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The Dichotomy of Gold-catalyzed Interplay between Cyanamides and Ynamides: Controllable Switch from [2+2+2] to [4+2] Cycloaddition

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Abstract. The gold-catalyzed interplay between cyanamides and ynamides demonstrates condition-dependent mechanistic dichotomy. [2+2+2] Cycloaddition proceeds under kinetically controlled conditions to give 2,4,6-triaminopyrimidines (19 examples, up to 99%). Under thermodynamically controlled conditions, the reactivity switches from [2+2+2]- to [4+2] cycloaddition; the latter [4+2] reaction accomplishes 1,3-diaminoisoquinolines (19 examples, up to 97%). The advantages of both methods include regioselectivity, mild reaction conditions (even for the thermodynamically controlled [4+2] reaction) and the possibility of introducing a variety of dialkyl, diaryl, and heterocyclic amino substituents into the target pyrimidine and isoquinoline cores. The reactions were conducted on gram scales and the versatility of the obtained products was demonstrated by post-functionalizations.

Keywords: Cycloaddition; Heterocycles; Synthetic methods; Homogeneous catalysis; Gold catalysis

Introduction

Compared to other transition metals, cationic gold species are especially useful for the activation of carbon–carbon triple bonds due to a superior affinity of Au centers toward the C≡C functionality. This affinity is accompanied with expressed kinetic lability of C–Au bonds, thus providing high turnover in Au-catalyzed reactions.[1,2] It is not therefore unusual that gold-based catalysis[3–10] opened up great opportunities for the application of alkynes in the construction of molecular complexity.[11–13]

Among the variety of acetylenic substrates, heteroatom-substituted alkynes occupy a remarkable place.[14–18] In particular, amino-functionalized alkynes, namely ynamides RC≡CN(R′)EWG,[19,20] are privileged substrates in view of high reactivity and controllable regioselectivity of their transformations.[21] Also a pivotal advantage of using ynamides as synthetic building blocks is the ability to introduce useful nitrogen-containing fragments into target molecules.[22] Often such desired synthetic goals are azaheterocycles, including amino-substituted systems, which often serve as important components of natural products and synthetic pharmaceuticals.[23,24] Notably the chemistry of ynamides is relevant to the chemistry of isomeric allenamides, also actively studied especially in recent years.[25,26]

Taking all of the above into account, it is hardly unexpected that a plethora of ynamide-based synthetic approaches to amino-substituted azaheterocycles have been developed in the past decade.[27–34] An interesting example of such transformations is the atom- economic synthesis of 4-aminopyrimidines via gold-catalyzed intermolecular formal [2+2+2] cycloaddition of *two discrete nitriles* to internal ynamides developed by Liu and co-workers (Scheme 1*a*).[35] Later, the same group showed that the structure of the ynamide substrate dramatically affects the direction of the gold-catalyzed reaction. In contrast to internal ynamides, Au-catalyzed intermolecular [2+2+2] cycloaddition of one nitrile to *two discrete terminal ynamides* leads to the generation of 2,4-diaminopyridine core (Scheme 1*b*).[36]

Inspired by these contrasting results achieved for two types of alkyne substrates, we hypothesized that a change in the essence of the nitrile component could have a significant effect on the direction of the interaction between nitriles and ynamides. In accord with this idea, we decided to study quite specific nitrile species, viz. cyanamides, as reaction partners for ynamides under gold-catalyzed conditions. The chemistry of cyanamides (belonging to a family of the so-called push-pull nitriles) is in many respects different from the chemistry of the conventional nitriles RCN (R = Alk, Ar) due to the dual nature of the cyanamide N–C≡N moiety featuring both nucleo-

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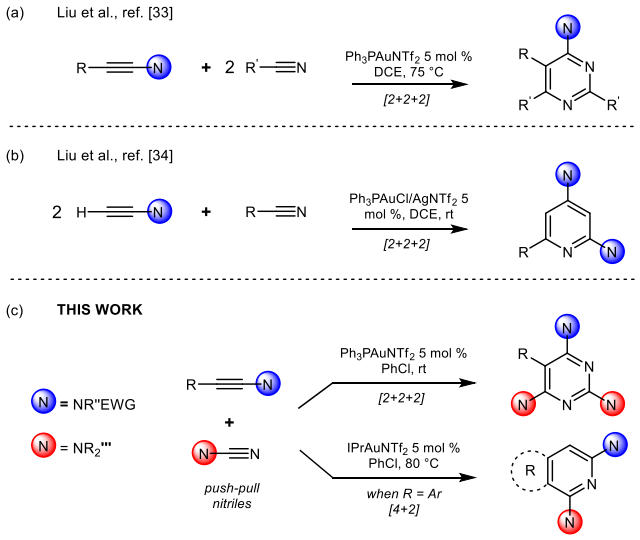


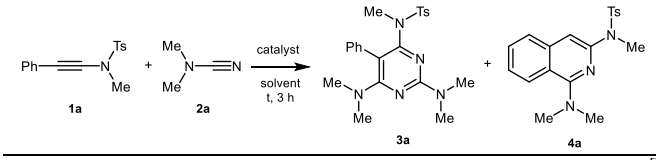
Scheme 1. Divergence in Au-catalyzed cycloaddition of nitrile species to ynamides.

philic and electrophilic nitrogen atoms.[37] Also the presence of amino groups in both ynamides and cyanamides allows the facile one-step introduction of some useful functional amino-based substituents into target molecules.[38,39] Herein we report on the dichotomy in gold-catalyzed interplay between cyanamides and ynamides. In addition to the known [2+2+2] reaction, we observed a new type of Au-catalyzed cycloaddition, namely [4+2] integration (Scheme 1*c*); the direction of the reaction can be easily switched by applying appropriate kinetic or thermodynamic controlled conditions.

Results and Discussion

We began our studies by exploring the reactivity of ynamide **1a** toward dimethylcyanamide (**2a**) using 5 mol % of the gold-containing Gagosz catalyst, $Ph_3PAuNTf_2$[40] (Table 1, entry 1). Surprisingly, in addition to 2,4,6-triaminopyrimidine **3a** (the structure was confirmed by X-ray crystallography)[41] derived from the 3-component [2+2+2] cycloaddition of **1a** and two molecules of **2a**, we obtained 1,3-diaminoisoquinoline **4a** that originates from the 2-component [4+2] cycloaddition. The yields of **3a** and **4a** were significantly increased when we employed the more thermally stable gold(I) NHC-complex $IPrAuNTf_2$[42] (entry 2). On the contrary, application of the gold(III) complex $PicAuCl_2$ gave poorer results (entry 3). Often, gold cationic species generated in situ from the gold chloride complexes and silver salts exhibit different reactivity compared to the corresponding well-defined catalysts.[43] Therefore we tested the IPrAuCl-based systems after the halide abstraction with AgOTf, $AgNTf_2$, or $AgBF_4$ in DCE, and again pyrimidine **3a** was obtained as a major product (entries 4–6). Control experiments indicated that the silver salts (AgOTf and $AgNTf_2$) alone do not catalyze the studied reactions (entry 7). Solvent replacement (toluene, PhCl, THF) has almost no effect on product ratios (entries 8–10).

Table 1. Optimization of the synthesis of 3a and 4a.[a]



Entry	Catalyst, 5 mol %	Solvent	**2a**, equiv	t, °C	Yields, %[b] **3a**	**4a**
1	$Ph_3PAuNTf_2$	DCE	5	60	31	21
2	$IPrAuNTf_2$	DCE	5	60	46	48
3	$PicAuCl_2$	DCE	5	60	13	4
4	IPrAuCl/ AgOTf	DCE	5	60	50	43
5	IPrAuCl/ $AgNTf_2$	DCE	5	60	60	33
6	IPrAuCl/ $AgBF_4$	DCE	5	60	25	10
7	AgOTf or $AgNTf_2$	DCE	5	60	–	–
8	IPrAuCl/ $AgNTf_2$	PhMe	5	60	56	36
9	IPrAuCl/ $AgNTf_2$	PhCl	5	60	61	38
10	IPrAuCl/ $AgNTf_2$	THF	5	60	59	35
11	$IPrAuNTf_2$	PhCl	5	80	35	56
12[c]	**$IPrAuNTf_2$**	**PhCl**	**1.5**	**80**	13	**81**
13[c]	$Ph_3PAuNTf_2$	PhCl	1.5	80	10	53
14	$IPrAuNTf_2$	PhCl	5	40	52	41
15	$IPrAuNTf_2$	PhCl	5	**RT**	63	26
16[d]	**$Ph_3PAuNTf_2$**	**PhCl**	**5**	**RT**	**76**	18
17[d]	$Ph_3PAuNTf_2$	PhCl	5	0	58	14
18[d]	$Ph_3PAuNTf_2$	PhCl	4	RT	73	22
19[d]	$Ph_3PAuNTf_2$	PhCl	2	RT	42	29
20[d]	$Ph_3PAuNTf_2$	PhCl	10	RT	63	15

[a] All reactions were carried out on a 0.1 mmol scale (0.2 M). [b] Estimated by ^{1}H NMR spectroscopy using durene as an internal standard. [c] **2a** was introduced into the reaction mixture slowly using a syringe pump. [d] 24 h.

