JOC The Journal of Organic Chemistry
Cite This: J. Org. Chem. XXXX, XXX, XXX−XXX
Article
pubs.acs.org/joc

Synthesis of 1*H*-Pyrazol-5-yl-pyridin-2-yl-[1,2,4]triazinyl Soft-Lewis Basic Complexants via Metal and Oxidant Free [3 + 2] Dipolar Cycloaddition of Terminal Ethynyl Pyridines with Tosylhydrazides

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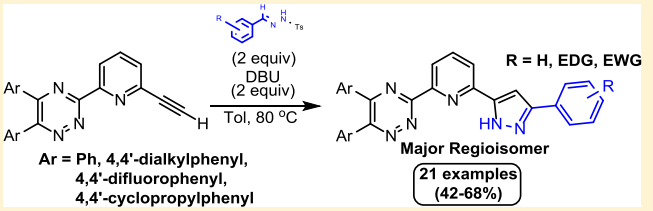
Supporting Information

ABSTRACT: Soft-Lewis basic complexants that facilitate chemoselective separation of the minor actinides from the lanthanides are critical to the closure of the nuclear fuel cycle. Complexants that modulate covalent orbital interactions with relevant metals of interest can facilitate desired outcomes in liquid−liquid separation, allowing for further transmutative processes that decrease issues related with storage of spent nuclear fuel from energy and weapons production. Synthesis of previously unexplored scaffolds seeks to improve performance over benchmark complexants. In the current work, an intermolecular, thermally initiated, and DBU-assisted [3 + 2] cycloaddition of 3-(6-ethynyl-pyridin-2-yl)-5,6-diphenyl-[1,2,4]triazine dipolarophiles with structurally diverse 4-methylbenzenesulfono-hydrazides afforded 21 yet-to-be reported examples in 42−68% yield and modest regioselectivity for the desired regioisomer. Preparation of requisite starting materials, method definition, dipole and dipolarophile scope, ten-fold scale-up reaction, and downstream functional group interconversion are reported herein.



INTRODUCTION

Dipolar cycloaddition reactions incorporating 4-methylsulfonohydrazides are widely employed for the production of pyrazoles,[1] 1,2,3-triazoles,[2] and other heteroarenes.[3] This versatile heterocycle exists in natural products,[4] biologically active compounds,[5] materials,[6] and has been utilized as a ligand for C−C bond-forming transformations.[7] Hydrazide dipoles can also be used in cross-coupling reactions.[8] Recently, efforts have focused on the construction of Lewis basic[9] motifs with relevance to catalytic carbon−carbon bond-forming transformations involving more earth-abundant metals[10] and complexation of various metals in general, by using soft-donor scaffolds containing donor atoms other than phosphorus.

Heteroarene complexants containing 1,2,4-triazine and related structures have demonstrated marked potential in separation science related to critical materials[11] and spent nuclear fuel (SNF).[12] Closure of the nuclear fuel cycle to facilitate recovery of relevant fission products by liquid−liquid extraction and subsequent downstream transmutation is a strategic goal to improve the overall efficiency of nuclear energy.[13] Sequestration of strong neutron-absorbing cross sections of the lanthanides post PUREX[14] by the removal of the minor actinides via SANEX[15] or TALSPEAK[16] for downstream transmutation decreases the heat load and long-term radiotoxicity of SNF.[17] Studies in this laboratory have focused on convergent synthetic access to previously unstudied soft-Lewis basic donor complexant scaffolds based on the CHON principle[18] to expand current knowledge and fundamentally understand differential chemoselectivity in separations processes of simulated SNF. Pursuant to the aforementioned, we were interested in ascertaining the utility of 1*H*-pyrazol-5-yl-pyridin-2-yl-[1,2,4] triazine cores. 1*H*-pyrazole nitrogen atom's diminished Brønsted basicity relative to a pyridinyl, or 1,2,4-triazinyl nitrogen, was proposed to potentially diminish third-phase interfacial phenomena in liquid−liquid separations of organic complexant solutions contacted in acidic media. Before evaluating solubility and separation performance of the desired complexant scaffold, a viable synthetic pathway to generate the desired complexant cores had to be realized. In this paper, we disseminate an effective method for generation of the desired core, leveraging a dipolar cycloaddition strategy. Preparation of requisite synthons, method optimization, substrate and tosylhydrazone scope, scale up, and computational evaluation of the participating reactants are reported herein.

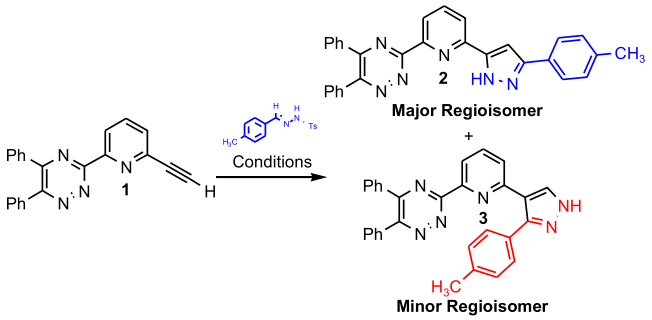
RESULTS AND DISCUSSION

Table 1 summarizes the empirical investigation toward construction of the desired complexant core. Strategies from

Received: July 30, 2019

DOI: 10.1021/acs.joc.9b02088
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 1. [3 + 2] Dipolar Cycloaddition Method Development[a]



entry	Lewis acid	additive	solvent	temp (°C)	time (h)	result	regio-selectivity (**2:3**)
1	Ag_2CO_3 (1 equiv)		Tol	100	10	**1**	
2	Li_2CO_3 (1 equiv)		Tol	100	10	**1**	
3	$Cu(OAc)_2$(10 mol %)	PvOH (1 equiv)	Tol	100	10	**1**	
4		I_2 (2 equiv)	DMSO	100	10	**1**	
5	CuI (20 mol %)	TEA (1 equiv)	Tol	100	10	<20%	
6		K_2CO_3 (2 equiv)	Tol	100	5	**2:3**	2.1:1[b]
7		K_2CO_3 (2 equiv)	CPMe	110	3.5	**2:3**	2.1:1[b]
8	$Cu(OAc)_2$ (10 mol %)	K_2CO_3 (2 equiv)	Tol	100	10	<10%	
9		Sodium ascorbate (2 equiv)	Tol	100	10	**1**	
10		TEA (2 equiv)	Tol	80	10	**1**	
11		DABCO (2 equiv)	Tol	110	3.5	**1**[c]	
12		DBU (2 equiv)	Tol	80	2	**2:3**	3.4:1[b]
13		DBU (2 equiv)	CPMe	80	1.5	**2:3**	2.3:1[b]
14		DBU (2 equiv)	2-MeTHF	80	4.5	**2:3**	1.3:1[b]
15		DBU (2 equiv)	DME	80	2.5	**2:3**[b]	3.0:1[b]
16			Tol	80	2.5	**1**[d]	
17		DBU (2 equiv)	Tol	80	2	**SM**[e]	

[a]Reaction conditions: In an 8 mL reaction vial with a magnetic stirring bar at ambient temperature was charged **1** (0.15 mmol) and 4-methylbenzenesulfonohydrazide (0.30 mmol) in the solvent indicated (0.3 M), for temperature and time indicated. [b]Complete conversion of **1**. [c]Degradation of hydrazone observed. [d]Control experiment with hydrazone and without DBU. [e]5,6-Diphenyl-3-(6-*p*-tolylethynyl-pyridin-2-yl)-[1,2,4]triazine employed as the substrate, no conversion of the starting material (SM) was observed.

previously disclosed work from this laboratory[19] afforded the preparation of terminal alkyne **1** by leveraging a two-step sequence via Sonogashira coupling and subsequent desilylation from the necessary 3-(6-bromo-pyridin-2-yl)-5,6-diphenyl-[1,2,4]triazine. The necessary prodiazo synthons were constructed via condensation of tosylhydrazide with various benzaldehyde derivatives using established literature precedent,[20] or the application thereof.[21] With the preparation of dipolarophile (**1**) secured, focus shifted toward defining suitable experimental parameters to affect the desired intermolecular [3 + 2] cycloaddition with *N*′-(4-methylbenzylidene)-4-methylbenzene-sulfonohydrazide. A series of experiments were conceived which varied Lewis acid, additive, solvent, and temperature toward the definition of a coherently adaptable synthetic strategy.

Preliminary efforts focused on the use of Lewis acid initiators Ag_2CO_3, Li_2CO_3, and $Cu(OAc)_2$, entries 1−3, respectively, all of which resulted in return of starting material (**1**). Intermolecular oxidative electrocyclization conditions mediated by I_2 (entry 4) were also unsuccessful in the present work.[22] The first productive experiment in terms of generation of **2:3** was observed in entry 5. LC/MS substantiated the regioisomeric ratios of **2:3** for examples which afforded the desired product. Spectroscopic intuition, with respect to the postulated major regioisomer **2**, was unambiguously confirmed via single-crystal X-ray crystallography of both regioisomers (**2** and **3**) and presented in Figure 1 below. Amending the base to

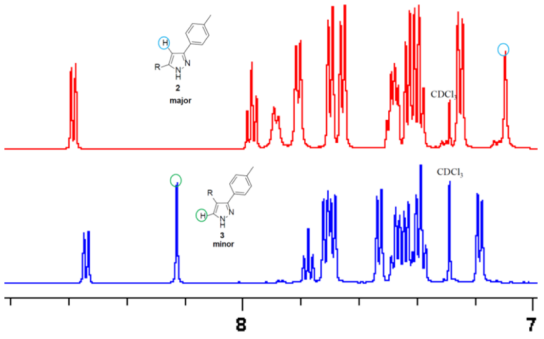


Figure 1. ^{1}H NMR spectra of regioisomeric products.

an insoluble inorganic example, K_2CO_3,[23] in toluene as the solvent resulted in complete conversion of **1** and afforded a 2:1 ratio of the regioisomer with respect to **2:3** (entry 6). Adjustment of the solvent to cyclopentylmethyl ether (CPME) and concomitantly increasing the reaction temperature to 110 °C afforded a faster reaction time but did not improve the observed regiochemistry (entry 7). Attempts to optimize the current transformation with Cs_2CO_3 and *N*,*N*-dimethylformamide as the solvent led to dipole degradation in this case.[24] Performing the same experiment as entry 7 in toluene as the solvent led to hydrazone degradation. Combining K_2CO_3 with Lewis acid resulted in substantively lower conversion.

DOI: 10.1021/acs.joc.9b02088
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Confident that development was trending in the right direction, a series of bases soluble in the organic solvent were evaluated next. Thus, triethylamine (TEA) returned **1** (entry 10) after an extended reaction time, and 1,4-diazabicyclo[2.2.2]octane (DABCO) resulted in degradation of the hydrazone (entry 11). Gratifyingly, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded complete conversion of **1** after 2 h at 80 °C in a 3.4:1 ratio of **2:3** (entry 12). Subsequent attempts to modulate performance by exploring solvent effects in ethereal solvents (entries 13−15) resulted in poor regioselectivity. A control experiment negating the use of DBU (entry 16) was performed in the interest of due diligence and, as expected, failed to convert **1** to **2**. Experimentation which heated *N*′-(4-methylbenzylidene)-4-methylbenzene-sulfonohydrazide to promote formation of the dipole in advance of addition of **1** to study the impact in regiochemistry resulted in dipole degradation and preclusion of product formation. Attempts to adapt this procedure to unsymmetrically disubstituted alkynes were unsuccessful. With a thorough evaluation of necessary [3 + 2] dipolar cycloaddition reaction parameters completed, a shift in focus centered on evaluating the scope of both dipole and dipolarophile to ascertain method limitations of the method.

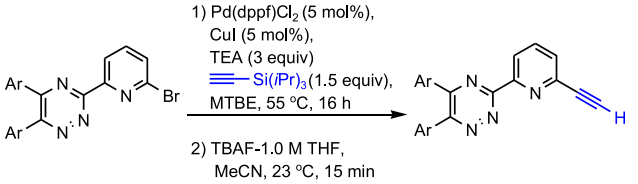
Complexants used in liquid−liquid separation of the minor actinides are prioritized if soluble in process-relevant solvents such as decane, ISOPAR, or 1-octanol. Maintaining effective concentrations of polar, heteroarene complexants in nonpolar, or mostly nonpolar diluents without incorporating phase modifiers is challenging. Evaluation of aliphatic-substituted moieties in the current work was diligently pursued commensurate with the aforementioned. Additional terminal alkyne substrates were prepared as delineated in Table 2.

Access to the 3-(6-bromo-pyridin-2-yl)-5,6-diphenyl-[1,2,4]-triazine precursors required was accomplished in two to three synthetic steps from commercially available 6-bromo-2-pyridinecarbonitrile via methods previously disclosed by this laboratory.[25] Sonogashira coupling with triisopropylsilylethyne and subsequent deprotection with tetrabutylammonium fluoride under standard conditions[26] afforded the desired substrates for cycloaddition (**1**, **4**−**8**) with various alkyl substitutions in good to excellent yield over two synthetic steps and one purification step. While alkyl, weak-electron-donating substituents afforded the best yields, deactivating substituents such as −F in the case of (**6**) afforded the poorest yields. The two-step sequence described above was attempted for the 3,3′-dimethoxy variant of **1** and resulted in poor performance. The success of the examples achieved in Table 2 established a solid foundation to investigate the dipole scope of the method. Table 3 highlights the types of dipoles employable in the described transformation.

