JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

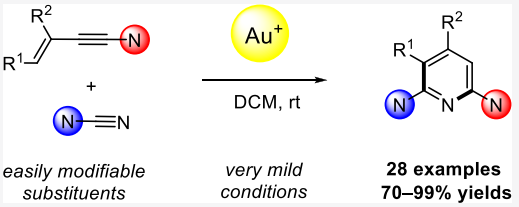
Hetero-Tetradehydro-Diels–Alder Cycloaddition of Enynamides and Cyanamides: Gold-Catalyzed Generation of Diversely Substituted 2,6-Diaminopyridines

Nikolay V. Shcherbakov, Dmitry V. Dar'in, Vadim Yu. Kukushkin,* and Alexey Yu. Dubovtsev*

Cite This: J. Org. Chem. 2021, 86, 7218–7228 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

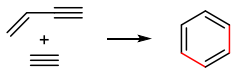
ABSTRACT: Gold(I)-catalyzed hetero-tetradehydro-Diels–Alder cycloaddition of enynamides and cyanamides comprises an efficient route to diversely substituted 2,6-diaminopyridines (28 examples; yields up to 99%). The reaction proceeds under very mild conditions (DCM, rt) with high functional group tolerance. The obtained 2,6-diaminopyridines represent a useful synthetic platform with an easily modulated substitution pattern for subsequent functionalizations of both the pyridine core and the *N*-substituents.



INTRODUCTION

In the field of Diels–Alder (DA) reactions, [4 + 2] cycloadditions of substrates featuring triple bonds are commonly categorized as dehydro-DAs,[1−3] while the cycloaddition of enynes and alkynes is subclassified as tetradehydro-Diels–Alder (TDDA) reactions (Scheme 1).

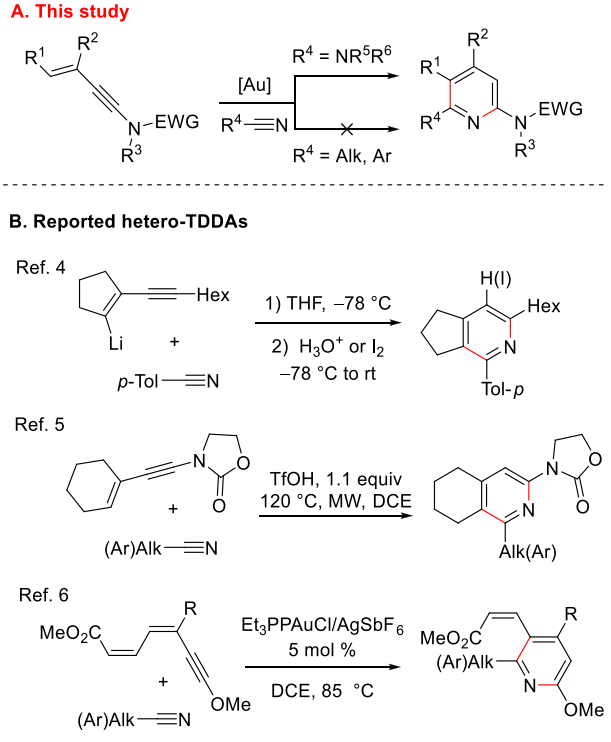
Scheme 1. TDDA Reaction between Enynes and Alkynes



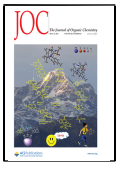
Practical application of TDDA reactions are severely limited, because they usually require harsh conditions, and/or complex prefunctionalized substrates (for the intramolecular variants). However, because TDDA cycloadditions allow the creation of benzene ring(s) in a single step, there is a demand for development of new practically feasible routes to such [4 + 2] integrations. While TDDA reactions in general are rare, *hetero*-TDDA reactions that provide access to aromatic heterocycles are almost unique. Only three examples of hetero-TDDA cycloadditions have been reported (Scheme 2B). These include the nucleophilic addition of 1-lithium-1-en-3-ynes to *p*-tolunitrile[4] and the TfOH-promoted interaction of enynyloxazolidin-2-ones with nitriles[5] giving in both cases fused pyridines. These two methods have a limited scope and involve the use of equivalent amounts of highly aggressive reagents, namely BuLi[4] or TfOH.[5] In contrast, the single known catalytic method allows the formation of 2-methoxypyridines from ynol ethers and nitriles under relatively mild conditions using the gold-based catalytic system $Et_3PAuCl/AgSbF_6$.[6] Notably, in all these cases[4−6] conventional nitriles RCN (R = Alk, Ar) were used as coreactants.

Based on these results[4−6] and considering the relevant successful examples of Au-catalyzed carbo-TDDA cyclo-

Scheme 2. Hetero-TDDA Reactions



Received: March 9, 2021
Published: May 7, 2021



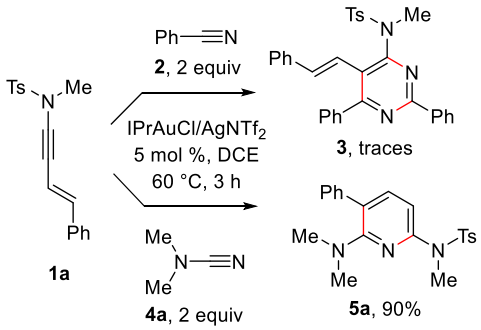
https://doi.org/10.1021/acs.joc.1c00558
J. Org. Chem. 2021, 86, 7218–7228

additions,[7,8] we now attempted gold-catalyzed *hetero*-TDDA reactions with such activated alkynes as enynamides. First, the application of gold for various catalytic conversions of alkynes is a cutting-edge research area[9−17] and the focus of the upcoming special issue of *Chemical Reviews* scheduled for Aug. 2021; the first articles[18−27] have already been published. Second, ynamides[28−33] are widely used synthetic building blocks that combine high reactivity and various substitution patterns, but at the same time, the reactions of enynamides[34−38] are poorly explored. As the initial idea for this study, we assumed that enynamides can also be involved in the intermolecular hetero-TDDA cycloaddition with nitriles RCN and that this integration should lead to 2-aminopyridines (Scheme 2A). All our results relevant to this novel synthetic route are disclosed in sections that follow.

RESULTS AND DISCUSSION

To prove our hypothesis, we first attempted the gold-catalyzed interaction between enynamide **1a** and conventional nitriles (MeCN, PhCN), but no hetero-TDDA reaction species were detected (Scheme 3). A complex reaction mixture was

Scheme 3. Gold-Catalyzed Cycloadditions of Enynamide 1a



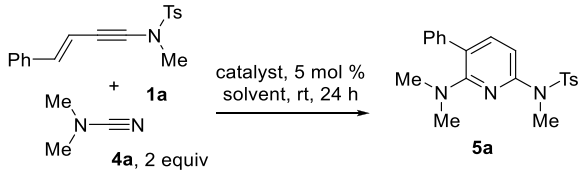
obtained in the case of acetonitrile. When benzonitrile was used, the only identified product was pyrimidine **3** derived from the known[39,40] [2 + 2 + 2] cycloaddition of one ynamide and two PhCN; the alkene fragment of **1a** remained intact.

It is known[41] (and it is also our experience[40,42,43]) that the chemistry of cyanamides[44,45] is often dramatically different from the chemistry of conventional organonitriles; this different reactivity is typically associated with the push−pull nature of cyanamides. Hence, as the next step, we replaced nitriles **2**, unreactive in the attempted hetero-TDDA reaction, with dimethylcyanamide **4a**. In line with our expectations, in the case of Me_2NCN, the desired 2,6-diaminopyridine **5a** was obtained as the only product. Inspired by these results, we optimized conditions of this novel hetero-TDDA reaction and extended its scope.

To optimize the reaction conditions, some popular gold-based catalysts were tested: these experiments included ligand and counterion variations (Table 1, entries 1−6).[46,47] The system IPrAuCl/$AgNTf_2$ demonstrated the best results (entry 2); $AgNTf_2$ alone does not catalyze the reaction (entry 7).

Among the employed solvents (entries 2, 8−10), DCM gave the highest yield. Interestingly, when neat acetonitrile was used as a solvent, the [4 + 2] and [2 + 2 + 2] cycloaddition products of **1a** and MeCN were not detected, again confirming that conventional nitriles are unreactive in the hetero-TDDA cycloaddition. The reaction can also be performed at 60 °C in DCE in just 3 h (entry 11). The catalyst loading can be

Table 1. Optimization of the Synthesis of 5a[a]



entry	Catalyst	Solvent	Yield,[b] %
1	$Ph_3PAuCl/AgNTf_2$	DCM	84
2	IPrAuCl/$AgNTf_2$	DCM	89
3	JohnPhosAuCl/$AgNTf_2$	DCM	88
4	IPrAuCl/AgOTf	DCM	71
5	IPrAuCl/$AgSbF_6$	DCM	81
6	IPrAuNTf_2	DCM	87
7	$AgNTf_2$	DCM	–
8	IPrAuCl/$AgNTf_2$	PhMe	80
9	IPrAuCl/$AgNTf_2$	THF	63
10	IPrAuCl/$AgNTf_2$	MeCN	83
11	IPrAuCl/$AgNTf_2$	DCE	90[c]
12	IPrAuCl/$AgNTf_2$	DCM	85[d]
13	IPrAuCl/$AgNTf_2$	DCM	92[e]

[a]All reactions were carried out on a 0.1 mmol scale (0.2 M). [b]Estimated by ^1H NMR spectroscopy using durene as an internal standard. [c]60 °C, 3 h. [d]3 mol % of IPrAuCl/$AgNTf_2$ was used. [e]1.5 equiv of Me_2NCN was used.

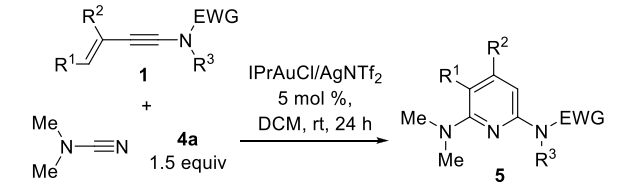
reduced to 3 mol % without significant loss of the yield (entry 12). In summary, the best synthetic results to achieve **5a** from enynamide **1a** were obtained with only 1.5 equiv of **4a** and 5 mol % of IPrAuCl/$AgNTf_2$ in DCM at rt for 24 h (entry 13).

