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## HFIP-mediated, regio- and stereoselective hydrosulfenylation of ynamides: a versatile strategy for accessing ketene *N,S*-acetals†

Appanapalli N. V. Satyanarayana, Paramita Pattanayak and Tanmay Chatterjee \*

Herein, we report an HFIP-mediated, versatile, sustainable, atom-economical, and regio- and stereoselective hydro-functionalization of ynamides with various *S*-nucleophiles (1 equiv.) such as thiols, thio-carboxylic acids, carbamates, xanthates, and *O,O*-diethyl *S*-hydrogen phosphorothioate to access a wide variety of stereodefined trisubstituted ketene *N,S*-acetals under mild conditions. This protocol requires only HFIP, which plays multiple roles, such as acting as a Brønsted acid to protonate the ynamide regioselectively at the *beta* carbon to generate the reactive keteniminium intermediate, stabilizing the intermediate as solvent through H-bonding. After the nucleophilic attack of the *S*-nucleophile on the keteniminium intermediate and deprotonation, HFIP is regenerated in most of the cases and can be easily recovered and recycled, revealing the high sustainability of the protocol. Remarkably, all the reactions are highly efficient and furnish ketene *N,S*-acetals in excellent yields and in many cases pure products were obtained just by washing the crude reaction mixture with pentane. Significantly, the green chemistry metrics of the protocol are found to be excellent.

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## Introduction

Ketene *N,S*-acetals represent valuable entities in the realm of organic synthesis and exhibit a wide range of applications across multiple fields, including pharmaceuticals,<sup>1,2</sup> agrochemicals<sup>3,4</sup> and materials science. This class of molecules serves as valuable building blocks in numerous organic transformations, thereby facilitating the synthesis of diverse heterocycles.<sup>5–8</sup> Furthermore, certain cyclic ketene *N,S*-acetals demonstrate enhanced efficacy in various applications. For instance, nithiazine A, a neonicotinoid insecticide,<sup>3,4,8</sup> ranks among the most widely utilized insecticides globally. Additionally, compounds such as etozolin B and ralitoline C are employed in the treatment of neurological disorders and hypertension (Fig. 1).<sup>1,2</sup> Thiazole Orange (TO) D functions as a probe for the early detection of cancer cell labelling,<sup>9,10</sup> while SYBR Safe E is an effective probe for investigating interactions between G-quadruplexes and their ligands (Fig. 1).<sup>10,11</sup> Although several strategies have been developed for the hydrosulfenylation of alkynes to synthesize functionalized vinyl sul-

phides, the synthesis of ketene *N,S*-acetals, a special class of vinyl sulphides, was found underdeveloped.<sup>12</sup> Previous studies have documented various multi-step synthetic methodologies for the synthesis of a very specific type of ketene *N,S*-acetal bearing an electron-withdrawing carbonyl functional group.<sup>5,8</sup>

In 2023, the Taillefer group reported the synthesis of only one example of ketene *N,S*-acetals, with moderate yield (62%) and poor stereoselectivity (*E/Z* = 70 : 30) (Scheme 1).<sup>13</sup> In 2008, Koichiro Oshima first reported the direct synthesis of ketene *N,S*-acetal derivatives (only 10 examples) from ynamides using diphenyldithiophosphinic acid in dimethoxyethane at ambient temperature (Scheme 1).<sup>14</sup>

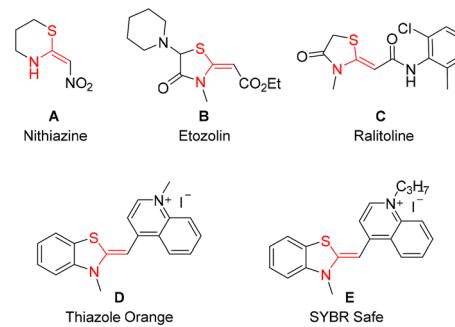
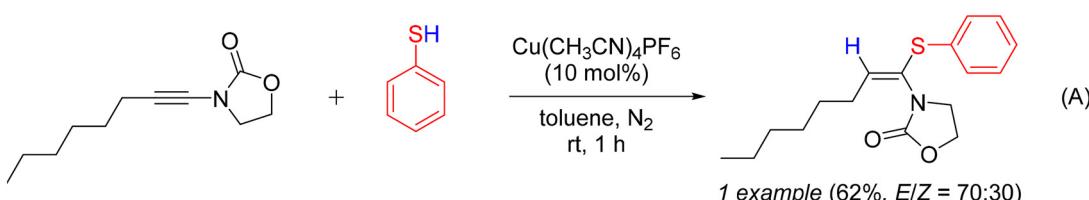


Fig. 1 Some important ketene *N,S*-acetal-containing drugs, insecticides, and probes.