Numerous combinations of 4-substituted hydrazide dipoles were evaluated including alkyl donor (**2**), resonance donors (**13** and **14**), as well as inductively electron-withdrawing and deactivating substituents including **10**−**12**. Strongly deactivating dipoles such as the 2,4,6-trifluoro-substituted example in entry 10 also proved competent in the transformation. Sterically demanding functionality on the dipole including a 2-iodo (**16**) and 3,5-di-*tert*-butyl (**18**) substituents did not provide demonstrable impediments to the desired synthesis goals. A heteroarene dipole in the form of 4-pyridinyl hydrazide (**19**) was also successful. Products **12** and **16** afford the potential opportunity for subsequent downstream functional group interconversion directly. Regioselectivity in the examples screened ranged from 1.7:1 in the case of entry 8 to 3.4:1 in the case of entry 10 as validated using LC/MS. Yields for the isolated major regioisomer upon chromatographic purification ranged from 45 to 65% and appeared consistently within the referenced range regardless of an electronic or steric environment of the dipole. It is also worth noting that an additional five examples, not listed in Table 3, with the following discrete dipoles including *N*′-(4-*tert*-butylbenzylidene)-4-methylbenzene sulfonohydrazide (**H6**), *N*′-(2,4,6-trimethoxy-benzylidene)-4-methyl-benzene-sulfonohydrazide (**H7**), *N*′-(6-bromo-pyridin-2-yl-methylene)-4-methylbenzene-sulfono-hydrazide (**H8**), and *N*′-(2-bromo-4-*tert*-butyl-6-phenol benzylidene)-4-methyl-benzenesulfonohydrazide (**H9**) were all successful from the perspective of starting material consumption and product formation.

Unfortunately, purification to publication standards for these combinations remained elusive even after extensive optimization attempts. Utilization of 2-ethynyl pyridine as dipolarophile was successful with the reaction method, affording the [3 + 2] cycloaddition adduct in 62% yield and 5.3:1 regioselectivity.[27] This result suggests that the 1,2,4-triazine moiety bears an unfavorable influence on product regioselectivity as the aforementioned was the highest regioselectivity observed. Aliphatic hydrazides were unsuccessful in the transformation. After establishing a broad dipole scope for the desired cycloaddition, efforts were transitioned to studying the impact of variance in the dipole and dipolarophile components of [3 + 2] cycloaddition to evaluate the limits of the method.

Table 2. Preparation of Dipolarophile Synthons[a]



Entry	Product	Yield[b]
1	**1** R = H	**1** (85)
2	**4** R = CH_3	**4** (64)
3	**5** R = $(CH_2)_3CH_3$	**5** (56)
4	**6** R′ = F	**6** (45)
5		**7** (80)
6		**8** (85)

[a]Reaction conditions: 3-(6-bromo-pyridin-2-yl)-5,6-diphenyl-[1,2,4]-triazine (0.13 mmol), $Pd(dppf)Cl_2$ (0.007 mmol), CuI (0.007 mmol), TEA (0.39 mmol), alkyne (0.20 mmol), slurried in MTBE (0.25 M), and heated for 16 h. Crude materials were telescoped to desilylation directly. TBAF—1.0 M in THF (0.59 mmol), 0.90 M in MeCN for 15 min at 23 °C. [b]Isolated, purified yield over two synthetic steps.

DOI: 10.1021/acs.joc.9b02088
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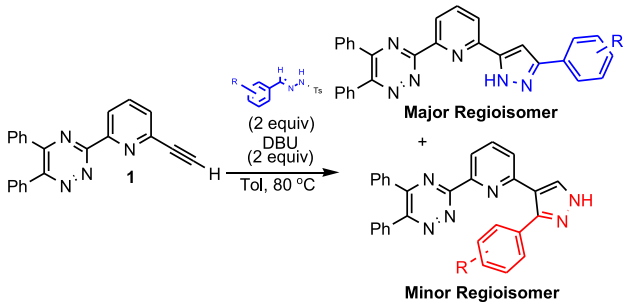
Table 3. Scope with 4-Methyl-benzenesulfono-hydrazides[a]



Entry		Regioselectivity	Product	Yield[b]
1	**9** R = H	(3.2:1)		**9** (58)
2	**2** R = CH_3	(3.3:1)		**2** (54)
3	**10** R = F	(2.5:1)		**10** (52)
4	**11** R = CF_3	(2.5:1)		**11** (56)
5	**12** R = Br	(1.6:1)		**12** (55)
6	**13** R = $N(CH_3)_2$	(3.1:1)		**13** (62)
7	**14** R = OCH_3	(2.0:1)		**14** (64)
8		(1.7:1)		**15** (42)[c]
9		(2.5:1)		**16** (60)[c]
10		(3.4:1)		**17** (60)
11		(1.5:1)		**18** (55)[c]
12		(3.0:1)		**19** (65)[d]

[a]Reaction conditions: alkyne (**1**) (0.15 mmol), tosylhydrazone (0.30 mmol), and DBU (0.30 mmol) in anhydrous toluene (0.5 mL) for 2 h. [b]Isolated and purified yield. [c]2.5 h reaction time. [d]4 h reaction time.

Table 4 highlights the strategic experiments which sought to produce complexants with potential for increased solubility in process-relevant solvents, in addition to ascertaining the feasibility of matched and mismatched electronic effects between the discrete cycloaddition precursors. Therefore, cyclopropyl alkyne (**8**) was combined with 4-methylbenzenesulfono-hydrazides containing phenyl, 2-iodo, and 2,4,6-trifluoro substituents, respectively, to afford **20**–**21** and **28** in moderate yield and regioselectivity. The alkyl donation of the 4,4′-cyclopropyl moieties against a backdrop of strongly electron-withdrawing 4-methylbenzenesulfonohydrazide provided an electronically matched system for normal-electron demand [3 + 2] cycloaddition and had a positive impact on cycloaddition. A 4-bromo-substituted 4-methylbenzenesulfono-hydrazide was screened with **4**–**5** and **7** to provide the aliphatic-substituted derivatives **22**, **23**, and **26** which presented opportunities for subsequent derivatization. Mismatched electronic effects in the case of sterically demanding, electron-donating 3,5-di-*tert*-butyl-4-methylbenzenesulfono-hydrazide toward **25** and the 4-*tert*-benzenesulfonolhydrazide example **24** provided the desired products in comparable regioselectivity to previous examples and a slightly lower overall yield in the case of the former and higher yield in the case of the latter. An inverse-electron demand experiment which employed a more electron-poor dipolarophile (**6**) in concert with an electron-rich dipole afforded the desired product, **27**, on par with previous combinations explored without substantial deterioration of yield or regioselectivity and demonstrated the electronic tolerance of transformation for both electronic environments of reactants.

Scalability of a given complexant scaffold is important toward producing significant quantities of material for solubility, acid contact, separation, and fluorimetric assays toward validation, and a tenfold scale-up experiment was attempted as described in Scheme 1. Thus, the treatment of **1** under the standard conditions discussed in Table 1 above with 4-methylbenzenesulfonohydrazide on a 1.5 mmol scale afforded the desired end product in 58% yield and comparable regioselectivity to the development scale discussed previously in Table 3 for **2**.

Flexibility, to further enhance the physical properties of the desired complexant produced as a result of the dipolar cycloaddition described, streamlines efficiency toward modulating performance. A series of functional group interconversions of bromo-substituted products were explored leading to the synthesis of **29** via Sonogashira coupling of **12** with 4-*tert*-butylphenylethyne which afforded the desired product in an unoptimized 65% yield (Scheme 2).[17] Further attempts to derivatize **12** via Pd-catalyzed amination[25a,c] in addition to Suzuki–Miyaura cross-coupling[25b] employing methods developed in this lab for similar, but not literal, substrates were unsuccessful.

Single-crystal X-ray diffraction (XRD) was performed on both regioisomers (**2** and **3**) of the original method development transformation (Table 1) to benchmark results obtained from LC/MS and NMR. XRD studies unambiguously determined the discrete connectivity of atoms and their respective orientations in three dimensions in the solid state. These results also established that the major tautomer existed with the 1,2-pyrazole hydrogen atom connected to N2. Polymorphism of the crystalline material presented challenges for obtaining quality crystals, but employment of a vapor deposition technique utilizing tetrahydrofuran (THF) and hexanes afforded quality material for analysis.[28] Both ethanol, from previous crystallization efforts, and THF were cocrystallized with **2**. XRD studies validated previous hypotheses regarding the chemical shift of pyrazolyl methine hydrogen (Figure 1).

The chemical shift of pyrazolyl methine hydrogen connected to C9 (δ 7.29 ppm in $CDCl_3$) was postulated to coincide with the C10–C11 bond of the newly formed heterocycle (**2**) and be of lower chemical shift, given the remote proximity to the electron-withdrawing N–N bond and the subsequent deshielding inductive effect. Alternatively, the minor regioisomer **3** was postulated to possess more strongly deshielded pyrazolyl methine hydrogen (δ 8.22 ppm in $CDCl_3$), given the closer location to the inductively deshielding N–N bond. XRD unambiguously benchmarked these hypotheses.

In order to better understand the regioselectivity of [3 + 2] dipolar cycloaddition, density functional theory (DFT)[29] at the B3LYP[30] exchange–correlation functional in concert with DFT-optimized DZVP2 basis sets[31] was utilized to optimize

DOI: 10.1021/acs.joc.9b02088
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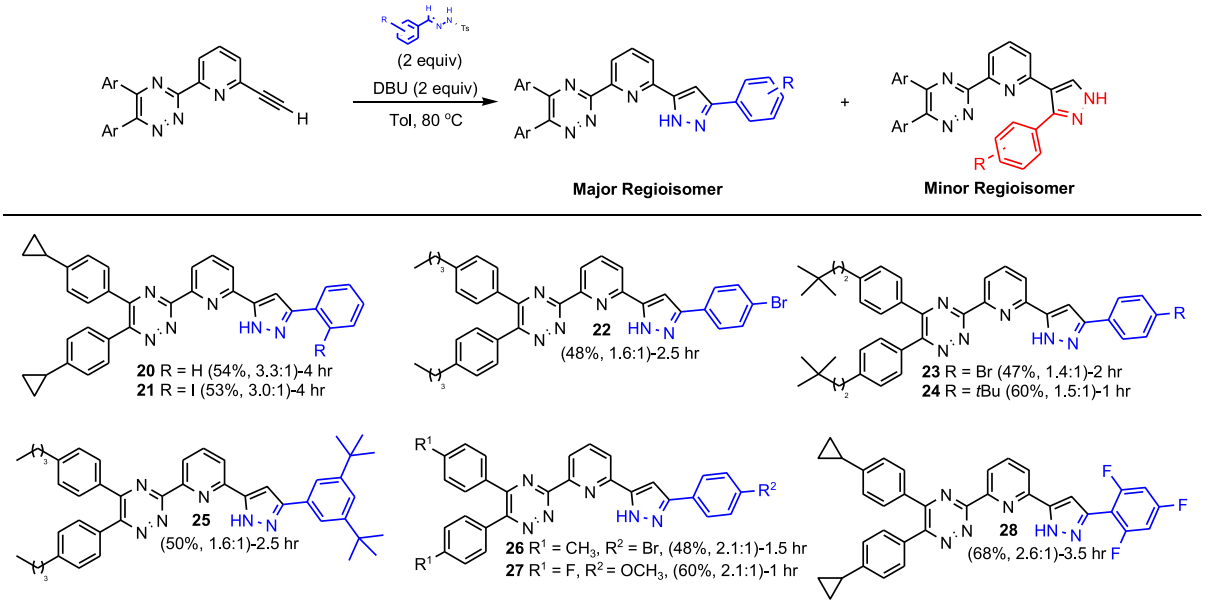
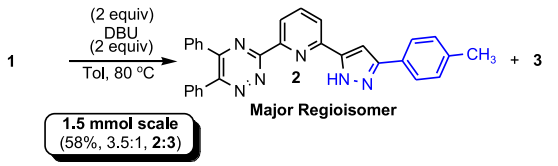
Table 4. Strategic Diversification of Various Scaffolds and 4-Methylbenzenesulfonohydrazides[a]

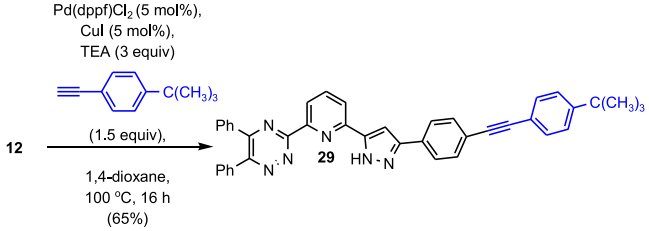


[a]Reaction conditions: alkyne (0.15 mmol), tosylhydrazide (0.30 mmol), and DBU (0.30 mmol) in anhydrous Tol (0.5 mL) for the time indicated. Isolated and purified yield.

