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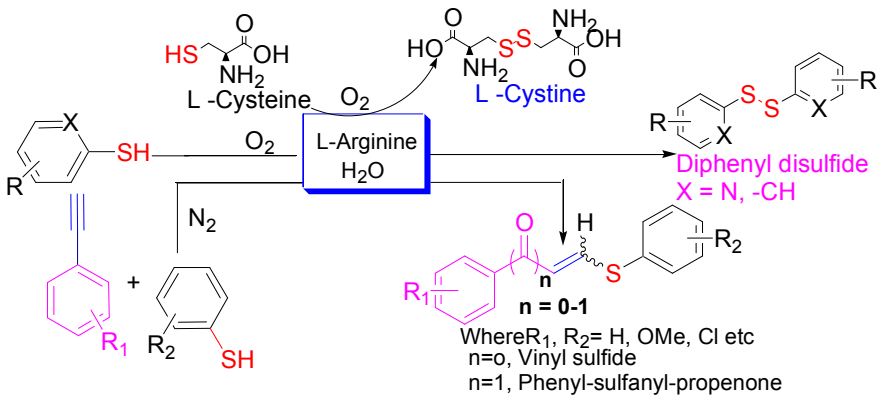
Graphical Abstract



Arginine in conjunction with water has been employed as an effective and recyclable organocatalyst for oxidative coupling of thiophenols and hydrothiolation of alkynes.

Amino Acid and Water-Driven Tunable Green Protocol to Access S-S/C-S Bonds via Aerobic Oxidative Coupling and Hydrothiolation

Amit Shard,[a,b] Rajesh Kumar,[a] Saima,[a,c] Nidhi Sharma[a] and Arun K. Sinha*[a, b, c]

Abstract

A green methodology utilizing natural auxiliary like L-Arginine in conjunction with water and oxygen led to oxidative coupling of thiols into disulfides (S-S bond) whereas thiol-yne coupling (TYC) to access vinyl sulfides (C-S bond) was facilitated in nitrogen atmosphere. The tunable protocol offers several advantages like low catalyst loading, high yields, clean reaction, no over-oxidation of S-S bond besides being metal/base/waste-free. The synthesis of ubiquitous cystine and GSSG in the same catalytic system is an added advantage and the catalytic system has been recycled up to seven times.

Keywords: Amino acids / Oxidative coupling / Vinyl sulfides / Waste-free

Introduction

Nature[1] has nurtured the mankind with an infinite repository of diverse[1a] type of biochemicals and carries out innumerable biochemical processes utilizing the native solvent of cell i.e. water.[1b] Additionally water in conjunction with air leads to the complexity of the biochemical world. The use of water as a new paradigm to innovate eco-sustainable chemical reactions are also gaining momentum because either its release[1c] as a by-product or its use as a solvent,[1d-e] will clearly have the least impact on the environment. Nevertheless, conducting reactions in water is still challenging because

most of the organic reactants are insoluble in water. Further, water may deteriorate the catalytic activity besides disruption of polar interaction among catalyst and substrate molecules. Therefore, the development of water-compatible organocatalyst and their application to chemical reactions using water as the reaction medium is of considerable interest. Furthermore, it is also highly desirable to develop environmentally benign chemical[1f] processes that use oxygen from air in aqueous medium without requirement of any metal oxidant.

Besides water, L-amino acids also dominate the natural world[2] and display a central theme in biological systems.[3] Recently, they are efficiently employed as organocatalysts in triggering a variety of chemical reactions[4] like synthesis[5] of Pfizer's anti-glaucoma drug latanoprost[5a] and anticancer drug carboplatin.[5b] Interestingly, under physiological conditions, sulphur containing amino acids like cysteine and glutathione, undergo oxidative coupling to form ubiquitous cystine and GSSG having disulphide (S-S) bond of high practical value.[6] Likewise, an alicyclic disulfide known as lipoic acid[6a] also acts as an essential cofactor of mitochondrial enzymatic complexes which highlights the importance of S-S bond. Some of the medicinally significant examples of disulphide bond[6b-c] are shown below (Fig. 1).

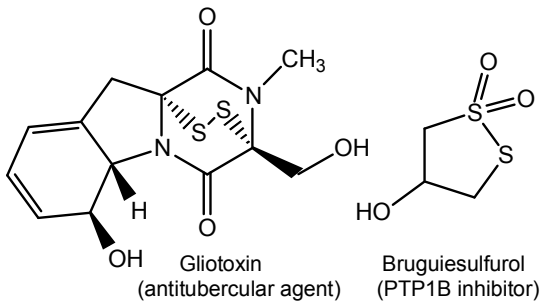


Fig. 1 Medicinally significant disulphides.

The disulfide bond has widespread occurrence in flora and fauna.[7] It also plays substantial roles in design of rechargeable lithium batteries, in a number of chemical reactions[8] and catalysis.[9] Further, many of the next generation[10] pharmaceuticals incorporating disulfide bonds have already hit the market. In this context, a large number of oxidative coupling protocols[11-13] mediated by gold nanoparticles[11a] or rhenium[13b] metal as an effective catalyst have emerged for the synthesis of disulphides. However, most of the approaches suffer from inadequacies such as low selectivity due to over oxidation[13a] of final product into sulphoxides/sulphones, expensive nature of catalyst with poor recovery and finally laborious work up procedures. Recently, environmentally benign approaches to synthesize heterocyclic disulfides[13g] have also been surfaced using a cocktail of enzymes, buffer and methanol. Besides this supported iron oxide nanoparticles[13h] are also used to synthesize disulfides but these methods not truly fall under the periphery of green reactions due to use of organic solvent and expensive nature of reagents. So there is a strong need to develop such a catalytic system for the chemoselective oxidation of thiols to disulfides which comprises all, that is, green catalyst, solvent, and reagent besides recyclability of catalytic system and waste-free green-approach in comparison to relentless conventional protocols[13b-f] (which utilize metal oxidant/base/organic solvent).

