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# Copper-catalyzed room-temperature cross-dehydrogenative coupling of secondary amides with terminal alkynes: a chemoselective synthesis of ynamides†

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A copper-catalyzed aerobic oxidative cross-dehydrogenative coupling reaction between secondary amides and terminal alkynes has been developed. With the aid of ligands and 3 Å molecular sieves, ynamides can be efficiently synthesized at room temperature and conveniently scaled up. A legitimate mechanism involving nitrogen-centred radicals and copper trivalent intermediates has been proposed.

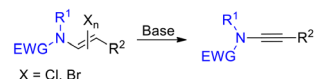
## Introduction

Ynamides are highly versatile synthetic building blocks. Despite that their first preparation was accomplished by Viehe and coworkers half a century ago,<sup>1</sup> the extensive utility of ynamides in organic synthesis has been realized only recently and the field continues to stimulate high research interest. Ynamides can serve as precursors of keteniminium salts<sup>2</sup> and  $\alpha$ -imino-metal carbenes,<sup>3</sup> and pave the foundation for a number of novel ynamide-mediated addition reactions,<sup>4</sup> annulation (cycloaddition and cycloisomerization) reactions,<sup>5</sup> metal-catalyzed cross-coupling reactions,<sup>6</sup> and free radical reactions.<sup>7</sup> In addition, useful synthetic reagents can be designed based on the unique reactivity of ynamides, as demonstrated recently by Zhao's group with their efficient and mild racemization-free coupling reagents for the synthesis of amides and peptides.<sup>8</sup> Structurally diverse ynamides serve as a crucial foundation for the advancement of ynamide chemistry. The synthesis of such compounds has attracted significant attention, leading to the development of a series of methods<sup>9</sup> that can be classified into three main categories: the elimination reaction of halogenated enamides (Scheme 1-1), copper-catalyzed (mediated) coupling reaction of halogenated olefins with amides (Scheme 1-2), and copper-catalyzed (mediated) coupling reaction of alkynes or alkyne derivatives with amides (Scheme 1-3). However, these reactions either require harsh

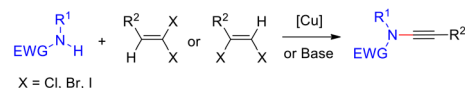
conditions, inconvenient starting materials, or a large excess of coupling partners. The development of greener, safer, more economical and efficient synthesis methods for ynamides remains a challenging topic.

Cross-dehydrogenative coupling (CDC) represents a class of atom- and step-economical methods.<sup>10</sup> The copper-catalyzed or -mediated CDC reaction of terminal alkynes and amides under an oxygen atmosphere is a highly effective strategy for the synthesis of ynamides,<sup>11</sup> owing to the direct use of readily available terminal alkynes and amides as substrates. However,

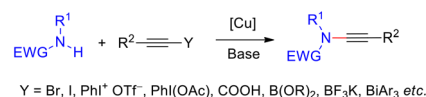
1) Synthesis of ynamides via elimination of halogen enamides:



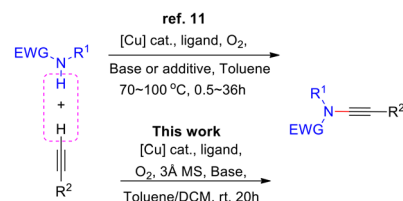
2) Synthesis of ynamides via cross coupling of amides with dihalogen alkenes:



3) Synthesis of ynamides via cross coupling of amides with substituted alkynes:



4) Synthesis of ynamides via CDC reaction of amides with alkynes:



Scheme 1 Synthesis of ynamides.

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the low reactivity of these substrates necessitates heating for these reactions to occur, leading to undesired alkyne homo-coupling dimers. On the other hand, the mechanism of this reaction remains elusive. Therefore, there is an urgent need for improving the chemoselectivity of this reaction toward ynamides and gaining further insight into its mechanism. Here, we report a facile synthesis of ynamides through a copper-catalyzed CDC reaction of terminal alkynes and amides under an oxygen atmosphere (Scheme 1-4). Promoted by ligands and 3 Å molecular sieves, the reaction can proceed smoothly at room temperature, potentially involving nitrogen-centred radicals and Cu(III) complexes as key intermediates.

## Results and discussion

### Copper-catalyzed CDC reaction of terminal alkynes and amides

Our investigation into the CDC protocol commenced with the optimization of the model reaction between *N*-methyl-*p*-toluenesulfonamide **1a** and phenylacetylene **2a**. It was observed that many copper(II) salts exhibit catalytic activity in the presence of an oxygen atmosphere. After examining several types of ligands, 1-methylbenzimidazole was found to provide the desired ynamide **3aa** with an excellent yield at room temperature. Interestingly, we discovered that molecular sieves are an indispensable additive to promote this reaction, and 3 Å molecular sieves gave the optimal results. Other optimization studies involving bases and solvents were performed (see ESI Tables S1–4†). Finally, the CDC reaction of *N*-methyl-*p*-toluenesulfonamide **1a** (3.0 equiv.) and phenylacetylene **2a** (1.0 equiv.) was conducted using Cu(OTf)<sub>2</sub> (0.2 equiv.) as the catalyst and 1-methylbenzimidazole (0.4 equiv.) as the ligand in the presence of 3 Å molecular sieves (360 mg for 1.0 mmol of alkyne) in toluene (0.25 M), under an oxygen atmosphere at room temperature for 20 hours, resulting in the desired ynamide **3aa** with 93% yield (Table 1, entry 1). In the absence of the ligand or molecular sieve additive, the reaction failed to provide any

detectable product (Table 1, entries 2–4). Other solvents such as dichloromethane led to diminished yields (Table 1, entry 5).

With these optimized conditions in hand, we next investigated the scope of terminal alkynes. As demonstrated in Table 2, CDC reactions of aryl, alkyl and silyl monosubstituted acetylenes (**2a–2o**) with *N*-methyl-*p*-toluenesulfonamide **1a** gave the desired ynamides (**3aa–3ao**) in moderate to good yields (57–93%). For *para*-substituted aromatic terminal alkynes, both electron-donating and electron-withdrawing groups gave the corresponding ynamides in high yields of 80–93% (**3aa–3ag**). Sterically more demanding *ortho*- and *meta*-substituted aromatic terminal alkynes provided diminished yields of 57–69% (**3ah–3ak**). Additionally, the reaction conditions are also suitable for aliphatic and heterocyclic terminal alkynes, affording the desired ynamides in 73–75% yields (**3al–3ao**). Notably, for cyclopropyl and silyl-substituted terminal alkynes, higher yields (**3am** and **3an**: 71% and 75%) were obtained when dichloromethane was used as solvent instead of toluene (**3am** and **3an**: 45% and 55%), and no discernible dimerization byproducts of alkyne were observed. Notably, this mild protocol enables the synthesis of thermolabile ynamides **3ap** and **3aq**. To our satisfaction, a gram-scale synthesis of **3aa** was achieved in 83% yield from 5.0 mmol of alkyne **2a** by following the standard procedure.

We also explored the scope of amides bearing various electron-withdrawing protecting groups on the nitrogen. In general, the CDC reactions between most secondary amides and phenylacetylene **2a** can provide the corresponding ynamides smoothly (Table 3), even for very low reactive  $\gamma$ -lactams (**3ha–3ja**).<sup>11d</sup> However, the reaction does not occur with primary amides like *p*-toluenesulfonamide. For secondary amides or alkynes that exhibit poor solubility in toluene, switching the solvent to dichloromethane (**3ba** and **3ma**), a 1 : 1 mixture of toluene and dichloromethane (**3ca**, **3da**, **3ea**,

Table 1 Control experiments

Entry	Variation from standard conditions	Yield <sup>a</sup> (%)
1		93
2	No ligand	0
3	No 3 Å molecular sieves	0
4	Anhydrous silica gel/MgSO <sub>4</sub> instead of 3 Å MS	0
5	DCM instead of toluene	72

<sup>a</sup> Isolated yield.

Table 2 Copper-catalyzed CDC reaction of sulfonamide **1a** and terminal alkynes<sup>a</sup>

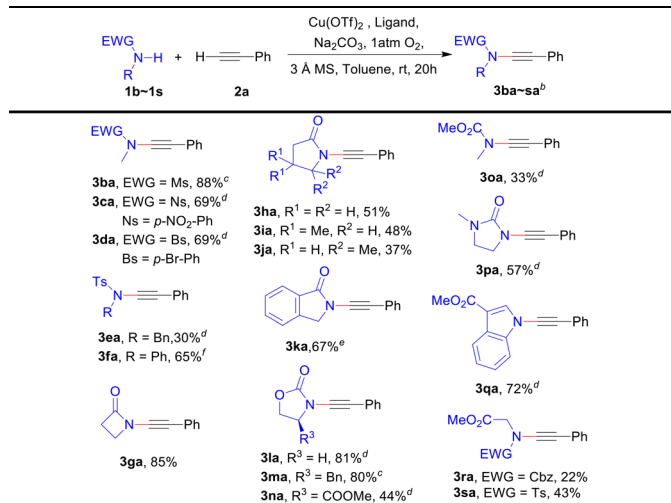
<b>3aa</b> , R' = H, 93%; <b>3ab</b> , R' = <i>p</i> -OMe, 93%; <b>3ac</b> , R' = <i>p</i> -CF <sub>3</sub> , 90%; <b>3ad</b> , R' = <i>p</i> -F, 80%; <b>3ae</b> , R' = <i>p</i> -Cl, 88%; <b>3af</b> , R' = <i>p</i> -Br, 91%; <b>3ag</b> , R' = <i>p</i> -COOMe, 87%; <b>3ah</b> , R' = <i>o</i> -OMe, 57%; <b>3ai</b> , R' = <i>o</i> -CF <sub>3</sub> , 69%; <b>3aj</b> , R' = <i>m</i> -OMe, 61%; <b>3ak</b> , R' = <i>m</i> -d/CF <sub>3</sub> , 64%	<b>3al</b> , 73%; <b>3am</b> , 75% <sup>c</sup> <b>3an</b> , 71% <sup>c</sup>	<b>3ao</b> , 74%; <b>3ap</b> , 57% <sup>c</sup> <b>3aq</b> , 58% <sup>d</sup>

<sup>a</sup> General method: amide (1.5 mmol), 1-methylbenzimidazole (0.2 mmol), Cu(OTf)<sub>2</sub> (0.1 mmol), Na<sub>2</sub>CO<sub>3</sub> (1.5 mmol), and 3 Å molecular sieves (180 mg) were dissolved in dry solvent (2.0 mL) and the terminal alkyne (0.5 mmol) was successively added. The mixture was stirred at room temperature for 20 h under an oxygen atmosphere.