Further experiments showed that the reaction temperature and a ratio between the reactants are key factors determining the type of the Au^I-catalyzed heterocyclization. Thus, under the thermodynamically controlled conditions (80 °C; 1.5 equivalents of **2a** was added for 3 h to the reaction mixture using a syringe pump), we increased the yield of isoquinoline **4a** to 81% (entry 12). At the same time, kinetic control leads to an increase in the proportion of the pyrimidine over the isoquinoline. When the reaction was conducted at room temperature using 5 equivalents of the cyanamide (the Gagosz catalyst was the most efficient in this case), the yield of **3a** was 76% (entry 16). A further decrease of the reaction temperature to 0 °C suppresses both processes (entry 15). A decrease in the amount of **2a** slows down the pyrimidine formation (entries 18–19). It is noteworthy that an

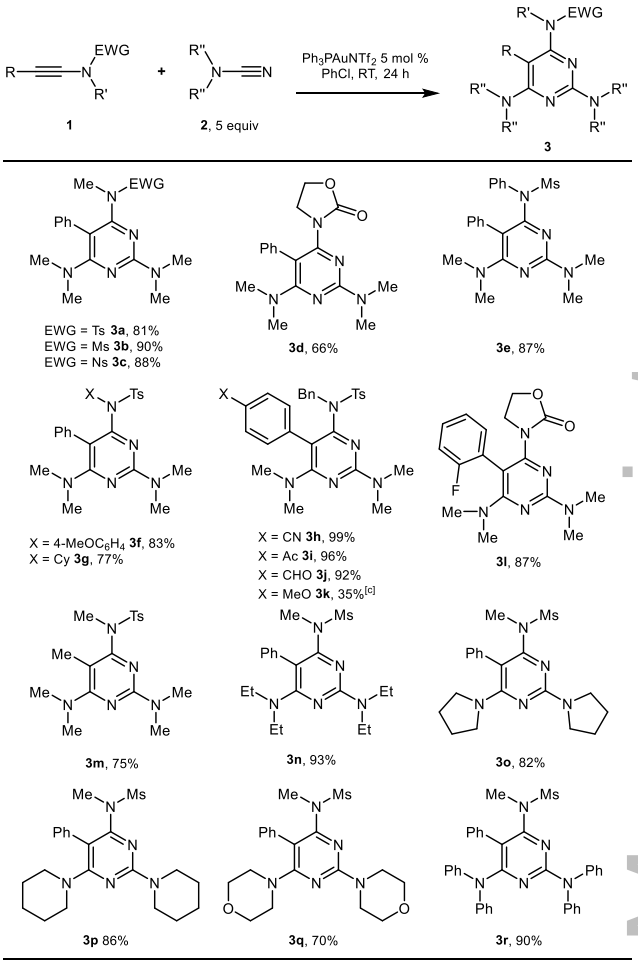
increase in the amount of the cyanamide to 10 equivalents also negatively affects the reaction (entry 20); this is probably because of the coordination of **2a** to gold(I).

The effect of temperature on the ratio of products was explicitly verified when the same gold catalyst ($IPrAuNTf_2$) is used for both cycloadditions. Along with a stepwise decrease in reaction temperature from 80 °C to RT, the yield of the pyrimidine decreased, and the yield of the isoquinoline increased (Entries 11, 2, 13, and 14). Predictably, the nature of the catalyst is also important, but it turned out that its variation is not crucial. In particular, $Ph_3PAuNTf_2$ works better than $IPrAuNTf_2$ in the synthesis of the pyrimidine at RT (Entries 15 and 16). However, in the synthesis of both heterocyclic systems conducted at 60–80 °C, $Ph_3PAuNTf_2$ is less catalytically active than $IPrAuNTf_2$. The low efficiency of $Ph_3PAuNTf_2$ at elevated temperatures was also demonstrated in our previous work.[44] Summing up the optimization experiments, we found that upon the reaction of ynamide **1** and dimethylcyanamide catalyzed by the gold complexes, either [2+2+2], or [4+2] heterocyclization occurred selectively, depending on kinetic or thermodynamic control, correspondingly.

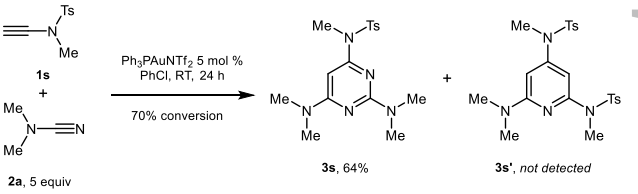
With the optimal conditions at hand, the substrate scope and limitations for the synthesis of 2,4,6-triaminopyrimidines **3** were examined (Table 2). First, we tested numerous ynamides **1** in their reaction with dimethylcyanamide. The reaction proceeds smoothly with various electron-withdrawing *N*-sulfonyl substituents (Ts, Ms, Ns, **3a**–**c**). Alkyne **1d** bearing a cyclic carbamate substituent can also be used in the heterocyclization. Ynamides featuring both alkyl and aryl groups at NR′EWG all delivered the corresponding pyrimidines in good yields (**3e**–**g**). The reaction conditions were applicable to the ynamides with diverse R-substituents (Ar, Alk). Pyrimidines containing electron-deficient aromatic substituents in the 5-position were obtained in excellent yields (**3h**–**k**). On the contrary, when the electron-rich *p*-MeO-phenyl substituted ynamide was used, the yield of pyrimidine **3l** was only 35%. In this case, the prevailing process was the [4+2] cycloaddition to grant corresponding isoquinoline **4**. Then, a number of cyanamides have been tested in the [2+2+2] heterocyclization. The found conditions were effective for introducing into the pyrimidine core a substantial diversity of amino groups, including five- and six- heterocyclic fragments (**3o**–**q**) or even two bulky diphenylamino substituents (**3r**).

We also tested terminal ynamide **1s** as a substrate (Scheme 2). Unexpectedly, by contrast to the Liu et al.[36] results for the cycloaddition involving conventional nitriles (Scheme 1*b*), pyrimidine **3s** was obtained selectively in the reaction with the cyanamide and generation of pyridine **3s′** was not observed. Probably, the cycloaddition of two cyanamides to one ynamide is preferable due to the greater nucleophilicity of cyanamides in comparison with that of conventional nitriles.

Table 2. Scope for the synthesis of 2,4,6-triaminopyrimidines **3**.[a,b]



[a] All reactions were carried out on a 0.2 mmol scale (0.2 *M*). [b] Isolated yield. [c] The corresponding isoquinoline was the major reaction product.

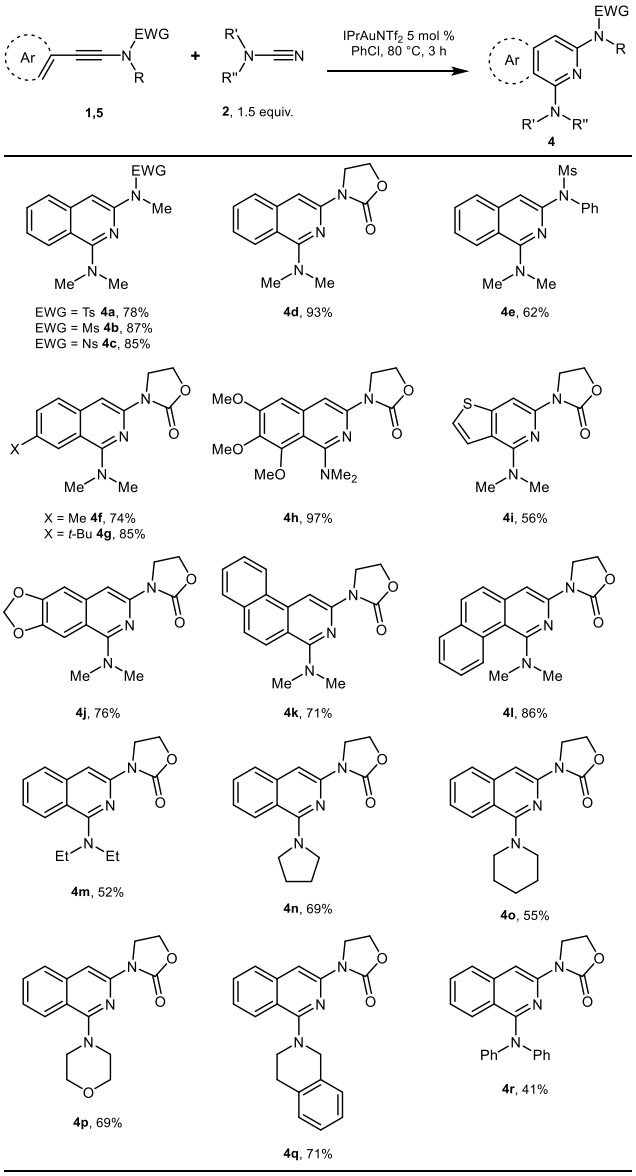


Scheme 2. The heterocyclization of terminal ynamide **1r**.

After the successful synthesis of pyrimidines, we studied the [4+2] gold-catalyzed heterocyclization to achieve 1,3-diaminoisoquinolines **4** (Table 3). Various *N*-sulfonyl groups tolerate the reaction conditions (**4a**–**c**), and in the case of the oxazolidin-2-one substituent, the yield of isoquinoline reached 93% (**4d**). The key factor determining the occurrence of [4+2] heterocyclization is the electronic parameters of the aromatic fragment Ar in ArC≡CN(R)EWG. Thus, in the presence of even weak electron-withdrawing groups (e.g., halogens) in the Ar-substituent, the [4+2] products were not detected, while the corresponding [2+2+2] adducts

were formed selectively. On the other hand, isoquinolines can be smoothly obtained by introducing electron-donating alkyl substituents into the aromatic rings of the starting ynamides (**4f**,**g**). For example, isoquinoline **4h** bearing three MeO-substituents was obtained in almost quantitative yield. The thermodynamically controlled [4+2] heterocyclization has been successfully applied for syntheses of difficult-to-obtain thieno[3,2-*c*]pyridine **4i** and polycyclic azaheterocycles **4j–l**. The structure of isoquinoline **4k** was confirmed by X-ray crystallography.[41] Variation of cyanamides allows the generation of heterocycles **4m–r** bearing various amino-functionalities, including pyrrolidine, pyrimidine, morpholine, isoquinoline fragments, in the 1-position of isoquinoline core.

