JOC The Journal of Organic Chemistry

Subscriber access provided by EDINBURGH UNIVERSITY LIBRARY | @ http://www.lib.ed.ac.uk

Note

Oxidative dehydrosulfurative cross-coupling of 3,4-dihydropyrimidine-2-thiones with alkynes for access to 2-alkynylpyrimidines

Ngoc Son Le Pham, Hyunik Shin, Jun Yong Kang, and Jeong-Hun Sohn

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c00091 • Publication Date (Web): 11 Mar 2020

Downloaded from pubs.acs.org on March 12, 2020

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Oxidative Dehydrosulfurative Cross-Coupling of 3,4-Dihydropyrimidine-2-thiones with Alkynes for Access to 2-Alkynylpyrimidines

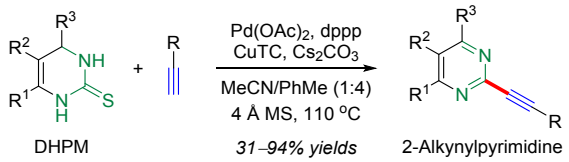
Ngoc Son Le Pham,[§] Hyunik Shin,[†] Jun Yong Kang,[‡] and Jeong-Hun Sohn[§]*

[§]Department of Chemistry, Chungnam National University, Daejeon 34134, Republic of Korea. [†]Yonsung Fine Chemicals R&D Center, Suwon 16675, Republic of Korea. [‡]Department of Chemistry and Biochemistry, University of Nevada, Las Vegas, 4505 South Maryland Parkway, Las Vegas, Nevada, 89154-4003

E-mail: sohnjh@cnu.ac.kr

KEYWORDS: dehydrosulfurative coupling, Sonogashira coupling, alkynylpyrimidine, 3,4-dihydropyrimidine-2-thione, oxidative dehydrogenation

ABSTRACT: A reaction method is described for the one-step synthesis of 2-alkynylpyrimidines from 3,4-dihydropyrimidin-1*H*-2-thiones (DHPMs) via dehydrosulfurative Sonogashira cross-coupling with concomitant oxidative dehydrogenation using a Pd/Cu catalytic system. Together with the ready availability of DHPMs possessing various substituents at the C4–C6 positions, this transformation offers a rapid and general access to diverse 2-alkynylpyrimidine derivatives.



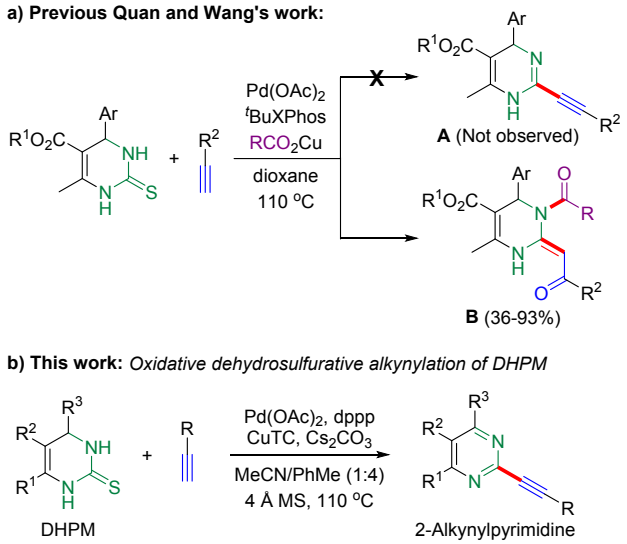
Transition metal-catalyzed cross-coupling reactions with organohalides have been widely used to form new carbon–carbon and carbon–heteroatom bonds with broad substrate tolerance.[1] Recently, organosulfur compounds have emerged as promising alternative electrophilic partners to the commonly used organo(pseudo)halides.[2] In 2000, Liebeskind and Srogl reported Pd-catalyzed/Cu-mediated cross-coupling between thioesters and boronic acids to produce ketones.[3] Since then, this desulfurative cross-coupling reaction has been extended to coupling with various nucleophilic partners to yield valuable C-C bonds that are unattainable by traditional C–C bond-forming reactions.[4] Notable examples include the direct dehydrosulfurative C–C cross-coupling reactions of thioamide moieties with boronic acids, stannanes, or siloxanes.[5] These reactions efficiently prohibit the traditionally favoured C-S cross-coupling reactions with such substrates.[6]

With growing interests in desulfurative coupling reactions, we recently developed a dehydrosulfurative arylation with concomitant oxidative dehydrogenation of 3,4-dihydropyrimidin-1*H*-2-thiones (DHPMs) with boronic acids to produce 2-arylpyrimidines.[7] In addition, we demonstrated that this cascade reaction protocol could be extended to oxidative dehydrosulfurative C–N or C–O cross-coupling reaction of DHPMs with amines or boric esters to generate 2-aminopyrimidines and 2-alkoxypyrimidines, respectively.[8] These results led us to envision an oxidative dehydrosulfurative alkynylation reaction of DHPMs with terminal alkynes to yield 2-alkynylpyrimidines. This reaction method would enable the rapid generation of diverse 2-alkynylpyrimidine derivatives because DHPMs bearing various substituents at the C4–C6 positions can be readily prepared by the well-known Biginelli three-component reaction.[9] Although pyrimidine motifs are important substructures of many commercialized medicines such as rosuvastatin, imatinib, ruxolitinib, tofacitinib, voriconazole, and baricitinib,[10] the precedent synthetic strategies toward various pyrimidine derivatives are limited, especially for the rapid access to potential pharmaceutical agents.

Since the development of the Sonogashira reaction,[11] terminal alkynes have been widely used in various C–C cross-coupling reactions with organo(pseudo)halide electrophiles. There have been many efforts to extend Sonogashira coupling to organosulfur electrophilic partners such as thiono or mercapto

electrophiles as alternatives to the (pseudo)halides. For example, Tatibouët group reported the dehydrosulfurative alkynylation of 1,3-oxazolidine-2-thiones or 1,3-oxazoline-2-thiones,[12] which was applied to the total synthesis of (+)-neopeltolide by Roulland and co-workers.[13] In addition, Hintermann group[14] and Suzenet group[15] extended the dehydrosulfurative alkynylation protocol to six-membered 2-mercaptopyrimidines and thioamide-type pyridines (quinolones) containing cyano or methoxy group at C3 position, respectively.

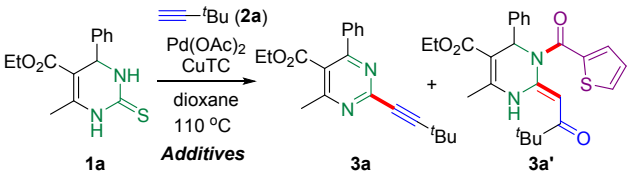
Recently, Quan and Wang group attempted the cross-coupling reaction between DHPMs and terminal alkynes in the presence of $Pd(OAc)_2$/Xphos and copper carboxylate, but obtained the substituted dihydropyrimidine **B** instead of the desired alkynylated product **A** (Scheme 1a).[16] According to the mechanism proposed by Quan and Wang, the product **B** was generated from the alkynylated product **A** via acylation and hydration subsequently. In this reaction, the copper carboxylate acted not only as a co-factor but also as an acylating agent. The proposition led us to focus on suppressing the acylation and hydration to yield the desired 2-alkynylpyrimidines. On the basis of the proposed mechanism, we hypothesized that the undesired acylation process could be restrained by the addition of a base to capture the carboxylic acid generated from the copper carboxylate and involved in the acylation under base-free conditions. To prevent the hydration by in-situ generated water, molecular sieves should be used. In addition, over the course of our previous studies on the cross-coupling reactions of DHPMs, we found that the dehydrosulfurative cross-coupling reactions using Pd/Cu catalytic system accompanied oxidative dehydrogenation under argon atmosphere, presumably due to the Cu species present in the reaction.[7,8,17] Thus, we envisaged that the dehydrosulfurative alkynylation of DHPMs would also undergo with concomitant oxidative dehydrogenation under similar reaction conditions. Herein, we report the oxidative dehydrosulfurative Sonogashira coupling of DHPMs with terminal alkynes to produce 2-alkynylpyrimidines (Scheme 1b).



Scheme 1. Oxidative dehydrosulfurative alkynylation of DHPMs with alkynes to produce 2-alkynylpyrimidines

We tested our hypothesis with the reaction between DHPM **1a** and alkyne **2a** using $Pd(OAc)_2$ and Cu(I)-thiophene-2-carboxylate (CuTC) in the presence or absence of Cs_2CO_3 and 4 Å molecular sieves under Ar (Table 1).

Table 1. Initial studies[a]



Entry	Additives	Yield (%)[b]	
		3a	**3a'**
1	-	0	63
2	4 Å MS	trace	70
3	Cs_2CO_3	11	0
4	4 Å MS/Cs_2CO_3	24	0

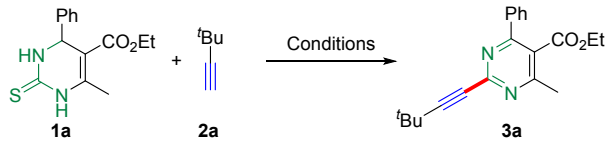
[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.38 mmol), CuTC (0.40 mmol), $Pd(OAc)_2$ (0.025 mmol), 1,4-dioxane (1.5 mL) at 110 °C. [b]Isolated yields.

When the reaction was carried out in the absence of both Cs_2CO_3 and 4 Å molecular sieves, only **3a′** was generated (entry 1, Table 1). However, the desired product **3a** was produced in the presence of either

4 Å molecular sieves or Cs_2CO_3, and **3a′** was not generated in the presence of Cs_2CO_3 (entries 2 and 3). These results led us to test a reaction using both 4 Å molecular sieves and Cs_2CO_3, which resulted in an increased yield of **3a** without forming **3a′** (entry 4).