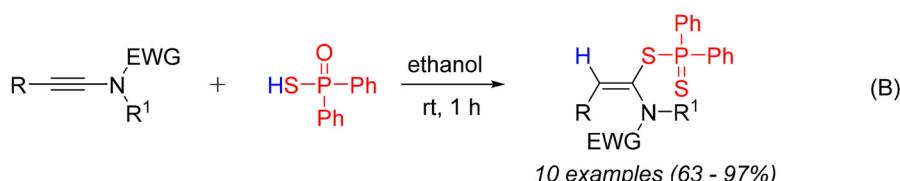
Department of Chemistry, Birla Institute of Technology and Science, Pilani,  
Hyderabad Campus, Jawahar Nagar, Hyderabad – 500078, India.  
E-mail: tanmay@hyderabad.bits-pilani.ac.in

† Electronic supplementary information (ESI) available: Experimental procedures, analytical data of the synthesized molecules, and <sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F spectra of the synthesized compounds. See DOI: <https://doi.org/10.1039/d4ob01984a>

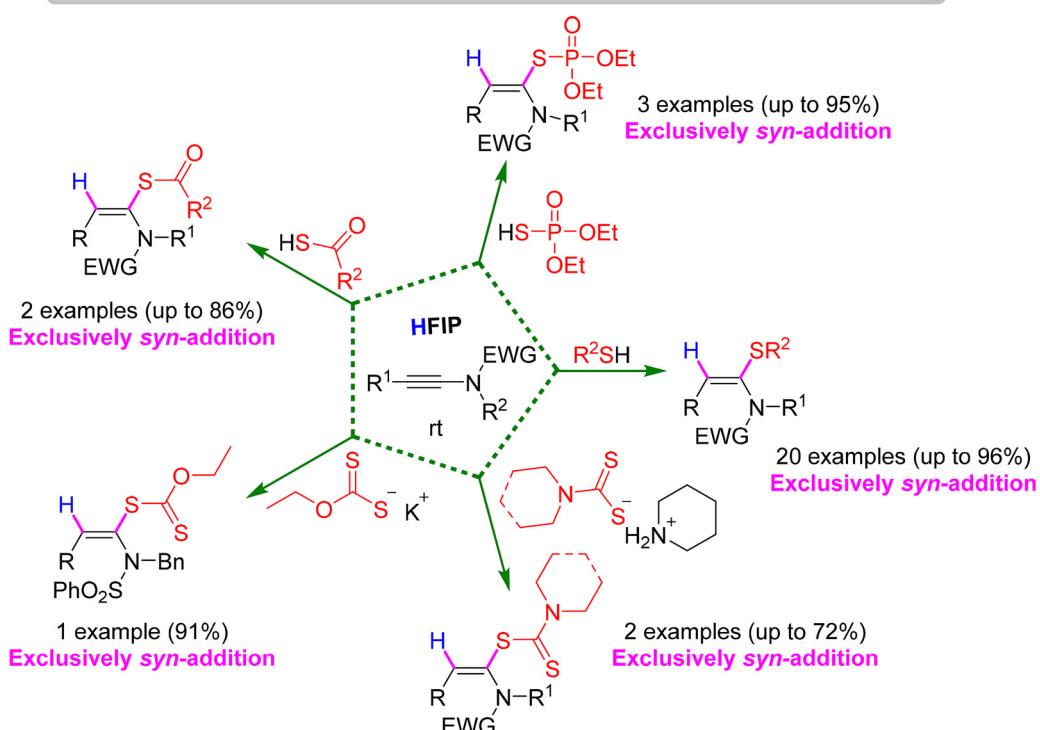


----- **Previous work: Metal-catalyzed or acid-mediated syn-hydrosulfenylation of ynamides** -----

- only one example
- poor stereoselectivity
- requirement of transition metal and inert conditions



- limited to only diphenylphosphinothioic S-acid as nucleophile
- poor stereoselectivity for some cases
- limited substrate scope

----- **This work: Reusable HFIP mediated versatile syn-hydrosulfenylation of ynamides** -----

- versatile synthetic strategy
- broad substrate scope
- high regio- and stereoselectivity
- easy recovery and reusability of the only reagent, HFIP
- HFIP as the unique solvent
- mild reaction conditions
- excellent green chemistry metrics including high atom economy

**Scheme 1** Synthetic strategies to access ketene *N,S*-acetals.

However, these methodologies suffer from some serious limitations, such as limited substrate scope, use of only diphenyldithiophosphinic acid as the *S*-nucleophile (limited scope), poor stereoselectivity, and the need for a transition metal. A

straightforward, one-pot, regio- and stereoselective synthesis of ketene *N,S*-acetals is underdeveloped. Recently, various regio- and stereoselective difunctionalization and hydrofunctionalization methods of ynamides have been developed by several



research groups to access various functionalized enamides.<sup>15–17</sup> As part of our continued interest in developing metal-free and sustainable synthetic methodologies,<sup>18–23</sup> in particular, exploring hexafluoroisopropanol (HFIP) and ynamides in organic synthesis,<sup>19</sup> and based on the importance of ketene *N,S*-acetals, we developed a metal-free, HFIP-mediated highly regio- and stereoselective hydrosulfonylation of ynamides for the sustainable and versatile synthesis of a wide variety of ketene *N,S*-acetals under mild reaction conditions such as room temperature and aerobic atmosphere.