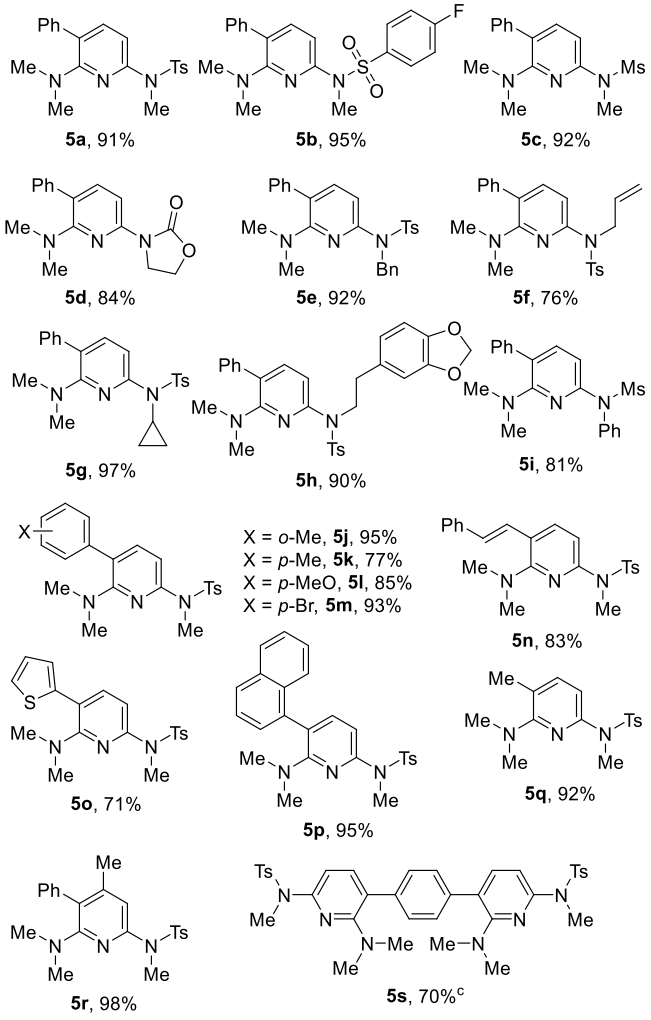
With the optimal conditions at hand, the substrate scope and limitations for the synthesis of 2,6-diaminopyridines **5** were examined. We tested various enynamides **1** in their reactions with dimethylcyanamide (Table 2). The cycloadditions proceed smoothly with the reactants featuring various electron-withdrawing *N*-sulfonyl substituents (**5a−c**). Pyridine **5d** bearing a cyclic carbamate substituent was obtained in good yield, and its structure was further confirmed by single-crystal X-ray diffraction (CCDC 2062892). Ynamides featuring *N*-phenyl and functional-substituted *N*-alkyl groups delivered the corresponding pyridines in good to excellent yields (**5e−i**). The reaction conditions were applicable to the hetero-TDDA cycloadditions of ynamides with diverse R^1-substituents. Thus, diversified functionalities can be introduced into the fifth position of pyrimidine ring, including aryl (**5j−5m**, **5p**), heteroaryl (**5o**), and alkyl (**5q**) fragments. The conjugated dienynamide **1n** was successfully converted to the corresponding 5-alkenylpyridine **5n**. The pyridine bearing a methyl substituent in the 4-position (**5r**) was obtained in excellent yield. The cycloaddition was carried out in a bidirectional manner giving bispyridine benzene **5s**.

The cyanamide scope of the studied hetero-TDDA reaction is shown in Table 3. All tested disubstituted cyanamides gave the corresponding pyridines in good and excellent yields. Our protocol was applicable for introducing a variety of cyclic amino-functionalities, such as, pyrrolidine, piperidine, morpholine, and tetrahydroisoquinoline fragments into the sixth position of the pyridine core (**6f−i**). Complex reaction mixtures were obtained when we used cyanamides containing free NH-fragments (NH_2CN, PhNHCN, *n*-BuNHCN). These facts are probably related to the competing gold-catalyzed hydroamination of starting ynamides.[48] Nevertheless, pyridines

https://doi.org/10.1021/acs.joc.1c00558
J. Org. Chem. 2021, 86, 7218−7228

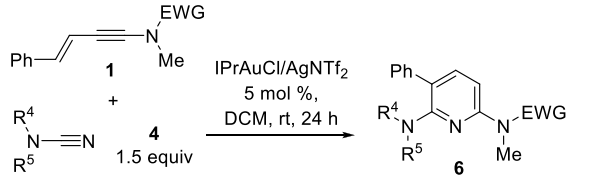
Table 2. Reactivity Screening for Ynamides 1[a,b]

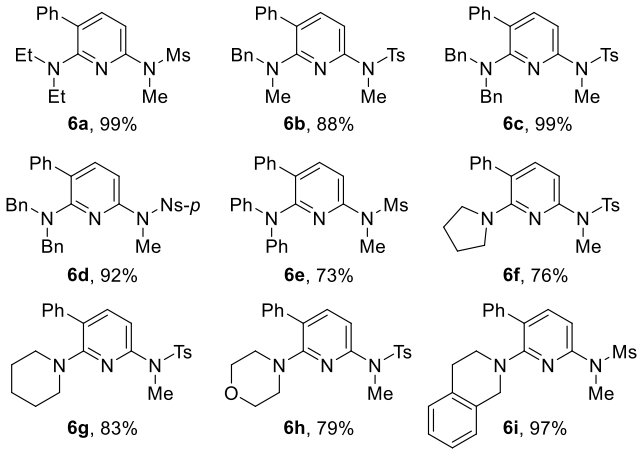




[a]All reactions were carried out on a 0.2 mmol scale (0.2 M). [b]Isolated yield. [c]15 mol % of IPrAuCl/AgNTf$_2$ was used.

Table 3. Reactivity Screening for Cyanamides 4[a,b]





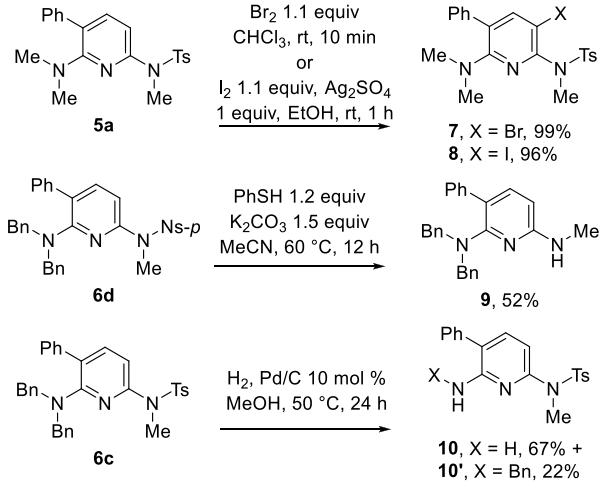
[a]All reactions were carried out on a 0.2 mmol scale (0.2 M). [b]Isolated yield.

6b−d, bearing easily cleavable benzyl *N*-protective groups, were obtained in excellent yields. Also, we scaled the synthesis of **6c** up to 1.0 mmol, and the isolated yield was 95%. The preparation of **5a** can be conducted on a gram scale (91% isolated yield).

The 2-aminopyridine and 2,6-diaminopyridine motifs are widely represented among natural compounds, such as α-carbolines,[49,50] and numerous synthetic drug candidates.[51−54] Moreover, these heterocycles are used in organometallic chemistry as ligands[55] and in materials chemistry as macromolecular linkers.[56] Although the synthetic routes to simply substituted 2-aminopyridines are known (e.g., Chichibabin reaction,[57] Buchwald−Hartwig aminations of halopyridines,[58,59] and various multicomponent condensations),[60−62] the preparation of target compounds with complex substitution patterns is typically a challenging task.[41,63]

Having developed a new efficient method for the construction of the 2,6-diaminopyridine core, we then focused on studying its postmodifications (Scheme 4). Pyridine **5a** was

Scheme 4. Post-functionalizations of Pyridines 5 and 6

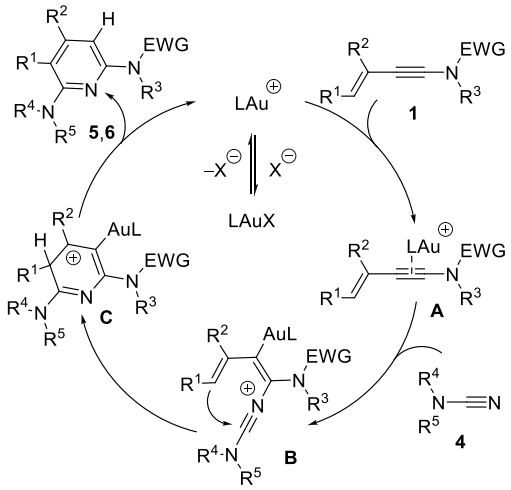


easily halogenated in the third position; the resulting bromo- and iodo- pyridines (**7** and **8**) could serve as precursors for cross-coupling strategies. The modification of the amino substituent in the second position is demonstrated by the denosylation of compound **6d**. Finally, pyridine **6c** gave the di- and mono-debenzylation products (**10** and **10′**) under the catalytic hydrogenolysis conditions.

A plausible mechanism[64−67] for the gold-catalyzed hetero-TDDA reaction is given in Scheme 5. The coordination of the cationic gold to the enynamide triple bond gives π-complex **A**, whereupon cyanamide **4** attacks **A** to give nitrilium ion **B**. Next, cyclization of **B** followed by aromatization/protodeaura-

https://doi.org/10.1021/acs.joc.1c00558
J. Org. Chem. 2021, 86, 7218−7228

Scheme 5. Plausible Mechanism for Generation of 5 and 6



tion leads to pyridine **5**, whereas the catalyst is regenerated. Unlike conventional nitriles Alk(Ar)CN giving only the pyrimidine species (Scheme 3),[39] cyanamide *sp*-carbon of the key intermediate **B** is sufficiently electrophilic for intramolecular attack by the alkene fragment. Thus, the employment of push−pull cyanamides is a crucial factor for this gold-catalyzed hetero-TDDA cycloaddition. In contrast to our method that utilizes exclusively cyanamides, Barluenga and Aguilar succeeded in employing the conventional nitriles in the gold-catalyzed TDDA reaction with enyne ethers (Scheme 2).[6] We assume that this reaction occurred due to the push−pull nature of the employed alkyne substrates, where the methoxy substituents at the triple bonds are conjugated with the ester fragments (see the postulated mechanism in ref 6). In another work, these authors also noted this effect.[68] Very likely, for the conductance of the TDDA reaction, one of the substrates (viz., enyne or nitrile) should exhibit the push−pull character.

The above reaction scheme (Scheme 5) is relevant to the gold-catalyzed formal [4 + 2] cycloaddition *β*-arylynamides and cyanamides to furnish 1,3-diaminoisoquinolines, which we reported earlier.[40] In contrast to enynamides **1**, which react with cyanamides at room temperature to give 2,6-diaminopyrimidines, the cyclization of nitrilium ions generated from *β*-arylynamides and cyanamides is not easy and it requires harsh conditions (80 °C). This is probably related to the need for dearomatization of the aryl substituent, whereas, for enynamides **1**, cyclization of the nitrile cation **B** is preferable. For the same reason, in a large number of cases, the competing [2 + 2 + 2] cycloaddition of one alkyne and two cyanamides becomes prevalent for *β*-arylynamides. For enynamides **1** even traces of the possible side products (derived from the [2 + 2 + 2] reaction) were not detected.

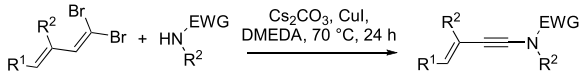
CONCLUSIONS

In summary, we reported a new example of a rare hetero-TDDA cycloaddition. Our method is based on the integration of enynamides and cyanamides under the gold catalysis conditions. In contrast to a few previously reported cases of hetero-TDDA transformations involving conventional nitriles, the application of push−pull cyanamides, as the reaction partners of enynamides, leads to the formation of a pyridine backbone under essentially mild conditions allowing high functional group tolerance. The advantages of the proposed method also include scalability and the possibility of further modifications of the obtained heterocyclic products. In conclusion, we showed the uniqueness of the chemical behavior of enynamides in comparison with *β*-aryl-substituted analogues. We hope that the use of enynamides will open up new frontiers in gold catalysis.