On the basis of the initial studies, the optimization of reaction conditions was performed in the presence of both base and molecular sieves (Table 2). When $Pd(OAc)_2$ was replaced by other Pd sources such as $PdCl_2$ and $Pd(PPh_3)_4$, the desired product was not formed (entries 1 and 2). Other Cu sources such as CuMeSal, CuI, and a mixture of CuTC and CuI did not provide the desired product (entries 3–5). With respect to solvents, MeCN was found to be more effective than other solvents such as dioxane, DMF, PhMe, NMP, DMA, and DMSO (entries 6–11). We found that the addition of a bidentate ligand such as 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl (Tol-BINAP) or 1,3-bis(diphenylphosphino)propane (dppp) improved the yield of the desired product (52% and 57%, respectively; entries 12 and 15). Further optimization using MeCN-PhMe cosolvent system increased the product yield up to 85% (entries 16 and 17). With respect to bases, Et_3N, K_3PO_4, K_2CO_3, and LiHMDS were not as effective as Cs_2CO_3 (entries 18–21).[18]

Table 2. Optimization of reaction conditions[a,b]



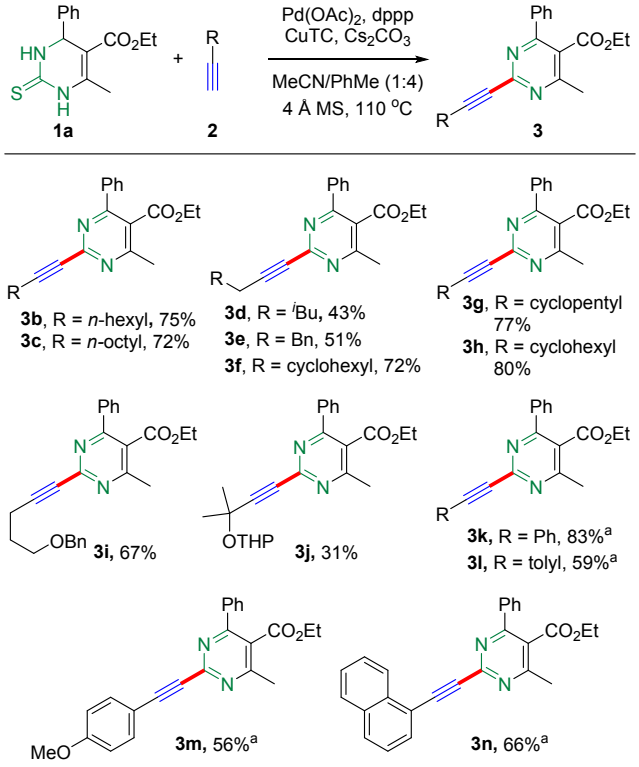
Entry	Pd/ Ligand	Cu/Base	Solvent	Yield (%)
1	$PdCl_2$	CuTC/ Cs_2CO_3	dioxane	0
2	$Pd(PPh_3)_4$	CuTC/ Cs_2CO_3	dioxane	0
3	$Pd(OAc)_2$	CuMeSal/ Cs_2CO_3	dioxane	0
4	$Pd(OAc)_2$	CuI/ Cs_2CO_3	dioxane	0
5	$Pd(OAc)_2$	CuTC-CuI /Cs_2CO_3	dioxane	0
6	$Pd(OAc)_2$	CuTC/ Cs_2CO_3	DMF	trace
7	$Pd(OAc)_2$	CuTC/ Cs_2CO_3	PhMe	trace

8	$Pd(OAc)_2$	CuTC/ Cs_2CO_3	NMP	7
9	$Pd(OAc)_2$	CuTC/ Cs_2CO_3	DMA	trace
10	$Pd(OAc)_2$	CuTC/ Cs_2CO_3	DMSO	trace
11	$Pd(OAc)_2$	CuTC/ Cs_2CO_3	MeCN	35
12	$Pd(OAc)_2$/ Tol-BINAP	CuTC/ Cs_2CO_3	MeCN	52
13	$Pd(OAc)_2$/ $P(o\text{-}tolyl)_3$	CuTC/ Cs_2CO_3	MeCN	17
14	$Pd(OAc)_2$/ PPh_3	CuTC/ Cs_2CO_3	MeCN	35
15	$Pd(OAc)_2$/ dppp	CuTC/ Cs_2CO_3	MeCN	57
16	$Pd(OAc)_2$/ dppp	CuTC/ Cs_2CO_3	MeCN/PhMe (1:20)	78
17	$Pd(OAc)_2$/ dppp	CuTC/ Cs_2CO_3	MeCN/PhMe (1:4)	85
18	$Pd(OAc)_2$/ dppp	CuTC/ Et_3N	MeCN/PhMe (1:4)	trace
19	$Pd(OAc)_2$/ dppp	CuTC/ K_2CO_3	MeCN/PhMe (1:4)	trace
20	$Pd(OAc)_2$/ dppp	CuTC/ K_3PO_4	MeCN/PhMe (1:4)	trace
21	$Pd(OAc)_2$/ dppp	CuTC/ LiHMDS	MeCN/PhMe (1:4)	42

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.38 mmol), Pd catalyst (0.025 mmol), phosphine ligand (0.030 mmol), Cu (0.40 mmol), base (0.25 mmol) and 4 Å molecular sieves in solvent (1.5 mL) at 110 °C for 16 h under Ar. [b]Isolated yields.

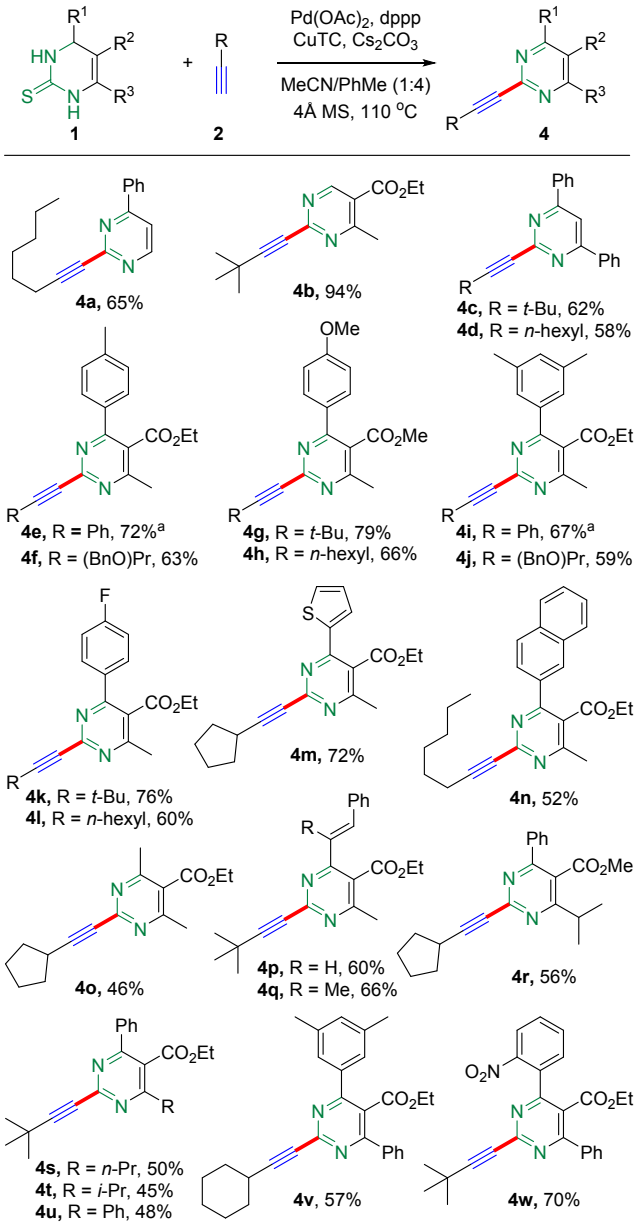
Under the optimal reaction conditions, we assessed the scope of the reaction with various DHPMs and terminal alkynes (Scheme 2). With respect to the alkynes, we found that both alkyl- and aryl-substituted alkynes were suitable substrates. When DHPM **1a** was reacted with the alkynes containing linear alkyl groups such as *n*-hexylacetylene and *n*-octylacetylene, the corresponding products **3b** and **3c** were produced in 75% and 72% yields, respectively. In the case of alkynes bearing branched alkyl groups such as *i*-pentylacetylene, phenethylacetylene, and cyclohexylmethylacetylene, the desired products **3d–f**, respectively, were obtained in 43–72% yields. Cyclopentylacetylene and cyclohexylacetylene, providing **3g** (77%) and **3h** (80%), respectively, were also compatible with the reaction method. We also examined alkynes possessing functionalized alkyl groups such as benzyl- or tetrahydropyranyl (THP)-protected

hydroxyl group. The benzyl ether provided **3i** in 67% yield while the THP ether furnished **3j** in 31% yield, which is presumably attributed to the labile character of the –OTHP group. In the case of aryl-substituted alkynes, we found that the desired products were produced in moderate to good yields in the absence of phosphine ligand.[19] For example, phenylacetylene, tolylacetylene, and anisoylacetylene afforded the corresponding products **3k–m**, respectively, in 56–83% yields. 1-Naphthylacetylene was also suitable substrate to generate **3n** in 66% yield.



Scheme 2. Scope of the reaction with respect to alkynes. Reaction conditions: **1a** (0.25 mmol), **2** (0.38 mmol), $Pd(OAc)_2$ (0.025 mmol), dppp (0.030 mmol), CuTC (0.40 mmol), Cs_2CO_3 (0.25 mmol) and 4 Å molecular sieves in MeCN/PhMe (1/4 v/v, 1.5 mL) at 110 °C for 16 h under Ar. Yields are isolated yields. [a]No P ligand was used.

Next, we evaluated the reactivity of DHPMs possessing various substituents at the C4–C6 positions (Scheme 3). The reaction of DHPM lacking substituents at both C5 and C6 positions with *n*-hexylacetylene produced **4a** in 65% yield. For DHPM having no substituent at the C4 position, the desired product **4b** was generated in high yield (94%) when reacted with *t*-butylacetylene. In the case of no substituent at the C5 position, the corresponding products **4c** (62%) and **4d** (58%) were obtained in the reactions with *t*-butylacetylene and *n*-hexylacetylene, respectively.

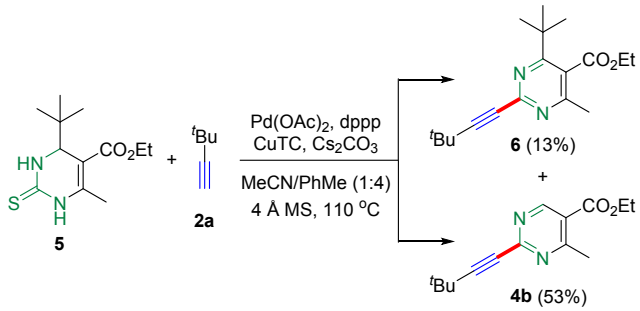


Scheme 3. Scope of the reaction with respect to DHPMs and alkynes. Reaction conditions: **1** (0.25 mmol), **2** (0.38 mmol), $Pd(OAc)_2$ (0.025 mmol), dppp (0.030 mmol), CuTC (0.40 mmol), Cs_2CO_3 (0.25 mmol) and 4 Å molecular sieves in MeCN/PhMe (1/4 v/v, 1.5 mL) at 110 °C for 16 h under Ar. Yields are isolated yields. [a]No P ligand was used.