## Results and discussion

We commenced our investigation by reacting *N*-benzyl-*N*-(phenylethynyl)benzenesulfonamide (**1a**) with thiophenol **2a** in the presence of HFIP (0.6 M) at ambient temperature under an aerobic atmosphere and gratifyingly, **1a** underwent *syn*-hydrosulfonylation with **2a** to furnish the desired product, (*E*)-*N*-benzyl-*N*-(2-phenyl-1-(phenylthio)vinyl)benzenesulfonamide **3** in an excellent yield of 92% and with exclusive (*E*)-stereoselectivity (entry 1, Table 1). When the loading of HFIP was decreased to 10 equiv., we observed that the solubility of **1a** decreased, resulting in an unsuccessful reaction. To check the feasibility of the reaction using HFIP as only the reagent, not as the solvent, we treated **1a** with HFIP (1 equiv.) in toluene

(0.6 M) at ambient temperature and also at 70 °C; however, only trace amounts of **3** were formed in both cases (entries 3 and 4, Table 1). When another Brønsted acid, such as acetic acid, was used instead of HFIP, the acetic acid addition product of **1a** was formed instead of **3** (entry 5, Table 1). Similarly, when TfOH was used instead of HFIP, the TfOH addition product of **1a** was formed along with **3** (entry 6, Table 1). With the change of the solvent from HFIP to trifluoroethanol and ethanol, the reaction was unsuccessful, and **1a** was recovered fully (entries 7 and 8, Table 1). When pentafluorophenol (0.6 M) was used as the solvent instead of HFIP, the hydro-pentafluorophenoxylation product of **1a**, *i.e.*, **X** (major), was formed along with the formation of **3** (minor amounts) in a 9 : 1 ratio with an overall quantitative yield (see Scheme S1 in the ESI†). Hence, for the synthesis of **3** *via* the hydrosulfonylation of **1a**, the use of only one equiv. of **2a** in the presence of HFIP (0.6 M) was found to be optimum at room temperature under an aerobic atmosphere.

With the optimized conditions in hand, we next explored the scope of *syn*-hydrosulfonylation of ynamides with thiols first (Table 2). When the reaction of **1a** was performed with **2a** on a 0.3 mmol scale, the desired product **3** was formed without any compromise in yield (92%). Both electron-withdrawing (4-Br, 4-F, and 4-CF<sub>3</sub>) and electron-donating (4-Me and 4-OMe) group substituted aryl thiols underwent the *syn*-hydrosulfonylation reaction with **1a** smoothly to furnish the desired products (**4–8**) in excellent yields (85–96%, average yield: 91.8%). Next, we explored the scope of aliphatic thiols and, notably, both primary and secondary aliphatic thiols such as benzyl mercaptan, furan-2-ylmethanethiol, butane-1-thiol, and butane-2-thiol participated in the *syn*-hydrosulfonylation reaction of **1a** to afford the corresponding desired products (**9–12**) in excellent yields (88–92%, average yield = 90%). The scope of ynamides was explored next, and both electron-withdrawing (4-Br, 4-F, and 2-CN) and electron-donating (4-Me) group substituted aryl ynamides underwent the *syn*-hydrosulfonylation reaction with **2a** to afford the desired products (**13–16**) in good to excellent yields (80–93%). A heteroaryl, *i.e.*, 2-thienyl-substituted ynamide, participated in the *syn*-hydrosulfonylation reaction with **2a** and afforded the desired product **17** in 76% yield. Aliphatic ynamides, *i.e.*, *N*-benzyl-*N*-(cyclohexylethynyl)benzenesulfonamide and *N*-benzyl-*N*-(cyclohexylethynyl)methanesulfonamide, also reacted with **2a** to afford the desired products (**18** and **19**) in 94% and 87% yields, respectively. A variation in the sulfonamide part of ynamides did not affect the outcome of the *syn*-hydrosulfonylation reaction with **2a**, as the desired products (**20–22**) were formed in 88–92% yields (average yield = 90%). When an *N*-alkynyl carbamate, *i.e.*, methyl benzyl(phenylethynyl)carbamate **1m**, was treated with **2a** in HFIP, the desired product **23** was formed in 83% yield at room temperature; however, unfortunately, the ynamide 1-(2-phenylethynyl)-2-pyrrolidinone did not participate in the reaction with **2a** and the desired product **24** was not formed.

Next, we explored the scope of dithiocarbamates and xanthates for the hydrosulfonylation reaction with ynamides to access a new class of ketene *N,S*-acetals. When **1a** was treated