EXPERIMENTAL SECTION

General Information. NMR spectra were recorded at ambient temperature with a Bruker Avance III 400 instrument at 400.13 MHz (^{1}H NMR) and 100.61 MHz (^{13}C NMR) in $CDCl_3$. Chemical shifts (δ) are given in ppm relative to resonances of the solvents (^{1}H: δ = 7.26 for residual $CHCl_3$ peak; ^{13}C: δ = 77.2 for $CDCl_3$). Mass spectra were recorded on Bruker MicroTOF (ESI) and Bruker maXis HRMS-ESI-QTOF instruments. Chromatographic separation was carried out on Macherey−Nagel silica gel 60 M (0.04−0.063 mm). Analytical TLC was performed on unmodified Merck ready-to-use plates (TLC silica gel 60 F254); detection was achieved with a UV lamp. Melting points were measured with a Stuart smp30 apparatus. Gold complexes ($IPrAuNTf_2$,[69] Ph_3PAuCl,[70] JohnPhosAuCl[71]) were synthesized accordingly to the published protocols. Known enynamides **1** were prepared according to the literature procedures.[34,72] The solvents were purified using standard techniques and stored over activated 4 Å molecular sieves before use. Other reagents were purchased from commercial vendors and were used as received. For known compounds **1c−e,g,o** the ^{1}H and ^{13}C NMR spectra are consistent with previously reported literature.

General Procedure for the Synthesis of Starting Enynamides 1. A 50 mL round-bottom flask was charged with amide (1.0



mmol), 1,1-dibromo-1-alkene (1.2 mmol, 1.2 equiv), Cs_2CO_3 (1.30 g, 4.0 mmol, 4.0 equiv), and copper(I) iodide (24 mg, 0.125 mmol, 12.5 mol %). The flask was fitted with a rubber septum, evacuated under high vacuum, and backfilled with argon. Dry and degassed DMF (5 mL) and *N*,*N*′-dimethylethylenediamine (22 mg, 0.25 mmol, 25 mol %) were next added, and the blue or green suspension was heated at 70 °C in an oil bath for 24 h 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 enynamides **1**.

*(E)-N,4-Dimethyl-N-(4-phenylbut-3-en-1-yn-1-yl)benzenesulfonamide (**1a**).*[72] Yellow solid (224 mg, 72%); mp 83.5−84.5 °C (hexane/EtOAc); R_f 0.30 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.3 Hz, 2H), 7.40−7.23 (m, 7H), 6.83 (d, J = 16.2 Hz, 1H), 6.22 (d, J = 16.2 Hz, 1H), 3.12 (s, 3H), 2.46 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 145.0, 139.8, 136.5, 133.4, 130.0, 128.8, 128.5, 127.9, 126.2, 107.6, 86.1, 68.9, 39.5, 21.8; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{17}NO_2SNa^+$, 334.0872; found, 334.0873.

*(E)-4-Fluoro-N-methyl-N-(4-phenylbut-3-en-1-yn-1-yl)benzenesulfonamide (**1b**).* Yellow solid (218 mg, 69%); mp 60.0−61.5 °C (hexane/EtOAc); R_f 0.30 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.93 (m, 2H), 7.39−7.23 (m, 7H), 6.85 (d, J = 16.2 Hz, 1H), 6.22 (d, J = 16.2 Hz, 1H), 3.14 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 165.9 (d, J_F = 256.4 Hz), 140.2, 136.3, 132.4 (d, J_F = 3.2 Hz), 130.6 (d, J_F = 9.6 Hz), 128.8, 128.6, 126.2, 116.7 (d, J_F = 22.7 Hz), 107.2, 85.6, 69.0, 39.4; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{17}H_{14}FNO_2SNa^+$, 338.0621; found, 338.0615.

*(E)-N-Methyl-N-(4-phenylbut-3-en-1-yn-1-yl)methanesulfonamide (**1c**).*[72] Brown solid (165 mg, 70%); mp 78.0−80.0 °C (hexane/EtOAc); R_f 0.40 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) 7.36−7.23 (m, 5H), 6.86 (d, J = 16.2 Hz, 1H), 6.21 (d, J = 16.2 Hz, 1H), 3.24 (s, 3H), 3.08 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 140.2, 136.4, 128.9, 128.6, 126.3, 107.3, 85.2, 69.3, 39.3, 36.9; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{13}NO_2SNa^+$, 258.0559; found, 258.0555.

https://doi.org/10.1021/acs.joc.1c00558
J. Org. Chem. 2021, 86, 7218−7228

*(E)-3-(4-Phenylbut-3-en-1-yn-1-yl)oxazolidin-2-one (**1d**).*[73] Brown solid (117 mg, 55%); mp 106.5−108.0 °C (hexane/EtOAc); R_f 0.40 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 6.93 (d, J = 16.2 Hz, 1H), 6.25 (d, J = 16.2 Hz, 1H), 4.49−4.45 (m, 2H), 3.99−3.95 (m, 2H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 156.6, 140.3, 136.3, 128.8, 128.6, 126.2, 107.0, 81.2, 71.0, 63.2, 47.1; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{11}NO_2Na^+$, 236.0682; found, 236.0680.

*(E)-N-Benzyl-4-methyl-N-(4-phenylbut-3-en-1-yn-1-yl)benzenesulfonamide (**1e**).*[74] Yellowish solid (263 mg, 68%); mp 84.5−86 °C (hexane/EtOAc); R_f 0.30 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.33−7.24 (m, 12H), 6.71 (d, J = 16.2 Hz, 1H), 6.15 (d, J = 16.2 Hz, 1H), 4.56 (s, 2H), 2.45 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 144.8, 139.6, 136.6, 135.0, 134.7, 129.9, 128.9, 128.8, 128.7, 128.48, 128.47, 127.9, 126.2, 107.7, 84.9, 71.2, 55.9, 21.8; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{24}H_{21}NO_2SNa^+$, 410.1185; found, 410.1180

*(E)-N-Allyl-4-methyl-N-(4-phenylbut-3-en-1-yn-1-yl)benzenesulfonamide (**1f**).* Brown oil (135 mg, 40%); R_f 0.30 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 2H), 7.41−7.22 (m, 7H), 6.83 (d, J = 16.2 Hz, 1H), 6.24 (d, J = 16.2 Hz, 1H), 5.78 (ddt, J = 16.6, 10.1, 6.3 Hz, 1H), 5.33−5.22 (m, 2H), 4.03 (d, J = 6.3 Hz, 2H), 2.46 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 144.8, 139.6, 136.4, 134.7, 130.9, 129.9, 128.7, 128.4, 127.7, 126.0, 120.1, 107.5, 84.4, 70.6, 54.4, 21.6; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{20}H_{19}NO_2SNa^+$, 360.1029; found, 360.1022.

*(E)-N-Cyclopropyl-4-methyl-N-(4-phenylbut-3-en-1-yn-1-yl)benzenesulfonamide (**1g**).*[75] Brown oil (250 mg, 74%); R_f 0.30 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.3 Hz, 2H), 7.40−7.24 (m, 7H), 6.84 (d, J = 16.2 Hz, 1H), 6.25 (d, J = 16.2 Hz, 1H), 2.81 (tt, J = 7.0, 3.6 Hz, 1H), 2.46 (s, 3H), 0.92−0.85 (m, 2H), 0.83−0.75 (m, 2H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 144.9, 139.6, 136.5, 134.0, 129.9, 128.8, 128.4, 128.1, 126.1, 107.6, 84.1, 70.3, 33.0, 21.8, 6.6; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{20}H_{19}NO_2SNa^+$, 360.1029; found, 360.1022.

*(E)-N-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-4-methyl-N-(4-phenylbut-3-en-1-yn-1-yl)benzenesulfonamide (**1h**).* Brown oil (267 mg, 60%); R_f 0.35 (hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.3 Hz, 2H), 7.37−7.23 (m, 7H), 6.82 (d, J = 16.2 Hz, 1H), 6.71−6.59 (m, 3H), 6.25 (d, J = 16.2 Hz, 1H), 5.89 (s, 2H), 3.59−3.53 (m, 2H), 2.90−2.84 (m, 2H), 2.43 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 147.8, 146.5, 144.8, 139.8, 136.6, 134.9, 131.3, 129.9, 128.9, 128.5, 127.7, 126.2, 122.1, 109.5, 108.5, 107.7, 101.1, 84.3, 71.2, 53.2, 34.4, 21.8; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{23}NO_4SNa^+$, 468.1240; found, 468.1238.

*N,4-Dimethyl-N-((3E,5E)-6-phenylhexa-3,5-dien-1-yn-1-yl)benzenesulfonamide (**1n**).* Yellow solid (280 mg, 83%); mp 117.0−118.5 °C (hexane/EtOAc); R_f 0.40 (hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.3 Hz, 2H), 7.41−7.37 (m, 4H), 7.32 (t, J = 7.6 Hz, 2H), 7.25−7.22 (m, 1H), 8.80 (dd, J = 15.6, 10.8 Hz, 1H), 6.67−6.56 (m, 2H), 5.78 (d, J = 15.2 Hz, 1H), 3.11 (s, 3H), 2.47 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 144.9, 140.4, 137.0, 134.1, 133.5, 130.0, 128.8, 128.2, 128.0, 127.9, 126.7, 110.8, 87.2, 69.2, 39.5, 21.8; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{20}H_{19}NNaO_2S^+$, 360.1034; found, 360.1029.

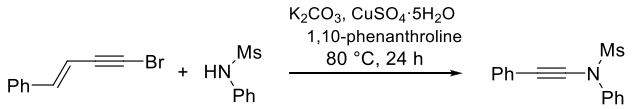
*(E)-N,4-Dimethyl-N-(4-(thiophen-2-yl)but-3-en-1-yn-1-yl)benzenesulfonamide (**1o**).*[72] Yellow oil (167 mg, 53%); R_f 0.50 (hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.17 (dd, J = 4.8, 1.5 Hz, 1H), 6.99−6.95 (m, 2H), 6.93 (d, J = 15.9 Hz, 1H), 6.03 (d, J = 15.9 Hz, 1H), 3.10 (s, 3H), 2.46 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 144.9, 141.5, 133.4, 132.9, 130.00, 127.9, 127.8, 126.7, 125.2, 106.8, 86.4, 68.5, 39.40 21.8; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{16}H_{15}NNaO_2S_2^+$, 340.0436; found, 340.0441.

*(E)-N,4-Dimethyl-N-(4-(naphthalen-1-yl)but-3-en-1-yn-1-yl)benzenesulfonamide (**1p**).* Brown oil (300 mg, 83%); R_f 0.35 (hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 1.8 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 6.6 Hz, 1H), 7.60 (s, 1H), 7.57−7.48 (m, 2H), 7.45 (t, J = 7.7 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 6.30 (d, J = 16.0 Hz, 1H), 3.17 (s, 3H), 2.47 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 145.0, 136.8, 134.0, 133.9, 133.6, 131.0, 130.1, 128.9, 128.8, 128.0, 126.5, 126.1, 125.7, 123.7, 123.4, 110.3, 86.1, 69.3, 39.5, 21.9; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{22}H_{19}NO_2SNa^+$, 384.1029; found, 384.1025.

*(E)-N,4-Dimethyl-N-(pent-3-en-1-yn-1-yl)benzenesulfonamide (**1q**).* Colorless solid (204 mg, 82%); mp 78.5−80.0 °C (hexane/EtOAc); R_f 0.50 (hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 6.09−6.00 (m, 1H), 5.54−5.49 (m, 1H), 3.04 (s, 3H), 2.44 (s, 3H), 1.76 (dd, J = 6.8, 1.8 Hz, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 144.8, 139.1, 133.4, 129.8, 127.9, 109.9, 82.1, 67.7, 39.4, 21.7, 18.6; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{13}H_{15}NNaO_2S^+$, 272.0716; found, 272.0720.