We also investigated the scope of the reaction with fully substituted DHPMs. The DHPMs possessing electron-donating substituents such as methyl and methoxy group at the para position of the C4 aryl provided **4e**–**h** in 63–79% yields. The DHPMs with the 3,5-dimethyl group on the C4 aryl were efficiently transformed to the desired products **4i** and **4j** in 59% and 67% yields, respectively. The electron-withdrawing fluoride group at the para position of the C4 aryl was also compatible under the reaction

conditions, yielding **4k** (76%) and **4l** (60%). When the heterocyclic thiophenyl group or bicyclic naphthyl group was attached at the C4 position of DHPM, the desired products **4m** and **4n** were produced in 72% and 52% yields, respectively. Instead of aryl group, methyl or styryl group at the C4 position was also proven to be suitable for the reaction and yielded **4o**, or **4p** and **4q**, respectively. With respect to substituents at the C5 and C6 positions of DHPM, methoxycarbonyl group at the C5 position furnished **4r** in 56% yield and both alky and aryl substituents such as *n*-propyl, *i*-propyl, and phenyl group at the C6 position afforded the corresponding products **4s**–**w**, respectively, in 45–70% yields.[20]

When the DHPM **5** possessing a *t*-Bu group at the C4 position was reacted with *t*-butylacetylene, the debutylated product **4b** was generated as the major product (Scheme 4). This result supports that the aromatization involved the generation of a radical intermediate,[21] as described in the previous oxidative dehydrogenation of 2-alkylthiodihydropyrimidine,[17a,22] and oxidative dehydrosulfurative arylation[7] and -alkoxylation[8b] of DHPM, bearing the *t*-Bu group at the C4 position.[23,24]



Scheme 4. Reaction of DHPM containing *t*-Bu group at the C4 position with alkyne

In summary, we have developed an oxidative dehydrosulfurative Sonogashira cross-coupling reaction using a Pd/Cu catalytic system to synthesize 2-alkynylpyrimidines from DHPMs in a single step. The reaction proceeded efficiently with a wide range of DHPM compounds and terminal alkynes. Together with the facile preparation of the DHPM substrates by the Biginelli three-component reaction, this transformation enables a highly concise synthesis of diverse 2-alkynylpyrimidine derivatives. Considering the biological significance of the pyrimidine derivatives, this synthetic protocol provides a new platform for a rapid and wide access to valuable drug candidate substructures.

EXPERIMENTAL SECTION

General. Common solvents were purified before use. Toluene (PhMe) was purified by distillation from sodium-benzophenone ketyl. Acetonitrile (MeCN, AcroSeal) was used as received. All reagents were reagent grade and purified where necessary. Reactions were monitored by thin layer chromatography (TLC) using Whatman pre-coated silica gel plates. Flash column chromatography was performed over ultra-pure silica gel (230-400 mesh) from Merck. Melting points (mp) were determined in opened capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker AVANCE 300 (300 MHz) or 600 (600 MHz) spectrometer using residual solvent peaks as an internal standard ($CHCl_3$: δ 7.26 ppm for proton and δ 77.16 ppm for carbon). Multiplicities for ^{1}H NMR are designated as: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext =sextet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet and br = broad. Infrared spectra (IR) were recorded on JASCO FT/IR-4100 spectrometer and are reported in reciprocal centimeter (cm^{-1}). High resolution mass spectra (HRMS) were obtained on BrukermicroTOF-Q.

Synthesis of DHPMs. Following the literature procedure,[25] ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(**1a**),[25] 4-phenyl-3,4-dihydropyrimidine-2(1H)-thione (**1b**),[26] ethyl 6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1c**),[27] 4,6-diphenyl-3,4-dihydropyrimidine-2(1H)-thione (**1d**),[28] ethyl 6-methyl-2-thioxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1e**),[25] methyl 4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1f**),[29] ethyl 4-(3,5-dimethylphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1g**), ethyl 4-(4-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1h**),[25] ethyl 6-methyl-4-(thiophen-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1i**),[30] ethyl 6-methyl-4-(naphthalen-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1j**),[31] ethyl 4,6-dimethyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1k**),[32] ethyl (E)-6-methyl-4-styryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1l**),[33] ethyl (E)-6-methyl-4-(1-phenylprop-1-en-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1m**), methyl 6-isopropyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

(**1n**),[34] ethyl 4-phenyl-6-propyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1o**), ethyl 6-isopropyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1p**),[35] ethyl 4,6-diphenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1q**),[36] ethyl 4-(3,5-dimethylphenyl)-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1r**), ethyl 4-(2-nitrophenyl)-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1s**)[37] were prepared.

Ethyl 4-(3,5-dimethylphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1g**). Recrystallized from a mixture of EtOH and H_2O (1:1). Yield: 2.46 g, 81% (10.0 mmol scale), white solid, mp 202-204 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.25 (s, 1H), 9.56 (s, 1H), 6.88 (d, J = 25.5 Hz, 3H), 5.13 (d, J = 3.8 Hz, 1H), 4.04 (dd, J = 7.1, 3.5 Hz, 2H), 2.28 (d, J = 14.7 Hz, 9H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 174.1, 165.1, 144.8, 143.5, 137.4, 129.1, 124.1, 100.7, 59.5, 54.0, 21.0, 17.2, 14.0; IR (film) cm^{-1}: 3175, 1658, 1570, 1456, 1280, 1184, 1094, 849, 749; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{21}N_2O_2S$ 305.1324; Found 305.1296.

Ethyl (E)-6-Methyl-4-(1-phenylprop-1-en-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1m**). Recrystallized from a mixture of EtOH and H_2O (1:1). Yield: 2.31 g, 73% (10.0 mmol scale), Yellow solid, mp 112-114 °C. ^{1}H NMR (300 MHz, DMSO-d_6): 10.22 (s, 1H), 9.41 (s, 1H), 7.43 – 7.11 (m, 5H), 6.33 (s, 1H), 4.87 – 4.67 (m, 1H), 4.08 (q, J = 7.1 Hz, 2H), 2.28 (s, 3H), 1.77 (s, 3H), 1.18 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d$_6$) δ 174.6, 165.2, 145.4, 137.8, 136.7, 128.8, 128.3, 126.7, 126.3, 98.7, 59.4, 58.6, 17.1, 14.1, 13.1; IR (film) cm^{-1}: 3182, 1661, 1566, 1452, 1369, 1331, 1275, 1164, 1110, 1012, 756, 699, 642; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{21}N_2O_2S$ 317.1324; Found 317.1284.

Ethyl 4-phenyl-6-propyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1o**). Recrystallized from a mixture of EtOH and H_2O (1:1). Yield: 1.77 g, 58% (10.0 mmol scale), white solid, mp 120-122 °C. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 10.30 (s, 1H), 9.63 (s, 1H), 7.57 – 7.02 (m, 5H), 5.19 (d, J = 3.2 Hz, 1H), 4.03 (q, J = 6.4 Hz, 2H), 2.84 – 2.58 (m, 2H), 1.71 – 1.39 (m, 2H), 1.12 (t, J = 6.8 Hz, 3H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d$_6$) δ 174.4, 164.9, 149.0, 143.5, 128.5, 127.7, 126.3,

100.5, 59.6, 54.0, 31.6, 21.8, 13.9, 13.6; IR (film) cm^{-1}: 3180, 1684, 1643, 1575, 1454, 1367, 1328, 1275, 1104, 825, 757, 699, 647; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{21}N_2O_2S$ 305.1324; Found 305.1295.

Ethyl 4-(3,5-dimethylphenyl)-6-phethyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1r**). Recrystallized from a mixture of EtOH and H_2O (1:1). Yield: 2.09 g, 57% (10.0 mmol scale), white solid, mp 244-246 °C. ^1H NMR (300 MHz, DMSO): δ 10.42 (s, 1H), 9.69 (s, 1H), 7.56 – 7.25 (m, 5H), 6.97 (s, 3H), 5.21 (d, *J* = 4.0 Hz, 1H), 3.75 (q, *J* = 6.8 Hz, 2H), 2.29 (s, 6H), 0.75 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6) δ 174.3, 164.8, 145.6, 143.0, 137.6, 134.1, 129.2, 129.1, 128.6, 127.7, 124.2, 101.8, 59.4, 54.1, 21.1, 13.3; IR (film) cm^{-1}: 3338, 1679, 1561, 1460, 1368, 1331, 1276, 1198, 1131, 759, 735, 696; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{23}N_2O_2S$ 367.1480; Found 367.1491.

Synthesis of Alkynes. All alkynes except ((pent-4-yn-1-yloxy)methyl)benzene (**2i**) and 2-((2-methylbut-3-yn-2-yl)oxy)tetrahydro-2*H*-pyran (**2j**) were commercially available. Alkynes **2i**[38] and **2j**[39] were prepared by the literature procedures.

General procedure for the synthesis of 2-alkynylpyrimidine from DHPM and alkyne. To an oven-dried test tube with a magnetic stirring bar were added DHPM **1** (0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol %), dppp (12.4 mg, 0.030 mmol, 12 mol %), CuTC (76 mg, 0.40 mmol), Cs_2CO_3 (81 mg, 0.25 mmol), and 4Å molecular sieves (100 mg). The reaction vessel was flushed with argon three times. To the reaction mixture was added a solution of alkyne **2** (0.38 mmol) in MeCN/PhMe (1/4 v/v, 1.5 mL), and the resulting mixture was allowed to stir at 110 °C in oil bath for 16 h. The mixture was diluted with EtOAc (30 mL) and filtered through a Celite pad. The filtrate was washed with brine (5 mL), dried over MgSO4, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel; eluent: *n*-hexane/EtOAc, 20/1 to 10/1) to give the corresponding 2-alkynylpyrimidine **3** or **4.**

Ethyl 2-(3,3-dimethylbut-1-ynyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**3a**).[40] Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 68.4 mg, 85%. ^1H NMR (300 MHz, $CDCl_3$): δ 7.67-7.57 (m, 2H), 7.48-7.38 (m, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 2.61 (s, 3H), 1.37 (s, 9H), 1.04 (t, *J* = 7.2 Hz, 3H);

$^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 167.8, 165.5, 164.1, 152.7, 137.5, 130.2, 128.6, 128.4, 124.1, 98.7, 79.0, 62.0, 30.6, 28.1, 22.7, 13.7.