<sup>b</sup> Isolated yield. <sup>c</sup> Solvent: DCM. <sup>d</sup> Solvent: toluene : DCM = 1 : 1.



When using *N*-methyl methylsulfonamide **1b** as a secondary amide substrate, either electron-rich or electron-deficient aromatic terminal alkynes, as well as alkyl-/silyl-substituted terminal alkynes can undergo CDC reactions with satisfactory yields, the same as for the secondary amide substrate 2-oxazolidinone **1l** (**3lb–3lr**). Notably, thermolabile ynamides **3lp** and **3lq** can also be prepared in moderate yields (79% and 42%). Compared with **1l**, more sterically hindered (*S*)-4-benzyl-2-oxazolidinone **1m** or (*R*)-4-methylester-2-oxazolidinone **1n** provided diminished reaction yields (**3lb–r** vs. **3mb–3nc**). With poorly active  $\gamma$ -lactams **1h** and **1i** and glycine derivative **1s** coupling with terminal alkynes can also give the desired products (**3hm**, **3ib–3im** and **3sb–3sm**). Interestingly, electron-deficient aromatic alkyne **2c** can provide higher yields than the electron-rich aromatic alkyne **2b** (**3ib** vs. **3ic** and **3sb** vs. **3sc**). Satisfactorily, a gram-scale synthesis of **3bn** was performed with an 88% yield from 6.0 mmol of **2n**.

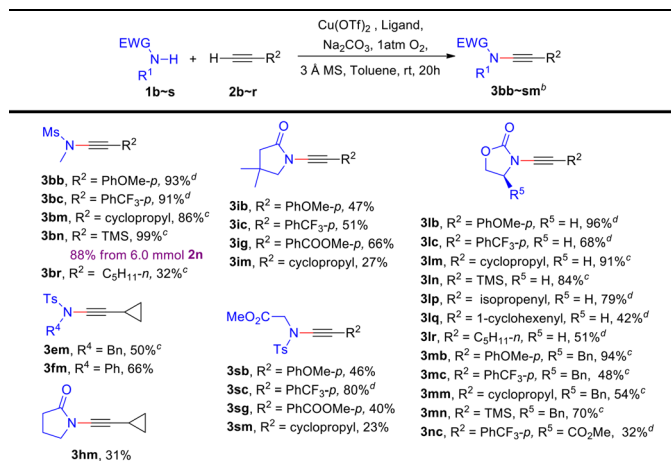


<sup>a</sup>General method. <sup>b</sup>Isolated yield. <sup>c</sup>Solvent: DCM. <sup>d</sup>Solvent: toluene : DCM = 1 : 1. <sup>e</sup>Solvent: THF. <sup>f</sup>Na<sub>2</sub>HPO<sub>4</sub> instead of Na<sub>2</sub>CO<sub>3</sub>.

**3la**, **3na**, **3oa**, **3pa** and **3qa**), or tetrahydrofuran (**3ka**) can result in improved yields. Additionally, base is a significant factor in some cases. For instance,  $\text{Na}_2\text{HPO}_4$  as a base resulted in a higher yield of ynamide **3fa** compared to  $\text{Na}_2\text{CO}_3$  (65% vs. 45%), which suggests that the deprotonation of amides may be crucial. Notably, *N*-Cbz and Ts glycine methyl esters can also be used to obtain the corresponding ynarnides **3ra** and **3sa**.

Moreover, we conducted a more comprehensive investigation into the CDC reactions of various amides and terminal alkynes under the general conditions. Table 4 demonstrates the favourable applicability of this protocol towards a wide range of ynamides in moderate to high yields (23%–99%).

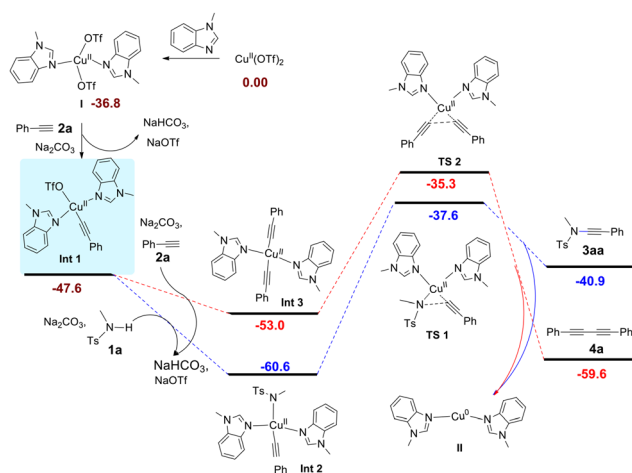
**Table 4** Copper-catalyzed CDC reaction of amides and terminal alkynes<sup>a</sup>



<sup>a</sup>General method. <sup>b</sup>Isolated yield. <sup>c</sup>Solvent: DCM. <sup>d</sup>Solvent: toluene : DCM = 1 : 1.

### Mechanistic studies of the copper-catalyzed CDC reaction

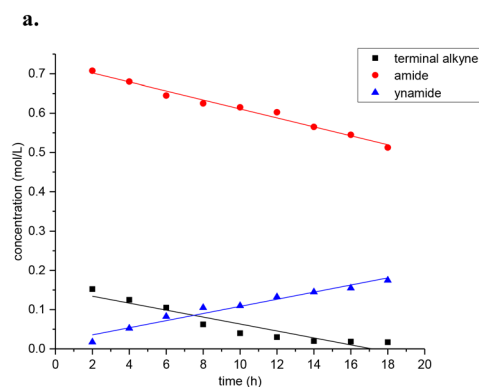
After establishing the broad substrate scope of this transformation, we next turned our attention to mechanistic investigations, and a plausible reaction mechanism was established with the aid of density functional theory (DFT) calculations. As listed in Fig. 1, Cu(II) complex **I** is taken as the starting point of this reaction, which is formed from Cu(OTf)<sub>2</sub> and two 1-methylbenzimidazoles. Complex **I** then reacts with terminal alkyne **2a** in the presence of a base to generate the copper alkyne intermediate **Int1**, which further forms Cu(II) complex **Int2** (−60.6 kcal mol<sup>−1</sup>) upon interaction with an amide anion [the formation of the homo-coupling precursor **Int3** from **Int1** is less favorable (−53.0 kcal mol<sup>−1</sup>)]. However, the reductive elimination of **Int2** towards ynamide **3aa** requires a relatively high activation barrier (*via* **TS1**,  $\Delta G^\ddagger = 23.0$  kcal mol<sup>−1</sup>), which is not in agreement with the facile product formation at room temperature.



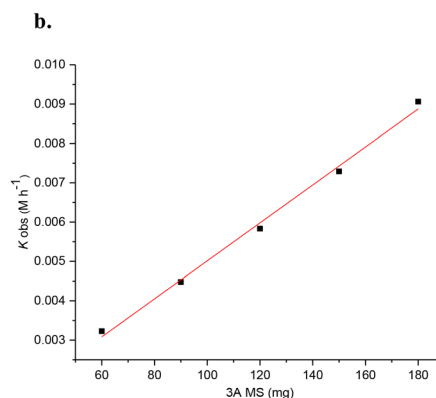
**Fig. 1** DFT calculations on the assumed Cu(II)-mediated CDC process (the values shown are relative free energies in kcal mol<sup>-1</sup>).

Alternatively, we assumed that **Int2** undergoes single-electron oxidation with a nitrogen-centred radical<sup>12</sup> generated by the synergistic oxidative system of copper complex, 3 Å molecular sieves and oxygen prior to reductive elimination. Indeed, DFT calculations indicated that after the nitrogen-centred radical **III** oxidizes the Cu(II) intermediate **Int2** to the thermodynamically stable Cu(III) intermediate **Int4**, the reductive elimination towards ynamide **3aa** and Cu(I) complex **IV** has a much lower barrier of 12.6 kcal mol<sup>-1</sup>, and thus occurs at room temperature (Fig. 2, transition state **TS3**, for details see ESI Fig. S2–4†). However, the calculation results indicate that the reductive elimination of **Int5** towards the homo-coupling dimer of alkyne **4a** is a spontaneous process due to a very low activation barrier (transition state **TS5** cannot be located by DFT calculations, see ESI Fig. S6†). This seems to imply that the generation of ynamide **3aa** is not a feasible process. Considering the experimental results, the generation of nitrogen-centred radical **III** rather than the reductive elimination of Cu(III) intermediates **Int4** and **Int5** may be the rate-determining step of the reaction.

In order to verify the reaction mechanism described by DFT calculations and obtain a more comprehensive understanding of the impact of reaction substrates and molecular sieves on the CDC reaction, kinetic studies were conducted. As shown in Fig. 3a, the plots of [amide], [alkyne] and [ynamide] versus time gave three straight lines which indicates that the CDC reaction can be considered zero-order for secondary amide and terminal alkyne in the presence of excess of amides, and thus can be deemed a typical surface-catalyzed reaction (also see ESI Table S5 and Fig. S8†). Interestingly, when the amount of 3 Å MS was changed in the general conditions, a plot of  $k_{\text{obs}}$  versus [weight of 3 Å MS] also exhibits a linear relationship (Fig. 3b, also see ESI Table S6 and Fig. S9†). Additionally, since molecular sieves cannot be replaced with dry silica gel or anhydrous magnesium sulfate, and the promotional effect of 3 Å MS on the reaction surpasses that of 4 Å MS, the essential role of molecular sieves in the CDC reaction should be a promoter rather than a desiccant. According to the aforementioned, it can be reasonably inferred that the oxidation process of sec-

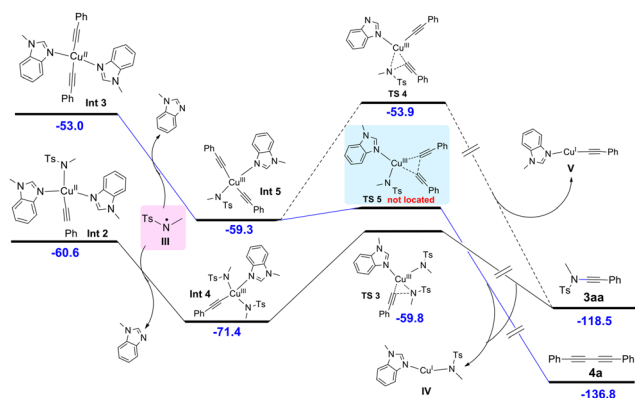


Reaction progress profiles for the CDC reaction between amide **1a** and alkyne **2g** to yield ynamide **3ag** under general conditions.



