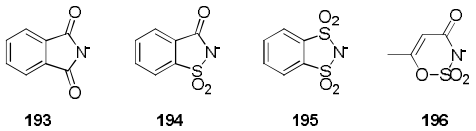
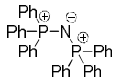


Figure 6. Imide-based anions **193-196**

In view of their application in emerging technologies as stable electrolytes in super capacitors, batteries and fuel cells, a large library of ionic liquids has been investigated in relation to chemical and radiation stability, by means of a variety of computational methods.[61] Whereas the cation stability was shown to be related to alkyl chain length and branching, the anion stability depended on ion size and

electronegativity. In a related paper, the same combinations of cations and anions in ionic liquids were computationally studied in order to predict the electrochemical potential window of thousands of their combinations. While predicted and experimental values were in good agreement, the anion of the *o*-benzenedisulfonimide proved to be among the five most stable ones.[62]

The high-temperature thermal stability of fourteen ionic liquids based on a perarylated stable cation **197** (PPN^+, commercially available) (Figure 7) has been studied by measuring not only the percent mass loss, by heating at three different elevated temperatures for 96 hours, but also the structural integrity of the evaluated salts by NMR spectroscopy.[63] Non-fluorinated imidate anions, including the OBS anion, were the most stable.

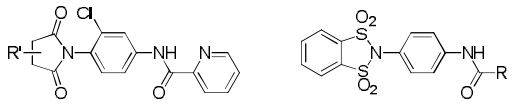


197, PPN^+

Figure 7. PPN^+ **197**.

5. Miscellaneous studies on *o*-benzenedisulfonimide derivatives

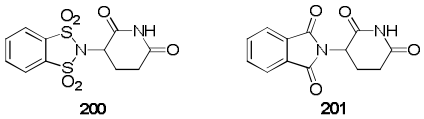
In recent years the *o*-benzenedisulfonimide scaffold has been considered as an interesting moiety in compounds already known for their biological activity. All derivatives were synthesized starting from *o*-benzenedisulfonyl chloride **4** and the suitable aminoderivative following the above mentioned literature procedures.[10] In this context, a new class of *N*-4-(2,5-dioxopyrrolidin-1-yl)-phenylpicolinamides **198** was synthesised as a result of drug design starting from a lead compound bearing *N*-(4-carboxamidophenyl)-*o*-benzenedisulfonimide scaffold **199** (Figure 8). These compounds were evaluated as positive allosteric modulators of the mGlu4 receptor for the treatment of Parkinson's disease.[64]



198 **199**

Figure 8.

The *o*-benzenedisulfonimide analogue **200** of thalidomide **201** (Figure 9) was synthesised and evaluated as inhibitor of the pro-inflammatory protein TNF-α, for the treatment of neurodegenerative disorders associated with neuroinflammation.[65] It showed more potency than the parent compound, along with improved tolerability.

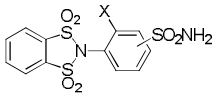


200 **201**

Figure 9.

Benzenesulfonamides substituted with the *o*-benzenedisulfonimido moiety **202** (Figure 10) were prepared and evaluated as inhibitors of human cytosolic CA enzymes isoforms I and II (hCA I and hCA II, and of the tumor-associated carbonic anhydrase isoforms CA IX and CA XII.[66] The tested compounds showed interesting activity, better than that of acetazolamide, the reference compound in clinical use. This finding was explained by molecular docking *via* favorable hydrogen-bonding interactions of the *o*-benzenedisulfonimide moiety with binding aminoacid residues.

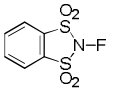
In 2017, Cheng published the first systematic computational evaluation of the N-F bond strength in a wide series of *N*-fluoro reagents.[67]



202; 5 examples

Figure 10.

The fluorination of organic compounds has recently been realised by many electrophilic and nucleophilic methods; conversely, radical pathway is limited by the scarcity of radical fluorinating agents. DFT calculations and N-F homolytic bond dissociation energies calculations were performed on 88 electrophilic N-F compounds, in acetonitrile; *N*-fluoro-*o*-benzenedisulfonimide **203** (Figure 11) showed to be a good donor of atomic fluorine.



203

Figure 11.