Ethyl 4-methyl-2-(oct-1-ynyl)-6-phenylpyrimidine-5-carboxylate (**3b**).[40] Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 65.6 mg, 75%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67-7.59 (m, 2H), 7.48-7.39 (m, 3H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.61 (s, 3H), 2.47 (t, *J* = 7.2 Hz, 2H), 1.69-1.64 (m, 2H), 1.48-1.41 (m, 2H), 1.28-1.23 (m, 4H), 1.05 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 6.7 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 167.8, 165.6, 164.1, 152.5, 137.4, 130.3, 128.7, 128.5, 124.2, 91.9, 80.2, 62.1, 31.5, 28.9, 28.1, 22.7, 22.6, 19.6, 14.2, 13.8.

Ethyl 2-(dec-1-yn-1-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**3c**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 68.0 mg, 72%; yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 – 7.60 (m, 2H), 7.48 – 7.38 (m, 3H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.60 (s, 3H), 2.46 (t, *J* = 7.2 Hz, 2H), 1.72 – 1.59 (m, 2H), 1.48 – 1.39 (m, 2H), 1.27 (m, 8H), 1.04 (t, *J* = 7.5 Hz, 3H), 0.86 (t, *J* = 6.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 167.8, 165.6, 164.1, 152.5, 137.4, 130.3, 128.6, 128.5, 124.2, 91.6, 80.2, 62.1, 32.0, 29.3, 29.26, 29.23, 28.1, 22.8, 22.7, 19.6, 14.2, 13.8; IR (film) cm^{-1}: 3054, 2987, 2305, 1723, 1265, 896, 735, 704; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{31}N_2O_2$ 379.2386; Found 379.2356.

Ethyl 4-methyl-2-(5-methylhex-1-yn-1-yl)-6-phenylpyrimidine-5-carboxylate (**3d**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 36.1 mg, 43%; yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.46 – 7.41 (m, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 2.60 (s, 3H), 2.47 (t, *J* = 7.4 Hz, 2H), 1.78 – 1.70 (m, 1H), 1.57 (q, *J* = 7.3 Hz, 2H), 1.05 (t, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 167.8, 165.6, 164.2, 152.5, 137.4, 130.3, 128.7, 128.5, 91.9, 80.1, 62.1, 37.0, 29.8, 27.5, 22.7, 22.3, 17.6, 13.8; IR (film) cm^{-1}: 3052, 2854, 2253, 1723, 1534, 1266, 907, 730, 649; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{25}N_2O_2$ 337.1916; Found 337.1870.

Ethyl 4-methyl-6-phenyl-2-(4-phenylbut-1-yn-1-yl)pyrimidine-5-carboxylate (**3e**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 47.1 mg, 51%, yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.3 Hz, 2H), 7.50 – 7.45 (m, 3H), 7.33 – 7.31 (m, 2H), 7.28 – 7.27 (m, 2H), 7.25 – 7.22 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.02 (t, *J* = 7.7 Hz, 2H), 2.78 (t, *J* = 7.8 Hz, 2H), 2.63 (s, 3H), 1.08 (t, *J* =

7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 167.8, 165.7, 164.1, 152.4, 140.4, 137.4, 130.3, 128.674, 128.673, 128.51, 128.50, 126.6, 124.4, 90.6, 80.6, 62.1, 34.6, 22.7, 21.8, 13.8; IR (film) cm^{-1}: 3053, 2986, 2253, 1721, 1538, 1264, 907, 730, 650; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{23}N_2O_2$ 371.1760; Found 371.1712.

Ethyl 2-(3-cyclohexylprop-1-yn-1-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**3f**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 65.2 mg, 72%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 – 7.58 (m, 2H), 7.47 – 7.38 (m, 3H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.60 (s, 3H), 2.37 (d, *J* = 6.8 Hz, 2H), 1.92-1.87 (m, 2H), 1.75-1.59 (m, 5H), 1.32 – 1.15 (m, 4H), 1.04 (t, *J* = 7.1 Hz, 4H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 167.8, 165.6, 164.1, 152.5, 137.5, 130.2, 128.6, 128.5, 124.2, 90.8, 81.1, 62.1, 37.2, 33.1, 27.4, 26.3, 26.2, 22.7, 13.7; IR (film) cm^{-1}: 2936, 2859, 2230, 1724, 1532, 1259, 1092, 772, 704; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{27}N_2O_2$ 363.2073; Found 363.2053.

Ethyl 2-(cyclopentylethynyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**3g**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 46.3 mg, 77%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 – 7.57 (m, 2H), 7.49 – 7.38 (m, 3H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.97-2.81 (m, 1H), 2.60 (s, 3H), 2.11-1.95 (m, 2H), 1.88-1.72 (m, 4H), 1.63 – 1.57 (m, 2H), 1.04 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 167.8, 165.6, 164.2, 152.7, 137.5, 130.2, 128.6, 128.5, 124.1, 95.7, 79.8, 62.1, 33.5, 30.7, 25.5, 22.7, 13.7; IR (film) cm^{-1}: 3053, 2254, 1718, 1263, 907, 730, 650; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{23}N_2O_2$ 335.1760; Found 335.1704.

Ethyl 2-(cyclohexylethynyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**3h**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 69.6 mg, 80%, yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.47 – 7.41 (m, 3H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.66 – 2.62 (m, 1H), 2.61 (s, 3H), 1.99-1.91 (m, 2H), 1.80-1.74 (m, 2H), 1.64-1.53 (m, 3H), 1.36-1.28 (m, 3H), 1.04 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 167.8, 165.5, 164.2, 152.6, 137.5, 130.3, 128.7, 128.5, 124.1, 95.4, 80.1, 62.1, 32.1, 29.9, 25.9, 25.2, 22.7, 13.8; IR (film) cm^{-1}: 2932, 2854, 2231, 1725, 1532, 1259, 1092, 772, 704; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{25}N_2O_2$ 349.1916; Found 349.1937.

Ethyl 2-(5-(benzyloxy)pent-1-yn-1-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**3i**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 69.3 mg, 67%, yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 – 7.61 (m, 2H), 7.48 – 7.40 (m, 3H), 7.36 – 7.29 (m, 5H), 4.52 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.62 (t, *J* = 6.1 Hz, 2H), 2.66 – 2.56 (m , 2H), 2.61 (s, 3H), 1.98 (quint, *J* = 6.7 Hz, 2H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.8, 165.6, 164.1, 152.4, 138.6, 137.4, 130.3, 128.7, 128.5, 127.8, 127.7, 124.3, 91.0, 80.4, 73.1, 69.0, 62.1, 28.4, 22.7, 16.6, 13.8; IR (film) cm^{-1}: 3053, 2305, 1723, 1264, 895, 733, 704; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{27}N_2O_3$ 415.2022; Found 415.1935.

Methyl 4-methyl-2-(3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)but-1-yn-1-yl)-6-phenylpyrimidine-5-carboxylate (**3j**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 31.7 mg, 31%, yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.64 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.50 – 7.42 (m, 3H), 5.23 – 5.17 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.01 – 3.95 (m, 1H), 3.57 – 3.52 (m, 1H), 2.62 (s, 3H), 1.88 – 1.82 (m, 1H), 1.80 – 1.75 (m, 1H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 -1.51 (m, 4H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.7, 165.6, 164.0, 152.1, 137.3, 130.4, 128.7, 128.5, 124.6, 96.5, 91.3, 83.1, 71.4, 63.4, 62.2, 32.0, 30.4, 29.7, 25.5, 22.7, 20.5, 13.8; IR (film) cm^{-1}: 3153, 2987, 2253, 1549, 1264, 905, 726, 649; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{29}N_2O_4$ 409.2127; Found 409.2095.

Ethyl 4-methyl-6-phenyl-2-(phenylethynyl)pyrimidine-5-carboxylate (**3k**).[40] Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 71.0 mg, 83%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74-7.62 (m, 4H), 7.51-7.44 (m, 3H), 7.41-7.35 (m, 3H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.66 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.7, 165.8, 164.3, 152.6, 137.4, 132.9, 130.4, 129.9, 128.7, 128.524, 128.522, 124.4, 121.4, 88.7, 88.3, 62.2, 22.8, 13.8.

Ethyl 4-methyl-6-phenyl-2-(p-tolylethynyl)pyrimidine-5-carboxylate (**3l**).[16c,40] Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 52.5 mg, 59%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71-7.63 (m, 2H), 7.59 (d, *J* = 7.8 Hz, 2H), 7.51-7.42 (m, 3H), 7.18 (d, *J* = 7.7 Hz, 2H), 4.2 (q, *J* = 7.1 Hz, 2H), 2.66 (s, 3H), 2.38 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.8, 165.7, 164.3, 152.7, 140.4, 137.4, 132.9, 130.4, 129.3, 128.7, 128.5, 124.2, 118.3, 89.3, 87.9, 62.2, 22.8, 21.8, 13.8.

Ethyl 2-((4-methoxyphenyl)ethynyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**3m**). Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 52.1 mg, 56%, yellow viscous oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.68 – 7.62 (m, 4H), 7.49 – 7.43 (m, 3H), 6.89 (d, *J* = 8.9 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 2.65 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.8, 165.7, 164.3, 161.0, 152.8, 137.5, 134.7, 130.3, 128.7, 128.5, 124.1, 114.3, 113.4, 89.4, 87.6, 62.1, 55.5, 22.8, 13.8; IR (film) cm^{-1}: 2984, 2212, 1715, 1250, 905, 727, 649; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{21}N_2O_3$ 373.1552; Found 373.1479.

Ethyl 4-methyl-2-(naphthalen-1-ylethynyl)-6-phenylpyrimidine-5-carboxylate (**3n**). Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 63.3 mg, 66%, yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (d, *J* = 8.3 Hz, 1H), 8.00 – 7.85 (m, 3H), 7.77 – 7.69 (m, 2H), 7.68 – 7.46 (m, 6H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.71 (s, 3H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.8, 165.8, 164.2, 152.7, 137.4, 133.7, 133.2, 132.4, 130.5, 130.4, 128.8, 128.6, 128.4, 127.4, 126.8, 126.5, 125.3, 124.4, 119.1, 93.0, 86.9, 62.2, 22.8, 13.8; IR (film) cm^{-1}: 3062, 2212, 1715, 1256, 905, 727, 649; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{21}N_2O_2$ 393.1603; Found 393.1635.