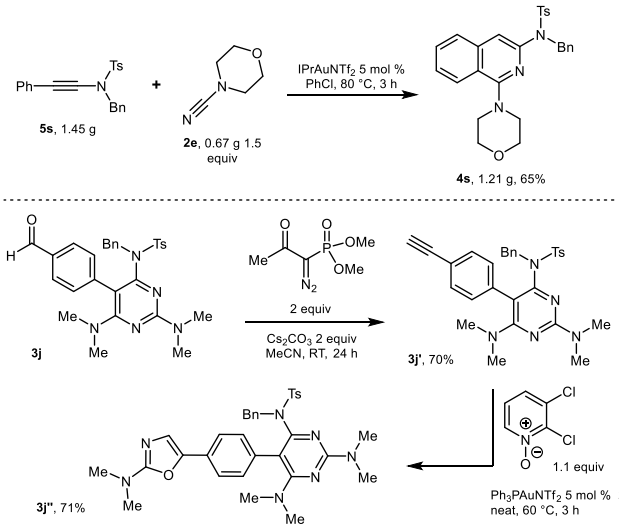
Table 3. Scope for the synthesis of 1,3-diaminoisoquinolines **4**.[a,b]



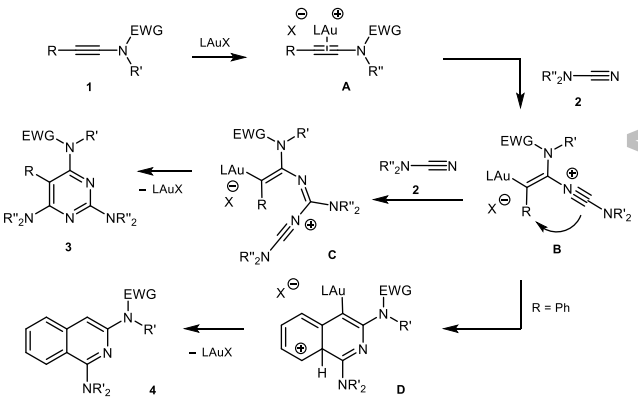
[a] All reactions were carried out on a 0.2 mmol scale (0.2 *M*). [b] Isolated yield.

Given the value of 2,4,6-triaminopyrimidine[45–48] and 1,3-diaminoisoquinoline[49–51] motifs (e.g. the commercial pyrimidine drug *Minoxidil*[52]), we were eager to demonstrate the utility of our synthetic approaches. First, the gram-scale reaction between **5s** and **2e** gave isoquinoline **4s** in 65% yield (Scheme 3, top). Second, the high synthetic potential of the obtained heterocycles was exemplified by the post-functionalizations of pyrimidine **3j** (Scheme 3, bottom). The aldehyde fragment of **3j** could be converted to an alkynyl group under the action of the Ohira–Bestmann reagent. The obtained alkyne **3j′** was further involved in the [2+2+1] gold-catalyzed synthesis[53] of oxazole **3j″** upon treatment with dimethylcyanamide and 2,3-dichloropyridine *N*-oxide.[54]

Plausible mechanisms of the gold-catalyzed reactions are given in Scheme 4. First, coordination of the cationic gold to the ynamide triple bond gives an alkyne complex (**A**), whereupon the cyanamide attacks **A** to give adduct **B**. In turn, two reactionary possibilities for intermediate **B** could be assumed.



Scheme 3. Gram-scale synthesis of **4s** and important transformations of **3j**.



Scheme 4. A plausible mechanism for generation of **3** and **4**.

This adduct may be attacked by another cyanamide followed by cyclization to pyrimidine **3** accompanied with the regeneration of the catalyst. The second possibility is a Friedel–Crafts-like cyclization of **B**, with further aromatization/protodeauration of **D** to isoquinoline **4**.

Conclusion

Summarizing, we observed the reaction dichotomy in the gold-catalyzed cycloaddition of cyanamides to ynamides. The direction of the cycloaddition can be easily switched from [2+2+2]- to [4+2] routes by conductance the reaction under either kinetic, or thermodynamic control and tuning the gold catalyst. The developed methods operate under mild conditions (even for the thermodynamically controlled [4+2] reaction), utilize easily available substrates, and open up a convenient atom-economical route to two families of valuable azaheterocycles, containing the 2,4,6-triaminoyrimidine and 1,3-diaminoisoquinoline motifs.

Experimental Section

General Procedure for the Synthesis of Pyrimidines 3

$Ph_3PAuNTf_2$ (7.4 mg, 10.0 μmol, 5 mol %) was added to the solution of ynamide (**1**, 0.2 mmol) and cyanamide (**2**, 1.0 mmol, 5.0 equiv) in PhCl (0.5 mL). The resulting solution was stirred at RT for 24 h. Then all volatile components were removed *in vacuo* and the residue was purified by silica gel chromatography eluting with hexane/EtOAc to afford pyrimidines **3**.

***N*-(2,6-Bis(dimethylamino)-5-phenylpyrimidin-4-yl)-*N*,4-dimethylbenzenesulfonamide (3a)**: white solid (68.9 mg, 81%); mp 202.3–204.2 °C (hexane/ethyl acetate); R_f 0.40 (hexane/ethyl acetate 6:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.3 Hz, 2H, Ar), 7.43–7.36 (m, 4H, Ph), 7.29–7.26 (m, 1H, Ph), 7.24 (d, J = 8.0 Hz, 2H, Ar), 3.00 (s, 6H, NMe_2), 2.72 (s, 6H, NMe_2), 2.64 (s, 3H, NMe), 2.41 (s, 3H, Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.1, 160.2, 160.0, 142.8, 136.8 (×2), 131.0, 129.0, 128.9, 128.2, 126.7, 107.3, 40.6, 37.0, 36.8, 21.6; **IR** (KBr, pellet): $\tilde{\nu}$ 2924, 1577, 1348, 1153, 990, 812 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{22}H_{28}N_5O_2S^+$: 426.1958; found: 426.1970.

***N*-(2,6-Bis(dimethylamino)-5-phenylpyrimidin-4-yl)-*N*-methylmethanesulfonamide (3b)**: white solid (62.9 mg, 90%); mp 126.3–127.4 °C (hexane/ethyl acetate); R_f 0.30 (hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 4H, Ph), 7.23 (t, J = 6.8 Hz, 1H, Ph), 3.19 (s, 3H, MeS), 3.13 (s, 6H, NMe_2), 2.70 (s, 6H, NMe_2), 2.69 (s, 3H, NMe); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.9, 160.2 (×2), 136.4, 130.8, 128.1, 126.6, 106.3, 40.5, 38.4, 36.90, 36.88; **IR** (KBr, pellet): $\tilde{\nu}$ 3434, 1582, 1511, 1389, 1335, 1146, 960, 707 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{16}H_{24}N_5O_2S^+$: 350.1645; found: 350.1649.

***N*-(2,6-Bis(dimethylamino)-5-phenylpyrimidin-4-yl)-*N*-methyl-4-nitrobenzenesulfonamide (3c)**: yellow solid (80.3 mg, 88%); mp 188.2–190.0 °C (hexane/ethyl acetate); R_f 0.45 (hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.9 Hz, 2H, Ar), 8.14 (d, J = 8.9 Hz, 2H, Ar), 7.40 (d, J = 4.4 Hz, 4H, Ar), 7.34–7.29 (m, 1H, Ar), 2.97 (s, 6H, NMe_2), 2.74 (s, 6H, NMe_2), 2.71 (s, 3H, NMe); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.8, 159.9, 149.9, 145.6, 136.2, 130.9, 130.2, 128.4, 127.1, 124.2, 123.6, 107.3, 40.7, 37.3, 36.8; **IR** (KBr, pellet): $\tilde{\nu}$ 1597, 1526, 1395, 1348, 1149, 741 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{21}H_{25}N_6O_4S^+$: 457.1653; found: 457.1651.

3-(2,6-Bis(dimethylamino)-5-phenylpyrimidin-4-yl)oxazolidin-2-one (3d): white solid (43.2 mg, 66%); mp 139.2–141.0 °C (hexane/ethyl acetate); R_f 0.30 (hexane/ethyl acetate 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.29 (m, 4H, Ph), 7.27–7.23 (m, 1H, Ph), 4.17–4.13 (m, 2H, CH_2), 3.62–3.58 (m, 2H, CH_2), 3.15 (s, 6H, NMe_2), 2.72 (s, 6H, NMe_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.6, 160.2, 157.1, 155.8, 136.8, 130.4, 128.3, 127.0, 106.3, 62.7, 46.3, 40.6, 37.1; **IR** (KBr, pellet): $\tilde{\nu}$ 3420, 2925, 2854, 1760, 1551, 1389, 1193, 703 cm^{-1}; **HRMS** (ESI): *m/z* [M + Na]$^+$ calcd. for $C_{17}H_{21}N_5NaO_2^+$: 350.1593; found: 350.1593.

***N*-(2,6-Bis(dimethylamino)-5-phenylpyrimidin-4-yl)-*N*-phenylmethanesulfonamide (3e)**: white solid (71.6 mg, 87%); mp 140.1–141.8 °C (hexane/ethyl acetate); R_f 0.50 (hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19–7.17 (m, 3H, Ph), 7.11–7.00 (m, 5H, Ph), 6.93–6.90 (m, 2H, Ph), 3.30 (s, 3H, MeS), 3.22 (s, 6H, NMe_2), 2.68 (s, 6H, NMe_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.6, 160.0, 159.9, 139.6, 136.4, 131.3, 128.4, 127.9, 127.7, 127.1, 126.6, 106.8, 40.7, 40.0, 37.2; **IR** (KBr, pellet): $\tilde{\nu}$ 1571, 1513, 1380, 1350, 1156, 709 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{21}H_{25}N_5O_2S^+$: 412.1802; found: 412.1807.