Apart from making disulfide (S-S) bond, thiols are also known to participate in hydrothiolation,[14] with alkynes *via* thiol-yne click[14a] (TYC) reactions to generate vinyl sulphide (C-S bond) having miscellaneous medicinal and physicochemical applications.[14b] Some of the medicinally significant examples of vinyl sulfides[14c] are shown below (Fig. 2).

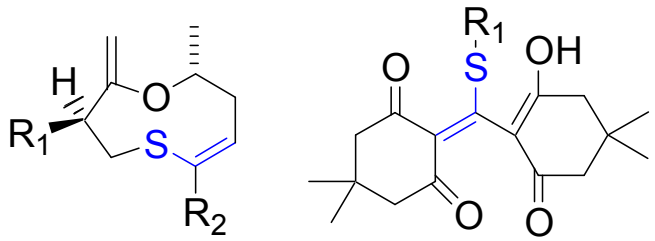


Fig. 2 Important drug intermediates with C-S bond.

In this article, we disclose for the first time, a waste free and atom economical protocol for direct oxidative coupling of thiols to disulfides utilizing quasi natural rudiments[14d] (amino acid/water/air) precluding any oxidant, base or metal. Among the various tested amino acids, arginine (Arg) provided chemoselective access to disulfides including ubiquitous cystine and GSSG in ample yield with recyclability of catalytic system up to seven cycles. Additionally, the zwitterionic character of Arg also worked as a driving force towards rapid hydrothiolation of alkynes i.e. thiol-yne coupling (TYC) thus leading to an environmentally benign synthesis of vinyl sulfides (C-S bond). Interestingly, our tunable catalytic system also clearly demonstrated that C-S bond formation is faster than S-S bond in nitrogen atmosphere (Fig. 3).

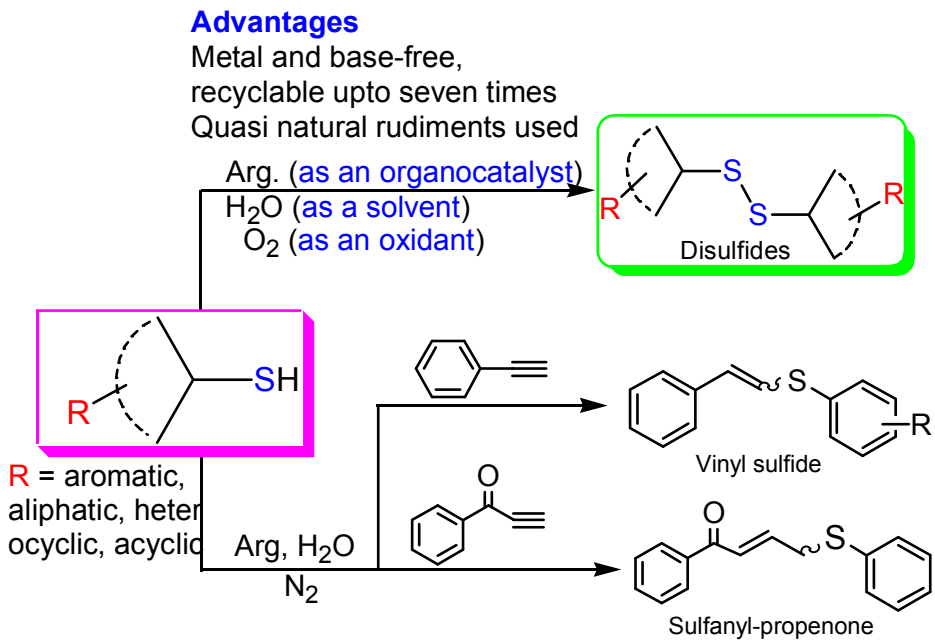


Fig. 3 Arginine/H_2O catalysed oxidation of thiols and hydrothiolation of alkynes.

Results and Discussion

In continuation of our interest in the development[15] of greener approaches,[15a-c] our group has recently reported ambiphillicity (cationic and anionic character) of [hmim]Br (1-hexyl 3-methyl imidazolium bromide), a neutral ionic liquid (I.L.),[15d] was found imperative for oxidative coupling of thiophenol into disulfides (S-S bond). Enthused by this, we now attempted to perform oxidative coupling of thiols to disulfides in histidine, a versatile amino acid[16] with imidazolium ring analogous to the heterocyclic core of [hmim]Br, having zwitterionic character[16a] in water (Fig. 4) and is more environmentally benign, safe and abundant in comparison to I.L.

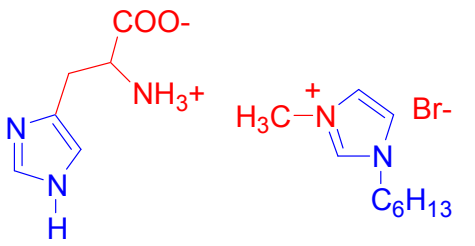
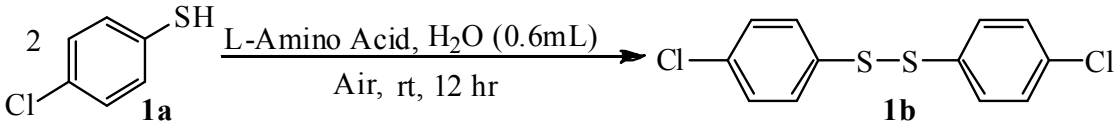


Fig. 4 Diagram showing analogy between zwitterionic histidine and ambiphillic [hmim]Br.