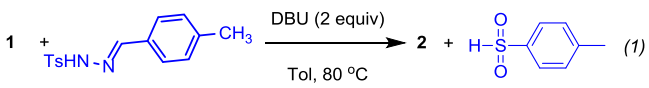
Scheme 1. Tenfold Scale-Up Experiment



Scheme 2. Downstream Functional Group Interconversion

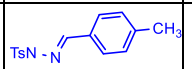
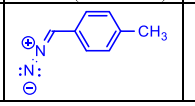


the geometries of the reactants and to predict inherent electronic properties, such as orbital energies and locations. All the calculations were done using Gaussian-16.[32] First, the reactants and products delineated in Table 1 given above were evaluated. The major product (**2**) is 8.1 kcal·mol^{-1} more stable (ΔH_{298K}) than its N1 tautomer generated by equilibrated transposition of the hydrogen from N2. The minor product **3** is 8.6 kcal·mol^{-1} higher in energy than **2**. This is in qualitative agreement with the experiment, although the calculated energy difference is larger than the qualitative value from the experiment. The calculated values are in the gas phase, as compared to experimental values in solution. The reaction energy for the [3 + 2] reaction is $\Delta H_{298K} = -63.4$ kcal·mol^{-1} at the B3LYP/DZVP2 level (eq 1).



The orbital energies and the HOMO−LUMO gap are given in Table 5 and the key orbitals are shown in Figure 2.[33] The

Table 5. Orbital Energies and Gap in eV

entry	Structure	HOMO (eV)	LUMO (eV)	HOMO / LUMO Gap (eV)
1	**1**	−6.43 / −6.98 (HOMO−2)	**−2.32 / −1.54 (LUMO+2)**	4.11 / 5.44
2		**−6.29**	−1.65	4.64
3	**2** (Major Regioisomer)	−5.79	−2.42	3.37
4	**2** (Major Tautomer)	−6.07	−2.11	3.96
5	**3** (Minor Regioisomer)	−5.75	−2.30	3.45
6	C_5NH_4-CCH	−6.98	−1.73	5.36
7	*p*-Me-C_6H_5-CCH	−6.40	−1.11	5.29
8	Product (C_5NH_4-CCH)	−5.88	−1.66	4.22
9		−5.57	−1.84	3.73

HOMO for **1** is localized on the triazine and the HOMO−1 is as well with some contribution from one of the two phenyl

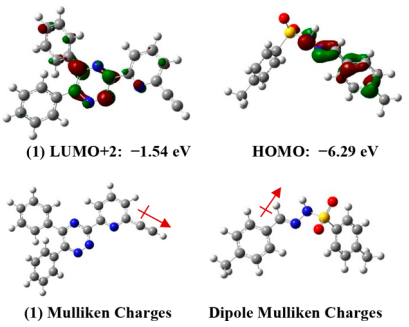


Figure 2. Reacting orbitals in [3 + 2] cycloaddition.

DOI: 10.1021/acs.joc.9b02088
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groups. The HOMO−2 is localized on the acetylenic group and on the adjacent ring with one N. The energy difference between the HOMO and HOMO−2 is 0.55 eV. The LUMO and LUMO+1 are localized on the triazine, and the LUMO+2 is the first orbital to have a character on the acetylenic group. The LUMO+2 is 0.78 eV above the LUMO and is still negative. It is proposed that the unoccupied orbital on the acetylenic group (entry 1) into which an occupied orbital on the dipolar species (entry 2) adds in the [3 + 2] cycloaddition under normal-electron demand is facilitated in the current work. The HOMO of the dipolar reactant has its electron density split between the C═N−N moiety and the adjacent phenyl ring, so it can add to the acetylene of **1**. The energy difference between the HOMO on the dipolar species and the LUMO+2 on **1** is 4.75 eV (Figure 2).

Figure 2 delineates the proposed electronic properties governing reactivity. The LUMO+2 for **1** and the HOMO for the dipolar species and HOMO are postulated to represent the reacting Frontier MOs for the transformation of interest. Mulliken charges for **1** for C1 and C2 of the alkyne are 0.10 e and −0.18 e, respectively. The dipolar species also affirmed the observed selectivity for the major regioisomer with respect to the direction of the localized dipole in the reacting region with Mulliken charges of −0.04 e and −0.20 e for the R−C═N−N(H)−S(O)$_2$R portion of the moiety. Calculation of the diazo dipole, devoid of the H−S(O$_2$)−Ph(Me) subunit, mediated through DBU was also performed. The HOMO for this moiety was −5.79 eV, rendering a HOMO−LUMO gap of 4.03 eV (entry 9) was slightly lower than 4.75 eV calculated for tosylhydrazide (eq 1). Mulliken charges of 0.13 e and −0.14 e were predicted, respectively, for N1 and N2 of the dipole in this scenario and also reinforced predicted regiochemistry of the major product **2**.

CONCLUSIONS

In summary, we have described a convergent strategy toward the production of yet undisclosed tridentate soft-Lewis basic complexant scaffolds featuring a 1,2-pyrazole moiety in concert with a pyridin-2-yl-[1,2,4]-triazine via a normal electron demand [3 + 2] dipolar cycloaddition of requisite terminal alkynes and 4-methylbenzenesulfonohydrazides. The twenty-one examples disseminated broadly evaluated the scope of electronic demand and steric combinations of both discrete components toward the production of the desired end products in satisfactory yield and workable regioselectivity after chromatographic separation. The transformation proved scalable for one example and functional group interconversion was also possible. XRD confirmed the three-dimensional structure of the major regioisomer. DFT calculations supported the experimental observations with respect to reacting frontier molecular orbitals, regioselectivity, and predominant tautomer in the major product. Studies evaluating the utility of the described complexants in SNF separations are ongoing and will be reported in due course.

EXPERIMENTAL SECTION

General Considerations. All the reagents were purchased from U.S. chemical suppliers, stored according to published protocols, and used as received unless indicated otherwise. All the experiments were performed in oven- or flame-dried glassware. Reaction progress was monitored using thin-layer chromatography on glass-backed silica gel plates and/or ^{1}H NMR analysis of crude reaction mixtures. R_f values for compounds that resulted in a concentrically observed spot on normal-phase silica gel are reported using the conditions listed. Melting point data listed are for a single, uncorrected experiment unless noted otherwise. All reported yields listed are for pure compounds and corrected for the residual solvent, if applicable, from ^{1}H NMR spectroscopy unless otherwise indicated. Regioselectivity of the dipolar cycloaddition reactions were determined using LC/MS on a Varian HPLC with ProStar 210 solvent-delivery modules and a Varian ES-320 mass spectrometric detector using an Agilent Eclipse Plus C18 3.0 × 150 mm, 3 μm, or C8 3.0 × 100 mm, 3.5 μm column with the CH_3CN/H_2O (50:50) gradient mobile phase. Infrared spectral data were acquired from the (form) listed. All ^{1}H and ^{13}C NMR data were acquired from a 500 or 900 MHz multinuclear spectrometer with a broad-band N_2 cryoprobe. Chemical shifts are reported using the δ scale and are referenced to the residual solvent signal: $CDCl_3$ (δ 7.26), CD_3CN (1.94), $(CD_3)_2C{=}O$ (2.05), and $(CD_3)_2S{=}O$ (2.50) for ^{1}H NMR and $CDCl_3$ (δ 77.15), CD_3CN (1.32), and $(CD_3)_2C{=}O$ (29.84) for $^{13}C\{^1H\}$ NMR.[34] Splittings are reported as follows: (br) = broad, (s) = singlet, (d) = doublet, (t) = triplet, (dd) = doublet of doublets, (dt) = doublet of triplets, and (m) = multiplet. ^{13}C NMR spectra were corrected for ringdown using linear back prediction. High-resolution mass spectrometry (HRMS) data were obtained utilizing electron impact ionization (EI) with a magnetic sector (EBE trisector), double focusing-geometry mass analyzer.

General Procedure for the Preparation of Requisite Hydrazides. To a 100 mL round-bottom flask equipped with a magnetic stirring bar at ambient temperature was charged the required aldehyde (1.705 g, 9.15 mmol, 1.00 equiv) in anhydrous ethanol (20.5 mL, 0.45 M) at 23 °C. The resulting clear solution was treated with tosylhydrazide (9.15 mmol, 1.00 equiv). The resulting mixture was continued at 23 °C until the starting aldehyde was consumed as evidenced from TLC analysis (1−2 h). Afterward, the crude reaction mixture was reduced by half using rotary evaporation at 23 °C followed by cooling of the crude mixture in an ice bath at 0 °C. The resulting slurry was filtered under reduced pressure to afford the title compounds as crystalline solids. In cases where precipitation was not significant at 0 °C, addition of pentane (5 mL) would facilitate precipitation.

Spectroscopic data obtained were congruent with the previously reported data for the following required examples: *N*′-(benzylidene)-4-methylbenzenesulfonohydrazide to form **9**,[20a] *N*′-(4-fluorobenzylidene)-4-methylbenzenesulfonohydrazide to form **10**,[20b] *N*′-(4-trifluoromethyl-benzy-lidene)-4-methylbenzenesulfono-hydrazide to form **11**,[20b] *N*′-(4-bromobenzylidene)-4-methyl-benzenesulfonohydrazide to form **12**,[20a,b] *N*′-(4-methoxy-benzylidene)-4-methylbenzene-sulfonohydrazide to form **14**,[35] methyl 3-((2-tosylhydrazono)-methyl)benzoate to form **15**,[20a] and *N*′-(2,4,6-trifluorobenzylidene)-4-methyl-benzenesulfonohydrazide to form **17**.[35] Functionalized hydrazides are delineated in the order of appearance in the manuscript.

N′*-(4-Methylbenzylidene)-4-methylbenzenesulfonohydrazide (**H1**).* H1 was prepared according to the general procedure discussed above with 4-methylbenzaldehyde (1.100 g, 9.16 mmol) and tosylhydrazide, R_f = 0.70, 50% ethyl acetate/hexanes; isolated yield 1.80 g, 68%; white solid; melting point = 140.0−142.0 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 11.33 (br-s, 1H), 7.86 (s, 1H), 7.75 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 2.35 (s, 3H), 2.29 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2SO$): δ 147.1, 143.4, 139.9, 136.2, 131.0, 129.8, 129.3, 127.2, 126.7, 20.96, 20.95; IR (ATR-solid): $\bar{\upsilon}_{max}$ = 3211, 2916, 1603, 1432, 1359, 1307, 1157, 1043, 942, 812 cm^{-1}; HRMS (EI) m/z: $[M]^+$ calcd for $C_{15}H_{16}N_2O_2S$, 288.0932; found, 288.0936.

N′*-(N,N-Dimethylaminobenzylidene)-4-methyl-benzenesulfonohydrazide (**H2**).* H2 was prepared according to the general procedure discussed above with 4-*N*,*N*-dimethylaminobenzaldehyde (1.366 g, 9.16 mmol) and tosylhydrazide, R_f = 0.61, 50% ethyl acetate/hexanes; isolated yield 2.25 g, 78%; white solid; melting point = 162.0−164.0 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 10.96 (br-s, 1H), 7.377 (s, 1H), 7.74 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 6.68 (d, J = 8.3 Hz, 2H), 2.92 (s, 6H), 2.35 (s, 3H);

DOI: 10.1021/acs.joc.9b02088
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$^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2SO$): δ 151.4, 148.2, 143.2, 136.3, 129.5, 128.0, 127.2, 121.0, 111.65, 40× overlaps with residual $(CH_3)_2SO$, 20.96; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3174, 2892, 1600, 1535, 1360, 1315, 1158, 814 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{16}H_{19}N_3O_2S$, 317.1198; found, 317.1212.

*N′-(2-Iodobenzylidene)-4-methylbenzenesulfonohydrazide (**H3**).* H3 was prepared according to the general procedure discussed above with 2-iodobenzaldehyde (0.500 g, 2.16 mmol) and tosylhydrazide, R_f = 0.85, 50% ethyl acetate/hexanes; isolated yield 0.760 g, 87%; white solid; melting point = 176.5−178.5 °C; ^1H NMR (500 MHz, $(CD_3)_2SO$): δ 11.75 (br-s, 1H), 8.12 (s, 1H), 7.88−7.84 (m, 1H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.65 (br-d, *J* = 8.0 Hz, 1H), 7.44−7.36 (m, 3H), 7.16−7.09 (m, 1H), 2.36 (s, 3H)-overlaps with residual $(CH_3)_2SO$; $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2SO$): δ 149.5, 143.6, 139.6, 136.0, 135.0, 131.8, 129.7, 128.6, 127.2, 126.6, 99.6, 21.0; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3189, 1594, 1425, 1347, 1162, 1062, 938, 818, 764 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{14}H_{13}IN_2O_2S$, 399.9742; found, 399.9759.

*N′-(3,5-Di-tert-butylbenzylidene)-4-methylbenzenesulfono-hydrazide (**H4**).* H4 was prepared according to the general procedure discussed above with 3,5-di-*tert*-butylbenzaldehyde (0.500 g, 2.29 mmol) and tosylhydrazide, R_f = 0.88, 50% ethyl acetate/hexanes; isolated yield 0.600 g, 68.0%; white solid; melting point = 172.0−173.2 °C; ^1H NMR (500 MHz, $(CD_3)_2SO$): δ 11.32 (br-s, 1H), 7.89 (s, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.43−7.38 (m, 3H), 7.37−7.35 (m, 2H), 2.35 (s, 3H), 1.27 (s, 18H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2SO$): δ 150.8, 147.8, 143.4, 136.0, 133.0, 129.5, 127.3, 124.0, 120.9, 34.5, 31.0, 20.9; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3175, 2957, 1589, 1460, 1357, 1313, 1161, 1065, 906 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{22}H_{30}N_2O_2S$, 386.2028; found, 386.2015.