Apparent first-order reaction rate in 3 Å MS for the CDC reaction between amide **1a** and alkyne **2g** to yield ynamide **3ag** under general conditions.

**Fig. 3** Kinetic studies of the copper-catalyzed CDC reactions of acetylenes and amides under an oxygen atmosphere.



**Fig. 2** DFT calculations on the assumed Cu(III)-mediated CDC process (the values shown are relative free energies in kcal mol<sup>-1</sup>).

ondary amides to nitrogen-centred radicals occurs on the surface of molecular sieves and represents the rate-determining step. Therefore, the formation of the homo-coupling dimer **4a** from **Int5**, which is generated by nitrogen-centred radical oxidation of **Int3**, can be facilitated by the presence of small amounts of secondary amide **1a** (~6% **4a** obtained in the absence of **1a**). However, Cu(II) intermediate **Int2** will be overwhelmingly favored over **Int3** in the presence of excess amides, leading to the nitrogen-centred radical-mediated generation of Cu(III) intermediate **Int4** and ultimately resulting in ynamide **3aa** formation (Fig. 4, also see ESI Table S4 and Fig. S1, S5–7†).

On the basis of DFT calculations and kinetic studies, the reaction mechanism was postulated as follows (Fig. 5): Cu(II) complex **I** is initially formed from Cu(OTf)<sub>2</sub> and two 1-methylbenzimidazoles. This complex then reacts with terminal alkyne **2** in the presence of a base to generate copper alkyne intermediate **Int1**, which subsequently forms Cu(II) complex **Int2** upon interaction with amide **1** in the presence of a base. Furthermore, **Int2** undergoes single-electron oxidation with nitrogen-centred radical **III** generated by the [Cu(II)Ln-MS-O<sub>2</sub>]





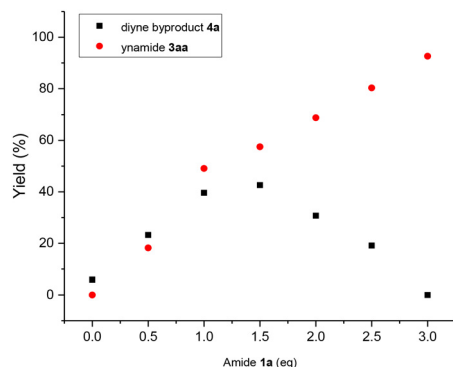


Fig. 4 The effect of amide loadings on the CDC reaction between amide **1a** and alkyne **2a** to yield ynamide **3aa** under general conditions.

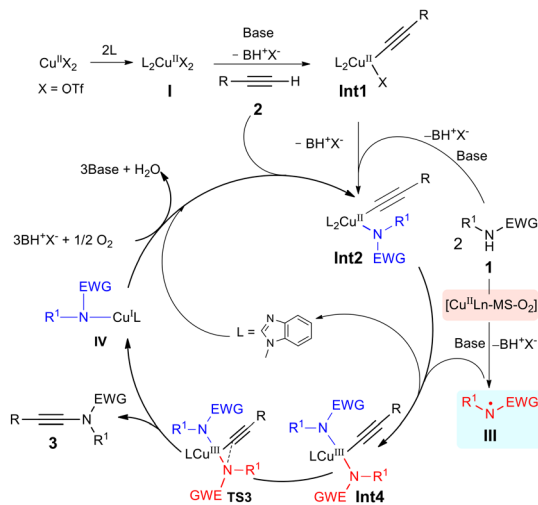


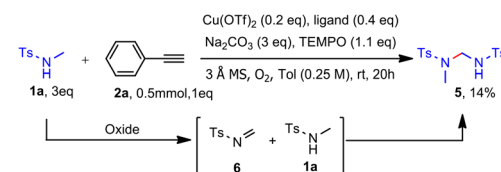
Fig. 5 Plausible mechanism for the CDC reaction of amides and terminal alkynes.

system to form Cu(III) intermediate **Int4**. The reductive elimination of **Int4** produces the desired ynamide **3** and Cu(I) complex **IV** via the transition state **TS3**. Finally, Cu(II) complex **Int2** is regenerated via aerobic oxidation of Cu(I) complex **IV** followed by ligand and alkyne coordination.

Notably, the involvement of nitrogen-centred radical was also supported by several controlled experiments. Upon the addition of a stoichiometric amount of TEMPO to the CDC reaction, the formation of ynamide and the homo-coupling dimer of alkyne was completely suppressed; alternatively, an unexpected *gem*-diamido compound **5** was obtained with a yield of 14%. We speculated that the compound could be formed through the dimerization of amide **1a**, wherein one molecule of amide is oxidized to imine **6** followed by the nucleophilic addition of another molecule of **1a** (Scheme 2a).

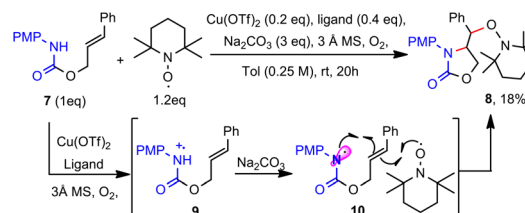
The presence of imine **6** suggests an oxidative-elimination mechanism from amide **1a**. Under aerobic oxidative conditions, it is rational that amide **1a** may undergo oxidation by the  $[\text{Cu(II)Ln-MS-O}_2]$  system to generate the nitrogen radical

#### a) The inhibition of TEMPO for the CDC reaction



Control experiments: a. no Cu(OTf)<sub>2</sub> or ligand or MS or O<sub>2</sub>, **5**, 0%; b. no base, **5**, 5%.

#### b) A nitrogen-centred radical-mediated intramolecular cyclization



Control experiments: a. Cu(OTf)<sub>2</sub> (0.5 eq) and ligand (1.0 eq), **8**, 28%; b. no base, **8**, 5%; c. no Cu(OTf)<sub>2</sub> or ligand or MS or O<sub>2</sub>, **8**, 0%.

Scheme 2 Control experiments for nitrogen radicals.

cation, followed by deprotonation to form the proposed nitrogen-centred radical, leading to imine **6** by TEMPO oxidation. Indeed, we synthesized carbamate **7** and subjected it to oxidation by  $[\text{Cu(II)Ln-MS-O}_2]$  system under CDC general conditions. The corresponding nitrogen radical cation **9** was first generated by the  $[\text{Cu(II)Ln-MS-O}_2]$  system, which then underwent deprotonation to form nitrogen-centred radical **10**. Subsequent 5-*exo-trig* radical cyclization of **10** followed by capture with TEMPO<sup>13</sup> gave the desired product **8** in 18% yield and the yield dropped to 5% in the absence of base; furthermore, no product **8** was afforded in the absence of any one of Cu/ligand/MS/O<sub>2</sub> (Scheme 2b).

## Conclusions

In summary, we have developed a copper-catalyzed aerobic oxidative CDC reaction between secondary amides and terminal alkynes. Through the synergistic promotion of appropriate ligands and 3 Å molecular sieves, ynamides can be efficiently prepared at room temperature and conveniently scaled up. Moreover, a mechanism involving the generation of nitrogen-centred radicals and reductive elimination of copper trivalent intermediates has been proposed legitimately. This also provides an explanation for substrate proportions, as well as the roles of ligands, molecular sieves and bases. Taking advantage of this catalytic mechanism, homo-coupling reactions of alkynes were predominantly suppressed. Furthermore, a preliminary mechanistic application was conducted for the cyclization reaction mediated by a nitrogen-centred radical. These deep insights revealed the potential copper-catalyzed aerobic oxidative process occurring on the surface of molecular sieves, which can inspire further research and application of related reactions.



## Experimental

### General information

Melting points (mp) were determined on SGW® X-4A micro-melting point apparatus and were uncorrected. Infrared (IR) spectra were measured with a Bruker Alpha spectrometer using film KBr pellet techniques.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance III 600 MHz spectrometer. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts are expressed in parts per million ( $\delta$ ) referenced to either the internal standard  $\text{Me}_4\text{Si}$  or solvent signals ( $\text{Me}_4\text{Si}$  at 0 ppm for  $^1\text{H}$  NMR and  $\text{CDCl}_3$  at 77.0 ppm for  $^{13}\text{C}$  NMR). The NMR data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, dt = doublet of triplet, dq = doublet of quartet, td = triplet of doublet, qd = quartet of doublet, ddd = doublet of doublet of doublet, m = multiplet, br s = broad singlet), coupling constant (Hz) and integration. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q Exactive LC-MS mass spectrometer.

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. Toluene was treated with  $\text{CaCl}_2$ . DCM was purchased from Energy Chemical (extra dry, with molecular sieves, water  $\leq 50$  ppm, in a resealable bottle) and THF was purchased from Energy Chemical (extra dry, with molecular sieves, water  $\leq 30$  ppm, in a resealable bottle). Flash column chromatography was performed using 200–300 mesh silica gel. All reactions were carried out in flame-dried glassware under a dry oxygen atmosphere. Reactions were monitored by TLC and visualized using a dual short wave/long wave UV lamp.

### General procedure for the copper-catalyzed CDC reaction of amides with terminal alkynes

In a 25 mL round bottom flask, the amide (1.5 mmol, 3.0 equiv.), 1-methylbenzimidazole (0.2 mmol, 0.4 equiv.), Cu ( $\text{OTf}$ ) $_2$  (0.1 mmol, 0.2 equiv.),  $\text{Na}_2\text{CO}_3$  (1.5 mmol, 3.0 equiv.), and 3 Å molecular sieves (180 mg) were dissolved in dry solvent (2 mL) and the terminal alkyne (0.5 mmol, 1.0 equiv.) was successively added. The mixture was degassed three times by applying vacuum and backfilling with oxygen while stirring vigorously. The mixture was stirred at room temperature for 20 h, filtered using diatomaceous earth over a plug of silica gel (washed with EtOAc), and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography over silica gel.