Initially, 4-chloro thiophenol (0.25 mmol), water (0.6 mL) and L-histidine (50 mol%) were taken in a round bottom flask and stirred at room temperature for 12 h. To our delight the desired 4,4'-dichloro diphenyl disulfide (**1b**) was formed in 64% yield (on GC-MS basis). It is worth mentioning that our green oxidative coupling process comprised of histidine-water-air might be corroborating with biochemical process where intracellular[16b] disulfide bond forms in presence of amino acids like cysteine. However, well known amino acid L-proline (Table 1, entry 2) provided **1b** in poor yield (37%). Thereafter, a series of neutral, acidic and basic amino acids were screened (Table 1), out of which Arg, a basic amino acid with pka = 2.488 provided **1b** in good yield (70%, 12 h) in air (Table 1, entry 10) whereas reaction using O_2 balloon provided **1b** in same yield in shorter reaction time of 5 h (Table 1, entry 15).

Table 1 Screening of different amino acids for the formation of disulphide.[a]

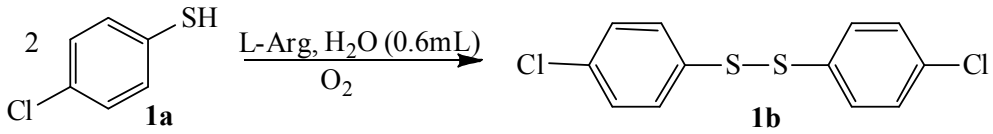


Entry	Amino acid	Yield[b](%)	Entry	Amino acid	Yield[b](%)
1	Histidine	64	11	Glycine	42
2	Proline	37	12	Aspartic acid	15
3	Serine	33	13	Glutamic Acid	14
4	Phenylalanine	23	14	Cysteine	traces
5	Glutamine	33	**15**	**Arginine[c]**	**70**
6	Valine	61	16	Arginine[d]	traces
7	Leucine	60	17	Arginine[e]	nd
8	Alanine	25	18	Arginine[f]	nd
9	Isoleucine	42	19[g]	-	nd
10	Arginine	70			

[a] The reaction conditions involved usage of 0.25 mmol of 1a, atmospheric O_2, 50 mol% of L-Amino acid, 0.6 mL of HPLC grade water. [b] Yields on the basis of GC-MS. [c] In O_2 atmosphere the reaction got completed in 5 hr . [d] N_2 atmosphere. [e] Ethanol was used as solvent. [f] Chloroform was used as solvent. [g] No Arg used.

As expected, **1b** was obtained in traces in nitrogen atmosphere (Table 1, entry 16) whereas replacement of water with ethanol or chloroform did not form **1b** (entry 17-18). This is possibly because of lack of formation of hydrogen bonding and inefficient generation of zwitterion in organic solvents. Following the above lead, amount of Arginine and effect of temperature for the synthesis of **1b** was optimized (Table 2).

Table 2 Optimization of the reaction conditions for formation of **1b** under O_2 atmosphere.



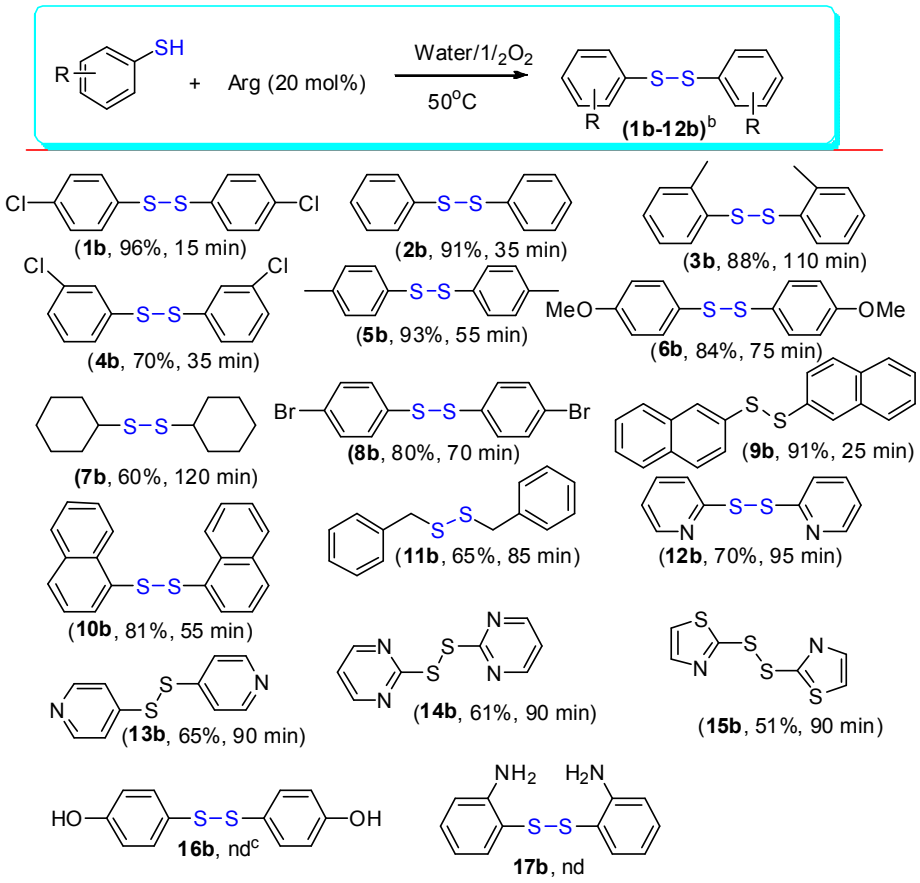
S.No	Amount of Organocatalyst (L-Arginine)	Temp in ^oC	Time	% Yield (on GC basis)
1.	50 mol%	R.T.	5 hr	92
2.	100 mol%	R.T.	5 hr	91
3.	30 mol%	R.T.	5 hr	92
4.	20 mol%	R.T.	5 hr	93
5.	10 mol%	R.T.	8 hr	70
6.	**20 mol%**	**50**	**15 min**	**98**
7.	20 mol%	40	90 min	90
8.	20 mol%	70	20 min	92
9.	20 mol%	80	15 min	80

