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## H-bond network-facilitated, diversity-oriented, green synthesis of valuable organic compounds *via* atom-economic, regio- and stereo-selective reactions involving ynamides and anilines

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Diversity-oriented synthesis (DOS) enables synthetic organic chemists to fabricate structurally diverse classes of molecules, which is highly desirable in the context of medicinal chemistry, thus leading to drug discovery. Herein, we report the H-bonding network-mediated DOS of five structurally diverse classes of molecules, such as acetimidamides, ketene *N,N*-acetals,  $\alpha$ -arylenamides, some heterocycles, such as quinolines, and 3,4-dihydroquinolin-4-ols, starting from readily available ynamides and anilines in the presence of HFIP as the only reagent/solvent. 2-Amidoindoles were also synthesized *via* a one-pot, two-step process starting from ynamides and primary anilines using  $\text{CuCl}_2$ . The significant benefits of this protocol compared with the previously established synthetic methods are the following: (a) a cost-effective, straightforward, and unified approach for diversity-oriented, green synthesis of various classes of valuable molecules from ynamides and all types of aromatic amines (1°, 2°, and 3°); (b) a metal-free, environmentally friendly, and scalable protocol; (c) mild reaction conditions; (d) 100% atom-economic transformations; (e) HFIP being the sole reagent necessary for the transformations; (f) the dual functionality of HFIP as both a Brønsted acid and a solvent; (g) the regeneration of HFIP post-reaction and its straightforward and effective recovery from the reaction mixture through distillation; (h) the reusability and efficient recyclability of HFIP without compromising the subsequent reaction's results; and (i) the ability to obtain pure products under various conditions without the need for column chromatography (green synthesis).

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### Sustainability spotlight

We developed a diversity-oriented, versatile synthetic method to access five different classes of valuable organic molecules from readily available ynamides and all types of aromatic amines (1°, 2°, and 3°) with excellent yield and regio- and stereo-selectivity using only HFIP, which was efficiently recovered after the reaction, reused and recycled (five runs) without any compromise on the reaction outcome. Most of the reactions are 100% atom-economic, and pure products were obtained without the need for work-up and column chromatography, resulting in minimal waste generation. Thus, the generality, practicality, cost-effectiveness, sustainability, and circular economy of this protocol were found to be significantly better than those of all existing protocols. This protocol is highly environmentally benign and greener.

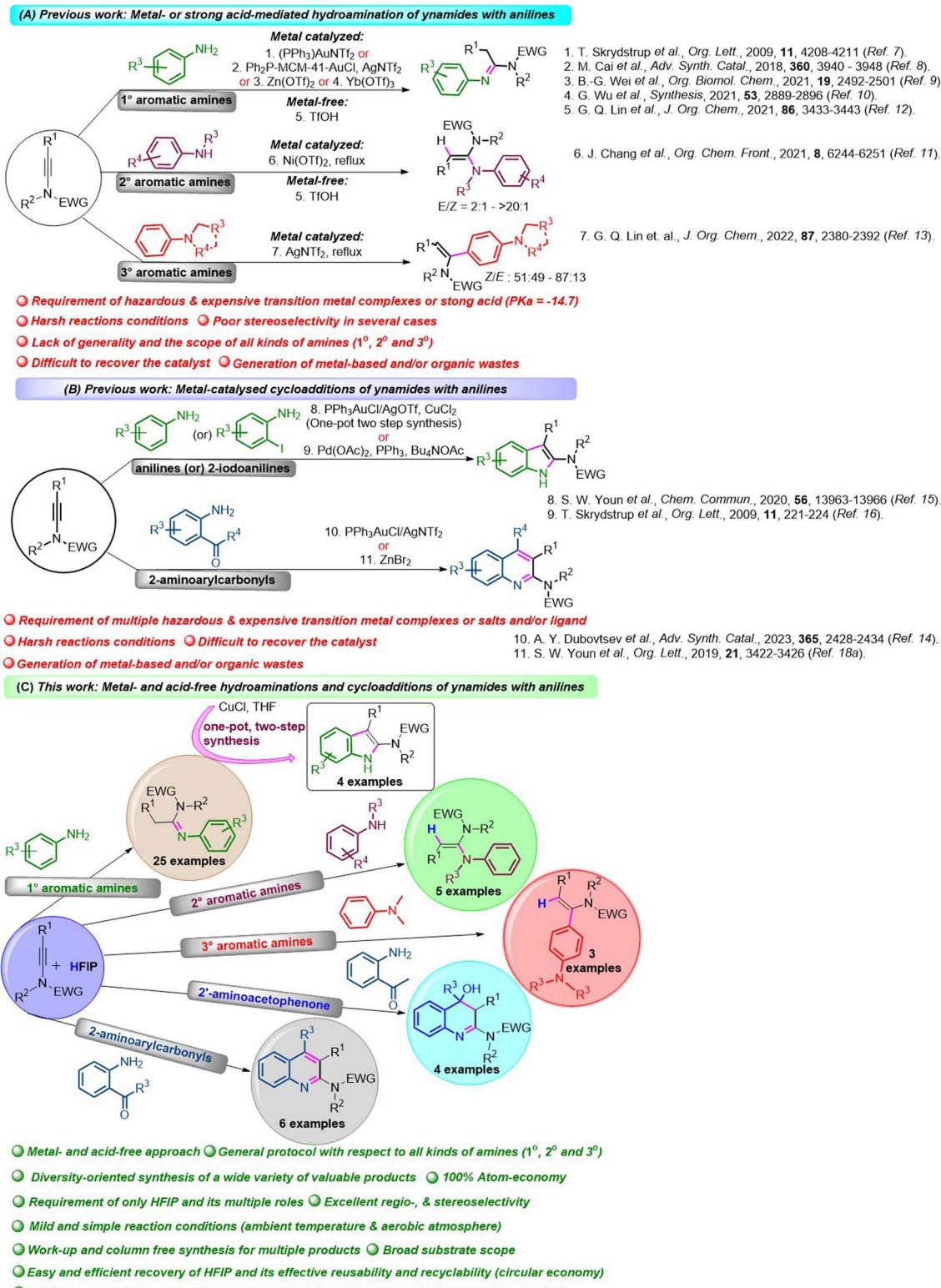
## Introduction

Diversity-oriented synthesis (DOS) mainly aims to produce skeletally diverse small molecules in an efficient manner.<sup>1</sup> It is a very important and unique tool in medicinal chemistry and drug discovery, which require the synthesis of libraries of structurally diverse small molecules.<sup>2</sup> Over the past few decades, ynamides, a unique type of unsymmetrical nitrogen-containing internal alkynes, have garnered significant interest from synthetic organic chemists as valuable building blocks for the