*(E)-N,4-Dimethyl-N-(3-methyl-4-phenylbut-3-en-1-yn-1-yl)benzenesulfonamide (**1r**).* Yellowish solid (215 mg, 66%); mp 57.5−59.5 °C (hexane/EtOAc); R_f 0.30 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.3 Hz, 2H), 7.41−7.32 (m, 4H), 7.28−7.22 (m, 3H), 6.73 (s, 1H), 3.13 (s, 3H), 2.47 (s, 3H), 2.47 (d, J = 1.4 Hz, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 144.9, 137.0, 134.6, 133.5, 130.0, 129.0, 128.4, 128.0, 127.2, 119.3, 83.4, 73.1, 39.5, 21.8, 19.5; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{19}NO_2SNa^+$, 348.1029; found, 348.1024.

Synthesis of Enynamide 1i. A 50 mL round-bottom flask was charged with *N*-phenylmethanesulfonamide (171 mg, 1.0 mmol),



K_2CO_3 (415 mg, 3.0 mmol, 3.0 equiv), 1,10-phenanthroline monohydrate (59.5 mg, 0.3 mmol, 30 mol %), and $CuSO_4{\cdot}5H_2O$ (49.9 mg, 0.2 mmol, 20 mol %). The flask was fitted with a rubber septum, evacuated under high vacuum, and backfilled with argon. Dry and degassed toluene (10 mL) and (*E*)-(4-bromobut-1-en-3-yn-1-yl)benzene (228 mg, 1.1 mmol, 1.1 equiv) were next added, and the suspension was heated at 80 °C in an oil bath for 12 h 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 enynamides **1i**.

*(E)-N-Phenyl-N-(4-phenylbut-3-en-1-yn-1-yl)methanesulfonamide (**1i**).*[34] Brown solid (40.0 mg, 13%); mp 89.0−91.0 °C (hexane/EtOAc); R_f 0.35 (hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.1 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.39−7.27 (m, 6H), 6.94 (d, J = 16.2 Hz, 1H), 6.30 (d, J = 16.2 Hz, 1H), 3.15 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 140.8, 138.9, 136.4, 129.7, 128.9, 128.7, 128.6, 126.3, 125.8, 107.2, 84.1, 70.7, 37.1; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{17}H_{15}NO_2SNa^+$, 320.0716; found, 320.0709.

General Procedure for the Gold(I)-Catalyzed Synthesis of Pyridines 5 and 6. IPrAuCl (6.2 mg, 10.0 μmol, 5 mol %) and $AgNTf_2$ (3.9 mg, 10.0 μmol, 5 mol %) in one portion were added to the solution of enynamide (**1**, 0.2 mmol) and cyanamide **4** (0.3 mmol, 1.5 equiv) in DCM (1.0 mL). The resulting mixture was stirred at room temperature for 24 h. After completion, all volatile components were removed in vacuo, and the residue was purified by silica gel chromatography eluting with hexane/EtOAc to afford pyridines **5** and **6**.

*N-(6-(Dimethylamino)-5-phenylpyridin-2-yl)-N,4-dimethylbenzenesulfonamide (**5a**).* Colorless solid (69.4 mg, 91%); mp 113.0−115.0 °C (hexane/EtOAc); R_f 0.30 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.3 Hz, 2H), 7.44−7.36 (m, 5H), 7.30−7.27 (m, 1H), 7.24 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 7.9 Hz, 1H), 3.32 (s, 3H), 2.53 (s, 6H), 2.40 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 157.6, 150.3, 143.6, 141.7, 140.1, 135.4, 129.5, 128.8, 128.2, 127.7, 127.1, 122.0, 110.3, 41.3, 35.6, 21.7; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{21}H_{23}N_3O_2SNa^+$, 404.1403; found, 404.1403.

*N-(6-(Dimethylamino)-5-phenylpyridin-2-yl)-4-fluoro-N-methylbenzenesulfonamide (**5b**).* Colorless solid (73.2 mg, 95%); mp 103.0−105.0 °C (hexane/EtOAc); R_f 0.50 (hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 8.9, 5.1 Hz, 2H), 7.45−7.35

https://doi.org/10.1021/acs.joc.1c00558
J. Org. Chem. 2021, 86, 7218−7228

(m, 5H), 7.29 (t, J = 7.0 Hz, 1H), 7.12 (t, J = 8.6 Hz, 2H), 7.06 (d, J = 7.9 Hz, 1H), 3.31 (s, 3H), 2.52 (s, 6H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 165.3 (d, J_F = 254.4 Hz), 158.2, 150.0, 141.7, 140.4, 134.3 (d, J_F = 3.3 Hz), 130.5 (d, J_F = 9.3 Hz), 128.8, 128.1, 127.1, 122.2, 116.0 (d, J_F = 22.5 Hz), 110.4, 41.1, 35.8; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{20}H_{20}FN_3O_2SNa^+$, 408.1152; found, 408.1162.

*N-(6-(Dimethylamino)-5-phenylpyridin-2-yl)-N-methylmethanesulfonamide (**5c**).* Colorless solid (56.2 mg, 92%); mp 124.5−126.5 °C (hexane/EtOAc); R_f 0.35 (hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.37 (m, 5H), 7.29 (tt, J = 6.4, 1.9 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 3.40 (s, 3H), 3.16 (s, 3H), 2.72 (s, 6H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 158.2, 150.8, 142.1, 140.3, 128.8, 128.1, 127.0, 121.8, 107.9, 41.3, 38.2, 35.8; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{15}H_{19}N_3O_2SNa^+$, 328.1090; found, 328.1102

*3-(6-(Dimethylamino)-5-phenylpyridin-2-yl)oxazolidin-2-one (**5d**).* Colorless solid (47.6 mg, 84%); mp 144.0−145.5 °C (hexane/EtOAc); R_f 0.45 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.1 Hz, 1H), 7.49−7.42 (m, 3H), 7.38 (t, J = 7.6 Hz, 2H), 7.29−7.25 (m, 1H), 4.47 (t, J = 8.2 Hz, 2H), 4.33 (t, J = 8.3 Hz, 2H), 2.71 (s, 6H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 157.7, 157.2, 147.8, 142.1, 140.5, 128.7, 128.2, 126.8, 119.9, 103.2, 62.2, 44.2, 41.3; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{16}H_{17}N_3O_2Na^+$, 306.1213; found, 306.1222.

*N-Benzyl-N-(6-(dimethylamino)-5-phenylpyridin-2-yl)-4-methylbenzenesulfonamide (**5e**).* Yellow oil (84.2 mg, 92%); R_f 0.30 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.2 Hz, 2H), 7.41−7.32 (m, 7H), 7.31−7.23 (m, 5H), 7.20 (t, J = 7.2 Hz, 1H), 7.00 (d, J = 7.9 Hz, 1H), 5.08 (s, 2H), 2.50 (s, 6H), 2.42 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 158.1, 148.6, 143.5, 141.6, 140.2, 137.6, 136.6, 129.5, 128.7, 128.4, 128.2, 128.1, 127.8, 127.3, 127.0, 122.5, 112.3, 51.4, 41.2, 21.7; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{27}H_{27}N_3O_2SNa^+$, 480.1716; found, 480.1711.

*N-Allyl-N-(6-(dimethylamino)-5-phenylpyridin-2-yl)-4-methylbenzenesulfonamide (**5f**).* Yellowish oil (61.9 mg, 76%); R_f 0.35 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.3 Hz, 2H), 7.45−7.35 (m, 5H), 7.30−7.27 (m, 1H), 7.24 (d, J = 8.1 Hz, 2H), 7.02 (d, J = 7.9 Hz, 1H), 5.92 (ddt, J = 16.0, 10.3, 5.8 Hz, 1H), 5.25 (dd, J = 17.2, 1.5 Hz, 1H), 5.11 (dd, J = 10.2, 1.4 Hz, 1H), 4.49 (dt, J = 5.7, 1.2 Hz, 2H), 2.52 (s, 6H), 2.41 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 158.3, 148.9, 143.4, 141.6, 140.5, 136.7, 134.0, 129.4, 128.7, 128.1, 127.8, 127.0, 122.2, 117.9, 111.3, 50.7, 41.2, 21.7; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{23}H_{25}N_3O_2SNa^+$, 430.1560; found, 430.1566.

*N-Cyclopropyl-N-(6-(dimethylamino)-5-phenylpyridin-2-yl)-4-methylbenzenesulfonamide (**5g**).* Yellowish oil (79.1 mg, 97%); R_f 0.30 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.3 Hz, 2H), 7.48−7.36 (m, 5H), 7.31−7.28 (d, 1H), 7.26 (d, J = 8.1 Hz, 2H), 6.85 (d, J = 7.7 Hz, 1H), 2.77 (tt, J = 6.9, 3.6 Hz, 1H), 2.50 (s, 6H), 2.43 (s, 3H), 0.90−0.85 (m, 2H), 0.79−0.74 (m, 2H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 158.6, 151.3, 143.4, 141.4, 140.5, 135.8, 129.2, 128.7, 128.6, 128.1, 127.0, 123.2, 113.4, 41.1, 30.5, 21.7, 8.4; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{23}H_{25}N_3O_2SNa^+$, 430.1560; found, 430.1551.

*N-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-N-(6-(dimethylamino)-5-phenylpyridin-2-yl)-4-methylbenzenesulfonamide (**5h**).* Colorless oil (92.8 mg, 90%); R_f 0.45 (hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.3 Hz, 2H), 7.47−7.36 (m, 5H), 7.29 (t, J = 7.2 Hz, 1H), 7.21 (d, J = 8.1 Hz, 2H), 7.02 (d, J = 7.8 Hz, 1H), 6.72−6.62 (m, 3H), 5.90 (s, 2H), 4.03−3.97 (m, 2H), 2.88−2.82 (m, 2H), 2.55 (s, 6H), 2.39 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 158.4, 148.8, 147.7, 146.2, 143.4, 141.6, 140.4, 136.5, 132.9, 129.4, 128.8, 128.1 127.7, 127.0, 122.4, 122.0, 112.2, 109.5, 108.4, 101.0, 49.7, 41.3, 35.6, 21.7; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{29}H_{29}N_3O_4SNa^+$, 538.1771; found, 538.1777.

*N-(6-(Dimethylamino)-5-phenylpyridin-2-yl)-N-phenylmethanesulfonamide (**5i**).* Yellow solid (59.5 mg, 81%); mp 168.0−170.0 °C (hexane/EtOAc); R_f 0.35 (hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.35 (m, 9H), 7.32−7.27 (m, 2H), 6.19 (d, J = 7.9 Hz, 1H), 3.55 (s, 3H), 2.77 (s, 6H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 158.2, 152.3, 142.2, 140.5, 139.9, 129.7, 129.7, 128.8, 128.6, 128.2, 127.0, 121.4, 108.2, 41.5. 41.3; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{20}H_{21}N_3O_2SNa^+$, 390.1247; found, 390.1244.

*N-(6-(Dimethylamino)-5-(o-tolyl)pyridin-2-yl)-N,4-dimethylbenzenesulfonamide (**5j**).* Colorless oil (75.1 mg, 95%); R_f 0.35 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 7.8 Hz, 1H), 7.24−7.18 (m, 6H), 7.03 (d, J = 7.8 Hz, 1H), 3.32 (s, 3H), 2.49 (s, 6H), 2.40 (s, 3H), 2.09 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 157.5, 150.3, 143.5, 141.9, 140.3, 136.2, 135.3, 130.2, 129.8, 129.3, 127.8, 127.3, 126.1, 121.1, 109.0, 40.3, 35.7, 21.7, 19.8; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{22}H_{25}N_3O_2SNa^+$, 418.1560; found, 418.1557.