Hence a decreased catalyst load of 20 mol% in presence of O_2 was found to be efficient for promoting the synthesis of **1b** in 15 min at 50^{o}C (Table 2, entry 6). Further impact of the contemporary tools viz. microwave and ultrasonicator were evaluated (See S.I). Unfortunately, reaction conducted in microwave[12g] (50°C, 80W) had no profound effect in efficient construction of **1b** in shorter reaction time (up to 45 min) as it led to several side products. Interestingly, reaction conducted in ultrasonicator[12f] provided the desired **1b** in 98% yield in 10 min (See S.I). However, owing to the malodorous smell[17] of thiols, the oxidative coupling was conducted under conventional conditions in well ventilated hood.

Finally, optimized conditions using 20 mol% of Arg in 0.6 ml of water, 0.25 mmol of **1a** and $1/_2O_2$ resulted **1b** in 96% yield (isolated) at 50^{o}C in 15 min (Table 3, 1b). The

substrate scope was explored using electronically versatile thiols which provided diverse types of disulfides (Table 3, 1b-11b) in moderate to excellent yields (up to 96%)

Table 3 Substrate scope of oxidative coupling of thiols in water-Arg-Oxygen [a]



[a] Reaction conditions involved usage of 0.25 mmol of thiol, 20 mol % of L-Arg, 0.6 mL of HPLC grade water, O_2. [b] Isolated Yields. [c] nd = not detected.

and their NMR well matched with those of the reported values.[11,15d] After the synthesis of aromatic and alicyclic disulfides (Table 3, 1b-11b) the synthesis of heterocyclic disulfide (12b-15b) was inspired by previous report by Abdel-Mohsen[13g] *et al*. which utilizes laccases/buffer/methanol for oxidative coupling of thiophenols into a series of heterocyclic disulfides. The heterocyclic compounds have numerous added benefits over carbocyclic ones. To our delight our catalytic system provided heterocyclic disulfides in up to 70% yield. Unfortunately, **16b** or **17b** (Table 3) could not be obtained possibly due

to feeble zwitterionic interaction of Arg with thiol as well as electron rich hydroxy or amine groups. Thereafter, we looked forward towards establishing the mechanism for the synthesis of disulfides using Arg-O_2-H_2O catalytic system.

Mechanism

It is known that in aqueous medium Arg interacts with water through cation-π interactions[18] which in turn interact with aromatic charged residues of thiophenol. The guanidinium group of Arg is the most polar of all the common amino acid side chains and plays a vital role in the binding of negatively charged substrates.[18b] The water provides an enhanced π-stacking as a result of the hydrophobic effect.[18c] The amino acid side chain of zwitterionic[19] Arg consists of a 3-carbon aliphatic straight chain in which the distal end is capped by a +vely charged complex guanidinium[19a] group. The delocalized positive charge on guanidinium group enables the formation of multiple hydrogen bonds with water (Fig. 5).

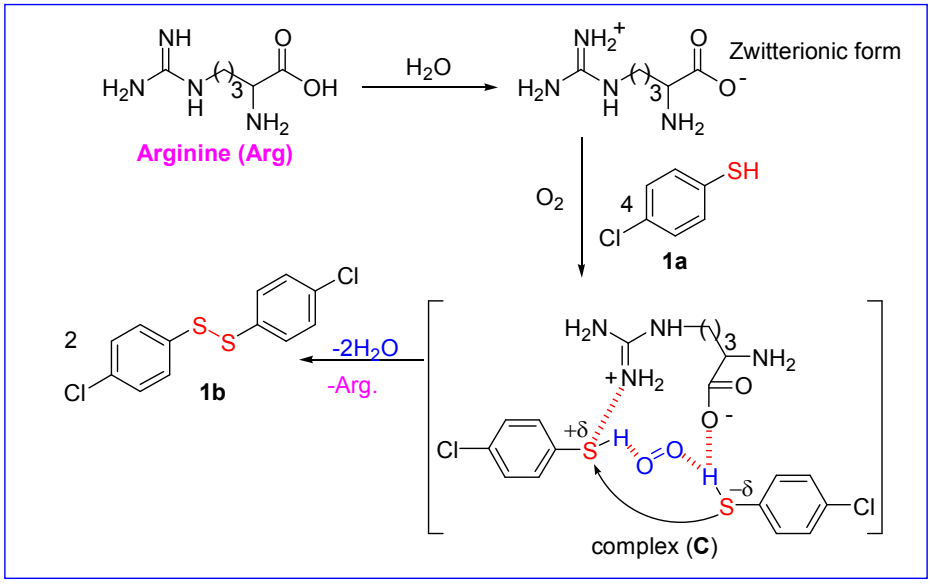


Fig. 5 The plausible mechanism of the formation of diphenyl disulfide via oxidative coupling of thiophenol.