synthesis of various important classes of molecules.<sup>3</sup> The polarization of the nitrogen lone pair renders the  $\beta$ -carbon of the ynamides nucleophilic, while  $\alpha$ -carbon exhibits electrophilic character. This distinction creates a unique environment that is conducive to regioselective difunctionalization reactions, facilitating the synthesis of tetrasubstituted alkenes. Consequently, several synthetic strategies have been developed for the difunctionalization of ynamides and the synthesis of functionalized enamides.<sup>4,5</sup> The synthesis of enamides has garnered considerable interest among synthetic organic chemists due to their prevalence in depsipeptides, pharmaceuticals, and notable natural products.<sup>6</sup> Furthermore, enamides serve as versatile reactants in various contexts, including transition metal catalysis, photochemistry, and asymmetric catalysis. To

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**Scheme 1** (A) Metal- or strong-acid mediated hydroamination of ynamides with anilines (previous work), (B) metal-catalysed cycloadditions of ynamides with anilines (previous work), and (C) metal- and acid-free hydroaminations and cycloadditions of ynamides with anilines (this work).

date, some synthetic strategies have been developed for the hydroamination/hydroarylation and cycloaddition reactions of ynamides with anilines. Several metals such as Au,<sup>7</sup> Ag,<sup>8</sup> Zn,<sup>9</sup>

and Yb<sup>10</sup> have been used to catalyze the hydroamination of ynamides with primary aromatic amines for the synthesis of acetimidamides (Scheme 1A). A metal-free, acid-mediated



hydroamination of ynamide with primary and secondary aromatic amines was reported by Junbiao Chang *et al.* using TfOH (0.5 equiv.) for the synthesis of acetimidamides and  $\alpha$ -aminoenamides, respectively (Scheme 1A).<sup>11</sup> Moreover, Guo-Qiang Lin *et al.* developed a Ni-catalysed hydroamination of ynamides with secondary aromatic amines for the synthesis of  $\alpha$ -aminoenamides using Ni(OTf)<sub>2</sub> as the metal-catalyst under refluxing conditions (Scheme 1A).<sup>12</sup> However, when tertiary aromatic amines such as 1-phenylpyrrolidine and *N,N*-di-alkylanilines were reacted with ynamides in the presence of AgNTf<sub>2</sub> (10 mol%), hydroarylation of ynamides occurred instead of hydroamination (Scheme 1A).<sup>13</sup> Dubovtsev *et al.* disclosed an Au-catalyzed annulation of 2-aminobenzaldehydes and 2-amino ketones with ynamides using Ph<sub>3</sub>PAuCl/AgNTf<sub>2</sub> and molecular sieves for the synthesis of valuable *N*-heteroaromatics, *i.e.*, 2-aminoquinolines (Scheme 1B).<sup>14</sup> Moreover, a few synthetic strategies have been developed for the direct or one-pot, two-step synthesis of 2-aminoindoles from ynamides and anilines or 2-iodoanilines under Au-catalysis or Pd-catalysis. Youn *et al.* reported a one-pot two-step synthesis of 2-aminoindoles from ynamides and anilines using catalytic PPh<sub>3</sub>AuCl and AgOTf in the first step, furnishing the corresponding acetimidamides, which then underwent a Cu-mediated intramolecular oxidative annulation in the second step to produce 2-aminoindoles (Scheme 1B).<sup>15</sup> The Ruhland and Skrydstrup group disclosed the Pd-catalyzed direct synthesis of 2-aminoindoles from 2-iodoaniline and terminal ynamides *via* Sonogashira coupling followed by a base-mediated intramolecular cyclization reaction using Pd(OAc)<sub>2</sub> (5 mol%), PPh<sub>3</sub> (20 mol%) and NaOAc (4 equiv.).<sup>16</sup>

Despite the notable advancements, the developed strategies suffered from several serious limitations, including the requirements of highly expensive and hazardous transition metal complexes and ligands, or strong acids (TfOH), and harsh reaction conditions, poor stereoselectivity in some cases, and the generation of metal-based and/or organic wastes. Moreover, no synthetic strategy has been developed to date for the diversity-oriented, versatile synthesis of valuable products involving ynamides and all types of aromatic amines (1°, 2°, and 3°) under metal-free and sustainable conditions, which is highly desirable in the context of green and sustainable chemistry. HFIP is an excellent alternative to the noble metals mentioned above and also eliminates the need for harsh reaction conditions.<sup>17</sup> Herein, we report a H-bond network-mediated hydroamination or hydroarylation of ynamides with (hetero)aromatic amines (1°, 2°, and 3°) and also cascade hydroamination followed by intramolecular cyclization strategies for the DOS of various useful classes of molecules such as acetimidamides,  $\alpha$ -aminoenamides,  $\alpha$ -arylenamides, and various bioactive heteroaromatics, such as 2-quinolines and hydroxyquinolines, and indoles, just by using HFIP at room temperature (Scheme 1C). This strategy offers several advantages and overcomes the limitations of the previously developed synthetic methods.