Finally, in a continuation of a high number of studies dealing with crystal structure of onium salts or uncharged hydrogen-bonded complexes of OBS, previously rewieved,[3] Jones published two papers on the crystal structures of secondary amines and aniline complexes with silver *o*-benzenedisulfonimide.[68-69]

6. Conclusions

o-Benzenedisulfonimide represents a very versatile reagent in many common organic conversions. As widely documented in literature, it serves both itself as a strong Brønsted acid catalyst and its conjugated base as a counter-ion of high stability for reactive intermediates. From the mechanistic point of view, in reactions which follow a radical pathway, the imide anion has been proved to act as an electron transfer agent. Furthermore, the imide scaffold is suitable to structural modifications which lead to chiral derivatives, bearing type C2 symmetry, whose usefulness as catalysts in asymmetric conversions has already been demonstrated. Finally, in recent years, the *o*-benzenedisulfonimide scaffold has attracted attention for incorporation in bioactive molecules.

Acknowledgements

This work was financially supported by the Italian MIUR and by the Università degli Studi di Torino.

References

1. Holleman, A. F. *Recl. Trav. Chim. Pays-Bas Belg.* **1921**, *40*, 446-450.
2. Hurtley, W. R. H.; Smiles, S. *J. Chem. Soc.* **1926**, 1821-1828.
3. Barbero, M.; Bazzi, S.; Cadamuro, S.; Dughera, S. *Curr. Org. Chem.* **2011**, *15*, 576-599.
4. Hendrickson, J. B.; Okano, S.; Bloom, R. K. *J. Org. Chem.* **1969**, *34*, 3434-3438.
5. King, J. F. In *Chem. Sulphonic Acids, Esters Their Deriv.*, Patai, S., Ed., Wiley, 1991, 249-259.
6. Zerbe, E.-M.; Woelper, C.; Pinol, S. R.; Jones, P. G.; Blaschette, A. *Z. Anorg. Allg. Chem.* **2007**, *633*, 593-602.
7. Barbero, M.; Berto, S.; Cadamuro, S.; Daniele, P. G.; Dughera, S.; Ghigo, G. *Tetrahedron* **2013**, *69*, 3212-3217.
8. Barbero, M.; Crisma, M.; Degani, I.; Fochi, R.; Perracino, P. *Synthesis* **1998**, *1998*, 1171-1175.
9. Barbero, M.; Degani, I.; Fochi, R.; Regondi, V. *Gazz. Chim. Ital.* **1986**, *116*, 165-166
10. Davis, F. A.; Sundarababu, G.; Qi, H., *Org. Prep. Proced. Int.* **1998**, *30*, 107-109.
11. Barbero, M.; Cadamuro, S.; Dughera, S.; Venturello, P. *Synlett* **2007**, *2007*, 2209-2212.
12. Barbero, M.; Bazzi, S.; Cadamuro, S.; Dughera, S. *Tetrahedron Lett.* **2010**, *51*, 6356-6359.
13. Barbero, M.; Bazzi, S.; Cadamuro, S.; Dughera, S. *Tetrahedron Lett.* **2010**, *51*, 2342-2344.