Thereafter, in the aqueous charged[19b] pool, hydrogen atom of one molecule of thiophenol starts interacting with the –vely charged carboxyl terminal of the arginine whereas sulphur atom of another molecule of thiophenol interacts with the +vely charged guanidinium group. This complex interplay of subtle non-covalent interactions led to efficient union of two molecules of 4-chlorothiophenol and was studied using UV spectrophotometer (Fig. 6). The study revealed that λ_{max} of 4-chlorothiophenol (**1a**) and Arg appeared at 246.5 nm and 207.5 nm respectively. However, when the substrates were stirred, the spectral analysis clearly indicated that **1a** and an aqueous solution of zwitterionic Arg led to immediate initiation of complexation evident by bathochromic shift from λ_{max} 246.5 nm to 274.6 nm. It was observed that complexation between iminium-ion of arginine and the heteroatom (S) of thiophenol exponentially increased up to 9 min leading to a hyperchromic shift which probably is an indicative of increase in concentration of complex "C" (Fig. 5). Diminution in the absorbance (hypochromic shift) of C appeared after 12 min with initiation of formation of **1b** which finally completed in 110 min at room temperature (see S.I. for details).

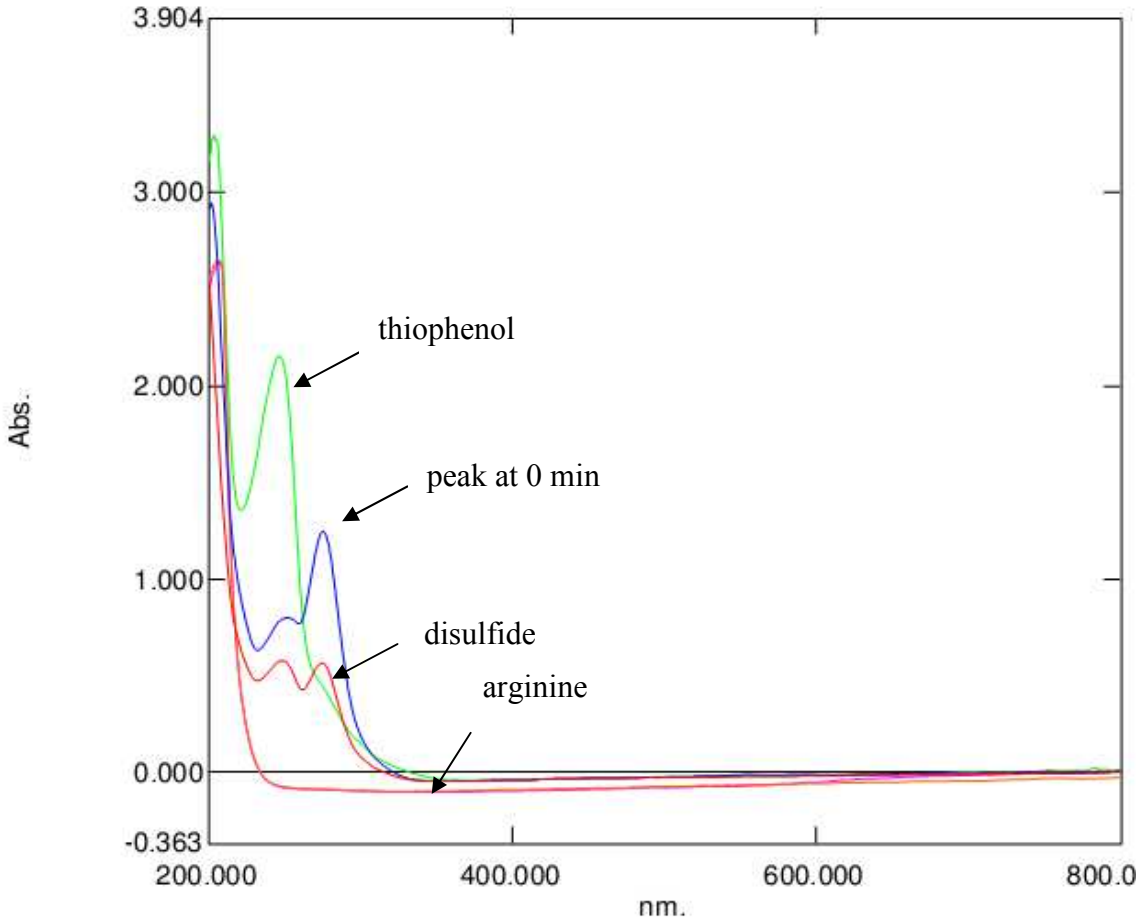


Fig. 6 Absorption profiles of thiophenol, arginine, complexation and 4, 4' diphenyl disulfide at 0 min and at the completion of reaction (after 110 min).

Recyclability of the catalytic system is an important factor in context of green chemistry as it has both economical as well as ecological benefits. In this experiment, 0.25 mmol of **1a**, 20 mol % of Arg, O_2 and 0.6 mL of water were heated at 50^{o}C, the resulting product **1b** was formed in 20 min. The aqueous solution containing Arg and **1b** was extracted using ethyl acetate. The ethyl acetate layer was vacuum evaporated to obtain **1b**, whereas the same aqueous solution containing Arg was used repeatedly for carrying out the oxidative coupling for a number of times. Profitably, the product could be easily recovered from the aqueous medium merely by extracting with ethyl acetate. The remaining aqueous solution of Arg was reused up to seven consecutive cycles (98-91%)

(Fig. 7). Thereafter, there was considerable fall in the yield of disulfide. Interestingly, addition of 5 mol% of Arg in the above catalytic cycle further increased the yield of **1b** up to 96% (up to ten cycles) due to rejuvenation of the organocatalytic system

