JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Intramolecular Inverse Electron-Demand [4 + 2] Cycloadditions of Ynamides with Pyrimidines: Scope and Density Functional Theory Insights

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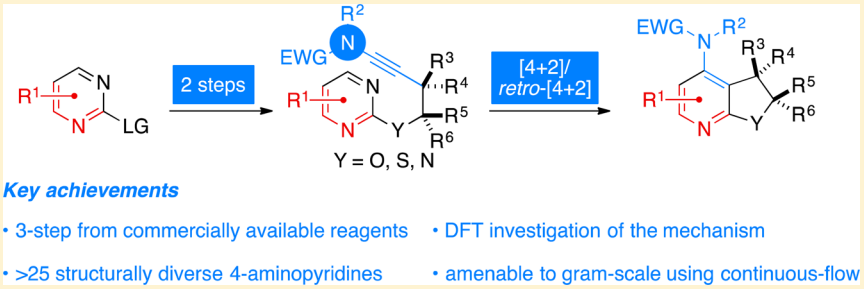
Supporting Information



ABSTRACT: 4-Aminopyridines are valuable scaffolds for the chemical industry in general, from life sciences to catalysis. We report herein a collection of structurally diverse polycyclic fused and spiro-4-aminopyridines that are prepared in only three steps from commercially available pyrimidines. The key step of this short sequence is a [4 + 2]/*retro*-[4 + 2] cycloaddition between a pyrimidine and an ynamide, which constitutes the first examples of ynamides behaving as electron-rich dienophiles in [4 + 2] cycloaddition reactions. In addition, running the *ih*DA/*r*DA reaction in continuous mode in superheated toluene, to overcome the limited scalability of MW reactions, results in a notable production increase compared to batch mode. Finally, density functional theory investigations shed light on the energetic and geometric requirements of the different steps of the *ih*DA/*r*DA sequence.

INTRODUCTION

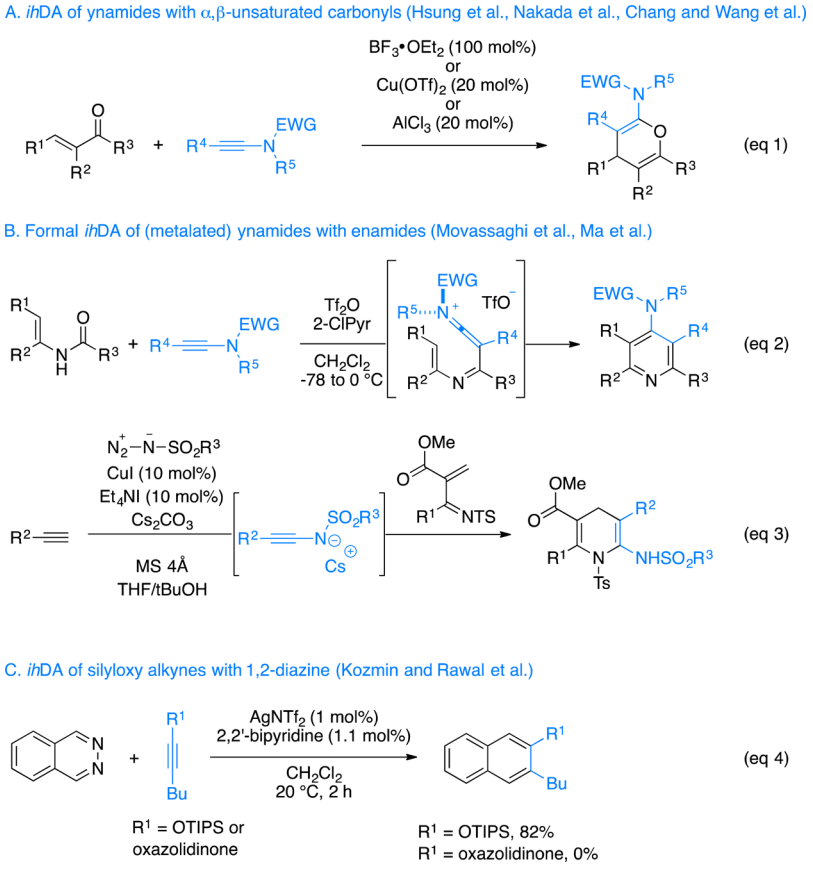
Ynamides are versatile building blocks in synthetic organic chemistry, as they possess the delicate balance between stability and reactivity, associated with an ever-increasing ease of preparation from commercially available reactants.[1−4] Cycloaddition and formal cycloaddition reactions involving ynamides have been the focus of many research groups, and this field has been thoroughly reviewed up to early 2013 by Hsung.[4,5] In the past three years, elegant studies continued to be reported on all classes of pericyclic reactions of ynamides, including [2 + 2],[6,7] [2 + 2 + 2],[8,9] [3 + 2],[6b,10,11] [4 + 2],[6b,8b,12] [4 + 3][13] benzannulation strategies[14] and hexadehydro-[4 + 2] Diels−Alder reactions.[15]

In this arsenal of pericyclic reactions of ynamides, the inter- and intramolecular [4 + 2] Diels−Alder[4,5,8] and formal Diels−Alder[4,5,12] reactions are of special note since they lead to valuable nitrogenated heterocycles such as pyridines, quinolines, carbazoles, dihydroindolines, or anilines. In almost all of these instances, the ynamide π system comprises the electron-deficient 2π component of the [4 + 2] cycloaddition reaction, and only a few examples of (formal) inverse electron-demand hetero-Diels−Alder (*ih*DA) of ynamides have been reported to the best of our knowledge (Scheme 1). Indeed, Hsung,[16] Nakada,[17] and Chang and Wang[18] have reported that ynamides could undergo an *ih*DA reaction with methylvinylketone, cyclic α-alkylidene β-oxo imides, or with *ortho*-quinone methides under Lewis acid catalysis (Scheme 1, eq 1). Movassaghi[19] reported an efficient synthesis of polysubstituted 4-aminopyridines, starting with amides that are activated using triflic

Received: December 14, 2016
Published: January 6, 2017

DOI: 10.1021/acs.joc.6b02986
J. Org. Chem. 2017, 82, 1726−1742

Scheme 1. Inverse Electron-Demand (Formal) [4 + 2] Cycloaddition Reactions of Ynamides



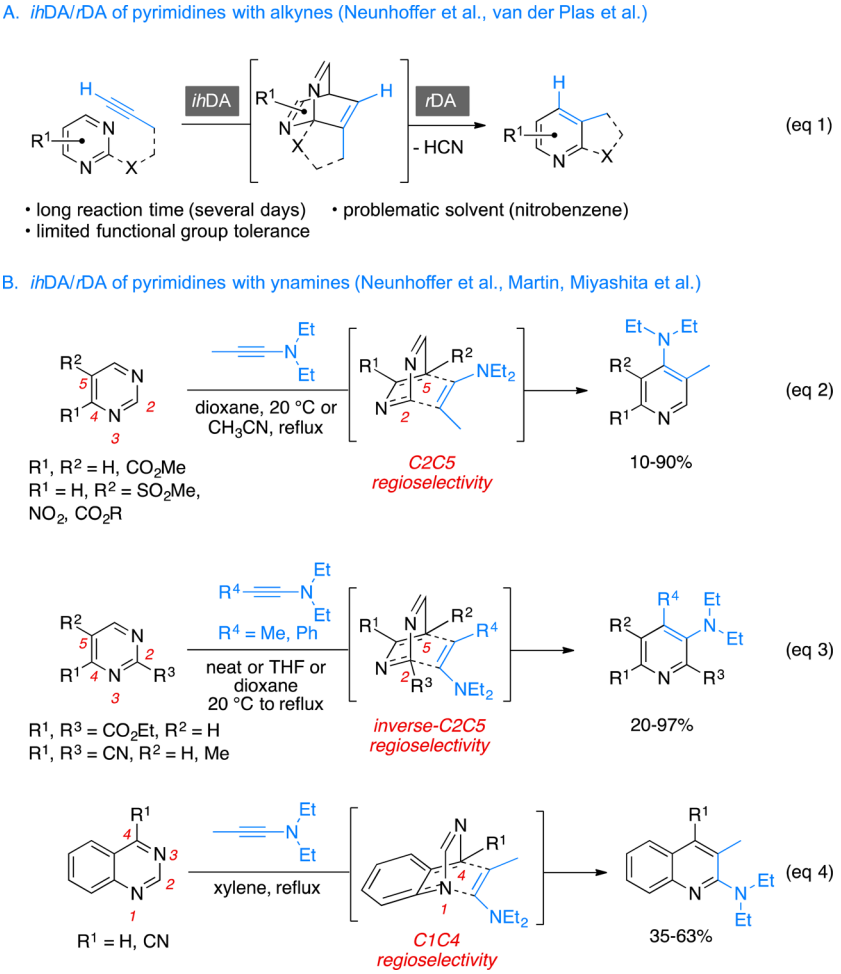
anhydride and 2-chloropyridine (Scheme 1, eq 2). The ensuing activated iminium is then trapped by an ynamide, leading to a keteniminium ion of which 6π electrocyclization delivered a 4-aminopyridine. Besides this elegant cascade reaction, Ma[12a] described the synthesis of 2-sulfonamido-1,4-dihydropyridines through a three-component reaction between a sulfonyl azide, a terminal alkyne, and an electron-deficient 1-aza-diene that rely on the *in situ* generation of a metalated ynamide (Scheme 1, eq 3). This formal *ih*DA also uncovered the crucial role of a Lewis acid (e.g., the cesium cation in Scheme 1, eq 3) on the outcome of the reaction. Finally, it should be noted that an oxazolidinone-derived ynamide was reported by Kozmin and Rawal to be unreactive in *ih*DA with 1,2-diazines under Ag(I) catalysis, which stands in sharp contrast with the comparably nucleophilic silyloxy alkynes that delivered a collection of silyl protected 2-naphthols in good yields at room temperature (Scheme 1, eq 4).[20] This last study demonstrates that [4 + 2] cycloadditions of ynamides with diazines could be particularly challenging.

[4 + 2] Cycloadditions of heterocyclic azadienes such as diazines, triazines, and tetrazines are enabling transformations that allow rapid access to nitrogen-containing heterocycles.[21] The reactivity of the azadiene is directly correlated to the number of nitrogen atoms, each nitrogen reducing the activation barrier of the [4 + 2] cycloaddition due to favorable orbital interaction and to a reduction in distortion energy that is correlated to the out-of-plane bending of the heteroaromatic diene in the transition state.[22,23] Among the heterocyclic azadienes, pyrimidines are prototypical low-reactivity electron-deficient azadienes, and their cycloaddition reactions have been only scarcely studied compared to triazines or tetrazines.[21]

In the 1970s and 1980s, the groups of Neunhoeffer[24] and van der Plas[21c,25] explored the inter- and intramolecular *ih*DA cycloaddition of pyrimidines with terminal alkynes (Scheme 2A). The first pericyclic event is followed by a spontaneous *retro*-Diels–Alder (*r*DA) that delivers (fused) pyridines. This *ih*DA/*r*DA sequence proceeds at an elevated temperature (up to 210 °C) in nitrobenzene, as the preferred solvent to give moderate yields after an extended period of time (up to several days). To overcome the use of such solvents and the extended heating at elevated temperature, Martin showed that van der Plas' *ih*DA/*r*DA reaction could be conducted under continuous flow in superheated solvents (toluene, 310 °C).[26] However, a nonsolved limitation of van der Plas' *ih*DA/*r*DA sequence is the nature of the dienophile: the terminal alkyne accounts for the vast majority of the reported 2π components, and only a handful of methyl-, silyl- or aryl-substituted alkynes were reported.[21,26] Along the same lines, heterosubstituted alkynes have rarely been used in this *ih*DA/*r*DA reaction. Ynol ethers are not reactive partners,[25e] and only a few examples of intermolecular cycloadditions using two ynamines, (1-diethylamino)-prop-1-yne (Scheme 2B, eqs 2–4) and (1-diethylamino)-2-phenylprop-1-yne (Scheme 2B, eq 3), have been reported (Scheme 2B).[24,25d,e,27,28] Finally, with a quite narrow functional group tolerance and harsh reaction conditions, this *ih*DA/*r*DA reaction has not found a widespread use in medicinal chemistry or total synthesis besides a few reports to construct penta-substituted pyridines such as the C-ring of streptonigrin[27] or the central 1-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine scaffold of some chain-breaking antioxidant.[29] Applications of this sequence can also be found in the elaboration of the

DOI: 10.1021/acs.joc.6b02986
J. Org. Chem. 2017, 82, 1726–1742

Scheme 2. Inverse Electron-Demand [4 + 2] Cycloaddition Reactions of Pyrimidines and Alkynes (A) and Ynamines (B)



tetra-substituted pyridine rings of the monoterpenic alkaloid actinidine[30] or the 4-aza analog of ramelteon.[31]

In continuation of our investigations of hetero-Diels–Alder cycloaddition reactions,[32] we recently disclosed for the first time the use of ynamides in *ih*DA reactions for the synthesis of aminopyridines (Scheme 3).[33] Pyrimidines were selected as electron-deficient heterodienes, since a broad range of these nitrogenated heterocycles are commercially available or can be prepared from simple reactants in a few steps, thus a general *ih*DA/*r*DA sequence based on pyrimidines as dienes is of high interest. Remarkably, starting with C2-substituted pyrimidines led to fused 4-aminopyridines in high yields, whether tetra- or pentasubstituted, and a good functional group tolerance was observed.[34]

Indeed, 4-amino pyridines are privileged scaffolds[35] that have attracted the attention of both the agrochemical and pharmaceutical industry due to their intrinsic biological activities[36] and potential for skeleton diversity.[37] In spite of their attractiveness, the synthesis of this class of 4-amino pyridines is still hampered by shortcomings, although insightful methods have been recently designed by Macgregor and Whittlesey[38] and Reissig[39] based on the catalytic hydrodefluorination reaction of fluorinated pyridines. Therefore, a general *ih*DA/*r*DA reaction of ynamides with pyrimidines could be a direct entry into a class of highly valuable but synthetically challenging amino-pyridines.