## Results and discussion

We commenced our investigation by reacting aniline (**2a**) with *N*-benzyl-*N*-(phenylethynyl)benzenesulfonamide (**1a**) in the

Table 1 Optimisation of the reaction conditions<sup>a</sup>

Entry	Bronsted acid	Solvent (conc.)	Yield <sup>b</sup> (%)
1	<b>HFIP</b>	<b>HFIP 0.6 M</b>	95%
2	TFE	TFE (0.6 M)	ND <sup>c</sup>
3	1 equiv. TFA	Toluene (0.6 M)	61%
4	1 equiv. CH <sub>3</sub> COOH	Toluene (0.6 M)	22%
5	1 equiv. TfOH	Toluene (0.6 M)	13%
6	2 equiv. HFIP	Toluene (0.6 M)	ND <sup>c</sup>
7	2 equiv. HFIP	TFE (0.6 M)	ND <sup>c</sup>

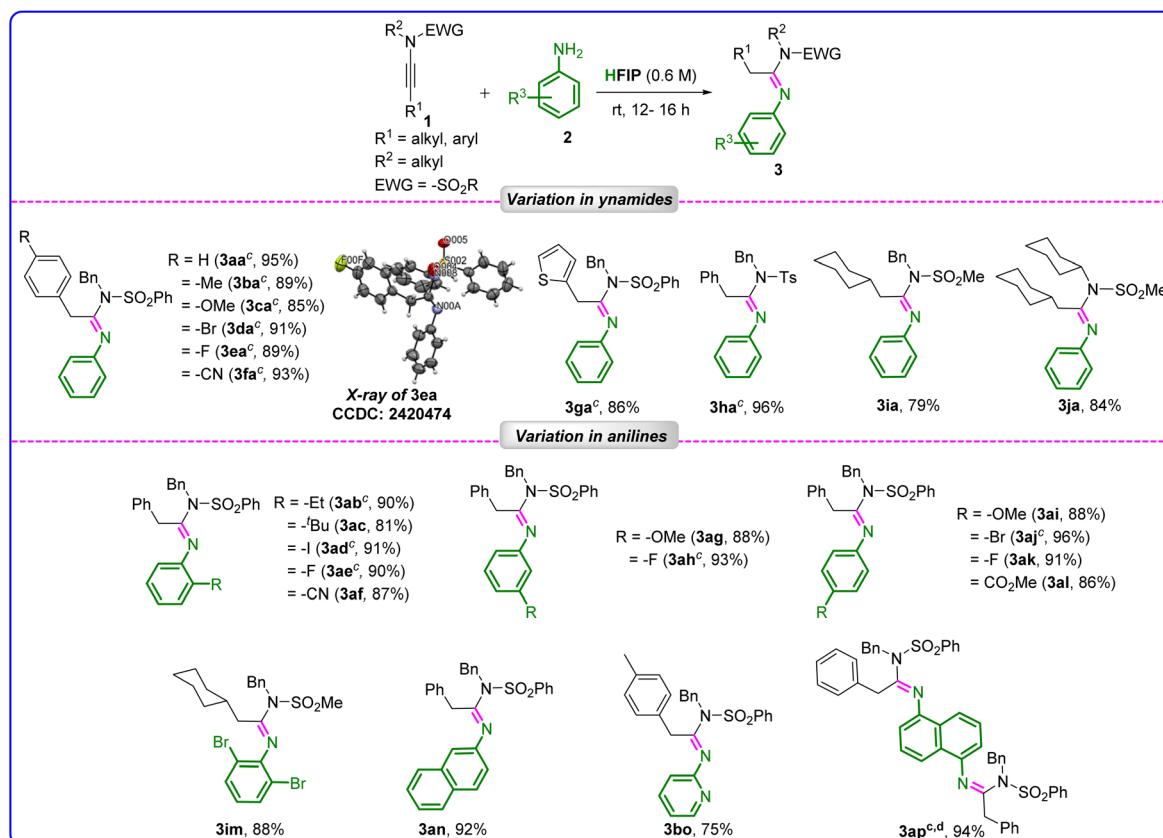
<sup>a</sup> Reactions are conducted on a 0.1 mmol scale. <sup>b</sup> The NMR yield is reported. <sup>c</sup> Starting materials are recovered.

presence of HFIP (0.6 M) at ambient temperature, and gratifyingly, the desired product, (*E*)-*N*-benzyl-*N'*,2-diphenyl-*N*-(phenylsulfonyl)acetimidamide **3aa**, was obtained in an excellent yield of 95% (entry 1, Table 1). However, when HFIP was replaced with trifluoroethanol as the solvent, the reaction did not proceed, and the starting material (**1a**) was completely recovered (entry 2, Table 1). When the reaction was conducted in the presence of a Brønsted acid, *i.e.*, trifluoroacetic acid (1 equiv.), in toluene as the solvent, **3aa** was formed in 61% yield, suggesting that HFIP played a crucial role as the Brønsted acid (entry 3, Table 1). Other Brønsted acids, such as acetic acid (1 equiv.) and triflic acid (1 equiv.), also in toluene, provided **3aa**, but in lower yields, *i.e.*, 22% and 13%, respectively (entries 4 and 5, Table 1). Notably, when HFIP (2 equiv.) was used as only a Brønsted acid but not as a solvent, the reaction was unsuccessful in toluene (entry 6, Table 1), resulting in the full recovery of the starting material (**1a**). When HFIP (2 equiv.) was employed only as a reagent in the presence of trifluoroethanol (TFE) as the solvent, the reaction did not proceed well, and the starting material was fully recovered, which revealed the indispensable role of HFIP as a solvent for this transformation. Thus, the addition of **2a** (0.1 mmol) and **1a** (0.1 mmol) in HFIP (0.6 M) at room temperature was found to be the optimized reaction conditions where HFIP played the dual roles of a Brønsted acid and the solvent.

With the optimized conditions in hand, we explored the scope of the reaction (Table 2). The reaction of *N*-benzyl-*N*-(phenylethynyl)benzenesulfonamide (**1a**) with aniline (**2a**) on a 0.3 mmol scale produced **3aa** without any loss in its yield (95%).

We then explored the scope of various ynamides for the hydroamination reaction with aniline. *N*-Benzyl-*N*-(arylethynyl)benzenesulfonamides bearing various substituents, such as 4-Me, 4-OMe, 4-Br, 4-F, and 4-CN, in the aryl ring were initially examined, and all reactions proceeded well, irrespective of the electronic nature of the substituents, producing the desired



Table 2 Hydroamination of ynamides with primary aromatic amines<sup>a,b</sup>

<sup>a</sup> Reaction conditions: **1** (0.3 mmol), **2** (0.3 mmol), HFIP (0.6 M), rt. <sup>b</sup> Yield of the isolated product is reported. <sup>c</sup> No column chromatographic purification. <sup>d</sup> 0.6 mmol (2 equiv.) of ynamide **1a** is used.