*N′-(Pyridin-4-yl-benzylidene)-4-methylbenzenesulfono-hydrazide (**H5**).*[36] H5 was prepared according to the general procedure discussed above with pyridine-4-carbaldehyde (0.981 g, 9.16 mmol) and tosylhydrazide, R_f = 0.40, 10% CH_3OH/CH_2Cl_2; isolated yield 1.90 g, 78%; white solid; melting point = 115.0−116.0 °C; ^1H NMR (500 MHz, $(CD_3)_2SO$): δ 11.87 (br-s, 1H), 8.59−8.57 (m, 2H), 7.89 (s, 1H), 7.79−7.75 (m, 2H), 7.50−7.48 (m, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 151.2, 145.2, 145.0, 142.0, 137.3, 130.5, 125.9, 121.6, 21.4; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 9047, 2883, 2761, 1656, 1589, 1486, 1370, 1168, 1077, 939, 821 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{13}H_{13}N_3O_2S$, 275.0728; found, 275.0734.

*N′-(4-tert-Butylbenzylidene)-4-methylbenzenesulfonohydrazide (**H6**).* H6 was prepared according to the general procedure discussed above with 4-*tert*-butylbenzaldehyde (1.485 g, 9.15 mmol) and tosylhydrazide, R_f = 0.79, 50% ethyl acetate/hexanes; isolated yield 1.99 g, 60%; white solid; melting point = 130.5−132.5 °C; ^1H NMR (500 MHz, $(CD_3)_2SO$): δ 11.33 (br-s, 1H), 7.88 (br-s, 1H), 7.77−7.74 (m, 2H), 7.49−7.46 (m, 2H), 7.41−7.38 (m, 4H), 2.35 (s, 3H), 1.25 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2SO$): δ 152.8, 146.9, 143.3, 136.1, 131.0, 129.6, 127.2, 126.5, 125.5, 34.5, 30.9, 21.0; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3163, 2957, 1605, 1448, 1309, 1155, 1047, 951, 819 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{18}H_{22}N_2O_2S$, 330.1402; found, 330.1398.

*N′-(2,4,6-Trimethoxybenzylidene)-4-methylbenzenesulfono-hydrazide (**H7**).* H7 was prepared according to the general procedure discussed above with 2,4,6-trimethoxybenzaldehyde (1.796 g, 9.15 mmol) and tosylhydrazide, R_f = 0.42, 50% ethyl acetate/hexanes; isolated yield 2.82 g, 85%; white solid; melting point = 140.5−142.5 °C; ^1H NMR (500 MHz, $(CD_3)_2SO$): δ 10.87 (br-s, 1H), 7.98 (s, 1H), 7.79−7.75 (m, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 6.22 (s, 2H), 3.80 (s, 3H), 3.74 (s, 6H), 2.38 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2SO$): δ 162.2, 159.6, 143.0, 136.5, 129.2, 127.3, 103.4, 91.0, 55.9, 55.4, 21.0; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3091, 2944, 1687, 1598, 1457, 1320, 1217, 1155, 1121, 811, 739 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{17}H_{20}N_2O_5S$, 364.1093; found, 364.1088.

*N′-(C-6-bromo-pyridin-2-yl-benzylidene)-4-methylbenzenesulfono-hydrazide (**H8**).* H8 was prepared according to the general procedure discussed above with 6-bromo-pyridine-2-carbaldehyde (1.703 g, 9.16 mmol) and tosylhydrazide, R_f = 0.76, 50% ethyl acetate/hexanes; isolated yield 2.46 g, 76%; white solid; melting point = 148.0−150.0 °C; ^1H NMR (500 MHz, $(CD_3)_2SO$): δ 11.97 (s, 1H), 7.82 (s, 1H), 7.79−7.73 (m, 4H), 7.63 (dt, *J* = 7.3, 1.3 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 2H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2SO$): δ 153.6, 145.0, 143.8, 141.0, 140.2, 135.9, 129.8, 128.6, 127.2, 119.0, 21.0; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3051, 2865, 2773, 1556, 1435, 1358, 1159, 1070, 947, 848 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{13}H_{12}{}^{81}BrN_3O_2S$, 353.9861; found, 354.0110 [M + H].

*N′-(2-Bromo-4-tert-butyl-6-phenol Benzylidene)-4-methyl-benzenesulfono-hydrazide (**H9**).* H9 was prepared according to the general procedure discussed above with 3-bromo-5-*tert*-butyl-2-hydroxy-benzaldehyde (0.250 g, 0.972 mmol) and tosylhydrazide, R_f = 0.76, 50% ethyl acetate/hexanes; isolated yield 0.380 g, 92.0%; white solid; melting point = 127.0−130.0 °C; ^1H NMR (500 MHz, DMSO-d_6): δ 11.88 (br-s, 1H), 10.88 (br-s, 1H), 8.13 (br-s, 1H), 7.76−7.72 (m, 2H), 7.54 (d, *J* = 2.3 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 2.3 Hz, 1H), 2.37 (s, 3H), 1.22 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2SO$): δ 151.1, 148.9, 144.0, 143.5, 135.3, 131.4, 129.9, 127.1, 126.5, 118.8, 109.8, 33.9, 30.9, 21.0; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3184, 2957, 1460, 1323, 1267, 1160, 1079, 897, 814, 679 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{18}H_{21}BrN_2O_3S$, 424.0456; found, 424.0470.

General Procedure for the Preparation of Ethynyl Scaffolds. General procedures for the preparation of the requisite 3-(6-bromo-pyridin-2-yl)-5,6-diphenyl-[1,2,4]triazine starting materials for Sonogashira coupling, including the hydrazonamide and condensation products, have been reported.[19,25b,c]

To a 100 mL round-bottom flask equipped with a magnetic stir bar at ambient temperature was charged the requisite (6-bromo-pyridin-2-yl)-[1,2,4]triazine (1000 mg, 2.569 mmol, 1.00 equiv) in anhydrous *tert*-butylmethyl ether (MTBE) (10.3 mL, 0.25 M). The resulting solution was treated sequentially with $Pd(dppf)Cl_2$ (94 mg, 0.129 mmol, 5 mol %), CuI (24.5 mg, 0.129 mmol, 5 mol %), and triethylamine [TEA] (1.1 mL, 7.749 mmol, 3 equiv). The resulting mixture was heated to 55 °C for 16 h, upon which time the crude mixture was cooled to ambient temperature and concentrated under reduced pressure to remove TEA. The resulting dark-brown residue was partitioned between ethyl acetate (50 mL) and water (20 mL). The organic layer was separated and the aqueous layer was back-extracted with (2 × 50 mL) portions of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and then concentrated to afford the crude mixture which was judged to be sufficiently pure by ^1H NMR and subsequently telescoped to the deprotection step.

To a 250 mL round-bottom flask equipped with a magnetic stir bar at ambient temperature was charged the requisite trisiopropylsilyl-protected 3-(6-ethynyl-pyridin-2-yl)-[1,2,4]triazine followed by dissolution with CH_3CN (50 mL, 0.05 M). The resulting solution was treated with tetrabutyammonium fluoride-1.0 M in THF (3.7 mL, 12.84 mmol, 5.0 equiv) drop wise at 23 °C and continued until the starting material was consumed by TLC analysis of the crude reaction mixture (15 min). Afterward, the reaction mixture was concentrated under reduced pressure and the crude mass was taken up in ethyl acetate (100 mL). The organic layer was successively washed with a saturated, aqueous sodium bicarbonate solution (25 mL) followed by washing with a saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated to afford the crude mixture which was absorbed on silica gel and purified using automated flash column chromatography under the discrete conditions for each described compound to afford the pure compound in the listed yield over two synthetic steps from the (6-bromo-pyridin-2-yl)-[1,2,4]triazine.

*3-(6-Ethynyl-pyridin-2-yl)-5,6-diphenyl-[1,2,4]triazine (**1**).* Compound **1** was prepared according to the general procedure discussed above with 3-(6-bromo-pyridin-2-yl)-5,6-diphenyl-[1,2,4]triazine (1.00 g, 2.57 mmol) and ethynyltriisopropylsilane, R_f = 0.42, 50% ethyl acetate/hexanes; eluent, ethyl acetate/hexanes (gradient); isolated yield 0.750 g, 85%; yellow solid; melting point = 157.0−159.0 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.65 (d, *J* = 8.0 Hz, 1H), 7.92 (t, *J* = 8.0 Hz, 1H), 7.72−7.69 (m, 2H), 7.67 (d, *J* = 8.0 Hz, 1H),

DOI: 10.1021/acs.joc.9b02088
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7.65−7.62 (m, 2H), 7.47−7.33 (m, 6H), 3.23 (s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 160.4, 156.7, 156.4, 153.6, 143.2, 137.4, 135.6, 135.4, 130.9, 130.2, 130.0, 129.7, 129.3, 128.8, 128.7, 124.0, 82.7, 78.2; IR (ATR-solid): $\bar{\upsilon}_{max}$ = 3203, 3061, 2103, 1579, 1566, 1488, 1443, 1413, 1390, 1353, 766, 690 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{22}H_{14}N_4$, 334.1218; found, 334.1219.

*3-(6-Ethynyl-pyridin-2-yl)-5,6-di-p-tolyl-[1,2,4]triazine (**4**).* Compound **4** was prepared according to the general procedure discussed above with 3-(6-bromo-pyridin-2-yl)-5,6-di-*p*-tolyl-[1,2,4]triazine (0.500 g, 1.38 mmol) and ethynyltriisopropylsilane, R_f = 0.32, 50% ethyl acetate/hexanes; eluent, ethyl acetate/hexanes (gradient); isolated yield 0.280 g, 64%; yellow solid; melting point = 158.0−160.0 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.63 (d, *J* = 8.0 Hz, 1H), 8.04 (t, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz), 7.52 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 3.60 (s, 1H), 2.42 (s, 3H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 160.1, 156.5, 156.2, 153.8, 143.2, 141.5, 140.1, 137.4, 132.9, 132.7, 130.1, 129.54, 129.52, 126.4, 129.1, 123.9, 82.8, 78.1, 21.7, 21.6; IR (ATR-solid): $\bar{\upsilon}_{max}$ = 3202, 2107, 1608, 1580, 1564, 1491, 1380, 819 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{24}H_{18}N_4$, 362.1531; found, 362.1523.

*5,6-Bis-(4-butyl-phenyl)-3-(6-ethynyl-pyridin-2-yl)-[1,2,4]triazine (**5**).* Compound **5** was prepared according to the general procedure discussed above with 3-(6-bromo-pyridin-2-yl)-5,6-bis-(4-butyl-phenyl)-[1,2,4]triazine (0.930 g, 1.86 mmol) and ethynyltriisopropylsilane, R_f = 0.58, 50% ethyl acetate/hexanes; eluent, ethyl acetate/hexanes (gradient); isolated yield 0.465 g, 56%; yellow solid; melting point = 107.0−110.0 °C; ^1H NMR (500 MHz, $(CD)_3CO$): δ 8.63 (dd, *J* = 8.0, 0.9 Hz, 1H), 8.10 (t, *J* = 7.9 Hz, 1H), 7.77 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.66−7.64 (m, 2H), 7.60−7.57 (m, 2H), 7.31−7.28 (m, 2H), 7.27−7.24 (m, 2H), 3.87 (s, 1H), 2.72−2.64 (m, 4H), 1.68−1.58 (m, 4H), 1.42−1.32 (m, 4H), 0.96−0.91 (m, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 161.0, 157.4, 156.6, 154.8, 146.8, 145.5, 143.7, 138.5, 134.28, 134.26, 130.8, 130.3, 129.7, 129.4, 129.3, 124.5, 83.7, 79.2, 35.99, 35.97, 34.2, 34.1, 22.94, 22.92, 14.2, 14.1; IR (ATR-solid): $\bar{\upsilon}_{max}$ = 3191, 3058, 2954, 2928, 2869, 2859, 2103, 1609, 1579, 1489, 1378, 813 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{30}H_{30}N_4$, 446.2470; found, 446.2473.

*3-(6-Ethynyl-pyridin-2-yl)-5,6-bis-(4-fluoro-phenyl)-[1,2,4]-triazine (**6**).* Compound **6** was prepared according to the general procedure discussed above with 3-(6-bromo-pyridin-2-yl)-5,6-bis-(4-fluoro-phenyl)-[1,2,4]triazine (1.00 g, 2.70 mmol) and ethynyltriisopropylsilane, R_f = 0.32, 50% ethyl acetate/hexanes; eluent, ethyl acetate/hexanes (gradient); isolated yield 0.395 g, 45%; yellow solid; melting point = 189.0−191.0 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.64 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.92 (t, *J* = 8.0 Hz, 1H), 7.75−7.71 (m, 2H), 7.68 (dd, *J* = 1.0, 7.8 Hz, 1H), 7.65−7.62 (m, 2H), 7.14−7.05 (m, 4H), 3.23 (s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 165.3 (*J* = 302.2 Hz), 163.3 (*J* = 295.6 Hz), 160.3, 155.3, 155.2, 153.3, 143.3, 137.5, 132.4 (*J* = 35.0 Hz), 131.7 (*J* = 33.6 Hz), 131.5 (*J* = 12.8 Hz), 131.3 (*J* = 12.1 Hz), 129.4, 123.9, 116.2 (*J* = 47.9 Hz), 116.1 (*J* = 47.9 Hz), 82.7, 78.3; IR (ATR-solid): $\bar{\upsilon}_{max}$ = 3200, 3065, 1602, 1580, 1509, 1487, 1355, 1230, 1155, 937 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{22}H_{12}F_2N_4$, 370.1030; found, 370.1046.