***N*-(4-Dimethyl-*N*-(phenylethynyl)benzenesulfonamide (3aa).** Following the general procedure, the reaction of **1a** and **2a** afforded **3aa** as a white solid (eluent: EtOAc/PE = 1/8; 93% yield): mp 62.4–64.2 °C; IR (film)  $\nu_{\text{max}}$ : 2232, 1597, 1366, 1275, 1168, 1089  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.83 (d,  $J$  = 8.22 Hz, 2H), 7.35 (d,  $J$  = 8.16 Hz, 4H), 7.31–7.23 (m, 3H), 3.13 (s, 3H), 2.44 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  144.8, 133.0, 131.3, 129.7, 128.2, 127.8, 127.7, 122.5, 83.8, 68.9, 39.2, 21.5; HRMS (ESI) calcd for  $[\text{C}_{16}\text{H}_{15}\text{NO}_2\text{SNa}]^+$  ( $M + \text{Na}^+$ ): 308.0716, Found: 308.0712.

***N*-(4-Methoxyphenyl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (3ab).** Following the general procedure, the reaction of **1a** and **2b** afforded **3ab** as a white solid (eluent: EtOAc/PE = 1/7; 93% yield): mp 62.4–66.3 °C; IR (film)  $\nu_{\text{max}}$ : 2236, 1606, 1366, 1279, 1261, 1189, 1167, 1093  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.82 (d,  $J$  = 8.16 Hz, 2H), 7.36 (d,  $J$  = 8.16 Hz, 2H), 7.30 (d,  $J$  = 8.70 Hz, 2H), 6.81 (d,  $J$  = 8.70 Hz, 2H), 3.78 (s, 3H), 3.12 (s, 3H), 2.44 (s, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  159.4, 144.6, 133.3, 132.9, 129.6, 127.7, 114.3, 113.8, 82.4, 68.5, 55.1, 39.3, 21.5; HRMS (ESI) calcd for  $[\text{C}_{17}\text{H}_{17}\text{NO}_3\text{SNa}]^+$  ( $M + \text{Na}^+$ ): 338.0821, Found: 338.0804.

***N*,4-Dimethyl-*N*-((4-(trifluoromethyl)phenyl)ethynyl)-benzenesulfonamide (3ac).** Following the general procedure, the reaction of **1a** and **2c** afforded **3ac** as a white solid (eluent: EtOAc/PE = 1/7; 90% yield): mp 87.8–90.7 °C; IR (film)  $\nu_{\text{max}}$ : 2236, 1602, 1365, 1277, 1269, 1189, 1167, 1093  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (d,  $J$  = 8.28 Hz, 2H), 7.42 (d,  $J$  = 8.28 Hz, 2H), 7.33 (d,  $J$  = 8.22 Hz, 2H), 7.27 (d,  $J$  = 8.22 Hz, 2H), 3.07 (s, 3H), 2.35 (s, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  145.1, 133.0, 130.9, 129.9, 129.1 (q,  $J$  = 32.8 Hz), 127.7, 126.7, 125.1 (q,  $J$  = 3.4 Hz), 123.9 (q,  $J$  = 271.3 Hz), 86.4, 68.3, 39.0, 21.5; HRMS (ESI) calcd for  $[\text{C}_{18}\text{H}_{19}\text{F}_3\text{NO}_3\text{S}]^+$  ( $M + \text{MeOH} + \text{H}^+$ ): 386.1032, Found: 386.1032.

***N*-(4-Fluorophenyl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (3ad).** Following the general procedure, the reaction of **1a** and **2d** afforded **3ad** as a white solid (eluent: EtOAc/PE = 1/8; 80% yield): mp 80.1–81.7 °C; IR (film)  $\nu_{\text{max}}$ : 2235, 1606, 1512, 1367, 1273, 1255, 1165, 1090  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.83 (d,  $J$  = 8.28 Hz, 2H), 7.38 (d,  $J$  = 8.28 Hz, 2H), 7.35–7.31 (m, 2H), 6.98 (t,  $J$  = 9.00 Hz, 2H), 3.14 (s, 3H), 2.46 (s, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  162.2 (d,  $J$  = 247.8 Hz), 144.9, 133.4 (d,  $J$  = 8.2 Hz), 133.1, 129.8, 127.8, 118.6 (d,  $J$  = 3.8 Hz), 115.5 (d,  $J$  = 22.5 Hz), 83.5, 67.9, 39.2, 21.6; HRMS (ESI) calcd for  $[\text{C}_{16}\text{H}_{17}\text{FNO}_3\text{S}]^+$  ( $M + \text{H}_2\text{O} + \text{H}^+$ ): 322.0908, Found: 322.0904.

***N*-(4-Chlorophenyl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (3ae).** Following the general procedure, the reaction of **1a** and **2e** afforded **3ae** as a white solid (eluent: EtOAc/PE = 1/8; 88% yield): mp 93.2–95.8 °C; IR (film)  $\nu_{\text{max}}$ : 2235, 1602, 1510, 1359, 1280, 1263, 1167, 1090  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.82 (d,  $J$  = 8.28 Hz, 2H), 7.37 (d,  $J$  = 8.28 Hz, 2H), 7.29–7.23 (m, 4H), 3.14 (s, 3H), 2.45 (s, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  144.9, 133.7, 133.0, 132.5, 129.8, 128.5, 127.7, 121.1, 84.7, 68.0, 39.1, 21.6; HRMS (ESI) calcd for  $[\text{C}_{17}\text{H}_{19}\text{ClNO}_3\text{S}]^+$  ( $M + \text{MeOH} + \text{H}^+$ ): 352.0769, Found: 352.0765.

***N*-(4-Bromophenyl)ethynyl)-*N*,4-dimethylbenzenesulfonamide (3af).** Following the general procedure, the reaction of **1a** and **2f** afforded **3af** as a white solid (eluent: EtOAc/PE = 1/8; 91% yield): mp 117.1–118.4 °C; IR (film)  $\nu_{\text{max}}$ : 2237, 1598, 1510, 1363, 1276, 1259, 1167, 1092  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.82 (d,  $J$  = 8.15 Hz, 2H), 7.41 (d,  $J$  = 8.49 Hz, 2H), 7.37 (d,  $J$  = 8.15 Hz, 2H), 7.21 (d,  $J$  = 8.49 Hz, 2H), 3.14 (s, 3H), 2.46 (s, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  144.9, 133.1, 132.7, 131.5, 129.8, 127.7, 121.9, 121.6, 84.9, 68.1, 39.2, 21.6; HRMS (ESI) calcd for  $[\text{C}_{17}\text{H}_{19}\text{BrNO}_3\text{S}]^+$  ( $M + \text{MeOH} + \text{H}^+$ ): 396.0264, Found: 396.0261.



**Methyl 4-(((N,4-dimethylphenyl)sulfonamido)ethynyl)benzoate (3ag).** Following the general procedure, the reaction of **1a** and **2g** afforded **3ag** as a white solid (eluent: EtOAc/PE = 1/6; 87% yield): mp 94.3–95.9 °C; IR (film)  $\nu_{\text{max}}$ : 2239, 1600, 1508, 1365, 1282, 1259, 1167, 1088  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.96 (d,  $J$  = 8.43 Hz, 2H), 7.84 (d,  $J$  = 8.43 Hz, 2H), 7.41–7.36 (m, 4H), 3.91 (s, 3H), 3.18 (s, 3H), 2.46 (s, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  166.5, 145.0, 133.1, 130.5, 129.9, 129.4, 128.7, 127.7, 127.6, 87.0, 69.0, 52.1, 39.1, 21.6; HRMS (ESI) calcd for  $[\text{C}_{19}\text{H}_{22}\text{NO}_5\text{S}]^+$  ( $\text{M} + \text{MeOH} + \text{H}^+$ ): 376.1213, Found: 376.1214.

**N-((2-Methoxyphenyl)ethynyl)-N,4-dimethylbenzenesulfonamide (3ah).** Following the general procedure, the reaction of **1a** and **2h** afforded **3ah** as a white solid (eluent: EtOAc/PE = 1/6; 57% yield): mp 70.3–72.8 °C; IR (film)  $\nu_{\text{max}}$ : 2235, 1600, 1508, 1363, 1278, 1263, 1167, 1092  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.90 (d,  $J$  = 8.19 Hz, 2H), 7.36 (d,  $J$  = 8.19 Hz, 2H), 7.32 (dd,  $J$  = 7.54, 1.59 Hz, 1H), 7.25 (td,  $J$  = 8.13, 1.79 Hz, 1H), 6.88 (td,  $J$  = 7.34, 0.79 Hz, 1H), 6.85 (d,  $J$  = 8.34 Hz, 1H), 3.86 (s, 3H), 3.15 (s, 3H), 2.45 (s, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  159.7, 144.6, 133.2, 133.1, 129.6, 129.2, 127.9, 120.3, 111.8, 110.6, 87.6, 65.3, 55.7, 39.3, 21.6; HRMS (ESI) calcd for  $[\text{C}_{18}\text{H}_{22}\text{NO}_4\text{S}]^+$  ( $\text{M} + \text{MeOH} + \text{H}^+$ ): 348.1264, Found: 348.1259.

**N,4-Dimethyl-N-((2-(trifluoromethyl)phenyl)ethynyl)-benzenesulfonamide (3ai).** Following the general procedure, the reaction of **1a** and **2i** afforded **3ai** as a white solid (eluent: EtOAc/PE = 1/7; 69% yield): mp 89.7–91.4 °C; IR (film)  $\nu_{\text{max}}$ : 2235, 1602, 1510, 1369, 1280, 1261, 1163, 1092  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.85 (d,  $J$  = 8.34 Hz, 2H), 7.60 (d,  $J$  = 7.92 Hz, 1H), 7.50 (d,  $J$  = 7.74 Hz, 1H), 7.45 (t,  $J$  = 7.56 Hz, 1H), 7.37 (d,  $J$  = 8.34 Hz, 2H), 7.33 (d,  $J$  = 7.50 Hz, 1H), 3.17 (s, 3H), 2.44 (s, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  145.0, 133.2, 132.9, 131.3, 130.2 (q,  $J$  = 30.1 Hz), 129.8, 127.7, 127.1, 125.7 (q,  $J$  = 4.7 Hz), 123.5 (q,  $J$  = 273.2 Hz), 121.2 (q,  $J$  = 1.9 Hz), 89.4, 65.8, 39.1, 21.6; HRMS (ESI) calcd for  $[\text{C}_{18}\text{H}_{19}\text{F}_3\text{NO}_3\text{S}]^+$  ( $\text{M} + \text{MeOH} + \text{H}^+$ ): 386.1032, Found: 386.1031.