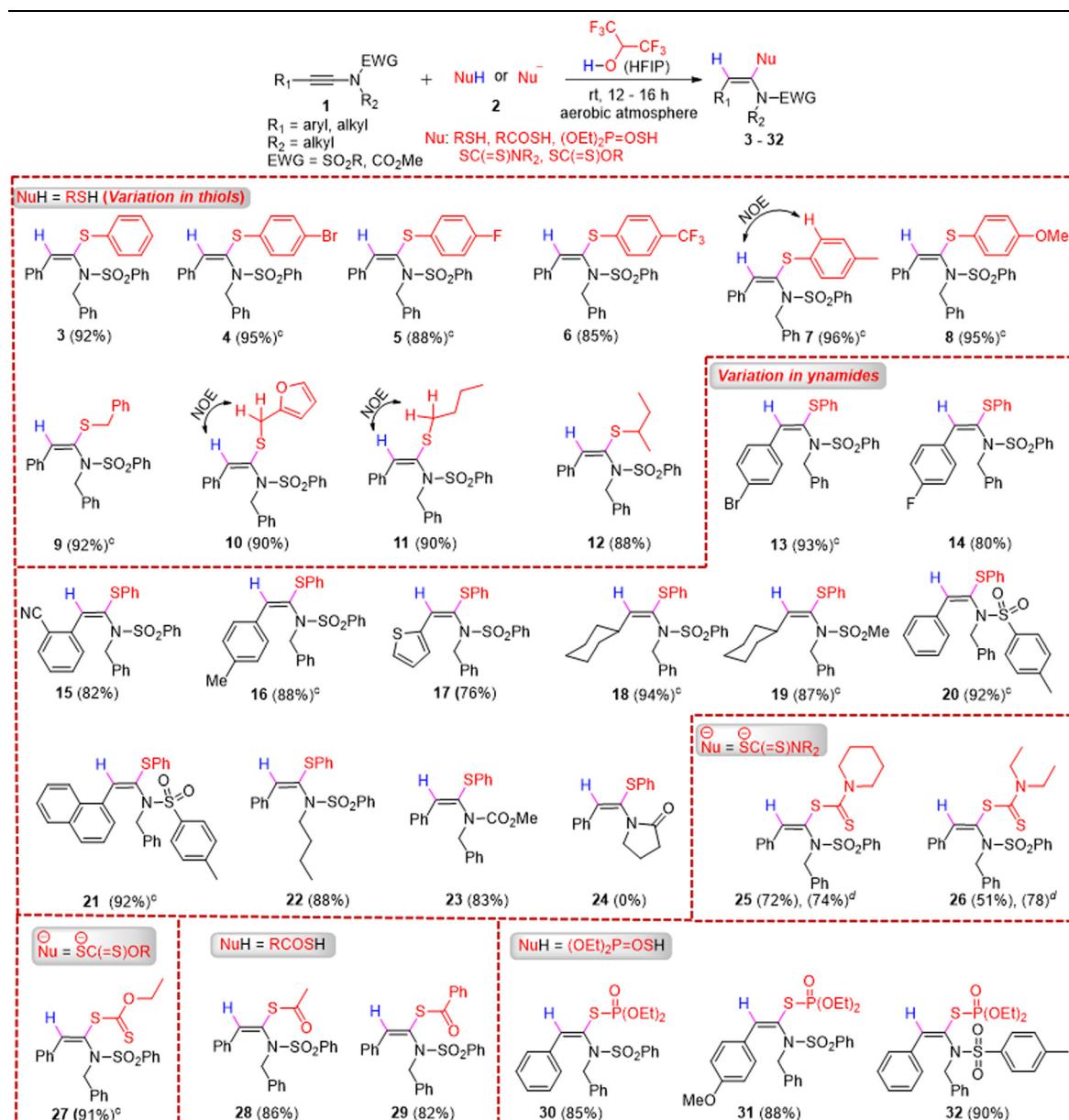
Table 1 Optimization of reaction conditions<sup>a</sup>

| Entry | Variation in conditions from the scheme                                      | Temperature (°C) | Yield <sup>b</sup> (%) |
|-------|--|------------------|------------------------|
| 1     | None   | rt               | 92                     |
| 2     | 10 equiv of HFIP was used  | rt               | Trace                  |
| 3     | HFIP (1 equiv) and toluene (0.6 M) were used                                 | rt               | Trace                  |
| 4     | HFIP (1 equiv) and toluene (0.6 M) were used                                 | 70               | Trace                  |
| 5     | CH <sub>3</sub> COOH (2 equiv) and toluene (0.6 M) were used instead of HFIP | rt               | 0 <sup>c</sup>         |
| 6     | TfOH (1 equiv) and toluene (0.6 M) were used instead of HFIP                 | rt               | 20 <sup>d</sup>        |
| 7     | Trifluoroethanol was used instead of HFIP                                    | rt               | 0                      |
| 8     | Ethanol was used instead of HFIP   | rt               | 0                      |
| 9     | Pentafluorophenol was used instead of HFIP                                   | rt               | 10 <sup>e</sup>        |

<sup>a</sup> All the reactions were conducted on a 0.1 mmol scale. <sup>b</sup> Yield of the product was determined by <sup>1</sup>H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. <sup>c</sup> Acetic acid addition product of **1a** was formed exclusively. <sup>d</sup> TfOH addition product of **1a** was formed along with the formation of **3** (messy NMR).

<sup>e</sup> Pentafluorophenol addition product of **1a**, *i.e.* **X**, was formed along with the formation of **3** (X : 3 = 9 : 1) in a quantitative yield and the product **X** was isolated when the reaction was performed on a 0.3 mmol scale and characterized by NMR (see the ESI†).



Table 2 Substrate scope<sup>a,b</sup>

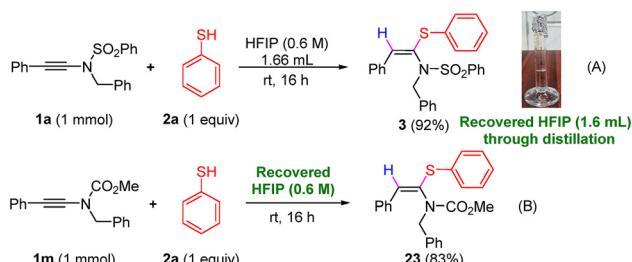
<sup>a</sup> All reactions were conducted on a 0.3 mmol scale using 1 equiv. of nucleophile in HFIP (0.6 M). <sup>b</sup> Yield of isolated products is reported. <sup>c</sup> No column chromatographic purification was performed. <sup>d</sup> 2-Equiv. of nucleophile (2k or 2l) was used.