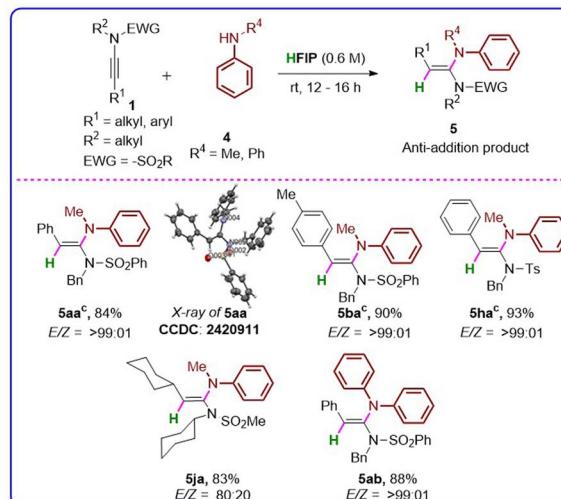
acetimidamides **3ba**–**3fa** in good to excellent yields (85–93%, average yield ~90%) and also in pure form without the requirement of any workup and column chromatography. The structure and the stereochemistry of **3ea** were confirmed by X-ray crystal structure determination (Fig. S1 and Table S1, SI). It is noteworthy that a heteroaromatic (thiophene)-substituted ynamide participated in the reaction, delivering the corresponding product **3ga** in 86% yield. Different EWG-substituted (–Ts, and –SO<sub>2</sub>Me) ynamides (**1h**, **1i**) participated in the reaction, furnishing the desired products **3ha** and **3ia** in excellent yields of 96% and 79%, respectively. Aliphatic ynamide (**1j**) reacted with commercially available aniline (**2a**) to furnish **3aj** in 84% yield. Notably, both electron-donating (–Et, –<sup>t</sup>Bu, and –OMe) and electron-withdrawing (–I, –Br, –F, –CN, and –CO<sub>2</sub>Me), group-substituted anilines **2** smoothly participated in the reaction with **1a**, and a series of desired *N*-arylimines (**3ab**–**3al**) was formed in excellent yield, ranging from 81% to 96%. Neither the electronic effect of the substituents nor their positional variations (*ortho*, *meta*, and *para*) impacted the outcome of the reaction. Sterically crowded, 2,6-dibromoaniline also participated in the hydroamination reaction with cyclohexyl-substituted ynamide (**1i**) without any difficulties and furnished the desired product, **3im**, in 88% yield. Naphthalen-2-

amine (**2n**) reacted smoothly with **1a** to afford the desired product **3an** in 92% yield. Furthermore, the extension of this hydroamination reaction to heteroaryl amines, such as pyridin-2-amine **2o** (a poor nucleophile) with **1b**, was successful, yielding the desired product **3bo** with a 75% yield.

Interestingly, when naphthalene-1,5-diamine (**2p**) was reacted with **1a** (2 equiv.), the *bis*-functionalization of **2p** occurred with **1a**, achieving the desired novel product **3ap** in a very high yield of 94%. Significantly, most of the reactions were highly efficient and clean, leading to the formation of pure products in yields ranging from very high to excellent, which were then obtained in pure form through a simple washing of the crude product with a small amount (2 × 2 mL) of cold ethanol.

Subsequently, we examined the scope and limitations of the hydroamination of secondary amines with ynamides (Table 3). Interestingly, we observed that unlike primary amines, secondary amines underwent a highly regio- and stereoselective anti-hydroamination with ynamides under the same optimized conditions. Initially, *N*-methylaniline **4a** was reacted with **1a** under optimized conditions, resulting in the formation of (*E*)-*N*-benzyl-*N*-(1-(methyl(phenyl)amino)-2-phenylvinyl)benzenesulfonamide (**5aa**) with a yield of 84% and an excellent *E/Z* ratio of >99 : 01 (exclusively *E*-stereoselectivity). The

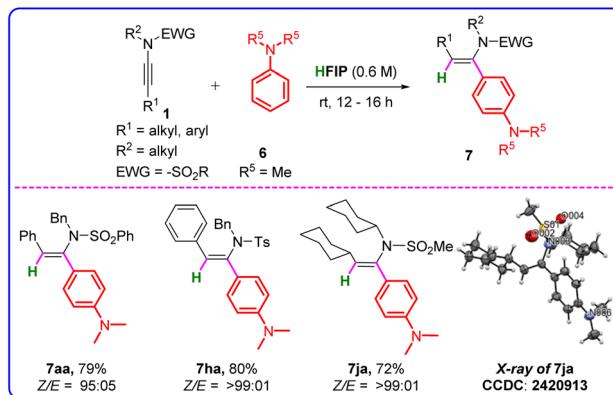


Table 3 Anti-selective hydroamination of ynamides with secondary amines<sup>a,b</sup>

<sup>a</sup> Reaction conditions: **1** (0.3 mmol), **4** (0.3 mmol), HFIP (0.6 M), rt. <sup>b</sup> Yield of the isolated product is reported. <sup>c</sup> No column chromatographic purification.

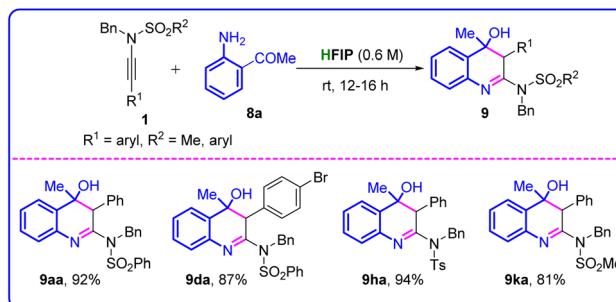
structure of **5aa** was confirmed by X-ray crystal structure determination (Fig. S2 and Table S1, SI). Various substituted ynamides (both aryl and alkyl ynamides), *i.e.*, **1b**, **1h**, and **1j**, smoothly participated in the reaction with *N*-methyl aniline (**4a**), resulting in the desired products (**5ba**, **5ha**, **5ja**) with good to excellent yields ranging from 83% to 93% and good to excellent *E*-stereoselectivity (*E/Z* = 80 : 20 to >99 : 1). Diphenylamine (**4b**) also successfully participated in the reaction with **1a**, producing the desired product (**5ab**) in 88% yield, and exclusive *E*-stereoselectivity (*E/Z* > 99 : 01). Notably, most of the reactions of ynamides with secondary amines were clean, and pure products were obtained by the simple cold ethanol washing of the crude product. In our efforts to broaden the substrate scope

of the hydroamination of ynamides, we employed tertiary amines to react with ynamides under the optimized conditions, and the results are presented in Table 4. *N,N*-Dimethylaniline (**6a**) underwent *syn*-selective hydroarylation at its *para* position with ynamide **1a**, leading to the formation of the target compound, (*Z*)-*N*-benzyl-*N*-(1-(4-(dimethylamino)phenyl)-2-phenylvinyl)benzenesulfonamide (**7aa**), with a 79% yield and excellent *Z*-stereoselectivity (*Z/E* = 95 : 05). Both aromatic (**1h**) and aliphatic ynamides (**1j**) smoothly underwent the hydroarylation reaction with **6a** to afford the desired products **7ha** and **7ja** in good yields (72–80%) and excellent stereoselectivity (*Z/E* > 99 : 1).