**N-((3-Methoxyphenyl)ethynyl)-N,4-dimethylbenzenesulfonamide (3aj).** Following the general procedure, the reaction of **1a** and **2j** afforded **3aj** as a white solid (eluent: EtOAc/PE = 1/6; 61% yield): mp 68.4–70.1 °C; IR (film)  $\nu_{\text{max}}$ : 2238, 1602, 1508, 1367, 1276, 1263, 1169, 1092  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.83 (d,  $J$  = 8.28 Hz, 2H), 7.36 (d,  $J$  = 8.28 Hz, 2H), 7.19 (t,  $J$  = 7.92 Hz, 1H), 6.95 (td,  $J$  = 7.62, 1.02 Hz, 1H), 6.88 (dd,  $J$  = 2.64, 1.32 Hz, 1H), 6.83 (dd,  $J$  = 8.35, 2.78 Hz, 1H), 3.78 (s, 3H), 3.14 (s, 3H), 2.45 (s, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  159.2, 144.8, 133.0, 129.8, 129.2, 127.7, 123.8, 123.6, 116.2, 114.2, 83.7, 68.9, 55.2, 39.2, 21.6; HRMS (ESI) calcd for  $[\text{C}_{18}\text{H}_{22}\text{NO}_4\text{S}]^+$  ( $\text{M} + \text{MeOH} + \text{H}^+$ ): 348.1264, Found: 348.1260.

**N-((3,5-Bis(trifluoromethyl)phenyl)ethynyl)-N,4-dimethylbenzenesulfonamide (3ak).** Following the general procedure, the reaction of **1a** and **2k** afforded **3ak** as a white solid (eluent: EtOAc/PE = 1/8; 64% yield): mp 97.4–99.2 °C; IR (film)  $\nu_{\text{max}}$ : 2235, 1600, 1510, 1371, 1282, 1261, 1171, 1094  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.84 (d,  $J$  = 8.34 Hz, 2H), 7.75 (s, 2H), 7.74 (s, 1H), 7.41 (d,  $J$  = 8.34 Hz, 2H), 3.20 (s, 3H), 2.48 (s, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  145.3, 133.1, 131.8 (q,  $J$  = 32.8 Hz),

130.6 (q,  $J$  = 3.4 Hz), 130.0, 127.7, 125.3, 122.9 (q,  $J$  = 273.0 Hz), 120.8 (app. quintet,  $J$  = 3.7 Hz), 87.4, 67.2, 39.0, 21.6; HRMS (ESI) calcd for  $[\text{C}_{19}\text{H}_{18}\text{F}_6\text{NO}_3\text{S}]^+$  ( $\text{M} + \text{MeOH} + \text{H}^+$ ): 454.0906, Found: 454.0903.

**N,4-Dimethyl-N-(4-phenylbut-1-yn-1-yl)benzenesulfonamide (3al).** Following the general procedure, the reaction of **1a** and **2l** afforded **3al** as a white solid (eluent: EtOAc/PE = 1/8; 73% yield): mp 66.2–68.4 °C; IR (film)  $\nu_{\text{max}}$ : 2237, 1596, 1510, 1369, 1271, 1259, 1167, 1092  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.68 (d,  $J$  = 8.28 Hz, 2H), 7.31–7.25 (m, 4H), 7.22–7.16 (m, 3H), 2.96 (s, 3H), 2.78 (t,  $J$  = 7.44 Hz, 2H), 2.54 (t,  $J$  = 7.44 Hz, 2H), 2.43 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  144.4, 140.4, 133.0, 129.6, 128.4, 128.2, 127.6, 126.1, 75.5, 67.7, 39.2, 35.1, 21.5, 20.4; HRMS (ESI) calcd for  $[\text{C}_{18}\text{H}_{20}\text{NO}_2\text{S}]^+$  ( $\text{M} + \text{H}^+$ ): 314.1209, Found: 314.1206.

**N-(Cyclopropylethynyl)-N,4-dimethylbenzenesulfonamide (3am).** Following the general procedure, the reaction of **1a** and **2m** afforded **3am** as a white solid (eluent: EtOAc/PE = 1/6; 75% yield): mp 46.4–48.9 °C; IR (film)  $\nu_{\text{max}}$ : 2924, 2212, 1757, 1689, 1363, 1281, 1259, 1228  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.68 (d,  $J$  = 8.28 Hz, 2H), 7.28 (d,  $J$  = 8.28 Hz, 2H), 2.91 (s, 3H), 2.37 (s, 3H), 1.19 (m, 1H), 0.69 (m, 2H), 0.54 (m, 2H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  144.4, 133.0, 129.5, 127.7, 72.8, 70.3, 39.3, 21.5, 8.6, –1.0; HRMS (ESI) calcd for  $[\text{C}_{13}\text{H}_{15}\text{NO}_2\text{SNa}]^+$  ( $\text{M} + \text{Na}^+$ ): 272.0716, Found: 272.0721.

**N,4-Dimethyl-N-((trimethylsilyl)ethynyl)benzenesulfonamide (3an).** Following the general procedure, the reaction of **1a** and **2n** afforded **3an** as a white solid (eluent: EtOAc/PE = 1/6; 71% yield): mp 53.5–56.1 °C; IR (film)  $\nu_{\text{max}}$ : 2928, 2212, 1753, 1687, 1355, 1287, 1259  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.78 (d,  $J$  = 8.22 Hz, 2H), 7.36 (d,  $J$  = 8.22 Hz, 2H), 3.05 (s, 3H), 2.46 (s, 3H), 0.15 (s, 9H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  144.8, 133.0, 129.6, 127.8, 96.5, 71.2, 39.0, 21.6, 0.0; HRMS (ESI) calcd for  $[\text{C}_{13}\text{H}_{19}\text{NO}_2\text{SSiNa}]^+$  ( $\text{M} + \text{Na}^+$ ): 304.0798, Found: 304.0795.

**N,4-Dimethyl-N-(thiophen-2-ylethynyl)benzenesulfonamide (3ao).** Following the general procedure, the reaction of **1a** and **2o** afforded **3ao** as a pale yellow solid (eluent: EtOAc/PE = 1/6; 74% yield): mp 78.2–80.4 °C; IR (film)  $\nu_{\text{max}}$ : 2237, 1604, 1510, 1367, 1273, 1259, 1169, 1085  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.82 (d,  $J$  = 8.28 Hz, 2H), 7.38 (d,  $J$  = 8.28 Hz, 2H), 7.25 (dd,  $J$  = 5.30, 1.08 Hz, 1H), 7.16 (dd,  $J$  = 3.62, 1.14 Hz, 1H), 6.95 (q,  $J$  = 2.82, 1.56 Hz, 1H), 3.13 (s, 3H), 2.46 (s, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  144.9, 133.0, 132.9, 129.8, 127.7, 126.9, 122.6, 87.3, 62.4, 39.2, 21.6; HRMS (ESI) calcd for  $[\text{C}_{15}\text{H}_{18}\text{NO}_3\text{S}_2]^+$  ( $\text{M} + \text{MeOH} + \text{H}^+$ ): 324.0723, Found: 324.0724.

**N,4-Dimethyl-N-(3-methylbut-3-en-1-yn-1-yl)benzenesulfonamide (3ap).** Following the general procedure, the reaction of **1a** and **2p** afforded **3ap** as a pale yellow oil (eluent: EtOAc/PE = 1/8; 57% yield): IR (film)  $\nu_{\text{max}}$ : 3006, 2362, 2229, 1457, 1276, 1261, 1170  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J$  = 8.10 Hz, 2H), 7.29 (d,  $J$  = 8.10 Hz, 2H), 5.07 (d,  $J$  = 16.2 Hz, 2H), 3.00 (s, 3H), 2.39 (s, 3H), 1.80 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  144.7, 131.1, 129.7, 127.8, 126.0, 119.8, 83.2, 70.5, 39.2, 23.5, 21.6; HRMS (ESI) calcd for  $[\text{C}_{13}\text{H}_{15}\text{NO}_2\text{SNa}]^+$  ( $\text{M} + \text{Na}^+$ ): 272.0716, Found: 272.0706.



***N*-(Cyclohex-1-en-1-ylethynyl)-*N*,4-dimethylbenzenesulfonamide (3aq).** Following the general procedure, the reaction of **1a** and **2q** afforded **3aq** as a white solid (eluent: EtOAc/PE = 1/8; 58% yield): decomposed at 170 °C; IR (film)  $\nu_{\max}$ : 3006, 2986, 2360, 2223, 1276, 1261  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.77 (d,  $J$  = 8.40 Hz, 2H), 7.46 (d,  $J$  = 8.40 Hz, 2H), 5.95 (m, 1H), 3.01 (s, 3H), 2.46 (s, 3H), 2.09–2.03 (m, 4H), 1.65–1.57 (m, 4H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  146.5, 134.8, 134.3, 130.9, 129.0, 121.1, 82.6, 71.4, 40.0, 30.5, 26.6, 23.5, 22.6, 21.6; HRMS (ESI) calcd for  $[\text{C}_{16}\text{H}_{19}\text{NO}_2\text{SNa}]^+$  ( $\text{M} + \text{Na}^+$ ): 312.1029, Found: 312.1017.

***N*-Methyl-*N*-(phenylethynyl)methanesulfonamide (3ba).** Following the general procedure, the reaction of **1b** and **2a** afforded **3ba** as a white solid (eluent: EtOAc/PE = 1/6; 88% yield): mp 55.9–58.7 °C; IR (film)  $\nu_{\max}$ : 2934, 2238, 1597, 1444, 1358, 1326, 1159, 1116  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43–7.39 (m, 2H), 7.32–7.28 (m, 3H), 3.30 (s, 3H), 3.13 (s, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  131.5, 128.3, 128.1, 122.3, 83.0, 69.5, 39.2, 36.8; HRMS (ESI) calcd for  $[\text{C}_{10}\text{H}_{11}\text{NO}_2\text{SNa}]^+$  ( $\text{M} + \text{Na}^+$ ): 232.0402, Found: 232.0401.