***N*-(2,6-Bis(dimethylamino)-5-phenylpyrimidin-4-yl)-*N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide (3f)**: yellowish solid (85.9 mg, 83%); mp 167.3–168.4 °C (hexane/ethyl acetate); R_f 0.30 (hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.3 Hz, 2H, Ar), 7.29–7.18 (m, 5H, Ph), 7.11 (d, J = 8.1 Hz, 2H, Ar), 6.59 (d, J = 9.0 Hz, 2H, Ar), 6.47 (d, J = 9.0 Hz, 2H, Ar), 3.66 (s, 3H, OMe), 3.02 (s, 6H, NMe_2), 2.66 (s, 6H, NMe_2), 2.35 (s, 3H, Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.7, 160.1, 160.0, 158.7, 142.7, 137.6, 136.8, 132.0, 131.5 130.1, 129.3, 128.6, 128.1, 126.7, 113.3, 107.6, 55.4, 40.7, 37.0, 21.7; **IR** (KBr, pellet): $\tilde{\nu}$ 1580, 1504, 1386, 1347, 1164, 703 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{28}H_{32}N_5O_3S^+$: 518.2220; found: 518.2209.

***N*-(2,6-Bis(dimethylamino)-5-phenylpyrimidin-4-yl)-*N*-cyclohexyl-4-methylbenzenesulfonamide (3g)**: white solid (76.0 mg, 77%); mp 220.0–222.0 °C (hexane/ethyl acetate); R_f 0.50 (hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.3 Hz, 2H, Ar), 7.71–7.21 (m, 5H, Ph), 7.23 (d, J = 8.1 Hz, 2H, Ar), 3.33–3.26 (m, 1H, CH), 3.06 (s, 6H, NMe_2), 2.71 (s, 6H, NMe_2), 2.42 (s, 3H, Me), 1.59–1.14 (m, 7H, $3CH_2$+CH), 0.93–0.88 (m, 2H, CH_2), 0.76–0.70 (m, 1H, CH), **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.9, 159.6, 156.8, 142.7, 139.0, 137.3, 131.7, 129.3, 128.8, 128.0, 126.6, 110.6, 61.0, 40.8, 36.9, 26.4 (×2), 25.4, 21.7; **IR** (KBr, pellet): $\tilde{\nu}$ 3422, 2930, 2851, 1573, 1387, 1339, 1160, 1089, 1014, 709, 687, 655, 569 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{27}H_{36}N_5O_2S^+$: 494.2590; found: 494.2590.

***N*-Benzyl-*N*-(5-(4-cyanophenyl)-2,6-bis(dimethylamino)pyrimidin-4-yl)-4-methylbenzenesulfonamide (3h)**: white solid (104.3 mg, 99%); mp 202.1–203.5 °C (hexane/ethyl acetate); R_f 0.30 (hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2H, Ar), 7.39 (d, J = 8.0 Hz, 2H, Ar), 7.28 (d, J = 8.0 Hz, 2H, Ar), 7.12–6.96 (m, 5H, Ar), 6.70 (d, J = 7.2 Hz, 2H, Ar), 4.27 (s, 2H, CH_2), 3.01 (s, 6H, NMe_2), 2.61 (s, 6H, NMe_2), 2.44 (s, 3H, Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.0, 160.1, 157.9, 143.5, 142.0, 135.9, 134.5, 131.7, 131.3, 129.5, 129.4, 129.0, 128.1, 127.5, 119.5, 109.3, 108.0, 54.2, 40.7, 36.7, 21.7; **IR** (KBr, pellet): $\tilde{\nu}$ 3400, 2924, 2224, 1571, 1384, 1335, 1158, 1089 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{29}H_{31}N_6O_2S^+$: 527.2224; found: 527.2240.

***N*-(5-(4-Acetylphenyl)-2,6-bis(dimethylamino)pyrimidin-4-yl)-*N*-benzyl-4-methylbenzenesulfonamide (3i)**: yellowish solid (104.4 mg, 96%); mp 182.0–184.0 °C (hexane/ethyl acetate); R_f 0.40 (hexane/ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.2 Hz, 2H, Ar), 7.75 (d, J = 7.8 Hz, 2H, Ar), 7.26 (d, J = 8.1 Hz, 2H, Ar), 7.11–7.07 (m, 3H, Ar), 6.94 (t, J = 7.5 Hz, 2H, Ar), 6.71 (d, J = 7.1 Hz, 2H, Ar), 4.27 (s, 2H, CH_2), 3.02 (s, 6H, NMe_2), 2.63 (s, 3H, Me), 2.62 (s, 6H, NMe_2), 2.43 (s, 3H, Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.2, 165.2, 160.1, 158.0, 143.3, 142.3, 136.3, 134.7, 131.4, 129.5 (×2), 128.9, 128.1, 127.7, 127.4, 108.6, 54.1, 40.6, 36.7, 26.8, 21.7 (one carbon merged with others); **IR** (KBr, pellet): $\tilde{\nu}$ 2920, 2872, 1678, 1578, 1389, 1342, 1268, 1161 cm^{-1}; **HRMS** (ESI): *m/z* [M + Na]$^+$ calcd. for $C_{30}H_{33}N_5NaO_3S^+$: 566.2202; found: 566.2218.

***N*-Benzyl-*N*-(2,6-bis(dimethylamino)-5-(4-formylphenyl)pyrimidin-4-yl)-4-methylbenzenesulfonamide (3j)**: yellowish solid (97.5 mg, 92%); mp 207.2–208.5 °C (hexane/ethyl acetate); R_f 0.50 (hexane/ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.00 (s, 1H, CHO), 7.79 (d, J = 8.4 Hz, 2H, Ar), 7.65 (d, J = 8.4 Hz, 2H, Ar), 7.27 (d, J = 8.1 Hz, 2H, Ar), 7.10–7.06 (br. m, 3H, Ar), 6.93 (t, J = 7.6 Hz, 2H, Ar), 6.70 (d, J = 7.2 Hz, 2H, Ar), 4.27 (s, 2H, CH_2), 3.02 (s, 6H, NMe_2), 2.61 (s, 6H, NMe_2), 2.43 (s, 3H, Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 192.4, 165.1, 160.1, 158.0, 143.8, 143.4, 136.1, 134.6, 134.0, 131.7, 129.5, 129.4, 129.0, 128.9, 128.1, 127.4, 108.4, 54.1, 40.6, 36.7, 21.7; **IR** (KBr, pellet): $\tilde{\nu}$ 2923, 1730, 1577, 1386, 1331, 1158, 1091 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{29}H_{32}N_5O_3S^+$: 530.2220; found: 530.2232.

***N*-Benzyl-*N*-(2,6-bis(dimethylamino)-5-(4-methoxyphenyl)pyrimidin-4-yl)-4-methylbenzenesulfonami-de (3k)**: white solid (37.2 mg, 35%); mp 177.7–179.0 °C (hexane/ethyl acetate); R_f 0.40 (hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.9 Hz, 2H, Ar), 7.23 (d, J = 8.0 Hz, 2H, Ar), 7.09 (t, J = 7.4 Hz, 1H, Ar), 7.00 (t, J = 7.5 Hz, 2H, Ar), 6.89–6.73 (m, 6H, Ar), 4.28 (s, 2H, CH_2), 3.84 (s, 3H, OMe), 3.03 (s, 6H, NMe_2), 2.65 (s, 6H, NMe_2), 2.42 (s, 3H, Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.4, 159.6, 158.2, 158.0, 143.1, 136.8, 135.1, 132.4, 129.5, 129.4, 128.9, 128.6, 127.9, 127.2, 113.2, 109.3, 55.3, 53.9, 40.6, 36.8, 21.7; **IR** (KBr, pellet): $\tilde{\nu}$ 3448, 2925, 1580, 1499, 1388, 1339, 1238, 1162, 1089, 1031 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{29}H_{34}N_5O_3S^+$: 532.2377; found: 532.2389.

3-(2,6-Bis(dimethylamino)-5-(2-fluorophenyl)pyrimidin-4-yl)oxazolidin-2-one (3l): colorless oil (60.1 mg, 87%); R_f 0.35 (hexane/ethyl acetate 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (td, J = 7.6, 1.8 Hz, 1H, Ar), 7.32–7.27 (m, 1H, Ar), 7.14 (d, J = 7.5, 1.3 Hz, 1H, Ar), 7.05 (t, J = 8.9 Hz, 1H, Ar), 4.29–3.56 (br. m, 4H, $2CH_2$), 3.19 (s, 6H, NMe_2), 2.79 (s, 6H, NMe_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.0, 161.5, 159.1, 156.2, 133.3 (d, J_F = 2.7 Hz), 129.6 (d, J_F = 8.1 Hz), 124.2 (d, J_F = 3.7 Hz), 123.9, 123.8, 115.2 (d, J_F = 22.3 Hz), 99.6, 63.0, 46.1, 40.4, 37.3; **IR** (KBr, pellet): $\tilde{\nu}$ 2922, 2261, 1766, 1583, 1512, 1389, 1212, 1032, 756 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{17}H_{21}FN_5O_2^+$: 346.1674; found: 346.1670.

***N*-(2,6-Bis(dimethylamino)-5-methylpyrimidin-4-yl)-*N*,4-dimethylbenzenesulfonamide (3m)**: yellow solid (54.5 mg, 75%); R_f 0.40 (hexane/ethyl acetate 4:1); mp 89.7–91.5 °C (hexane/ethyl acetate); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.2 Hz, 2H, Ar), 7.24 (d, J = 8.1 Hz, 2H, Ar), 3.00 (s, 6H, NMe_2), 2.98 (s, 3H, Me), 2.91 (s, 6H, NMe_2), 2.40 (s, 3H, Me), 2.24 (s, 3H, Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.2, 160.5, 159.4, 143.1, 135.2, 129.0, 128.7, 102.6, 40.6, 36.6 (×2), 21.6, 15.2; **IR** (KBr, pellet): $\tilde{\nu}$ 3445, 2925, 2859, 1585, 1388, 1341, 1152, 1047, 1020 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{17}H_{26}N_5O_2S^+$: 364.1802; found: 364.1802.