*5,6-Bis-[4-(3,3-dimethyl-butyl)-phenyl]-3-(6-ethynyl-pyridin-2-yl)-[1,2,4]triazine (**7**).* Compound 7was prepared according to the general procedure discussed above with 3-(6-bromo-pyridin-2-yl)-5,6-bis-[4-(3,3-dimethyl-butyl)-phenyl]-[1,2,4]triazine (0.660 g, 1.19 mmol) and ethynyltriisopropylsilane, R_f = 0.58, 50% ethyl acetate/hexanes; eluent, ethyl acetate/hexanes (gradient); isolated yield 0.357 g, 80%; dark green solid; melting point = 117.0−120.0 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.63 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.90 (t, *J* = 7.9 Hz, 1H), 7.67−7.63 (m, 3H), 7.58−7.54 (m, 2H), 7.23−7.20 (m, 2H), 7.19−7.16 (m, 2H), 3.22 (s, 1H), 2.65−2.57 (m, 4H), 1.56−1.47 (m, 4H), 0.97 (s, 9H), 0.96 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 160.1, 156.6, 156.3, 153.8, 146.4, 145.1, 143.2, 137.4, 133.1, 132.8, 130.1, 129.5, 129.1, 128.8, 128.7, 123.9, 82.8, 78.1, 35.7, 35.6, 33.4, 33.3, 27.5, 22.4, 14.1, 14.0; IR (ATR-solid): $\bar{\upsilon}_{max}$ = 3272, 2950, 2901, 2865, 1610, 1574, 1562, 1490, 1406, 1392, 1356, 853, 832 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{34}H_{38}N_4$, 502.3096; found, 502.3080.

*5,6-Bis-(4-cyclopropyl-phenyl)-3-(6-ethynyl-pyridin-2-yl)-[1,2,4]-triazine (**8**).* Compound **8** was prepared according to the general procedure discussed above with 3-(6-bromo-pyridin-2-yl)-5,6-bis-[4-(cycloproplyl)-phenyl]-[1,2,4]triazine (1.00 g, 2.14 mmol) and ethynyltriisopropylsilane, R_f = 0.42, 50% ethyl acetate/hexanes; eluent, ethyl acetate/hexanes (gradient); isolated yield 0.750 g, 85%; yellow solid; melting point = 117.0−120.0 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.60 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.88 (t, *J* = 8.0 Hz, 1H), 7.65−7.61 (m, 3H), 7.56−7.53 (m, 2H), 7.08−7.05 (m, 2H), 7.04−7.01 (m, 2H), 3.20 (s, 1H), 1.95−1.85 (m, 2H), 1.05−0.99 (m, 4H), 0.77−0.71 (m, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 160.9, 157.2, 156.3, 154.8, 148.6, 147.1, 143.7, 138.4, 133.9, 133.8, 130.8, 130.3, 129.7, 126.4, 126.2, 124.5, 83.7, 79.2, 16.0, 15.9, 10.6, 10.4; IR (ATR-solid): $\bar{\upsilon}_{max}$ = 3283, 3217, 3080, 3002, 2105, 1609, 1580, 1566, 1486, 1455, 1380, 821, 805 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{28}H_{22}N_4$, 414.1844; found, 414.1857.

General Procedure for the Dipolar Cycloaddition of Alkynes and Hydrazides. To an 8 mL reaction vial equipped with a magnetic stirring bar at 23 °C was charged the 3-(6-ethynyl-pyridin-2-yl)-triazine derivative (0.15 mmol, 1.00 equiv) in anhdrous toluene (0.50 mL, 0.30 M). The resulting solution was treated sequentially with the required 4-methylbenzene-sulfonohydrazide (0.30 mmol, 2.00 equiv) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.30 mmol, 2.00 equiv). The resulting mixture was heated to 80 °C for the indicated time upon which the starting alkyne was observed to be consumed by TLC benchmarked with ^1H NMR. The resulting mixture was cooled to 23 °C and absorbed onto Celite and purified using automated flash-column chromatography using the mobile phase system indicated. The desired fractions were retained and concentrated under reduced pressure at 30 °C to afford the title compound in the morphology and yield listed. Characterization data for the major (desired) regioisomer are listed.

Special Instructions. It should be noted that some compounds in this class described demonstrate significant sensitivity to the residual acidity in chloroform and dichloromethane-even when buffered, in addition to dimethyl sulfoxide in certain cases. Pursuant to the aforementioned, these solvents should be avoided where possible for the purposes of chromatographic purification, transfer, and/or NMR analysis. Acetone and acetonitrile were suitable alternatives for this work.

Additionally, prepared materials readily incorporate the residual solvent into the crystal lattice which is challenging to remove via standard reduced pressure techniques. Azeotropic removal with acetone for dichloromethane and acetonitrile in the case of ethyl acetate proved competent solutions to this issue.

Finally, ^{13}C NMR data for prepared cycloaddition adducts below negate the presence of 4−6 carbon resonances most likely due to phasing out of these resonances during acquisition. Similar outcomes have been observed by Manna,[37] Valdes,[38] Wang,[39] and others.[40] Notwithstanding the ^{13}C acquisition data, in all the cases, the remaining supporting analytical characterization data demonstratively support the preparation of the molecules described. Each compound below which this phenomena was observed lists the number of ^{13}C resonances not observed.

*5,6-Diphenyl-3-[6-(5-phenyl-2H-pyrazol-3-yl)-pyridin-2-yl]-[1,2,4]triazine (**9**).* Compound **9** was prepared according to the general procedure discussed above with 3-(6-ethynyl-pyridin-2-yl)-5,6-diphenyl-[1,2,4]triazine (**1**) (1.00 equiv) and *N*′-(benzylidene)-4-methylbenzenesulfono-hydrazide (2.00 equiv), regioisomeric ratio (3.2:1); R_f = 0.42, 10% CH_3OH/CH_2Cl_2; eluent, 2-propanol/CH_2Cl_2 (gradient); isolated yield 0.0393 g, 58%; yellow solid; melting point = 187.0−190.0 °C; ^1H NMR (500 MHz, CD_3CN): δ 8.57 (br-d, *J* = 8.9 Hz, 1H), 8.12−8.07 (m, 2H), 7.88 (br-d, *J* = 6.5 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.63−7.60 (m, 2H), 7.53−7.36 (m, 9H), 7.33 (s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 161.6, 157.5, 156.7, 153.9, 138.9, 136.89, 136.87, 131.5, 131.0, 130.5, 129.6, 126.4, 129.3, 128.7, 126.3, 126.3× (overlaps with 126.3), 122.4, 101.9, four ^{13}C resonances were phased out during acquisition and not observed;

DOI: 10.1021/acs.joc.9b02088
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IR (ATR-solid): $\bar{\upsilon}_{max}$ = 3058, 1595, 1568, 1491, 1445, 1378, 1358, 813, 763, 693 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{29}H_{20}N_6$, 452.1749; found, 452.1756.

*5,6-Diphenyl-3-[6-(5-p-tolyl-2H-pyrazol-3-yl)-pyridin-2-yl]-[1,2,4]triazine (**2**).* Compound **2** was prepared according to the general procedure discussed above with 3-(6-ethynyl-pyridin-2-yl)-5,6-diphenyl-[1,2,4]triazine (**1**) (1.00 equiv) and *N*′-(4-methylbenzylidene)-4-methylbenzenesulfonohydrazide (**H1**) (2.00 equiv), regioisomeric ratio (3.3:1); R_f = 0.46, 10% CH_3OH/CH_2Cl_2; eluent, 2-propanol/CH_2Cl_2 (gradient); isolated yield 0.0377 g, 54%; yellow solid; melting point = 169.0−172.0 °C; ^1H NMR (500 MHz, CD_3CN): δ 8.56 (br-d, *J* = 8.8 Hz, 1H), 8.12−8.06 (m, 2H), 7.78−7.72 (br-m, 2H), 7.69 (d, *J* = 7.8 Hz, 2H), 7.67−7.60 (m, 2H), 7.53−7.47 (m, 2H), 7.46−7.39 (m, 4H), 7.32−7.27 (m, 3H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 161.6, 157.5, 156.7, 153.9, 138.9, 136.92, 136.9× (overlaps with 136.92), 131.5, 131.0, 130.48, 130.46, 130.2, 129.4, 129.3, 126.2, 123.7, 122.3, 101.7, 21.2, six ^{13}C resonances were phased out, or overlapped, during acquisition and not observed; IR (ATR-solid): $\bar{\upsilon}_{max}$ = 3428, 3059, 2993, 2904, 2843, 1596, 1570, 1503, 1445, 1377, 827, 764, 697 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{30}H_{22}N_6$, 466.1906; found, 466.1917.

*5,6-Diphenyl-3-[6-(3-p-tolyl-1H-pyrazol-4-yl)-pyridin-2-yl]-[1,2,4]triazine (**3**).* Compound **3** was prepared according to the general procedure discussed above with 3-(6-ethynyl-pyridin-2-yl)-5,6-diphenyl-[1,2,4]triazine (**1**) (1.00 equiv) and *N*′-(4-methylbenzylidene)-4-methylbenzenesulfonohydrazide (2.00 equiv), and isolated as the minor regioisomer to **2** during automated flash-column chromatography; R_f = 0.64, 10% CH_3OH/CH_2Cl_2; eluent, 2-propanol/CH_2Cl_2 (gradient); isolated yield 0.0132 g, 19%; yellow solid; melting point = 220.5−222.5 °C; ^1H NMR (500 MHz, CD_3CN): δ 12.28 (br-s, 1H), 8.35 (dd, *J* = 0.9, 7.8 Hz, 1H), 8.11 (br-s, 1H), 7.81 (t, *J* = 7.8 Hz, 1H), 7.71−7.55 (m, 6H), 7.46−7.30 (m, 7H), 7.07 (d, *J* = 8.1 Hz, 2H), 2.21 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 162.0, 157.3, 156.8, 154.7, 153.9, 138.0, 137.1, 137.0, 131.4, 130.9, 130.5, 130.4, 130.0, 129.9, 129.4, 129.3, 124.3, 122.1, 117.6, 21.3, four ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\bar{\upsilon}_{max}$ = 3163, 3061, 3027, 2976, 2951, 1589, 1565, 1508, 1456, 1442, 1382, 826, 813 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{30}H_{22}N_6$, 466.1906; found, 466.1899.

*3-{6-[5-(4-Fluoro-phenyl)-2H-pyrazol-3-yl]-pyridin-2-yl}-5,6-diphenyl-[1,2,4]triazine (**10**).* Compound **10** was prepared according to the general procedure discussed above with 3-(6-ethynyl-pyridin-2-yl)-5,6-diphenyl-[1,2,4] triazine (**1**) (1.00 equiv) and *N*′-(4-fluorobenzylidene)-4-methylbenzenesulfonohydrazide (2.00 equiv), regioisomeric ratio (2.5:1); R_f = 0.21, 10% CH_3OH/CH_2Cl_2; eluent, CH_3CN; isolated yield 0.0366 g, 52%; yellow solid; melting point = 232.0−235.0 °C; ^1H NMR (500 MHz, CD_3CN): δ 8.56 (br-d, *J* = 8.8 Hz, 1H), 8.10 (t, *J* = 7.7 Hz, 1H), 8.08−8.02 (br-m, 2H), 7.93−7.87 (br-m, 2H), 7.70−7.66 (m, 2H), 7.62−7.59 (m, 2H), 7.46−7.38, (m, 4H), 7.30 (s, 1H), 7.24−7.18 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)CO$): δ 164.3, 161.5, 157.5, 156.8, 153.9, 139.1, 136.86, 136.84, 131.5, 131.0, 130.5, 129.4, 129.3, 128.3, 128.2, 123.9, 122.4, 116.3 (*J* = 89.1 Hz), 101.8, four ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\bar{\upsilon}_{max}$ = 3375, 3077, 2987, 2902, 2837, 1596, 1571, 1529, 1495, 1452, 1378, 1218, 845, 769, 695 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{29}H_{19}FN_6$, 470.1655; found, 470.1673.

*5,6-Diphenyl-3-{6-[5-(4-trifluoromethyl-phenyl)-2H-pyrazol-3-yl]-pyridin-2-yl}-[1,2,4]triazine (**11**).* Compound **11** was prepared according to the general procedure discussed above with 3-(6-ethynyl-pyridin-2-yl)-5,6-diphenyl-[1,2,4] triazine (**1**) (1.00 equiv) and *N*′-(4-trifluoromethylbenzylidene)-methylbenzene-sulfonohydrazide (2.00 equiv), regioisomeric ratio (2.5:1); R_f = 0.24, 10% CH_3OH/CH_2Cl_2; eluent, CH_3CN; isolated yield 0.0436 g, 56%; yellow solid; melting point = 222.0−225.0 °C; ^1H NMR (500 MHz, CD_3CN): δ 8.57 (d, *J* = 8.0 Hz, 1H), 8.14−8.03 (br-m, 4H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.53−7.47 (m, 2H), 7.46−7.38 (m, 5H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 161.4, 157.5, 156.7, 153.9, 139.2, 136.8, 136.7, 131.6, 131.0, 130.49, 130.46, 129.4, 129.3, 126.7, 126.5, 124.0, 122.6, 102.6, five ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\bar{\upsilon}_{max}$ = 3061, 2893, 2832, 1619, 1596, 1570, 1504, 1377, 1323, 1162, 1106, 1067, 847, 765, 694 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{30}H_{19}F_3N_6$, 520.1623; found, 520.1646.