Herein, we report a full account of our investigations, with a thorough study of the scope of the reaction sequence including a scale-up *ih*DA/*r*DA procedure using flow conditions in superheated toluene. In addition, density functional theory (DFT) calculations at the M06-2X/6-311+G(d,p) level were used to gain insights into the mechanism of this reaction.

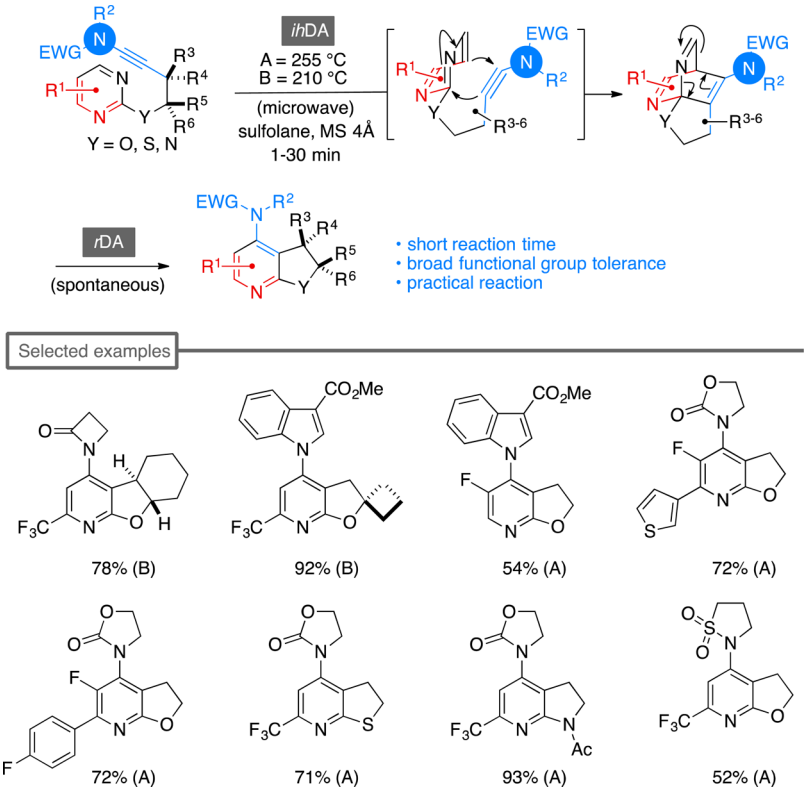
RESULTS AND DISCUSSION

A three-step sequence to synthesize structurally diverse 4-amino pyridines was thus designed, starting from pyrimidines of general structure **A**, possessing a leaving group in the C2-position (Scheme 4). Nucleophilic aromatic substitution with homopropargylic alcohols, amines, or *N*-hydroxycarbamates leads to alkynyl pyrimidines **B**, whose terminal alkynes could be further transformed into the corresponding ynamides **C**.[40] The key *ih*DA/*r*DA would then allow the formation of polycyclic 4-aminopyridines **D**. To evaluate the relevance and generality of this three-step sequence to nitrogen-containing heterocycles **D**, we first focused on the synthesis of the cycloaddition precursors.

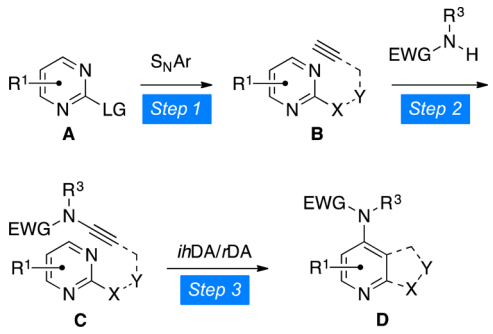
Synthesis of Cycloaddition Precursors. We began our investigations by the synthesis of a diversity of cycloaddition precursors that differ by the nature of the substituents on the pyrimidine ring as well as the ynamide moiety (carbamate, sulfonamide, indole and sultam). The length and substitution of the tether between the azadiene and the ynamide were also investigated. To this end, we focused on a first series of 2-alkoxypyrimidines **3**, **5**, **7**, and **9** prepared via a S_NAr reaction of the appropriate 2-chloropyrimidine with a sodium alkoxide in THF (Schemes 5 and 6).

DOI: 10.1021/acs.joc.6b02986
J. Org. Chem. 2017, 82, 1726–1742

Scheme 3. Inverse Electron-Demand [4 + 2] Cycloaddition Reactions of Pyrimidines and Ynamides



Scheme 4. A Three-Step Synthesis of Structurally Diverse 4-Aminopyridines Using *ih*DA/*r*DA as a Key Step



For the simplest pyrimidines such as the 2-chloro- and 2-chloro-4-trifluoromethylpyrimidines **1a** and **1b**, the S_NAr reaction proceeded smoothly at room temperature, leading to the corresponding alkynyl-pyrimidines **3a–i** in 32–97% yield (Scheme 5A).

Pyrimidines substituted in the 5-position by an electron-withdrawing atom (F in **5a–c**, Cl in **5d**, or Br in **5e**) or electron-withdrawing group (CN in **5f**, CF_3 in **5g**) were also prepared by S_NAr of the corresponding 2-chloropyrimidines with the relevant homopropargylic sodium alkoxide (Scheme 5B). Heating to 130 °C (microwave irradiation) led to a marginal increase in the yield, as can be seen for **5a** (79% (A) vs 94% (B)) and **5e** (74% (A) vs 89% (B)). Pyrimidine **5f** bearing a cyano-group in the 5-position was prepared by the palladium-catalyzed cyanation reaction of **5e** ($Pd(dba)_2$ (10 mol %), dppf (20 mol %), $Zn(CN)_2$, DMF, 90 °C).[41]

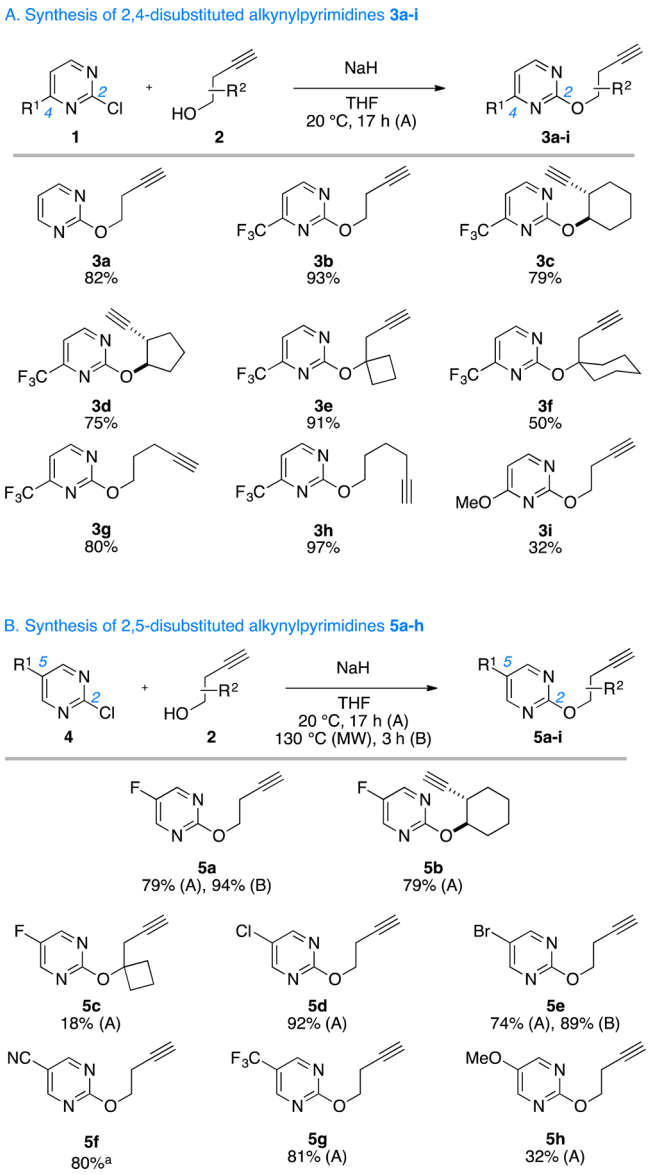
2,4,5 and 2,4,6-Trisubstituted pyrimidines were prepared from pyrimidines possessing a leaving group in the 2-position (either a methanesulfonyl in **6a** or a chlorine atom in **6b** and **8a–e**) and homopropargylic sodium alkoxide in THF (Scheme 6). For the symmetrical pyrimidines **7a** and **7b**, the 4- and 6-positions were substituted by electron-withdrawing chlorine atoms or electron-donating methoxy groups, respectively (Scheme 6A). In the case of 2,4,5-trisubstituted pyrimidines **9a–e**, the 5-fluoro substituent was kept identical, while the 4-position differed by the nature of the aromatic (phenyl in **9a** and 4-fluorophenyl in **9b**) or heteroaromatic ring (imidazo[1,2-*a*]pyridinyl in **9c**, 1-methyl-1*H*-pyrazol-5-yl in **9d**, and thiophen-3-yl in **9e**) (Scheme 6B).

We finally turned our attention to a last series of three alkynyl pyrimidines **11**, **13**, and **15** that possess one or two heteroatoms in the tether (Scheme 7). Methyl *N*-propargyl-*N*-(pyrimidin-2-yloxy)carbamate **11** was prepared in two steps from commercially available 2-chloro-4-trifluoromethylpyrimidine **1b** by S_NAr followed by propargylation of the nitrogen atom under basic conditions (Scheme 7, eq 1). Starting from **1b**, a different strategy was used for the synthesis of *N*-propargyl-*N*-(pyrimidin-2-yl)acetamide (**13**). Nucleophilic displacement of the C2-chlorine atom of **1b** by the sodium anion of but-3-yn-1-amine led to **12**, whose nitrogen atom was protected using acetic anhydride with 1 mol % of sulfuric acid (Scheme 7, eq 2).[25b,42] Finally, 2-(propargylthio)-4-trifluoromethylpyrimidine **15** was prepared in a single step in 93% yield by propargylation of commercially available **14**, under basic heterogeneous conditions (Scheme 7, eq 3).

