ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

Chemo- and Stereoselective Synthesis of Substituted Thiazoles from *tert*-Alcohols Bearing Alkene and Alkyne Groups with Alkaline Earth Catalysts

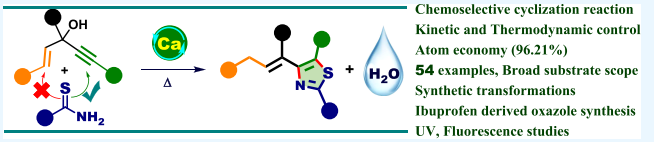
Srinivasarao Yaragorla* and Dandugula Sneha Latha

Cite This: *ACS Omega* 2022, 7, 34693−34706

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: We report here that thioamides can distinguish C−C double bonds and C−C triple bonds chemoselectively when subjected to a reaction with pent-1-en-4-yn-3-ol derivatives in the presence of $Ca(OTf)_2$. This protocol offers a fast, efficient, and high-yielding synthesis of functionalized thiazoles. Interestingly, this reaction offers a time-dependent formation of kinetic and thermodynamic products. The products showed stereoselectivity concerning the alkene geometry. Further, we extended this protocol to synthesize oxazoles from propargyl alcohols and ibuprofen (NSAID) was converted into amide and then subjected to oxazole formation with *tert*-propargyl alcohols.



INTRODUCTION

Thiazoles and oxazoles are important structural moieties, often found in natural products and biologically active or pharmaceutical compounds (Figure 1).[1] For example, thiazole natural products, such as the mycothiazole,[2] and cystothiazole A[3] exhibit a diverse range of biological activities. Additionally, there is increasing interest in these scaffolds for material applications. Thus, the discovery of their significant pharmacological activities and their pivotal role as building blocks/synthetic intermediates have attracted the attention of chemists both in academia and industry, which stimulated the substantial interest in the chemistry and synthesis of thiazoles and of course their bio-isosteres.[4] Since the popular Hantzsch thiazole synthesis,[5] several catalytic methods have been developed.[6,8,9] In recent years, propargyl alcohols are serving as key building blocks for constructing various organic molecules.[7] Their utility was also extensively studied for the oxazole synthesis by treating with amides.[7,8] However, a limited number of studies were done for thiazole synthesis from *sec*-propargyl alcohols as well as a couple of reports with *tert*-propargyl alcohols using silver triflate[9a] and *p*-toluenesulfonic acid.[9b] On the other hand, calcium salts have been identified as sustainable Lewis acid catalysts for various organic reactions due to their large abundance, biodegradability, nontoxic, less expensive, and moisture-stable features.[10,11] Over the past 5 years, our group has been actively engaged in utilizing the Ca(II) catalysts for activating propargyl alcohols toward developing various synthetic methodologies.[11a−c] With this experience, we desired to develop a catalytic, synthetic method for thiazole synthesis by treating propargyl alcohols and thioamides in the presence of a Ca(II) catalyst, thereby extending this to the oxazole synthesis. Further, to advance the synthetic protocol, we wanted to subject the propargyl alcohol bearing a vinyl substitution on the propargylic carbon to reaction with thioamide; this will lead us to investigating the chemoselective cyclization of thioamides with alkene and alkyne (Scheme 1).

RESULTS AND DISCUSSION

As proposed (Scheme 1), we commenced the reaction of compound **1a** (prepared using a reported procedure)[12] and thiobenzamide **2a** with $Ca(OTf)_2/Bu_4NPF_6$ in 1,2-dichloroethane at rt. Since the reaction showed <5% product formation at rt (entry 1), we heated the reaction mixture in DCE (entry 2). Delightfully, 40% of the product was isolated in 6 h. Continuing beyond 6 h could not increase the product yield. Encouraged by this observation, we planned to screen the reaction conditions to increase the product yield. Accordingly, we have heated the reaction mixture in various solvents, such as acetonitrile, THF, ethanol, hexafluoroisopropanol (HFIP), and toluene (entries 3−7). Thus, we observed that the maximum yield of **3a** (85%, entry 7) was obtained in toluene in 40 min. While reproducing this result, it was observed that a positional isomer **3s** was initially formed (double bond away from thiazole ring, kinetic product) in 10 min, slowly isomerizing to a more conjugated system **3a** (thermodynamically more stable).[13] Nevertheless, in both products, the spectral data indicates that the alkyne was involved in the

Received: August 9, 2022
Accepted: September 5, 2022
Published: September 15, 2022

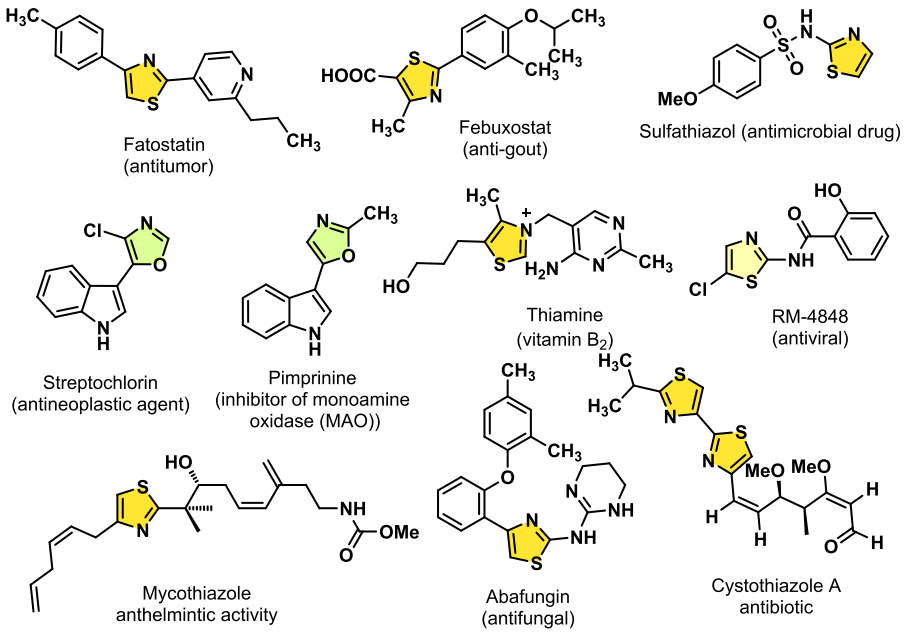
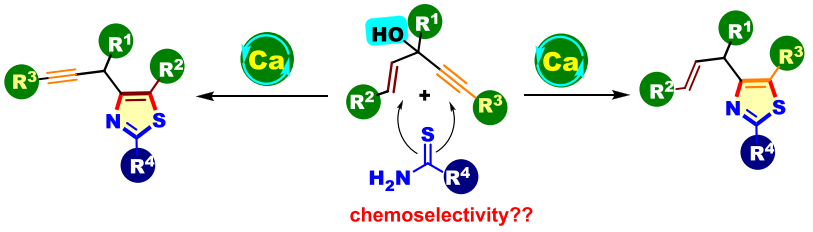


Figure 1. Representative examples of natural and biologically potent thiazoles and oxazoles.

Scheme 1. Possible Ways of Chemoselective Thiazole Formation with the Substrate Having Alkene and Alkyne Groups

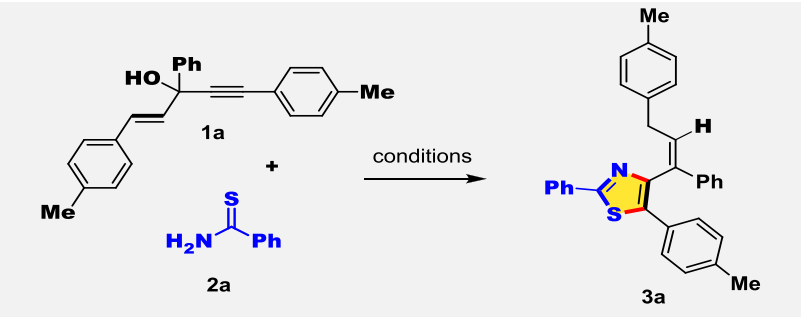


thiazole formation keeping the alkene intact. The chemical shift of the olefinic proton at 6.33 δ ppm in the ^{1}H NMR spectrum indicated the stereoselective olefin (Z) formation of **3a** (which was later supported by the single-crystal X-ray data). Continuing the reaction for a long time did not show any increase in the yield of **3a**; also, decreasing or increasing the reaction temperature was not fruitful in obtaining a better yield. Surprisingly, the reaction also produced **3a** in 60% yield by heating at 120 °C under solvent-free conditions but it took 24 h (entry 9). There was no reaction observed in the absence of a catalyst (entry 10). For other alkaline earth catalysts, Mg $(OTf)_2$ gave a 40% yield in 24 h, and Ca $(NTf_2)_2$ gave a complex TLC (entries 11 and 12). The Brønsted acid catalyst (*p*-TSA) gave 58% product formation (entry 13). Transition-metal catalysts $FeCl_3$, Cu $(OTf)_2$, and Cu $(OAc)_2$ were not found to be suitable under these conditions (entries 14−16). Based on these optimization studies, we realized that entry 7 (Table 1) is the best condition to obtain the maximum yield of **3a**.

Having the optimum reaction conditions in hand, we then planned to check the generality of this protocol (Scheme 2). Initially, we treated propargyl alcohol **1a** with *para*-substituted thiobenzamides bearing trifluoromethyl, methyl, and methoxy groups under standard conditions and witnessed that all of them showed excellent reactivity and furnished the corresponding fully conjugated 4-vinyl thiazoles **3a**-**3d** in good yields. Further, a gram-scale synthesis of **3d** (1.14 g) was performed, and its single crystal-X-ray data was obtained to confirm the structure to avoid ambiguity.[14] Next, we subjected (*E*)-1,3,5-triphenylpent-1-en-4-yn-3-ol (**1b**) and substituted thiobenzamides under the reaction conditions to obtain the more conjugated thiazoles **3e** to **3h** in good yields. The other substrate (*E*)-3-(4-chlorophenyl)-1,5-diphenylpent-1-en-4-yn-3-ol (**1c**) also showed excellent reactivity with thiobenzamide and 4-methyl thiobenzamide to furnish the corresponding fully conjugated thiazoles **3i** and **3j**. Next, we synthesized thiazole **3k** in 81% yield from (*E*)-1,5-diphenyl-3-(*p*-tolyl)pent-1-en-4-yn-3-ol (**1d**) and thiobenzamide **2a** under standard conditions. Another fully conjugated thiazole **3l** was prepared from (*E*)-1,5-diphenyl-3-(thiophen-2-yl)pent-1-en-4-yn-3-ol (**1e**) with thiobenzamide **2a** in 80% yield after 2 h. During the synthesis of these thermodynamically more stable products (a trisubstituted olefin in conjugation with thiazoles) **3a** to **3l**, we observed that in all the cases, another product (a fast forming isomer) was forming, which slowly converts to the compounds mentioned above with time. Therefore, we also wanted to isolate these fast-forming isomers (kinetic products). Accordingly, (*E*)-3-(4-ethoxyphenyl)-1,5-diphenylpent-1-en-4-yn-3-ol (**1f**) was subjected to standard reaction conditions with thiobenzamide **2a** and isolated the first product **3m** in 86% yield after 25 min. The ^{1}H NMR spectrum of **3m** indicated that the disubstituted alkene is not in conjugation with thiazole and has a *trans* geometry. Similarly, (*E*)-3-(furan-2-yl)-1,5-diphenylpent-1-en-4-yn-3-ol (**1g**) was also investigated against a variety of thioamides under the reaction conditions and produced the corresponding initial thiazole compounds **3n** to

https://doi.org/10.1021/acsomega.2c05085
ACS Omega 2022, 7, 34693−34706

Table 1. Optimization of Reaction Conditions[a]



entry	reaction conditions	yield (%)[b]
1	$Ca(OTf)_2/Bu_4NPF_6$ (5/5), DCE, rt., 24 h	<5
2	$Ca(OTf)_2/Bu_4NPF_6$ (5/5), DCE, 90 °C, 6 h	40
3	$Ca(OTf)_2/Bu_4NPF_6$ (5/5), CH_3CN, 90 °C, 5 h	60
4	$Ca(OTf)_2/Bu_4NPF_6$ (5/5), THF, 90 °C, 2 h	80
5	$Ca(OTf)_2/Bu_4NPF_6$ (5/5), EtOH, 90 °C, 3 h	40
6	$Ca(OTf)_2/Bu_4NPF_6$ (5/5), HFIP, 80 °C, 4 h	63
7[c]	$Ca(OTf)_2/Bu_4NPF_6$ (5/5), toluene, 120 °C, 40 min	85
8	$Ca(OTf)_2/Bu_4NPF_6$ (5/5), toluene, 100 °C, 4 h	75
9	$Ca(OTf)_2/Bu_4NPF_6$ (5/5), neat, 120 °C, 24 h	60
10	toluene, 120 °C, 24 h	nr
11	$Mg(OTf)_2/Bu_4NPF_6$ (5/5), toluene, 120 °C, 24 h	40
12	$Ca(NTf_2)_2/Bu_4NPF_6$ (5/5), toluene, 120 °C, 1 h	$
13	*p*-TSA (5), toluene, 120 °C, 6 h	58
14	$FeCl_3$ (5), toluene, 120 °C, 5 h	$
15	$Cu(OTf)_2$ (5), toluene, 120 °C, 24 h	35
16	$Cu(OAc)_2$ (5), toluene, 120 °C, 24 h	<5

[a]Reaction conditions: **1a** (0.28 mmol), **2a** (0.42 mmol), all reactions were monitored up to 24 h; oil bath temperatures mentioned. [b]Isolated yields. [c]Optimum condition. $ = complex TLC; nr = no reaction.

3p in good yields in 40−50 min. The same observation was also made with **1g** and 4-(trifluoromethyl) benzothioamide in 40 min; further continuing the reaction up to 70 min produced an inseparable mixture of products **3q** and **3r** in a 1: 1.25 ratio, which again confirms that with time, **3q** is isomerizing to a more conjugated system **3r**.[15] As **3a** was formed from **1a** and **2a** after 40 min, we repeated this reaction again and stopped the reaction after 10 min to isolate the thiazole **3s** in 75% yield. It was also observed that under the standard conditions, **3s** was converted to **3a**. After developing the reactions of **1** with various thioamides, we tried to extend the same with benzamide; however, compound **1** gave an inseparable mixture of compounds with benzamide under these conditions.