14. Barbero, M.; Cadamuro, S.; Dughera, S. *Arkivoc* **2012**, *2012*, 262-279.
15. Subba Reddy, B. V.; Ghanty, S. *Synth. Commun.* **2014**, *44*, 2545-2554.
16. Maleki, B. *Org. Prep. Proced. Int.* **2016**, *48*, 303-318.
17. Maleki, B. *Org. Prep. Proced. Int.* **2016**, *48*, 81-87.
18. Maleki, B.; Rooky, R.; Rezaei-Seresht, E.; Tayebee, R. *Org. Prep. Proced. Int.* **2017**, *49*, 557-567.
19. Barbero, M.; Bazzi, S.; Cadamuro, S.; Dughera, S.; Piccinini, C. *Synthesis* **2010**, *2010*, 315-319.
20. Barbero, M.; Bazzi, S.; Cadamuro, S.; Dughera, S.; Magistris, C.; Smarra, A.; Venturello, P. *Org. Biomol. Chem.* **2011**, *9*, 2192-2197.
21. Garcia-Garcia, P.; Lay, F.; Garcia-Garcia, P.; Rabalakos, C.; List, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 4363-4366.
22. Cheon, C. H.; Yamamoto, H. *Tetrahedron* **2010**, *66*, 4257-4264.
23. Cheon, C. H.; Yamamoto, H. *Tetrahedron Lett.* **2009**, *50*, 3555-3558.
24. Barbero, M.; Cadamuro, S.; Dughera, S. *Synth. Commun.* **2013**, *43*, 758-767.
25. Barbero, M.; Cadamuro, S.; Dughera, S.; Magistris, C.; Venturello, P. *Org. Biomol. Chem.* **2011**, *9*, 8393-8399.
26. Chierotti, M. R.; Gaglioti, K.; Gobetto, R.; Barbero, M.; Nervi, C. *CrystEngComm* **2012**, *14*, 6732-6737.
27. Barbero, M.; Cadamuro, S.; Dughera, S.; Rucci, M.; Spano, G.; Venturello, P. *Tetrahedron* **2014**, *70*, 1818-1826.
28. Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500-9512.
29. Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66-77.
30. Mayr, H.; Lakhdar, S.; Maji, B.; Ofial, A. R. *Beilstein J. Org. Chem.* **2012**, *8*, 1458-1478.
31. Mayer, R. J.; Hampel, N.; Mayer, P.; Ofial, A. R.; Mayr, H. *Eur. J. Org. Chem.* **2019**, *2019*, 412-421; and references therein.
32. Jin, Y.; Ji, Y.; He, X.; Kan, S.; Xia, H.; Liang, B.; Chen, J.; Wu, H.; Guo, K.; Li, Z. *Polym. Chem.* **2014**, *5*, 3098-3106.
33. Wu, H.; Ji, Y.; Li, Z.; Wang, X.; Zhang, Q.; Cui, S.; Wu, W.; Liu, J.; Guo, K. *J. Polym. Sci., Part A: Polym. Chem.* **2015**, *53*, 729-736.
34. Farahani, N.; Akbari, J. *Lett. Org. Chem.* **2017**, *14*, 483-487.
35. Barbero, M.; Bazzi, S.; Cadamuro, S.; Di Bari, L.; Dughera, S.; Ghigo, G.; Padula, D.; Tabasso, S. *Tetrahedron* **2011**, *67*, 5789-5797.
36. Barbero, M.; Cadamuro, S.; Dughera, S.; Ghigo, G. *Org. Biomol. Chem.* **2012**, *10*, 4058-4068.
37. Barbero, M.; Cadamuro, S.; Dughera, S.; Torregrossa, R. *Org. Biomol. Chem.* **2014**, *12*, 3902-3911.
38. Barbero, M.; Cadamuro, S.; Dughera, S. *Tetrahedron: Asymmetry* **2015**, *26*, 1180-1188.
39. Barbero, M.; Cadamuro, S.; Dughera, S. *Green Chem.* **2017**, *19*, 1529-1535.
40. Ratjen, L.; van Gemmeren, M.; Pesciaioli, F.; List, B. *Angew. Chem. Int. Ed.* **2014**, *53*, 8765-8769.
41. Barbero, M.; Cerrato, G.; Laurenti, E.; Zanol, S.; Dughera, S. *ChemistrySelect* **2017**, *2*, 3178-3183.
42. Barbero, M.; Bazzi, S.; Cadamuro, S.; Dughera, S.; Magistris, C.; Venturello, P. *Synlett* **2010**, *2010*, 1803-1806.
43. James, T.; van Gemmeren, M.; List, B. *Chem. Rev.* **2015**, *115*, 9388-9409.
44. Bekdemir, Y.; Eren, B.; Kutuk, H. *Phosphorus, Sulfur Silicon Relat. Elem.* **2012**, *187*, 689-696.
45. Gutierrez, D. A.; Dean, D. R.; Laxamana, C. M.; Migliozzi-Smith, M.; O'Brien, C. J.; O'Neill, C. L.; Li, J. J. *Arkivoc* **2016**, *2016*, 261-276.
46. Sakakibara, Y.; Ito, E.; Fukushima, T.; Murakami, K.; Itami, K. *Chem. Eur. J.* **2018**, *24*, 9254-9258.
47. Patel, B.; Carlisle, J.; Bottle, S. E.; Hanson, G. R.; Kariuki, B. M.; Male, L.; McMurtrie, J. C.; Spencer, N.; Grainger, R. S. *Org. Biomol. Chem.* **2011**, *9*, 2336-2344.
48. Barbero, M.; Cadamuro, S.; Dughera, S. *Org. Biomol. Chem.* **2016**, *14*, 1437-1441.
49. Barbero, M.; Cadamuro, S.; Dughera, S. *Tetrahedron* **2014**, *70*, 8010-8016.
50. Barbero, M.; Cadamuro, S.; Dughera, S. *Eur. J. Org. Chem.* **2014**, *2014*, 598-605.
51. Barbero, M.; Dughera, S. *Org. Biomol. Chem.* **2018**, *16*, 295-301.
52. Barbero, M.; Dughera, S. *Tetrahedron* **2018**, *74*, 5758-5769.