With a diversity of alkynylpyrimidines in hand, we next turned our attention to their elaboration into the corresponding ynamides (Schemes 8–10). To this end, several classical synthetic strategies for the copper-mediated synthesis of ynamides were evaluated, such as Stahl's methods (C: $CuCl_2$, pyridine, Na_2CO_3, O_2 in toluene at 70 °C; D: $CuCl_2$, Cs_2CO_3, O_2, DMSO, 70 °C) and Evano's method (E: CuI, Cs_2CO_3, NH_4OH/EtOH

DOI: 10.1021/acs.joc.6b02986
J. Org. Chem. 2017, 82, 1726–1742

Scheme 5. Synthesis of 2,4- and 2,5-Disubstituted Alkynyl Pyrimidines 3 and 5



[a]Prepared from **5e**, $Pd(dba)_2$ (10 mol %), dppf (20 mol %), $Zn(CN)_2$, DMF, 90 °C, 48 h.

then TMEDA, MeCN, 20 °C).[2−4,43−45] It is worth noting that the ynamides precursors **3**, **5**, **7**, **9**, **11**, **13**, and **15** are challenging substrates for copper-mediated transformations, owing to the chelating potential of pyrimidines in general (and more specifically 2-alkoxypyrimidines) that could negatively impact the yield of the desired copper mediated C−N bond formation.[46,47] For most of the substrates, several methods were screened in parallel, and only the best results are reported in Schemes 8−10. Unfortunately, no general trends were observed in the synthesis of these ynamides.

Starting from 2,4-disubstituted alkynyl pyrimidines **3**, methods D and E proved the most efficient using diverse nitrogenated nucleophiles such as oxazolidinone, azetidinone, sultame, 3-carboxymethylindole, and *N*-methyl arylsulfonamides (Scheme 8). The 16 desired ynamides **16a−q** were obtained in 11−77% yield. The structure of ynamide **16k** was unambiguously confirmed by X-ray diffraction.[48] In addition to methods D and E, method C was used for the synthesis of 10 additional ynamides **17a−i** starting from 2,5-disubstituted alkynyl pyrimidines **5** (Scheme 9).

Finally, a last set of 10 ynamides was prepared from terminal alkynes **7**, **9**, **11**, **13**, and **15** (Scheme 10). Except for the case of ynamide **18e** for which none of the desired ynamide was detected (which could be traced back to the chelation potentials of the imidazo[1,2-*a*]pyridinyl and 2-alkoxypyrimidine motifs in **9c**), the targeted ynamides **18** were obtained in 25−79% yield. The more challenging ynamide **19a** was obtained with a low (but reproducible) yield of 12%. Moderate to good yields were obtained for **19b−d** that possess either a 2-acetamido (**19b**, 54% and **19c**, 75%) or a 2-thio (**19d**, 69%) substituent on the pyrimidine ring.

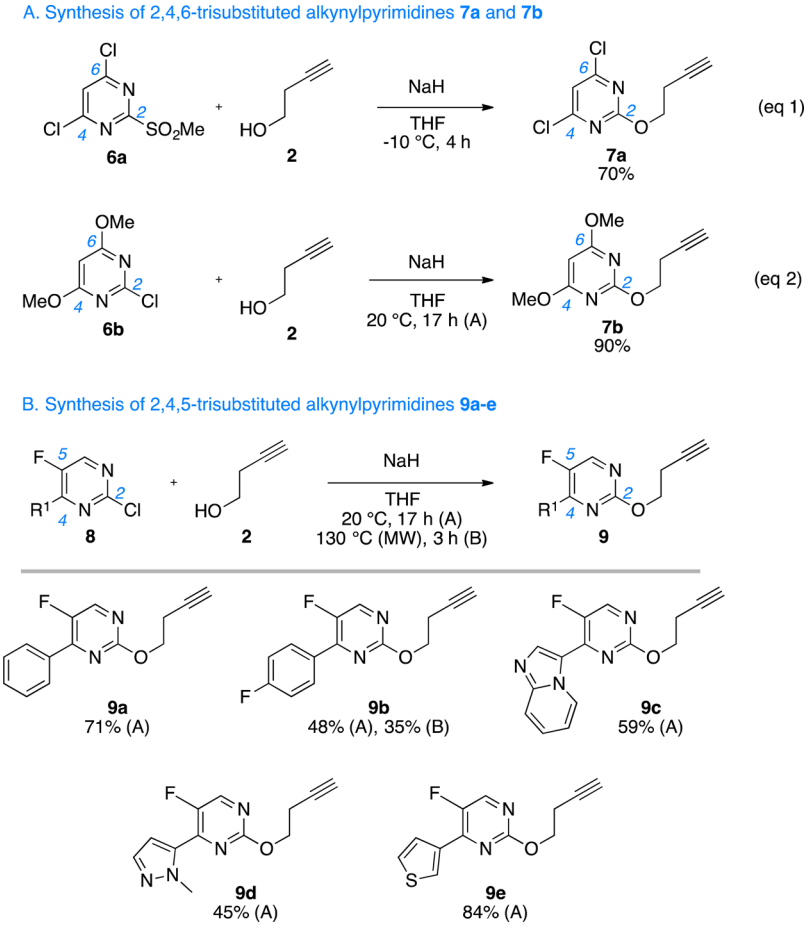
Having prepared a set of 36 structurally differentiated ynamides (**16−19**), the reactivity of these compounds in the intramolecular *ih*DA/*r*DA was evaluated.

Intramolecular *ih*DA/*r*DA of Ynamides. The ynamides **16a−q** were selected for the first series of intramolecular *ih*DA/*r*DA under the optimized reaction conditions: dry sulfolane using microwave irradiation at 255 °C for 1 min (method F) or 210 °C for 30 min (method G) (Scheme 11).[33] The need for an electron-withdrawing group on the azadiene partner became quickly evident as none of the pyridine **20a** was obtained from compound **16a** under conditions F or G. The latter was fully recovered without any traces of decomposition. On the other hand, introducing a strongly electron-deficient motif such as a trifluoromethyl group in the 4-position of the pyrimidine led to a productive cycloaddition sequence, as evidenced by 4-aminopyridines **20b−e** and **20i−n**, which were obtained cleanly and in moderate to good yields. In line with these results, a 4-methoxy substituent on the pyrimidine ring, as in **16q**, did not lead to the desired fused pyridine **20q**. A similar lack of reactivity was observed with the 2,4,6-trialkoxy pyrimidine **18a** (vide infra, Scheme 13). The efficiency of this *ih*DA/*r*DA sequence is also strongly impacted by the nature of the ynamide, which should not be too strongly electron-deficient. Indeed, it was found that for comparable substrates, good yields of the fused 4-aminopyridines were obtained using ynamides derived from oxazolidinone (**20b**,**i−k**,**n**) azetidinone (**20d**), sultame (**20c**), and indole (**20e** and **20m**), whereas ynamides derived from methylsulfonamide led to poor yield of the cycloadducts (**20f**, 21%) or suffer from complete decomposition in the case of strongly electron-withdrawing substituent on the nitrogen atom of the ynamide (**20g** and **20h**, 0%). A last parameter that influenced the reactivity in this *ih*DA/*r*DA sequence is the nature and length of the tether between the pyrimidine and the ynamide. Whereas a three-atom tether was perfectly tolerated (as in **20b**, for example), a four- or five-atom tether was detrimental to the reactivity, no cycloadducts being formed in the case of **20o** and **20p** (for a DFT investigation of the reactivity of **20o**, see the Experimental Section and Supporting Information). Quite logically, substitution of the tether entropically favored the first, rate-limiting [4 + 2] cycloaddition step (vide infra, Figure 2). Tricyclic pyridines **20i−n** were thus obtained and in some cases with greatly improved yields (**20b**, 60% vs **20k**, 91%; **20e**, 49% vs **20m**, 86%; and **20f**, 21% vs **20l**, 60%). Finally, it should be noted that an X-ray structure of cycloadduct **20m** was obtained, thus unambiguously establishing the fused 4-aminopyridine scaffolds arising from the *ih*DA/*r*DA cascade of **16m**.[33]

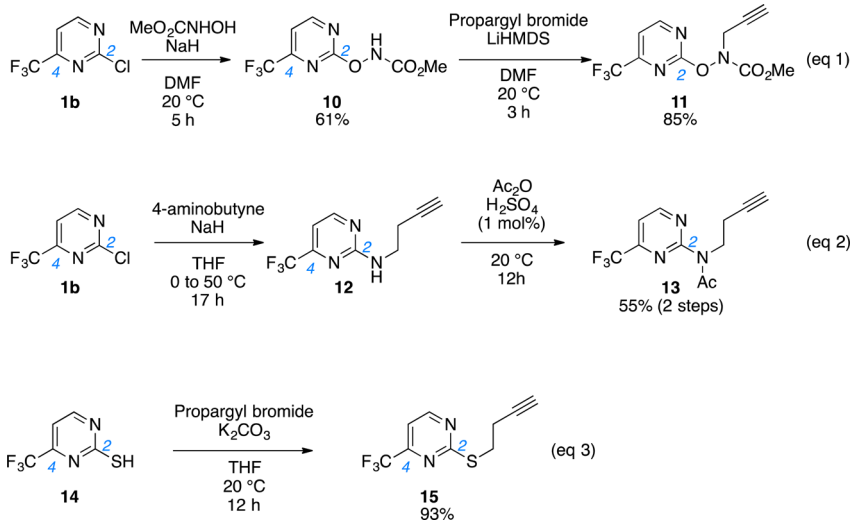
In a second series of studies, we focused on the 2,5-disubstituted ynamidyl pyrimidines **17** (Scheme 12) to probe the

DOI: 10.1021/acs.joc.6b02986
J. Org. Chem. 2017, 82, 1726−1742

Scheme 6. Synthesis of 2,4,6- and 2,4,5-Trisubstituted Alkynyl Pyrimidines 7 and 9



Scheme 7. Synthesis of 2,4-Disubstituted Alkynyl Pyrimidines 11, 13, and 15



efficiency of the *ih*DA/*r*DA sequence using 5-substituents on the pyrimidine that possess opposite steric and electronic properties. Indeed, substitution of this 5-position was reported by van der Plas and Neunhoeffer to have a strong impact on the yields of the cycloadducts.[21,24,25] In our observation, moderate to excellent yields of the desired 4-aminopyridines **21** were obtained in cases of **21a**−**e** whose C5-position is substituted by a fluorine atom, except in the case of **21c** for which only decomposition of the cycloaddition precursor was observed. This difference in reactivity could be attributed to the more sterically and electronically demanding electron-withdrawing group on the nitrogen atom of the ynamide that severely impacts the transition state of the initial [4 + 2] cycloaddition. This hypothesis is further supported by the decrease in yields observed with the increase of steric bulk of the electron-withdrawing group of the ynamide (**21d** 90%, **21a** 71%, **21e** 54%, and **21c** 0%).

DOI: 10.1021/acs.joc.6b02986
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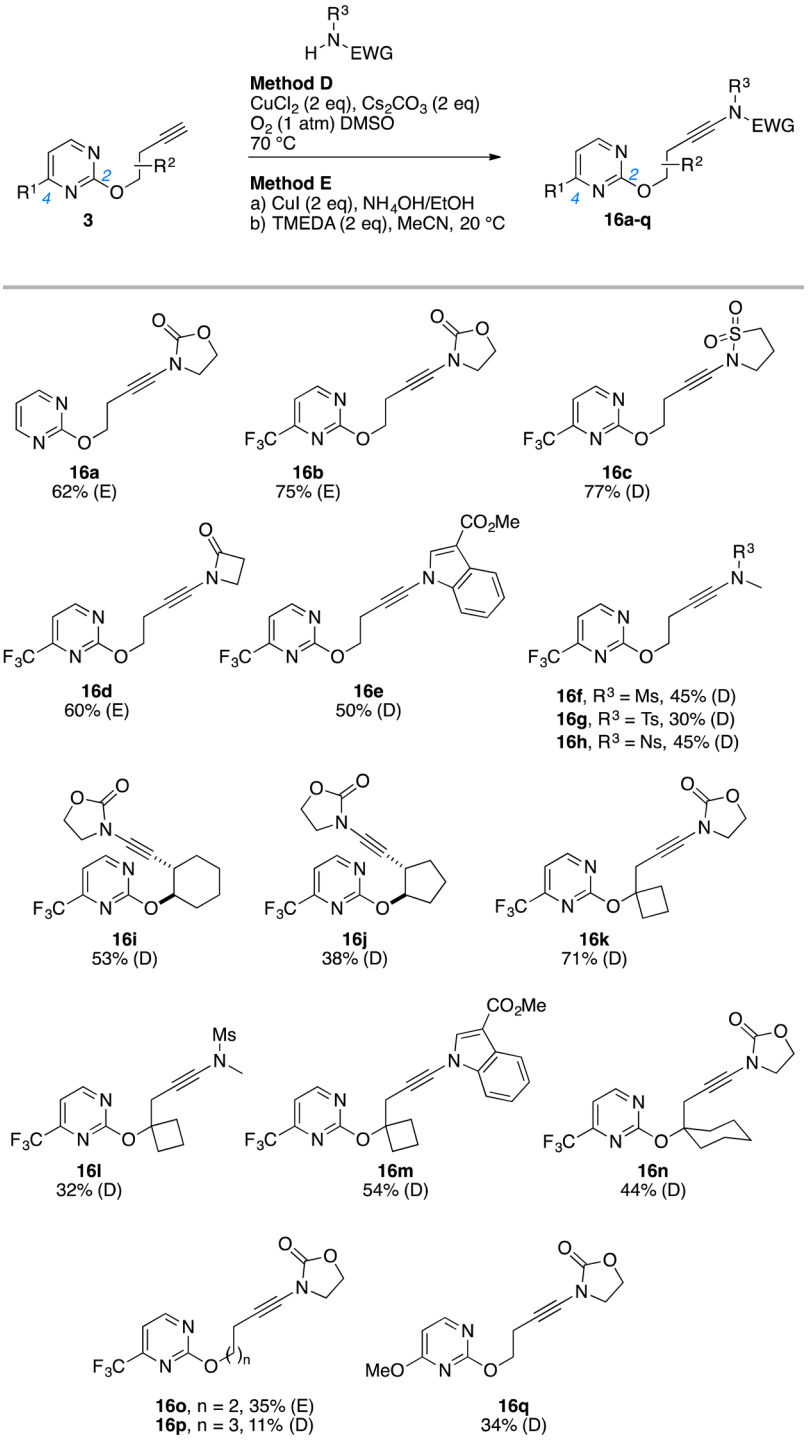
Scheme 8. Synthesis of 2,4-Disubstituted Ynamidyl Pyrimidines 16