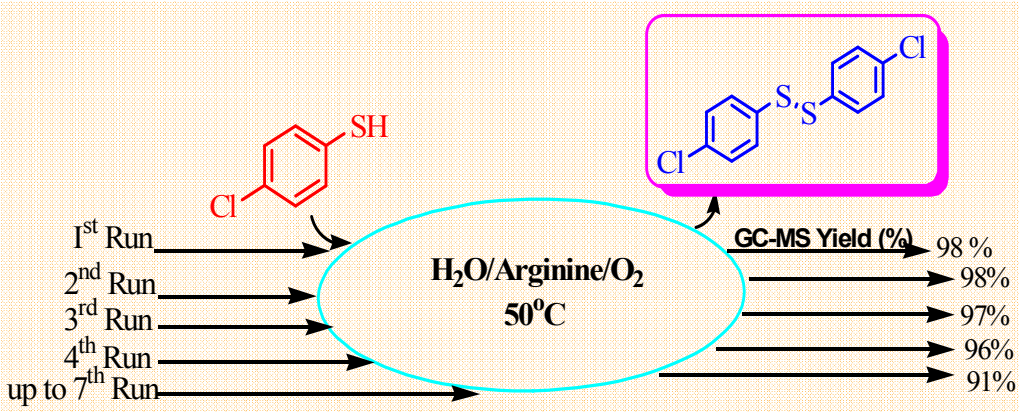


Fig. 7 Recyclability studies using the same catalytic water/Arg/Oxygen system up to seven cycles.

It is well known that oxidized glutathione (GSSG) with cisplatin is a well-tolerated therapeutic adjuvant called NOV-002 in standard anticancer therapy.[20a] Likewise cystine is also a physiological disulfide of clinical importance. Recent biocatalytic protocol highlights laccases[13g] catalyzed disulfides but does not disclose the generality towards synthesis of physiological disulfides i.e. cystine and GSSG. Thus in parlance of their medicinal significance and to test the generosity of our protocol, we attempted to synthesize physiological disulfides i.e. cystine and GSSG under similar conditions documented in Table 3. It is prudent to state that oxidations of cysteine and related compounds have been extensively studied, utilizing metal pthalocyanines[20b] and expensive noble metals,[13a] however, their synthesis utilizing perfectly benign conditions sill remains a significant challenge.[21] Interestingly, the developed organocatalytic system of "Arg-Water-Oxygen" successfully led to the formation of dimmers (18b and 19b) of

aminothiols viz. L-cysteine and L-glutathione in appreciable yields of 71% and 76% respectively at 50°C in longer reaction times of 4 h (Fig. 8).

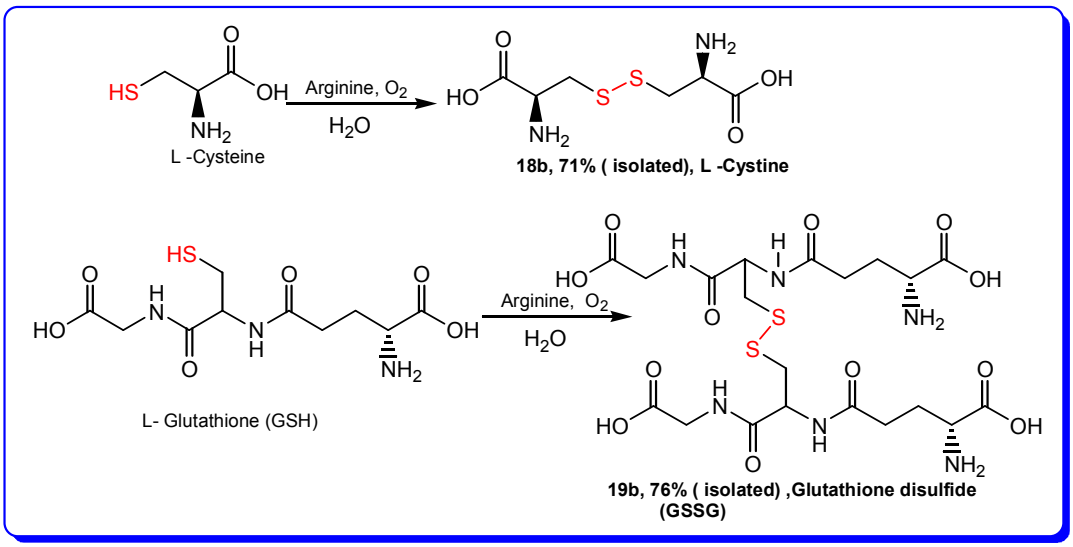


Fig. 8 Synthesis of Cystine (18b) and GSSG (19b) using natural rudiments like arginine-water-oxygen.

Like S-S bonds, C-S[22] bonds are another critical[22a-f] and ubiquitous[22g] constituents of many pharmaceuticals[22h-i] and natural products[22j] e.g allicin, anthelmintic drug levamisole, and antibiotics like penicillins etc. To construct the C-S bonds, popular 'click'-procedures like thiol-yne coupling (TYC) or hydrothiolation has become an outstanding tool for the functionalization[23] of molecules. The TYC unarguably yields useful synthetic intermediates having applications in organic[24a] transformations ranging from Diels−Alder, thio−Claisen, acting as Michael acceptors and as versatile synthons in olefin metathesis. Certain reports reveal the synthesis of vinyl sulfides using strong base[24b] and ammonia.[24c]