Table 4 *Syn*-selective hydroarylation of ynamides with tertiary aromatic amines<sup>a,b</sup>

<sup>a</sup> Reaction conditions: **1** (0.3 mmol), **6** (0.3 mmol), HFIP (0.6 M), rt. <sup>b</sup> Yield of the isolated product is reported.



Table 5 Cycloaddition of ynamides with 2-aminoaryl carbonyls<sup>a,b</sup>

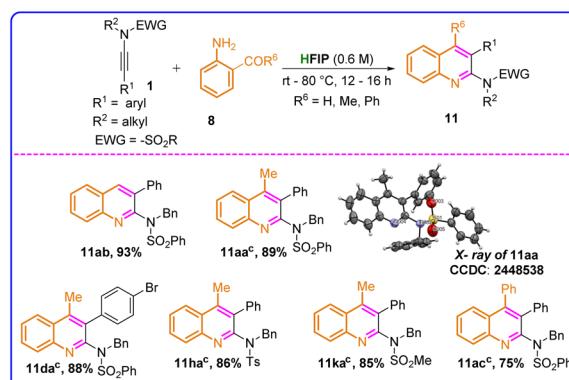
<sup>a</sup> Reaction conditions: **1** (0.3 mmol), **8** (0.3 mmol), HFIP (0.6 M), rt. <sup>b</sup> Yield of the isolated product is reported.

The structure of **7aj** was confirmed by X-ray crystal structure determination (Fig. S3 and Table S1, SI).

Under the optimized conditions, 2-aminocarbonyls **8** underwent cycloaddition reaction rather than a hydroamination reaction. We then examined the scope of ynamides **1** for the cycloaddition reactions (Table 5). Ynesulfonamide **1a** smoothly underwent the cycloaddition reaction with 1-(2-aminophenyl)ethan-1-one (**8a**) to furnish the desired product *N*-benzyl-*N*-(4-hydroxy-4-methyl-3-phenyl-3,4-dihydroquinolin-2-yl)benzenesulfonamide **9aa** in an excellent yield, 93%. The mild electron-withdrawing (–Br) group-substituted aryl-ynesulfonamides (**1d**) also reacted with **8a** without any difficulties to furnish the desired product **9da** in 87% yield. Upon substituting electron-withdrawing groups (EWG) such as –Ts and –Ms in ynesulfonamides, the reaction proceeded efficiently, yielding the desired products (**9ha**–**9ka**) with excellent yields ranging from 81% to 94%.

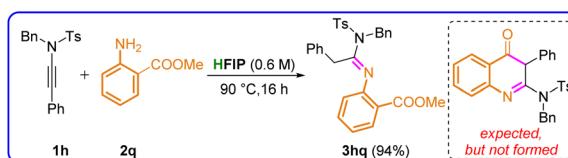
The synthesis of highly functionalized heterocycles in a single step is always challenging and has drawn significant interest from synthetic organic chemists. Ynamide chemistry is an excellent platform to construct different kinds of

heterocycles in a single step.<sup>18</sup> Among all heterocycles, 2-aminoquinolines represent a significant class of heterocycles, known for their valuable medicinal properties.<sup>19</sup> The synthesis of 2-aminoquinolines in a single step through a sustainable approach is highly desirable. When 2-aminobenzaldehyde was reacted with ynamide **1** under the optimized conditions, we unexpectedly obtained an aromatized cyclic product, specifically, a substituted 2-aminoquinoline (Table 6). Phenyl-substituted ynesulfonamide, *i.e.*, *N*-benzyl-*N*-(4-bromophenyl)ethynylbenzenesulfonamide **1d**, reacted with 1-(2-aminophenyl)ethan-1-one **8a** to furnish *N*-benzyl-*N*-(4-methyl-3-phenylquinolin-2-yl)benzenesulfonamide **11da** in 88% yield. Under optimized conditions, the reaction of 1-(2-aminophenyl)ethan-1-one (**8a**) with ynamide (**1a**) initially yielded a non-aromatized product. Upon heating the reaction mixture at 80 °C for 5 hours, the final desired product, *N*-benzyl-*N*-(4-methyl-3-phenylquinolin-2-yl)benzenesulfonamide (**11aa**), was obtained in an 89% yield. The structure of **11aa** was confirmed by X-ray crystal structure determination (Fig. S4 and Table S1, SI). Upon substituting electron-withdrawing groups (EWG) such as –Ts and –Ms in ynesulfonamides, the reaction proceeded

Table 6 Quinoline synthesis<sup>a,b</sup>

<sup>a</sup> Reaction conditions: **1** (0.3 mmol), **10** (0.3 mmol), HFIP (0.6 M), rt. <sup>b</sup> Yield of the isolated product is reported. <sup>c</sup> The reaction mixture was heated at 80 °C.