In addition, low yields were obtained in cases with sterically demanding 5-chloro or 5-trifluoromethyl groups or the electron-rich 5-methoxy substituent (leading, respectively, to **21f** 17%, **21i** 11%, and **21j** 21%). No cycloadducts were obtained starting from 5-bromo- and 5-cyano-substituted pyrimidines (leading, respectively, to the putative **21g** and **21h**). An X-ray structure of cycloadduct **21e** revealed unambiguously the structure of the cycloadduct obtained from **17e**.[33]

Finally, the *ih*DA/*r*DA reaction of ynamides **18** and **19** was studied with the potential to give access to tetra- or penta-substituted pyridines, annulated to an oxygen-, nitrogen- or sulfur-containing five-membered heterocycle (Scheme 13). Cycloaddition reaction of the 2,4,6-trisubstituted pyrimidine **18a** led to only a low yield of the tetra-substituted aminopyridine **22a** (21%) in 5 min at 255 °C. Although cycloaddition precursor **18a** is quite electron-deficient, the steric requirement of the two C4- and C6-chlorine atoms seems to negatively impact the yield of the *ih*DA/*r*DA sequence. In the case of the 2,4,6-trisubstituted pyrimidine **18b**, the electronics of the azadiene do not favor the cycloaddition at all, and no cycloadduct **20q** was detected. This result is coherent with the lack of reactivity of pyrimidine **16q** possessing a single C4-methoxy group on the pyrimidine ring

DOI: 10.1021/acs.joc.6b02986
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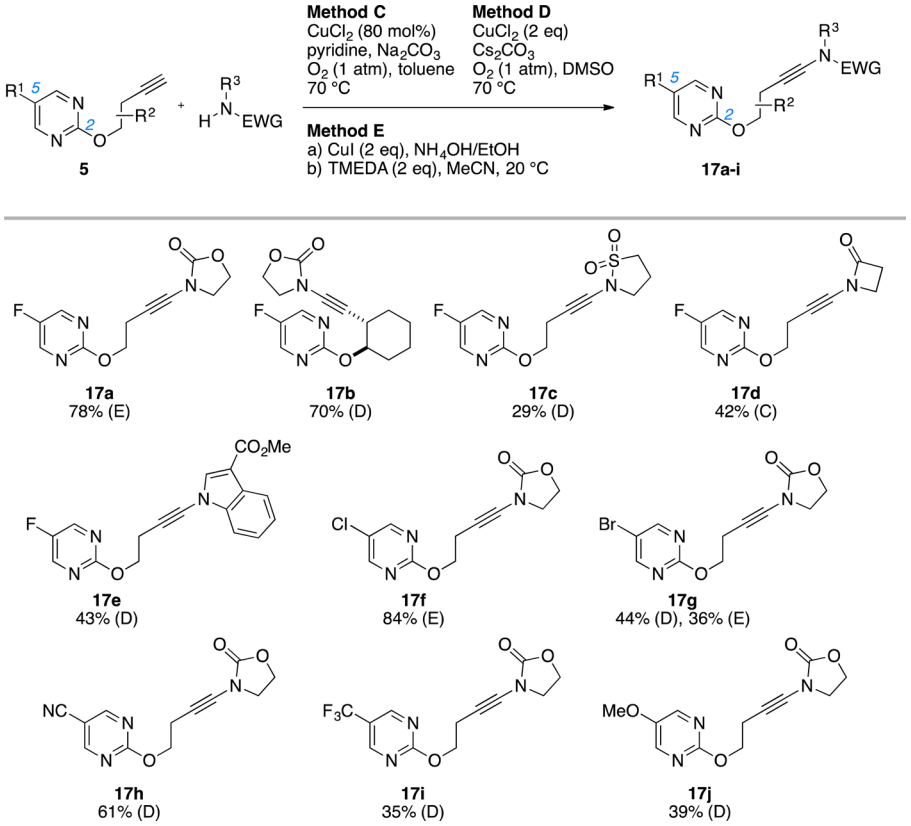
Scheme 9. Synthesis of 2,5-Disubstituted Ynamidyl Pyrimidines 17



(see Scheme 12). It should also be noted that ynamide **18g** possessing a 1-methyl-1*H*-pyrazol-5-yl motif at C4 of the pyrimidine led to complete decomposition at 255 °C for 1 min, and no cycloadduct **22f** could be detected in the crude reaction mixture. In sharp contrast, pentasubstituted pyridines **22c**, **22d**, and **22g** were obtained in 82%, 72%, and 72% yields, respectively, thus demonstrating that the *ih*DA/*r*DA of ynamides constitute a valuable approach to these densely functionalized pyridines. When two successive heteroatoms are present in the tether of the cycloaddition precursor as in **19a**, the *ih*DA/*r*DA reaction could be conducted at lower temperature (180 °C), leading to the high value 2,3-dihydroisoxazolo[5,4-*b*]pyridine scaffold, albeit in 21% NMR yield (unoptimized). The last three cycloadducts, **23b**−**d**, were obtained in good to excellent yields, thus highlighting that this method could be applied to the preparation of 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridines (such as **23b** and **23c**) or 2,3-dihydrothieno[2,3-*b*]pyridine (such as **23d**).

Scale-Up of *ih*DA/*r*DA of Ynamides under Continuous Flow Conditions. In continuation of our investigations, we were keen to demonstrate that the *ih*DA/*r*DA reaction sequence was easily scalable using continuous flow technology. Even if microwave dielectric heating is an efficient technology for small-scale experiments, some limitations arise when multigrams of products are required within a short time.[49] With regards to scale-up, an established alternative to microwave irradiation is thermal heating in continuous flow, a safe synthetic tool that gained momentum in the past few years due to its excellent heat and mass transfer capacities.[50] Indeed, Martin et al. demonstrated that inverse electron demand Diels−Alder cycloadditions,[26] such as the Kondrat'eva reaction,[51] can be conducted efficiently under continuous flow in superheated solvents (toluene, 230−310 °C). Our recently reported *ih*DA/*r*DA of ynamides with pyrimidines is also amenable to continuous flow conditions using a very simple setup,[52] as demonstrated in Scheme 14. At 300 °C in superheated toluene, cyanhydric acid polymers might obstruct the reactor. This potential clogging is efficiently prevented using pentanone (1% v/v) as a cyanide trap.[26b] Under these conditions, **16b** is efficiently converted to **20b** on a multigram scale and in a very short reaction time (effective residence time: 7.4 min, corrected for the 35% thermal expansion of toluene at 300 °C). The increase of yield between microwave irradiation (60%, Scheme 11) and continuous flow (78%, Scheme 14) is also worth noting.

This easy-to-use technology thus overcomes the commonly observed limitations of microwave heating when it comes to synthesis up scaling. Although a systematic comparison of the cycloaddition yields using microwave irradiations and superheated toluene was beyond the scope of this study, the rapid preparation of 2.4 g of the fused pyridine **20b** proves that this sequence is relevant to the preparative synthesis of valuable polycyclic pyridines.

DFT Investigations of the *ih*DA/*r*DA Sequence of Ynamides. Besides developing a practical access to multigrams of the representative cycloadduct **20b**, we have been interested in the understanding of the reaction pathway of the *ih*DA/*r*DA of ynamides with pyrimidines. Actually, the exploration of the Diels−Alder reactions of pyridine, di-, tri-, and tetrazines with 2π components with DFT have been reported recently by Ess and Bickelhaupt[22] and Houk.[23] As discussed in the Introduction, it was shown that the reactivity of azadienes is directly correlated to the number of nitrogen atoms; each substitution of a C−H bond by a nitrogen atom decreases the σ

DOI: 10.1021/acs.joc.6b02986
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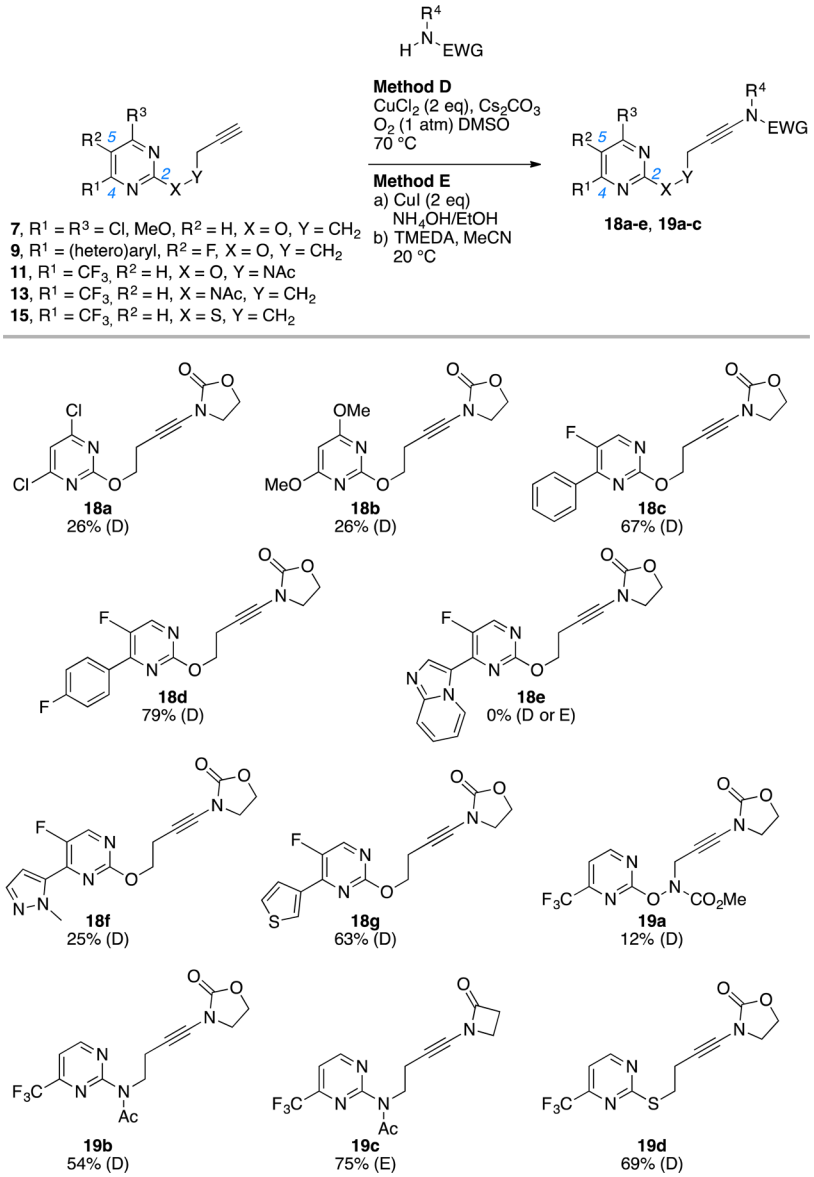
Scheme 10. Synthesis of Ynamidyl Pyrimidines 18 and 19



aromaticity of the heteroaromatics. In addition, distortion energies and interaction energies of the diene and dienophile were shown to be of prime importance. To gain some insight into the mechanism of the *ih*DA of ynamides with pyrimidines, DFT computations were carried out at the M06-2X/6-311+G(d,p) level taking sulfolane into account (PCM method) using three representative substrates: **3b** (Figure 1A), **16b** and **17a** (Figure 1B).[51]