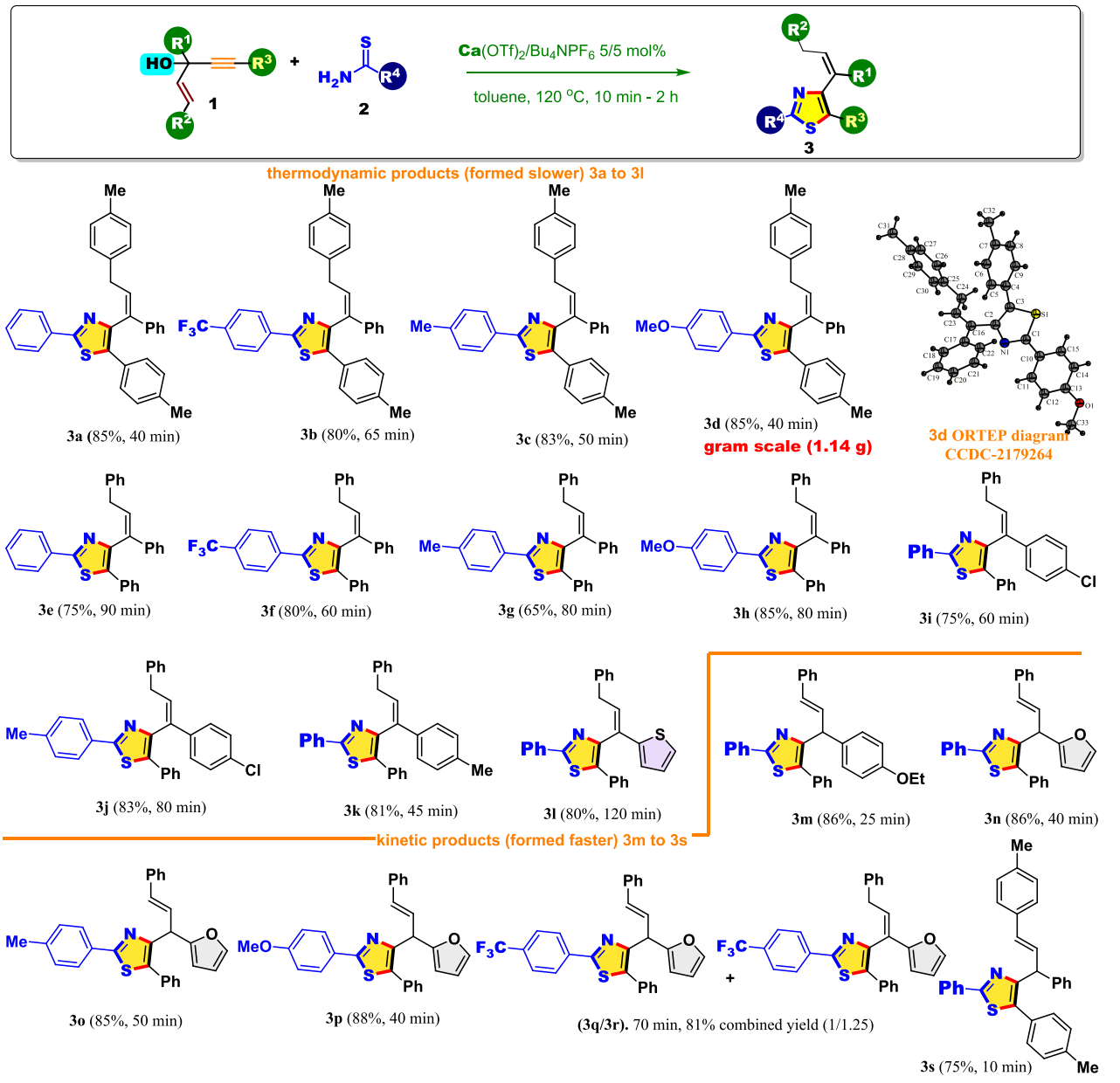
We then investigated the reactivity of tertiary propargyl alcohol **4** in the thiazole formation under standard conditions (Scheme 3). Gratefully, the reaction of 1,1,3-triphenylprop-2-yn-1-ol (**4a**) gave a nearly quantitative yield of thiazole **5a** under standard reaction conditions. When we replaced toluene with water, the reaction gave the same yield but took 24 h. Interestingly, solvent-free conditions provided a similar yield of **5a** in 25 min. Albeit the three conditions (heating in toluene, water, and neat) gave comparable yields, the reaction in the water took a long time. Next, we studied that substituted aryl thioamides **2** bearing electron-donating groups gave higher yields than electron-withdrawing groups (though the difference is slight) to furnish thiazoles **5a−5d** under standard conditions. Then, we switched to see the scope of various substituted propargyl alcohols having aryl, alicyclic, and aliphatic groups and observed the excellent reactivity and the yields of corresponding thiazoles **5e−5p**. It is worth noting that compounds **5a**, **5e**, **5j**, **5 k**, **5l**, **5 m**, **5n**, and **5o** were also produced in similar yields under solvent-free conditions. Surprisingly, the reaction of 1-(phenylethynyl)cycloheptan-1-ol with benzothiamide did not result in the desired thiazole formation in toluene; instead, the propargyl alcohol underwent a rapid Rupe elimination[13] to give the corresponding 1,3-enyne **5q**. Nevertheless, we have circumvented this problem by performing the reaction under the solvent-free condition to get the desired thiazole **5r** in 81% yield.

After the successful demonstration of thiazole synthesis, we were curious to extend this strategy to the oxazole synthesis by treating propargyl alcohols **4** with amide **6** (Scheme 4). Initial attempts under solvent-free conditions gave the oxazole **7a** in 85% yield and in aqueous conditions gave poor yields (<10%) even after 24 h. The standard conditions (heating in toluene) provided a nearly quantitative yield of **7a** in 30 min. The structure of **7a** was further confirmed by obtaining its single-crystal X-ray data.[14] With the success of this example, we have studied the scope of both the substituted aryl amides **6** and propargyl alcohols **4** and obtained the desired oxazoles **7b−7o** in excellent yields (Scheme 4). It is worth mentioning that the *ortho*-substituted (methyl) benzamide, when reacted with propargyl alcohol **4a**, furnished the corresponding oxazole **7e**, which showed the atropisomerism in the ^{1}H NMR spectrum; we have also obtained the crystal structure of **7e**.[14]

Additionally, we have converted ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), to corresponding amide **8** quantitatively by treating with thionyl chloride and aqueous ammonia. Then, the ibuprofen amide **8** was subjected to standard reaction conditions with propargyl alcohol **4a** and the

https://doi.org/10.1021/acsomega.2c05085
ACS Omega 2022, 7, 34693−34706

Scheme 2. Substrate Scope of Functionalized Thiazoles 3



corresponding thiazole **9** was obtained in a 65% yield. Similarly, compound **10** was also made in a 69% yield (Scheme 5).

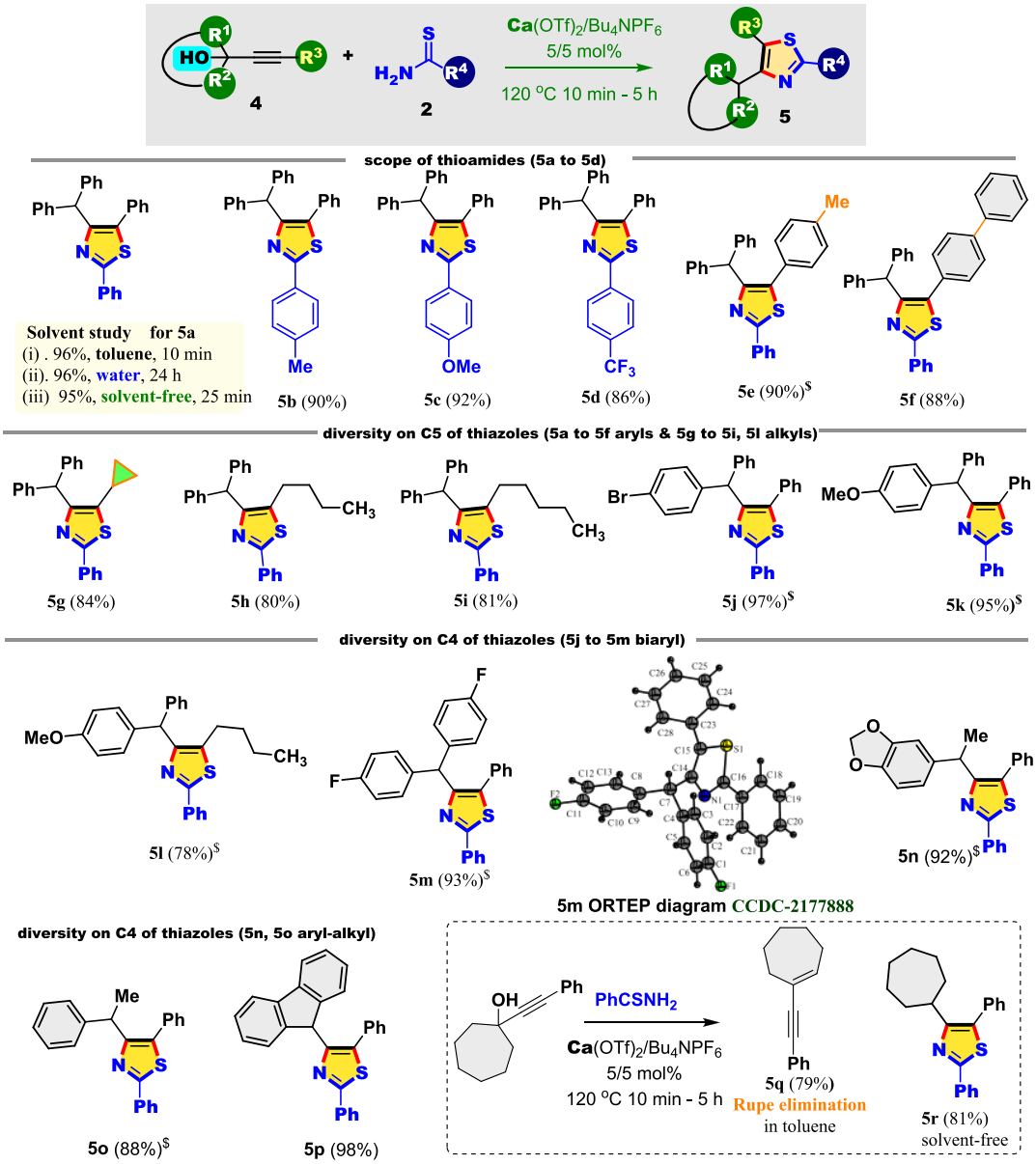
Next, we subjected thiazole **3d** to dioxidation with an excess of *m*-chloroperbenzoic acid and obtained the corresponding thiazole *S*, *S*-dioxide **11** in 81% yield after 12 h (Scheme 6).[16] It is important to note that the double bond of **3d** did not react with *m*-CPBA even after 12 h, probably due to the extended conjugation obtained.

The reaction mechanism for this chemo- and stereoselective cyclization reaction is depicted in Scheme 7. Initially, the tautomer of thioamide reacts with activated (with calcium catalyst) propargyl alcohol **1** to form allene (**A**) by removing water. Then, an intramolecular, regioselective 5-*exo dig* cyclization of allene produces the thiazole **3**. With time, the double bond isomerizes to a highly conjugated (thermodynamically stable) thiazole **3′**.

While synthesizing these thiazoles, we observed the luminescence of all the products under long UV light. Hence, we have selected 10 compounds to study their photophysical properties such as UV−visible and fluorescence characteristics. Four of them were benzhydryl thiazoles (**5a**, **5d**, **5f**, **5h**), one was cycloheptyl thiazole (**5r**), one was phenyl alkyl thiazole (**5o**), two were vinyl thiazoles (**3c** and **3e**), and the last two were furyl allyl thiazoles (**3p** and **3o**). The UV−Visible spectra of these compounds in acetonitrile exhibited the maximum absorption wavelength (λ_{max}) at 252−328 nm, as shown in Table 2 and Figure 2. It should be noted that the λ_{max} covered all of the UV region, i.e., **5d**, **5f**, **3c**, and **3e** showed in the UV-A region with wavelengths above 315 nm, **5a**, **5o**, and **3o** showed in the UV-B region at 312, 310, and 314 nm, respectively, and **5h** and **5r** showed in the UV-C region at 297 and 252 nm, respectively. Thiazoles having extended conjugation on C4, such as furyls (**3o**, **3p**), vinyl (**3c**, **3e**), and benzhydryl (**5a**, **5o**, **5d**, **5f**), exhibited an enhanced red

https://doi.org/10.1021/acsomega.2c05085
ACS Omega 2022, 7, 34693−34706

Scheme 3. Substrate Scope of *tert*-Propargyl Alcohols with Thioamides for the Synthesis of Thiazoles[a]



[a]Unless mentioned, all the reactions were heated in toluene at 120 °C (oil bath temperature); $ = heated at 120 °C under solvent-free conditions.