***N*-Methyl-4-nitro-*N*-(phenylethynyl)benzenesulfonamide (3ca).** Following the general procedure, the reaction of **1c** and **2a** afforded **3ca** as a white solid (eluent: EtOAc/PE = 1/6; 69% yield): mp 143.4–146.5 °C; IR (film)  $\nu_{\max}$ : 2235, 1598, 1366, 1276, 1168, 1090  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.35 (d,  $J$  = 8.76 Hz, 2H), 8.06 (d,  $J$  = 8.76 Hz, 2H), 7.30–7.27 (m, 2H), 7.24–7.23 (m, 3H), 3.15 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  150.7, 141.5, 131.6, 129.0, 128.4, 124.4, 121.8, 82.4, 69.7, 39.6; HRMS (ESI) calcd for  $[\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_4\text{S}]^+$  ( $\text{M} + \text{H}^+$ ): 317.0591, Found: 317.0586.

**4-Bromo-*N*-methyl-*N*-(phenylethynyl)benzenesulfonamide (3da).** Following the general procedure, the reaction of **1d** and **2a** afforded **3da** as a white solid (eluent: EtOAc/PE = 1/8; 69% yield): mp 66.8–69.2 °C; IR (film)  $\nu_{\max}$ : 2239, 1596, 1366, 1278, 1168, 1089  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.81 (d,  $J$  = 8.64 Hz, 2H), 7.71 (d,  $J$  = 8.64 Hz, 2H), 7.37–7.35 (m, 2H), 7.30–7.28 (m, 3H), 3.16 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  135.0, 132.5, 131.4, 129.2, 129.0, 128.3, 128.1, 122.2, 83.2, 69.3, 39.4; HRMS (ESI) calcd for  $[\text{C}_{15}\text{H}_{13}\text{NO}_2\text{SBr}]^+$  ( $\text{M} + \text{H}^+$ ): 349.9845, Found: 349.9840.

***N*-Benzyl-4-methyl-*N*-(phenylethynyl)benzenesulfonamide (3ea).** Following the general procedure, the reaction of **1e** and **2a** afforded **3ea** as a white solid (eluent: EtOAc/PE = 1/8; 30% yield): mp 75.4–77.5 °C; IR (film)  $\nu_{\max}$ : 2234, 1602, 1366, 1275, 1263, 1191, 1167  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79 (d,  $J$  = 8.22 Hz, 2H), 7.39–7.21 (m, 12H), 4.58 (s, 2H), 2.44 (s, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  144.6, 134.6, 134.4, 131.1, 129.7, 128.9, 128.5, 128.3, 128.2, 127.7, 127.6, 122.7, 82.6, 71.3, 55.7, 21.6; HRMS (ESI) calcd for  $[\text{C}_{22}\text{H}_{19}\text{NO}_2\text{SNa}]^+$  ( $\text{M} + \text{Na}^+$ ): 384.1029, Found: 384.1032.

**4-Methyl-*N*-phenyl-*N*-(phenylethynyl)benzenesulfonamide (3fa).** Following the general procedure, the reaction of **1f** and **2a** afforded **3fa** as a white solid (eluent: EtOAc/PE = 1/8; 65% yield): mp 85.4–87.1 °C; IR (film)  $\nu_{\max}$ : 2236, 1597, 1366, 1281, 1261, 1187, 1167  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44 (d,  $J$  = 8.16 Hz, 2H), 7.22–7.09 (m, 12H), 2.26 (s, 3H).  $^{13}\text{C}$  NMR

(150 MHz,  $\text{CDCl}_3$ )  $\delta$  145.0, 138.9, 132.8, 131.4, 129.5, 129.1, 128.2, 128.0, 126.2, 122.5, 82.9, 70.4, 21.7; HRMS (ESI) calcd for  $[\text{C}_{21}\text{H}_{17}\text{NO}_2\text{SNa}]^+$  ( $\text{M} + \text{Na}^+$ ): 370.0872, Found: 370.0866.

**1-(Phenylethynyl)azetidin-2-one (3ga).** Following the general procedure, the reaction of **1g** and **2a** afforded **3ga** as a pale yellow solid (eluent: EtOAc/PE = 1/5; 85% yield): mp 83.8–86.8 °C; IR (film)  $\nu_{\max}$ : 2232, 1595, 1366, 1281, 1259, 1189, 1167, 1091  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 (dd,  $J$  = 7.17, 3.66 Hz, 2H), 7.33–7.26 (m, 3H), 3.67 (t,  $J$  = 4.83 Hz, 2H), 3.06 (t,  $J$  = 4.83 Hz, 2H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  166.6, 131.2, 128.2, 128.0, 122.0, 78.6, 69.6, 43.0, 37.8; HRMS (ESI) calcd for  $[\text{C}_{11}\text{H}_{10}\text{NO}]^+$  ( $\text{M} + \text{H}^+$ ): 172.0757, Found: 172.0762.

**1-(Phenylethynyl)pyrrolidin-2-one (3ha).** Following the general procedure, the reaction of **1h** and **2a** afforded **3ha** as a colorless oil (eluent: EtOAc/PE = 1/5; 51% yield): IR (film)  $\nu_{\max}$ : 2922, 2218, 1755, 1697, 1693, 1363, 1263, 1168  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.46–7.42 (m, 2H), 7.32–7.27 (m, 3H), 3.77 (t,  $J$  = 7.20 Hz, 2H), 2.47 (t,  $J$  = 8.28 Hz, 2H), 2.16 (m,  $J$  = 8.28, 7.20 Hz, 2H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  175.8, 131.4, 128.1, 127.8, 122.5, 80.3, 72.5, 50.1, 29.6, 18.8; HRMS (ESI) calcd for  $[\text{C}_{12}\text{H}_{11}\text{NONa}]^+$  ( $\text{M} + \text{Na}^+$ ): 208.0733, Found: 208.0724.

**4,4-Dimethyl-1-(phenylethynyl)pyrrolidin-2-one (3ia).** Following the general procedure, the reaction of **1i** and **2a** afforded **3ia** as a white solid (eluent: EtOAc/PE = 1/5; 48% yield): mp 99.4–103.9 °C; IR (film)  $\nu_{\max}$ : 3004, 2988, 2964, 2362, 2247, 1718, 1402, 1386, 1276, 1261  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45–7.43 (m, 2H), 7.31–7.28 (m, 3H), 3.50 (s, 2H), 2.31 (s, 2H), 1.23 (s, 6H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  175.2, 131.5, 128.2, 127.9, 122.5, 80.5, 72.1, 62.9, 44.8, 33.8, 27.4; HRMS (ESI) calcd for  $[\text{C}_{14}\text{H}_{15}\text{NONa}]^+$  ( $\text{M} + \text{Na}^+$ ): 236.1046, Found: 236.1038.

**5,5-Dimethyl-1-(phenylethynyl)pyrrolidin-2-one (3ja).** Following the general procedure, the reaction of **1j** and **2a** afforded **3ja** as a white solid (eluent: EtOAc/PE = 1/5; 37% yield): mp 50.1–52.3 °C; IR (film)  $\nu_{\max}$ : 3004, 2988, 2358, 2240, 1717, 1541, 1276, 1261  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40–7.38 (m, 2H), 7.24–7.21 (m, 3H), 2.47 (t,  $J$  = 8.09 Hz, 2H), 1.95 (t,  $J$  = 8.09 Hz, 2H), 1.36 (s, 6H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  175.0, 131.5, 128.2, 127.8, 122.8, 78.1, 74.9, 62.7, 33.5, 29.5, 26.5; HRMS (ESI) calcd for  $[\text{C}_{14}\text{H}_{15}\text{NONa}]^+$  ( $\text{M} + \text{Na}^+$ ): 236.1046, Found: 236.1037.

**2-(Phenylethynyl)isoindolin-1-one (3ka).** Following the general procedure, the reaction of **1k** and **2a** afforded **3ka** as a pale yellow solid (eluent: EtOAc/PE = 1/5; 67% yield): mp 128.9–131.7 °C; IR (film)  $\nu_{\max}$ : 2244, 1719, 1447, 1276, 1124  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.90 (d,  $J$  = 7.62 Hz, 1H), 7.62 (t,  $J$  = 7.62 Hz, 1H), 7.51–7.48 (m, 3H), 7.46 (d,  $J$  = 7.62 Hz, 1H), 7.33–7.29 (m, 3H), 4.75 (s, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  168.5, 140.9, 133.0, 131.4, 129.7, 128.6, 128.2, 127.9, 124.5, 122.9, 122.6, 80.4, 73.5, 52.6; HRMS (ESI) calcd for  $[\text{C}_{16}\text{H}_{12}\text{NO}]^+$  ( $\text{M} + \text{H}^+$ ): 234.0913, Found: 234.0910.

**3-(Phenylethynyl)oxazolidin-2-one (3la).** Following the general procedure, the reaction of **1l** and **2a** afforded **3la** as a white solid (eluent: EtOAc/PE = 1/5; 81% yield): mp 80.3–84.0 °C; IR (film)  $\nu_{\max}$ : 2236, 1600, 1366, 1279,





1167  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45–7.41 (m, 2H), 7.32–7.23 (m, 3H), 4.43 (t,  $J$  = 8.31 Hz, 2H), 3.95 (t,  $J$  = 8.31 Hz, 2H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  155.9, 131.3, 128.2, 128.0, 122.0, 78.9, 70.9, 63.0, 46.8; HRMS (ESI) calcd for  $[\text{C}_{11}\text{H}_9\text{NO}_2\text{Na}]^+$  ( $\text{M} + \text{Na}^+$ ): 210.0525, Found: 210.0517.