*N-(6-(Dimethylamino)-5-(p-tolyl)pyridin-2-yl)-N,4-dimethylbenzenesulfonamide (**5k**).* Colorless oil (60.9 mg, 77%); R_f 0.40 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 7.9 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 7.07 (d, J = 7.9 Hz, 1H), 3.31 (s, 3H), 2.52 (s, 6H), 2.40 (s, 3H), 2.38 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 158.2, 150.0, 143.5, 141.5, 137.5, 136.7, 135.4, 129.43, 129.42, 128.0, 127.8, 121.9, 110.1, 41.1, 35.6, 21.7, 21.4; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{22}H_{25}N_3O_2SNa^+$, 418.1560; found, 418.1557.

*N-(6-(Dimethylamino)-5-(4-methoxyphenyl)pyridin-2-yl)-N,4-dimethylbenzenesulfonamide (**5l**).* Colorless oil (70.0 mg, 85%); R_f 0.50 (hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 7.9 Hz, 1H), 6.93 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H), 3.30 (s, 3H), 2.53 (s, 6H), 2.40 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 158.7, 158.0, 149.9, 143.5, 141.4, 135.3, 132.5, 129.4, 129.2, 127.8, 122.0, 114.2, 110.5, 55.4, 41.2, 35.6, 21.7; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{22}H_{26}N_3O_3S^+$, 412.1689; found, 412.1668.

*N-(5-(4-Bromophenyl)-6-(dimethylamino)pyridin-2-yl)-N,4-dimethylbenzenesulfonamide (**5m**).* Colorless oil (85.6 mg, 93%); R_f 0.30 (hexane/ethyl acetate 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 7.9 Hz, 1H), 3.32 (s, 3H), 2.54 (s, 6H), 2.40 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 158.1, 150.5, 143.6, 141.4, 139.4, 135.5, 131.9, 129.7, 129.5, 127.7, 120.8, 120.3, 109.9, 41.2, 35.6, 21.7; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{21}H_{22}BrN_3O_2SNa^+$, 482.0508; found, 482.0507.

*(E)-N-(6-(Dimethylamino)-5-styrylpyridin-2-yl)-N,4-dimethylbenzenesulfonamide (**5n**).* Colorless oil (67.6 mg, 83%); R_f 0.25 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1 Hz, 1H), 7.56−7.50 (m, 4H), 7.36 (t, J = 7.6 Hz, 2H), 7.28−7.24 (m, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 16.4 Hz, 1H), 6.95 (d, J = 16.3 Hz, 1H), 3.29 (s, 3H), 2.74 (s, 6H), 2.40 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 159.5, 150.4, 143.6, 137.7, 137.1, 135.1, 129.4, 128.9, 128.5, 127.8, 127.7, 126.5, 125.6, 120.0, 111.9, 42.2, 35.6, 21.7; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{23}H_{25}N_3NaO_2S^+$, 430.1560; found, 430.1565.

*N-(6-(Dimethylamino)-5-(thiophen-2-yl)pyridin-2-yl)-N,4-dimethylbenzenesulfonamide (**5o**).* Colorless solid (55.0 mg, 71%); mp 88.5−89.5 °C (hexane/EtOAc); R_f 0.35 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.56 (m, 3H), 7.29 (dd, J = 5.1, 1.2 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.18 (dd, J = 3.5, 1.2 Hz, 1H), 7.13 (dd, J = 3.5, 1.2 Hz, 1H), 7.04 (dd, J = 5.2, 3.6 Hz, 1H), 3.31 (s, 3H), 2.59 (s, 6H), 2.40 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 158.6, 150.5, 143.6, 141.3, 141.0, 135.3, 129.5, 127.7, 127.1, 125.5, 125.4, 116.3, 110.6, 41.4, 35.5, 21.7; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{19}H_{21}N_3NaO_2S_2^+$, 410.0967; found, 410.0974.

*N-(6-(Dimethylamino)-5-(naphthalen-1-yl)pyridin-2-yl)-N,4-dimethylbenzenesulfonamide (**5p**).* Yellowish solid (82.0 mg, 95%); mp 146.0−148.0 °C (hexane/EtOAc); R_f 0.40 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.4 Hz, 1H), 7.52−7.48 (m, 2H), 7.45−7.38 (m, 3H), 7.28 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 7.9 Hz, 1H), 3.39 (s, 3H), 2.43 (s, 3H), 2.41 (s, 6H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 158.0, 150.7, 143.5, 142.9, 138.4, 135.5, 133.8, 131.6, 129.4, 128.5, 127.79, 127.76, 127.0, 126.2, 126.1, 126.0, 125.7,

https://doi.org/10.1021/acs.joc.1c00558
J. Org. Chem. 2021, 86, 7218−7228

119.0, 108.4, 40.3, 35.7, 21.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{25}N_3O_2SNa^+$, 454.1560; found, 454.1563.

*N-(6-(Dimethylamino)-5-methylpyridin-2-yl)-N,4-dimethylbenzenesulfonamide (**5q**).* Colorless oil (52.4 mg, 92%); R_f 0.45 (hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 7.8 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 7.8 Hz, 1H), 3.22 (s, 3H), 2.63 (s, 6H), 2.39 (s, 3H), 2.24 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 160.6, 149.3, 143.3, 141.1, 135.0, 129.3, 127.8, 120.5, 112.9, 41.5, 35.8, 21.6, 18.7; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{16}H_{21}N_3NaO_2S^+$, 342.1247; found, 342.1253.

*N-(6-(Dimethylamino)-4-methyl-5-phenylpyridin-2-yl)-N,4-dimethylbenzenesulfonamide (**5r**).* Colorless solid (77.5 mg, 98%); mp 125.0−126.0 °C (hexane/EtOAc); R_f 0.30 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.3 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 6.9 Hz, 2H), 6.96 (s, 1H), 3.27 (s, 3H), 2.41 (s, 3H), 2.40 (s, 6H), 2.05 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 159.0, 149.9, 148.7, 143.4, 138.9, 135.5, 130.3, 129.3, 128.6, 127.9, 126.9, 122.7, 112.7, 41.3, 35.7, 21.7, 21.1; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{26}N_3O_2S^+$, 396.1740; found, 396.1728.

*N,N′-(1,4-Phenylenebis(6-(dimethylamino)pyridine-5,2-diyl))bis-(N,4-dimethylbenzenesulfonamide) (**5s**).* Was additionally recrystallized from hexane/EtOAc and obtained as a yellow solid with an 85% purity (NMR assay; with an admixture of IPr[76]), 104.0 mg, 70%; mp 208.0−210.0 °C (hexane/EtOAc); R_f 0.50 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.2 Hz, 4H), 7.47−7.45 (m, 6H), 7.30−7.24 (m, 6H), 7.11 (d, J = 7.9 Hz, 2H), 3.33 (s, 6H), 2.56 (s, 12H), 2.41 (s, 6H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 159.5, 150.4, 143.6, 137.7, 137.1, 135.1, 129.4, 128.9, 128.5, 127.8, 127.7, 126.5, 125.6, 120.0, 111.9, 42.2, 35.6, 21.7; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{36}H_{40}N_6NaO_4S_2^+$, 707.2445; found, 707.2451.

*N-(6-(Diethylamino)-5-phenylpyridin-2-yl)-N-methylmethanesulfonamide (**6a**).* Colorless oil (66.0 mg, 99%); R_f 0.30 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.36 (m, 5H), 7.32−7.27 (m, 1H), 6.86 (d, J = 7.9 Hz, 1H), 3.39 (s, 3H), 3.13 (q, J = 7.0 Hz, 4H), 3.09 (s, 3H), 0.96 (t, J = 7.0 Hz, 6H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 157.6, 150.8, 142.1, 140.5, 128.8, 128.2, 127.2, 123.7, 109.1, 44.4, 37.6, 35.9, 12.9; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{17}H_{23}N_3O_2SNa^+$, 356.1403; found, 356.1402.

*N-(6-(Benzyl(methyl)amino)-5-phenylpyridin-2-yl)-N,4-dimethylbenzenesulfonamide (**6b**).* Yellow oil (80.5 mg, 88%); R_f 0.30 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 7.9 Hz, 1H), 7.43 (d, J = 7.1 Hz, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.30−7.26 (m, 1H), 7.24−7.15 (m, 6H), 7.04−6.99 (m, 2H), 4.19 (s, 2H), 3.22 (s, 3H), 2.43 (s, 3H), 2.38 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 157.4, 150.4, 143.5, 142.1, 140.2, 138.9, 135.3, 129.5, 128.8, 128.34, 128.33, 128.0, 127.7, 127.1, 126.9, 122.0, 110.7, 56.1, 39.3, 35.6, 21.7; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{27}H_{27}N_3O_2SNa^+$, 480.1716; found, 480.1725.

*N-(6-(Dibenzylamino)-5-phenylpyridin-2-yl)-N,4-dimethylbenzenesulfonamide (**6c**).* Colorless oil (105.7 mg, 99%); R_f 0.30 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.47 (m, 5H), 7.40 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.1 Hz, 1H), 7.24−7.19 (m, 7H), 7.14 (d, J = 8.1 Hz, 2H), 6.95 (dd, J = 6.9 Hz, J = 2.3 Hz, 4H), 4.05 (s, 4H), 3.09 (s, 3H), 2.37 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 157.2, 150.6, 143.5, 142.1, 140.0, 139.0, 135.1, 129.5, 129.0, 128.3 (×2), 128.1, 127.8, 127.4, 126.9, 123.5, 112.0, 53.5, 35.6, 21.7; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{33}H_{31}N_3O_2SNa^+$, 556.2029; found, 556.2019.

*N-(6-(Dibenzylamino)-5-phenylpyridin-2-yl)-N-methyl-4-nitrobenzenesulfonamide (**6d**).* Orange solid (103.9 mg, 92%); mp 61.5−63.0 °C (hexane/EtOAc); R_f 0.50 (hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.9 Hz, 2H), 7.70 (d, J = 8.8 Hz, 1H), 7.55−7.51 (m, 3H), 7.43 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 7.4 Hz, 2H), 7.25−7.19 (m, 6H), 7.16 (d, J = 7.9 Hz, 1H), 6.93 (dd, J = 6.5 Hz, J = 2.8 Hz, 4H), 4.00 (s, 4H), 3.09 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 157.3, 150.1, 149.9, 143.8, 142.5, 139.7, 138.6, 129.2, 129.0, 128.5, 128.2, 128.0, 127.8, 127.2, 124.7, 124.0, 112.5, 53.6, 36.0; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{32}H_{28}N_4O_4SNa^+$, 587.1723; found, 587.1740.

*N-(6-(Diphenylamino)-5-phenylpyridin-2-yl)-N-methylmethanesulfonamide (**6e**).* Yellowish oil (62.7 mg, 73%); R_f 0.35 (hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 6.4 Hz, 2H), 7.12−7.05 (m, 8H), 6.92−6.83 (m, 6H), 3.26 (s, 3H), 2.80 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 155.4, 152.6, 146.7, 142.7, 137.9, 128.9, 128.8, 128.5, 128.2, 127.1, 124.4, 123.3, 112.9, 39.2, 35.8; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{23}N_3O_2SNa^+$: 452.1403; found, 452.1405.