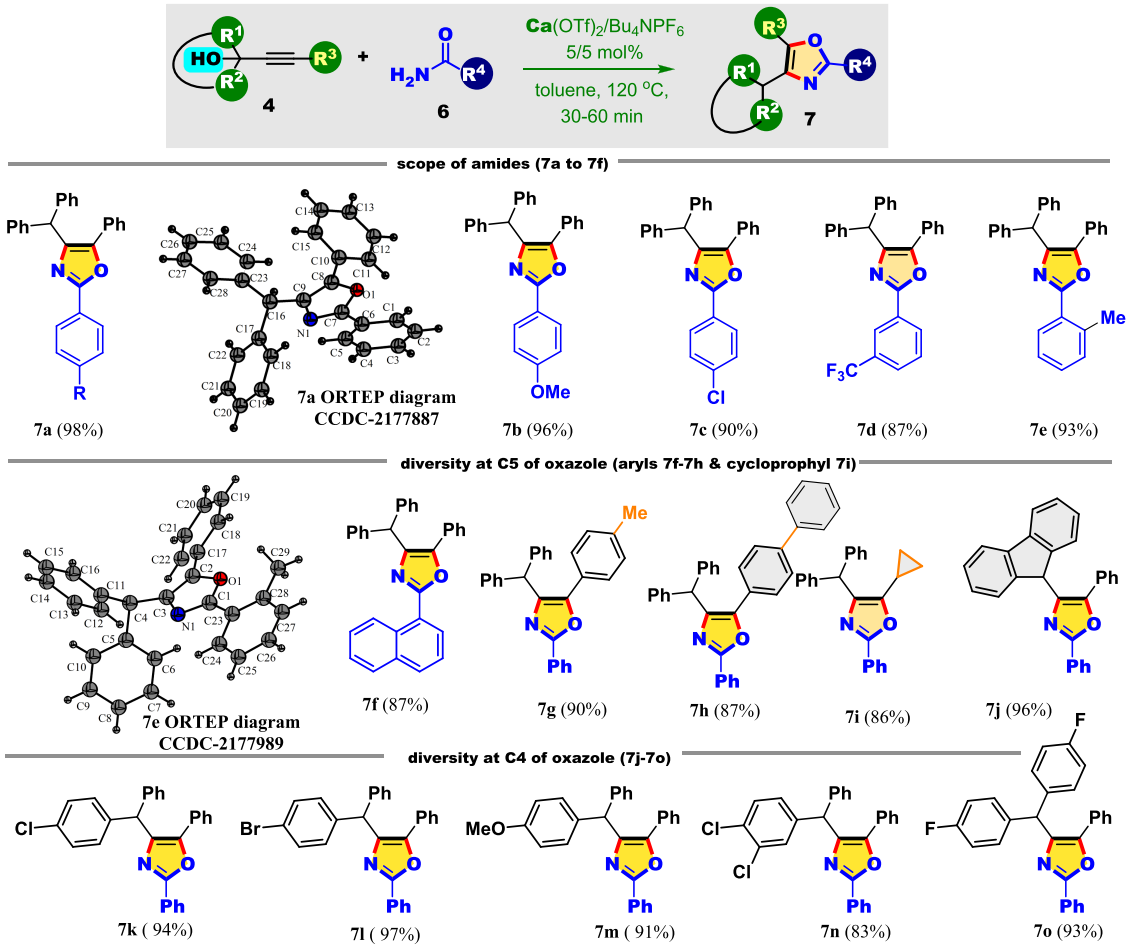
shift compared to those with alkyl and aromatic substitutions (**5h**, **5r**) due to the diminishment of the energy gap between $\pi \rightarrow \pi^*$ interactions. The fluorescence spectra of **5h** and **5r** showed the emission maxima (λ_{em}) at 367 and 355 nm, respectively; the remaining **5a**, **5o**, **5d**, **5f**, **3c**, **3p**, **3e**, and **3o** emitted at 399−418 nm, which indicates the role of the electron-donating group on the thiazole rings. The absorption peak wavelengths (λ_{abs}), calculated molar extinction coefficient (ε), and emission peak wavelengths in acetonitrile are summarized in Table 2. Based on these observations, these compounds may be suitable for appropriate modifications so that they may be useful in the future as fluorescent probes.[17]

CONCLUSIONS

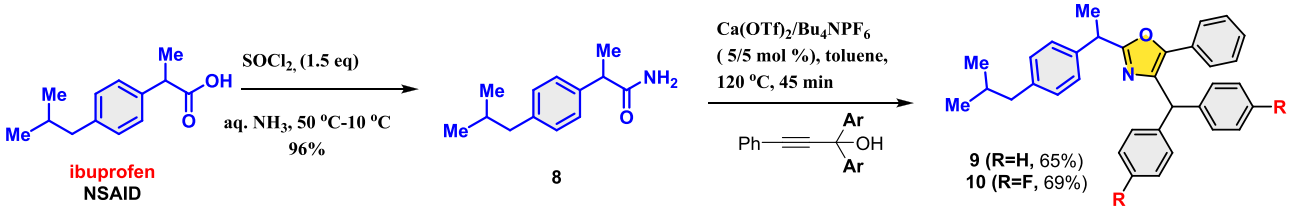
In conclusion, we have described chemo- and stereoselective thiazole synthesis from propargyl alcohols bearing alkene at the propargylic carbon. Interestingly, the reaction showed the formation of time-dependent kinetic and thermodynamic products. The products formed were also stereoselective concerning the geometry of the olefins. This reaction was found to be selective toward alkyne over alkene. We also extended this protocol to the solvent-free synthesis of selected thiazoles with *tert*-propargyl alcohols, further proving that the reaction conditions were used to make the oxazoles from amides by heating them in toluene. A gram-scale synthesis was demonstrated. A non-steroidal anti-inflammatory drug (NSAID), ibuprofen, was converted into amide and subjected to the corresponding oxazole formation using this protocol. Selective oxidation of **3d** to corresponding *S*,*S*-dioxide was achieved. Preliminary photophysical properties were also studied. The selective reactivities, fast and high reaction yields, broad substrate scope, use of an alkaline earth catalyst, and atom economy (96.21%) are the other highlights of the work.

https://doi.org/10.1021/acsomega.2c05085
ACS Omega 2022, 7, 34693−34706

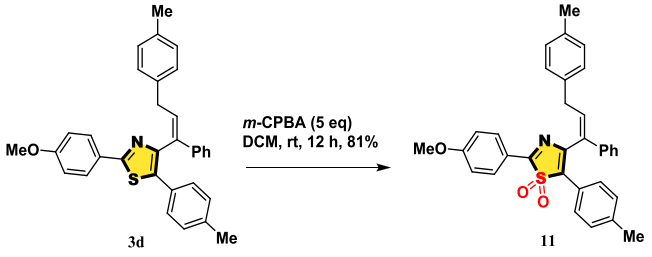
Scheme 4. Substrate Scope of *tert*-Propargyl Alcohols with Amides for the Synthesis of Oxazoles



Scheme 5. Amidation of Ibuprofen and Application to Oxazole Synthesis Using Our Protocol



Scheme 6. Dioxidation of Thiazole 3d



EXPERIMENTAL SECTION

General. Unless otherwise noted, all reagents were used as received from commercial suppliers. Reactions were performed in oven-dried glassware with magnetic stirring. All the reactions were monitored using TLC with aluminum sheets of silica gel 60 F254 from Merck. TLC plates were visualized with UV light (254 nm), iodine treatment, and a *p*-anisaldehyde stain. Column chromatography was carried out using silica gel 100−200 mesh as the stationary phase. NMR spectra were recorded at 500 and 400 MHz (^{1}H) and at 125 and 100 MHz (^{13}C), respectively, on the Avance Bruker spectrometer. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in $CDCl_3$ (^{1}H: δ = 7.26 and ^{13}C: δ = 77.16 ppm) as an internal standard and coupling constants (J) are given in Hz. HRMS spectra were recorded using ESI-TOF techniques. Melting points were measured with LABINDIA mepa melting apparatus. Single crystal X-ray diffraction data were collected in a Bruker D8-Quest diffractometer. Unless mentioned, all the chemicals were purchased from commercial sources. Propargyl alcohols were prepared using the reported procedures.[12,19]

General Experimental Procedure (1) for the Synthesis of Thiazole 3. To a mixture of propargyl alcohol **1** (0.28 mmol) and thiobenzamide **2** (0.42 mmol) was added $Ca(OTf)_2/Bu_4NPF_6$ (5/5 mol %) and heated in toluene at

https://doi.org/10.1021/acsomega.2c05085
ACS Omega 2022, 7, 34693−34706

Scheme 7. Proposed Reaction Mechanism

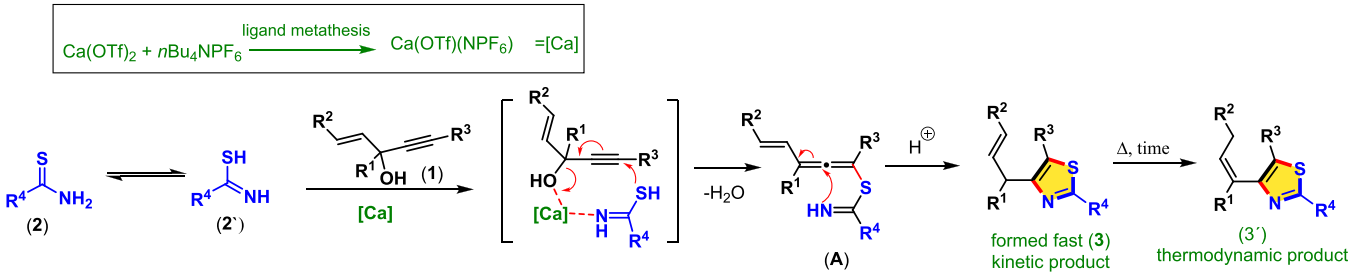


Table 2. Absorbance, Extinction Coefficient (ε), and Emission Wavelengths of Listed Compounds

entry	compound	λ_{abs} (nm)[a]	absorbance at λ_{max}	λ_{emm} (nm)[b]	ε (1×10^4 M^{-1} cm^{-1})
1	**5a**	317	0.33	399	1.00
2	**5o**	310	0.34	400	1.03
3	**5d**	319	0.36	408	1.09
4	**5f**	318	0.65	418	1.96
5	**5h**	297	0.41	367	1.24
6	**5r**	252	0.33	355	1.00
7	**3c**	328	0.42	418	1.27
8	**3p**	273	0.96	410	2.90
9	**3e**	273	0.43	415	1.30
10	**3o**	320	0.40	406	1.21

120 °C. After completion of the reaction (monitored by TLC), the crude product was purified by silica-gel column chromatography (1% EtOAc in petroleum ether) to obtain the corresponding thiazole **3** as a pure product.

General Experimental Procedure (2) for the Synthesis of Thiazole 5. To a mixture of propargyl alcohol **4** (0.35 mmol) and thiobenzamide **2** (0.52 mmol) was added $Ca(OTf)_2/Bu_4NPF_6$ (5/5 mol %) and heated at 120 °C under neat conditions or heated in toluene (as specified). After completion of the reaction (monitored by TLC), the crude product was purified by silica-gel column chromatography (1% EtOAc in petroleum ether) to obtain the corresponding thiazole **5** as a pure product.

General Experimental Procedure (3) for the Synthesis of Oxazole 7. To a mixture of propargyl alcohol **4** (0.35 mmol) and benzamide **6** (0.52 mmol) was added $Ca(OTf)_2/Bu_4NPF_6$ (5/5 mol %) and heated at 120 °C in toluene (as specified). After completion of the reaction (monitored by TLC), the crude product was purified by silica-gel column chromatography (1% EtOAc in petroleum ether) to obtain the corresponding thiazole **7** as a pure product.

*(E)-2-Phenyl-4-(1-phenyl-3-(p-tolyl)prop-1-en-1-yl)-5-(p-tolyl)thiazole (**3a**).* Following the general experimental procedure (**1**), compound **3a** was obtained as a white solid (115 mg, 85%); mp: 83−84 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93−7.91 (m, 2H), 7.36−7.31 (m, 6H), 7.21−7.18 (m, 2H), 7.14−7.10 (m, 2H), 7.01 (d, J = 7.60 Hz, 2H), 6.91 (d, J = 6.95 Hz, 2H), 6.79 (d, J = 7.85 Hz, 2H), 6.33−6.29 (m, 1H), 3.16 (d, J = 7.20 Hz, 2H), 2.26 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 149.0, 138.1, 137.1, 136.0, 135.5, 135.4, 133.8, 132.0, 130.0, 129.5, 129.1, 129.0, 128.9, 128.6, 128.4, 128.3, 127.3, 126.7, 126.6, 125.4, 35.9, 21.3, 21.1 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{32}H_{28}NS]^+$: 458.1937; found: 458.1933.; IR (film): ν_{max} 3014, 2918, 2850, 1598, 1492, 813, 755, 716 cm^{-1}.

*(E)-4-(1-Phenyl-3-(p-tolyl)prop-1-en-1-yl)-5-(p-tolyl)-2-(4-(trifluoromethyl)phenyl)thiazole (**3b**).* Following the general experimental procedure (**1**), compound **3b** was obtained as a brown liquid (124 mg, 80%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, J = 8.10 Hz, 2H), 7.68 (d, J = 8.25 Hz, 2H), 7.40−7.38 (m, 4H), 7.29−7.25 (m, 2H), 7.23−7.20 (m, 1H), 7.09 (d, J = 7.95 Hz, 2H), 6.98 (d, J = 7.80 Hz, 2H), 6.85 (d, J = 7.90 Hz, 2H), 6.40 (t, J = 7.30 Hz, 1H), 3.21 (d, J = 7.35 Hz, 2H), 2.33 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 149.5, 140.1, 138.5, 137.3, 136.9 (2), 135.5, 135.3, 132.2, 129.7, 129.6, 129.2, 129.1, 128.6, 128.5, 128.3, 127.4, 126.7, 126.6, 126.4, 125.9, 124.4, 122.7, 35.9, 21.3, 21.1

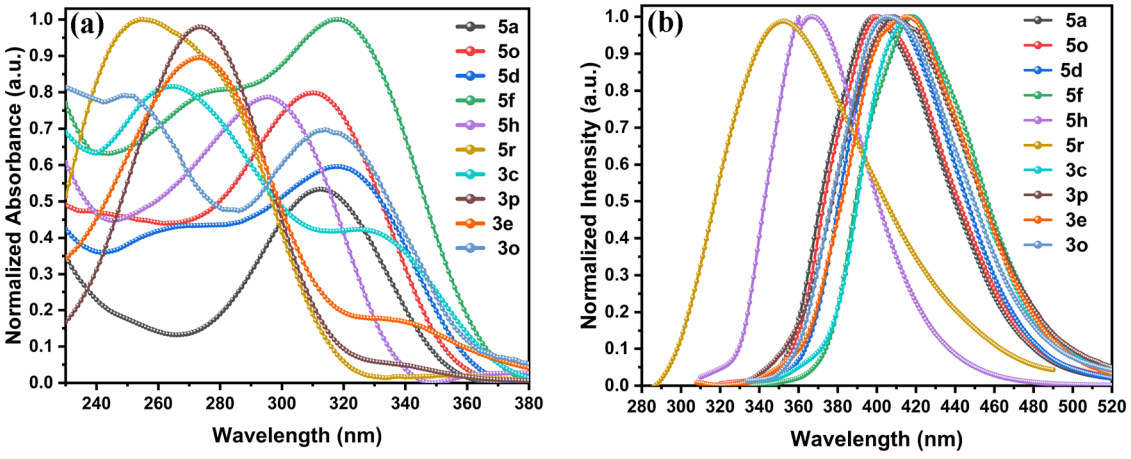


Figure 2. Absorbance (a) and fluorescence emission (b) spectra of compounds **5a**, **5o**, **5d**, **5f**, **5h**, **5r**, **3c**, **3p**, **3e**, and **3o** in acetonitrile recorded at a concentration of 3.3×10^{-5} M at room temperature (25 °C).

https://doi.org/10.1021/acsomega.2c05085
ACS Omega 2022, 7, 34693−34706

ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ − 62.6 (s); HRMS (ESI-TOF) m/z: [M + H]$^+$calculated for $[C_{33}H_{27}F_3NS]^+$: 526.1811; found: 526.1810.