*3-{6-[5-(4-Bromo-phenyl)-2H-pyrazol-3-yl]-pyridin-2-yl}-5,6-diphenyl-[1,2,4]triazine (**12**).* Compound **12** was prepared according to the general procedure discussed above with 3-(6-ethynyl-pyridin-2-yl)-5,6-diphenyl-[1,2,4] triazine (**1**) (1.00 equiv) and *N*′-(4-bromobenzylidene)-4-ethylbenzenesulfonohydrazide (2.00 equiv), regioisomeric ratio (1.6:1); R_f = 0.48, 10% CH_3OH/CH_2Cl_2; eluent, CH_3CN; isolated yield 0.0436 g, 55%; yellow solid; melting point = 171.0−173.0 °C; ^1H NMR (500 MHz, CD_3CN): δ 8.58 (d, *J* = 7.5 Hz, 1H), 8.11 (t, *J* = 7.7 Hz, 1H), 8.09−8.03 (br-s, 1H), 7.82 (br-d, *J* = 8.0 Hz, 2H), 7.72−7.67 (m, 2H), 7.66−7.60 (m, 4H), 7.54−7.48 (m, 2H), 7.47−7.39 (m, 4H), 7.34 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 161.5, 157.5, 156.8, 154.0, 139.1, 136.9, 136.9, 132.6, 131.55, 131.5× (overlaps with 131.55), 131.0, 130.5, 129.4, 129.3, 128.2, 123.9, 122.4, 121.9, 102.1, four ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\bar{\upsilon}_{max}$ = 3413, 3138, 3089, 2850, 1644, 1595, 1574, 1505, 1488, 1445, 1376, 774, 763, 696 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{29}H_{19}BrN_6$, 530.0855; found, 530.0872.

*(4-{5-[6-(5,6-Diphenyl-[1,2,4]triazin-3-yl)-pyridin-2-yl]-1H-pyrazol-3-yl}-phenyl)-dimethylamine (**13**).* Compound **13** was prepared according to the general procedure discussed above with 3-(6-ethynyl-pyridin-2-yl)-5,6-diphenyl-[1,2,4] triazine (**1**) (1.00 equiv) and *N*′-(4-*N*,*N*-dimethylaminobenzylidene)-4-methyl-benzene-sulfonohydrazide (**H2**) (2.00 equiv), regioisomeric ratio (3.1:1); R_f = 0.23, 10% CH_3OH/CH_2Cl_2; eluent, CH_3CN; isolated yield 0.046 g, 62%; orange solid; melting point = 157.0−160.0 °C; ^1H NMR (500 MHz, CD_3CN): δ 8.53 (d, *J* = 8.0 Hz, 1H), 8.25−8.11 (br-s, 1H), 8.06 (br-t, *J* = 8.0 Hz, 1H), 7.71−7.64 (br-m, 4H), 7.63−7.59 (br-m, 2H), 7.52−7.47 (m, 2H), 7.46−7.38 (m, 4H), 7.16 (br-s, 1H), 6.84−6.80 (br-s, 2H), 2.98 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 161.7, 157.4, 156.6, 153.8, 151.4, 138.5, 136.9, 136.8× (overlaps with 136.9), 131.5, 130.9, 130.5, 130.4, 129.4, 129.3, 127.2, 123.5, 122.1, 113.2, 100.6, 40.5, four ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\bar{\upsilon}_{max}$ = 3410, 3059, 2891, 2800, 1615, 1593, 1568, 1537, 1493, 1377, 1356, 807, 767, 695 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{31}H_{25}N_7$, 495.2171; found, 495.2179.

*3-{6-[5-(4-Methoxy-phenyl)-2H-pyrazol-3-yl]-pyridin-2-yl}-5,6-diphenyl-[1,2,4]triazine (**14**).* Compound **14** was prepared according to the general procedure discussed above with 3-(6-ethynyl-pyridin-2-yl)-5,6-diphenyl-[1,2,4] triazine (1.00 equiv) and *N*′-(4-methoxybenzylidene)-4-methyl-benzene-sulfonohydrazide (2.00 equiv), regioisomeric ratio (2.0:1); R_f = 0.22, 10% CH_3OH/CH_2Cl_2; eluent, CH_3CN; isolated yield 0.046 g, 64%; yellow solid; melting point = 150.0−153.0 °C; ^1H NMR (500 MHz, CD_3CN): δ 8.56 (br-d, *J* = 8.7 Hz, 1H), 8.14−8.05 (br-m, 2H), 7.80 (br-d, *J* = 7.8 Hz, 2H), 7.72−7.68 (m, 2H), 7.64−7.60 (m, 2H0), 7.53−7.47 (m, 2H), 7.46−7.40 (m, 4H), 7.25 (s, 1H), 7.05−7.00 (m, 2H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, D_3CCN): δ 161.7, 160.8, 157.9, 157.4, 153.8, 139.2, 136.9, 136.87, 131.6, 130.9, 130.6, 130.5, 129.5, 129.4, 127.8, 124.0, 122.6, 115.2, 101.3, 56.0, four ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\bar{\upsilon}_{max}$ = 3409, 3242, 3150, 3051, 3027, 2911, 2862, 1618, 1592, 1570, 1513, 14567, 1442, 1379, 1257, 1173, 829, 771, 762, 695 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{30}H_{22}N_6O$, 482.1855; found, 482.1859.

*3-{5-[6-(5,6-Diphenyl-[1,2,4]triazin-3-yl)-pyridin-2-yl]-1H-pyrazol-3-yl}-benzoic Acid Methyl Ester (**15**).* Compound **15** was prepared according to the general procedure discussed above with 3-(6-ethynyl-pyridin-2-yl)-5,6-diphenyl-[1,2,4] triazine (**1**) (1.00 equiv) and *N*′-(3-benzoic acid methyl ester)-4-methylbenzenesulfonohydrazide (2.00 equiv), regioisomeric ratio (1.7:1); R_f = 0.21, 10% CH_3OH/CH_2Cl_2; eluent, CH_3CN; isolated yield 0.032 g, 42%; yellow solid; melting point = 221.0−224.0 °C; ^1H NMR (500 MHz, CD_3CN): δ 8.62 (br-d, *J* = 8.2 Hz, 1H), 8.56 (br-s, 1H), 8.19−8.12

DOI: 10.1021/acs.joc.9b02088
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(br-m, 3H), 8.03 (br-d, J = 8.0 Hz, 1H), 7.76−7.73 (br-m, 2H), 7.68−7.61 (m, 3H), 7.58−7.52 (m, 2H), 7.51−7.46 (m, 4H), 7.45 (br-s, 1H), 3.97 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)CO$): δ 167.2, 161.5, 157.5, 156.7, 154.0, 139.1, 136.89, 136.8× (overlaps with 136.86), 131.8, 131.6, 131.0, 130.6, 130.5, 129.9, 129.4, 129.3, 127.0, 124.0, 122.5, 102.2, 52.5, six ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3442, 3066, 2950, 2847, 1716, 1570, 1508, 1433, 1375, 1283, 1266, 757, 695 cm^{-1}; HRMS (EI) m/z: $[M]^+$ calcd for $C_{31}H_{22}N_6O_2$, 510.1804; found, 510.1810.

*3-{6-[5-(2-Iodo-phenyl)-2H-pyrazol-3-yl]-pyridin-2-yl}-5,6-diphenyl-[1,2,4]triazine (**16**).* Compound **16** was prepared according to the general procedure discussed above with 3-(6-ethynyl-pyridin-2-yl)-5,6-di-*p*-tolyl-[1,2,4]triazine (**1**) (1.00 equiv) and *N*′-(2-iodobenzylidene)-4-methylbenzene-sulfonohydrazide (**H3**) (2.00 equiv), regioisomeric ratio (2.5:1); R_f = 0.29, 10% CH_3OH/CH_2Cl_2; eluent, CH_3CN; isolated yield 0.0519 g, 60%; yellow solid; melting point = 198.0−201.0 °C; ^1H NMR (500 MHz, CD_3CN): δ 8.58 (br-d, J = 8.8 Hz, 1H), 8.13−8.07 (br-m, 2H), 8.04 (dd, J = 1.0, 7.9 Hz, 1H), 7.70−7.67 (m, 2H), 7.62−7.60 (m, 2H), 7.58 (dd, J = 1.2, 7.8 Hz, 1H), 7.52−7.47 (m, 3H), 7.46−7.39 (m, 4H), 7.26 (s, 1H), 7.16 (dt, J = 1.5, 7.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 161.6, 157.5, 156.7, 153.9, 141.0, 138.9, 136.9, 136.8, 131.7, 131.5, 130.9, 130.7, 130.5, 129.4, 129.3, 129.2, 123.7, 122.3, 105.5, 97.8, four ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3405, 1594, 1568, 1493, 1444, 1377, 1358, 1010, 813, 759, 694 cm^{-1}; HRMS (EI) m/z: $[M]^+$ calcd for $C_{29}H_{19}IN_6$, 578.0716; found, 578.0737.

*5,6-Diphenyl-3-{6-[5-(2,4,6-trifluoro-phenyl)-2H-pyrazol-3-yl]-pyridin-2-yl}-[1,2,4]triazine (**17**).* Compound **17** was prepared according to the general procedure discussed above with 3-(6-ethynyl-pyridin-2-yl)-5,6-diphenyl-[1,2,4] triazine (**1**) (1.00 equiv) and *N*′-(2,4,6-trifluorobenzylidene)-4-methylbenzenesulfonohydrazide (2.00 equiv), regioisomeric ratio (3.4:1); R_f = 0.31, 10% CH_3OH/CH_2Cl_2; eluent, 2-propanol/CH_2Cl_2 (gradient); isolated yield 0.0454 g, 60%; yellow solid; melting point = 163.0−166.0 °C; ^1H NMR (500 MHz, CD_3CN): δ 8.57 (d, J = 8.8 Hz, 1H), 8.20−8.12 (br-s, 1H), 8.10 (br-t, J = 7.6 Hz, 1H), 7.70−7.66 (br-m, 2H), 7.63−7.60 (br-m, 2H), 7.53−7.47 (m, 2H), 7.46−7.39 (m, 4H), 7.32−7.27 (br-s, 1H), 7.02 (t, J = 9.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 161.5, 157.6, 156.8, 153.9, 139.0, 136.88, 136.8× (overlaps with 136.88), 131.54, 131.5× (overlaps with 131.54), 131.0, 130.5, 129.4, 129.3, 123.9, 122.4, 106.6, 101.7, six ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3471, 3143, 3099, 2901, 2847, 1640, 1598, 1574, 1516, 1489, 1440, 1380, 1121, 1033, 999, 852, 770, 696 cm^{-1}; HRMS (EI) m/z: $[M]^+$ calcd for $C_{29}H_{17}F_3N_6$, 506.1467; found, 506.1485.

*3-{6-[5-(3,5-Di-tert-butyl-phenyl)-2H-pyrazol-3-yl]-pyridin-2-yl}-5,6-diphenyl-[1,2,4]triazine (**18**).* Compound **18** was prepared according to the general procedure discussed above with 3-(6-ethynyl-pyridin-2-yl)-5,6-diphenyl-[1,2,4] triazine (**1**) (1.00 equiv) and *N*′-(3,5-di-*tert*-butylbenzylidene)-4-methylbenzenesulfonohydrazide (**H4**) (2.00 equiv), regioisomeric ratio (1.5:1); R_f = 0.50, 10% CH_3OH/CH_2Cl_2; eluent, CH_3CN; isolated yield 0.0464 g, 55%; yellow solid; melting point = 144.0−147.0 °C; ^1H NMR (500 MHz, CD_3CN): δ 8.60 (br-d, J = 7.8 Hz, 1H), 8.21−8.16 (br-m, 1H), 8.13 (t, J = 7.8 Hz, 1H), 7.75−7.71 (m, 4H), 7.67−7.63 (br-m, 2H), 7.57−7.52 (m, 3H0), 7.50−7.42 (m, 4H), 7.40 (s, 1H), 1.43 (s, 18H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 161.6, 157.5, 156.7, 153.8, 152.0, 138.8, 136.9, 131.5, 131.0, 130.5, 130.46, 130.4× (overlaps with 130.46), 129.4, 129.3, 123.6, 122.9, 122.2, 120.7, 102.0, 35.6, 31.8, four ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3434, 3062, 2960, 2902, 2865, 1594, 1569, 1493, 1445, 1378, 1360, 1249, 768, 695 cm^{-1}; HRMS (EI) m/z: $[M]^+$ calcd for $C_{37}H_{36}N_6$, 564.3001; found, 564.2990.