2-(Oct-1-yn-1-yl)-4-phenylpyrimidine (**4a**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 42.9 mg, 65%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.69 (d, *J* = 4.8 Hz, 1H), 8.13 – 8.03 (m, 2H), 7.58 (d, *J* = 5.3 Hz, 1H), 7.55 – 7.43 (m, 3H), 2.49 (t, *J* = 7.2 Hz, 2H), 1.67 (m, 2H), 1.48 (m, 2H), 1.39 – 1.25 (m, 4H), 0.90 (t, *J* = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 164.6, 157.8, 153.6, 136.3, 131.3, 129.1, 127.5, 115.3, 90.5, 80.5, 31.5, 28.9, 28.2, 22.7, 19.6, 14.2; IR (film) cm^{-1}: 2959, 2253, 1567, 1264, 906, 729, 649; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{21}N_2$ 265.1705; Found 265.1679. **Scale-up synthesis**. To an oven-dried round-bottom flask with a magnetic stirring bar were added DHPM **1b** (1.00 g, 3.60 mmol), $Pd(OAc)_2$ (81 mg, 0.36 mmol, 10 mol %), dppp (179 mg, 0.434 mmol, 12 mol %), CuTC (1.10 g, 5.76 mmol), Cs_2CO_3 (1.43 g, 3.60 mmol), and 4 Å molecular sieves (1.5 g). The reaction vessel was sealed by septum and degassed with argon three times. To the reaction mixture was added a solution of 1-octyne (0.80 mL, 5.4 mmol) in MeCN/PhMe (1/4 v/v, 22 mL), and the resulting mixture was allowed to stir at 110 °C in oil bath for 16 h. The mixture was filtered through a Celite pad and rinsed

with EtOAc (100 mL). The filtrate was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (*n*-hexane/EtOAc, 20/1) to give **4a** (922 mg, 79%)**.**

Ethyl 2-(3,3-dimethylbut-1-yn-1-yl)-4-methylpyrimidine-5-carboxylate (**4b**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 57.8 mg, 94%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.04 (s, 1H), 4.38 (q, J = 7.1 Hz, 2H), 2.79 (s, 3H), 1.39 (t, , J = 7.1 Hz, 3H), 1.36 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.2, 164.6, 158.9, 154.4, 121.6, 100.6, 78.9, 61.8, 30.5, 28.2, 24.5, 14.3; IR (film) cm^{-1}: 3053, 2982, 2226, 1719, 1265, 908, 731, 649; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{19}N_2O_2$ 247.1447; Found 247.1409.

2-(3,3-Dimethylbut-1-yn-1-yl)-4,6-diphenylpyrimidine (**4c**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 48.3 mg, 62%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 – 8.10 (m, 4H), 7.95 (s, 1H), 7.60 – 7.43 (m, 6H), 1.43 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.2, 153.8, 136.8, 131.0, 129.0, 127.5, 111.4, 96.9, 79.6, 30.7, 28.1; IR (film) cm^{-1}: 3053, 2975, 2228, 1569, 1265, 908, 730, 650; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{21}N_2$ 313.1705; Found 313.1731.

2-(Oct-1-yn-1-yl)-4,6-diphenylpyrimidine (**4d**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 49.3 mg, 58%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 – 8.08 (m, 4H), 7.96 (s, 1H), 7.57 – 7.45 (m, 6H), 2.52 (t, J = 7.2 Hz, 2H), 1.71 (quint, J = 7.2 Hz, 2H), 1.57 – 1.42 (m, 2H), 1.40 – 1.23 (m, 4H), 0.91 (t, J = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.2, 153.7, 136.8, 131.1, 129.0, 127.5, 111.4, 89.9, 80.8, 31.5, 28.9, 28.2, 22.7, 19.7, 14.2; IR (film) cm^{-1}: 3056, 2935, 2232, 1570, 1264, 906, 729, 649; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{25}N_2$ 341.2018; Found 341.1986.

Ethyl 4-methyl-2-(phenylethynyl)-6-(p-tolyl)pyrimidine-5-carboxylate (**4e**). Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 64.1 mg, 72%, yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 – 7.67 (m, 2H), 7.59 (d, J = 8.1 Hz, 2H), 7.43 – 7.35 (m, 3H), 7.27 – 7.25 (m, 2H), 4.23 (q, J = 7.1 Hz, 2H), 2.64 (s, 3H), 2.41 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.9, 165.5, 164.1, 152.5, 140.8, 134.4, 132.9, 129.8, 129.5, 128.5, 124.2, 121.5, 88.6, 88.3, 62.2, 22.7, 21.6, 13.9; IR (film) cm^{-1}:

2958, 2221, 1705, 1263, 907, 730, 649; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{21}N_2O_2$ 357.1603; Found 357.1633.

Ethyl 2-(5-(benzyloxy)pent-1-yn-1-yl)-4-methyl-6-(p-tolyl)pyrimidine-5-carboxylate (**4f**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 67.4 mg, 63%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 4.3 Hz, 4H), 7.34 – 7.30 (m, 1H), 7.29 (d, *J* = 2.5 Hz, 2H), 4.56 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.66 (t, *J* = 6.1 Hz, 2H), 2.65 (t, *J* = 7.0 Hz, 2H), 2.63 (s, 3H), 2.43 (s, 3H), 2.01 (quint, *J* = 6.7 Hz, 2H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.0, 165.4, 163.9, 152.3, 140.7, 138.5, 134.4, 129.4, 128.50, 128.48, 127.8, 127.7, 124.1, 90.7, 80.4, 73.1, 69.0, 62.1, 28.3, 22.7, 21.6, 16.6, 13.8; IR (film) cm^{-1}: 2865, 2239, 1721, 1263, 907, 730, 649; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{29}N_2O_3$ 429.2178; Found 429.2207.

Methyl 2-(3,3-dimethylbut-1-yn-1-yl)-4-(4-methoxyphenyl)-6-methylpyrimidine-5-carboxylate (**4g**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 66.8 mg, 79%, yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 3.85 (s, 3H), 3.74 (s, 3H), 2.57 (s, 3H), 1.38 (s, 9H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.9, 165.3, 163.2, 161.6, 152.7, 130.2, 129.7, 123.2, 114.3, 98.5, 79.1, 55.5, 52.8, 30.6, 28.1, 22.7; IR (film) cm^{-1}: 3052, 2858, 2228, 1730, 1513, 1268, 909, 732, 647; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{23}N_2O_3$ 339.1709; Found 339.1674.

Methyl 4-(4-methoxyphenyl)-6-methyl-2-(oct-1-yn-1-yl)pyrimidine-5-carboxylate (**4h**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 65.3 mg, 66%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 3.74 (s, 3H), 2.56 (s, 3H), 2.46 (t, *J* = 7.2 Hz, 2H), 1.66 (quint, *J* = 7.3 Hz, 2H), 1.44 (m, 2H), 1.32 – 1.24 (m, 4H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.8, 165.4, 163.2, 161.6, 152.5, 130.1, 129.5, 123.2, 114.2, 91.6, 80.2, 55.5, 52.6, 31.5, 28.9, 28.1, 22.7, 22.6, 19.6, 14.2; IR (film) cm^{-1}: 2932, 2858, 2236, 1727, 1510, 1256, 909, 732, 647; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{27}N_2O_3$ 367.2022; Found 367.1987.

Ethyl 4-(3,5-dimethylphenyl)-6-methyl-2-(phenylethynyl)pyrimidine-5-carboxylate (**4i**). Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 61.9 mg, 67%, white solid, mp 164-166 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87 – 7.83 (m, 2H), 7.59 – 7.51 (m, 3H), 7.44 – 7.40 (m, 3H), 4.38 (q, *J* = 7.1 Hz, 2H),

2.80 (s, 3H), 2.51 (s, 6H), 1.27 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 167.8, 165.5, 164.6, 152.4, 138.4, 137.1, 132.9, 132.1, 129.9, 128.5, 126.3, 124.4, 121.5, 88.8, 88.3, 62.1, 22.7, 21.4, 13.8; IR (film) cm^{-1}: 2958, 2925, 2871, 2222, 1705, 1529, 1247, 908, 734, 650; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{23}N_2O_2$ 371.1760; Found 371.1779.

Ethyl 2-(5-(benzyloxy)pent-1-yn-1-yl)-4-(3,5-dimethylphenyl)-6-methylpyrimidine-5-carboxylate (**4j**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 65.1 mg, 59%, yellow oil. ^1H NMR (600 MHz, $CDCl_3$): δ 7.51 – 7.41 (m, 8H), 4.70 (s, 2H), 4.38 (q, J = 7.1 Hz, 2H), 3.79 (t, J = 6.1 Hz, 2H), 2.79 (t, J = 6.1 Hz, 2H), 2.77 (s, 3H), 2.51 (s, 6H), 2.15 (quint, J = 6.7 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 167.9, 165.4, 164.4, 152.3, 138.6, 138.3, 137.2, 132.0, 128.5, 127.8, 127.7, 126.3, 124.3, 90.8, 80.4, 73.1, 69.0, 62.0, 28.4, 22.7, 21.4, 16.6, 13.8;IR (film) cm^{-1}: 2861, 2240, 1723, 1249, 907, 729, 648; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{31}N_2O_3$ 443.2335; Found 443.2287.

Ethyl 2-(3,3-dimethylbut-1-yn-1-yl)-4-(4-fluorophenyl)-6-methylpyrimidine-5-carboxylate (**4k**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 64.6 mg, 76%, yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.71 – 7.57 (m, 2H), 7.13 (t, J = 8.7 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 2.60 (s, 3H), 1.37 (s, 9H), 1.10 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.8, 165.7, 164.2 (d, J = 249 Hz), 162.8, 152.7, 133.5, 130.7, 130.7 (d, J = 8.3 Hz), 124.0, 115.8 (d, J = 22 Hz), 98.9, 78.9, 62.2, 30.6, 28.1, 22.8, 13.9; $^{19}F\{^1H\}$ NMR (565 MHz, $CDCl_3$) δ -110.29 (s); IR (film) cm^{-1}: 2979, 2227, 1720, 1267, 907, 730, 649; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{22}FN_2O_2$ 341.1665; Found 341.1693.