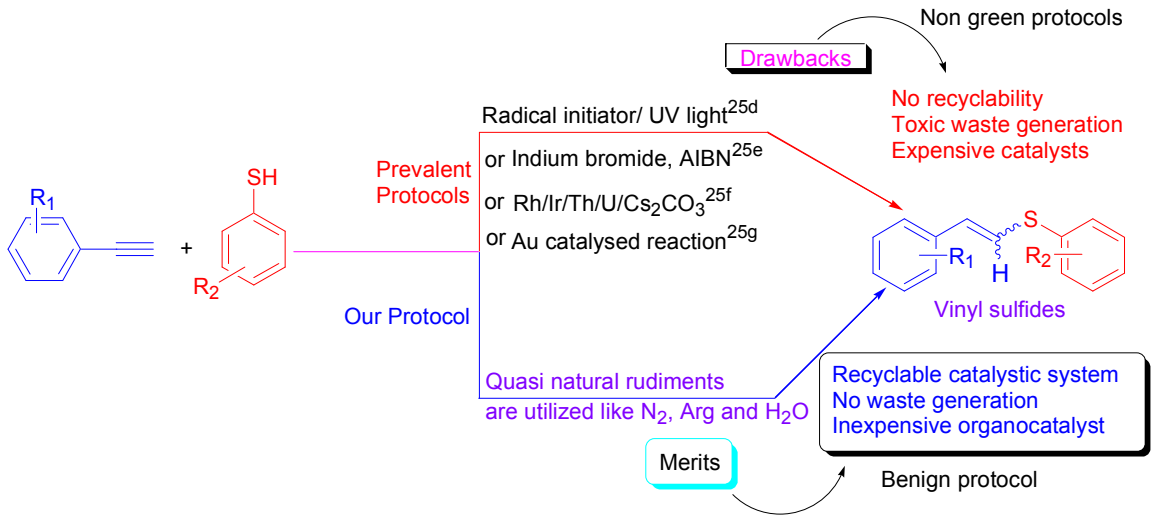
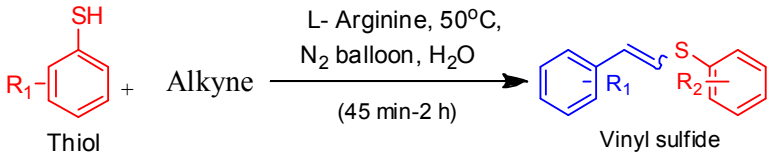
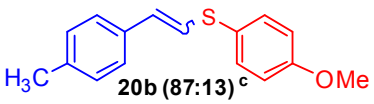
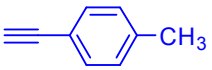
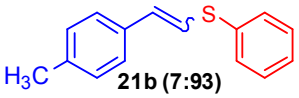
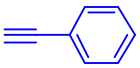
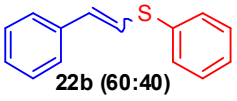
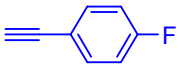
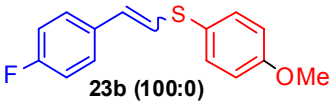
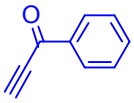
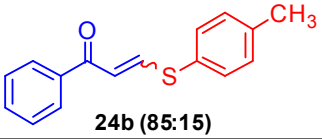


Fig. 9 Comparison of prevalent protocols with our method for TYC.

There are also numerous reported methods[25] for hydrothiolation of terminal alkynes to form vinyl sulfides using various transition metals like Wilkinson's catalyst, lanthanides, late transition metal catalysts and various free radical initiators (Fig. 9). However, a method employing mild, environmentally compatible, efficient[25c] and in particular selective route towards synthesis of C- S bond is yet awaited. Therefore, in light of their expected utility,[26] hydrothiolation between alkyne and thiophenol in Arg/water to generate vinyl sulfides was carried out in nitrogenous atmosphere (replacing the oxygen atmosphere to ward off the formation of S-S bond). However, GC analysis of the crude product confirms the formation of vinyl sulphide (**20b**) in 20% yield only along with unwanted S-S bond (30-35%) and unreacted thiol. Interestingly, the sequence of addition of reactants was found very crucial, hence addition of thiophenol to a well stirred

Table 4 Substrate scope of alkenylative cross-coupling of alkynes and thiophenols to form vinyl sulfides.[a]



S.No	Thiol	Alkyne	Alkenyl sulfide (Z/E)	Yield[b]
1.	R_1= 4 -OCH_3		 **20b (87:13)** [c]	81
2.	R_1= H		 **21b (7:93)**	71
3	R_1= H		 **22b (60:40)**	75
4	R_1= OCH_3		 **23b (100:0)**	85
5	R_1= 4 -CH_3		 **24b (85:15)**	80

[a] Reaction conditions involved usage of 50 mg of thiol, alkyne (1.1 equiv), N_2, 20 mol % of L-Arg, 0.6 mL of HPLC grade water. [b] Yields of isolated product. [c] *E:Z* ratio on NMR basis. (See S.I for details)

mixture of phenylacetylene and water/Arg in N_2 atmosphere efficiently provided vinyl sulphide (C-S bond) **20b** (Table 4) in 45 min in 81% yield as *E:Z* isomeric mixture.[23e] The catalytic system has been successfully extended for anti-Markovnikov products (21b-24b)[23e] with variable appendages attached to the aromatic ring of thiophenol and alkyne in varying yields up to 85%. The catalytic system also led to the synthesis of 1-Phenyl-3-*p*-tolylsulfanyl-propenone (24b) a unique and significant[26c] scaffold with *α,β*-unsaturated carbonyl moiety (O=C-C=C-S) [26e-f] which might find applications in biomedical,

materials chemistry and bioconjugation realms.[26g] The plausible mechanism for the formation of *E/Z* vinyl sulfides is presented in Fig 10. Here it is presumed that zwitterionic Arg in water interacts with the thiophenol by carboxylate terminal and the negatively charged sulfur atom interacts with the terminal alkyne resulting in formation of vinyl sulfide. The exact mechanism of the formation of *E/Z* vinyl sulfides is currently under investigation.