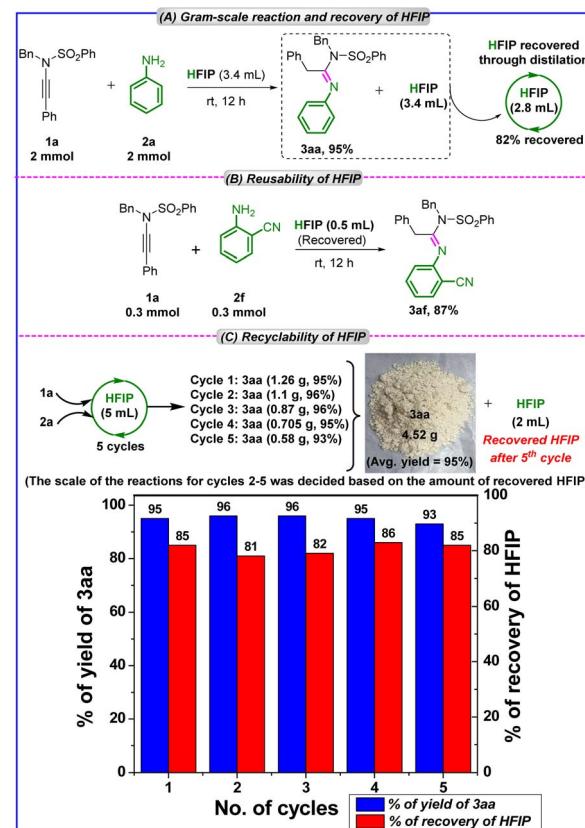


Scheme 2 Reaction between ynamide (**1h**) and methyl 2-amino benzoate (**2q**) in the presence of HFIP.

efficiently, affording the desired products (**11ha**–**11ka**) with excellent yields ranging from 85% to 86%. (2-Amino-phenyl)(phenyl)methanone (**8c**) also underwent the reaction with ynamide (**1a**) and produced the desired product, *N*-benzyl-*N*-(3,4-diphenylquinolin-2-yl)benzenesulfonamide (**11ac**), in good yield (75%).

We then explored the feasibility of the cycloaddition reaction of ynamides **1** with *ortho*-aminobenzoic acid esters for the potential synthesis of 2-amidoquinolin-4(3*H*)-one. When yne-sulfonamide **1h** was treated with methyl 2-aminobenzoate (**2q**), the reaction did not proceed as anticipated, and we observed the formation of the hydroamination product only, **3hq**, in 94% yield without the formation of the expected cycloaddition product, suggesting that HFIP could not effectively activate the ester carbonyl group, which is required for cyclization (Scheme 2).

To demonstrate the potential application of our green synthetic protocol, we developed a one-pot, direct synthetic strategy to access highly substituted 2-amidoindoles, a highly potent and biologically active class of molecules, starting from easily accessible ynamides and anilines (Table 7). In the presence of HFIP, **1a** and aniline furnished the desired product **3aa** in almost quantitative yield. After the evaporation of HFIP,  $\text{CuCl}_2$  and THF were added to the same pot, and the reaction mixture was heated at 100 °C, which furnished the desired highly substituted 2-amidoindole, *i.e.*, *N*-benzyl-*N*-(3-phenyl-1*H*-indol-2-yl)benzenesulfonamide **12aa** in 76% yield. The one-pot direct synthesis of indole from ynamides and aniline was found to be efficient, and the electronic effect of ynamides and substituted anilines did not affect the outcome, resulting in various 2-amidoindoles **12aa**–**12aj** in good to excellent yields

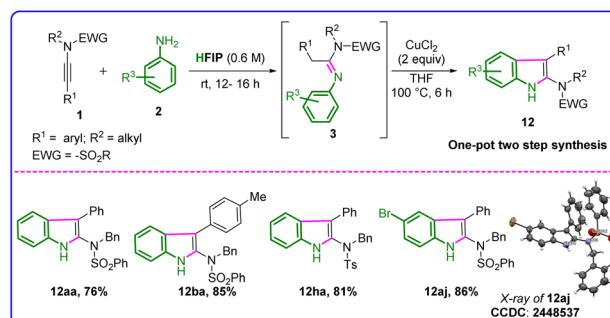


Scheme 3 (A) Scale-up batch reaction and recovery of HFIP. (B) Reusability of HFIP. (C) Recyclability of HFIP.

(76–86%). The structure of **12aj** was confirmed by X-ray crystal structure determination (Fig. S5 and Table S1, SI).

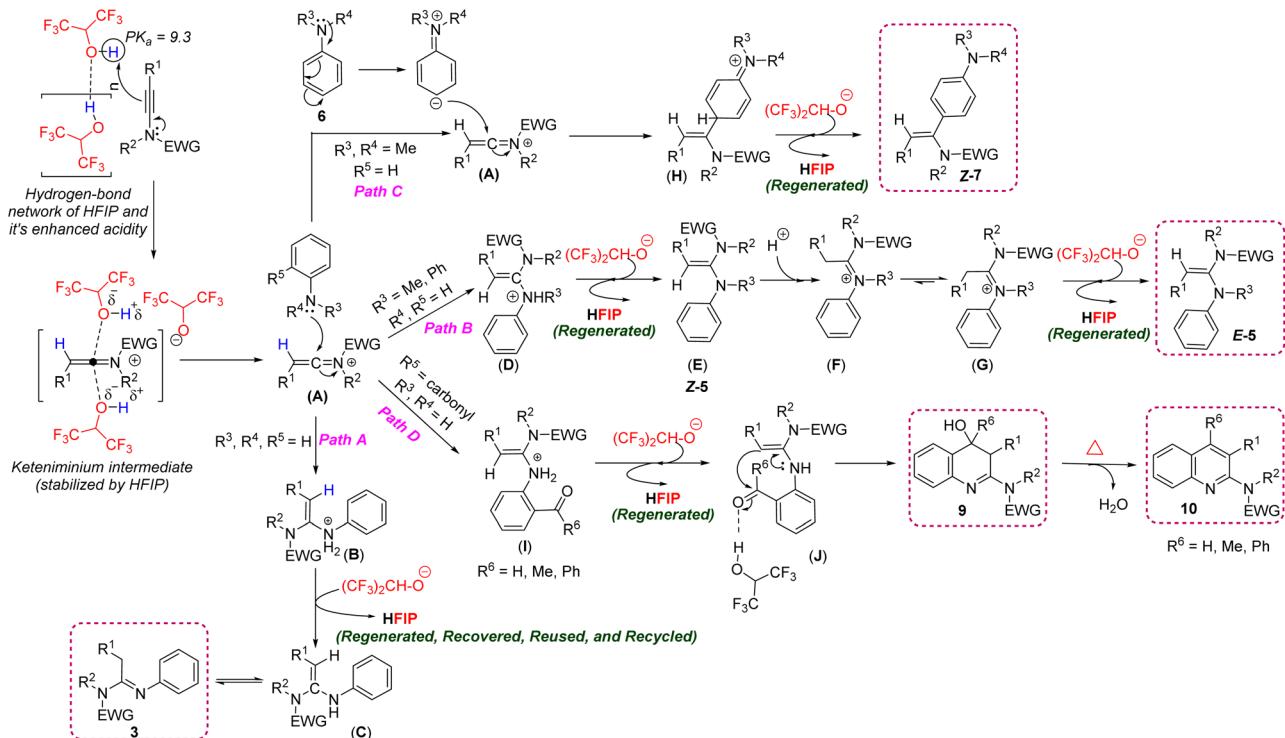
To demonstrate the practicality of our developed protocol, we conducted the model reaction between **1a** and **2a** on a gram scale (2 mmol scale), successfully obtaining the desired final product without sacrificing yield (Scheme 3A). Upon completion of the reaction, the solvent was recovered *via* distillation at 50 °C under 400 mbar pressure. The recovery process was efficient, yielding 2.8 mL of HFIP (82% recovery). To demonstrate the reusability of the recovered HFIP, we conducted the reaction