with *in situ*-generated dithiocarbamates, formed by the reaction of  $\text{CS}_2$  and amines, in the presence of HFIP, the desired *syn*- $\alpha$ -hydro-dithiocarbamation products of **1a**, *i.e.*, **25** and **26**, were formed respectively in moderate to good yields. Both primary and secondary (cyclic and acyclic) amines (piperidine and diethyl amine) underwent the reaction smoothly. When potassium *O*-ethyl carbonodithioate was treated with **1a**, the desired product **27** was formed in 91% yield. Other sulphur nucleophiles such as ethanethioic *S*-acid and benzothioic *S*-acid were employed for the hydrosulfenylation of **1a**, and notably another new class of products, *i.e.*, (*E*)-*S*-(1-(*N*-benzyl-

phenylsulfonamido)-2-phenylvinyl) ethanethioate **28** and (*E*)-*S*-(1-(*N*-benzylphenylsulfonamido)-2-phenylvinyl) benzothioate **29**, were formed in excellent yields (82–86%) under the optimized conditions. Finally, *O,O*-dimethyl *S*-hydrogen phosphorothioate was subjected to reaction with various ynamides, *i.e.*, **1a**, **1f**, and **1j**, under the optimized conditions, and the desired products **30–32** were also formed in excellent yields (85–90%).

The stereochemistry of various products, such as **7**, **10**, and **11**, was confirmed by NOE difference spectroscopy (see the ESI†). Interestingly, most of the reactions were very clean, and several products such as **4**, **5**, **7**, **8**, **9**, **13**, **16**, **18**, **19**, **20**, **21**, and

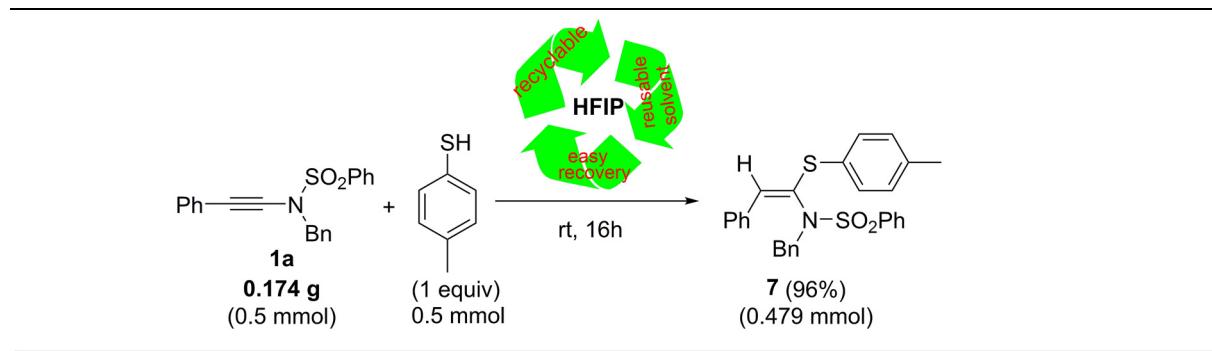




Scheme 2 (A) Recovery and (B) reusability of HFIP.

27 were obtained pure just by evaporating the solvent (HFIP) first after the reaction and then washing the crude product with a small amount of cold pentane or cold ethanol; no work-up or column chromatography was required. Thus, the requirement of huge amounts of organic solvents in purifying the product from the crude reaction mixture *via* work-up and column chromatographic techniques was avoided, which certainly revealed the high sustainability of our developed protocol. Moreover, the recovered HFIP could be reused for subsequent reactions (Scheme 2).<sup>19</sup>

Table 3 Evaluation of the green metrics of our protocol for the synthesis of 7 from 1a and 2e



Yield of desired product = 96%

$$\text{Atom Economy (\%)} = \frac{\text{M.wt. of desired product}}{\text{M.wt. of all reactants}} \times 100 = \frac{471.63}{347.43 + 124.20} \times 100 = 100\%$$

$$\text{Atom Efficiency (\%)} = (\% \text{yield of product} \times \% \text{atom economy}) \times 100 = (96\% \times 100\%) \times 100 = 96\%$$

$$\text{Carbon Efficiency (\%)} = \frac{(\text{moles of 6} \times \text{no. of carbons in 6}) \times 100}{(\text{moles of 1a} \times \text{carbons in 1a}) + (\text{moles of 2b} \times \text{carbons in 2b})} = \frac{(0.479 \times 28) \times 100}{(0.5 \times 21) + (0.5 \times 7)} = 95.8\%$$

$$\text{Reaction Mass Efficiency (\%)} = \frac{\text{mass of isolated product}}{\text{mass of all reactants}} \times 100 = \frac{0.226}{0.174 + 0.062} \times 100 = 95.76\%$$

|                    |  |         |            |           |
|--------------------|--|---------|------------|-----------|
| Reactant 1:        | <i>N</i> -benzyl- <i>N</i> -(phenylethynyl)benzenesulfonamide (1a)                                       | 0.174 g | 0.5 mmol   | FW 347.43 |
| Reactant 2:        | 4-methylbenzenethiol (2b)  | 0.062 g | 0.50 mmol  | FW 124.20 |
| Solvent:           | 1,1,1,3,3,3-hexafluoropropan-2-ol  | 1.34 g  | 8 mmol     | FW 168.04 |
| Recovered solvent: | 1,1,1,3,3,3-hexafluoropropan-2-ol  | 1.3 g   | 7.75 mmol  | FW 168.04 |
| Product:           | ( <i>E</i> )- <i>N</i> -benzyl- <i>N</i> -(2-phenyl-1-( <i>p</i> -tolylthio)vinyl)benzenesulfonamide (7) | 0.226 g | 0.479 mmol | FW 471.63 |

$$\text{E-factor} = \frac{\text{total waste (g)}}{\text{total product (g)}} = \frac{(0.174 + 0.062 + 1.34) - (0.226 + 1.3)}{0.226} = 0.22 \text{ g waste/g pdt}$$

To demonstrate the recovery and reusability of HFIP, we performed the reaction between **1a** and **2a** on a 1 mmol scale, and after the completion of the reaction, 96% HFIP (1.6 mL) was recovered through simple distillation at 65 °C in an oil bath (Scheme 2A). The recovered HFIP was recycled for the synthesis of **23**, and the result was reproducible (Scheme 2B).