*N,4-Dimethyl-N-(5-phenyl-6-(pyrrolidin-1-yl)pyridin-2-yl)-benzenesulfonamide (**6f**).* Brownish oil (61.9 mg, 76%); R_f 0.40 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.3 Hz, 2H), 7.38−7.27 (m, 6H), 7.24 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 7.9 Hz, 1H), 3.33 (s, 3H), 2.97−2.92 (m, 4H), 2.40 (s, 3H), 1.70−1.64 (m, 4H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 154.9, 150.4, 143.4, 141.6, 140.5, 135.7, 129.4, 129.2, 128.1, 127.8, 126.7, 119.8, 107.6, 50.1, 35.6, 25.7, 21.7; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{23}H_{25}N_3O_2SNa^+$, 430.1560; found, 430.1572.

*N,4-Dimethyl-N-(5-phenyl-6-(piperidin-1-yl)pyridin-2-yl)-benzenesulfonamide (**6g**).* Colorless oil (70.0 mg, 83%); R_f 0.45 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 7.1 Hz, 2H), 7.44 (d, J = 7.9 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 7.9 Hz, 1H), 3.29 (s, 3H), 2.89−2.84 (m, 4H), 2.40 (s, 3H), 1.45−1.39 (m, 2H), 1.38−1.31 (m, 4H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 158.6, 150.4, 143.5, 141.3, 140.1, 135.2, 129.4, 128.8, 127.83, 127.79, 127.2, 123.4, 111.5, 50.0, 35.7, 25.5, 24.7, 21.7; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{24}H_{27}N_3O_2SNa^+$, 444.1716; found, 444.1717.

*N,4-Dimethyl-N-(6-morpholino-5-phenylpyridin-2-yl)benzenesulfonamide (**6h**).* Orange oil (66.9 mg, 79%); R_f 0.50 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 7.3 Hz, 2H), 7.47 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 7.27−7.24 (m, 2H), 7.22 (d, J = 8.1 Hz, 1H), 3.52−3.48 (m, 4H), 3.30 (s, 3H), 2.90−2.86 (m, 4H), 2.41 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 157.6, 150.6, 143.7, 141.5, 139.4, 135.2, 129.5, 128.9, 127.9, 127.7, 127.5, 123.4, 112.3, 66.6, 49.1, 35.6, 21.7; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{23}H_{25}N_3O_3SNa^+$, 446.1509; found, 446.1505.

*N-(6-(3,4-Dihydroisoquinolin-2(1H)-yl)-5-phenylpyridin-2-yl)-N-methylmethanesulfonamide (**6i**).* Yellowish oil (76.3 mg, 97%); R_f 0.35 (hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.2 Hz, 2H), 7.48 (d, J = 7.9 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.3 Hz, 1H), 7.15−7.11 (m, 2H), 7.07−7.02 (m, 2H), 6.94 (d, J = 7.9 Hz, 1H), 4.40 (s, 2H), 3.41 (s, 3H), 3.32 (t, J = 5.8 Hz, 2H), 3.03 (s, 3H), 2.66 (t, J = 5.7 Hz, 2H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 157.9, 151.0, 142.1, 139.9, 135.2, 134.8, 129.0, 128.9, 128.0, 127.4, 126.7, 126.3, 126.0, 123.3, 109.8, 50.7, 47.5, 37.7, 35.8, 28.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{23}N_3O_2SNa^+$, 416.1403; found, 416.1404.

Synthesis of 6c (1 mmol Scale). IPrAuCl (31.0 mg, 50.0 μmol, 5 mol %) and $AgNTf_2$ (19.5 mg, 50.0 μmol, 5 mol %) in one portion were added to the solution of ynamide **1a** (311 mg, 1.0 mmol) and *N,N*-dibenzylcyanamide (333 mg, 1.5 mmol, 1.5 equiv) in DCM (5.0 mL). The resulting mixture was stirred at room temperature for 24 h. After completion, DCM was removed in vacuo and the residue was purified by silica gel chromatography eluting with hexane/EtOAc to afford pyridine **6c** (507 mg, 95%).

Synthesis of 5a (Gram Scale). IPrAuCl (155 mg, 0.25 mmol, 5 mol %) and $AgNTf_2$ (97.5 mg, 0.25 mmol, 5 mol %) in one portion were added to the solution of **1a** (1.56 g, 5.0 mmol) and *N,N*-dimethylcyanamide (526 mg, 7.5 mmol, 1.5 equiv) in DCM (5.0 mL). The resulting mixture was stirred at room temperature for 24 h. After completion, DCM was removed in vacuo and the residue was purified by silica gel chromatography eluting with hexane/EtOAc to afford pyridine **5a** (1.74 g, 91%).

Bromination of 5a. The solution of bromine (17.6 mg, 0.11 mmol, 1.1 equiv) in $CHCl_3$ (1.0 mL) was added dropwise to the solution of **5a** (38.5 mg, 0.1 mmol) in $CHCl_3$ (1.0 mL) with stirring at room temperature. When the color of bromine ceased to disappear, the reaction was quenched by the addition of 10% aqueous solution of

https://doi.org/10.1021/acs.joc.1c00558
J. Org. Chem. 2021, 86, 7218−7228

$Na_2S_2O_3$ (5 mL) and was extracted with DCM (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in vacuo and the residue was purified by silica gel chromatography, eluting with hexane/EtOAc (8/1) to afford bromopyridine **7**.

*N-(3-Bromo-6-(dimethylamino)-5-phenylpyridin-2-yl)-N,4-dimethylbenzenesulfonamide (**7**).* Colorless solid (45.6 mg, 99%); mp 164.5−166.5 °C (hexane/EtOAc); R_f 0.30 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.3 Hz, 2H), 7.66 (s, 1H), 7.43−7.39 (m, 4H), 7.36−7.28 (m, 3H), 3.10 (s, 3H), 2.49 (s, 6H), 2.44 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 157.7, 148.3, 145.3, 143.5, 138.9, 135.7, 129.3, 128.90, 128.88, 128.0, 127.7, 126.4, 109.0, 41.0, 37.0, 21.7; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{21}H_{22}BrN_3O_2SNa^+$, 484.0488; found, 484.0496.

Iodination of 5a. Iodine (25.4 mg, 0.11 mmol, 1.1 equiv) was added to the solution of **5a** (38.5 mg, 0.1 mmol) and Ag_2SO_4 (31.2 mg, 0.1 mmol, 1.0 equiv) in EtOH (1.0 mL) with stirring at room temperature. The resulting mixture was stirred for 1 h. When the reaction was quenched by the addition of 10% aqueous solution of $Na_2S_2O_3$ (5 mL) and was extracted with DCM (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in vacuo and the residue was purified by silica gel chromatography, eluting with hexane/EtOAc (8/1) to afford iodopyridine **8**.

*N-(6-(Dimethylamino)-3-iodo-5-phenylpyridin-2-yl)-N,4-dimethylbenzenesulfonamide (**8**).* Colorless solid (48.7 mg, 96%); mp 178.5−180.5 °C (hexane/EtOAc); R_f 0.30 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.81 (d, J = 8.3 Hz, 2H), 7.41−7.37 (m, 4H), 7.35−7.28 (m, 3H), 3.08 (s, 3H), 2.47 (s, 6H), 2.44 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 158.5, 151.7, 151.1, 143.4, 138.9, 135.6, 129.2, 129.0, 128.9, 128.0, 127.7, 126.5, 81.7, 40.9, 37.2, 21.7; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{21}H_{22}IN_3O_2SNa^+$, 530.0370; found, 530.0367.

Denosylation of 5a. PhSH (13.2 mg, 0.12 mmol, 1.2 equiv) and K_2CO_3 (20.7 mg, 0.15 mmol, 1.5 equiv) were added to the solution of **6d** (56.4 mg, 0.1 mmol) in MeCN (1.0 mL). The resulting mixture was stirred at 60 °C in an oil bath for 12 h. After completion, all volatile components were removed in vacuo and the residue was purified by silica gel chromatography eluting with hexane/EtOAc (8/1) to afford pyridine **9**.

*N^2,N^2-Dibenzyl-N^6-methyl-3-phenylpyridine-2,6-diamine (**9**).* Yellow solid (19.7 mg, 52%); mp 97.0−98.5 °C (hexane/EtOAc); R_f 0.40 (hexane/EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 7.3 Hz, 2H), 7.37−7.29 (m, 3H), 7.25−7.16 (m, 7H), 7.10 (d, J = 6.8 Hz, 4H), 6.01 (d, J = 8.1 Hz, 1H), 4.33 (br. s, 1H, NH), 4.21 (s, 4H), 2.89 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 157.9, 157.5, 142.2, 141.6, 139.7, 128.7, 128.6, 128.5, 128.2, 126.7, 126.1, 115.5, 97.6, 53.4, 29.4; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{26}N_3^+$, 380.2121; found, 380.2130.

Debenzylation of 6c. A 50 mL round-bottom flask containing **6c** (53.4 mg, 0.1 mmol) and 10% palladium on carbon (10.6 mg, 0.01 mmol, 10 mol %) was fitted with a rubber septum, evacuated under high vacuum and backfilled with hydrogen. Degassed MeOH (5 mL) was next added. The flask was equipped with a hydrogen balloon, and the black suspension was heated at 50 °C in an oil bath for 24 h with stirring. After completion, all volatile components were removed in vacuo and the residue was purified by silica gel chromatography eluting with hexane/EtOAc (4/1) to afford di- and monodebenzylated pyridines **10** and **10′** respectively.

*N-(6-Amino-5-phenylpyridin-2-yl)-N,4-dimethylbenzenesulfonamide (**10**).* Colorless solid (23.7 mg, 67%); mp 85.0−86.3 °C (hexane/EtOAc); R_f 0.25 (hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.3 Hz, 2H), 7.47−7.41 (m, 4H), 7.37 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 8.0 Hz, 1H), 4.42 (s, 2H), 3.27 (s, 3H), 2.41 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 154.5, 151.6, 143.6, 139.6, 137.8, 135.4, 129.5, 129.2, 128.8, 127.8, 127.8, 118.6, 109.8, 35.6, 21.7.; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{20}N_3O_2S^+$, 354.1271; found, 354.1278.

*N-(6-(Benzylamino)-5-phenylpyridin-2-yl)-N,4-dimethylbenzenesulfonamide (**10′**).* Colorless oil (9.8 mg, 22%); R_f 0.50 (hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.3 Hz, 2H), 7.46−7.35 (m, 5H), 7.32 (d, J = 7.8 Hz, 1H), 7.24−7.12 (m, 7H), 6.96 (d, J = 7.8 Hz, 1H), 4.97 (t, J = 5.8 Hz, 1H), 4.35 (d, J = 5.8 Hz, 2H), 3.20 (s, 3H), 2.37 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 154.1, 151.5, 143.3, 140.3, 139.1, 137.6, 135.6, 129.4, 129.4, 129.0, 128.5, 127.9, 127.7, 127.2, 126.9, 119.0, 108.3, 45.3, 35.7, 21.7; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{26}H_{25}N_3NaO_2S^+$, 466.1560; found, 466.1563.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00558.

Experimental procedures, copies of ^{1}H and ^{13}C{1H} NMR spectra and XRD data (PDF)

FAIR data, including the primary NMR FID files, for compounds **1a−1i**; **1n−1r**; **5a−5s**; **6a−6i**; **7−10**; and **10′** (ZIP)

Accession Codes

CCDC 2062892 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Vadim Yu. Kukushkin − *Saint Petersburg State University, 199034 Saint Petersburg, Russian Federation; South Ural State University, 454080 Chelyabinsk, Russian Federation;* orcid.org/0000-0002-2253-085X; Email: v.kukushkin@spbu.ru

Alexey Yu. Dubovtsev − *Saint Petersburg State University, 199034 Saint Petersburg, Russian Federation;* orcid.org/0000-0001-6576-814X; Email: a.dubovtsev@spbu.ru

Authors

Nikolay V. Shcherbakov − *Saint Petersburg State University, 199034 Saint Petersburg, Russian Federation*

Dmitry V. Dar'in − *Saint Petersburg State University, 199034 Saint Petersburg, Russian Federation*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c00558

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

A.Yu.D. thanks the Russian Science Foundation for support of these studies (Grant 20-73-10022). We are much obliged to the Center for Magnetic Resonance, Center for Chemical Analysis and Material Research, Center for X-ray Diffraction Studies (all belonging to Saint Petersburg State University) for physicochemical measurements. V.Yu.K. thanks South Ural State University (Act 211 Government of the Russian Federation, Contract 02.A03.21.0011) for putting facilities at the author's disposal.