(E)-4-(1-Phenyl-3-(p-tolyl)prop-1-en-1-yl)-2,5-di-p-tolylthiazole ***(3c)***. Following the general experimental procedure (**1**), compound **3c** was obtained as white solid (116 mg, 83%); mp: 167−168 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, J = 7.95 Hz, 2H), 7.41−7.37 (m, 4H), 7.27 (d, J = 7.25 Hz, 2H), 7.24−7.20 (m, 3H), 7.07 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 7.85 Hz, 2H), 6.85 (d, J = 7.80 Hz, 2H), 6.37 (t, J = 7.25 Hz, 1H), 3.22 (d, J = 7.30 Hz, 2H), 2.39 (s, 3H) 2.32 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 148.8, 140.3, 140.2, 137.9, 137.2, 135.6, 135.4, 131.9, 131.2, 129.6, 129.4, 129.0, 128.6, 128.4, 128.2, 127.3, 126.7, 126.5, 35.9, 21.5, 21.3, 21.1 ppm; HRMS (ESI-TOF) m/z: [M + H]$^+$calculated for $[C_{33}H_{30}NS]^+$; 472.2093; Found; 472.2099.

(E)-2-(4-Methoxyphenyl)-4-(1-phenyl-3-(p-tolyl)prop-1-en-1-yl)-5-(p-tolyl)thiazole ***(3d)***. Following the general experimental procedure (**1**), compound **3d** was obtained as yellow solid (123 mg, 85%); mp: 134−135 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93−7.91 (m, 2H), 7.41−7.37 (m, 4H), 7.27−7.23 (m, 2H), 7.21−7.18 (m, 1H), 7.06 (d, J = 8.0 Hz, 2H), 6.97−6.93 (m, 4H), 6.85 (d, J = 7.95 Hz, 2H), 6.36 (t, J = 7.30 Hz, 1H), 3.84 (s, 3H), 3.23 (d, J = 7.25 Hz, 2H) 2.31 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 161.2, 148.6, 140.3, 137.9, 137.2, 135.6, 135.4, 135.0, 131.9, 129.4, 129.0, 128.6, 128.4, 128.2, 128.1, 127.3, 126.8, 126.7, 114.3, 55.5, 35.9, 21.3, 21.1 ppm; HRMS (ESI-TOF) m/z: [M + H]$^+$calculated for $[C_{33}H_{30}NOS]^+$: 488.1970; found: 488.2046.; IR (film): ν_{max} 2918, 1686, 1602, 1248, 819, 740 cm^{-1}.

(E)-4-(1,3-Diphenylprop-1-en-1-yl)-2,5-diphenylthiazole ***(3e)***. Following the general experimental procedure (**1**), compound **3e** was obtained as a yellow liquid (104 mg, 75%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01−7.99 (m, 2H), 7.51−7.49 (m, 2H), 7.43−7.40 (m, 5H), 7.28−7.25 (m, 5H), 7.22−7.18 (m, 2H), 7.16−7.10 (m, 3H), 6.96 (d, J = 6.90 Hz, 2H), 6.40 (t, J = 7.30 Hz, 1H), 3.28 (d, J = 7.35 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 149.3, 140.2, 135.9, 135.7, 133.7, 131.8, 130.1, 129.6, 129.0, 128.8, 128.7, 128.5, 128.4, 128.1, 127.4, 126.7, 126.6, 126.0, 36.4 ppm; HRMS (ESI-TOF) m/z: [M + H]$^+$calculated for $[C_{30}H_{24}NS]^+$: 430.1624; found; 430.1643.

(E)-4-(1,3-Diphenylprop-1-en-1-yl)-5-phenyl-2-(4-(trifluoromethyl)phenyl)thiazole ***(3f)***. Following the general experimental procedure (**1**), compound **3f** was obtained as a brown liquid (128 mg, 80%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 8.25 Hz, 2H), 7.69 (d, J = 8.45 Hz, 2H), 7.51−7.49 (m, 2H), 7.29−7.28 (m, 3H), 7.24−7.22 (m, 2H), 7.20−7.17 (m, 2H), 7.15−7.12 (m, 2H), 6.96 (d, J = 7.05 Hz, 2H), 6.42 (t, J = 7.35 Hz, 1H), 3.27 (d, J = 7.35 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7, 149.9, 140.0, 137.2, 136.8, 135.5, 132.0, 131.4, 128.9, 128.7, 128.5, 127.5, 126.7, 127.3, 126.8, 126.7, 126.1, 126.0, 36.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): −62.7 ppm; HRMS (ESI-TOF) m/z: [M + H]$^+$calculated for $[C_{31}H_{23}F_3NS]^+$: 498.1498; found: 498.1499.

(E)-4-(1,3-Diphenylprop-1-en-1-yl)-5-phenyl-2-(p-tolyl)-thiazole ***(3g)***. Following the general experimental procedure (**1**), compound **3g** was obtained as a yellow liquid (93 mg, 65%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98−7.96 (m, 2H), 7.89 (d, J = 8.20 Hz, 2H), 7.50−7.48 (m, 2H), 7.41 (d, J = 7.25 Hz, 2H), 7.31−7.28 (m, 3H), 7.27−7.26 (m, 2H), 7.23−7.22 (m, 3H), 7.18−7.14 (m, 2H), 6.97−6.95 (m, 2H), 6.39 (t, J = 7.30 Hz, 1H), 3.28 (d, J = 7.30 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 185.9, 165.9, 149.2, 145.6, 140.4, 140.2, 135.8, 135.3, 132.9, 131.9, 131.8, 131.2, 129.7 (2), 128.8, 128.7, 128.4 (2), 128.3, 128.0, 127.3, 126.7, 126.6, 126.0, 36.4, 21.9 ppm; HRMS (ESI-TOF) m/z: [M + H]$^+$calculated for $[C_{31}H_{26}NS]^+$: 444.1780; found: 444.1777.

(E)-4-(1,3-Diphenylprop-1-en-1-yl)-2-(4-methoxyphenyl)-5-phenylthiazole ***(3h)***. Following the general experimental procedure (**1**), compound **3h** was obtained as a yellow liquid (126 mg, 85%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94−7.92 (m, 2H), 7.49−7.48 (m, 2H), 7.42−7.40 (m, 2H), 7.28−7.22 (m, 2H), 7.17−7.11 (m, 4H), 6.96−6.94 (m, 5H), 6.39 (t, J = 7.30 Hz, 1H), 3.85 (s, 3H), 3.28 (d, J = 7.30 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6, 161.3, 149.0, 140.2, 135.8, 134.9, 131.9, 131.7, 129.3, 128.8, 128.7, 128.4 (2), 128.3, 128.2, 127.9, 127.3, 126.7, 126.0, 114.3, 55.5, 36.4 ppm; HRMS (ESI-TOF) m/z: [M + H]$^+$calculated for $[C_{31}H_{26}NOS]^+$: 460.1730; found: 460.1734.

(E)-4-(1-(4-Chlorophenyl)-3-phenylprop-1-en-1-yl)-2,5-diphenylthiazole ***(3i)***. Following the general experimental procedure (**1**), compound **3i** was obtained as a yellow liquid (104 mg, 75%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00−7.98 (m, 2H), 7.46−7.40 (m, 5H), 7.32−7.30 (m, 2H), 7.27−7.25 (m, 3H), 7.23−7.20 (m, 2H), 7.18−7.15 (m, 2H), 7.13−7.11 (m, 1H), 6.97−6.95 (m, 2H), 6.37 (t, J = 7.35 Hz, 1H), 3.28 (d, J = 7.30 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 148.8, 139.9, 138.7, 136.1, 134.7, 133.6, 133.1, 132.4, 131.6, 130.2, 129.0, 128.8, 128.7, 128.6, 128.5, 128.3 (2), 127.9, 126.6, 126.1, 36.4 ppm; HRMS (ESI-TOF) m/z: [M + H]$^+$calculated for $[C_{30}H_{23}ClNS]^+$: 464.1234; found: 464.1235; IR (film): ν_{max} 3059, 3026, 2922, 2852, 2188, 1686, 1596, 1490, 760, 692 cm^{-1}.

(E)-4-(1-(4-Chlorophenyl)-3-phenylprop-1-en-1-yl)-5-phenyl-2-(p-tolyl)thiazole ***(3j)***. Following the general experimental procedure (**1**), compound **3j** was obtained as a yellow liquid (112 mg, 83%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, J = 8.05 Hz, 2H), 7.46−7.44 (m, 2H), 7.33−7.31 (m, 2H), 7.28−7.27 (m, 3H), 7.24−7.21 (m, 4H), 7.18−7.15 (m, 2H), 6.96 (d, J = 7.35 Hz, 2H), 6.37 (t, J = 7.35 Hz, 1H), 3.28 (d, J = 7.30 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1, 148.6, 140.5, 140.0, 138.7, 135.6, 134.7, 133.1, 132.4, 131.7, 131.0, 130.2, 129.7, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 128.0, 126.6, 126.1, 36.4, 21.6 ppm; HRMS (ESI-TOF) m/z: [M + H]$^+$calculated for $[C_{31}H_{25}ClNS]^+$: 478.1391; found; 478.1392.

(E)-2,5-Diphenyl-4-(3-phenyl-1-(p-tolyl)prop-1-en-1-yl)-thiazole ***(3k)***. Following the general experimental procedure (**1**), compound **3k** was obtained as a colorless liquid (113 mg, 81%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93−7.91 (m, 2H), 7.44−7.41 (m, 2H), 7.36−7.32 (m, 4H), 7.23−7.21 (m, 2H), 7.19−7.16 (m, 3H), 7.09−7.06 (m, 2H), 7.04−6.69 (m, 2H), 6.87 (t, J = 10.65 Hz, 2H), 6.29−6.26 (m, 1H), 3.17 (d, J = 7.25 Hz, 2H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6, 149.5, 140.3, 137.3, 137.1, 135.7, 135.6, 133.8, 131.8, 130.8, 130.1, 129.2, 129.0, 128.8, 128.7, 128.5, 128.4 (2), 128.1, 126.7, 126.5, 126.0, 36.3, 21.2 ppm; HRMS (ESI-TOF) m/z: [M + H]$^+$calculated for $[C_{31}H_{26}NS]^+$: 444.1780; found: 444.1780.

(E)-2,5-Diphenyl-4-(3-phenyl-1-(thiophen-2-yl)prop-1-en-1-yl)thiazole ***(3l)***. Following general experimental procedure (**1**), compound **3l** was obtained as a yellow liquid (111 mg, 80%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02−8.00 (m, 2H), 7.53−7.51 (m, 2H), 7.45−7.42 (m, 3H), 7.31−7.28 (m, 3H),

https://doi.org/10.1021/acsomega.2c05085
ACS Omega 2022, 7, 34693−34706

7.17−7.15 (m, 1H), 7.14−7.09 (m, 3H), 6.94−6.92 (m, 2H), 6.90−6.88 (m, 1H), 6.83−6.82 (m, 1H), 6.35 (t, J = 7.45 Hz, 1H), 3.23 (d, J = 7.40 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 148.2, 144.8, 139.8, 136.0, 133.7, 131.6, 130.4, 130.3, 130.2, 129.0, 128.9, 128.7, 128.4 (2), 128.3, 127.5, 126.6, 126.1, 125.2, 124.3, 36.0 ppm; HR-MS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{28}H_{22}NS_2]^+$: 436.1188; found: 436.1182.

*(E)-4-(1-(4-Ethoxyphenyl)-3-phenylallyl)-2,5-diphenylthiazole (**3m**).* Following the general experimental procedure (**1**), compound **3m** was obtained as a yellow liquid (116 mg, 86%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99−7.98 (m, 2H), 7.46−7.43 (m, 5H), 7.41−7.39 (m, 3H), 7.37 (d, J = 7.45 Hz, 2H), 7.33 (d, J = 8.65 Hz, 2H), 7.26 (t, J = 7.40 Hz, 2H), 7.17 (t, J = 7.3 Hz, 1H), 6.89 (q, J = 15.85 Hz, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.39 (d, J = 18.95 Hz, 1H), 4.98 (d, J = 8.05 Hz, 1H), 4.00 (q, J = 14.00 Hz, 2H), 1.38 (t, J = 6.95 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 157.7, 153.3, 137.5, 135.0, 134.0, 133.1, 131.8, 130.3, 129.9, 129.8, 129.4, 128.9, 128.8, 128.5, 128.3, 127.2, 126.6, 126.5, 114.5, 63.5, 47.9, 15.0 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{32}H_{28}NOS]^+$: 474.1886; found: 474.1882.

*(E)-4-(1-(Furan-2-yl)-3-phenylallyl)-2,5-diphenylthiazole (**3n**).* Following the general experimental procedure (**1**), compound **3n** was obtained as a yellow liquid (118 mg, 86%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98−7.96 (m, 2H), 7.53−7.51 (m, 2H), 7.46−7.44 (m, 2H), 7.43−7.42 (m, 1H), 7.42−7.40 (m, 2H), 7.40−7.37 (m, 3H), 7.35 (d, J = 0.95 Hz, 1H), 7.29−7.24 (m, 2H), 7.21−7.18 (m, 1H), 6.80 (q, J = 15.85 Hz, 1H), 6.47 (d, J = 16.35 Hz, 1H), 6.33−6.32 (m, 1H), 6.23−6.22 (m, 1H), 5.12 (d, J = 8.05 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 155.6, 150.7, 141.7, 137.2, 133.9, 131.6, 131.5, 130.0, 129.8, 129.2, 128.9, 128.5 (2), 127.5, 126.6, 110.5, 106.8, 43.1 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{28}H_{22}NOS]^+$: 420.1417; found; 420.1415.; IR(film): ν_{max} 2937, 2251, 1599, 1445, 1245, 760, 692 cm^{-1}.