*5,6-Diphenyl-3-[6-(5-pyridin-4-yl-2H-pyrazol-3-yl)-pyridin-2-yl]-[1,2,4]triazine (**19**).* Compound **19** was prepared according to the general procedure discussed above with 3-(6-ethynyl-pyridin-2-yl)-5,6-diphenyl-[1,2,4] triazine (**1**) (1.00 equiv) and *N*′-(pyridin-4-yl-benzylidene)-4-methylbenzenesulfonohydrazide (**H5**) (2.00 equiv), regioisomeric ratio (3.0:1); R_f = 0.24, 10% CH_3OH/CH_2Cl_2; eluent, CH_3CN; isolated yield 0.044 g, 65%; yellow solid; melting point = 180.0−183.0 °C; ^1H NMR (500 MHz, CD_3CN): δ 8.65−8.63 (br-m, 2H), 8.60 (br-d, J = 8.0 Hz, 1H), 8.14 (t, J = 7.8 Hz, 1H), 8.09−8.03 (br-m, 1H), 7.84−7.81 (m, 2H), 7.73−7.68 (m, 2H), 7.64−7.60 (m, 2H), 7.55−7.48 (m, 2H), 7.47−7.40 (m, 5H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 161.5, 157.6, 156.8, 154.1, 151.2, 139.3, 136.87, 136.8× (overlaps with 136.87), 131.6, 131.0, 130.53, 130.49, 129.5, 129.4, 124.1, 122.6, 120.5, 102.9, four ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3427, 3145, 1661, 1601, 1570, 1509, 1489, 1430, 1381, 770, 703, 695 cm^{-1}; HRMS (EI) m/z: $[M]^+$ calcd for $C_{28}H_{19}N_7$, 453.1702; found, 453.1718.

*5,6-Bis-(4-cyclopropyl-phenyl)-3-[6-(5-phenyl-2H-pyrazol-3-yl)-pyridin-2-yl]-[1,2,4]triazine (**20**).* Compound **20** was prepared according to the general procedure discussed above with 5,6-bis-(4-cyclopropyl-phenyl)-3-(6-ethynyl-pyridin-2-yl)-[1,2,4]triazine (**8**) (1.00 equiv) and *N*′-(benzylidene)-4-methylbenzenesulfonohydrazide (2.00 equiv), regioisomeric ratio (3.3:1); R_f = 0.24, 10% CH_3OH/CH_2Cl_2; eluent, CH_3CN; isolated yield 0.043 g, 54%; yellow solid; melting point = 154.5−157.5 °C; ^1H NMR (500 MHz, $(CD_3)_2CO$): δ 8.53 (br-d, J = 8.5 Hz, 1H), 8.25−8.10 (m, 2H), 7.95 (br-d, J = 6.6 Hz, 2H), 7.71−7.67 (m, 2H), 7.61−7.57 (m, 2H), 7.51−7.43 (m, 3H), 7.40−7.32 (m, 1H), 7.20−7.17 (m, 2H), 7.16−7.13 (m, 2H), 2.03−1.96 (m, 2H), 1.08−1.03 (m, 4H), 0.81−0.75 (m, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 161.2, 157.1, 156.2, 154.0, 148.7, 147.1, 138.9, 133.9, 133.8, 130.9, 130.3, 129.6, 128.7, 126.4, 126.3, 126.2, 123.6, 122.2, 101.9, 16.0, 15.9, 10.6, 10.4, four ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3005, 1608, 1568, 1489, 1455, 1379, 1359, 1189, 1044, 822, 806, 764 cm^{-1}; HRMS (EI) m/z: $[M]^+$ calcd for $C_{35}H_{28}N_6$, 532.2375; found, 532.2396.

*5,6-Bis-(4-cyclopropyl-phenyl)-3-{6-[5-(2-iodo-phenyl)-2H-pyrazol-3-yl]-pyridin-2-yl}-[1,2,4]triazine (**21**).* Compound **21** was prepared according to the general procedure discussed above with 5,6-bis(4-cyclopropyl-phenyl)-3-(6-ethynyl-pyridin-2-yl)-[1,2,4]-triazine (**8**) (1.00 equiv) and *N*′-(2-iodobenzylidene)-4-methylbenzenesulfono-hydrazide (**H3**) (2.00 equiv), regioisomeric ratio (3:1); R_f = 0.24, 10% CH_3OH/CH_2Cl_2; eluent, CH_3CN; isolated yield 0.0525 g, 53%; yellow solid; melting point = 183.0−186.0 °C; ^1H NMR (500 MHz, CD_3CN): δ 8.55 (br-d, J = 8.4 Hz, 1H), 8.14−8.06 (m, 2H), 8.05 (d, J = 8.0 Hz, 1H), 7.61−7.56 (m, 3H), 7.52−7.48 (m, 3H), 7.25 (s, 1H), 7.19−7.15 (m, 1H), 7.14 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 1.99−1.93 (m, 2H), 1.07−1.00 (m, 4H), 0.78−0.71 (m, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 161.2, 157.1, 156.2, 154.1, 148.7, 147.2, 141.0, 138.9, 134.0, 133.9, 131.7, 130.9, 130.7, 130.3, 129.2, 126.4, 126.2, 123.6, 122.2, 105.5, 16.0, 15.9, 10.6, 10.4, five ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3270, 3000, 2916, 1666, 1607, 1567, 1495, 1443, 1427, 1381, 1360, 1189, 1014, 825, 807, 760 cm^{-1}; HRMS (EI) m/z: $[M]^+$ calcd for $C_{35}H_{27}IN_6$, 658.1342; found, 658.1316.

*3-{6-[5-(4-Bromo-phenyl)-2H-pyrazol-3-yl]-pyridin-2-yl}-5,6-bis-(4-butyl-phenyl)-[1,2,4]triazine (**22**).* Compound **22** was prepared according to the general procedure discussed above with 5,6-bis-(4-butyl-phenyl)-3-(6-ethynyl-pyr-idin-2-yl)-[1,2,4] triazine (**5**) (1.00 equiv) and *N*′-(4-bromolbenzylidene)-4-methylbenzenesulfonohydrazide (2.00 equiv), regioisomeric ratio (1.6:1); R_f = 0.44, 10% CH_3OH/CH_2Cl_2; eluent, CH_3CN; isolated yield 0.0463 g, 48%; yellow solid; melting point = 141.0−144.0 °C; ^1H NMR (500 MHz, CD_3CN): δ 8.59 (d, J = 8.0 Hz, 1H), 8.13 (t, J = 7.7 Hz, 1H), 8.07 (br-d, J = 7.7 Hz, 1H), 7.85 (br-d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.36 (s, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 2.72 (t, J = 7.8 Hz, 2H0), 2.69 (t, J = 7.8 Hz, 2H), 1.70−1.60 (m, 4H), 1.45−1.35 (m, 4H), 0.98 (t, J = 7.4 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 161.1, 157.3, 156.5, 153.9, 146.9, 145.5, 139.0, 134.3, 134.2, 132.6, 130.9, 130.3, 129.4, 129.3, 128.2, 123.8, 122.4, 121.9, 102.0, 36.0, 35.99, 34.2, 34.1, 22.97, 22.9× (overlaps with 22.97), 14.18, 14.16, four ^{13}C resonances were phased

DOI: 10.1021/acs.joc.9b02088
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out during acquisition and not observed; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3468, 3374, 3133, 3018, 2956, 2926, 2857, 1642, 1608, 1574, 1498, 1389, 1375, 827, 797 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{37}H_{35}BrN_6$, 642.2107; found, 642.2097.

*3-{6-[5-(4-Bromo-phenyl)-2H-pyrazol-3-yl]-pyridin-2-yl}-5,6-bis-[4-(3,3-dimethyl-butyl)-phenyl]-[1,2,4]triazine (**23**).* Compound **23** was prepared according to the general procedure discussed above with 5,6-bis-[4-(3,3-dimethyl-butyl)-phenyl]-3-(6-ethynyl-pyridin-2-yl)-[1,2,4]triazine (**7**) (1.00 equiv) and *N*′-(4-bromobenzylidene)-4-methyl-benzenesulfono-hydrazide (2.00 equiv), regioisomeric ratio (1.5:1); R_f = 0.44, 10% CH_3OH/CH_2Cl_2; eluent, 2-propanol/CH_2Cl_2 (gradient); isolated yield 0.0491 g, 47%; yellow solid; melting point = 197.0−200.0 °C; ^{1}H NMR (500 MHz, CD_3CN): δ 8.54 (d, *J* = 8.0 Hz, 1H), 8.09 (t, *J* = 8.0 Hz, 1H), 8.04 (br-s, 1H), 7.82−7.77 (br-m, 2H), 7.64−7.57 (br-m, 4H), 7.51 (br-d, *J* = 7.6 Hz, 2H0), 7.31 (br-s, 1H), 7.27 (br-d, *J* = 8.0 Hz, 2H), 7.22 (br-d, *J* = 7.8 Hz, 2H), 2.69−2.60 (m, 4H), 1.56−1.46 (m, 4H), 0.98 (s, 9H), 0.97 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 160.2, 156.4, 155.5, 153.0, 146.8, 145.4, 138.1, 133.3, 133.2, 131.7, 130.1, 129.4, 128.5, 128.4, 127.3, 122.9, 121.6, 121.0, 101.2, 45.9, 45.8, 30.89, 30.85, 30.24, 30.22, 28.8, 28.7, four ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3136, 2951, 2904, 2864, 1609, 1596, 1570, 1489, 1466, 1444, 1363, 1009, 831 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{41}H_{43}BrN_6$, 698.2733; found: 698.2751.

*3-{6-[5-(4-tert-Butyl-phenyl)-2H-pyrazol-3-yl]-pyridin-2-yl}-5,6-bis-[4-(3,3-dimethyl-butyl)-phenyl]-[1,2,4]triazine (**24**).* Compound **24** was prepared according to the general procedure discussed above with 5,6-bis-[4-(3,3-dimethyl-butyl)-phenyl]-3-(6-ethynyl-pyridin-2-yl)-[1,2,4]triazine (**7**) (1.00 equiv) and *N*′-(4-*tert*-butylbenzylidene)-4-methylbenzenesulfono-hydrazide (2.00 equiv), regioisomeric ratio (1.5:1); R_f = 0.35, 10% CH_3OH/CH_2Cl_2; eluent, 2-propanol/CH_2Cl_2 (gradient); isolated yield 0.0609 g, 60%; yellow solid; melting point = 240.0−243.0 °C; ^{1}H NMR (500 MHz, CD_3CN): δ 8.43 (d, *J* = 8.1 Hz, 1H), 8.08 (br-s, 1H), 8.01 (br-t, *J* = 7.9 Hz, 1H), 7.76 (br-d, *J* = 6.9 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.31 (s, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 2.61−2.51 (m, 4H), 1.50−1.39 (m, 4H), 1.25 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 161.4, 157.2, 156.3, 154.1, 151.6, 147.7, 146.3, 138.8, 134.34, 134.28, 131.0, 130.4, 129.4, 129.3, 126.5, 126.1, 123.6, 122.1, 101.7, 46.9, 46.8, 35.2, 31.8, 31.7, 31.6, 31.1, three ^{13}C resonances were phased out during acquisition and not observed, three ^{13}C resonances appeared in the range of the residual solvent resonances with significant overlap; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3236, 3032, 2951, 2903, 2864, 1609, 1591, 1495, 1466, 1386, 1364, 1352, 835, 799 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{45}H_{52}N_6$, 676.4253; found, 676.4283.

*5,6-Bis-(4-butyl-phenyl)-3-{6-[5-(3,5-di-tert-butyl-phenyl)-2H-pyrazol-3-yl]-pyridin-2-yl}-[1,2,4]triazine (**25**).* Compound **25** was prepared according to the general procedure discussed above with 5,6-bis-(4-butyl-phenyl)-3-(6-ethynyl-pyr-idin-2-yl)-[1,2,4] triazine (**5**) (1.00 equiv) and *N*′-(3,5-di-*tert*-butylbenzylidene)-4-methylbenzenesulfonohydrazide (**H4**) (2.00 equiv), regioisomeric ratio (1.6:1); R_f = 0.42, 10% CH_3OH/CH_2Cl_2; eluent, CH_3CN; isolated yield 0.051 g, 50%; yellow solid; melting point = 129.0−132.0 °C; ^{1}H NMR (500 MHz, CD_3CN): δ 8.43 (br-d, *J* = 7.9 Hz, 1H), 8.13−8.07 (br-m, 1H0), 8.03−7.98 (br-m, 1H), 7.71 (br-s, 2H), 7.61−7.55 (br-m, 2H), 7.52−7.45 (br-m, 2H), 7.39 (br-s, 1H), 7.21−7.09 (br-m, 5H), 2.62−2.52 (m, 4H), 1.58−1.46 (m, 4H), 1.32−1.23 (m, 22H), 0.85−0.80 (m, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 161.4, 157.3, 156.4, 153.9, 152.0, 146.9, 145.5, 138.7, 134.4, 134.3, 130.9, 130.3, 129.4, 129.3, 123.5, 122.8, 122.1, 120.7, 102.0, 36.01, 35.98, 35.55, 34.2, 34.1, 31.8, 22.96, 22.9× (overlaps with 22.96), 14.18, 14.17, four ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 2954, 2929, 2860, 1608, 1594, 1569, 1493, 1477, 1414, 1378, 1360, 1249, 1185, 804 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{45}H_{52}N_6$, 676.4253; found, 676.4225.