■ REFERENCES

(1) Wessig, P.; Müller, G. The Dehydro-Diels−Alder Reaction. *Chem. Rev.* **2008**, *108* (6), 2051−2063.

(2) Li, W.; Zhou, L.; Zhang, J. Recent Progress in Dehydro-(Genative) Diels–Alder Reaction. *Chem. - Eur. J.* **2016**, *22* (5), 1558–1571.
(3) Wessig, P.; Matthes, A.; Pick, C. The Photo-Dehydro-Diels–Alder (PDDA) Reaction. *Org. Biomol. Chem.* **2011**, *9* (22), 7599–7605.
(4) Dubbaka, S. R.; Kienle, M.; Mayr, H.; Knochel, P. Copper(I)-Mediated Oxidative Cross-Coupling between Functionalized Alkynyl Lithium and Aryl Magnesium Reagents. *Angew. Chem., Int. Ed.* **2007**, *46* (47), 9093–9096.
(5) Xie, L.-G.; Niyomchon, S.; Mota, A. J.; González, L.; Maulide, N. Metal-Free Intermolecular Formal Cycloadditions Enable an Orthogonal Access to Nitrogen Heterocycles. *Nat. Commun.* **2016**, *7* (1), 10914.
(6) Barluenga, J.; Fernández-Rodríguez, M. Á.; García-García, P.; Aguilar, E. Gold-Catalyzed Intermolecular Hetero-Dehydro-Diels–Alder Cycloaddition of Captodative Dienynes with Nitriles: A New Reaction and Regioselective Direct Access to Pyridines. *J. Am. Chem. Soc.* **2008**, *130* (9), 2764–2765.
(7) Zhao, Q.; León Rayo, D. F.; Campeau, D.; Daenen, M.; Gagosz, F. Gold-Catalyzed Formal Dehydro-Diels–Alder Reactions of Ene-Ynamide Derivatives Bearing Terminal Alkyne Chains: Scope and Mechanistic Studies. *Angew. Chem., Int. Ed.* **2018**, *57* (41), 13603–13607.
(8) Zamani, F.; Babaahmadi, R.; Yates, B. F.; Gardiner, M. G.; Ariafard, A.; Pyne, S. G.; Hyland, C. J. T. Dual Gold-Catalyzed Cycloaromatization of Unconjugated (E)-Enediynes. *Angew. Chem., Int. Ed.* **2019**, *58* (7), 2114–2119.
(9) Hashmi, A. S. K. Dual Gold Catalysis. *Acc. Chem. Res.* **2014**, *47* (3), 864–876.
(10) Hashmi, A. S. K. Gold-Catalyzed Organic Reactions Gold-Catalyzed Organic Reactions. *Chem. Rev.* **2007**, *107*, 3180–3211.
(11) Hashmi, A. S. K.; Hutchings, G. J. Gold Catalysis. *Angew. Chem., Int. Ed.* **2006**, *45* (47), 7896–7936.
(12) Yeom, H. S.; Shin, S. Catalytic Access to α-Oxo Gold Carbenes by N-O Bond Oxidants. *Acc. Chem. Res.* **2014**, *47* (3), 966–977.
(13) Shin, S. The Effect of Acceptor-Substituted Alkynes in Gold-Catalyzed Intermolecular Reactions. *Pure Appl. Chem.* **2014***86* (3), 373–379..
(14) Kim, H.; Choi, S. Y.; Shin, S. Asymmetric Synthesis of Dihydropyranones via Gold(I)-Catalyzed Intermolecular [4 + 2] Annulation of Propiolates and Alkenes. *Angew. Chem., Int. Ed.* **2018**, *57* (40), 13130–13134.
(15) Dubovtsev, A. Y.; Shcherbakov, N. V.; Dar'in, D. V.; Kukushkin, V. Y. Nature of the Nucleophilic Oxygenation Reagent Is Key to Acid-Free Gold-Catalyzed Conversion of Terminal and Internal Alkynes to 1,2-Dicarbonyls. *J. Org. Chem.* **2020**, *85* (2), 745–757.
(16) Dubovtsev, A. Y.; Dar'in, D. V.; Kukushkin, V. Y. Gold(I)-Catalyzed Oxidation of Acyl Acetylenes to Vicinal Tricarbonyls. *Org. Lett.* **2019**, *21* (11), 4116–4119.
(17) Dubovtsev, A. Y.; Dar'in, D. V.; Krasavin, M.; Kukushkin, V. Y. Gold-Catalyzed Oxidation of Internal Alkynes into Benzils and Its Application for One-Pot Synthesis of Five-, Six-, and Seven-Membered Azaheterocycles. *Eur. J. Org. Chem.* **2019**, *2019*, 1856–1864.
(18) Mato, M.; Franchino, A.; García-Morales, C.; Echavarren, A. M. Gold-Catalyzed Synthesis of Small Rings. *Chem. Rev.* **2020**. DOI: 10.1021/acs.chemrev.0c00697.
(19) Wang, T.; Hashmi, A. S. K. 1,2-Migrations onto Gold Carbene Centers. *Chem. Rev.* **2020**. DOI: 10.1021/acs.chemrev.0c00811.
(20) Reyes, R. L.; Iwai, T.; Sawamura, M. Construction of Medium-Sized Rings by Gold Catalysis. *Chem. Rev.* **2020**. DOI: 10.1021/acs.chemrev.0c00793.
(21) Rocchigiani, L.; Bochmann, M. Recent Advances in Gold(III) Chemistry: Structure, Bonding, Reactivity, and Role in Homogeneous Catalysis. *Chem. Rev.* **2020**. DOI: 10.1021/acs.chemrev.0c00552.
(22) Ye, L.-W.; Zhu, X.-Q.; Sahani, R. L.; Xu, Y.; Qian, P.-C.; Liu, R.-S. Nitrene Transfer and Carbene Transfer in Gold Catalysis. *Chem. Rev.* **2020**. DOI: 10.1021/acs.chemrev.0c00348.
(23) Campeau, D.; Rayo, D. F. L.; Mansour, A.; Muratov, K.; Gagosz, F. Gold-Catalyzed Reactions of Specially Activated Alkynes, Allenes, and Alkenes. *Chem. Rev.* **2020**. DOI: 10.1021/acs.chemrev.0c00788.
(24) Li, D.; Zang, W.; Bird, M. J.; Hyland, C. J. T.; Shi, M. Gold-Catalyzed Conversion of Highly Strained Compounds. *Chem. Rev.* **2020**. DOI: 10.1021/acs.chemrev.0c00624.
(25) Hendrich, C. M.; Sekine, K.; Koshikawa, T.; Tanaka, K.; Hashmi, A. S. K. Homogeneous and Heterogeneous Gold Catalysis for Materials Science. *Chem. Rev.* **2020**. DOI: 10.1021/acs.chemrev.0c00824.
(26) Lu, Z.; Li, T.; Mudshinge, S. R.; Xu, B.; Hammond, G. B. Optimization of Catalysts and Conditions in Gold(I) Catalysis—Counterion and Additive Effects. *Chem. Rev.* **2021**. DOI: 10.1021/acs.chemrev.0c00713.
(27) Witzel, S.; Hashmi, A. S. K.; Xie, J. Light in Gold Catalysis. *Chem. Rev.* **2021**. DOI: 10.1021/acs.chemrev.0c00841.
(28) Hu, Y.-C.; Zhao, Y.; Wan, B.; Chen, Q.-A. Reactivity of Ynamides in Catalytic Intermolecular Annulations. *Chem. Soc. Rev.* **2021**, *50*, 2582.
(29) Evano, G.; Michelet, B.; Zhang, C. The Anionic Chemistry of Ynamides: A Review. *C. R. Chim.* **2017**, *20* (6), 648–664.
(30) Evano, G.; Coste, A.; Jouvin, K. Ynamides: Versatile Tools in Organic Synthesis. *Angew. Chem., Int. Ed.* **2010**, *49* (16), 2840–2859.
(31) Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P. Ynamides in Ring Forming Transformations. *Acc. Chem. Res.* **2014**, *47* (2), 560–578.
(32) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. Ynamides: A Modern Functional Group for the New Millennium. *Chem. Rev.* **2010**, *110* (9), 5064–5106.
(33) Tian, X.; Song, L.; Hashmi, A. S. K. α-Imino Gold Carbene Intermediates from Readily Accessible Sulfilimines: Intermolecular Access to Structural Diversity. *Chem. - Eur. J.* **2020**, *26* (15), 3197–3204.
(34) Shu, C.; Wang, Y.-H.; Shen, C.-H.; Ruan, P.-P.; Lu, X.; Ye, L.-W. Gold-Catalyzed Intermolecular Ynamide Amination-Initiated Aza-Nazarov Cyclization: Access to Functionalized 2-Aminopyrroles. *Org. Lett.* **2016**, *18* (13), 3254–3257.
(35) Singh, R. R.; Liu, R.-S. Gold-Catalyzed Imination/Mannich Reaction Cascades of 3-En-1-Ynamides with Anilines and Aldehydes to Enable 1,5-Nitrogen Functionalizations. *Adv. Synth. Catal.* **2016**, *358* (9), 1421–1427.
(36) Dateer, R. B.; Pati, K.; Liu, R.-S. Gold-Catalyzed Synthesis of Substituted 2-Aminofurans via Formal [4 + 1]-Cycloadditions on 3-En-1-Ynamides. *Chem. Commun.* **2012**, *48* (57), 7200–7202.
(37) Nguyen, Q. H.; Nguyen, N. H.; Kim, H.; Shin, S. Synthesis of γ-Substituted Carbonyl Compounds from DMSO-Mediated Oxidation of Enynamides: Mechanistic Insights and Carbon- and Hetero-Functionalizations. *Chem. Sci.* **2019**, *10* (38), 8799–8805.
(38) Nguyen, N. H.; Nguyen, Q. H.; Biswas, S.; Patil, D. V.; Shin, S. β-Oxidation of Ynamides into N,O-Acetals by MCPBA: Application in Enantioselective Intermolecular Transacetalization. *Org. Lett.* **2019**, *21* (22), 9009–9013.
(39) Karad, S. N.; Liu, R.-S. Regiocontrolled Gold-Catalyzed [2 + 2+2] Cycloadditions of Ynamides with Two Discrete Nitriles to Construct 4-Aminopyrimidine Cores. *Angew. Chem., Int. Ed.* **2014**, *53* (34), 9072–9076.
(40) Dubovtsev, A. Y.; Shcherbakov, N. V.; Dar'in, D. V.; Kukushkin, V. Y. The Dichotomy of Gold-Catalyzed Interplay between Cyanamides and Ynamides: Controllable Switch from [2 + 2+2] to [4 + 2] Cycloaddition. *Adv. Synth. Catal.* **2020**, *362* (13), 2672–2682.
(41) Lane, T. K.; D'Souza, B. R.; Louie, J. Iron-Catalyzed Formation of 2-Aminopyridines from Diynes and Cyanamides. *J. Org. Chem.* **2012**, *77* (17), 7555–7563.