*(E)-4-(1-(Furan-2-yl)-3-phenylallyl)-5-phenyl-2-(p-tolyl)-thiazole (**3o**).* Following the general experimental procedure (**1**), compound **3o** was obtained as a colorless liquid (122 mg, 85%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, J = 8.15 Hz, 2H), 7.52−7.50 (m, 2H), 7.46−7.43 (m, 2H), 7.41−7.39 (m, 2H), 7.37−7.35 (m, 2H), 7.29−7.25 (m, 2H), 7.23−7.18 (m, 3H), 6.80 (q, J = 15.85 Hz, 1H), 6.46 (d, J = 15.85 Hz, 1H), 6.33−6.32 (m, 1H), 6.22 (d, J = 3.2 Hz, 1H), 5.11 (d, J = 8.10 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 155.6, 150.5, 141.6, 140.2, 137.2, 133.4, 131.6, 131.3, 129.8, 129.6, 129.3, 128.9, 128.5, 128.4, 127.5, 126.6, 126.5, 110.5, 106.8, 43.1, 22.1 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{29}H_{24}NOS]^+$: 434.1573; found: 434.1572. ; IR (film): ν_{max} 3024, 2919, 2849, 1595, 1499, 1483, 815, 751, 691 cm^{-1}.

*(E)-4-(1-(Furan-2-yl)-3-phenylallyl)-2-(4-methoxyphenyl)-5-phenylthiazole (**3p**).* Following the general experimental procedure (**1**), compound **3p** was obtained as a colorless liquid (132 mg, 88%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91−7.90 (m, 2H), 7.51−7.49 (m, 2H), 7.45−7.42 (m, 2H), 7.40−7.35 (m, 4H), 7.29−7.25 (m, 2H), 7.21−7.18 (m, 1H), 6.94−6.93 (m, 2H), 6.79 (q, J = 15.85 Hz, 1H), 6.46 (d, J = 15.85 Hz, 1H), 6.33−6.32 (m, 1H), 6.22−6.21 (m, 1H), 5.10 (d, J = 8.05 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 161.1, 155.6, 150.4, 141.6, 137.2, 132.9, 131.6, 129.8, 129.2, 128.9, 128.5, 128.3, 128.1, 127.5, 126.9, 126.6, 114.2, 110.5, 106.8, 55.5, 43.1 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{29}H_{24}NO_2S]^+$: 450.1522; found: 450.1527.

*(E)-4-(1-(Furan-2-yl)-3-phenylallyl)-5-phenyl-2-(4-(trifluoromethyl)phenyl)thiazole (**3q/3r**).* Following the general experimental procedure (**1**), compounds **3q**/**3r** were obtained as an inseparable mixture (1:1.25) and colorless liquid (129 mg, 81%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11−8.06 (m, 4H), 7.70−7.66 (m, 4H), 7.53−7.49 (m, 4H), 7.47−7.41 (m, 3H), 7.40−7.34 (m, 4H), 7.33−7.31 (m, 3H), 7.29−7.26 (m, 3H), 7.22−7.19 (m, 1H), 7.17−7.14 (m, 2H), 7.12−7.09 (m, 1H), 6.94 (d, J = 7.25 Hz, 2H), 6.81−6.76 (m, 1H), 6.54 (t, J = 7.65 Hz, 1H), 6.47 (d, J = 15.85 Hz, 1H), 6.33−6.30 (m, 2H), 6.22−6.21 (m, 1H), 5.99 (d, J = 2.9 Hz, 1H), 5.13 (d, J = 8.00 Hz, 1H), 3.24 (d, J = 7.65 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 163.7, 155.4, 153.4, 151.4, 147.3, 142.2, 141.8, 139.8, 137.7, 137.0, 136.9, 136.7, 135.1, 131.9, 131.2, 131.0, 129.8, 129.2, 129.0, 128.8 (2), 128.6 (2), 128.5, 128.4, 127.6, 126.7, 126.6, 126.2, 126.1 (2), 111.5, 110.5, 108.2, 106.8, 43.0, 35.6 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{29}H_{21}F_3NOS]^+$: 488.1290; found: 488.1292.

*(E)-2-Phenyl-4-(1-phenyl-3-(p-tolyl)allyl)-5-(p-tolyl)-thiazole (**3s**).* Following the general experimental procedure (**1**), compound **3s** was obtained as a colorless liquid (102 mg, 75%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02−8.00 (m, 2H), 7.47−7.43 (m, 5H), 7.38 (d, J = 8.10 Hz, 2H), 7.35−7.34 (m, 2H), 7.32−7.31 (m, 3H), 7.26−7.22 (m, 2H), 7.11 (t, J = 9.50 Hz, 2H), 6.89 (dd, J = 15.85, 8.2 Hz, 1H), 6.38 (d, J = 16.3 Hz, 1H), 5.04 (d, J = 8.15 Hz, 1H), 2.44 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.5, 152.9, 143.3, 138.3, 137.0, 134.7, 134.1, 133.4, 131.7, 130.4, 129.8, 129.7, 129.5, 129.2, 128.9, 128.5, 127.6, 126.5, 126.4, 48.7, 21.4, 21.2 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{32}H_{28}NS]^+$: 458.1937; found: 458.1940.

*4-Benzhydryl-2,5-diphenylthiazole (**5a**)*[9a,8m]. Following the general experimental procedure (**2**), compound **5a** was obtained as a yellow solid (135 mg, 95%); mp: 153−154 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95−7.93 (m, 2H), 7.43−7.41 (m, 4H), 7.41−7.40 (m, 2H), 7.38−7.37 (m, 6H), 7.28 (d, J = 7.40 Hz, 4H), 7.19 (d, J = 7.45 Hz, 2H), 5.56 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.5, 152.9, 143.6, 134.1, 134.0, 131.8, 129.9 (2), 129.3, 128.9, 128.4, 128.3, 126.5, 126.4, 50.4 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{28}H_{22}NS]^+$: 404.1467; found: 404.1472; IR (film): ν_{max} 3058, 1597, 1452, 744, 689 cm^{-1}.

*4-Benzhydryl-5-phenyl-2-(p-tolyl)thiazole (**5b**).* Following the general experimental procedure (**2**), compound **5b** was obtained as a colorless solid (133 mg, 90%); mp: 211−212 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, J = 8.10 Hz, 2H), 7.42−7.41 (m, 4H), 7.40−7.36 (m, 5H), 7.28−7.24 (m, 4H), 7.21−7.17 (m, 4H), 5.55 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 152.7, 143.7, 140.0, 133.5, 132.0, 131.5, 129.9, 129.5, 129.3, 128.8, 128.3, 126.5, 126.4, 50.4, 21.5 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{29}H_{24}NS]^+$: 418.1624; found: 418.1623.; IR (film): ν_{max} 3024, 1598, 1492, 1450, 745, 695 cm^{-1}.

*4-Benzhydryl-2-(4-methoxyphenyl)-5-phenylthiazole (**5c**).* Following the general experimental procedure (**2**), compound **5c** was obtained as a colorless solid (140 mg, 92%); mp: 232−233 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, J = 8.70 Hz, 2H), 7.42−7.41 (m, 4H), 7.38−7.36 (m, 5H), 7.29−7.24 (m, 4H), 7.20−7.17 (m, 2H), 6.91 (d, J = 8.75 Hz, 2H), 5.54 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4, 161.1, 152.6, 143.7, 133.0, 132.0, 129.9, 129.4, 128.8, 128.3,

https://doi.org/10.1021/acsomega.2c05085
ACS Omega 2022, 7, 34693−34706

128.2, 128.0, 127.2, 126.4, 114.2, 55.5, 50.4 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{29}H_{24}NOS]^+$: 434.1573; found: 434.1577.

*4-Benzhydryl-5-phenyl-2-(4-(trifluoromethyl)phenyl)-thiazole (**5d**).* Following the general experimental procedure (**2**), compound **5d** was obtained as a pink solid (142 mg, 86%); mp: 199−200 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, J = 8.05 Hz, 2H), 7.65 (d, J = 8.10 Hz, 2H), 7.43 (s, 5H), 7.36 (d, J = 7.60 Hz, 4H), 7.29 (t, J = 7.45 Hz, 4H), 7.24−7.19 (m, 2H), 5.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 153.6, 143.4, 137.1, 135.3, 131.4, 129.9, 129.3, 129.0, 128.7, 128.4, 126.7, 126.5, 125.9, 50.3 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{29}H_{21}F_3NS]^+$: 472.1341; found: 472.1342.

*4-Benzhydryl-2-phenyl-5-(p-tolyl)thiazole (**5e**).* Following the general experimental procedure (**2**), compound **5e** was obtained as a white solid (127 mg, 90%); mp: 156−157 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94−7.92 (m, 2H), 7.41−7.38 (m, 3H), 7.38−7.37 (m, 4H), 7.33−7.31 (m, 2H), 7.29−7.27 (m, 4H), 7.24−7.22 (m, 2H), 7.21−7.17 (m, 2H), 5.55 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 152.7, 143.7, 138.4, 134.1, 129.8, 129.6, 129.3, 128.8, 128.3, 126.5, 126.4, 50.3, 21.4 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{29}H_{24}NS]^+$: 418.1624; found: 418.1626.

*5-([1,1′-Biphenyl]-4-yl)-4-benzhydryl-2-phenylthiazole (**5f**).* Following the general experimental procedure (**2**), compound **5f** was obtained as a brown solid (117 mg, 88%); mp: 184−185 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95−7.94 (m, 2H), 7.66−7.62 (m, 4H), 7.51−7.49 (m, 2H), 7.47−7.44 (m, 2H), 7.41−7.40 (m, 2H), 7.40−7.39 (m, 5H), 7.36−7.35 (m, 1H), 7.29 (t, J = 7.40 Hz, 4H), 7.22−7.18 (m, 2H), 5.63 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.5, 153.1, 143.6, 141.2, 140.4, 134.0, 133.7, 130.8, 130.2, 129.9, 129.4, 129.0, 128.9, 128.4, 127.7, 127.5, 127.2, 126.5, 126.4, 50.5 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{34}H_{26}NS]^+$; 480.1780; Found; 480.1781.

*4-Benzhydryl-5-cyclopropyl-2-phenylthiazole (**5g**).* Following the general experimental procedure (**2**), compound **5g** was obtained as pale yellow solid (125 mg, 84%); mp: 125−126 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (s, 2H), 7.40 (s, 4H), 7.36−7.33 (m, 3H), 7.31−7.28 (m, 4H), 7.22−7.19 (m, 2H), 5.77 (s, 1H), 2.00−1.97 (m, 1H), 1.03 (s, 2H), 0.71 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.7, 154.7, 143.3, 137.7, 134.3, 129.4, 129.3, 128.7, 128.3, 126.4, 126.3, 50.9, 9.7, 7.6 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{25}H_{22}NS]^+$; 368.1467; Found; 368.1465.; IR (film): ν_{max} 3060, 1597, 1530, 1448, 711, 695 cm^{-1}.

*4-Benzhydryl-5-butyl-2-phenylthiazole (**5h**).* Following the general experimental procedure (**2**), compound **5h** was obtained as yellow sticky compound (115 mg, 80%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, J = 7.05 Hz, 2H), 7.36−7.33 (m, 4H), 7.32−7.29 (m, 2H), 7.27−7.24 (m, 5H), 7.17 (t, J = 7.45 Hz, 2H), 5.52 (s, 1H), 2.80 (t, J = 7.70 Hz, 2H), 1.60−1.54 (m, 2H), 1.35−1.29 (m, 2H), 0.87 (t, J = 7.65 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.5, 152.9, 143.4, 134.8, 134.3, 132.4, 130.1, 129.4, 129.3, 128.7, 128.3, 128.2, 126.3 (2), 50.6, 31.4, 26.3, 22.4, 13.9 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{26}H_{26}NS]^+$; 384.1780; Found; 384.1777.

*4-Benzhydryl-5-pentyl-2-phenylthiazole (**5i**).* Following the general experimental procedure (**2**), compound **5i** was obtained as pale yellow sticky compound (116 mg, 81%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88−7.85 (m, 2H), 7.37−7.35 (m, 4H), 7.33−7.30 (m, 2H), 7.28−7.25 (m, 5H), 7.19−7.16 (m, 2H), 5.52 (s, 1H), 2.83−2.79 (m, 2H), 1.60 (s, 2H), 1.29−1.28 (m, 4H), 0.84−0.83 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.5, 152.9, 143.4, 134.8, 134.3, 129.4, 129.3, 128.7, 128.2, 126.3 (2), 50.5, 31.7, 31.4, 26.5, 22.4, 14.0 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{27}H_{28}NS]^+$; 398.1937; Found; 398.1939.

*4-((4-Bromophenyl)(phenyl)methyl)-2,5-diphenylthiazole (**5j**).* Following the general experimental procedure (**2**), compound **5j** was obtained as pink solid (130 mg, 97%); mp: 113−114 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93−7.91 (m, 2H), 7.42 (m, 1H), 7.41−7.40 (m, 4H), 7.40−7.38 (m, 5H), 7.35−7.33 (m, 2H), 7.30−7.27 (m, 2H), 7.24−7.21 (m, 3H), 5.49 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 152.3, 143.1, 142.7, 134.2, 133.9, 131.6, 131.4, 131.1, 130.0, 129.8, 129.2, 128.9 (2), 128.5 (2), 126.6, 126.5, 120.4, 49.8 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{28}H_{21}BrNS]^+$; 482.0573; Found; 483.0575.; IR (film): ν_{max} 3021, 1596, 1519, 1442, 759, 734, 687 cm^{-1}.

*4-((4-Methoxyphenyl)(phenyl)methyl)-2,5-diphenylthiazole (**5k**).* Following the general experimental procedure (**2**), compound **5k** was obtained as cream solid (132 mg, 95%); mp: 183−184 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94−7.92 (m, 2H), 7.42−7.41 (m, 4H), 7.39−7.37 (m, 3H), 7.36−7.34 (m, 3H), 7.31−7.28 (m, 2H), 7.26−7.22 (m, 2H), 7.19−7.16 (m, 1H), 6.83−6.81 (m, 2H), 5.51 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.5, 158.2, 153.3, 144.0, 135.8, 134.1, 133.8, 131.9, 130.3, 129.9, 129.8, 129.2, 128.8, 128.3 (2), 126.5, 126.3, 113.7, 55.3, 49.6 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{29}H_{24}NOS]^+$; 434.1573; Found; 434.1575.; IR (film): ν_{max} 2931, 2833, 1603, 1508, 1456, 740, 689 cm^{-1}.