***N*-(2,6-Bis(diethylamino)-5-phenylpyrimidin-4-yl)-*N*-methylmethanesulfonamide (3n)**: white solid (75.4 mg, 93%); mp 130.4–131.9 °C (hexane/ethyl acetate); R_f 0.30 (hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.31 (m, 4H, Ph), 7.27–7.23 (m, 1H, Ph), 3.57 (q, J = 7.0 Hz, 4H, $2CH_2$), 3.17 (s, 3H, MeS), 3.15 (q, J = 7.1 Hz, 4H, $2CH_2$), 2.69 (s, 3H, NMe), 1.20 (t, J = 7.0 Hz, 6H, 2Me) 0.92 (t, J = 7.0 Hz, 6H, 2Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.1, 160.4, 159.2, 136.8, 130.8, 128.2, 126.8, 106.7, 43.9, 42.1, 38.1, 37.0, 13.6, 13.1; **IR** (KBr, pellet): $\tilde{\nu}$ 3441, 2970, 1584, 1536, 1332, 1149, 972, 701 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{20}H_{32}N_5O_2S^+$: 406.2271; found: 406.2285.

***N*-Methyl-*N*-(5-phenyl-2,6-di(pyrrolidin-1-yl)pyrimidin-4-yl)methanesulfonamide (3o)**: white solid (65.9 mg, 82%); mp 169.5–170.5 °C (hexane/ethyl acetate); R_f 0.45 (hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 4H, Ph), 7.26–7.23 (m, 1H, Ph), 3.54 (br. s, 4H, $2CH_2N$), 3.23 (s, 3H, MeS), 3.10 (br. s, 4H, $2CH_2N$), 2.70 (s, 3H, NMe), 1.94 (br. s, 4H, $2CH_2$), 1.67 (br. s, 4H, $2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.7, 160.0, 158.8, 136.3, 131.8, 127.7, 126.8, 105.5, 49.5, 46.5, 38.7, 37.1, 25.6 (×2); **IR** (KBr, pellet): $\tilde{\nu}$ 2958, 2873, 1573, 1530, 1439, 1333, 1146 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{20}H_{28}N_5O_2S^+$: 402.1958; found: 402.1959.

***N*-Methyl-*N*-(5-phenyl-2,6-di(piperidin-1-yl)pyrimidin-4-yl)methanesulfonamide (3p)**: white solid (73.9 mg, 86%); mp 132.0–134.0 °C (hexane/ethyl acetate); R_f 0.25 (hexane/ethyl acetate 8:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (d, J = 6.8 Hz, 2H, Ph), 7.34 (t, J = 7.6 Hz, 2H, Ph), 7.22 (t, J = 7.3 Hz, 1H, Ph), 3.71 (t, J = 5.2 Hz, 4H, $2CH_2$), 3.16 (s, 3H, MeS), 3.14–3.12 (m, 4H, $2CH_2$), 2.68 (s, 3H, NMe), 1.67–1.59 (m, 6H, $3CH_2$), 1.48–1.44 (m, 2H, CH_2), 1.37–1.32 (m, 4H, $2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.9, 160.2, 159.8, 136.2, 130.1, 128.4, 126.7, 107.8, 48.7, 44.9, 38.5, 36.9, 25.7, 25.5, 24.9, 24.6; **IR** (KBr, pellet): $\tilde{\nu}$ 3445, 2930, 2850, 1581, 1440, 1340, 1235, 1126, 783, 701 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{22}H_{32}N_5O_2S^+$: 430.2271; found: 430.2282.

***N*-(2,6-Dimorpholino-5-phenylpyrimidin-4-yl)-*N*-methylmethanesulfonamide (3q)**: white solid (60.7 mg, 70%); mp 183.1–185.0 °C (hexane/ethyl acetate); R_f 0.30 (hexane/ethyl acetate 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41–7.35 (m, 4H, Ph), 7.28–7.24 (m, 1H, Ph), 3.77–3.70 (m, 8H, $4CH_2$), 3.49–3.47 (m, 4H, $2CH_2$), 3.17–3.14 (m, 4H, $2CH_2$), 3.12 (s, 3H, MeS), 2.70 (s, 3H, NMe); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.6, 160.5, 159.7, 135.2, 130.1, 128.7, 127.4, 109.0, 66.8, 66.5, 48.0, 44.4, 38.7, 36.9; **IR** (KBr, pellet): $\tilde{\nu}$ 1576, 1524, 1423, 1335, 1233, 1115 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{20}H_{28}N_5O_4S^+$: 434.1857; found: 434.1856.

***N*-(2,6-Bis(diphenylamino)-5-phenylpyrimidin-4-yl)-*N*-methylmethanesulfonamide (3r)**: white solid (107.8 mg, 90%); mp 196.5–197.5 °C (hexane/ethyl acetate); R_f 0.30 (hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19–7.18 (m, 8H, Ph), 7.12–7.01 (m, 10H, Ph), 6.99–6.93 (m, 3H, Ph), 6.88–6.86 (m, 4H, Ph), 2.59 (s, 3H, Me), 2.56 (s, 3H, Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.9, 162.2, 159.6, 145.9, 144.0, 133.5, 130.5, 128.8 (×2), 128.0, 127.2, 126.8, 126.0, 125.1, 124.3, 114.0, 38.5, 37.0; **IR** (KBr, pellet): $\tilde{\nu}$ 3063, 3024, 2925, 1587, 1566, 1523, 1488, 1376, 1337, 1277, 1145, 960, 696 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{36}H_{32}N_5O_2S^+$: 598.2271; found: 598.2275.

***N*-(2,6-Bis(dimethylamino)pyrimidin-4-yl)-*N*,4-dimethylbenzenesulfonamide (3s)**: white solid (44.7 mg, 64%); mp 118.0–119.5 °C (hexane/ethyl acetate); R_f 0.35 (hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.2 Hz, 2H, Ar), 7.22 (d, J = 8.1 Hz, 2H, Ar), 6.04 (s, 1H, Ar), 3.35 (s, 3H, NMe), 3.03 (s, 6H, NMe_2), 3.00 (s, 6H, NMe_2), 2.38 (s, 3H, Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.3, 161.3, 160.0, 143.5, 136.3, 129.4, 127.5, 82.5, 37.2, 36.7, 34.6, 21.6; **IR** (KBr, pellet): $\tilde{\nu}$ 3432, 2925, 1582, 1350, 1166, 1088, 991, 774 cm^{-1}; **HRMS** (ESI): *m/z*

$[M + H]^+$ calcd. for $C_{16}H_{24}N_5O_2S^+$: 350.1651; found: 350.1651.

General Procedure for the Synthesis of Isoquinolines 4

A solution of cyanamide (**2**, 0.3 mmol, 1.5 equiv) in 1.0 mL PhCl was added to a solution of ynamide (**1**,**5**, 0.2 mmol) and $IPrAuNTf_2$ (8.7 mg, 10.0 μmol, 5 mol %) in PhCl (0.5 mL) using a syringe pump for 3 hours at 80 °C with stirring. After completion all volatile components were removed in vacuo and the residue was purified by silica gel chromatography eluting with hexane/EtOAc to afford isoquinolines **4**.

***N*-(1-(Dimethylamino)isoquinolin-3-yl)-*N*,4-dimethylbenzenesulfonamide (4a)**: yellowish oil (55.5 mg, 78%); R_f 0.45 (hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.4 Hz, 1H, Ar), 7.75 (d, J = 8.2 Hz, 1H, Ar), 7.56 (t, J = 6.9 Hz, 1H, Ar), 7.52 (d, J = 8.4 Hz, 2H, Ar), 7.42 (t, J = 7.1 Hz, 1H, Ar), 7.39 (s, 1H, Ar), 7.18 (d, J = 8.0 Hz, 2H, Ar), 3.31 (s, 3H, NMe), 2.88 (s, 6H, NMe_2), 2.38 (s, 3H, Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.6, 146.0, 143.2, 139.9, 135.3, 129.8, 129.2, 127.9, 125.9, 125.3, 119.5, 110.2, 42.8, 36.1, 21.6; **IR** (KBr, pellet): $\tilde{\nu}$ 1755, 1558, 1479, 1392, 1186, 749 cm^{-1}; **HRMS** (ESI): *m/z* $[M + H]^+$ calcd. for $C_{19}H_{22}N_3O_2S^+$: 356.1433; found: 356.1433.

***N*-(1-(Dimethylamino)isoquinolin-3-yl)-*N*-methylmethanesulfonamide (4b)**: white solid (48.6 mg, 87%); mp 76.0–77.0 °C (hexane/ethyl acetate); R_f 0.30 (hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 1H, Ar), 7.71 (d, J = 8.1 Hz, 1H, Ar), 7.56 (t, J = 7.0 Hz, 1H, Ar), 7.42 (t, J = 7.0 Hz, 1H, Ar), 7.15 (s, 1H, Ar), 3.41 (s, 3H, MeS), 3.13 (s, 9H, NMe + NMe_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.0, 146.7, 140.2, 130.0, 127.5, 126.2, 125.3, 119.4, 108.2, 43.1, 37.9, 36.5; **IR** (KBr, pellet): $\tilde{\nu}$ 3435, 2929, 1584, 1557, 1506, 1390, 1340, 1147, 962, 760 cm^{-1}; **HRMS** (ESI): *m/z* $[M + H]^+$ calcd. for $C_{13}H_{18}N_3O_2S^+$: 280.1114; found: 280.1103.

***N*-(1-(Dimethylamino)isoquinolin-3-yl)-*N*-methyl-4-nitrobenzenesulfonamide (4c)**: orange solid (65.7 mg, 85%); mp 129.0–131.0 °C (hexane/ethyl acetate); R_f 0.40 (hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.9 Hz, 2H, Ar), 8.03 (d, J = 9.5 Hz, 1H, Ar), 7.85 (d, J = 8.9 Hz, 2H, Ar), 7.77 (d, J = 8.2 Hz, 1H, Ar), 7.60 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H, Ar), 7.46 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, Ar), 7.35 (s, 1H, Ar), 3.35 (s, 3H, Me), 2.87 (s, 6H, NMe_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.9, 150.1, 145.2, 144.3, 139.9, 130.1, 129.2, 127.7, 126.1, 125.8, 123.8, 119.7, 110.7, 42.8, 36.6; **IR** (KBr, pellet): $\tilde{\nu}$ 3445, 2931, 1596, 1526, 1348, 1148, 1085, 975, 740, 638, 598 cm^{-1}; **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{18}H_{18}N_4NaO_4S^+$: 409.0946; found: 409.0960.