To measure the greenness of our developed protocol quantitatively, we evaluated the green chemistry metrics<sup>17–19</sup> of our protocol for the synthesis of **7** from **1a** and **2e**, and the results are summarized in Table 3.

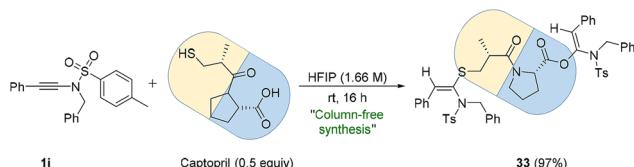
Notably, our protocol was found to possess 100% atom economy, 96% atom efficiency, 95.8% carbon efficiency, and 95.76% reaction mass efficiency (Table 3). Another important green parameter, *i.e.*, the *E*-factor,<sup>18</sup> which is based on the generated waste, is found to have a very low value of 1.22 g of waste generated per gram of product formed. These results demonstrated the high sustainability of our developed protocol.

Captopril (brand name: Capoten) is a marketed drug used for the treatment of hypertension. It possesses two functional groups, *i.e.*, thiol (–SH) and carboxylic acid (–COOH), offering scope for bis-late-stage functionalization (bis-LSF) for the drug with ynesulfonamide (Scheme 3).

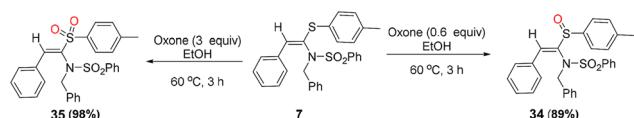
When **1j** was treated with Captopril (0.5 equiv.) in HFIP at room temperature, the desired bis-functionalized product **33** was formed in almost quantitative yield (97%), and notably, **33** was obtained pure without the requirement of column chromatography (Scheme 3).

Furthermore, to demonstrate the synthetic application of the products, we diversified one of the synthesized products, *i.e.*, **7**, into other useful classes of its derivatives, *i.e.*, the corresponding sulfoxide **34** and sulfone **35**, in 89% and 98% yields, respectively, *via* controlled oxidation of **7** using 0.6 and 3 equivalents of oxone in ethanol, respectively (Scheme 4).

Based on the literature reports,<sup>16b,19</sup> we proposed that at first, the keteniminium ion intermediate **A** was formed *via* the regioselective protonation of yensulfonamide **1a** at the  $\beta$ -position by HFIP, which was also stabilized by HFIP. Next, **A** underwent a favoured *syn*-attack by the nucleophile to furnish the desired *syn*-hydrosulfenylation product of the ynamide (**1a**), as the anti-attack is disfavoured due to the steric hindrance from the R-group (Scheme 5).



**Scheme 3** Bis-late-stage functionalization (bis-LSF) of captopril with ynamide **1j**.

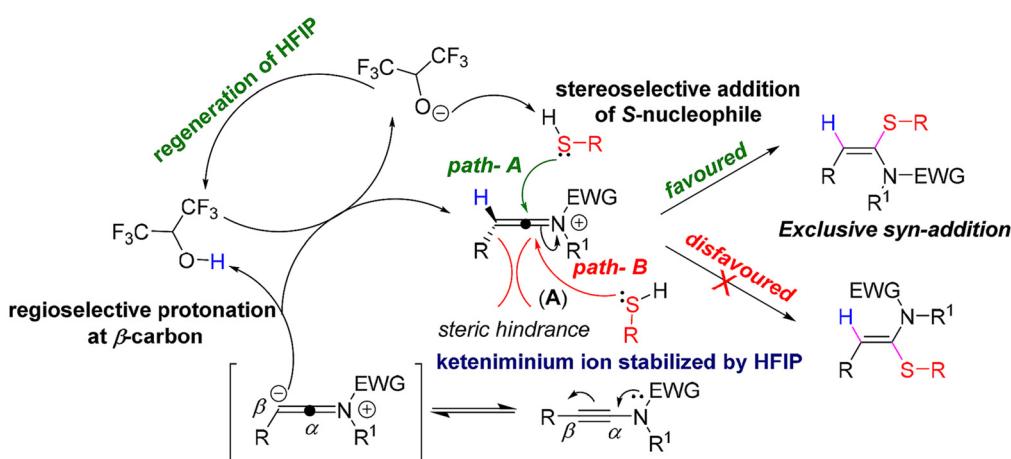


**Scheme 4** Oxone-mediated controlled oxidation of **7** to its corresponding sulfoxide (**34**) and sulfone (**35**).

## Conclusion

In conclusion, we developed an HFIP-mediated, highly regio- and stereoselective, and versatile protocol for the synthesis of a wide variety of stereodefined ketene *N,S*-acetals in good to excellent yields *via* the hydrosulfenylation of ynamides under mild reaction conditions such as room temperature and an aerobic atmosphere.