*5-Butyl-4-((4-methoxyphenyl)(phenyl)methyl)-2-phenylthiazole (**5l**).* Following the general experimental procedure (**2**), compound **5l** was obtained as colorless sticky compound (109 mg, 78%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86−7.84 (m, 2H), 7.34−7.33 (m, 3H), 7.30−7.26 (m, 4H), 7.26−7.23 (m, 2H), 7.17−7.13 (m, 1H), 6.81 (d, J = 8.80 Hz, 2H), 5.47 (s, 1H), 3.70 (s, 3H), 2.80 (t, J = 7.55 Hz, 2H), 1.60−1.54 (m, 2H), 1.37−1.30 (m, 2H), 0.87 (t, J = 7.35 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.5, 158.1, 153.2, 143.8, 135.6, 134.5, 134.3, 130.2, 129.3, 129.1, 128.7, 128.2, 126.2, 113.6, 55.2, 49.7, 34.1, 26.2, 22.3, 13.9 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{27}H_{28}NOS]^+$; 414.1886; Found; 414.1882.

*4-(bis(4-Fluorophenyl)methyl)-2,5-diphenylthiazole (**5m**).* Following the general experimental procedure (**2**), compound **5m** was obtained as white solid (129 mg, 93%); mp: 142−143 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93−7.91 (m, 2H), 7.43−7.42 (m, 2H), 7.41−7.40 (m, 3H), 7.39−7.36 (m, 3H), 7.31−7.28 (m, 4H), 6.96 (t, J = 8.75 Hz, 4H), 5.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 162.8, 160.4, 152.5, 139.2, 134.1, 133.8, 131.6, 130.7, 130.6, 130.0, 129.8, 129.0, 128.6, 126.5, 115.3, 115.1, 48.9 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{28}H_{20}F_2NS]^+$; 440.1279; Found; 440.1277.

*4-(1-(Benzo[d][1,3]dioxol-4-yl)ethyl)-2,5-diphenylthiazole (**5n**).* Following the general experimental procedure (**2**), compound **5n** was obtained as yellow solid (133 mg, 92%); mp: 99−100 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00−7.98 (m, 2H), 7.46−7.44 (m, 2H), 7.43−7.42 (m, 2H), 7.41−7.40 (m, 3H), 7.40−7.37 (m, 1H), 7.06 (d, J = 1.60 Hz, 1H), 6.82−6.80 (m, 1H), 6.73 (d, J = 8.00 Hz, 1H), 5.92 (d, J = 1.45 Hz,

https://doi.org/10.1021/acsomega.2c05085
ACS Omega 2022, 7, 34693−34706

1H), 5.90 (d, J = 1.45 Hz, 1H), 4.22 (q, J = 14.10 Hz, 1H), 1.67 (d, J = 7.05 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4, 155.6, 147.6, 145.8, 140.0, 134.1, 132.2, 132.0, 129.9, 129.8, 128.9, 128.7, 128.2, 126.5, 120.6, 108.5, 108.1, 100.9, 39.1, 23.5 ppm; HR-MS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{24}H_{20}NO_2S]^+$; 386.1209; Found; 386.1211.

2,5-Diphenyl-4-(1-phenylethyl)thiazole ***(5o)***. Following the general experimental procedure (**2**), compound **5o** was obtained as cream solid (135 mg, 88%); mp: 209−211 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00−7.99 (m, 2H), 7.44−7.43 (m, 3H), 7.41−7.40 (m, 2H), 7.39−7.38 (m, 4H), 7.36−7.35 (m, 1H), 7.29 (t, J = 7.50 Hz, 2H), 7.18 (t, J = 7.35 Hz, 1H), 7.29 (q, J = 14.10 Hz, 1H), 1.72 (d, J = 7.10 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 155.6, 145.9, 134.1, 132.3, 132.0, 129.9, 129.8, 128.9, 128.7, 128.5, 128.1, 127.8, 126.5, 126.2, 39.4, 23.2 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{23}H_{20}NS]^+$; 342.1311; Found; 342.1310.

4-(9H-Fluoren-9-yl)-2,5-diphenylthiazole ***(5p)***. Following the general experimental procedure (**2**), compound **5p** was obtained as white solid (140 mg, 98%); mp: 123−124 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81−7.80 (m, 2H), 7.75 (d, J = 7.60 Hz, 2H), 7.35−7.34 (m, 4H), 7.34−7.32 (m, 4H), 7.27−7.25 (m, 4H), 7.20 (d, J = 7.45 Hz, 2H), 5.53 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.0, 151.0, 146.4, 141.3, 134.8, 133.7, 131.5, 129.9, 129.7, 128.8, 128.5, 128.2, 127.3, 127.1, 126.6, 125.0, 120.0, 49.1 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{28}H_{20}NS]^+$; 402.1311; Found; 402.1311.; IR (film): ν_{max} 3051, 1597, 1442, 736, 697 cm^{-1}.

1-(Phenylethynyl)cyclohept-1-ene ***(5q)***. Following general experimental procedure **2**, compound **5q** was obtained as brown liquid (120 mg, 79%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34−7.32 (m, 2H), 7.22−7.20 (m, 1H), 7.19−7.17 (m, 2H), 6.32 (t, J = 6.70 Hz, 1H), 2.36−2.34 (m, 2H), 2.17−2.14 (m, 2H), 1.71−1.67 (m, 2H), 1.56−1.51 (m, 2H), 1.49−1.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 131.4, 128.8, 128.3, 127.7, 127.0, 125.4, 124.0, 93.0, 86.9, 34.4, 32.3, 29.4, 26.7, 26.6 ppm; HR-MS (ESI-TOF) m/z: [M + H] + calculated for $[C_{15}H_{17}]$+; 197.1325; Found; 197.1327.

4-Cycloheptyl-2,5-diphenylthiazole ***(5r)***. Following the general experimental procedure (**2**), compound **5r** was obtained as yellow liquid (125 mg, 81%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52−7.41 (m, 1H), 7.41−7.39 (m, 2H), 7.34−7.32 (m, 1H), 7.30−7.28 (m, 2H), 7.27−7.24 (m, 2H), 7.23−7.18 (m, 1H), 6.39 (t, J = 6.75 Hz, 1H), 2.82−2.69 (m, 1H), 2.43 (t, J = 5.55 Hz, 2H), 2.23 (q, J = 6.40 Hz, 2H), 1.79−1.74 (m, 1H), 1.73−1.71 (m, 1H), 1.67−1.65 (m, 1H), 1.63−1.59 (m, 2H), 1.56−1.52 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.3, 131.5, 128.8, 128.3, 127.7, 127.0, 126.8, 126.7, 125.4, 124.0, 34.4, 32.3, 29.4, 26.7 (2) ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$calculated for $[C_{22}H_{24}NS]^+$; 334.1624; Found; 334.1624.

4-Benzhydryl-2,5-diphenyloxazole ***(7a)***.[8h] Following the general experimental procedure (**3**), compound **7a** was obtained as white solid (134 mg, 98%); mp: 174−175 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09−8.07 (m, 2H), 7.80−7.79 (m, 1H), 7.62 (d, J = 7.35, 2H), 7.45−7.44 (m, 3H), 7.42−7.41 (m, 5H), 7.37−7.34 (m, 1H), 7.30 (t, J = 7.40, 4H), 7.24−7.20 (m, 2H), 5.64 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 146.6, 142.7, 138.5, 132.1, 130.2, 129.3, 128.9, 128.8, 128.7 (2), 128.4 (2), 127.8, 127.4, 126.6, 48.2; HRMS (ESI-TOF): m/z $[M + H]^+$ calculated for $[C_{28}H_{22}NO]^+$: 388.1696; found: 388.1702.

4-Benzhydryl-2-(4-methoxyphenyl)-5-phenyloxazole ***(7b)***. Following the general procedure **3**, compound **7b** was obtained as white color solid (141 mg, 96%); mp: 185−186 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, J = 8.95 Hz, 2H), 7.62−7.60 (m, 2H), 7.44−7.42 (m, 4H), 7.40−7.33 (m, 3H), 7.31−7.28 (m, 4H), 7.25−7.20 (m, 2H), 6.95−6.93 (m, 2H), 5.63 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 161.3, 160.1, 146.1, 142.8, 138.2, 129.3, 129.0, 128.9, 128.4, 128.3, 128.1, 126.6, 126.5, 120.7, 114.1, 55.5, 48.2 ppm; HRMS (ESI-TOF): m/z $[M + H]^+$ calculated for $[C_{29}H_{24}NO_2]^+$: 418.1802; found: 418.1802.

4-Benzhydryl-2-(4-chlorophenyl)-5-phenyloxazole ***(7c)***. Following the general procedure **3**, compound **7c** was obtained as white solid (133 mg, 90%); mp: 124−125 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, J = 8.50 Hz, 2H), 7.61 (d, J = 7.40 Hz, 2H), 7.46−7.43 (m, 2H), 7.41−7.39 (m, 6H), 7.37−7.35 (m, 1H), 7.30 (t, J = 7.40 Hz, 4H) 7.25−7.21 (m, 2H), 5.63 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$):159.2, 146.9, 142.6, 138.6, 136.3, 129.3, 129.0 (2), 128.6, 128.5 (2), 127.9, 126.7 (2), 126.3, 48.2; HRMS (ESI-TOF): m/z $[M + H]^+$ calculated for $[C_{28}H_{21}ClNO]^+$: 422.1306; found: 422.1302.

4-Benzhydryl-5-phenyl-2-(3-(trifluoromethyl)phenyl)-oxazole ***(7d)***. Following the general procedure (**3**), compound **7d** was obtained as a white solid (140 mg, 87%); mp: 120−121 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31−8.26 (m, 2H), 7.67−7.63 (m, 3H), 7.57−7.54 (m, 1H), 7.48−7.45 (m, 2H), 7.41−7.38 (m, 5H), 7.32 (t, J = 7.35 Hz, 4H), 7.25−7.22 (m, 2H), 5.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 147.3, 142.4, 138.8, 129.7, 129.3, 129.2, 129.0, 128.7, 128.5, 128.4, 126.8, 126.6, 123.4, 48.2 ppm; ^{19}F NMR (470 $CDCl_3$): δ − 62.7 HRMS (ESI-TOF): m/z $[M + H]^+$ calculated for $[C_{29}H_{21}F_3NO]^+$: 456.1570; found: 456.1571.

4-Benzhydryl-5-phenyl-2-(o-tolyl)oxazole ***(7e)***.[8h] Following the general procedure **3**, compound **7e** was obtained as white solid (131 mg, 93%); mp: 119−120 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05−8.04 (m, 1H), 7.64−7.63 (m ,2H), 7.46−7.45 (m, 2H), 7.44−7.43 (m, 4H), 7.37−7.34 (m, 1H), 7.31−7.30 (m, 3H), 7.28−7.24 (m, 4H), 7.22−7.19 (m, 2H), 5.64 (d, J = 1.95 Hz, 1H), 2.70 (d, J = 1.85 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 146.0, 142.9, 138.0, 137.8, 131.7, 129.8, 129.3, 129.0, 128.7, 128.4, 128.3, 126.6, 126.5, 125.9, 48.4, 22.3 ppm; HRMS (ESI-TOF): m/z $[M + H]^+$ calculated for $[C_{29}H_{24}NO]^+$: 402.1852; found: 402.1856.

4-Benzhydryl-2-(naphthalen-1-yl)-5-phenyloxazole ***(7f)***. Following the general procedure **3**, compound **7f** was obtained as white solid (134 mg, 87%); mp: 116−117 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.30 (d, J = 8.50 Hz, 1H), 8.28−8.26 (m, 1H), 7.93 (d, J = 8.15 Hz, 1H), 7.87 (d, J = 8.05 Hz, 1H), 7.69−7.68 (m, 2H), 7.59−7.52 (m, 3H), 7.50−7.48 (m, 4H), 7.47−7.46 (m, 2H), 7.40−7.37 (m, 1H), 7.35−7.32 (m, 4H), 7.25−7.22 (m, 3H), 5.71 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 146.3, 142.9, 138.3, 134.1, 131.1, 130.4, 129.3, 129.0, 128.8, 128.5 (2), 128.4, 127.7, 127.5, 126.7, 126.6, 126.3, 125.0, 124.1, 48.5 ppm; HRMS (ESI-TOF): m/z $[M + H]^+$ calculated for $[C_{32}H_{25}NO]^+$: 438.1852; found: 438.1850.

4-Benzhydryl-2-phenyl-5-(p-tolyl)oxazole ***(7g)***.[8h,j] Following the general procedure **3**, compound **7g** was obtained as pink solid (121 mg, 90%); mp: 140−141 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08−8.06 (m, 2H), 7.52−7.50 (m, 2H), 7.44−7.41 (m, 3H), 7.41−7.40 (m, 4H), 7.31−7.28 (m, 4H), 7.26−7.24 (m, 2H), 7.23−7.20 (m, 2H), 5.62 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 146.8, 142.8,

https://doi.org/10.1021/acsomega.2c05085
ACS Omega 2022, 7, 34693−34706

138.4, 137.9, 130.1, 129.6, 129.3, 128.7, 128.4, 127.9, 126.6, 126.0, 48.2, 21.5 ppm; HRMS (ESI-TOF): m/z [M + H]$^+$ calculated for [$C_{29}H_{24}NO$]$^+$: 402.1852; found: 402.1855.

*5-([1,1′-Biphenyl]-4-yl)-4-benzhydryl-2-phenyloxazole (**7h**).* Following the general procedure **3**, compound **7h** was obtained as yellow solid (113 mg, 87%); mp: 123−124 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11−8.09 (m, 2H), 7.71−7.67 (m, 4H), 7.63 (d, J = 7.15 Hz, 2H), 7.48−7.46 (m, 2H), 7.44 (s, 3H), 7.43 (s, 4H), 7.37 (t, J = 7.40 Hz, 1H), 7.32 (t, J = 7.50 Hz, 4H), 7.25−7.22 (m, 2H), 5.69 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 146.4, 142.7, 141.0, 140.4, 138.7, 130.2, 129.3, 129.0, 128.7, 128.5, 127.8, 127.7, 127.6, 127.1, 126.9, 126.7, 126.6, 48.4 ppm; HRMS (ESI-TOF): m/z [M + H]$^+$ calculated for [$C_{34}H_{26}NO$]$^+$: 464.2009; found: 464.2007.