Determination of the Gibbs free energies and of the geometries of transition states and intermediates of the *ih*DA of terminal alkyne **3b** is important since it allows a direct evaluation of the impact of the nitrogen atom connected to the alkyne on reactivity. The most stable conformations of **3b**, **16b**, and **17a** are dependent on the substitution pattern. Figure 1 shows the most stable ground-state conformations of the folded and stretched conformers of terminal alkyne **3b** (Figure 1A) as well as of the folded conformers of ynamides **16b** and **17a** (Figure 1B) at the M06-2X level. In the terminal alkyne **3b** (Figure 1A), the stretched isomer $\mathbf{3b_1}$ is the most stable by about 1 kcal/mol. This shows that the stabilization of the charge at C3 through alkyne electron transfer is quite negligible (respective charges at C2 and C3 are −0.020 and +0.750).[53] On the other hand, as can be seen in Figure 1B, the folded conformer $\mathbf{16b_2}$ is more stable than the stretched one $\mathbf{16b_1}$ by 3.8 kcal/mol at 528 K (255 °C). Inspection of the maximum electron density reveals a weak interaction between C2 at the alkyne moiety and C3 at the pyrimidine fragment (ρ_{max} = 0.009 e·Å^{-3}). This is consistent with the fact that C3 has a strong positive charge (+0.766), while C2 is more negatively charged (−0.070) than in **3b**.[52]

Two CF···H hydrogen bonds (ρ_{max} = 0.007 e·Å^{-3}) also account for the stabilization of $\mathbf{16b_2}$, these hydrogen bonds being mainly responsible for the stabilization of the folded isomer. In $\mathbf{17a_2}$, O-C5 electron density transfer was found at ρ_{max} = 0.005 e·Å^{-3}, while a very weak electron transfer from the alkyne moiety to C3 was computed at ρ_{max} = 0.003 e·Å^{-3}. The stretched isomer $\mathbf{17a_1}$ is less stable by 1.5 kcal/mol at 528 K.

For these substrates, three steps were considered (Figure 2): (i) [4 + 2] cycloaddition leading to **A3b** (from **3b**), **A16b** (from **16b**), and **A17a** (from **17a**); (ii) *retro*-[4 + 2]

DOI: 10.1021/acs.joc.6b02986
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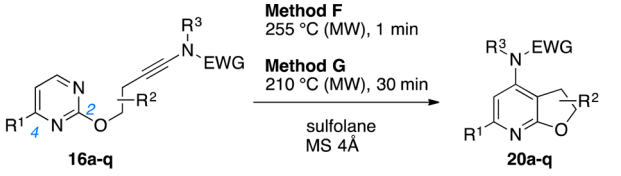
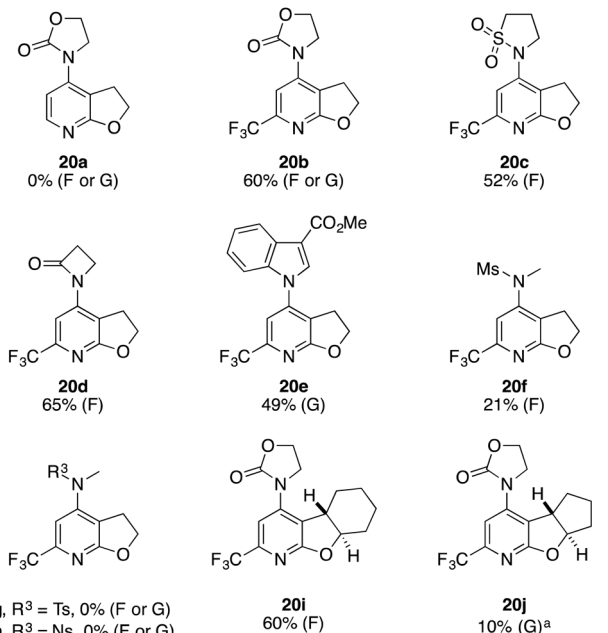
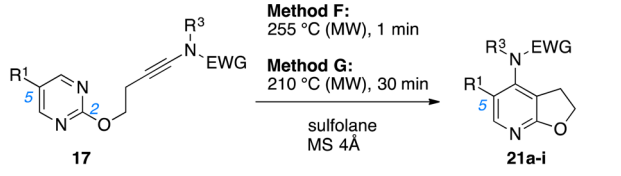
Scheme 11. Intramolecular *ih*DA/*r*DA of Ynamidyl Pyrimidines 16

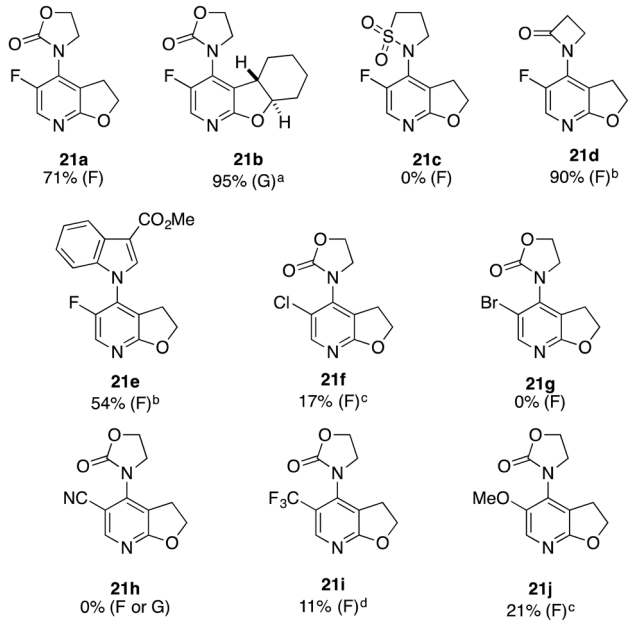




[a]NMR yield using **1b** as internal standard. [b]30 s. [c]1 h. [d]10 min. [e]3 h.

Scheme 12. Intramolecular *ih*DA/*r*DA of Ynamidyl Pyrimidines 17





[a]60 min. [b]2 min. [c]10 min. [d]NMR yields using **1b** or **4a** as internal standards.

cycloaddition of HCN (leading to **24**·HCN, **20b**·HCN or **21a**·HCN) or F_3CCN (leading to **24′**·HCN, **20b′**·HCN or **21a′**·HCN); and (iii) dissociation of the final cycloadduct from the HCN or F_3CCN complex. As after step ii the two fragments may still interact noncovalently, step iii is required to get a more precise estimation of the ΔG of the reaction. It should also be mentioned that even though only one product can be obtained from **17a**, two distinct HCN fragments can be eliminated from **A17a**, since R^1 = H.

Figure 2 summarizes the computed Gibbs free energies at 528 K related to steps i–iii for compounds **3b** (gray lines), **16b** (light blue lines), and **17a** (black lines). All values are relative to the most stable conformers $\mathbf{3b_1}$, $\mathbf{16b_2}$, and $\mathbf{17a_2}$.

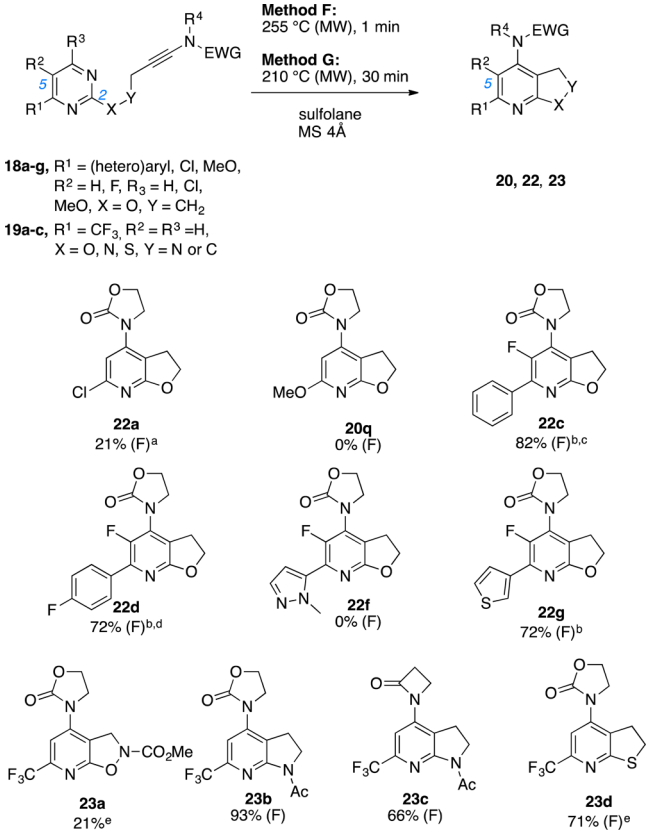
For the transformation of $\mathbf{16b_2}$, the [4 + 2] is achieved through the transition state TS3($\mathbf{16b_2}$ → **A16b**) and requires 32.4 kcal/mol of activation energy. The fact that the cyclization barrier does not change much by raising the temperature from 298 to 528 K is indicative of negative entropy changes.[54]

The adduct **A16b** is formed in an exergonic fashion (−10.6 kcal/mol). The free Gibbs activation energy for TS6 (**A16b** → **20b**·HCN) corresponding to the elimination of HCN is 21.8 kcal/mol. The formation of **20b**·HCN is strongly exergonic by 25.3 kcal/mol. Considering the strong energy difference between **20b**·HCN and TS6 (36 kcal/mol), the *retro*-[4 + 2] step is expected to be irreversible. Separation of the fragments costs 16.4 kcal/mol, but the overall process remains appreciably exergonic (−8.9 kcal/mol).

Elimination of F_3C-CN from **A16b** (red lines) is comparable to that of HCN kinetically (see TS7(**A16b** → **20b′**·F_3C-CN), 12.1 kcal/mol), but it is clearly disfavored thermodynamically (see **20b′**·F_3C-CN, −13.4 kcal/mol and **20b′** + F_3C-CN, +9 kcal/mol).[55] The same conclusion can be reached for **17a**. Lastly, calculations on terminal alkyne **3b** show that the use of ynamides instead of simple alkynes does not necessarily retard nor accelerate the [4 + 2] cycloaddition step. Indeed, TS2(**3b1** → **A3b**) actually lies 26.5 kcal/mol above $\mathbf{3b_1}$, which is less than the Gibbs free energy of activation for $\mathbf{16b_2}$ (32.4 kcal/mol), but more than that for $\mathbf{17a_2}$ (23.8 kcal/mol). Also worth mentioning, the barrier of the [4 + 2] cycloaddition increases significantly with a 4-atom tether as in **20o**

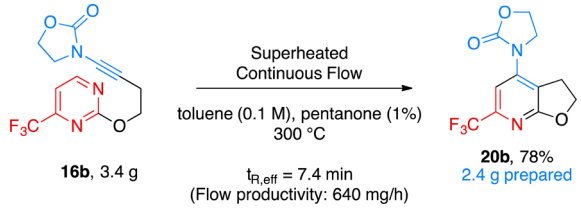
DOI: 10.1021/acs.joc.6b02986
J. Org. Chem. 2017, 82, 1726−1742

Scheme 13. Intramolecular *ih*DA/*r*DA of Ynamidyl Pyrimidines 18 and 19



[a]5 min. [b]10 min. [c]Ratio **21a**/**22a** = 82:18 by ^{19}F NMR. [d]Ratio **21a**/**22b** = 85:15 by ^{19}F NMR. [e]180 °C for 90 min. [f]2 min.

Scheme 14. Continuous Flow Scale-Up of the Synthesis of 20b in Superheated Toluene



(Scheme 11), the computed Gibbs free energy of activation at 528 K being 36.6 kcal/mol. This is corroborated by the absence of reactivity of **20o** under the experimental conditions.