Table 7 One-pot, two-step synthesis of 2-aminoindoles<sup>a,b</sup>



<sup>a</sup> Reaction conditions: **1** (0.3 mmol), **2** (0.3 mmol), HFIP (0.6 M), rt;  $\text{CuCl}_2$  (2 equiv.), THF (2 mL). <sup>b</sup> Yield of the isolated product is reported.





**Scheme 4** Plausible reaction mechanisms for the synthesis of acetimidamides (path A), ketene *N,N*-acetals (path B),  $\alpha$ -arylenamides (path C), and quinolines (path D), from ynamides and various anilines using HFIP only.

between **1a** and **2f** with the recovered HFIP, and the desired product, (*E*)-*N*-benzyl-*N'*-(2-cyanophenyl)-2-phenyl-*N*-(phenylsulfonyl)acetimidamide (**3af**), was obtained with reproducible yields of 87% (Scheme 3B). We also assessed the recyclability of HFIP by conducting a reaction between **1a** and **2a** on a 3 mmol scale using 5 mL of HFIP (Scheme 3C). After the completion of the reaction, we could recover 4.25 mL of HFIP (85% recovery) and reused it for the second cycle reaction (2.5 mmol scale reaction), which afforded **3aa** in 96% yield. After completing the second cycle, we recovered 3.44 mL of HFIP (81% recovery) and reused it for the third cycle reaction (2.06 mmol scale reaction), which afforded **3aa** in 96% yield. After completing the third cycle, we recovered 2.82 mL of HFIP (82% recovery) and reused it for the fourth cycle reaction (1.69 mmol scale reaction), which afforded **3aa** in 95% yield. After completing the fourth cycle, we recovered 2.42 mL of HFIP (86% recovery) and reused it for the fifth cycle reaction (1.45 mmol scale), which afforded **3aa** in 93% yield. After completing the fifth cycle, we recovered 2 mL of HFIP (85% recovery).

Notably, the recyclability of HFIP was found to be effective and efficient, as 4.52 g of **3aa** was synthesized in a total of five cycles with a reproducible yield of **3aa** in each cycle (average yield = 95%). These outcomes demonstrate the high sustainability, circular economy, practicality and cost-effectiveness of our protocol.

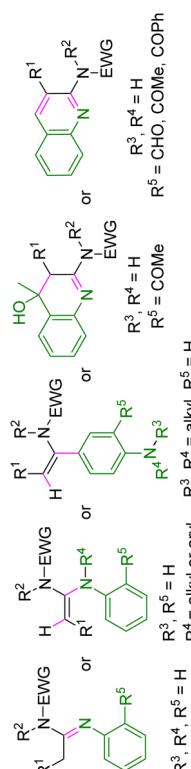
Based on previous literature reports on ynamide chemistry,<sup>4b,d</sup> the plausible mechanisms for this HFIP-mediated hydroamination and cycloaddition reaction are shown in Scheme 4. The H-bond network in HFIP, by increasing its acidity ( $pK_a = 9$ ), enables the activation of an ynamide via

regioselective protonation at its  $\beta$ -carbon, generating the reactive keteniminium ion intermediate **A**. For the HFIP-mediated hydroamination of ynamides with primary aromatic amines (path A), the *in situ*-generated **A** was subsequently trapped by the nitrogen atom of aromatic amines to afford **B**. Further deprotonation of **B** yielded **C**, which ultimately tautomerized to furnish the final product **3**. Similarly, for the hydroamination of ynamides with secondary aromatic amines, the keteniminium ion **A** was trapped by the nitrogen atom of the secondary aromatic amine **4** from the less hindered side of **A** to give **D** (path B). Subsequent deprotonation of species **D** produced **Z-5**, which is thermodynamically disfavored in most cases, and under the reaction conditions, it was easily converted to the thermodynamically stable product **E-5** via the intermediate **F** and **G**. Likewise, in the HFIP-mediated hydroarylation of ynamides with tertiary aromatic amines (path c), the resulting keteniminium ion **A** was trapped by the regioslective *para*-attack of the aromatic amines to yield intermediate **H**, followed by deprotonation to afford **Z-7**. Analogously, during the HFIP-mediated cycloaddition of ynamides with 2-amino aryl carbonyls (path d), the keteniminium ion is trapped by the amino nitrogen in 2-aminoaryl carbonyl **8** to produce **I**, which is then deprotonated to give **J**. At the same time, the carbonyl group is activated by HFIP, increasing the electrophilicity of carbon. Due to tautomerism, the electron density on the  $\beta$ -carbon increases, which favours intramolecular cyclization, yielding the cyclized product **9**, which is subsequently dehydrated to give **10**.