Interestingly, a wide variety of *S*-nucleophiles such as thiols, thio *S*-acids, carbamates, xanthates, and *O,O*-diethyl *S*-hydrogen phosphorothioate were employed, and all underwent the reaction smoothly with ynesulfonamides to furnish a



**Scheme 5** Proposed reaction mechanism.



wide variety of *N,S*-acetals. The transformation required only HFIP, which played multiple roles such as Brønsted acid, keteniminium ion stabilizer, and solvent. HFIP was regenerated after the reactions when thiols, thio *S*-acids, and *O,O*-diethyl *S*-hydrogen phosphorothioate were used as *S*-nucleophiles, and it could easily be recovered and reused for subsequent reactions.<sup>19</sup> Moreover, this protocol could be utilized for the late-stage functionalization of some drug molecules, such as captopril. Notably, this protocol features excellent green chemistry metrics including 100% atom economy, 96% atom efficiency, 95.8% carbon efficiency, and 95.76% reaction mass efficiency, and a very low value of *E*-factor, *i.e.*, 1.22 g waste generated per gram of product (7) formed. We believe that this sustainable and versatile strategy will find useful applications in accessing useful *N,S*-acetals.

## Experimental section

### General experimental procedure for the synthesis of ketene *N,S*-acetals (3–22) *via* the hydrothiolation of ynesulfonamides

**Representative experimental procedure for the synthesis of (E)-*N*-benzyl-*N*-(2-phenyl-1-(phenylthio)vinyl)benzenesulfonamide (3).** *N*-Benzyl-*N*-(phenylethynyl)benzenesulfonamide **1a** (0.104 g, 0.3 mmol, 1 equiv.) and thiophenol **2a** (0.033 g, 0.30 mmol, 1.0 equiv.) were taken in a round-bottom flask and then dry HFIP (0.5 mL, 0.6 M) was added to it. The reaction mixture was stirred at 25 °C. The progress of the reaction was monitored by TLC and the reaction was found to be complete in 12 h. After the completion of the reaction, the solvent was evaporated under reduced pressure and the crude reaction mixture was purified by flash column chromatography (100–200 silica) using hexane as an eluent to afford pure (E)-*N*-benzyl-*N*-(2-phenyl-1-(phenylthio)vinyl)benzenesulfonamide **3** (0.126 g, 0.27 mmol) as a yellow oil in 92% yield. However, several products such as **4**, **5**, **7**, **8**, **9**, **13**, **16**, **18**, **19**, **20**, and **21** were obtained pure by washing the crude product with cold pentane or cold ethanol.

### General experimental procedure for the synthesis of ketene *N,S*-acetals (25–26) *via* the hydro-dithiocarbamation of ynesulfonamides

**Representative experimental procedure for the synthesis of (E)-1-(*N*-benzylphenylsulfonamido)-2-phenylvinyl piperidine-1-carbodithioate (25).** *N*-Benzyl-*N*-(phenylethynyl)benzenesulfonamide **1a** (0.104 g, 0.3 mmol, 1 equiv.) was added to piperidin-1-ium piperidine-1-carbodithioate (0.082 g, 0.30 mmol, 1.0 equiv.), prepared *in situ* in a RBF by adding an amine (1 equiv.) in CS<sub>2</sub>, and then dry HFIP (0.5 mL, 0.6 M) was added to it. The reaction mixture was stirred at 25 °C. The progress of the reaction was monitored by TLC and the reaction was found to be complete in 16 h. After the completion of the reaction, the solvent was evaporated under reduced pressure and the crude reaction mixture was purified by flash column chromatography (100–200 silica) using hexane as an eluent to afford pure (E)-1-(*N*-benzylphenylsulfonamido)-2-phenylvinyl piperidine-1-carbodithioate (25) (0.110 g, 0.22 mmol) as a light yellow solid in 72% yield.

mido)-2-phenylvinyl piperidine-1-carbodithioate **25** (0.110 g, 0.22 mmol) as a light yellow solid in 72% yield.

**Experimental procedure for the synthesis of (E)-*S*-(1-(*N*-benzylphenylsulfonamido)-2-phenylvinyl) *O*-ethyl carbonodithioate (27).** *N*-Benzyl-*N*-(phenylethynyl)benzenesulfonamide **1a** (0.104 g, 0.3 mmol, 1 equiv.) and potassium *O*-ethyl carbonodithioate (0.048 g, 0.30 mmol, 1.0 equiv.)<sup>3</sup> were taken in a round-bottom flask and then HFIP (0.5 mL, 0.6 M) was added to it. The reaction mixture was stirred at 25 °C. The progress of the reaction was monitored by TLC and the reaction was found to be complete in 16 h. After the completion of the reaction, the solvent was evaporated under reduced pressure and the crude reaction mixture was purified by washing with cold pentane two times to afford pure (E)-*S*-(1-(*N*-benzylphenylsulfonamido)-2-phenylvinyl) *O*-ethyl carbonodithioate (27) (0.128 g, 91%) as a white crystalline solid in 91% yield.