The geometry of the computed [4 + 2] transition state of the *ih*DA of $\mathbf{16b_2}$ (TS3) is displayed in Figure 2 (bottom). As shown by the quite similar C1C5 and C2C3 distances, TS3 is essentially synchronous (whereas asynchronicity was observed in TS1 and TS2).[51] In addition, the F···H hydrogen bonds, which stabilized the folded isomer $\mathbf{16b_2}$, are lost in TS3. In the primary adduct **A16b**, the orientation of the oxazolidinone tends to minimize the electronic repulsion between the fluorine and oxygen lone pairs. The geometry of the *retro*-[4 + 2] transition state TS6 was also computed. Since a normal C−N bond is shorter than a C−C bond, this transition state is clearly asynchronous; the breaking of the C−N bond being more advanced than that of the C−C bond (a similar asynchronicity was observed for TS4 and TS5). The asynchronicity in the

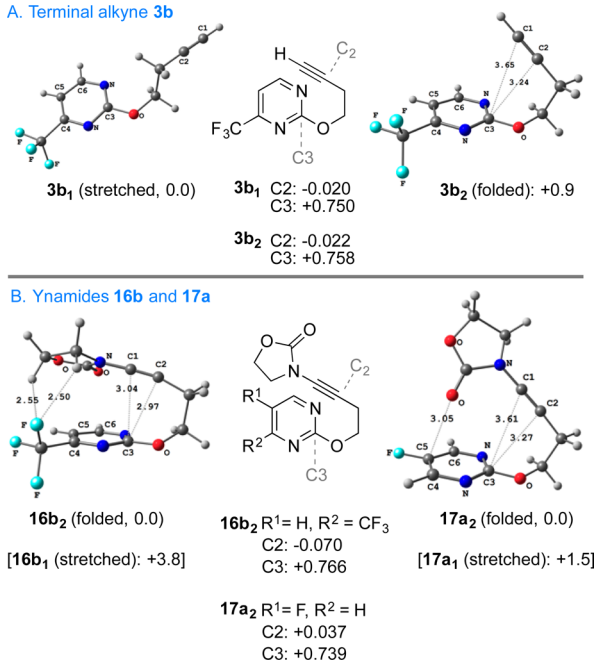


Figure 1. Lowest-energy conformations of terminal alkyne **3b** and ynamides **16b** and **17a**. Note: ΔG_{528} in kcal/mol; selected distances in Å; selected natural charges.

F_3C-CN elimination transition state TS7 is even more pronounced. Overall, for each case studied, the [4 + 2] cycloaddition is the rate-limiting step, and the selectivity between HCN or R^1CN elimination can be deduced from the Gibbs free energy of the reaction. The stabilization of the cycloaddition precursors through intramolecular noncovalent interactions, especially F···H hydrogen bonds that are lost in the [4 + 2] transition states, increases the cyclization barrier.

CONCLUSION

Capitalizing on previous cycloaddition reactions of terminal alkynes and pyrimidines reported in the 1970s and 1980s by Neunhoeffer and van der Plas, we have developed the first inverse electron demand hetero-Diels−Alder cycloadditions of ynamides with C2-substituted pyrimidines, in an intramolecular version, thus complementing the few examples of (formal) *ih*DA of ynamides known to date. In three simple steps from commercially available pyrimidine building blocks, an array of structurally diverse polycyclic-fused- and spiro-4-aminopyridines that could be further derivatized was synthesized. It should be noted that such a strategy could also be applied to C5-substituted pyrimidines, thereby opening the way to fused-3-aminopyridines. In addition, continuous flow conditions in superheated toluene enabled the synthesis of multigrams of cycloaddition product within very short times. Finally, DFT calculations shed light on the reaction sequence, which involves two consecutive transition states. The [4 + 2]-TS lies above the *retro*-TS that is highly asynchronous in nature. In addition, the HCN elimination appears to be favored both on thermodynamic and kinetic grounds.

This *ih*DA/*r*DA reaction sequence of ynamides is a useful addition to the ever-growing number of pericyclic reactions of heterosubstituted alkynes, and a comprehensive understanding of the intricate steps of this sequence will guide future investigations of intra- and intermolecular *ih*DA reactions of ynamides.

DOI: 10.1021/acs.joc.6b02986
J. Org. Chem. 2017, 82, 1726−1742

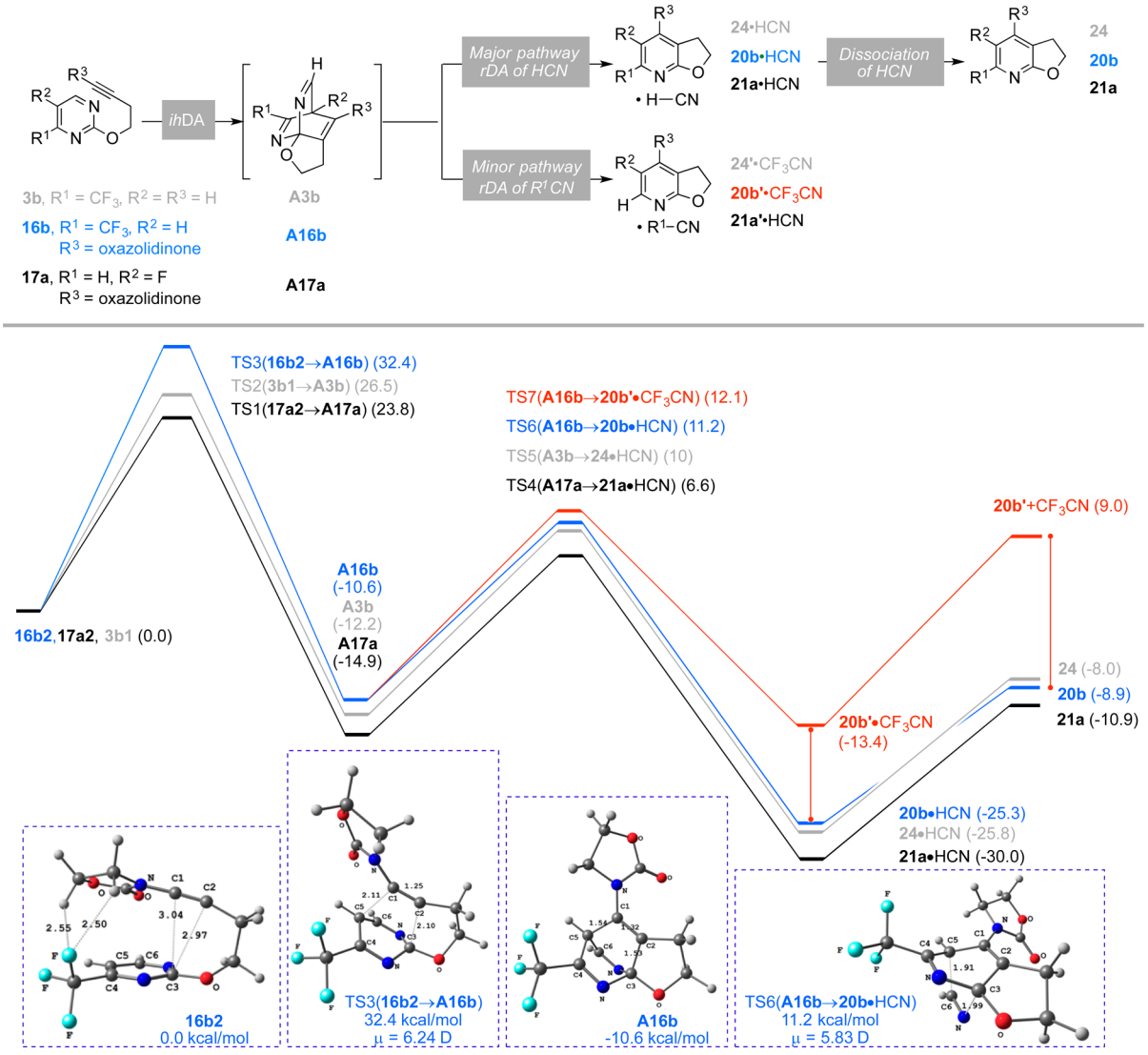


Figure 2. Free energy profile of the *ih*DA/*r*DA of **3b**, **16b**, and **17a**. Note: ΔG_{528} in kcal/mol, in sulfolane at the M06-2X/6-311+G(d,p) level.

EXPERIMENTAL SECTION

General Experimental Methods. NMR spectra were recorded at 300 or 400 MHz for ^{1}H NMR, at 75 or 100 MHz for ^{13}C NMR, and at 376 or 282 MHz for ^{19}F NMR. The spectra were calibrated using undeuterated solvent as an internal reference, unless otherwise indicated. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and b = broad. Coupling constant (*J*) were reported in Hertz. Microwave reactions were performed in a CEM Intelligent Explorer microwave (Model 541416). High-resolution mass spectra (HRMS) in positive mode were recorded using a multimode ion source in mixed mode that enables both electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI). Samples were directly infused into the source using 50/50-methanol/formic acid 0.2% in water. Despite repeated efforts, HMRS could not be secured for **3d**, **5b**, **11**, and **17b**. Melting points were recorded on a melting point apparatus. Tetrahydrofuran (THF) was distilled under nitrogen from sodium-benzophenone. Yields refer to chromatographically and spectroscopically (^{1}H, ^{13}C, and ^{19}F NMR) homogeneous materials, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on TLC silica gel aluminum plates, using UV light or potassium permanganate as visualizing agents. All separations were performed by chromatography on silica gel 60 (40−63 μm), on an automatic purification system on silica gel or by preparative TLC chromatography (layer thickness of 500 μm). Compounds **3a**,[26b] **3b**,**c**,**e**−**h**,[33] **3i**,[26b] **5a**,**c**,**d**,**f**,[33] **5f**,**g**,[26b] **7a**,[26b] **9a**,**b**,**e**,[33] **12**,[33] **13**,[33] **15**,[33] **16b**−**f**,**i**,**k**−**p**,[33] **18c**−**e**,**g**,[33] **19b**−**d**,[33] **20b**−**i**,**k**−**n**,[33] **21a**,**d**−**f**,**i**,[33] **22c**,**d**,**g**,[33] and **23b**−**d**[33] were either reported in our preliminary communication[33] or were prepared using known methods and their identities have been established by comparison of their ^{1}H NMR spectra with the reported data.

General Procedure A. Sodium hydride (1.4 equiv) was suspended in THF (0.3 M) at 0 °C under nitrogen in a round-bottomed flask equipped with a magnetic stirring bar. Homopropargylic alcohol (1.4 equiv) was then added, and the solution was left stirring for 30 min. 2-Chloropyrimidine (1 equiv) was then added dropwise, and a color change from yellow to deep red was observed. Once the addition was complete, the solution was left stirring at room temperature for 17 h until complete consumption of the starting materials as indicated by TLC. The reaction mixture was concentrated in vacuo, quenched with water, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified using flash chromatography on silica gel (petroleum ether/EtOAc = 9:1 to 6:4).

General Procedure B. Sodium hydride (1 equiv) was suspended in THF (0.3 M) at 0 °C under nitrogen in a microwaveable tube equipped with a magnetic stirring bar. Homopropargylic alcohol (1 equiv) was then added, and the solution was left stirring for 30 min. 2-Chloropyrimidine (1 equiv) was added dropwise, and a color change from yellow to deep red was observed. Once the addition was

DOI: 10.1021/acs.joc.6b02986
J. Org. Chem. 2017, 82, 1726−1742

complete, the solution was heated at 130 °C for 3 h. The reaction mixture was concentrated in vacuo, quenched with water, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified using flash chromatography on silica gel (petroleum ether/EtOAc = 9:1 to 6:4).

General Procedure C. In a round-bottomed flask flushed with oxygen and equipped with a magnetic stirrer bar were placed the nitrogen nucleophile (5 equiv), $CuCl_2$ (0.8 equiv), pyridine (0.8 equiv), and Na_2CO_3 (2 equiv). Toluene (0.2 M) was then added via syringe, and the suspension was heated at 70 °C, under an atmosphere of oxygen (balloon). A solution of alkyne (1 equiv) in toluene (0.2 M) was then slowly added to the reaction mixture via syringe pump addition over 4 h, and then stirring was continued at 70 °C until TLC showed complete consumption of alkyne. The reaction mixture was allowed to cool to room temperature, pyridine (50 equiv) was added, and the solution was stirred for 10 more minutes. The reaction mixture was quenched with water, and the aqueous layer was extracted using EtOAc. The combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified using flash chromatography on silica gel (petroleum ether/EtOAc = 7:3 to 1:1).