3-(1-(Dimethylamino)isoquinolin-3-yl)oxazolidin-2-one (4d): yellowish solid (47.9 mg, 93%); mp 138.0–140.0 °C (hexane/ethyl acetate); R_f 0.35 (hexane/ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.5 Hz, 1H, Ar), 7.91 (s, 1H, Ar), 7.71 (d, J = 8.3 Hz, 1H, Ar), 7.50 (t, J = 7.0 Hz, 1H, Ar), 7.32 (d, J = 8.4 Hz, 1H, Ar), 4.45 (ddd, J = 8.3, 7.1, 1.4 Hz, 2H, CH_2), 4.35 (ddd, J = 9.1, 7.3, 1.5 Hz, 2H, CH_2), 3.09 (s, 6H, NMe_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.3, 155.3, 143.6, 140.5, 129.7, 127.3, 125.9, 123.9, 117.8, 100.2, 62.1, 44.4, 42.9; **IR** (KBr, pellet): $\tilde{\nu}$ 3435, 1757, 1583, 1495, 1395, 1217, 1156, 1041, 707 cm^{-1}; **HRMS** (ESI): *m/z* $[M + H]^+$ calcd. for $C_{14}H_{16}N_3O_2^+$: 258.1237; found: 258.1237.

***N*-(1-(Dimethylamino)isoquinolin-3-yl)-*N*-phenylmethanesulfonamide (4e)**: white solid (42.5 mg, 62%); mp 143.0–144.5 °C (hexane/ethyl acetate); R_f 0.30 (hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, J = 9.0 Hz, 1H, Ar), 7.56–7.48 (m, 4H, Ar), 7.42–7.30 (m, 4H, Ar), 6.77 (s, 1H, Ar), 3.51 (s, 3H, MeS), 3.21 (s, 6H, NMe_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.8, 147.9, 140.9, 140.4, 130.0, 129.5, 129.0, 128.1, 127.3, 126.2, 125.3, 119.2, 109.0, 43.3, 41.0; **IR** (KBr, pellet): $\tilde{\nu}$ 1592, 1552, 1493, 1387, 1339, 1149, 966, 759 cm^{-1}; **HRMS** (ESI): *m/z* $[M + H]^+$ calcd. for $C_{18}H_{20}N_3O_2S^+$: 342.1271; found: 342.1271.

3-(1-(Dimethylamino)-7-methylisoquinolin-3-yl)oxazolidin-2-one (4f): white solid (40.2 mg, 74%); mp 134.0–136.0 °C (hexane/ethyl acetate); R_f 0.40 (hexane/ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (s, 1H, Ar), 7.83 (s, 1H, Ar), 7.64 (d, J = 8.4 Hz, 1H, Ar), 7.36 (d, J = 9.6 Hz, 1H, Ar), 4.48–4.44 (m, 2H, CH_2), 4.38–4.33 (m, 2H, CH_2), 3.08 (s, 6H, NMe_2), 2.49 (s, 3H, Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.7, 155.3, 143.0, 138.6, 134.0, 132.0, 127.3, 124.7, 118.2, 100.9, 62.1, 44.4, 43.1, 22.0; **IR** (KBr, pellet): $\tilde{\nu}$ 1742, 1588, 1559, 1404, 1383, 1248, 1178, 1113, 1033, 853 cm^{-1}; **HRMS** (ESI): *m/z* $[M + H]^+$ calcd. for $C_{15}H_{18}N_3O_2^+$: 272.1394; found: 272.1389.

3-(7-(*tert*-Butyl)-1-(dimethylamino)isoquinolin-3-yl)oxazolidin-2-one (4g): white solid (53.3 mg, 85%); mp 170.5–171.3 °C (hexane/ethyl acetate); R_f 0.40 (hexane/ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (s, 1H, Ar), 7.92 (s, 1H, Ar), 7.70–7.62 (m, 2H, Ar), 4.49–4.45 (m, 2H, CH_2), 4.39–4.35 (m, 2H, CH_2), 3.10 (s, 6H, NMe_2), 1.41 (s, 9H, 3Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.1, 155.3, 147.1, 143.2, 138.6, 128.7, 127.1, 120.8, 117.7, 100.6, 62.1, 44.4, 43.0, 35.1, 31.4; **IR** (KBr, pellet): $\tilde{\nu}$ 1745, 1590, 1557, 1434, 1405, 1393, 1249, 1120, 850 cm^{-1}; **HRMS** (ESI): *m/z* $[M + H]^+$ calcd. for $C_{18}H_{24}N_3O_2^+$: 314.1863; found: 314.1861.

3-(1-(Dimethylamino)-6,7,8-trimethoxyisoquinolin-3-yl)oxazolidin-2-one (4h): white solid (24.8 mg, 60%); mp 167.4–169.1 °C (hexane/ethyl acetate); R_f 0.35 (hexane/ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (s, 1H, Ar), 6.84 (s, 1H, Ar), 4.47 (t, J = 7.7 Hz, 2H, CH_2), 4.36 (t, J = 7.6 Hz, 2H, CH_2), 3.94 (s, 3H, OMe), 3.94 (s, 3H, OMe), 3.81 (s, 3H, OMe), 2.99 (s, 6H, NMe_2), **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.0, 156.1, 155.2, 149.7, 143.1, 140.9, 139.5, 107.4, 101.9, 98.9, 62.3, 62.1, 61.8 55.9, 44.2, 42.8; **IR** (KBr, pellet): $\tilde{\nu}$ 3444, 2921, 1755, 1488, 1383, 1251, 755 cm^{-1}; **HRMS** (ESI): *m/z* $[M + H]^+$ calcd. for $C_{17}H_{22}N_3O_5^+$: 348.1554; found: 348.1552.

3-(4-(Dimethylamino)thieno[3,2-*c*]pyridin-6-yl)oxazolidin-2-one (4i): white solid (29.5 mg, 56%); mp 154.0–156.0 °C (hexane/ethyl acetate); R_f 0.30 (hexane/ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (s, 1H, Ar), 7.54 (d, J = 5.7 Hz, 1H, Ar), 7.18 (d, J = 5.7 Hz, 1H, Ar), 4.46 (t, J = 8.6 Hz, 2H, CH_2), 4.33 (t, J = 8.3 Hz, 2H, CH_2), 3.24 (s, 6H, NMe_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.2, 154.1, 152.5, 144.3, 122.5, 122.4, 119.8, 96.4, 62.1, 44.6, 41.4; **IR** (KBr, pellet): $\tilde{\nu}$ 1747, 1569, 1546, 1431, 1394, 1221, 703 cm^{-1}; **HRMS** (ESI): *m/z* $[M + H]^+$ calcd. for $C_{12}H_{14}N_3O_2S^+$: 264.0801; found: 264.0816.

3-(4-(Dimethylamino)benzo[*f*]isoquinolin-2-yl)oxazolidin-2-one (4j): brownish solid (45.8 mg, 76%); mp 208.5–209.7 °C (dec., hexane/ethyl acetate); R_f 0.40 (hexane/ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (s, 1H, Ar), 7.35 (s, 1H, Ar), 7.02 (s, 1H, Ar), 6.04 (s, 2H, CH_2), 4.47 (t, J = 7.9 Hz, 2H, CH_2), 4.34 (t, J = 8.0 Hz, 2H, CH_2), 3.00 (s, 6H, NMe_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.4, 155.3, 150.6, 146.6, 143.2, 138.5, 114.4, 103.5, 102.2, 101.6, 101.5, 62.1, 44.4, 43.1; **IR** (KBr, pellet): $\tilde{\nu}$ 2933, 1751, 1499, 1453, 1430, 1227, 1125, 1040, 901, 750 cm^{-1}; **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{15}H_{15}N_3NaO_4^+$: 324.0955; found: 324.0957.

3-(4-(Dimethylamino)benzo[*f*]isoquinolin-2-yl)oxazolidin-2-one (4k): white solid (43.6 mg, 71%); mp 214.3–215.2 °C (dec., hexane/ethyl acetate); R_f 0.40 (hexane/ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.86 (s, 1H, Ar), 8.69–8.66 (m, 1H, Ar), 7.96 (d, J = 9.2 Hz, 1H, Ar), 7.87–7.83 (m, 1H, Ar), 7.67–7.62 (m, 3H, Ar),

4.53–4.48 (m, 2H, CH_2), 4.42–4.38 (m, 2H, CH_2), 3.10 (s, 6H, NMe_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.1, 155.3, 145.4, 139.7, 133.5, 129.4, 128.5, 128.3, 126.8, 124.9, 124.5, 122.9, 114.8, 97.8, 62.1, 44.4, 43.3; **IR** (KBr, pellet): $\tilde{\nu}$ 3423, 2925, 1750, 1584, 1456, 1226, 1040, 900 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{18}H_{18}N_3O_2^+$: 308.1394; found: 308.1395.

3-(1-(Dimethylamino)benzo[*h*]isoquinolin-3-yl)oxazolidin-2-one (4l): white solid (52.9 mg, 86%); mp 184.5–186.0 °C (dec., hexane/ethyl acetate); R_f 0.40 (hexane/ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.16 (d, *J* = 8.5 Hz, 1H, Ar), 8.02 (s, 1H, Ar), 7.81 (d, *J* = 9.0 Hz, 1H, Ar), 7.76 (d, *J* = 8.8 Hz, 1H, Ar), 7.63–7.58 (m, 2H, Ar), 7.52–7.48 (m, 1H, Ar), 4.52–4.48 (m, 2H, CH_2), 4.42–4.38 (m, 2H, CH_2), 2.93 (s, 6H, NMe_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.7, 155.3, 144.2, 141.9, 131.9, 131.4, 130.0, 128.4, 126.9, 126.1, 125.8, 125.6, 112.2, 102.2, 62.2, 44.2, 42.6; **IR** (KBr, pellet): $\tilde{\nu}$ 3447, 2915, 1745, 1573, 1395, 1217, 1118, 1058, 764 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{18}H_{18}N_3O_2^+$: 308.1394; found: 308.1393.