Ethyl 4-(4-fluorophenyl)-6-methyl-2-(oct-1-yn-1-yl)pyrimidine-5-carboxylate (**4l**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 55.1 mg, 60%, yellow oil. ^1H NMR (600 MHz, $CDCl_3$): δ 7.68 – 7.62 (m, 2H), 7.13 (t, J = 8.6 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 2.61 (s, 3H), 2.48 (t, J = 7.3 Hz, 2H), 1.70 – 1.64 (m, 2H), 1.48 – 1.42 (m, 2H), 1.34 – 1.28 (m, 4H), 1.11 (t, J = 7.1 Hz, 3H), 0.89 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 167.7, 165.7, 164.2 (d, J = 242 Hz), 162.9, 152.4, 133.5, 130.7 (d, J = 8.3 Hz), 124.1, 115.8 (d, J = 22 Hz), 92.3, 80.0, 62.2, 31.5, 28.9, 28.1, 22.67, 22.65, 19.7, 14.2, 13.9; $^{19}F\{^1H\}$ NMR (565 MHz, $CDCl_3$) δ -110.10 (s); IR (film) cm^{-1}: 2958, 2253, 1719, 1264, 907, 731, 650; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{26}FN_2O_2$ 369.1978; Found 369.2011.

Ethyl 2-(cyclopentylethynyl)-4-methyl-6-(thiophen-2-yl)pyrimidine-5-carboxylate (**4m**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 61.3 mg, 72%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, *J* = 5.0 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.12 – 7.07 (m, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.97-2.83 (m, 1H), 2.53 (s, 3H), 2.11 – 2.01 (m, 2H), 1.87 – 1.73 (m, 4H), 1.66 – 1.54 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.2, 165.0, 155.5, 152.5, 140.2, 131.1, 129.4, 128.4, 121.5, 95.5, 79.6, 62.5, 33.5, 30.7, 25.5, 22.5, 14.0; IR (film) cm^{-1}: 2959, 2869, 2233, 1727, 1532, 1260, 1088, 734, 649; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{21}N_2O_2S$ 341.1324; Found 341.1254.

Ethyl 4-methyl-6-(naphthalen-2-yl)-2-(oct-1-yn-1-yl)pyrimidine-5-carboxylate (**4n**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 51.9 mg, 52%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.96 – 7.82 (m, 3H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.54 (m, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.64 (s, 3H), 2.49 (t, *J* = 7.2 Hz, 2H), 1.68 (quint, *J* = 7.3 Hz, 2H), 1.52 – 1.40 (m, 2H), 1.34 – 1.25 (m, 4H), 0.99 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.0, 165.7, 163.9, 152.5, 134.7, 134.1, 133.0, 128.9, 128.8, 128.5, 127.9, 127.5, 126.7, 125.4, 124.4, 91.9, 80.2, 62.1, 31.5, 28.9, 28.1, 22.8, 22.6, 19.7, 14.2, 13.8; IR (film) cm^{-1}: 2957, 2926, 2871, 2241, 1724, 1534, 1257, 907, 732, 649; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{29}N_2O_2$ 401.2229; Found 401.2191.

Ethyl 2-(cyclopentylethynyl)-4,6-dimethylpyrimidine-5-carboxylate (**4o**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 31.3 mg, 46%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.42 (q, *J* = 7.1 Hz, 2H), 2.87 (quint, *J* = 7.4 Hz, 1H), 2.52 (s, 6H), 2.11 – 1.95 (m, 2H), 1.87 – 1.72 (m, 4H), 1.66 – 1.53 (m, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.3, 164.9, 152.5, 124.8, 95.6, 79.6, 62.1, 33.5, 30.6, 25.5, 23.0, 14.3; IR (film) cm^{-1}: 2958, 2925, 2872, 2253, 1725, 1541, 1263, 907, 734, 651; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{21}N_2O_2$ 273.1603; Found 273.1533.

Ethyl (E)-2-(3,3-dimethylbut-1-yn-1-yl)-4-methyl-6-styrylpyrimidine-5-carboxylate (**4p**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 52.2 mg, 60%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (d, *J* = 15.5 Hz, 1H), 7.62 – 7.52 (m, 2H), 7.43 – 7.34 (m, 3H), 7.12 (d, *J* = 15.6 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 2.55 (s, 3H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.40 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.4, 165.7, 152.5, 140.1, 135.8, 132.3, 129.8, 129.0, 128.1, 122.9, 121.8, 98.2, 79.1, 62.2, 30.6, 28.1,

23.2, 14.4; IR (film) cm^{-1}: 2967, 2228, 1723, 1524, 1237, 906, 729, 649; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{25}N_2O_2$ 349.1916; Found 349.1892.

Ethyl (E)-2-(3,3-dimethylbut-1-yn-1-yl)-4-methyl-6-(1-phenylprop-1-en-2-yl)pyrimidine-5-carboxylate (**4q**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 59.7 mg, 66%, yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.40 – 7.28 (m, 5H), 6.66 (d, *J* = 1.7 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.58 (s, 3H), 2.30 (d, *J* = 1.4 Hz, 3H), 1.38 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.9, 167.8, 165.6, 152.3, 136.7, 136.0, 133.1, 129.2, 128.4, 127.7, 123.8, 98.5, 79.0, 62.1, 30.6, 28.1, 22.8, 17.5, 14.3; IR (film) cm^{-1}: 2981, 2227, 1718, 1529, 1240, 906, 728, 649; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{27}N_2O_2$ 363.2073; Found 363.2031.

Methyl 2-(cyclopentylethynyl)-4-isopropyl-6-phenylpyrimidine-5-carboxylate (**4r**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 48.7 mg, 56%, yellow oil. ^1H NMR (600 MHz, $CDCl_3$): δ 7.65 – 7.61 (m, 2H), 7.45 – 7.41 (m, 3H), 3.68 (s, 3H), 3.13 (quint, *J* = 6.7 Hz, 1H), 2.90 (quint, *J* = 7.8 Hz, 1H), 2.09 – 2.01 (m, 2H), 1.86 – 1.76 (m, 4H), 1.64 – 1.56 (m, 2H), 1.33 (d, *J* = 6.7 Hz, 6H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 173.3, 168.7, 163.8, 153.2, 137.6, 130.2, 128.7, 128.4, 123.2, 95.0, 80.3, 52.8, 33.7, 33.5, 30.8, 25.5, 21.8; IR (film) cm^{-1}: 2968, 2872, 2231, 1719, 1530, 907, 729, 649; IR (film) cm^{-1}: 2968, 2872, 2231, 1719, 1530, 907, 729, 649; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{25}N_2O_2$ 349.1916; Found 349.1873.

Ethyl 2-(3,3-dimethylbut-1-yn-1-yl)-4-phenyl-6-propylpyrimidine-5-carboxylate (**4s**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 43.8 mg, 50%, yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 – 7.58 (m, 2H), 7.47 – 7.39 (m, 3H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.85 – 2.74 (m, 2H), 1.77 (sext, 7.5 Hz, 2H), 1.37 (s, 9H), 1.01 (dt, *J* = 14.0, 7.3 Hz, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.0, 167.9, 164.2, 152.9, 137.6, 130.2, 128.7, 128.5, 124.1, 98.4, 79.2, 62.0, 37.9, 30.6, 28.1, 23.0, 14.2, 13.8; IR (film) cm^{-1}: 3052, 2254, 1723, 1249, 907, 729, 650; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{27}N_2O_2$ 351.2073; Found 351.2034.

Ethyl 2-(3,3-dimethylbut-1-yn-1-yl)-4-isopropyl-6-phenylpyrimidine-5-carboxylate (**4t**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 39.4 mg, 45%, yellow solid, mp 108-110 °C. ^1H NMR

(300 MHz, $CDCl_3$): δ 7.65 – 7.57 (m, 2H), 7.46 – 7.40 (m, 3H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.17 (quint, *J* = 6.8 Hz, 1H), 1.38 (s, 9H), 1.33 (d, *J* = 6.7 Hz, 6H), 1.04 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 173.1, 168.1, 163.8, 153.1, 137.7, 130.0, 128.6, 128.4, 123.5, 97.9, 79.4, 62.0, 33.5, 30.6, 28.1, 21.8, 13.8; IR (film) cm^{-1}: 3052, 2253, 1723, 1264, 907, 729, 650; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{27}N_2O_2$ 351.2073; Found 351.2055.

Ethyl 2-(cyclohexylethynyl)-4,6-diphenylpyrimidine-5-carboxylate (**4u**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 44.1 mg, 43%, pale yellow solid, mp 118-120 °C. ^1H NMR (600 MHz, $CDCl_3$): δ 7.70 – 7.62 (m, 4H), 7.50 – 7.40 (m, 6H), 4.03 (q, *J* = 7.1 Hz, 2H), 2.70 – 2.57 (m, 1H), 2.01 – 1.91 (m, 2H), 1.81 – 1.73 (m, 2H), 1.64 – 1.54 (m, 3H), 1.37 – 1.28 (m, 3H), 0.92 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 167.8, 164.9, 152.9, 137.3, 130.2, 128.7, 128.6, 128.6, 95.4, 80.4, 62.1, 32.1, 29.9, 25.9, 25.2, 13.6; IR (film) cm^{-1}: 2958, 2925, 2860, 2255, 1725, 1463, 907, 734, 651; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{27}N_2O_2$ 411.2073; Found 411.2033.

Ethyl 2-(cyclohexylethynyl)-4-(3,5-dimethylphenyl)-6-phenylpyrimidine-5-carboxylate (**4v**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 62.4 mg, 57%, yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.88 – 7.78 (m, 2H), 7.68 – 7.66 (m, 3H), 7.44 (s, 3H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.86 – 2.73 (m, 1H), 2.51 (s, 6H), 2.18 – 2.05 (m, 2H), 1.99 – 1.90 (m, 2H), 1.84 – 1.71 (m, 3H), 1.51 – 1.41 (m, 3H), 1.14 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.9, 165.2, 164.7, 152.8, 138.3, 137.3, 137.1, 131.9, 130.2, 128.6, 128.5, 126.3, 123.8, 95.3, 80.4, 62.0, 32.1, 29.9, 25.9, 25.2, 21.5, 13.6; IR (film) cm^{-1}: 3052, 2986, 2254, 1723, 1264, 906, 728, 650; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{29}H_{31}N_2O_2$ 439.2386; Found 439.2418.