General Procedure D. In a round-bottomed flask flushed with oxygen and equipped with a magnetic stirrer bar were placed the nitrogen nucleophile (5 equiv), $CuCl_2$ (2 equiv), and Cs_2CO_3 (2 equiv). DMSO (0.2 M) was then added via syringe, and the suspension was heated at 70 °C, under an atmosphere of oxygen (balloon). A solution of alkyne (1 equiv) in DMSO (0.2 M) was then slowly added to the reaction mixture via syringe pump addition over 4 h, and then stirring was continued at 70 °C until TLC showed complete consumption of alkyne. The reaction mixture was allowed to cool to room temperature, pyridine (50 equiv) was added, and the solution was stirred for 10 more minutes. The reaction mixture was quenched with water, and the aqueous layer was extracted using EtOAc. The combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified using flash chromatography on silica gel (petroleum ether/EtOAc = 7:3 to 1:1).

General Procedure E. In a round-bottomed flask equipped with a magnetic stirrer was placed alkyne (1 equiv) dissolved in a mixture of ethanol (0.125 M) and ammonium hydroxide (32%, 0.1 M). The mixture was stirred for few minutes, then CuI (2 equiv) was added, and stirring was allowed to continue until complete consumption of the starting material. The crude green mixture was filtrated over a büchner funnel and washed with an aqueous solution of ammonium hydroxide solution (32%), H_2O, ethanol, and finally Et_2O.

In a 100 mL round-bottomed flask equipped with a magnetic stirrer were placed alkynylcopper (1 equiv) and 2-oxazolidinone (5 equiv). MeCN (0.4 M) was added, and the reaction mixture was allowed to stir under an oxygen atmosphere for few minutes. TMEDA (1 equiv) was finally added, and the mixture was stirred overnight at room temperature under an atmosphere of oxygen. The deep blue crude mixture was concentrated in vacuo and quenched with water. The aqueous phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 7:3 to 1:1).

General Procedures F and G. In a microwaveable tube equipped with a magnetic stirrer bar, ynamide (1 equiv) was dissolved in sulfolane (0.04 M) that had been dried over molecular sieves (4 Å). The tube was sealed, placed in the microwave, and heated at either 210 °C for 30 min (F) or 255 °C for 1 min (G), both with a maximal power of 300 W. After completion of the reaction, the mixture was then quenched with warm (50 °C) saturated aqueous solution of K_2CO_3. The aqueous phase was extracted with methyl *t*-butyl ether. The combined organic phases were washed with warm water (50 °C), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified using flash chromatography on silica gel (petroleum Ether/EtOAc = 4:6 to 2:8).

*2-(2-Ethynylcyclopentyloxy)-4-(trifluoromethyl)pyrimidine (**3d**).* Compound **3d** was obtained using general procedure A and recovered as colorless oil (210 mg, 75%) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (d, J = 5.0 Hz, 1H), 7.26 (d, J = 5.0 Hz, 1H), 5.49−5.45 (m, 1H), 3.07−3.00 (m, 1H), 2.32−2.18 (m, 2H), 2.14 (d, J = 2.6 Hz, 1H), 1.94−1.77 (m, 4H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 165.0; 161.9; 151.8 (q, J = 275.0 Hz); 120.1 (q, J = 37.4 Hz); 110.4 (q, J = 3.6 Hz); 85.3; 84.8; 70.0; 36.7; 31.5; 31.4; 22.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ 70.2.

*2-(2-Ethynylcyclohexyloxy)-5-fluoropyrimidine (**5b**).* Compound **5b** was obtained using general procedure A and recovered as colorless oil (553 mg, 79%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.33 (s, 2H), 5.01 (td, J = 3.6 Hz, 8.1 Hz, 1H), 2.76−2.68 (m, 1H), 2.15−2.05 (m, 2H), 1.99 (d, J = 3.6 Hz, 1H), 1.76−1.69 (m, 2H), 1.60−1.45 (m, 2H), 1.41−1.30 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 161.3; 154.3 (d, J = 154.3 Hz); 146.8 (d, J = 22.4 Hz); 85.3; 77.5; 70.1; 34.0; 29.9; 29.5; 23.7; 23.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ 150.3.

*2-(But-3-ynyloxy)-5-methoxypyrimidine (**5h**).* Compound **5h** was obtained using general procedure A and recovered as a colorless oil (100 mg, 32%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.19 (s, 2H); 4.23 (t, J = 7.2 Hz, 2H); 3.86 (s, 3H); 2.74 (dt, J = 2.7 Hz, 7.2 Hz, 2H); 2.01 (t, J = 2.7 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 159.8; 149.9; 146.0; 80.6; 70.2; 65.6; 56.8; 19.4; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_9H_{11}N_2O_2^+$: 179.0815, found: 179.0817.

*2-(But-3-ynyloxy)-4,6-dimethoxypyrimidine (**7b**).* Compound **7b** was obtained using general procedure A and recovered as colorless oil (570 mg, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.73 (s, 1H), 4.47 (t, J = 7.2 Hz, 2H), 3.93 (s, 6H), 2.73 (td, J = 7.2, 2.6 Hz, 2H), 2.03 (t, J = 2.6 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 173.1; 164.3; 84.1; 80.5; 65.4; 54.4; 19.4; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{10}H_{13}N_2O_3^+$: 209.0921, found: 209.0925.

*2-Chloro-5-fluoro-4-(1-methyl-1H-pyrazol-5-yl)pyrimidine (**8c**).* In a 50 mL round-bottomed flask equipped with a magnetic stirrer bar were dissolved 2,4-dichloro-5-fluoropyrimidine (1 equiv, 401 mg, 2.40 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.1 equiv, 196 mg, 0.24 mmol) in THF (10.8 mL), and then Na_2CO_3 (3 equiv, 764 mg, 7.20 mmol) in water (3.6 mL) is added to the stirring mixture followed by the addition of 1-methyl-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1 equiv, 500 mg, 2.40 mmol). The stirring mixture is refluxed overnight. After the completion of the reaction, the crude is concentrated and dissolved in EtOAc, the organic layer is washed with water, and the aqueous layers are gathered and extracted with EtOAc. The organic layers are combined dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude is finally purified by flash chromatography using petroleum ether/EtOAc gradient from (98:2) to (95:5) as solvent. **8c** was recovered as a white powder (501 mg, 98%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.55 (d, J = 2.1 Hz, 1H); 7.62 (d, J = 2.1 Hz, 1H); 7.04 (dd, J = 2.1 Hz, 4.5 Hz, 1H); 4.35 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 155.3 (d, J = 4.4 Hz); 154.8; 152.2; 148.2 (d, J = 24.9 Hz); 147.0 (d, J = 11.7 Hz); 139.0; 112.3 (d, J = 11.7 Hz); 41.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ 136.27; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_8H_7ClN_4^+$: 213.0338, found: 213.0339.

*2-Chloro-5-fluoro-4-(thiophen-3-yl)pyrimidine (**8d**).* In a 50 mL round-bottomed flask equipped with a magnetic stirrer bar were dissolved 2,4-dichloro-5-fluoropyrimidine (1 equiv, 537 mg, 3.2 mmol) and $Pd(PPh_3)_4$ (0.1 equiv, 310 mg, 0.24 mmol) in MeCN (13.7 mL), and then Na_2CO_3 (3.4 equiv, 972 mg, 9.20 mmol) in water (13.7 mL) is added to the stirring mixture, followed by the addition of 3-thiopheneboronic acid (1 equiv, 300 mg, 2.68 mmol). The stirring mixture is refluxed overnight. After the completion of the reaction, the crude is concentrated and dissolved in AcOEt, the organic layer is washed with water, and the aqueous layers are combined and extracted with EtOAc. The organic layers are combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude is finally purified by flash chromatography using petroleum ether/EtOAc gradient from (98:2) to (95:5) as solvent. **8d** was isolated as a white powder (304 mg, 57%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.48 (d, J = 2.9 Hz, 1H); 8.35 (q, J = 1.3 Hz, 1H); 7.9 (dt, J = 1.3 Hz, 5.04 Hz, 1H), 7.5 (dd, J = 2.9 Hz; 5.3 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz)

DOI: 10.1021/acs.joc.6b02986
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δ 155.5; 152.9; 150.5 (d, J = 11.0 Hz); 148.1 (d, J = 26.4 Hz); 134.1 (d, J = 5.1 Hz); 131.8 (d, J = 10.3 Hz); 127.8 (d, J = 5.9 Hz); 126.9. ^{19}F NMR ($CDCl_3$, 376 MHz) δ 140.09 ppm; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_8H_5ClFN_2S^+$: 214.9846, found: 214.9843.

*2-(But-3-ynyloxy)-5-fluoro-4-(1-methyl-1H-pyrazol-5-yl)-pyrimidine (**9c**).* Compound **7b** was obtained using general procedure A and recovered as a white solid (52 mg, 45%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44 (d, J = 2.5 Hz, 1H); 7.58 (d, J = 2.0 Hz, 1H); 6.97 (dd, 2.5 Hz, 4.3 Hz, 1H); 4.50 (t, J = 7.1 Hz, 2H); 4.34 (s, 3H); 2.75 (dt, 2.0 Hz, 7.3 Hz, 2H); 2.04 (t, 2.5 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 160.4; 152.3, 149.7, 148.2 (d, J = 24.9 Hz); 145.7 (d, J = 11.0 Hz); 138.8; 111.7 (d, J = 12.5 Hz); 80.1; 70.6; 63.3; 41.3; 19.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ 144.6; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{12}H_{12}FN_4O^+$: 247.0995, found: 247.0996.

*Methyl Prop-2-yn-1-yl((4-(trifluoromethyl)pyrimidin-2-yl)oxy)-carbamate (**11**).* To a round-bottomed flask equipped with a magnetic stirring bar, methyl((4-(trifluoromethyl)pyrimidin-2-yl)oxy)-carbamate **10** (1 equiv, 1.06 g, 4.49 mmol) was dissolved in DMF (9 mL) under nitrogen. LiHMDS (1 equiv, 1 M in THF, 4.49 mL, 4.49 mmol) was added at 0 °C, and a color change from yellow to brown was observed. Propargyl bromide (1.2 equiv, 0.581 mL, 5.39 mmol, 80% solution in toluene) was then added dropwise. Once the addition was complete, the solution was left stirring at room temperature until complete consumption of the starting materials as indicated by TLC. The reaction mixture was quenched with water, and the aqueous phase was extracted with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified using flash chromatography on silica gel (petroleum ether/EtOAc: 6:4). **11** was recovered as bright yellow oil (1.04 g, 85%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.87 (d, J = 4.9 Hz, 1 H); 7.46 (d, J = 4.9 Hz, 1 H); 4.57 (bs, 2 H); 3.82 (s, 3 H); 2.7 (t, J = 2.4 Hz, 1 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 166.0; 162.6; 157.8 (q, J = 49.4 Hz); 156.1; 121.6 (q, J = 365.1 Hz); 113.0; 76.3; 73.3; 54.0; 40.6; ^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ −69.96; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{10}H_9F_3N_3O_3^+$: 276.0596, found: 276.0590.

*3-(4-(Pyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**16a**).* Compound **16a** was obtained using general procedure E and recovered as a white solid (700 mg, 62%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (d, J = 4.5 Hz, 2H); 6.96 (t, J = 4.5 Hz, 1H); 4.49 (t, J = 7.0 Hz, 2 H); 4.42 (t, J = 7.9 Hz, 2H); 3.90 (t, J = 7.9 Hz, 2H); 2.87 (t, J = 7.0 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 164.8; 159.3; 159.2; 115.2; 67.2; 65.3; 64.9; 62.9; 46.9; 19.0; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{11}H_{12}N_3O_3^+$: 234.0879, found: 234.0876.

*N-methyl-N-(4-(4-(trifluoromethyl)pyrimidin-2-yloxy)but-1ynyl)-toluenesulfonamide (**16g**).* Compound **16g** was obtained using general procedure E and recovered as a white solid (270 mg, 30%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.80 (d, J = 4.4 Hz, 1H); 7.80 (d, J = 8.4 Hz, 2H); 7.36 (d, J = 8.4 Hz, 2H); 7.31 (d, J = 5.1 Hz, 1H); 4.50 (t, J = 7.1 Hz, 2H); 3.02 (s, 3H); 2.82 (t, J = 7.1 Hz, 2H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 165.4; 162.4; 157.9 (q, J = 36.4 Hz); 145.0; 133.2; 130.0; 128.1; 120.4 (q, J = 274.6 Hz); 110.9 (d, J = 1.8 Hz); 66.7; 65.9; 64.5; 39.4; 21.8; 19.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ 71.2; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{17}F_3N_3O_3S^+$: 400.0943, found: 400.0945.