**(S)-4-Benzyl-3-(phenylethynyl)oxazolidin-2-one (3ma).**

Following the general procedure, the reaction of **1m** and **2a** afforded **3ma** as a white solid (eluent: EtOAc/PE = 1/6; 80% yield): mp 88.9–91.7  $^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{27}$  +186.7 ( $c$  1.0, MeOH); IR (film)  $\nu_{\text{max}}$ : 2234, 1602, 1366, 1273, 1263, 1169, 1167  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49–7.42 (m, 2H), 7.37–7.20 (m, 8H), 4.33 (d,  $J$  = 4.32 Hz, 2H), 4.13 (q,  $J$  = 14.38, 4.32 Hz, 1H), 3.24 (dd,  $J$  = 14.38, 6.93 Hz, 1H), 2.99 (dd,  $J$  = 14.29, 6.93 Hz, 1H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  155.4, 134.1, 131.4, 129.3, 128.9, 128.2, 128.1, 127.3, 122.0, 77.9, 73.1, 67.3, 58.3, 37.8; HRMS (ESI) calcd for  $[\text{C}_{18}\text{H}_{16}\text{NO}_2]^+$  ( $\text{M} + \text{H}^+$ ): 278.1176, Found: 278.1174.

**Methyl (R)-2-oxo-3-(phenylethynyl)oxazolidine-4-carboxylate (3na).** Following the general procedure, the reaction of **1n** and **2a** afforded **3na** as a white solid (eluent: EtOAc/PE = 1/5; 44% yield): mp 78.3–82.4  $^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{27}$  +133.3 ( $c$  1.0, MeOH); IR (film)  $\nu_{\text{max}}$ : 3006, 2988, 2360, 2256, 1772, 1410, 1276, 1261  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45 (dd,  $J$  = 7.01, 4.09 Hz, 2H), 7.32–7.30 (m, 3H), 4.70–4.64 (m, 2H), 4.51 (dd,  $J$  = 8.47, 3.80 Hz, 1H), 3.90 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  168.3, 154.6, 131.8, 128.4, 128.3, 121.8, 77.4, 72.1, 65.4, 58.8, 53.4; HRMS (ESI) calcd for  $[\text{C}_{13}\text{H}_{11}\text{NO}_4\text{Na}]^+$  ( $\text{M} + \text{Na}^+$ ): 268.0580, Found: 268.0571.

**Methyl methyl(phenylethynyl)carbamate (3oa).** Following the general procedure, the reaction of **1o** and **2a** afforded **3oa** as a yellow solid (eluent: EtOAc/PE = 1/6; 33% yield): mp 39.8–42.5  $^\circ\text{C}$ ; IR (film)  $\nu_{\text{max}}$ : 2239, 1594, 1366, 1278, 1168, 1090  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 (d,  $J$  = 6.96 Hz, 2H), 7.31–7.27 (m, 3H), 3.84 (s, 3H), 3.27 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  155.9, 131.2, 128.2, 127.6, 123.0, 83.9, 69.4, 54.1, 37.9; HRMS (ESI) calcd for  $[\text{C}_{11}\text{H}_{12}\text{NO}_2]^+$  ( $\text{M} + \text{H}^+$ ): 190.0863, Found: 190.0860.

**1-Methyl-3-(phenylethynyl)imidazolidin-2-one (3pa).**

Following the general procedure, the reaction of **1p** and **2a** afforded **3pa** as a white solid (eluent: EtOAc/PE = 1/5; 57% yield): mp 101.3–104.0  $^\circ\text{C}$ ; IR (film)  $\nu_{\text{max}}$ : 2228, 1597, 1366, 1275, 1261, 1187, 1167, 1093  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 (dd,  $J$  = 8.19, 1.50 Hz, 2H), 7.29–7.22 (m, 3H), 3.75 (t,  $J$  = 7.86 Hz, 2H), 3.41 (t,  $J$  = 7.86 Hz, 2H), 2.83 (s, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  157.4, 131.0, 128.0, 127.1, 123.2, 82.2, 69.8, 44.5, 44.2, 31.0; HRMS (ESI) calcd for  $[\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}]^+$  ( $\text{M} + \text{H}^+$ ): 201.1022, Found: 201.1021.

**Methyl 1-(phenylethynyl)-1H-indole-3-carboxylate (3qa).**

Following the general procedure, the reaction of **1q** and **2a** afforded **3qa** as a pale pink solid (eluent: EtOAc/PE = 1/6; 72% yield): mp 98.2–101.0  $^\circ\text{C}$ ; IR (film)  $\nu_{\text{max}}$ : 2232, 1600, 1366, 1271, 1261, 1167  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.17 (d,  $J$  = 7.86 Hz, 1H), 7.93 (s, 1H), 7.61 (d,  $J$  = 7.86 Hz, 1H), 7.54 (dd,  $J$  = 7.00, 2.28 Hz, 2H), 7.40–7.32 (m, 5H), 3.91 (s, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  164.2, 138.3, 134.7, 131.5, 128.6, 128.5, 125.3, 124.4, 123.6, 121.9, 121.5, 111.4, 110.9, 79.0, 71.7, 51.3;

HRMS (ESI) calcd for  $[\text{C}_{18}\text{H}_{14}\text{NO}_2]^+$  ( $\text{M} + \text{H}^+$ ): 276.1019, Found: 276.1019.

**Methyl N-((benzyloxy)carbonyl)-N-(phenylethynyl)glycinate (3ra).** Following the general procedure, the reaction of **1r** and **2a** afforded **3ra** as a white solid (eluent: EtOAc/PE = 1/7; 22% yield): mp 41.6–44.1  $^\circ\text{C}$ ; IR (film)  $\nu_{\text{max}}$ : 3006, 2990, 2356, 1732, 1279, 1264  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36–7.19 (m, 10H), 5.22 (s, 2H), 4.24 (s, 2H), 3.72 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  168.1, 155.0, 135.4, 131.1, 128.5, 128.2, 127.7, 127.6, 122.8, 82.3, 70.3, 68.9, 52.5, 51.4; HRMS (ESI) calcd for  $[\text{C}_{19}\text{H}_{17}\text{NO}_4\text{Na}]^+$  ( $\text{M} + \text{Na}^+$ ): 346.1050, Found: 346.1036.

**Methyl N-(phenylethynyl)-N-tosylglycinate (3sa).** Following the general procedure, the reaction of **1s** and **2a** afforded **3sa** as a colorless oil (eluent: EtOAc/PE = 1/8; 43% yield): IR (film)  $\nu_{\text{max}}$ : 3006, 2988, 2358, 2242, 1759, 1364, 1276, 1261, 1167  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.78 (d,  $J$  = 8.22 Hz, 2H), 7.28–7.24 (m, 4H), 7.19–7.18 (m, 3H), 4.23 (s, 2H), 3.61 (s, 3H), 2.36 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  167.5, 144.9, 134.3, 131.5, 129.6, 128.1, 128.0, 127.9, 122.3, 81.9, 70.3, 52.4, 52.2, 21.6; HRMS (ESI) calcd for  $[\text{C}_{18}\text{H}_{17}\text{NO}_4\text{SNa}]^+$  ( $\text{M} + \text{Na}^+$ ): 366.0770, Found: 366.0756.

### Discovery of the nitrogen-centered radical in the copper-catalyzed CDC reaction

**TEMPO-inhibition control experiment I.** In a 25 mL round bottom flask, **1a** (1.5 mmol, 3.0 eq.), 1-methylbenzimidazole (0.2 mmol, 0.4 eq.),  $\text{Cu}(\text{OTf})_2$  (0.1 mmol, 0.2 eq.),  $\text{Na}_2\text{CO}_3$  (1.5 mmol, 3.0 eq.), TEMPO (0.55 mmol, 1.1 eq.) and 3 Å molecular sieves (180 mg) were dissolved in toluene (2 mL) and **2a** (0.5 mmol, 1.0 eq.) was successively added. The mixture was degassed three times by applying vacuum and backfilling with oxygen while stirring vigorously. The mixture was stirred at room temperature for 20 h, filtered using diatomaceous earth over a plug of silica gel (washed with EtOAc), and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography over silica gel to obtain **5**.

**N,4-Dimethyl-N-(((4-methylphenyl)sulfonamido)methyl)-benzenesulfonamide (5).** White solid (eluent: EtOAc/PE = 1/3; 15% yield): mp 116.3–117.8  $^\circ\text{C}$ ; IR (film)  $\nu_{\text{max}}$ : 3010, 1598, 1451, 1339, 1280, 1263, 1161  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.71 (d,  $J$  = 8.28 Hz, 2H), 7.62 (d,  $J$  = 7.28 Hz, 2H), 7.09 (dd,  $J$  = 8.22, 2.08 Hz, 4H), 5.32 (t,  $J$  = 6.84 Hz, 1H), 4.47 (d,  $J$  = 6.96 Hz, 2H), 2.72 (s, 3H), 2.43 (s, 6H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  144.0, 143.8, 137.8, 135.1, 129.9, 129.8, 127.1, 126.7, 58.9, 34.2, 21.5; HRMS (ESI) calcd for  $[\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_4\text{S}_2\text{Na}]^+$  ( $\text{M} + \text{Na}^+$ ): 391.0757, Found: 391.0753.

**TEMPO-capture control experiment II.** In a 25 mL round bottom flask, cinnamyl (4-methoxyphenyl)carbamate **7** (1.5 mmol, 3.0 eq.), 1-methylbenzimidazole (0.2 mmol, 0.4 eq.),  $\text{Cu}(\text{OTf})_2$  (0.1 mmol, 0.2 eq.),  $\text{Na}_2\text{CO}_3$  (1.5 mmol, 3.0 eq.), TEMPO (0.55 mmol, 1.1 eq.) and 3 Å molecular sieves (180 mg) were dissolved in toluene (2 mL). The mixture was degassed three times by applying vacuum and backfilling with oxygen while stirring vigorously. The mixture was stirred at room temperature for 20 h, filtered using diatomaceous earth over a



plug of silica gel (washed with EtOAc), and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography over silica gel to obtain **8**.

**3-(4-Methoxyphenyl)-4-(phenyl((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)oxazolidin-2-one (8)**. Pale yellow oil (eluent: EtOAc/PE = 1/4; 18% yield): IR (film)  $\nu_{\text{max}}$ : 3010, 2939, 1753, 1512, 1463, 1406, 1278, 1265, 1130  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43 (d,  $J$  = 9.06 Hz, 2H), 7.32–7.29 (m, 3H), 7.18 (dd,  $J$  = 6.87, 1.98 Hz, 2H), 6.89 (d,  $J$  = 9.06 Hz, 2H), 4.93 (d,  $J$  = 1.80 Hz, 1H), 4.93–4.89 (m, 1H), 4.76 (dd,  $J$  = 8.25, 4.56 Hz, 1H), 4.59 (t,  $J$  = 8.88 Hz, 1H), 3.80 (s, 3H), 1.53–0.87 (m, 16H), 0.25 (s, 2H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  156.7, 156.1, 138.2, 130.4, 129.1, 128.4, 128.1, 123.3, 114.1, 84.6, 63.3, 60.8, 60.6, 59.4, 55.4, 40.5 (br), 33.8 (br), 20.4, 16.9; HRMS (ESI) calcd for  $[\text{C}_{26}\text{H}_{35}\text{N}_2\text{O}_4]^+$  ( $\text{M} + \text{H}^+$ ): 439.2591, Found: 439.2597.