3-(1-(Diethylamino)isoquinolin-3-yl)oxazolidin-2-one (4m): white solid (29.7 mg, 52%); mp 95.0–96.0 °C (hexane/ethyl acetate); R_f 0.50 (hexane/ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.5 Hz, 1H, Ar), 7.93 (s, 1H, Ar), 7.72 (d, *J* = 8.3 Hz, 1H, Ar), 7.51 (t, *J* = 6.9 Hz, 1H, Ar), 7.32 (d, *J* = 7.0 Hz, 1H, Ar), 4.50–4.46 (m, 2H, CH_2), 4.37–4.33 (m, 2H, CH_2), 3.49 (q, *J* = 7.0 Hz, 4H, $2CH_2O$), 1.24 (t, *J* = 7.0 Hz, 6H, 2Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.5, 155.3, 143.6, 140.6, 129.8, 127.5, 125.5, 124.0, 119.1, 100.4, 62.1, 46.1, 44.4, 13.3; **IR** (KBr, pellet): $\tilde{\nu}$ 1761, 1587, 1554, 1480, 1397, 1321, 1230, 828, 750 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{16}H_{20}N_3O_2^+$: 286.1550; found: 286.1544.

3-(1-(Pyrrolidin-1-yl)isoquinolin-3-yl)oxazolidin-2-one (4n): yellowish solid (39.1 mg, 69%); mp 222.0–224.0 °C (hexane/ethyl acetate); R_f 0.35 (hexane/ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.6 Hz, 1H, Ar), 7.72 (s, 1H, Ar), 7.67 (d, *J* = 8.2 Hz, 1H, Ar), 7.47 (t, *J* = 7.5 Hz, 1H, Ar), 7.26–7.22 (m, 1H, Ar), 4.47–4.43 (m, 2H, CH_2), 4.36–4.33 (m, 2H, CH_2), 3.84–3.81 (m, 4H, $2CH_2$), 2.03–1.98 (m, 4H, $2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.4, 155.3, 143.9, 141.1, 129.4, 127.2, 125.9, 122.9, 117.0, 97.4, 62.1, 51.4, 44.4, 26.1; **IR** (KBr, pellet): $\tilde{\nu}$ 3478, 2971, 2866, 1752, 1594, 1398, 1341, 1245, 812 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{16}H_{18}N_3O_2^+$: 284.1394; found: 284.1391.

3-(1-(Piperidin-1-yl)isoquinolin-3-yl)oxazolidin-2-one (4o): white solid (32.7 mg, 55%); mp 179.0–180.5 °C (hexane/ethyl acetate); R_f 0.50 (hexane/ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.3 Hz, 1H, Ar), 8.00 (s, 1H, Ar), 7.73 (d, *J* = 8.2 Hz, 1H, Ar), 7.53 (t, *J* = 7.5 Hz, 1H, Ar), 7.36 (d, *J* = 7.6 Hz, 1H, Ar), 4.48 (t, *J* = 8.3 Hz, 2H, CH_2), 4.36 (t, *J* = 8.5 Hz, 2H, CH_2), 3.41–3.38 (m, 4H, $2CH_2$), 1.87–1.83 (m, 4H, $2CH_2$), 1.70 (p, *J* = 5.9 Hz, 2H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.3, 155.3, 143.8, 140.3, 130.0, 127.5, 125.6, 124.6, 118.6, 101.8, 62.1, 52.9, 44.5, 26.0, 24.9; **IR** (KBr, pellet): $\tilde{\nu}$ 3445, 2930, 1756, 1437, 1415, 1393, 1248, 1163, 1032, 833 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{17}H_{20}N_3O_2^+$: 298.1550; found: 298.1550.

3-(1-Morpholinoisoquinolin-3-yl)oxazolidin-2-one (4p): white solid (41.3 mg, 69%); mp 184.0–186.0 °C (hexane/ethyl acetate); R_f 0.35 (hexane/ethyl acetate 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (s, 1H, Ar), 8.02 (d, *J* = 8.4 Hz, 1H, Ar), 7.77 (d, *J* = 8.2 Hz, 1H, Ar), 7.56 (ddd, *J* = 8.2, 6.7, 1.2 Hz, 1H, Ar), 7.39 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H, Ar), 4.52–4.48 (m, 2H, CH_2), 4.39–4.34 (m, 2H, CH_2), 3.98–3.96 (m, 4H, $2CH_2$), 3.45–3.42 (m, 4H, $2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.5, 155.3, 143.8, 140.4, 130.3, 127.7, 125.1, 124.9, 118.3, 102.6, 66.9, 62.1, 52.0, 44.0; **IR** (KBr, pellet): $\tilde{\nu}$ 1745, 1561, 1444, 1394, 1224, 1115, 928, 753 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{16}H_{18}N_3O_3^+$: 300.1343; found: 300.1343.

3-(3',4'-Dihydro-1'*H*-[1,2'-biisoquinolin]-3-yl)oxazolidin-2-one (4q): white solid (49.0 mg, 71%); mp 138.5–140.5 °C (hexane/ethyl acetate); R_f 0.25 (hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05–8.02 (m, 2H, Ar), 7.75 (d, *J* = 8.2 Hz, 1H, Ar), 7.55 (t, *J* = 7.9 Hz, 1H, Ar), 7.38 (t, *J* = 8.2 Hz, 1H, Ar), 7.21–7.20 (m, 3H, Ar), 7.17–7.14 (m, 1H, Ar), 4.64 (s, 2H, CH_2), 4.48 (t, *J* = 8.3 Hz, 2H, CH_2), 4.32 (t, *J* = 8.4 Hz, 2H, CH_2), 3.77 (t, *J* = 5.9 Hz, 2H, CH_2), 3.12 (t, *J* = 5.9 Hz, 2H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.6, 155.2, 143.7, 140.4, 134.9, 134.6, 130.1, 129.0, 127.6, 126.6, 126.4, 126.1, 125.2, 124.6, 118.4, 101.5, 62.1, 52.4, 50.3, 44.4, 29.2; **IR** (KBr, pellet): $\tilde{\nu}$ 1746, 1566, 1444, 1394, 1245, 749 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{21}H_{20}N_3O_2^+$: 346.1550; found: 346.1545.

3-(1-(Diphenylamino)isoquinolin-3-yl)oxazolidin-2-one (4r): yellowish solid (31.3 mg, 41%); mp 187.0–189.0 °C (hexane/ethyl acetate); R_f 0.35 (hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (s, 1H, Ar), 7.79 (d, *J* = 8.3 Hz, 1H, Ar), 7.74 (d, *J* = 8.6 Hz, 1H, Ar), 7.51 (t, *J* = 7.5 Hz, 1H, Ar), 7.26 (t, *J* = 7.7 Hz, 4H, Ph), 7.18 (t, *J* = 7.7 Hz, 1H, Ar), 7.07 (t, *J* = 7.3 Hz, 2H, Ph), 7.03 (d, *J* = 7.9 Hz, 4H, Ph), 4.35 (t, *J* = 8.1 Hz, 2H, CH_2), 3.90 (t, *J* = 8.1 Hz, 2H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.2, 155.3, 148.3, 144.5, 141.0, 130.3, 129.2, 127.5, 126.3, 125.4, 124.7, 123.7, 120.7, 104.5, 62.2, 44.1; **IR** (KBr, pellet): $\tilde{\nu}$ 1755, 1583, 1488, 1402, 1345, 1117, 757 cm^{-1}; **HRMS** (ESI): *m/z* [M + Na]$^+$ calcd. for $C_{24}H_{19}N_3NaO_2^+$: 404.1369; found: 404.1370.

Gram-Scale Synthesis of 4s

A round-bottom flask (50mL) equipped with a magnetic stirrer bar was charged with ynamide **5s** (1.45 g, 4.0 mmol), $IPrAuNTf_2$ (173.4 mg, 0.2 mmol, 5 mol %) and PhCl (10 mL). Then a solution of morpholine-4-carbonitrile (**2e**, 0.67 g, 6.0 mmol, 1.5 equiv) in PhCl (10 mL) was added to this mixture using a syringe pump for 3 hours at 80 °C with stirring. After completion all volatile components were removed in vacuo and the residue was purified by silica gel chromatography eluting with chloroform to afford isoquinoline **4s**.

***N*-Benzyl-4-methyl-*N*-(1-morpholinoisoquinolin-3-yl)benzenesulfonamide (4s)**: yellowish oil (1.21 g, 65%); R_f 0.30 (hexane/ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 1H, Ar), 7.73 (d, *J* = 8.2 Hz, 1H, Ar), 7.58–7.52 (m, 3H, Ar), 7.47–7.41 (m, 2H, Ar), 7.34–7.32 (m, 2H, Ar), 7.23–7.18 (m, 4H, Ar), 7.13 (d, *J* = 7.2 Hz, 1H, Ar), 5.02 (s, 2H, $C\underline{H}_2Ph$), 3.84–3.82 (m, 4H, $2CH_2$), 3.17–3.15 (m, 4H, $2CH_2$), 2.41 (s, 3H, Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.8, 144.0, 143.5, 139.6, 137.0, 136.2, 130.1, 129.4, 128.4, 128.3, 128.0, 127.8, 127.4, 126.4, 125.1, 120.1, 115.3, 66.8, 51.8, 51.7, 21.6; **IR** (KBr, pellet): $\tilde{\nu}$ 2831, 1593, 1494, 1410, 1340, 1164, 1117, 1028, 737 cm^{-1}; **HRMS** (ESI): *m/z* [M + H]$^+$ calcd. for $C_{27}H_{28}N_3O_3S^+$: 474.1851; found: 474.1871.