*N-Methyl-4-nitro-N-(4-(4-(trifluoromethyl)pyrimidin-2-yloxy)but-1-ynyl)benzenesulfonamide (**16h**).* Compound **16h** was obtained using general procedure D and recovered as a white solid (85 mg, 45%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.81 (d, J = 4.8 Hz, 1H); 8.45 (ddd, J = 2.3, 4.3, and 9.2 Hz, 2H); 8.13 (ddd, J = 2.3, 4.4, and 9.3 Hz, 2H); 7.32 (d, J = 4.9 Hz, 1H); 4.50 (t, J = 6.6 Hz, 2H); 3.09 (s, 3H); 2.82 (t, J = 6.5 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 165.5; 162.5; 158.1 (q, J = 35.9 Hz); 151.0; 141.7; 129.5; 124.8; 120.4 (q, J = 275.8 Hz); 111.2 (d, J = 2.0 Hz); 75.6; 66.6; 66.0; 39.7; 19.3; ^{19}F NMR ($CDCl_3$, 376 MHz) δ 71.2; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{16}H_{14}F_3N_4O_5S^+$: 431.0637, found: 431.0638.

*3-((2-(4-(Trifluoromethyl)pyrimidin-2-yloxy)cyclopentyl)ethynyl)-oxazolidin-2-one (**16j**).* Compound **16j** was obtained using general procedure D and recovered as a white solid (47 mg, 38%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (d, J = 4.8 Hz, 1H), 7.26 (d, J = 4.8 Hz, 1H), 5.45 (m, 1H), 4.42 (t, J = 7.8 Hz, 2H), 3.88 (t, J = 7.8 Hz, 2H), 3.14 (m, 1H), 2.31−2.17 (m, 2H), 1.92−1.75 (m, 4H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 165.4; 162.3, 156.1 (q, J = 35.2 Hz); 156.6; 120.5 (q, J = 275.0 Hz); 110.8; 85.2; 77.6; 72.2; 63.1; 47.3; 37.1; 32.2; 31.8; 23.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ 71.1; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{15}F_3N_3O_3^+$: 342.1066, found: 342.1067.

*3-(4-(4-Methoxypyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**16q**).* Compound **16q** was obtained using general procedure D and recovered as a white solid (46 mg, 34%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, J = 5.7 Hz, 1H); 6.38 (d, J = 5.7 Hz); 4.46 (t, J = 7.3 Hz, 2H); 4.42 (dd, J = 7.3 Hz, 8.3 Hz, 2H); 3.96 (s, 3H); 3.88 (dd, J = 6.7 Hz, 8.1 Hz, 2H); 2.85 (t, J = 7.3 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 117.9; 165.0; 158.7; 156.8; 102.7; 71.8; 67.5; 65.7; 65.2; 54.2; 41.2; HRMS-ESI *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{14}N_3O_4$: 264.0984, found: 264.0985.

*3-((2-(5-Fluoropyrimidin-2-yloxy)cyclohexyl)ethynyl)oxazolidin-2-one (**17b**).* Compound **17b** was obtained using general procedure D and recovered as a white solid (97 mg, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.37 (s, 2H), 5.06 (td, J = 3.8 and 8.3 Hz, 1H), 4.37 (t, J = 8.3 Hz, 2H), 3.79 (td, J = 1.5 and 8.3 Hz, 2H), 2.89 (m, 1H), 2.20−2.03 (m, 2H), 1.88−1.66 (m, 2H), 1.66−1.50 (m, 2H), 1.49−1.32 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 161.4, 156.5, 154.4 (d, J = 253.1 Hz); 146.9 (d, J = 22 Hz); 77.6; 72.2; 72.1; 63.0; 47.3; 34.2; 30.2; 29.8; 24.0; 23.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ 150.2.

*3-(4-(5-Bromopyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**17g**).* Compound **17b** was obtained using general procedure D and recovered as a white solid (120 mg, 44%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.55 (s, 2H); 4.46 (t, J = 6.6 Hz, 2H); 4.43 (t, J = 6.6 Hz, 2H); 3.89 (t, J = 7.8 Hz, 2H); 2.85 (t, J = 7.8 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 163.8; 160.0; 156.8; 111.0; 71.9; 67.3; 66.4; 63.2; 47.2; 19.3; HRMS-ESI *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{11}BrN_3O_3$: 311.9984, found: 311.9985.

*2-(4-(2-Oxooxazolidin-3-yl)but-3-ynyloxy)pyrimidine-5-carbonitrile (**17h**).* Compound **17h** was obtained using general procedure D and recovered as a white solid (55 mg, 61%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.77 (s, 2H); 4.53 (t, J = 7.2 Hz, 2H); 4.40 (t, J = 7.2 Hz, 2H); 3.86 (t, J = 6.8 Hz, 2H); 2.84 (t, J = 6.8 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 165.6; 162.8; 156.7; 114.9; 103.3; 72.1; 66.9; 66.6; 63.3; 47.0; 19.1; HRMS-ESI *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{11}N_4O_3$: 259.0831, found: 259.0830.

*3-(4-(5-Methoxypyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**17j**).* Compound **17j** was obtained using general procedure D and recovered as a white solid (115 mg, 39%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (s, 2H); 4.45−439 (m, 4H); 3.89 (t, J = 8.8 Hz, 2H); 3.87 (s, 3H); 2.84 (t, J = 7.1 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 172.3; 165.4; 159.0; 103.1; 72.2; 68.0; 66.1; 63.6; 54.6; 47.6; 19.8; HRMS-ESI *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{14}N_3O_4$: 264.0984, found: 264.0985.

*3-(4-(4,6-Dichloropyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**18a**).* Compound **18a** was obtained using general procedure D and recovered as a white solid (22 mg, 26%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.06 (s, 1H); 4.50 (t, J = 6.0 Hz, 2H); 4.43 (t, J = 7.6 Hz, 2H); 3.89 (t, J = 7.6 Hz, 2H); 2.85 (t, J = 6.0 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 164.3; 163.4; 156.8; 115.1; 72.1; 67.1; 66.9; 63.3; 47.2; 19.3; HRMS-ESI *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}Cl_2N_3O_3$: 302.0099, found: 302.0098.

*3-(4-(4,6-Dimethoxypyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**18b**).* Compound **18b** was obtained using general procedure D and recovered as a white solid (272 mg, 26%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.73 (s, 1H), 4.46 (t, J = 7.5, 2H), 4.42 (t, J = 6.7, 2H), 3.93 (s, 6H), 3.89 (t, J = 7.5, 2H), 2.86 (t, J = 6.7 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 173.1; 164.4; 156.8; 84.1; 71.8; 67.6; 65.7; 63.2; 54.5; 47.2; 30.0; 19.4; HRMS-ESI *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{16}N_3O_5$: 294.1090, found: 294.1092.

*3-(4-(5-Fluoro-4-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yloxy)-but-1-ynyl)oxazolidin-2-one (**18f**).* Compound **18f** was obtained using general procedure D and recovered as a white solid (17 mg, 25%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.45 (s, 1H); 7.58 (d, J = 2.1 Hz, 1H); 7.97 (dd, J = 2.1 and 4.3 Hz, 1H); 4.49 (t, J = 7.2 Hz, 2H); 4.42 (t, J = 7.2 Hz, 2H); 4.33 (s, 3H); 3.89 (t, J = 7.0 Hz, 2H); 2.88 (t, J = 7.0 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 160.5;

DOI: 10.1021/acs.joc.6b02986
J. Org. Chem. 2017, 82, 1726−1742

156.4; 150.7 (d, J = 259.0 Hz); 148.0 (d, J = 26.4 Hz); 145.5 (d, J = 12.5 Hz); 138.5; 132.8 (d, J = 6.6 Hz); 111.4 (d, J = 12.5 Hz); 71.7; 66.9; 66.2; 62.9; 46.8; 41.0; 19.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ 144.63.

*Methyl 3-(2-Oxooxazolidin-3-yl)prop-2-ynyl(4-(trifluoromethyl)-pyrimidin-2-yloxy) carbamate (**19a**).* Compound **19a** was obtained using general procedure D and recovered as a white solid (76 mg, 12%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.87 (d, J = 4.7 Hz, 1H); 7.46 (d, J = 4.7 Hz, 1 H); 4.73 (s, 2 H); 4.43 (t, J = 8.1 Hz, 2 H); 3.89 (t, J = 8.1 Hz, 2 H); 3.81 (s, 3 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 166.1; 162.5; 158.2 (q, J = 37.2 Hz, CH); 156.1; 155.9; 119.8 (q, J = 274.1 Hz, CF_3); 113.0; 74.7; 64.7; 63.0; 54.1; 46.6; 41.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −70.0; HRMS-ESI m/z [M + H]$^+$ calcd for $C_{13}H_{12}F_3N_4O_5$: 361.0760, found: 361.0761.

*3-(3-Fluoro-4b,5,6,7,8,8a-hexahydrobenzofuro[2,3-b]pyridin-4-yl)oxazolidin-2-one (**21b**).* Compound **21b** was obtained using general procedure F and recovered as a white solid (23 mg, 84%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 (s, 1H), 4.57 (quint., J = 3.0 Hz, 2H), 4.3 (bs, 1H), 4.00 (dt, J = 3.0 and 11.9 Hz, 1H), 3.18−3.09 (t, J = 11.9 Hz, 1H), 3.1 (bs, 1H); 2.39−2.21 (m, 2H), 2.0−1.84 (m, 2H), 1.45 (m, 2H); 1.14 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 165.5; 155.3; 146.7; 133.9 (d, J = 41 Hz); 130.6; (d, 69.0 Hz); 129.8; 89.8; 63.0; 48.7; 46.4; 38.2; 30.35; 27.4; 25.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ 147.3; HRMS-ESI m/z [M + H]$^+$ calcd for $C_{14}H_{16}FN_2O_3$: 279.1145, found: 279.1143.

*3-(6-Chloro-2,3-dihydrofuro[2,3-b]pyridin-4-yl)oxazolidin-2-one (**22a**).* Compound **22a** was obtained using general procedure F for 5 min and recovered as a white solid (5 mg, 21%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.81 (s, 1H); 4.67 (t, J = 8.3 Hz, 2H); 4.54 (t, J = 7.2 Hz, 2H); 4.11 (t, J = 8.3 Hz, 2H); 3.37 (t, J = 7.2 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 170.2; 154.2; 149.6; 144.6; 110.1; 107.9; 70.2; 62.6; 46.1; 29.0; HRMS-ESI m/z [M + H]$^+$ calcd for $C_{10}H_{10}ClN_2O_3$: 241.0380, found: 241.0381.

*Methyl 4-(2-Oxo-1,3-oxazolidin-3-yl)-6-(trifluoromethyl)-2H,3H-[1,2]oxazolo[5,4b]pyridine-2-carboxylate (**23a**).* Compound **23a** was obtained using general procedures F and G but at 180 °C for 90 min. NMR yield (21%) was calculated using an internal standard (2-chloro-4-trifluoromethylpyrimidine), and analytical data were obtained after purification by preparative TLC. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18 (s, 1 H); 5.33 (s, 2 H); 4.62 (t, J = 7.6 Hz, 2 H); 4.18 (t, J = 7.6 Hz, 2 H); 3.89 (s, 3 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 166.6; 158.3; 153.7; 147.6 (q, J = 35.0 Hz); 142.9; 121.3 (q, J = 274.1 Hz); 109.5; 106.0 (d, J = 3.0 Hz) ; 62.4; 54.3; 53.7; 45.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −68.0; HRMS-ESI m/z [M + H]$^+$ calcd for $C_{12}H_{11}F_3N_3O_5$: 334.0651, found: 334.0654.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02986.

X-ray crystallographic data for compound **16k** (CCDC 1509490) (CIF)

^{1}H, ^{19}F, and ^{13}C spectra for all new compounds and DFT data for **3b**, **16b**, and **17a** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the Université de Strasbourg, the CNRS, the Université Paris-Sud, the Université Paris-Saclay, and the Région Alsace. We are grateful to Dr. Didier Le Nouën (Université de Haute-Alsace) for his NMR expertise and to Sophie Brogly (Hoffmann-La Roche, Ltd.) for HRMS analysis. V.G. thanks the Institut Universitaire de France (IUF).

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(55) We do not have a clear rationale for the fact that **20b′**·F_3C-CN lies 11.9 kcal/mol above **20b**·HCN.

DOI: 10.1021/acs.joc.6b02986
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