*4-Benzhydryl-5-cyclopropyl-2-phenyloxazole (**7i**).* Following the general procedure **3**, compound **7i** was obtained as a white solid (121 mg, 86%); mp: 102−103 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94−7.92 (m, 2H), 7.40−7.36 (m, 4H), 7.34 (s, 3H), 7.29 (t, J = 7.40 Hz, 4H), 7.25−7.19 (m, 2H), 5.50 (s, 1H), 1.62−1.60 (m, 1H), 0.92−0.89 (m, 2H), 0.88−0.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 149.1, 142.7, 137.8, 129.7, 129.2, 128.6, 128.4, 128.0, 126.5, 126.1, 48.3, 6.9, 6.2; HRMS (ESI-TOF): m/z [M + H]$^+$ calculated for [$C_{25}H_{22}NO$]$^+$: 352.1696; found: 352.1694.

*4-(9H-Fluoren-9-yl)-2,5-diphenyloxazole (**7j**).* Following the general procedure **3**, compound **7j** was obtained as a white color solid (131 mg, 96%); mp: 201−202 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05−8.03 (m, 2H), 7.84−7.80 (m, 3H), 7.55−7.45 (m, 3H), 7.43−7.41 (m, 4H), 7.40−7.38 (m, 2H), 7.32−7.28 (m, 2H), 7.26−7.21 (m, 2H), 5.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 147.4, 145.0, 141.3, 135.7, 132.2, 130.7, 128.8, 128.5, 128.3, 127.7, 127.5, 127.4, 126.9, 126.7, 126.4, 125.1, 120.2, 46.4; HRMS (ESI-TOF): m/z [M + H]$^+$ calculated for [$C_{28}H_{20}NO$]$^+$: 386.1539; found: 386.1540.

*4-((4-Chlorophenyl)(phenyl)methyl)-2,5-diphenyloxazole (**7k**).*[8f] Following the general procedure **3**, compound **7k** was obtained as a yellow solid (125 mg, 94%); mp: 123−124 °C; ^{1}H NMR (500 MHz, $CDCl_3$); δ 8.09−8.07 (m, 2H), 7.61−7.59 (m, 2H), 7.46−7.42 (m, 5H), 7.39−7.37 (m, 3H), 7.34−7.29 (m, 4H), 7.27−7.22 (m, 3H); 5.60 ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 160.2, 146.7, 142.2, 141.2, 137.9, 132.5, 130.7, 130.3, 129.1, 129.0, 128.7, 128.6, 128.5, 127.7, 126.8, 126.6 (2), 47.6; HRMS(ESI-TOF): m/z [M + H]$^+$ calculated for [$C_{28}H_{20}ClNO$]$^+$: 422.1306; found: 422.1303.

*4-((4-Bromophenyl)(phenyl)methyl)-2,5-diphenyloxazole (**7l**).*[8f] Following the general procedure **3**, compound **7l** was obtained as a white solid (124 mg, 97%); mp: 134−135 °C; ^{1}H NMR (500 MHz, $CDCl_3$); δ 8.08−8.07 (m, 2H), 7.61−7.59 (m, 2H), 7.46−7.42 (m, 5H), 7.41−7.35 (m, 4H), 7.32−7.29 (m, 3H), 7.27 (m, 1H), 7.25−.22 (m, 2H), 5.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 160.2, 146.7, 142.1, 141.8, 137.8, 131.5, 131.1, 130.3, 129.1, 129.0, 128.7, 128.6, 128.5, 127.7, 126.9, 126.6, 120.6, 47.7 ppm; HRMS (ESI-TOF): m/z [M + H]$^+$ calculated for [$C_{28}H_{21}BrNO$]$^+$: 466.0801; found: 466.0800.

*4-((4-Methoxyphenyl)(phenyl)methyl)-2,5-diphenyloxazole (**7m**).* Following the general procedure **3**, compound **7m** was obtained as a white solid (121 mg, 91%); mp: 180−181 °C; ^{1}H NMR (500 MHz, $CDCl_3$); δ 8.09−8.08 (m, 2H), 7.62 (d, J = 7.50 Hz, 2H), 7.46−7.40 (m, 5H), 7.39−7.36 (m, 2H), 7.34−7.30 (m, 4H), 7.26−7.20 (m, 2H), 6.85 (d, J = 8.55 Hz, 2H), 5.59 (s, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 160.0, 158.3, 146.4, 143.0, 138.7, 134.8, 130.3, 130.2, 129.1, 128.9, 128.7, 128.4, 128.3, 127.8, 126.6, 113.8, 55.3, 47.4; HRMS(ESI-TOF): m/z [M + H]$^+$ calculated for [$C_{29}H_{24}NO_2$]$^+$: 418.1802; found: 418.1801.

*4-((3,4-Dichlorophenyl)(phenyl)methyl)-2,5-diphenyloxazole (**7n**).* Following the general procedure **3**, compound **7n** was obtained as a white solid (107 mg, 83%); mp: 102−103 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09−8.07 (m, 2H), 7.60−7.58 (m, 2H), 7.48−7.47 (m, 1H), 7.46−7.43 (m, 4H), 7.40−7.38 (m, 3H), 7.37−7.31 (m, 3H), 7.27−7.23 (m, 3H), 5.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 160.3, 146.8, 143.0, 141.6, 137.3, 132.3, 131.2, 130.7, 130.4, 130.3, 129.1, 128.8, 128.6, 128.5, 127.6, 127.1, 126.6, 47.4 ppm; HRMS-(ESI-TOF): m/z [M + H]$^+$ calculated for [$C_{28}H_{20}ClNO$]$^+$: 456.0916; found: 456.0917.

*4-(bis(4-Fluorophenyl)methyl)-2,5-diphenyloxazole (**7o**).*[8f] Following the general procedure **3**, compound **7o** was obtained as a yellow solid (123 mg, 93%); mp: 140−141 °C; ^{1}H NMR (500 MHz, $CDCl_3$); δ 8.09−8.07 (m, 2H), 7.83−7.81 (m, 3H), 7.59−7.57 (m, 1H), 7.55−7.52 (m, 1H), 7.47 (m, 1H), 7.46−7.45 (m, 2H), 7.44 (m, 2H), 7.35−7.33 (m < 3H), 6.99 (t, J = 8.75 Hz, 3H), 5.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 170.1, 162.9, 160.5, 160.3, 146.6, 138.2, 137.9, 132.9, 132.3, 130.7, 130.6, 130.4, 129.0, 128.8, 128.7, 128.6, 128.5, 127.5, 127.4, 126.6, 126.5, 115.4, 115.2, 46.7 ppm; HRMS (ESI-TOF): m/z [M + H]$^+$ calculated for [$C_{28}H_{20}F_2NO$]$^+$: 424.1507; found: 424.1507.

*2-(4-Isobutylphenyl)propenamide (**8**).* To the stirred thionyl chloride (1.5 equiv), ibuprofen (1 equiv) was added slowly, the reaction mixture was warmed to 50 °C for 1 h and cooled to 10 °C in ice water, 25% aq ammonia (4 mL) was slowly and carefully added, and the solution was stirred for 30 min. The solid precipitated out was collected by filtration, washed with 10% sodium bicarbonate solution and water, dried, and purified by crystallization, and the pure product **8** was obtained as a pink solid (95 mg, 96%). mp: 195−196 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26−7.19 (m, 2H), 7.13−7.11 (m, 2H), 5.73 (s, 1H), 5.34 (s, 1H), 3.59−3.55 (m, 1H), 2.45 (d, J = 7.20 Hz, 2H), 1.86−1.82 (m, 1H), 1.51 (d, J = 7.15 Hz, 3H), 0.89 (d, J = 6.60 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3, 141.0, 138.8, 129.8, 127.4, 46.3, 45.1, 30.3, 22.4, 18.3, ppm; HR-MS (ESI-TOF) m/z: [M + H] + calculated for [$C_{13}H_{20}$ NO]$^+$: 206.1539; found: 206.1541.

*4-Benzhydryl-2-(1-(4-isobutylphenyl)ethyl)-5-phenyloxazole (**9**).* Following general experimental procedure **3**, compound **9** was obtained as a yellow sticky compound (150 mg, 65%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49−7.47 (m, 2H), 7.38−7.34 (m, 6H), 7.31−7.25 (m, 6H),7.23−7.20 (m, 4H), 7.07 (d, J = 7.95 Hz, 2H), 5.56 (s, 1H), 4.28 (q, J = 7.25 Hz, 2H), 2.43 (d, J = 7.20 Hz, 2H), 1.87−1.79 (m, 1H), 1.69 (d, J = 7.25 Hz, 3H), 0.90 (d, J = 3.80 Hz, 3H), 0.88 (d, J = 3.85 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.2, 146.4, 142.9, 142.8, 140.3, 139.5, 130.1, 129.9, 129.4, 129.3, 129.2, 128.8, 128.4, 127.2, 126.5, 48.1, 45.1, 39.4, 30.3, 22.5, 20.5 ppm; HR-MS (ESI-TOF) m/z: [M + H] + calculated for [$C_{34}H_{34}NO$]$^+$: 472.2635; found; 472.2637.

*4-(bis(4-Fluorophenyl)methyl)-2-(1-(4-isobutylphenyl)-ethyl)-5-phenyloxazole (**10**).* Following general experimental procedure **3**, compound **10** was obtained as a brown sticky compound (170 mg, 69%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, J = 7.75 Hz, 2H), 7.37 (t, J = 7.40 Hz, 2H), 7.32−7.27 (m, 5H), 7.22−7.20 (m, 2H), 7.08 (d, J = 8.00 Hz, 2H), 7.00−6.94 (m, 4H), 5.50 (s, 1H), 4.27 (q, J = 7.20 Hz, 2H), 2.43 (d,

https://doi.org/10.1021/acsomega.2c05085
ACS Omega 2022, 7, 34693−34706

J = 7.20 Hz, 2H), 1.86−1.79 (m, 1H), 1.69 (d, J = 7.25 Hz, 3H), 0.89 (d, J = 6.60 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4, 162.7, 160.7, 146.4, 140.4, 139.4, 138.5, 138.4 (2), 138.3, 136.3, 130.6 (2), 130.5, 129.4, 128.9, 128.3, 127.1, 126.5, 115.3, 115.2, 46.6, 45.1, 39.4, 30.3, 22.5, 20.4 ppm; HR-MS (ESI-TOF) m/z: [M + H] + calculated for $[C_{34}H_{32}F_2NO]^+$: 508.2446; found; 508.2444.

*(Z)-2-(4-Methoxyphenyl)-4-(1-phenyl-3-(p-tolyl)prop-1-en-1-yl)-5-(p-tolyl)thiazole 1,1-Dioxide (**11**).* To a mixture of **3d** (1equiv) in DCM was added *m*-CPBA (5 equiv) and stirred at room temperature for 12 h until complete conversion of **3d** monitored by TLC. The resulting solution was quenched with aqueous Na_2CO_3 and extracted with ethyl acetate thrice. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo, the crude was purified by column chromatography (100−200 silica gel, 1%, EtOAc in petroleum ether), and the product was obtained as a yellow solid (86 mg, 81%); mp: 122−123 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91−7.87 (m, 3H), 7.41−7.37 (m, 4H), 7.28−7.24 (m, 1H), 7.22−7.18 (m, 1H), 7.07 (d, J = 7.95 Hz, 2H), 6.97−6.92 (m, 4H), 6.86−6.83 (m, 3H), 6.37 (t, J = 7.30 Hz, 1H), 3.84 (s, 3H), 3.22 (d, J = 7.30 Hz, 2H), 2.32 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 163.0, 161.2, 148.6, 140.2, 137.9, 137.1, 135.5, 135.4, 135.0, 131.9, 129.4, 129.2, 129.0, 128.6, 128.4, 128.1 (2), 127.3, 126.6, 114.3, 113.6, 55.5, 35.9, 21.3, 21.0 ppm; HR-MS (ESI-TOF) m/z: [M + H] + calculated for $[C_{33}H_{30}NO_3S]^+$: 520.1941; found: 520.1946.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c05085.

Copies of ^{1}H and ^{13}C{H} NMR spectra for all compounds (PDF)

Details of single-crystal data of compound **3d** (CIF)

Details of single-crystal data of compound **5m** (CIF)

Details of single-crystal data of compound **7a** (CIF)

Details of single-crystal data of compound **7e** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Srinivasarao Yaragorla − *School of Chemistry, University of Hyderabad, Hyderabad 500046, India;* orcid.org/0000-0001-6152-5861; Email: srinivas.yaragorla@uohyd.ac.in, ysruoh@gmail.com

Author

Dandugula Sneha Latha − *School of Chemistry, University of Hyderabad, Hyderabad 500046, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.2c05085

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is financially supported by the IOE-UOH grant no UoH/IoE/RC1-08. D.S.L. is thankful to RGNF for the fellowship and Rathod Mahesh for the technical support in solving the crystal structures. The authors are thankful to the School of Chemistry, University of Hyderabad, for the facilities.

■ REFERENCES

(1) For selected reviews, see: (a) Lewis, J. R. Muscarine, oxazole, thiazole, imidazole, and peptide alkaloids, and other miscellaneous alkaloids. *Nat. Prod. Rep.* **1991**, *8*, 171−183. (b) Jagodziński, T. S. Thioamides as Useful Synthons in the Synthesis of Heterocycles. *Chem. Rev.* **2003**, *103*, 197−228. ((c)) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Applications*; 2nd ed.; Wiley-VCH: Weinheim, 2003. (d) Mustafa, S. M.; Nair, V. A.; Chittoor, J. P.; Krishnapillai, S. Synthesis of 1, 2, 4-Triazoles and Thiazoles from Thiosemicarbazide and its Derivatives. *Mini-Rev. Org. Chem.* **2004**, *1*, 375−385. ((e)) Wu, Y.-J.; Yang, B. V. Five-Membered Ring Systems: With N and S (Se, Te) Atoms. In *Progress in Heterocyclic Chemistry*; Gribble, G. W.; Joule, J. A., Eds.; Elsevier: Oxford, 2007, Vol. *18*, p 247. ((f)) Chen, B.; Heal, W. Five-Membered Rings with Two Heteroatoms, Each with Their Fused Carbocyclic Derivatives. In *Comprehensive Heterocyclic Chemistry III*; Katrizky, R.; Rees, C. W.; Scriven, E. F. V.; Taylor, R. J. K., Eds.; Pergamon: New York, 2008, Vol. *4*, p 635. (g) Jin, Z. Muscarine, imidazole, oxazole and thiazole alkaloids. *Nat. Prod. Rep.* **2009**, *26*, 382−445. (h) Lachia, M.; Moody, C. J. The synthetic challenge of diazonamide A, a macrocyclic indole bis-oxazole marine natural product. *Nat. Prod. Rep.* **2008**, *25*, 227−253.