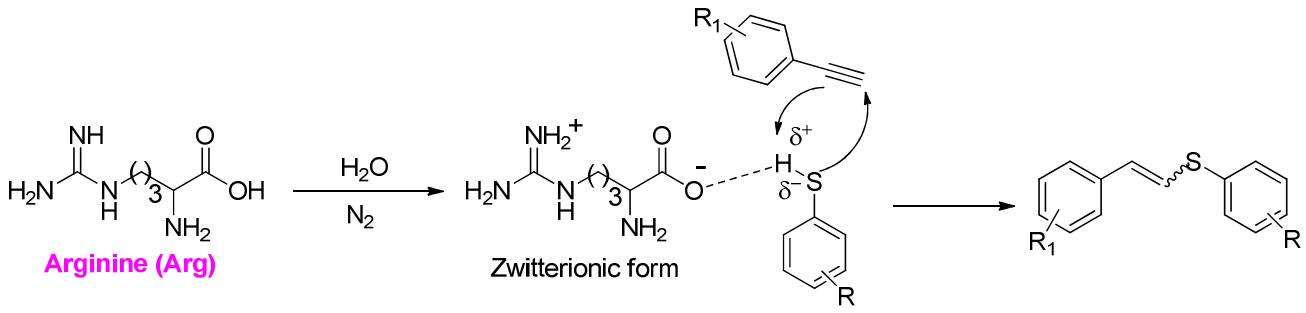


Fig 10. Plausible mechanism for the formation of Vinyl sulfides.

Conclusions

In conclusion, we have developed an ecologically compatible tunable catalytic system comprised of water and sub-stoichiometric amounts of organocatalyst arginine which is competent enough in promoting the chemoselective disulfide (S-S bond) synthesis via oxidative coupling of thiol in the presence of oxygen as well as carrying out hydrothiolation of alkynes/thiol to their alkenyl sulfides (C-S bond) under nitrogen atmosphere without requirements of any metallic salts and basic medium. Moreover, aerobic oxidative coupling of L-cysteine and L-glutathione into dimeric cystine and GSSG render our green oxidative process highly practical and appealing for its application in industrial process. Further, synthesis of vinyl sulfides (*E:Z* isomeric

mixture) having α, β-unsaturated carbonyl moiety (O=C-C=C-S) emphatically demonstrates the synthetic viability of the above catalytic system. Since the quest for such type of novel tunable catalytic systems is high, therefore, the method would find applications for the construction of aromatic (hetero)/alicyclic/aliphatic disulfides as well as vinyl sulfides by concurrently maintaining the criteria of catalysis, greenness, recyclability and selectivity.

Experimental Section

General procedure for the synthesis of disulfide: Initially 0.25 mmol of thiophenol (1a) was added to HPLC grade water (0.6 mL) containing arginine (20 mol%), and heated for 15 min at 50^{o}C in presence of O_2. After complete consumption of starting material (analysed by TLC), the reaction mixture was extracted with ethyl acetate (2x10 mL). The combined organic layers were dried over Na_2SO_4, filtered and vacuum evaporated. The GC-MS analysis confirmed the formation of disulfide (1b) in 98% yield (isolated 96%). The residue was purified using column chromatography (silica gel 60-120) with ethylacetate/hexane (0.5:9.5) as eluents to give the corresponding disulphide. The ^{1}H and ^{13}CNMR of disulfide (1b) well matched with the reported values.

General procedure for the synthesis of vinyl sulfides: 20 mol% of Arg was stirred for 5 minutes under nitrogen in HPLC grade water (0.6 mL) followed by addition of phenyl acetylene (1.1 equiv). Next, substituted thiophenol (0.25 mmol) was added to the above reaction mixture and stirred at 50^{o}C under N_2 atmosphere for 2 h till complete consumption of starting material (analysed by TLC). The crude reaction mixture was extracted with ethylacetate (2x10 mL) and the combined organic layers were dried over

Na_2SO_4, filtered and vacuum evaporated. The residue was purified using column chromatography (silica gel 60-120) with ethylacetate/hexane (1:9) as eluents to give the corresponding vinyl sulfide (*E:Z* isomeric mixture).

Supplementary Information (Detailed UV based mechanistic studies and NMR spectral values of compounds are provided.)

Notes and references

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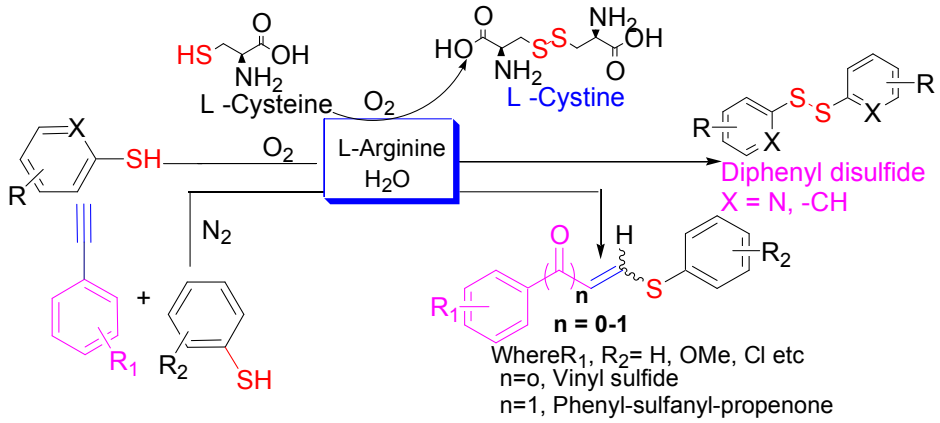
Graphical Abstract



Arginine in conjunction with water has been employed as an effective and recyclable organocatalyst for oxidative coupling of thiophenols and hydrothiolation of alkynes.