Ethyl 2-(3,3-dimethylbut-1-yn-1-yl)-4-(2-nitrophenyl)-6-phenylpyrimidine-5-carboxylate (**4w**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 75.1 mg, 70%, yellow solid, mp 154-156 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.58 (t, *J* = 2.0 Hz, 1H), 8.35 (dd, *J* = 8.2, 2.2 Hz, 1H), 8.06 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.75 – 7.61 (m, 3H), 7.54 – 7.39 (m, 3H), 4.08 (q, *J* = 7.1 Hz, 2H), 1.39 (s, 9H), 0.98 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.4, 165.5, 162.2, 153.1, 148.4, 138.7, 137.0, 134.8, 130.6, 129.8, 128.8, 128.6, 125.0, 123.9, 123.8, 99.9, 79.0, 62.6, 30.5, 28.2, 13.6; IR (film) cm^{-1}: 2958, 2925,

2860, 2255, 1725, 1463, 907, 734, 651; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{24}N_3O_4$ 430.1767; Found 430.1795.

Ethyl 4-(tert-butyl)-2-(3,3-dimethylbut-1-yn-1-yl)-6-methylpyrimidine-5-carboxylate (**6**). Eluent in chromatography: *n*-hexane/EtOAc 20:1. Yield: 9.8 mg, 13%, yellow solid, mp 108-110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.38 (q, *J* = 7.0 Hz, 2H), 2.43 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.36 (s, 18H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.6, 169.3, 164.1, 151.6, 124.2, 97.5, 79.1, 62.1, 39.8, 30.7, 29.6, 28.0, 22.3, 14.0; IR (film) cm^{-1}: 2926, 2230, 1729, 1524, 1364, 1266, 1085, 864; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{27}N_2O_2$ 303.2073; Found 303.2044.

ASSOCIATED CONTENT

Supporting Information. Plausible reaction mechanism, ^{1}H and ^{13}C NMR Spectra of compounds **1i, 1m, 1o**, **1v**, **3a-n**, **4a-w** and **6**, and ^{19}F NMR Spectra of **4k** and **4l**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* E-mail: sohnjh@cnu.ac.kr;

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by the NRF grant (NRF-2017R1A2B2003614) and the research fund of Chungnam National University.

REFERENCES

(1) (a) *Transition Metals for Organic Synthesis*, (Eds.: M. Beller, C. Bolm), 2nd ed., Wiley-VCH, Weinheim 2004. (b) *Metal-Catalyzed Cross-Coupling Reactions*, Vols. 1 and 2 (Eds.: A. de Meijere, F. Diederich), 2nd ed., Wiley-VCH, Weinheim 2004.

(2) For selected recent reviews, see: a) Ortgies, D. H.; A. Hassanpour, A.; Chen, F; Woo, S.; Forgione, P. Desulfination as an Emerging Strategy in Palladium-Catalyzed C–C Coupling Reactions. *Eur. J. Org. Chem.* **2016**, 408-425. (b) Yuan, K.; Soule, J. –F.; Doucet, H. Functionalization of C–H Bonds via Metal-Catalyzed Desulfitative Coupling: An Alternative Tool for Access to Aryl- or Alkyl-Substituted (Hetero)arenes. *ACS Catal.* **2015**, *5*, 978-991. (c) Aziz, J.; Messaoudi, S.; Alami, M.; Hamze, A. Sulfinate derivatives: dual and versatile partners in organic synthesis. *Org. Biomol. Chem.* **2014**, *12*, 9743-9759. (d) Wang, L.; He, W.; Yu, Z. Transition-metal mediated carbon–sulfur bond activation and transformations. *Chem. Soc. Rev.* **2013**, *42*, 599-621. (e) Modha, S. G.; Mehta, V. P.; Van der Eycken, E. Transition metal-catalyzed C–C bond formation *via* C–S bond cleavage: an overview. *Chem. Soc. Rev.* **2013**, *42*, 5042-5055. (f) Dubbaka, S. R.; Vogel, P. Organosulfur Compounds: Electrophilic Reagents in Transition-Metal-Catalyzed Carbon–Carbon Bond-Forming Reactions. *Angew. Chem. Int. Ed*. **2005**, ***44***, 7674–7684.

(3) Liebeskind, L. S.; Srogl, J. Thiol Ester−Boronic Acid Coupling. A Mechanistically Unprecedented and General Ketone Synthesis. *J. Am. Chem. Soc*. **2000**, *122*, 11260-11261.

(4) (a) Prokopcová, H.; Kappe, C. O. The Liebeskind–Srogl C–C Cross-Coupling Reaction. *Angew. Chem. Int. Ed*. **2009**, *48*, 2276-2286. (b) Cheng, H. –G.; Chen, H.; Liu, Y.; Zhou, Q. The Liebeskind-Srogl Cross-Coupling Reaction and its Synthetic Applications. *Asian J. Org. Chem*. **2018**, *7*, 490–508.

(5) (a) Lengar, A.; Kappe, C. O. Tunable Carbon−Carbon and Carbon−Sulfur Cross-Coupling of Boronic Acids with 3,4-Dihydropyrimidine-2-thiones. *Org. Lett*. **2004**, *6*, 771-774. (b) Prokopcova, H.; Kappe, C. O. Palladium(0)-Catalyzed, Copper(I)-Mediated Coupling of Boronic Acids with Cyclic Thioamides. Selective Carbon−Carbon Bond Formation for the Functionalization of Heterocycles. *J. Org. Chem.* **2007**, *72*, 4440-4448. (c) Arshad, N; Hashim, J.; Kappe, C. O. Palladium(0)-Catalyzed, Copper(I)-Mediated Coupling of Cyclic Thioamides with Alkenylboronic Acids, Organostannanes, and Siloxanes. *J. Org. Chem*. **2009**, *74*, 5118-5121. (d) Silva, S.; Tardy, S; Routier, S.; Suzenet, F.;

Tatibouët, A.; Rauter, A. P.; Rollin, P. 1,3-Oxazoline- and 1,3-oxazolidine-2-thiones as substrates in direct modified Stille and Suzuki cross-coupling. *Tetrahedron Lett.* **2008**, *49*, 5583-5586. (e) Sun, Q.; Suzenet, F.; Guillaumet, G. Desulfitative Cross-Coupling of Protecting Group-Free 2-Thiouracil Derivatives with Organostannanes. *J. Org. Chem.* **2010**, *75*, 3473-3476. (f) Sun, Q.; Suzenet, F.; Guillaumet, G. Optimized Liebeskind–Srogl coupling reaction between dihydropyrimidines and tributyltin compounds. *Tetrahedron Lett.* **2012**, *53*, 2694-2698.

(6) (a) Li, G. Y.; Zheng, G.; Noonan, A. F. Highly Active, Air-Stable Versatile Palladium Catalysts for the C−C, C−N, and C−S Bond Formations via Cross-Coupling Reactions of Aryl Chlorides. *J. Org. Chem.* **2001**, *66*, 8677-8681. (b) Kwong, F. Y.; Buchwald, S. L. A General, Efficient, and Inexpensive Catalyst System for the Coupling of Aryl Iodides and Thiols. *Org. Lett*. **2002**, *4*, 3517-3520. (c) Itoh, T.; Mase, T. A General Palladium-Catalyzed Coupling of Aryl Bromides/Triflates and Thiols. *Org. Lett.* **2004**, *6*, 4587-4590. (d) Fernández-Rodriges, M. A.; Shen, Q.; Hartwig, J. F. A General and Long-Lived Catalyst for the Palladium-Catalyzed Coupling of Aryl Halides with Thiols. *J. Am. Chem. Soc*. **2006**, *128*, 2180-2181.

(7) Kim, H.; Phan, N. H. T.; Shin, H.; Lee, H. S.; Sohn, J. -H. Dehydrosulfurative arylation with concomitant oxidative dehydrogenation for rapid access to pyrimidine derivatives. *Tetrahedron* **2017**, *73*, 6604-6613.

(8) (a) Phan, N. H. T.; Kim, H.; Shin, H.; Lee, H. -S.; Sohn, J. -H. Dehydrosulfurative C–N Cross-Coupling and Concomitant Oxidative Dehydrogenation for One-Step Synthesis of 2-Aryl(alkyl)aminopyrimidines from 3,4-Dihydropyrimidin-1*H*-2-thiones. *Org. Lett*. **2016**, *18*, 5154−5157. (b) Kim, H.; Lee, J.; Shin, H.; Sohn, J. -H. Boric Ester and Thiourea as Coupling Partners in a Copper-Mediated Oxidative Dehydrosulfurative Carbon–Oxygen Cross-Coupling Reaction. *Org. Lett*. **2018**, *20*, 1961−1965.

(9) (a) Singh, K.; Singh, K. Biginelli Condensation: Synthesis and Structure Diversification of 3,4-Dihydropyrimidin-2(1H)-one Derivatives. *Adv. Heterocycl. Chem*. **2012**, *105*, 223–308. (b) Suresh; Sandhu, J. S. Past, present and future of the Biginelli reaction: a critical perspective. *ARKIVOC* **2012**,

66–133. (c) Wan, J. P.; Liu, Y. Synthesis of Dihydropyrimidinones and Thiones by Multicomponent Reactions: Strategies Beyond the Classical Biginelli Reaction. *Synthesis* **2010**, *23*, 3943– 3953. (d) Kappe, C. O. Recent Advances in the Biginelli Dihydropyrimidine Synthesis. New Tricks from an Old Dog. *Acc. Chem. Res*. **2000**, *33*, 879– 888.

(10) (a) Capdeville, R.; Buchdunger, E; Zimmermann, J.; Matter, A. Glivec (STI571, imatinib), a rationally developed, targeted anticancer drug. *Nat. Rev. Drug. Discov.* **2002**, *1*, 493-502. (b) Scott, L. J.; Simpson, D. Voriconazole: A Review of Its Use in the Management of Invasive Fungal Infections. *Drugs* **2007**, *67*, 269-298. (c) Singh, P. K.; Singh, H.; Silakari, O. Glycolysis inhibition as a cancer treatment and its role in an anti-tumour immune response. *Biochim. Biophys. Acta, Rev. Cancer* **2016**, *1866*, 128-140. (d) Burmester, G. R.; Bijlsma, J. W.; Cutolo, M; McInnes, I. B. Managing rheumatic and musculoskeletal diseases−past, present and future. *Nat. Rev. Rheumatol.* **2017**, *13*, 443-448.

(11) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines. *Tetrahedron Lett.* **1975**, *16*, 4467–4470. (b) Chinchilla, R.; Najera, C. The Sonogashira reaction: a booming methodology in synthetic organic chemistry. *Chem. Rev.* **2007**, *107*, 874-922.