To have a better understanding of the overall sustainability of our developed protocol with respect to the previously



Table 8 Detailed comparison of previous works with this work

Research work	Starting material (required in excess)	Catalyst or reagent	Solvent	Temp. (°C)	Scope of amines	Synthesis of products	Yield (avg. Yield)	E-factor (g waste/g product) <sup>a,b</sup>	Catalyst or reagent recovery	Circular economy	Cost of the catalyst or reagent (1 g)
											
Ref. 7	—	(PPh <sub>3</sub> ) <sub>2</sub> AuNTf <sub>2</sub>	DCM	rt	Only 1°-anilines	Acetimidamides	89-98% (94%)	5.69	Difficult	Low	\$ 284.2
Ref. 8 (Cai)	Aniline (1.1 eq.)	Ph <sub>2</sub> P-MCM-41-AuCl, AgNTf <sub>2</sub> , Zn(Orf) <sub>2</sub>	DCM	rt	Only 1°-anilines	Acetimidamides	87-97% (92%)	3.56	Effective	High	\$ 340.7
Ref. 9 (Wei)	Ynamide (1.5 eq.)	Yb(OTf) <sub>3</sub>	Toluene	80	Only 1°-anilines	Acetimidamides	50-93% (68%)	25.1	Difficult	Low	\$ 9.3
Ref. 10 (Wu)	Aniline (2 eq.)	DCE	85	Only 1°-anilines	Acetimidamides	39-89% (75%)	21.3	Difficult	Low	\$ 27.1	
Ref. 11	Aniline (1.2 eq.)	TfOH	DCE	rt	Only 1°- and 2°-anilines	Acetimidamides and 2ketene N,N-acetals	65-99% (88%)	6.56	Difficult	Low	\$ 19.4
Ref. 12 (Lin)	Ynamide (1.5 eq.)	Ni(Orf) <sub>2</sub>	Toluene	80	Only 2°-amines	Ketene N,N-acetals	54-92% (72%)	10.7	Difficult	Low	\$ 24.8
Ref. 13 (Lin)	Ynamide (2.0 eq.)	AgNTf <sub>2</sub>	CHCl <sub>3</sub>	60-70	Only 3°-amines	α-Aryl enamides	52-90% (72%)	19.9	Difficult	Low	\$ 147.7
Ref. 14 (Dubovtsev)	—	PPh <sub>3</sub> AuCl/AgNTf <sub>2</sub> (extra 10 mol% MsOH required for ketones)	DCE	60	Only <i>ortho</i> carbonyl anilines	Quinolines	54-98% (77%)	13.1	Difficult	Low	PPh <sub>3</sub> AuCl (\$ 316) AgNTf <sub>2</sub> (\$ 148)
Ref. 18a (Youn)	Ynamide (1.2 eq.)	ZnBr <sub>2</sub>	Toluene	140	Only <i>ortho</i> carbonyl anilines and phenols	Quinolines and coumarins	84-95% (89%)	24.1	Difficult	Low	\$ 9.5
<b>This work</b>	—	<b>HFP</b>	<b>rt</b>		<b>1°, 2°, 3°-Amines, 1°-hetero aromatic amines, <i>ortho</i> amino</b>	<b>Acetimidamides, Ketene N,N-acetals, α-aryl enamides, quinolines, and 4-benzaldehydes, and hydroxy-3,4-dihydroquinolines</b>	<b>72%-96% (89%)</b>	<b>0.98-1.27</b>	<b>Easy and effective</b>	<b>High</b>	<b>\$ 0.5</b>

<sup>a</sup> For the *E*-factor calculation, the reaction which furnished the highest yield of product was considered. <sup>b</sup> solvent was considered for the *E*-factor calculation.

reported ones, we enlisted a detailed comparison of various parameters in Table 8, such as the requirement of the starting material being in excess, catalyst, and/or reagents, solvent, reaction temperature, scope of amines, synthesis of products, yield, *E*-factor, feasibility of the recovery of catalyst or reagent, cost of the catalyst or reagent (cost-effectiveness), and circular economy. This analysis revealed that our protocol is simpler, and more general, cost-effective, practical, sustainable, and environmentally benign, with a broader substrate scope, and has a significantly higher circular economy compared to previously reported protocols. Moreover, the stereoselectivity of this protocol was found to be superior to that of a few previously reported ones.

## Conclusions

The atom-economic, highly regio- and stereo-selective hydroamination of ynamides with primary, secondary, and tertiary aromatic and heteroaromatic amines has been successfully achieved under mild and sustainable reaction conditions. This sustainable protocol yields a wide variety of valuable products, including acetimidamides, ketene *N,N*-acetals, and  $\alpha$ -arylenamides, as well as various heterocycles such as quinolines and 3,4-dihydroquinolin-4-ols, starting from readily available ynamides involving all kinds of aromatic amines (1°, 2°, and 3°). This protocol is workup-free, and most of the pure final products were obtained through a simple organic washing using a small amount of ethanol. The scalability of the protocol is straightforward up to a gram-scale level without compromising reaction yields. The only species used in the reaction, except for the starting materials, was HFIP, which played a crucial dual role as both the activator of the ynamide and the stabiliser of the *in situ*-generated keteniminium ion, and was regenerated after the reaction. HFIP was recovered effectively through simple distillation and reused for another reaction without losing its properties. HFIP was also recycled efficiently for five consecutive reactions between **1a** and **2a**, and thus, 4.52 g of **3aa** was produced with a reproducible yield in each cycle (average yield = 95%), synthesised in five consecutive batches of reactions involving recycled HFIP. These results indicate that the protocol is highly sustainable in the context of green chemistry. We also described the synthesis of 2-aminoindoles from commercially available aromatic amines. We believe this Diversity-Oriented Synthesis (DOS) will be useful for crafting more powerful small molecules in a more sustainable and cost-effective manner, thereby paving the way for advancements in pharmaceutical development and materials chemistry.

## Author contributions

A. N. V. Satyanarayana carried out all the experiments, including optimization of the reaction conditions, synthesis of products, their synthetic diversifications, and mechanistic studies. T. Chatterjee conceived and supervised the work and wrote and edited the manuscript. All authors have given their approval to the manuscript's final version.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

CCDC 2420474, 2420911, 2420913, 2448538 and 2448537 contain the supplementary crystallographic data for this paper.<sup>20a–e</sup>

The data underlying this study are available in the published article, and its experimental and spectroscopic details are included as a part of the online supplementary information (SI). Supplementary information: experimental procedures, X-ray data, analytical data of the synthesized molecules, and  $^1\text{H}$ ,  $^{13}\text{C}$ , NOE spectra of the synthesized compounds. See DOI: <https://doi.org/10.1039/d5su00899a>.

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