Seyferth–Gilbert Homologation of 3j

A solution of dimethyl (1-diazo-2-oxopropyl)phosphonate (192.1 mg, 1.0 mmol, 2.0 equiv) in acetonitrile (1 mL) was added to the suspension of **3j** (264.8 mg, 0.5 mmol), Cs_2CO_3 (325.8 mg, 1.0 mmol) and acetonitrile (4 mL) at 0 °C. The resulting mixture was stirred at RT for 24 h. Then all volatile components were removed *in vacuo* and the residue was purified by silica gel chromatography eluting with hexane/EtOAc to afford alkyne **3j'**.

***N*-Benzyl-*N*-(2,6-bis(dimethylamino)-5-(4-ethynylphenyl)pyrimidin-4-yl)-4-methylbenzenesulfonamide (3j')**: white solid (184.0 mg, 70%); mp 172.4–173.9 °C (hexane/ethyl acetate); R_f 0.45

(hexane/ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.4 Hz, 2H, Ar), 7.29 (d, J = 8.1 Hz, 2H, Ar), 7.26 (d, J = 8.0 Hz, 2H, Ar), 7.10 (t, J = 7.4 Hz, 1H, Ar), 7.01–6.97 (br. m, 4H, Ar), 6.72 (d, J = 7.1 Hz, 2H, Ar), 4.27 (s, 2H, CH_2), 3.09 (s, 1H, CH), 3.02 (s, 6H, NMe_2), 2.62 (s, 6H, NMe_2), 2.43 (s, 3H, Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.3, 160.1, 158.0, 143.2, 137.6, 136.4, 134.8, 131.5, 131.2, 129.5, 129.4, 128.9, 128.1, 127.3, 119.5, 108.7, 84.3, 76.9, 54.0, 40.6, 36.7, 21.7; **IR** (KBr, pellet): $\tilde{\nu}$ 3282, 2925, 1580, 1388, 1333, 1158 cm^{-1}; **HRMS** (ESI): *m/z* $[M + H]^+$ calcd. for $C_{30}H_{35}N_5O_2S^+$: 526.2271; found: 526.2279.

Gold-Catalyzed Oxidative [2+2+1] Heterocyclization of 3j′

$Ph_3PAuNTf_2$ (7.4 mg, 10.0 μmol, 5 mol %) was added to the solution of alkyne **3j′** (105.1 mg, 0.2 mmol) and 2,3-dichloropyridine *N*-oxide (36.1 mg, 0.22 mmol, 1.1 equiv) in dimethylcyanamide (**2a**, 0.2 mL). The resulting solution was stirred at 60 °C for 3 h. Then all volatile components were removed *in vacuo* and the residue was purified by silica gel chromatography eluting with hexane/EtOAc to afford oxazole **3j″**.

***N*-Benzyl-*N*-(2,6-bis(dimethylamino)-5-(4-(2-(dimethylamino)oxazol-5-yl)phenyl)pyrimidin-4-yl)-4-methylbenzenesulfonamide (3j″)**: white solid (86.9 mg, 71%); mp 112.5–113.6 °C (hexane/ethyl acetate); R_f 0.35 (hexane/ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2H, Ar), 7.30–7.24 (m, 4H, Ar), 7.13–6.93 (br. m, 6H, Ar), 6.73 (d, J = 7.1 Hz, 2H, Ar), 4.26 (s, 2H, CH_2), 3.28 (s, 6H, NMe_2), 3.01 (s, 6H, NMe_2), 2.65 (s, 6H, NMe_2), 2.43 (s, 3H, Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.4, 160.1, 158.2, 145.9, 143.2, 136.5, 136.4, 134.9, 131.7, 129.5, 129.4, 128.9, 128.0, 127.3, 122.2, 108.8, 54.0, 40.6, 38.4, 36.7, 21.7 (three carbons merged with others); **IR** (KBr, pellet): $\tilde{\nu}$ 3401, 2925, 2857, 1623, 1578, 1389, 1339, 1202, 1138, 1058 cm^{-1}; **HRMS** (ESI): *m/z* $[M + H]^+$ calcd. for $C_{33}H_{38}N_7O_3S^+$: 612.2751; found: 612.2751.

Synthesis of Starting Ynamides 5

To an oven dried flask was added oxazolidin-2-one (287.3 mg, 3.3 mmol, 1.1 equiv), K_2CO_3 (1.244 g, 9.0 mmol, 3 equiv), $CuSO_4{\cdot}5H_2O$ (74.9 mg, 0.30 mmol, 10 mol %), 1,10-phenanthroline (108.1 mg, 0.60 mmol, 20 mol %) and this mixture was subsequently treated with anhydrous toluene (5 ml) and bromoalkyne (3.0 mmol). The flask was charged with nitrogen, and the solution was heated at 80°C for 24 hours. After completion, the crude reaction mixture was cooled to room temperatures, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with hexane/EtOAc to afford ynamides **5**.

3-((4-(*tert*-Butyl)phenyl)ethynyl)oxazolidin-2-one (5a): white solid (495.7 mg, 68%); mp 132.0–133.0 °C (hexane/ethyl acetate); R_f 0.30 (hexane/ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 4H, Ar), 4.46–4.42 (m, 2H, CH_2), 3.98–3.94 (m, 2H, CH_2), 1.29 (s, 9H, 3Me); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.0, 151.5, 131.4, 125.3, 119.1, 78.5, 71.2, 63.1, 47.2, 34.8, 31.2; **IR** (KBr, pellet): $\tilde{\nu}$ 2959, 2261, 1764, 1477, 1427, 1221, 1167, 1086, 1031, 836, 748 cm^{-1}; **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{15}H_{17}NNaO_2^+$: 266.1151; found: 266.1147.

3-((3,4,5-Trimethoxyphenyl)ethynyl)oxazolidin-2-one (5b): white solid (665.5 mg, 80%); mp 64.0–65.0 °C (hexane/ethyl acetate); R_f 0.20 (hexane/ethyl acetate 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.65 (s, 2H, Ar), 4.48–4.44 (m, 2H, CH_2), 4.40–3.96 (m, 2H, CH_2), 3.82 (s, 3H, OMe), 3.81 (s, 6H, 2OMe); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.0, 153.1, 138.8, 117.2, 108.9, 78.2, 71.3, 63.2, 61.0, 56.2, 47.1; **IR** (KBr, pellet): $\tilde{\nu}$ 1687, 1587, 1461, 1423, 1391, 1330, 1234, 1127, 992 cm^{-1}; **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{14}H_{15}NNaO_5^+$: 300.0842; found: 300.0842.

3-(Benzo[*d*][1,3]dioxol-5-ylethynyl)oxazolidin-2-one (5c): white solid (374.5 mg, 54%); mp 125.4–126.8 °C (hexane/ethyl acetate); R_f 0.35 (hexane/ethyl acetate 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.96 (d, J = 8.0 Hz, 1H, Ar), 6.88 (s, 1H, Ar), 6.73 (d, J = 8.1 Hz, 1H, Ar), 5.96 (s, 2H, CH_2), 4.46 (t, J = 8.0 Hz, 2H, CH_2), 3.97 (t, J = 8.0 Hz, 2H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.1, 148.1, 147.5, 126.7, 115.4, 112.0, 108.5, 101.4, 77.5, 71.1, 63.1, 47.2; **IR** (KBr, pellet): $\tilde{\nu}$ 2909, 2256, 11755, 1451, 1411, 1207, 1025, 811 cm^{-1}; **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{12}H_9NNa_2O_4^+$: 254.0424; found: 254.0424.

3-(Naphthalen-1-ylethynyl)oxazolidin-2-one (5d): white solid (505.4 mg, 71%); mp 120.1–121.9 °C (hexane/ethyl acetate); R_f 0.40 (hexane/ethyl acetate 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.4 Hz, 1H, Ar), 7.84 (d, J = 8.1 Hz, 1H, Ar), 7.80 (d, J = 8.3 Hz, 1H, Ar), 7.66 (dd, J = 7.2, 1.2 Hz, 1H, Ar), 7.58 (ddd, J = 8.3, 6.8, 1.4 Hz, 1H, Ar), 7.51 (ddd, J = 8.1, 6.9, 1.4 Hz, 1H, Ar), 7.41 (dd, J = 8.3, 7.1 Hz, 1H, Ar), 4.43–4.39 (m, 2H, CH_2), 4.01–3.95 (m, 2H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.0, 133.1, 133.0, 129.9, 128.5, 128.3, 126.9, 126.5, 126.1, 125.2, 119.9, 83.8, 69.5, 63.2, 47.0; **IR** (KBr, pellet): $\tilde{\nu}$ 3433, 2254, 1765, 1387, 1219, 1107, 1034, 801, 774 cm^{-1}; **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{15}H_{11}NNaO_2^+$: 260.0682; found: 260.0682.

3-(Naphthalen-2-ylethynyl)oxazolidin-2-one (5e): white solid (583.7 mg, 82%); mp 171.9–173.4 °C (hexane/ethyl acetate); R_f 0.40 (hexane/ethyl acetate 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (s, 1H, Ar), 7.81–7.76 (m, 3H, Ar), 7.50–7.47 (m, 3H, Ar), 4.51–4.47 (m, 2H, CH_2), 4.05–4.01 (m, 2H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.0, 133.1, 132.8, 131.4, 128.4, 128.1, 127.9, 127.8, 126.8, 126.7, 119.6, 79.4, 71.8, 63.2, 47.2; **IR** (KBr, pellet): $\tilde{\nu}$ 3500, 2253, 1755, 1587, 1474, 1424, 1218, 820, 742 cm^{-1}; **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{15}H_{11}NNaO_2^+$: 260.0682; found: 260.0687.

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FULL PAPER

The Dichotomy of Gold-catalyzed Interplay between Cyanamides and Ynamides: Controllable Switch from [2+2+2] to [4+2] Cycloaddition

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