https://doi.org/10.1021/acs.joc.1c00558
J. Org. Chem. 2021, 86, 7218–7228

(42) Zimin, D. P.; Dar'in, D. V.; Kukushkin, V. Yu.; Dubovtsev, A. Yu. Oxygen Atom Transfer as Key To Reverse Regioselectivity in the Gold(I)-Catalyzed Generation of Aminooxazoles from Ynamides. *J. Org. Chem.* **2021**, *86* (2), 1748−1757.
(43) Dubovtsev, A. Y.; Dar'in, D. V.; Kukushkin, V. Y. Three-Component [2 + 2+1] Gold(I)-Catalyzed Oxidative Generation of Fully Substituted 1,3-Oxazoles Involving Internal Alkynes. *Adv. Synth. Catal.* **2019**, *361*, 2926−2935.
(44) Prabhath, M.; Williams, L.; Bhat, S.; Sharma, P. Recent Advances in Cyanamide Chemistry: Synthesis and Applications. *Molecules* **2017**, *22* (4), 615.
(45) Larraufie, M.-H.; Maestri, G.; Malacria, M.; Ollivier, C.; Fensterbank, L.; Lacôte, E. The Cyanamide Moiety, Synthesis and Reactivity. *Synthesis* **2012**, *44* (09), 1279−1292.
(46) Schießl, J.; Schulmeister, J.; Doppiu, A.; Wörner, E.; Rudolph, M.; Karch, R.; Hashmi, A. S. K. An Industrial Perspective on Counter Anions in Gold Catalysis: Underestimated with Respect to "Ligand Effects. *Adv. Synth. Catal.* **2018**, *360* (13), 2493−2502.
(47) Schießl, J.; Schulmeister, J.; Doppiu, A.; Wörner, E.; Rudolph, M.; Karch, R.; Hashmi, A. S. K. An Industrial Perspective on Counter Anions in Gold Catalysis: On Alternative Counter Anions. *Adv. Synth. Catal.* **2018**, *360* (20), 3949−3959.
(48) Kramer, S.; Dooleweerdt, K.; Lindhardt, A. T.; Rottländer, M.; Skrydstrup, T. Highly Regioselective Au(I)-Catalyzed Hydroamination of Ynamides and Propiolic Acid Derivatives with Anilines. *Org. Lett.* **2009**, *11* (18), 4208−4211.
(49) Nakao, Y.; Yeung, B. K. S.; Yoshida, W. Y.; Scheuer, P. J.; Kelly-Borges, M. Kapakahine B, a Cyclic Hexapeptide with an.Alpha.-Carboline Ring System from the Marine Sponge Cribrochalina Olemda. *J. Am. Chem. Soc.* **1995**, *117* (31), 8271−8272.
(50) Kim, J.-S.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. Structure of Mescengricin, a Novel Neuronal Cell Protecting Substance Produced by Streptomyces Griseoflavus. *Tetrahedron Lett.* **1997**, *38* (19), 3431−3434.
(51) Veale, C. G. L.; Laming, D.; Swart, T.; Chibale, K.; Hoppe, H. C. Exploring the Antiplasmodial 2-Aminopyridines as Potential Antitrypanosomal Agents. *ChemMedChem* **2019**, *14* (24), 2034−2041.
(52) Kang, S.; Li, H.; Tang, W.; Martásek, P.; Roman, L. J.; Poulos, T. L.; Silverman, R. B. 2-Aminopyridines with a Truncated Side Chain To Improve Human Neuronal Nitric Oxide Synthase Inhibitory Potency and Selectivity. *J. Med. Chem.* **2015**, *58* (14), 5548−5560.
(53) González Cabrera, D.; Douelle, F.; Younis, Y.; Feng, T.-S.; Le Manach, C.; Nchinda, A.; Street, L. J.; Scheurer, C.; Kamber, J.; White, K. L.; Montagnat, O. D.; Ryan, E.; Katneni, K.; Mohammed Zabiulla, K.; Joseph, J. T.; Bashyam, S.; Waterson, D.; Witty, M. J.; Charman, S. A.; Wittlin, S.; Chibale, K. Structure−Activity Relationship Studies of Orally Active Antimalarial 3,5-Substituted 2-Aminopyridines. *J. Med. Chem.* **2012**, *55* (24), 11022−11030.
(54) Connolly, S.; Aberg, A.; Arvai, A.; Beaton, H. G.; Cheshire, D. R.; Cook, A. R.; Cooper, S.; Cox, D.; Hamley, P.; Mallinder, P.; Millichip, I.; Nicholls, D. J.; Rosenfeld, R. J.; St-Gallay, S. A.; Tainer, J.; Tinker, A. C.; Wallace, A. V. 2-Aminopyridines as Highly Selective Inducible Nitric Oxide Synthase Inhibitors. Differential Binding Modes Dependent on Nitrogen Substitution. *J. Med. Chem.* **2004**, *47* (12), 3320−3323.
(55) Flock, J.; Suljanovic, A.; Torvisco, A.; Schoefberger, W.; Gerke, B.; Pöttgen, R.; Fischer, R. C.; Flock, M. The Role of 2,6-Diaminopyridine Ligands in the Isolation of an Unprecedented, Low-Valent Tin Complex. *Chem. - Eur. J.* **2013**, *19* (46), 15504−15517.
(56) Shi, Z.; Li, Y.; Gong, H.; Liu, M.; Xiao, S.; Liu, H.; Li, H.; Xiao, S.; Zhu, D. Self-Assembly and Characterization of Supramolecular [60]Fullerene-Containing 2,6-Diacylamidopyridine with Uracil Derivative by Hydrogen-Bonding Interaction. *Org. Lett.* **2002**, *4* (7), 1179−1182.
(57) Mcgill, C. K.; Rappa, A. Advances in the Chichibabin Reaction. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: 1988; Vol. *44*, pp 1−79. DOI: 10.1016/S0065-2725(08)60261-5.
(58) Maiti, D.; Buchwald, S. L. Orthogonal Cu- and Pd-Based Catalyst Systems for the O- and N-Arylation of Aminophenols. *J. Am. Chem. Soc.* **2009**, *131* (47), 17423−17429.
(59) Shen, Q.; Hartwig, J. F. [(CyPF-TBu)$PdCl_2$]: An Air-Stable, One-Component, Highly Efficient Catalyst for Amination of Heteroaryl and Aryl Halides. *Org. Lett.* **2008**, *10* (18), 4109−4112.
(60) Teague, S. J. Synthesis of Heavily Substituted 2-Aminopyridines by Displacement of a 6-Methylsulfinyl Group. *J. Org. Chem.* **2008**, *73* (24), 9765−9766.
(61) Du, X.-X.; Zi, Q.-X.; Wu, Y.-M.; Jin, Y.; Lin, J.; Yan, S.-J. An Environmentally Benign Multi-Component Reaction: Regioselective Synthesis of Fluorinated 2-Aminopyridines Using Diverse Properties of the Nitro Group. *Green Chem.* **2019**, *21* (6), 1505−1516.
(62) Weng, Y.; Kuai, C.; Lv, W.; Cheng, G. Synthesis of 2-Aminopyridines via a Base-Promoted Cascade Reaction of N-Propargylic β-Enaminones with Formamides. *J. Org. Chem.* **2018**, *83* (9), 5002−5008.
(63) Londregan, A. T.; Jennings, S.; Wei, L. General and Mild Preparation of 2-Aminopyridines. *Org. Lett.* **2010**, *12* (22), 5254−5257.
(64) Hashmi, A. S. K. Homogeneous Gold Catalysis Beyond Assumptions and Proposals — Characterized Intermediates. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232−5241.
(65) Lauterbach, T.; Asiri, A. M.; Hashmi, A. S. K. Organometallic Intermediates of Gold Catalysis. In *Advances in Organometallic Chemistry*; Academic Press Inc.: 2014; Vol. *62*, pp 261−297. DOI: 10.1016/B978-0-12-800976-5.00005-9.
(66) Wang, Y.; Song, L.-J.; Zhang, X.; Sun, J. Metal-Free [2 + 2+2] Cycloaddition of Ynamides and Nitriles: Mild and Regioselective Synthesis of Fully Substituted Pyridines. *Angew. Chem., Int. Ed.* **2016**, *55* (33), 9704−9708.
(67) Xie, L.-G.; Shaaban, S.; Chen, X.; Maulide, N. Metal-Free Synthesis of Highly Substituted Pyridines by Formal [2 + 2+2] Cycloaddition under Mild Conditions. *Angew. Chem., Int. Ed.* **2016**, *55* (41), 12864−12867.
(68) Fernández-García, J. M.; Fernández-Rodríguez, M.; Aguilar, E. Catalytic Intermolecular Hetero-Dehydro-Diels−Alder Cycloadditions: Regio- and Diasteroselective Synthesis of 5,6-Dihydropyridin-2-Ones. *Org. Lett.* **2011**, *13* (19), 5172−5175.
(69) Ricard, L.; Gagosz, F. Synthesis and Reactivity of Air-Stable N-Heterocyclic Carbene Gold(I) Bis(Trifluoromethanesulfonyl)Imidate Complexes. *Organometallics* **2007**, *26* (19), 4704−4707.
(70) Rassadin, V. A.; Boyarskiy, V. P.; Kukushkin, V. Y. Facile Gold-Catalyzed Heterocyclization of Terminal Alkynes and Cyanamides Leading to Substituted 2-Amino-1,3-Oxazoles. *Org. Lett.* **2015**, *17* (14), 3502−3505.
(71) Minkler, S.; Isley, N.; Lippincott, D.; Krause, N.; Lipshutz, B. Leveraging the Micellar Effect: Gold-Catalyzed Dehydrative Cyclizations in Water at Room Temperature. *Org. Lett.* **2014**, *16* (3), 724−726.
(72) Gawade, S.; Huple, D.; Liu, R.-S. Zn(II)- or Ag(I)-Catalyzed 1,4-Metathesis Reactions between 3-En-1-Ynamides and Nitrosoarenes. *J. Am. Chem. Soc.* **2014**, *136* (8), 2978−2981.
(73) Davies, P. W.; Cremonesi, A.; Dumitrescu, L. Intermolecular and Selective Synthesis of 2,4,5-Trisubstituted Oxazoles by a Gold-Catalyzed Formal [3 + 2] Cycloaddition. *Angew. Chem., Int. Ed.* **2011**, *50* (38), 8931−8935.
(74) Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. Copper-Mediated Coupling of 1,1-Dibromo-1-Alkenes with Nitrogen Nucleophiles: A General Method for the Synthesis of Ynamides. *Angew. Chem.* **2009**, *121* (24), 4445−4449.
(75) Jadhav, A. M.; Gawade, S. A.; Vasu, D.; Dateer, R. B.; Liu, R. S. ZnII- and AuI-Catalyzed Regioselective Hydrative Oxidations of 3-En-1-Ynes with Selectfluor: Realization of 1,4-Dioxo and 1,4-Oxohydroxy Functionalizations. *Chem. - Eur. J.* **2014**, *20* (7), 1813−1817.

(76) Bantreil, X.; Nolan, S. P. Synthesis of N-Heterocyclic Carbene Ligands and Derived Ruthenium Olefin Metathesis Catalysts. *Nat. Protoc.* **2011**, *6* (1), 69−77.

https://doi.org/10.1021/acs.joc.1c00558
J. Org. Chem. 2021, 86, 7218−7228