## Author contributions

X. Zheng conceived this project. X. Zheng and J.-L. Ye supervised the investigation. S.-Y. Zhuo performed the research. J.-L. Ye conducted the DFT calculations. All authors wrote and revised the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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## References

- For the first synthesis of ynamides, see: (a) Z. Janousek, J. Collard and H. G. Viehe, *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 917–918. For some selected reviews, see: (b) D. Campeau, D. F. L. Rayo, A. Mansour, K. Muratov and F. Gagosz, *Chem. Rev.*, 2021, **121**, 8756–8867; (c) J. Luo, G.-S. Chen, S.-J. Chen, J.-S. Yu, Z.-D. Li and Y.-L. Liu, *ACS Catal.*, 2020, **10**, 13978–13992; (d) C. C. Lynch, A. Sripada and C. Wolf, *Chem. Soc. Rev.*, 2020, **49**, 8543–8583; (e) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang and R. P. Hsung, *Chem. Rev.*, 2010, **110**, 5064–5106; (f) G. Evano, A. Coste and K. Jouvin, *Angew. Chem., Int. Ed.*, 2010, **49**, 2840–2859.
- (a) Y.-B. Chen, P.-C. Qian and L.-W. Ye, *Chem. Soc. Rev.*, 2020, **49**, 8897–8909; (b) G. Evano, M. Lecomte, P. Thilmany and C. Theunissen, *Synthesis*, 2017, **49**, 3183–3214; (c) X.-J. Li, Y. Sun, L. Zhang and B. Peng, *Chin. J. Org. Chem.*, 2016, **36**, 2530–2544.
- (a) P. W. Davies, *Chem. Rec.*, 2021, **21**, 3964–3977; (b) G.-X. Ru, T.-T. Zhang, M. Zhang, X.-L. Jiang, Z.-K. Wan, X.-H. Zhu, W.-B. Shen and G.-Q. Gao, *Org. Biomol. Chem.*, 2021, **19**, 5274–5283; (c) D. V. Patil and S. Shin, *Asian J. Org. Chem.*, 2019, **8**, 63–73; (d) Y. Liao, L. Zhu, Y.-H. Yu, G. Chen and X.-L. Huang, *Chin. J. Org. Chem.*, 2017, **37**, 2785–2799.
- For reviews on addition reactions of ynamides, see: (a) B. Zhou, T.-D. Tan, X.-Q. Zhu, M. Shang and L.-W. Ye, *ACS Catal.*, 2019, **9**, 6393–6406; (b) X. Li, Y. Sun, L. Zhang and B. Peng, *Chin. J. Org. Chem.*, 2016, **36**, 2530–2544.
- For reviews on annulation reactions of ynamides, see: (a) Y.-C. Hu, Y. Zhao, B. Wan and Q.-A. Chen, *Chem. Soc. Rev.*, 2021, **50**, 2582–2625; (b) L. Li, W.-F. Luo and L.-W. Ye, *Synlett*, 2021, **32**, 1303–1308; (c) X. Zhou, Z. Liang and X.-N. Wang, *Chin. J. Org. Chem.*, 2021, **41**, 1288–1318; (d) F.-L. Hong and L.-W. Ye, *Acc. Chem. Res.*, 2020, **53**, 2003–2019; (e) G. Duret, V. L. Fouler, P. Bissereet and V. Bizet, *Eur. J. Org. Chem.*, 2017, 6816–6830; (f) B. Prabagar, N. Ghosh and A. K. Sahoo, *Synlett*, 2017, 2539–2555; (g) F. Pan, C. Shu and L.-W. Ye, *Org. Biomol. Chem.*, 2016, **14**, 9456–9465; (h) X.-N. Wang, H.-S. Yeom, L.-C. Fang, S. He, Z.-X. Ma, B. L. Kedrowski and R. P. Hsung, *Acc. Chem. Res.*, 2014, **47**, 560–578.
- For reviews on transition metal-catalyzed cross-coupling reactions of ynamides, see: (a) F.-L. Hong and L.-W. Ye, *Acc. Chem. Res.*, 2020, **53**, 2003–2019; (b) L. Li, T.-D. Tan, Y.-Q. Zhang, X. Liu and L.-W. Ye, *Org. Biomol. Chem.*, 2017, **15**, 8483–8492.
- For reviews on radical reactions of ynamides, see: (a) T.-D. Tan, Z.-S. Wang, P.-C. Qian and L.-W. Ye, *Small Methods*, 2021, **5**, 2000673; (b) C. Mahe and K. Cariou, *Adv. Synth. Catal.*, 2020, **362**, 4820–4832.
- For reviews on ynamide coupling reagents, see: (a) T. Liu, S.-L. Xu and J.-F. Zhao, *Chin. J. Org. Chem.*, 2021, **41**, 873–887; (b) Q. Song, L.-Y. Kong, L.-L. Zhu, R. Hong and S.-H. Huang, *Chin. J. Chem.*, 2021, **39**, 1022–1024; (c) L. Hu and J.-F. Zhao, *Synlett*, 2017, **28**, 1663–1670. For some selected reports, see: (d) S.-L. Xu, D.-D. Jiang, Z.-J. Peng, L. Hu, T. Liu, L.-L. Zhao and J.-F. Zhao, *Angew. Chem., Int. Ed.*, 2022, **61**, e202212247; (e) T. Liu, X. Zhang, Z.-J. Peng and J.-F. Zhao, *Green Chem.*, 2021, **23**, 9916–9921; (f) C.-C. Yao, J.-H. Yang, X.-B. Lu, S.-Y. Zhang and J.-F. Zhao, *Org. Lett.*, 2020, **22**, 6628–6631; (g) X.-W. Wang, Y. Yang, Y.-L. Zhao, S. Wang, W.-C. Hu, J.-M. Li, Z. Wang, F.-L. Yang and J.-F. Zhao, *J. Org. Chem.*, 2020, **85**, 6188–6194; (h) M. Yang, X.-W. Wang and J.-F. Zhao, *ACS Catal.*, 2020, **10**, 5230–5235; (i) J.-H. Yang, C.-L. Wang, C.-C. Yao, C.-Q. Chen, Y.-F. Hu, G.-F. He and J.-F. Zhao, *J. Org. Chem.*, 2020, **85**, 1484–1494; (j) J.-H. Yang, C.-L. Wang, S.-L. Xu and J.-F. Zhao, *Angew. Chem., Int. Ed.*, 2019, **58**, 1382–1386; (k) L. Hu, S.-L. Xu, Z.-G. Zhao, Y. Yang, Z.-Y. Peng, M. Yang, C.-L. Wang and J.-F. Zhao, *J. Am. Chem. Soc.*, 2016, **138**, 13135–13138.
- (a) Y.-L. Zhao, Y.-L. Tu, M.-Z. Cai and J.-F. Zhao, *Chin. J. Org. Chem.*, 2022, **42**, 85–99; (b) W.-X. Peng, E. Vessally, S. Arshad, A. Monfared, A. Hosseini and



- L. Edjlali, *Top. Curr. Chem.*, 2019, **377**, 20–41; (c) G. Evano, K. Jouvin and A. Coste, *Synthesis*, 2013, **45**, 17–26. For very recent selected reports, see: (d) K. Kagami, X.-Y. Liang, N. Ishibashi, S. Ohruai, M. Tayu and N. Saito, *Chem. Commun.*, 2023, **59**, 8274–8277; (e) R. Kawakami, S. Usui, N. Tada and A. Itoh, *Chem. Commun.*, 2023, **59**, 450–453.
- 10 For very recent selected reviews, see: (a) J.-B. Li, C.-Y. Huang and C.-J. Li, *Trends Chem.*, 2022, **4**, 479–494; (b) A. Bera, L. M. Kabadwal, S. Bera and D. Banerjee, *Chem. Commun.*, 2022, **58**, 10–28; (c) T. Tian, Z.-P. Li and C.-J. Li, *Green Chem.*, 2021, **23**, 6789–6862; (d) C. M. A. Afsina, T. Aneeraja, M. Neetha and G. Anilkumar, *Eur. J. Org. Chem.*, 2021, 1776–1808; (e) K. Peng and Z.-B. Dong, *Adv. Synth. Catal.*, 2021, **363**, 1185–1201; (f) W.-H. Zhuang, X.-F. Zhang and Q.-F. Huang, *Chin. J. Org. Chem.*, 2021, **41**, 529–542.
- 11 (a) For a review, see ref. 9b; (b) H. T. N. Le, T. V. Tran, N. T. S. Phan and T. Truong, *Catal. Sci. Technol.*, 2015, **5**, 851–859; (c) X.-J. Jin, K. Yamaguchi and N. Mizuno, *Chem. Commun.*, 2012, **48**, 4974–4976; (d) X.-G. Tong, G.-H. Ni, X. Deng and C.-F. Xia, *Synlett*, 2012, **23**, 2497–2500; (e) T. Hamada, X. Ye and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 833–835.
- 12 For reviews on nitrogen-centred radicals, see: (a) H. Song, X.-Y. Liu and Y. Qin, *Acta Chim. Sin.*, 2017, **75**, 1137–1149; (b) T. Xiong and T. Zhang, *Chem. Soc. Rev.*, 2016, **45**, 3069–3087; (c) J.-R. Chen, X.-Q. Hu, L.-Q. Lu and W.-J. Xiao, *Chem. Soc. Rev.*, 2016, **45**, 2044–2056; (d) S. Z. Zard, *Chem. Soc. Rev.*, 2008, **37**, 1603–1618.
- 13 F. Xu, L. Zhu, S.-B. Zhu, X.-M. Yan and H.-C. Xu, *Chem. – Eur. J.*, 2014, **20**, 12740–12744.