(12) Silva, S.; Sylla, B.; Suzenet, F.; Tatibouët, A.; Rauter, A. P.; Rollin, P. Oxazolinethiones and Oxazolidinethiones for the First Copper-Catalyzed Desulfurative Cross-Coupling Reaction and First Sonogashira Applications. *Org. Lett.* **2008**, *10*, 853-856.

(13) Guinchard, X.; Roulland, E. Total Synthesis of the Antiproliferative Macrolide (+)-Neopeltolide. *Org. Lett.* **2009**, *11*, 4700-4703.

(14) Maltsev, O. V.; Pöthig, A.; Hintermann, L. Synthesis of Soai Aldehydes for Asymmetric Autocatalysis by Desulfurative Cross-Coupling. *Org. Lett.* **2014**, *16*, 1282-1285.

(15) (a) Wu, Y.; Xing, Y.; Wang, J.; Sun, Q.; Kong, W.; Suzenet, F. Palladium-catalyzed desulfurative Sonogashira cross-coupling reaction of 3-cyano assisted thioamide-type quinolone derivatives with

alkynes. *RSC Adv.* **2015**, *5*, 48558–48562. (b) Zou, W.: Huang, Z.; Jiang,, K.; Wu, Y.; Xue, Y.; Suzenet, F.; Sun, Q.; Guillaumet, G. Chelation-assisted C-S activation/cascade heteroannulation of pyridine-2-thione derivatives in Pd-catalyzed cross-coupling reaction with alkynes. *Tetrahedron* **2017**, *73*, 5485-5492.

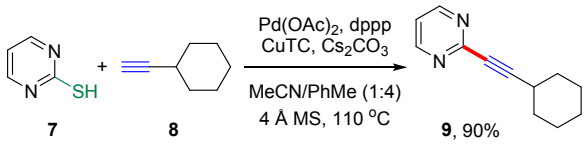
(16) (a) Quan, Z. -J.; Hu, W. H.; Jia, X. D.; Zhang, Z.; Da, Y. -X.; Wang, X. -C. A Domino Desulfitative Coupling/Acylation/Hydration Process Cocatalyzed by Copper(I) and Palladium(II): Synthesis of Highly Substituted and Functionalized Pyrimidines. *Adv. Synth. Catal.* **2012**, *354*, 2939-2948. (b) Yan, Z. F.; Quan, Z. -J.; Da, Y. -X.; Zhang, Z.; Wang, X. -C. A domino desulfurative coupling–acylation–hydration–Michael addition process for the synthesis of polysubstituted tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines. *Chem. Commun*. **2014**, *50*, 13555-13558. (c) Quan, Z. -J.; Lv, Y.; Jing, F. -Q.; Jia, X. D.; Huo, C. D.; Wang, X. -C. Chemoselective Carbon-Carbon Cross-Coupling *via* Palladium-Catalyzed Copper-Mediated C–S Cleavage of Disulfides. *Adv. Synth. Catal.* **2014**, *356*, 325–332.

(17) (a) Lee, O. S.; Lee, H. K.; Kim, H.; Shin, H; Sohn, J. -H. Copper-catalyzed aerobic cascade reaction for the conversion of 3,4-dihydropyrimidine-2(1*H*)-thiones to arylthiopyrimidines. *Tetrahedron* **2015**, *71*, 2936-2944. (b) Lee, O. S.; Kim, H.; Lee, H. -S.; Shin, H.; Sohn, J. -H. Synthesis of Arylthiopyrimidines by Copper-catalyzed Aerobic Oxidative C–S Cross-coupling. *Bull. Korean Chem. Soc.* **2016**, *37*, 242-245.

(18) Further efforts to stoichiometrically optimise the $Pd(OAc)_2$, CuTC and Cs_2CO_3 amounts did not improve the product yield.

(19) In the presence of P ligand, the desired products were produced in lower yields.

(20) Our reaction method also afforded the desired alkynylated pyrimidine **9** in high yield (90%) when 2-mercaptopyrmidine **7** was reacted with cyclohexylalkyne **8**, as described in the previous microwave-assisted dehydrosulfurative alkynylation of mercaptopyrimidine derivatives reported by Hintermann group.[14]



(21) (a) Yamamoto, K.; Chen, Y. G.; Buono, F. G. Oxidative Dehydrogenation of Dihydropyrimidinones and Dihydropyrimidines. *Org. Lett*. **2005**, *7*, 4673-4676. (b) Han, B.; Han, R. F.; Ren, Y. W.; Duan, X. Y.; Xu, Y. C.; Zhang, W. Efficient aerobic oxidative dehydrogenation of dihydropyrimidinones and dihydropyrimidines. *Tetrahedron* **2011**, *67*, 5615–5620.

(22) Phan, N. H. T.; Sohn, J. -H. Copper-catalyzed aerobic oxidative dehydrogenation for conversion of 2-(alkylthio)-1,4-dihydropyrimidines to 2-(alkylthio)pyrimidines. *Tetrahedron* **2014**, *70*, 7929-7935.

(23) (a) Yamamoto, K.; Chen, Y. G.; Buono, F. G. Oxidative Dehydrogenation of Dihydropyrimidinones and Dihydropyrimidines. *Org. Lett*. **2005**, *7*, 4673-4676. (b) Han, B.; Han, R. F.; Ren, Y. W.; Duan, X. Y.; Xu, Y. C.; Zhang, W. Efficient aerobic oxidative dehydrogenation of dihydropyrimidinones and dihydropyrimidines. *Tetrahedron* **2011**, *67*, 5615–5620.

(24) For a plausible reaction mechanism, see the Supporting Information.

(25) Khatri, C. K.; Potadar, S. M.; Chaturbhuj, G. U. A reactant promoted solvent free synthesis of 3,4-dihydropyrimidin-2(1H)-thione analogues using ammonium thiocyanate. *Tetrahedron Lett.* **2017**, *58*, 1778-1780.

(26) Sośnicki, J. G. Addition of Organolithium and Grignard Reagents to Pyrimidine-2(1H)-thione: Easy Access to 4-Substituted 3,4- Dihydropyrimidine-2(1H)-thiones. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2009**, *184*, 1946-1957.

(27) Cho, H.; Nishimura, Y.; Ikeda, H.; Asakura, M.; Toyota, S. Experimental and theoretical studies on thermodynamics and properties of tautomers of 2-substituted 6(4)-methyl-1,4(1,6)-dihydropyrimidine-5-carboxylates. *Tetrahedron* **2018**, *70*,2405-2413.

(28) Sekhar, T.; Thriveni, P.; Harikrishna, M.; Murali, K. One-Pot Synthesis of 3,4-Dihydropyrimidine-2(1*H*)-thione Derivatives Using DBU as Green and Recyclable Catalyst. *Asian J. Chem*. **2018**, *30*, 1243-1246.

(29) Matias, M.; Campos, G.; Santos, A. O.; Falcão, A.; Silvestre, S.; Alves, G. Synthesis, in vitro evaluation and QSAR modelling of potential antitumoral 3,4-dihydropyrimidin-2-(1*H*)-thiones. *Arab. J. Chem.* **2019**, *12*, 5086-5102.

(30) Sahoo, P. K.; Bose, A.; Mal, P. Solvent-Free Ball-Milling Biginelli Reaction by Subcomponent Synthesis. *Eur. J. Org. Chem*. **2015**, *32*, 6994–6998.

(31) Konkala, K.; Sabbavarapu, N. M.; Katla, R.; Durga, N. Y. V.; Reddy, V. K.; Prabhavathi Devi, B. L. A.; Prasad, R. B. N. Revisit to the Biginelli reaction: a novel and recyclable bioglycerol-basedsulfonic acid functionalized carbon catalyst for one-pot synthesis of substituted3,4-dihydropyrimidin-2-(1*H*)-ones. *Tetrahedron Lett.* **2012**, *53*, 1968-1973.

(32) Zang, W.; Wang. N.; Yang, Z. -J.; Li, Y. -R.; Yu, Y.; Pu, X. -M.; Yu, X. -Q. Lipase-Initiated Tandem Biginelli Reactions *via in situ*-Formed Acetaldehyde in One Pot: Discovery of Single-Ring Deep Blue Luminogens. *Adv. Synth. Catal*. **2017**, *359*, 3397-3406.

(33) Dilmaghani, K. A.; Zeynizadeh, B.; Amirpoor, M. Ultrasound-Mediated Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-Ones (or Thiones) with $NaHSO_4 \cdot H_2O$. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2013**, *188*, 1634-1642.

(34) Hang, Z.; Zhu, J.; Lian, X.; Xu, P.; Yu, H.; Han, S. A highly enantioselective Biginelli reaction using self-assembled methanoproline-thiourea organocatalysts: asymmetric synthesis of 6-isopropyl-3,4-dihydropyrimidines. *Chem. Commun*. **2016**, *52*, 80-83.

(35) Hayashi, M.; Okunaga, K. -I.; Nishida, S.; Kawamura, K.; Eda, K. Oxidative transformation of thiols to disulfides promoted by activated carbon-air system, *Tetrahedron Lett.* **2010**, *51*, 6734-6736.

(36) Pathak, P. Synthesis of S-alkyl/S-benzyl-1,4-dihydropyrimidines and evaluation of their biological activity. *J. Chem. Pharm. Res.* **2014**, *6*, 1207-1211.

(37) Jenner, G. Effect of high pressure on Biginelli reactions. Steric hindrance and mechanistic considerations. *Tetrahedron Lett.* **2004**, *45*, 6195-6198.

(38) Slack, E. D.; Gabriel, C. M.; Lipshutz, B. H. A Palladium Nanoparticle-Nanomicelle Combination for the Stereoselective Semihydrogenation of Alkynes in Water at Room Temperature. *Angew. Chem. Int. Ed*. **2014**, *53*, 14051-14054.

(39) Pimkov, I. V.; Serli-Mitasev, B.; Peterson, A. A.; Ratvasky, S. C.; Hammann, B. ; Basu, P. Designing the Molybdopterin Core through Regioselective Coupling of Building Blocks. *Chem. Eur. J*. **2015**, *21*, 17057–17072.

(40) Quan, Z. -J.; Jing, F. -Q.; Zhang, Z.; Da, Y. -X.; Wang, X. -C. Palladium(II) Catalyzed Suzuki/Sonogashira Cross-Coupling Reactions of Sulfonates: An Efficient Approach to C2-Functionalized Pyrimidines and Pyridines. *Eur. J. Org. Chem*. **2013**, 7175-7183.