### General experimental procedure for the synthesis of ketene *N,S*-acetals (28–29) with thio *S*-acids

**Experimental procedure for the synthesis of (E)-*S*-(1-(*N*-benzylphenylsulfonamido)-2-phenylvinyl) ethanethioate (28).** *N*-Benzyl-*N*-(phenylethynyl)benzenesulfonamide **1a** (0.104 g, 0.3 mmol, 1 equiv.) and ethanethioic *S*-acid **2n** (0.023 g, 0.30 mmol, 1.0 equiv.) were taken in a round-bottom flask and then HFIP (0.5 mL, 0.6 M) was added to it. The reaction mixture was stirred at 25 °C. The progress of the reaction was monitored by TLC and the reaction was found to be complete in 16 h. After the completion of the reaction, the solvent was evaporated under reduced pressure and the crude reaction mixture was purified by washing with cold pentane two times to afford pure (E)-*S*-(1-(*N*-benzylphenylsulfonamido)-2-phenylvinyl) ethanethioate (28) (0.109 g, 86%) as a white gummy oil in 86% yield.

### General experimental procedure for the synthesis of ketene *N,S*-acetals (30–32) with *O,O*-diethyl *S*-hydrogen phosphorothioate

**Experimental procedure for the synthesis of (E)-*S*-(1-(*N*-benzylphenylsulfonamido)-2-phenylvinyl) *O,O*-diethyl phosphorothioate (30).** *N*-Benzyl-*N*-(phenylethynyl)benzenesulfonamide **1a** (0.104 g, 0.3 mmol, 1 equiv.) and *O,O*-diethyl *S*-hydrogen phosphorothioate **2p** (0.051 g, 0.30 mmol, 1.0 equiv.) were taken in a round-bottom flask and then HFIP (0.5 mL, 0.6 M) was added to it. The reaction mixture was stirred at 25 °C. The progress of the reaction was monitored by TLC and the reaction was found to be complete in 16 h. After the completion of the reaction, the solvent was evaporated under reduced pressure and the crude reaction mixture was purified by washing with cold pentane two times to afford pure (E)-*S*-(1-(*N*-benzylphenylsulfonamido)-2-phenylvinyl) *O,O*-diethyl phosphorothioate (30) (0.140 g, 90%) as a white gummy oil in 90% yield.

**Experimental procedure for the synthesis of (E)-2-((*N*-benzyl-4-methylphenyl)sulfonamido)-1-phenylvinyl (3-((*E*)-1-((*N*-benzyl-4-methylphenyl)sulfonamido)-2-phenylvinyl)thio)-2-methylpropanoyl)proline (33).** *N*-Benzyl-4-methyl-*N*-(phenylethynyl)benzenesulfonamide **1j** (0.109 g, 0.3 mmol, 1 equiv.) and



(3-mercaptopropanoyl)proline **2q** (0.033 g, 0.15 mmol, 0.5 equiv.) were taken in a round-bottom flask and then dry HFIP (0.5 mL, 0.6 M) was added to it. The reaction mixture was stirred at 25 °C. The progress of the reaction was monitored by TLC and the reaction was found to be complete in 16 h. After the completion of the reaction, the solvent was evaporated under reduced pressure, and the crude reaction mixture was purified by flash column chromatography (100–200 silica) using ethyl acetate in hexane as an eluent to afford pure **33** (0.276 g, 0.294 mmol) as a colorless gummy oil in 97% yield.

**Experimental procedure for the synthesis of (E)-N-benzyl-N-(2-phenyl-1-(*p*-tolylsulfinyl)vinyl)benzenesulfonamide (34).** (E)-N-Benzyl-N-(2-phenyl-1-(*p*-tolylthio)vinyl)benzenesulfonamide **7** (0.1 g, 0.212 mmol, 1 equiv.) and Oxone (0.04 g, 0.13 mmol, 0.6 equiv.) were taken in a round-bottom flask and then EtOH (0.5 mL) was added to it. The reaction mixture was heated at 60 °C. The progress of the reaction was monitored by TLC and the reaction was found to be complete in 3 h. After the completion of the reaction, the solvent was evaporated under reduced pressure, and the crude reaction mixture was purified by flash column chromatography (100–200 silica) using ethyl acetate in hexane as an eluent to afford pure **34** (0.091 g, 0.188 mmol) as a white solid in 89% yield.

**Experimental procedure for the synthesis of (E)-N-benzyl-N-(2-phenyl-1-(*p*-tolylsulfinyl)vinyl)benzenesulfonamide (35).** (E)-N-Benzyl-N-(2-phenyl-1-(*p*-tolylthio)vinyl)benzenesulfonamide **7** (0.1 g, 0.212 mmol, 1 equiv.) and oxone (0.195 g, 0.636 mmol, 3 equiv.) were taken in a round-bottom flask and then EtOH (0.5 mL) was added to it. The reaction mixture was heated at 60 °C. The progress of the reaction was monitored by TLC and the reaction was found to be complete in 3 h. After the completion of the reaction, the solvent was evaporated under reduced pressure, and the crude reaction mixture was purified by flash column chromatography (100–200 silica) using ethyl acetate in hexane as an eluent to afford pure **35** (0.104 g, 0.2 mmol) as a white solid in 98% yield.

## Author contributions

A. N. V. Satyanarayana carried out most of the experiments, including optimization of the reaction conditions, synthesis of products, their synthetic diversifications, and mechanistic studies. P. Pattanayak also synthesized some of the ketene *N,S*-acetals. T. Chatterjee conceived and supervised the work and wrote and edited the manuscript. All the authors have given their final approval to the final version of the manuscript.

## Data availability

The data underlying this study are available in the published article, and its experimental and spectroscopic details are included as part of the online ESL.†

## Conflicts of interest

There are no conflicts to declare.

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