53. Boga, C.; Forlani, L.; Tozzi, S.; Del Vecchio, E.; Mazzanti, A.; Monari, M.; Zanna, N. *Curr. Org. Chem.* **2014**, *18*, 512-523.
54. Del Vecchio, E.; Boga, C.; Forlani, L.; Tozzi, S.; Micheletti, G.; Cino, S. *J. Org. Chem.* **2015**, *80*, 2216-2222.
55. Boga, C.; Cino, S.; Micheletti, G.; Padovan, D.; Prati, L.; Mazzanti, A.; Zanna, N. *Org. Biomol. Chem.* **2016**, *14*, 7061-7068.
56. Barbero, M.; Cadamuro, S.; Cauda, F.; Dughera, S.; Gervasio, G.; Venturello, P. *J. Org. Chem.* **2012**, *77*, 4278-4287.
57. Armenise, N.; Dughera, S.; Gualandi, A.; Mengozzi, L.; Barbero, M.; Cozzi, P. G. *Asian J. Org. Chem.* **2015**, *4*, 337-345.
58. Barbero, M.; Buscaino, R.; Cadamuro, S.; Dughera, S.; Gualandi, A.; Marabello, D.; Cozzi, P. G. *J. Org. Chem.* **2015**, *80*, 4791-4796.
59. Barbero, M.; Cadamuro, S.; Dughera, S.; Ghigo, G.; Marabello, D.; Morgante, P. *Tetrahedron Lett.* **2016**, *57*, 4758-4762.
60. Shkrob, I. A.; Marin, T. W.; Chemerisov, S. D.; Hatcher, J.; Wishart, J. F. *J. Phys. Chem. B* **2012**, *116*, 9043-9055.
61. Ilawe, N. V.; Fu, J.; Ramanathan, S.; Wong, B. M.; Wu, J. *J. Phys. Chem. C* **2016**, *120*, 27757-27767.
62. Lian, C.; Liu, H.; Li, C.; Wu, J. *AIChE J.* **2019**, *65*, 804-810.
63. Benchea, A.; Siu, B.; Soltani, M.; McCants, J. H.; Salter, E. A.; Wierzbicki, A.; West, K. N.; Davis, J. H., Jr. *New J. Chem.* **2017**, *41*, 7844-7848.
64. Jones, C. K.; Engers, D. W.; Thompson, A. D.; Field, J. R.; Blobaum, A. L.; Lindsley, S. R.; Zhou, Y.; Gogliotti, R. D.; Jadhav, S.; Zamorano, R.; Bogenpohl, J.; Smith, Y.; Morrison, R.; Daniels, J. S.; Weaver, C. D.; Conn, P. J.; Lindsley, C. W.; Niswender, C. M.; Hopkins, C. R.. *J. Med. Chem.* **2011**, *54*, 7639-7647.
65. Luo, W.; Yu, Q.-s.; Salcedo, I.; Holloway, H. W.; Lahiri, D. K.; Brossi, A.; Tweedie, D.; Greig, N. H. *Bioorg. Med. Chem.* **2011,** *19*, 3965-3972.
66. Guzel-Akdemir, O.; Akdemir, A.; Isik, S.; Vullo, D.; Supuran, C. T. *Bioorg. Med. Chem.* **2013**, *21*, 1386-1391.
67. Yang, J.-D.; Wang, Y.; Xue, X.-S.; Cheng, J.-P. *J. Org. Chem.* **2017**, *82*, 4129-4135.
68. Zerbe, E. M.; Wolper, C.; Jones, P. G. *Z. Naturforsch., B: J. Chem. Sci.* **2011**, *66*, 449-458.
69. Zerbe, E.-M.; Woelper, C.; Jones, P. G. *Z. Naturforsch., B: J. Chem. Sci.* **2012**, *67*, 1263-1272.