(2) (a) Crews, P.; Kakou, Y.; Quinoa, E. Mycothiazole, a polyketide heterocycle from a marine sponge. *J. Am. Chem. Soc.* **1988**, *110*, 4365−4368. (b) Cutignano, A.; Bruno, I.; Bifulco, G.; Casapullo, A.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. Dactylolide, a New Cytotoxic Macrolide from the Vanuatu Sponge Dactylospongia sp. *Eur. J. Org. Chem.* **2001**, 775−778.

(3) (a) Williams, D. R.; Patnaik, S.; Clark, M. P. Total Synthesis of Cystothiazoles A and C. *J. Org. Chem.* **2001**, *66*, 8463−8469. (b) DeRoy, P. L.; Charette, A. B. Total Synthesis of (+)-Cystothiazole A. *Org. Lett.* **2003**, *5*, 4163−4165. (c) Shao, J.; Panek, J. S. Total Synthesis of Cystothiazoles A and B. *Org. Lett.* **2004**, *6*, 3083−3085.

(4) For selected reviews on the synthesis of oxazoles and thiazoles, see: (a) Turchi, I. J. Oxazole chemistry. A review of recent advances. *Ind. Eng. Chem. Prod. Res. Dev.* **1981**, *20*, 32−76. (b) Ibrar, A.; Khan, I.; Abbas, N.; Farooq, U.; Khan, A. Transition-metal-free synthesis of oxazoles: valuable structural fragments in drug discovery. *RSC Adv.* **2016**, *6*, 93016−93047. (c) Zhang, H. Z.; Zhao, Z. L.; Zhou, C. H. Recent advance in oxazole-based medicinal chemistry. *Eur. J. Med. Chem.* **2018**, *144*, 444−492. (d) Zheng, X.; Liu, W.; Zhang, D. Recent Advances in the Synthesis of Oxazole-Based Molecules *via* van Leusen Oxazole Synthesis. *Molecules* **2020**, *25*, 1594−1611. (e) Neha, K.; Ali, F.; Haider, K.; Khasimbi, S.; Wakode, S. Synthetic approaches for oxazole derivatives: A review. *Synth. Commun.* **2021**, *51*, 3501−3519. (5) Hantzsch, A.; Weber, J. H. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 3118−3132.

(6) For selected recent examples, see: (a) Bach, T.; Heuser, S. Regioselective Cross-Coupling Reactions as an Entry into Biologically Relevant Bithiazoles: First Total Synthesis of Cystothiazole E. *Angew. Chem., Int. Ed.* **2001**, *40*, 3184−3185. (b) Ganesh, T.; Schilling, J. K.; Palakodety, R. K.; Ravindra, R.; Shanker, N.; Bane, S.; Kingston, D. G. I. Synthesis and biological evaluation of fluorescently labeled epothilone analogs for tubulin binding studies. *Tetrahedron* **2003**, *59*, 9979−9984. (c) Rivkin, A.; Cho, Y. S.; Gabarda, A. E.; Yoshimura, F.; Danishefsky, S. J. Application of Ring-Closing Metathesis Reactions in the Synthesis of Epothilones. *J. Nat. Prod.* **2004**, *67*, 139−143. (d) Kazmaier, U.; Ackermann, S. A straightforward approach towards thiazoles and endothiopeptides *via* Ugi reaction. *Org. Biomol. Chem.* **2005**, *3*, 3184−3187. (e) Kaleta, Z.; Makowski, B. T.; Soós, T.; Dembinski, R. Thionation Using Fluorous Lawesson's Reagent. *Org. Lett.* **2006**, *8*, 1625−1628. (f) Thomae, D.; Perspicace, E.; Xu, Z.; Henryon, D.; Schneider, S.; Hesse, S.; Kirsch, G.; Seck, P. One-pot synthesis of new 2,4,5-trisubstituted 1,3-thiazoles and 1,3-selenazoles. *Tetrahedron* **2009**, *65*, 2982−2988. (g) Shi, B.; Blake, A. J.; Lewis, W.; Campbell, I. B.; Judkins, B. D.; Moody, C. J. Rhodium

https://doi.org/10.1021/acsomega.2c05085
ACS Omega 2022, 7, 34693−34706

Carbene Routes to Oxazoles and Thiazoles. Catalyst Effects in the Synthesis of Oxazole and Thiazole Carboxylates, Phosphonates, and Sulfones. *J. Org. Chem.* **2010**, *75*, 152−161.

(7) For reviews on reactions of propargyl alcohols, see; (a) Zhu, Y.; Sun, L.; Lu, P.; Wang, Y. Recent Advances on the Lewis Acid-Catalyzed Cascade Rearrangements of Propargylic Alcohols and Their Derivatives. *ACS Catal.* **2014**, *4*, 1911−1925. (b) R Reddy, C.; Ranjan, R.; Kumaraswamy, P.; D Reddy, M.; Gree, R. 1-Aryl propargylic alcohols as handy synthons for the construction of heterocycles and carbocycles. *Curr. Org. Chem.* **2014**, *18*, 2603−2645. (c) Roy, D.; Tharra, P.; Baire, B. Intercepted Meyer−Schuster Rearrangements in Organic Synthesis. *Asian J. Org. Chem.* **2018**, *7*, 1015−1032. (d) Roy, R.; Saha, S. Scope and advances in the catalytic propargylic substitution reaction. *RSC Adv.* **2018**, *8*, 31129−31193. (e) Hua, R.; Nizami, T. A. Synthesis of Heterocycles by Using Propargyl Compounds as Versatile Synthons. *Mini-Rev. Org. Chem.* **2018**, *15*, 198−207. (f) Khan, T.; Yaragorla, S. Iodocyclization of Propargyl Alcohols: Highly Facile Approach to Hetero/Carbocyclic Iodides. *Eur. J. Org. Chem.* **2019**, 3989−4012. (g) Qian, H.; Huang, D.; Bi, Y.; Yan, G. 2-Propargyl Alcohols in Organic Synthesis. *Adv. Synth. Catal.* **2019**, *361*, 3240−3280. (h) Tsuji, H.; Kawatsura, M. Transition-Metal-Catalyzed Propargylic Substitution of Propargylic Alcohol Derivatives Bearing an Internal Alkyne Group. *Asian J. Org. Chem.* **2020**, *9*, 1924−1941. (i) Song, X. R.; Yang, R.; Xiao, Q. Recent Advances in the Synthesis of Heterocyclics *via* Cascade Cyclization of Propargylic Alcohols. *Adv. Synth. Catal.* **2021**, *363*, 852−876. (j) Justaud, F.; Hachem, A.; Grée, R. Recent Developments in the Meyer-Schuster Rearrangement. *Eur. J. Org. Chem.* **2021**, 514−542.

(8) (a) Arcadi, A.; Cacchi, S.; Cascia, L.; Fabrizi, G.; Marinelli, F. Preparation of 2,5-Disubstituted Oxazoles from N-Propargylamides. *Org. Lett.* **2001**, *3*, 2501−2504. (b) Milton, M. D.; Inada, Y.; Nishibayashi, Y.; Uemura, S. Ruthenium- and gold-catalysed sequential reactions: a straightforward synthesis of substituted oxazoles from propargylic alcohols and amides. *Chem. Commun.* **2004**, 2712−2713. (c) Kumar, M. P.; Liu, R.-S. $Zn(OTf)_2$-Catalyzed Cyclization of Proparyl Alcohols with Anilines, Phenols, and Amides for Synthesis of Indoles, Benzofurans, and Oxazoles through Different Annulation Mechanisms. *J. Org. Chem.* **2006**, *71*, 4951−4955. (d) Yoshimatsu, M.; Yamamoto, T.; Sawa, A.; Kato, T.; Tanabe, G.; Muraoka, O. α-Sulfanyl and α-Selanyl Propadienyl Cations: Regioselective Generations and Cycloadditions with Thioamides and Selemides Controlled by $MeNO_2$−H_2O System. *Org. Lett.* **2009**, *11*, 2952−2955. (e) Pan, Y. M.; Zheng, F.; Lin, H.; Zhan, Z. Brønsted Acid-Catalyzed Propargylation/Cycloisomerization Tandem Reaction: One-Pot Synthesis of Substituted Oxazoles from Propargylic Alcohols and Amides. *J. Org. Chem.* **2009**, *74*, 3148−3151. (f) Zhang, X.; Teo, W. T.; Chan, P. W. H. Efficient synthesis of di- and trisubstituted 2-aryloxazoles *via* ytterbium(III) triflate catalyzed cyclization of tertiary propargylic alcohols with aryl amides. *J. Organomet. Chem.* **2011**, *696*, 331−337. (g) Bartoli, G.; Cimarelli, C.; Cipolletti, R.; Diomedi, S.; Giovannini, R.; Mari, M.; Marsili, L.; Marcantoni, E. Microwave-Assisted Cerium(III)-Promoted Cyclization of Propargyl Amides to Polysubstituted Oxazole Derivatives. *Eur. J. Org. Chem.* **2012**, 630−636. (h) Cabrero-Antonino, J. R.; Leyva-Pérez, A.; Corma, A. Beyond Acid Strength in Zeolites: Soft Framework Counteranions for Stabilization of Carbocations on Zeolites and Its Implication in Organic Synthesis. *Angew. Chem., Int. Ed.* **2015**, *54*, 5658−5661. (i) Wang, B.; Chen, Y.; Zhou, L.; Wang, J.; Tung, C. H.; Xu, Z. Synthesis of Oxazoles by Tandem Cycloisomerization/Allylic Alkylation of Propargyl Amides with Allylic Alcohols: $Zn(OTf)_2$ as π Acid and σ Acid Catalyst. *J. Org. Chem.* **2015**, *80*, 12718−12724. (j) Peng, H.; Akhmedov, N. G.; Liang, Y.-F.; Jiao, N.; Shi, X. Synergistic Gold and Iron Dual Catalysis: Preferred Radical Addition toward Vinyl−Gold Intermediate over Alkene. *J. Am. Chem. Soc.* **2015**, *137*, 8912−8915.

(9) (a) Gao, X.; Pan, Y.; Lin, M.; Chen, L.; Zhan, Z.-P. Facile one-pot synthesis of three different substituted thiazoles from propargylic alcohols. *Org. Biomol. Chem.* **2010**, *8*, 3259−3266. (b) Zhang, X.; Teo, W. T.; Sally; Chan, P. W. H. Brønsted Acid Catalyzed Cyclization of Propargylic Alcohols with Thioamides. Facile Synthesis of Di- and Trisubstituted Thiazoles. *J. Org. Chem.* **2010**, *75*, 6290−6293.

(10) See for reviews on calcium catalysis: (a) Harder, S. From Limestone to Catalysis: Application of Calcium Compounds as Homogeneous Catalysts. *Chem. Rev.* **2010**, *110*, 3852−3876. (b) Begouin, J.-M.; Niggemann, M. Calcium-Based Lewis Acid Catalysts. *Chem. − Eur. J.* **2013**, *19*, 8030−8041. (c) Leboeuf, D.; Gandon, V. Carbon−Carbon and Carbon−Heteroatom Bond-Forming Transformations Catalyzed by Calcium(II) Triflimide. *Synthesis* **2017**, 1500−1508. (d) Sun, Y.; Hu, M.; Fu, S.; Liu, B. Recent advances in alkaline earth metal-enabled syntheses of heterocyclic compounds. *Org. Biomol. Chem.* **2020**, *18*, 6443−6466. ((e)) Rauser, M.; Schröder, S.; Niggemann, M. *Early Main Group Metal Catalysis: Concepts and Reactions*; Harder, S., Ed.; Wiley-VCH, 2020, 279 −310.

(11) See for selected reactions of propargyl alcohol activation with calcium(II) from our group: (a) Yaragorla, S.; Pareek, A.; Dada, R. Cycloisomerization of Oxindole-Derived 1,5-Enynes: A Calcium(II)-Catalyzed One-Pot, Solvent-free Synthesis of Phenanthridinones, 3-(Cyclopentenylidene)indolin-2-ones and 3-Spirocyclic Indolin-2-ones. *Adv. Synth. Catal.* **2017**, *359*, 3068−3075. (b) Yaragorla, S.; Dada, R.; Rajesh, P.; Sharma, M. Highly Regioselective Synthesis of Oxindolyl-Pyrroles and Quinolines *via* a One-Pot, Sequential Meyer−Schuster Rearrangement, Anti-Michael Addition/$C(sp^3)$−H Functionalization, and Azacyclization. *ACS Omega* **2018**, *3*, 2934−2946. (c) Yaragorla, S.; Latha, D. S.; Rajesh, P. Calcium-Catalyzed Intramolecular Hydroamination-Deacylation Reaction of in situ formed β-Amino Allenes. *Adv. Synth. Catal.* **2021**, *363*, 5486−5492.

(12) Wang, S.-H.; Tu, Y.-Q.; Chen, P.; Hu, X.-D.; Zhang, F.-M.; Wang, A.-X. KO^{t}Bu-Promoted Three-Component Coupling of Aldehydes and Alkynes: Highly Efficient Synthesis of 1-En-4-yn-3-ols and 2-En-4-yn-1-ols. *J. Org. Chem.* **2006**, *71*, 4343−4345.

(13) Product **3s** was formed in the first 10 min and slowly isomerized to **3a** in 40 min; see the Supporting Information for details.

(14) See the Supporting Information for the details of the crystal structure of **3d**, **5m**, **7a**, and **7e**.

(15) The ratio of **3q**/**3r** was determined by the ^{1}H NMR spectrum of the crude compound.

(16) Xi, J.; Yang, H.; Li, L.; Zhang, X.; Li, C.; Gu, Z. Atroposelective Kinetic Resolution of 8H-Indeno[1,2-c]thiophen-8-ols *via* Pd-Catalyzed C−C Bond Cleavage Reaction. *Org. Lett.* **2022**, *24*, 2387−2392.

(17) (a) Xie, H.; Rao, Y.; Ding, M.-W. Synthesis of fluorescent trisubstituted oxazoles *via* a facile tandem Staudinger/aza-Wittig/isomerization reaction. *Dyes Pigm.* **2017**, *139*, 440−447. (b) Suntsova, P. O.; Eltyshev, A. K.; Pospelova, T. A.; Slepukhin, P. A.; Benassi, E.; Belskaya, N. P. Design and synthesis of disubstituted and trisubstituted thiazoles as multifunctional fluorophores with large Stokes shifts. *Dyes Pigm.* **2019**, *166*, 60−71.

https://doi.org/10.1021/acsomega.2c05085
ACS Omega 2022, 7, 34693−34706