*3-{6-[5-(4-Bromo-phenyl)-2H-pyrazol-3-yl]-pyridin-2-yl}-5,6-di-p-tolyl-[1,2,4]triazine (**26**).* Compound **26** was prepared according to the general procedure discussed above with 3-(6-ethynyl-pyridin-2-yl)-5,6-di-*p*-tolyl-[1,2,4]triazine (**4**) (1.00 equiv) and *N*′-(4-bromobenzylidene)-4-methylbenzene-sulfonohydrazide (2.00 equiv), regioisomeric ratio (2.1:1); R_f = 0.50, 10% CH_3OH/CH_2Cl_2; eluent, 2-propanol/CH_2Cl_2 (gradient); isolated yield 0.0401 g, 48%; yellow solid; melting point = 187.0−190.0 °C; ^{1}H NMR (500 MHz, CD_3CN): δ 8.47−8.41 (br-s, 1H), 8.09−7.98 (br-s, 2H), 7.81 (br-d, *J* = 8.0 Hz, 2H), 7.61−7.44 (br-m, 6H), 7.38 (br-s, 1H), 7.18 (br-d, *J* = 7.5 Hz, 2H), 7.15 (br-d, *J* = 7.5 Hz, 2H), 2.30 (s, 3H), 2.28 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 161.2, 157.3, 156.4, 154.1, 142.0, 140.6, 139.0, 134.13, 134.07, 132.6, 130.9, 130.3, 130.1, 130.0, 128.1, 123.8, 122.3, 121.8, 102.1, 21.4, 21.3, four ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3482, 3373, 3187, 3129, 3069, 1646, 1609, 1599, 1501, 1490, 1387, 1375, 1006, 824, 796 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{31}H_{23}BrN_6$, 558.1168; found, 558.1154.

*5,6-Bis-(4-fluoro-phenyl)-3-{6-[5-(4-methoxy-phenyl)-2H-pyrazol-3-yl]-pyridin-2-yl}-[1,2,4]triazine (**27**).* Compound **27** was prepared according to the general procedure discussed above with 3-(6-ethynyl-pyridin-2-yl)-5,6-bis-(4-fluoro-phenyl)-[1,2,4] triazine (**6**) (1.00 equiv) and *N*′-(4-methoxybenzylidene)-4-methylbenzene-sulfonohydrazide (2.00 equiv), regioisomeric ratio (2.1:1); R_f = 0.21, 10% CH_3OH/CH_2Cl_2; eluent, 2-propanol/CH_2Cl_2 (gradient); isolated yield 0.0465 g, 60%; yellow solid; melting point = 194.0−197.0 °C; ^{1}H NMR (500 MHz, CD_3CN): δ 8.54 (br-d, *J* = 8.7 Hz, 1H), 8.18−8.11 (br-s, 1H), 8.08 (br-t, *J* = 7.5 Hz, 1H), 7.82−7.75 (br-s, 2H), 7.74−7.70 (m, 2H), 7.67−7.62 (m, 2H), 7.24−7.14 (m, 5H), 7.05−7.00 (m, 2H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 165.8 (*J* = 73.6 Hz), 163.8 (*J* = 72.2 Hz), 161.6, 160.6, 156.5, 155.7, 153.7, 138.8, 133.5 (*J* = 8.4 Hz), 133.1 (*J* = 3.1 Hz), 133.0 (*J* = 3.3 Hz), 132.8 (*J* = 8.1 Hz), 127.6, 123.7, 122.3, 116.5 (*J* = 11.0 Hz), 116.4 (*J* = 11.0 Hz), 115.0, 101.3, 55.6, four ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3059, 2925, 1652, 1619, 1590, 1569, 1491, 1380, 1323, 1164, 1120, 1066, 768, 695 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{30}H_{20}OF_2N_6$, 518.1667; found, 518.1665.

*5,6-Bis-(4-cyclopropyl-phenyl)-3-{6-[5-(2,4,6-trifluoro-phenyl)-2H-pyrazol-3-yl]-pyridin-2-yl}-[1,2,4]triazine (**28**).* Compound **28** was prepared according to the general procedure discussed above with 5,6-bis-(4-cyclopropyl-phenyl)-3-(6-ethynyl-pyridin-2-yl)-[1,2,4]triazine (**8**) (1.00 equiv) and *N*′-(2,4,6-trifluorobenzylidene)-4-methyl-benzenesulfonohydrazide (2.00 equiv), regioisomeric ratio (2.6:1); R_f = 0.24, 10% CH_3OH/CH_2Cl_2; eluent, CH_3CN; isolated yield 0.0593 g, 68%; yellow solid; melting point = 150.0−153.0 °C; ^{1}H NMR (500 MHz, CD_3CN): δ 8.54 (br-d, *J* = 8.8 Hz, 1H), 8.12−8.03 (br-m, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.51−7.48 (m, 2H), 7.28 (s, 1H), 7.15−7.12 (m, 2H), 7.11−7.08 (m, 2H), 7.01 (t, *J* = 9.0 Hz, 2H), 1.99−1.92 (m, 2H), 1.06−1.00 (m, 4H), 0.78−0.71 (m, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 161.0, 157.2, 156.3, 153.8, 148.7, 147.2, 139.0, 133.9, 133.7, 130.9, 130.3, 126.4, 126.2, 123.7, 122.4, 106.5, 101.7 (t, *J* = 27.0 Hz), 16.0, 15.9, 10.6, 10.4, six ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-solid): $\overline{\upsilon}_{max}$ = 3082, 3004, 1638, 1608, 1597, 1570, 1488, 1378, 1121, 1033, 1000, 822, 805, 609 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{35}H_{25}F_3N_6$, 586.2093; found, 586.2094.

*3-(6-{5-[4-(4-tert-Butyl-phenylethynyl)-phenyl]-2H-pyrazol-3-yl}-pyridin-2-yl)-5,6-diphenyl-[1,2,4]triazine (**29**).* To an 8 mL reaction vial equipped with a magnetic stir bar at 23 °C was charged the requisite (6-bromo-pyridin-2-yl)-[1,2,4]triazine (50 mg, 0.094 mmol, 1.00 equiv) in anhydrous 1,4-dioxane (0.38 mL, 0.25 M).[19] The resulting solution was treated sequentially with $Pd(dppf)Cl_2$ (3.4 mg, 0.0047 mmol, 5 mol %), CuI (0.9 mg, 0.0047 mmol, 5 mol %), and triethylamine [TEA] (390 μL, 0.282 mmol, 3 equiv). The resulting mixture was heated to 100 °C for 16 h, upon which time the crude mixture was cooled to ambient temperature and concentrated under reduced pressure to remove TEA. The resulting dark-brown residue was partitioned between ethyl acetate (5.0 mL) and water (1.0 mL). The organic layer was separated and the aqueous layer was back-extracted with (2 × 5.0 mL) portions of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and then

DOI: 10.1021/acs.joc.9b02088
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concentrated to afford the crude mixture which was purified using automated flash column chromatography to afford the title compound. R_f = 0.48, 10% CH_3OH/CH_2Cl_2; eluent, ethyl acetate/hexanes (gradient); isolated yield 0.033 g, 58%; yellow solid; melting point = 180.0−182.0 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 8.49−8.45 (m, 1H), 8.23−8.15 (m, 2H), 7.96 (d, J = 8.1 Hz, 2H), 7.88−7.84 (m, 1H), 7.74−7.59 (m, 6H), 7.57−7.37 (m, 11H), 1.31 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2CO$): δ 161.2, 157.6, 156.9, 153.6, 152.6, 139.2, 136.72, 136.69, 132.6, 132.6, 132.1, 131.6, 130.9, 130.5, 129.4, 129.3, 126.4, 126.3, 123.8, 123.3, 122.6, 121.8, 121.1, 102.2, 90.9, 89.6, 35.4, 31.4, three ^{13}C resonances were phased out during acquisition and not observed; IR (ATR-$CDCl_3$): $\overline{\upsilon}_{max}$ = 2955, 2904, 2864, 1595, 1571, 1502, 1448, 1377, 1009, 836, 767, 676 cm^{-1}; HRMS (EI) m/z: $[M]^+$ calcd for $C_{41}H_{32}N_6$, 608.2688; found, 608.2689.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b02088.

Copies of ^{1}H and ^{13}C NMR spectra, purification chromatograms, LC/MS chromatograms, XRD data, and computational data (PDF)

X-ray crystallographic data for major regioisomer **2** (CIF)

X-ray crystallographic data for minor regioisomer **3** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work was provided by an award from the U.S. Department of Energy, Basic Energy Sciences, Separations Program Award: DE-SC0018033. An award from the National Science Foundation (NSF) Major Research Instrumentation Program (1531870) is gratefully acknowledged for the acquisition of University's 500 MHz multinuclear NMR spectrometer with a broad-band N_2 cryoprobe. The authors would like to thank Dr. Qiaoli Liang, The University of Alabama, for acquisition of HRMS data, Gene Mullins, Tennessee Tech University, for method development and acquisition of LC/MS data to assist in confirming reaction regioselectivity, and Dr. Markus W. Voehler for acquisition of the ^{13}C NMR of 29, supported in part by grants for NMR instrumentation from the NSF (0922862), National Institutes of Health (S10 RR025677), and Vanderbilt University matching funds. D.A.D. also thanks the Robert Ramsay Chair Fund of The University of Alabama for support.

■ DEDICATION

The authors dedicate this work in memory of the TN Tech College of Arts and Sciences Associate Dean Dr. Kurt R. Eisen (1958−2019).

■ REFERENCES

(1) (a) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. A Novel One-Pot Method for the Preparation of Pyrazoles by 1,3-Dipolar Cycloadditions of Diazo Compounds Generated in Situ. *J. Org. Chem.* **2003**, *68*, 5381−5383. (b) Panda, S.; Pradhan, N.; Manna, D. Ring-opening of Indoles: An Unconventional Route for the Transformation of Indoles to 1H-Pyrazoles using Lewis Acid. *ACS Comb. Sci.* **2018**, *20*, 573−578. (c) He, S.; Chen, L.; Niu, Y.-N.; Wu, L.-Y.; Liang, Y.-M. 1,3-Dipolar Cycloaddition of Diazoacetate Compounds to Terminal Alkynes Promoted by $Zn(OTf)_2$: An Efficient Way to the Preparation of Pyrazoles. *Tetrahedron Lett.* **2009**, *50*, 2443−2445.

(2) (a) Chen, Z.; Yan, Q.; Liu, Z.; Xu, Y.; Zhang, Y. Copper-Mediated Synthesis of 1,2,3-Triazoles from N-Tosylhydrazones and Anilines. *Angew. Chem., Int. Ed.* **2013**, *52*, 13324−13328. (b) Chen, Z.; Yan, Q.; Liu, Z.; Zhang, Y. Metal-Free C N- and N N-bond Formation: Synthesis of 1,2,3-triazoles from Ketones, N-tosylhydrazines, and Amines in One Pot. *Chem.—Eur. J.* **2014**, *20*, 17635−17639.

(3) (a) Paraja, M.; Valdés, C. Pd-Catalyzed Autotandem Reactions with N-Tosylhydrazones. Synthesis of Condensed Carbo- and Heterocycles by Formation of a C−C Single Bond and a C=C Double Bond on the Same Carbon Atom. *Org. Lett.* **2017**, *19*, 2034−2037. (b) Wang, W.-L.; Feng, Y.-L.; Gao, W.-Q.; Luo, X.; Deng, W.-P. A Highly Efficient BF_3•Et_2O-catalysed Intramolecular [3+2] Cycloaddition for the Synthesis of 3,4-Dihydrobenzopyrano[3,4-c]-pyrazoles. *RSC Adv.* **2013**, *3*, 1687−1690. (c) Zheng, Y.; Zhang, X.; Yao, R.; Wen, Y.; Huang, J.; Xu, X. 1,3-Dipolar Cycloaddition of Alkyne-Tethered N-Tosylhydrazones: Synthesis of Fused Polycyclic Pyrazoles. *J. Org. Chem.* **2016**, *81*, 11072−11080.

(4) Kumar, V.; Kaur, K.; Gupta, G. K.; Sharma, A. K. Pyrazole Containing Natural Products: Synthetic Preview and Biological Significance. *Eur. J. Med. Chem.* **2013**, *69*, 735−753.

(5) Ansari, A.; Ali, A.; Asif, M.; Shamsuzzaman, S. Review: biologically active pyrazole derivatives. *New J. Chem.* **2017**, *41*, 16−41.

(6) (a) Cuerva, C.; Campo, J. A.; Ovejero, P.; Torres, M. R.; Cano, M. Polycatenar Pyrazole and Pyrazolate Ligands as Building Blocks of New Columnar Pd(II) Metallomesogens. *Dalton Trans.* **2014**, *43*, 8849−8860. (b) Lam, M. H. W.; Lee, D. Y. K.; Man, K. W.; Lau, C. S. W. A Luminescent pH Sensor Based on a Sol-Gel Film Functionalized with a Luminescent Organometallic Complex. *J. Mater. Chem.* **2000**, *10*, 1825−1828.

(7) Ojwach, S. O.; Darkwa, J. Pyrazole and (Pyrazol-1-yl)metal Complexes as Carbon-Carbon Coupling Catalysts. *Inorg. Chim. Acta* **2010**, *363*, 1947−1964.

(8) (a) Ye, F.; Ma, X.; Xiao, Q.; Li, H.; Zhang, Y.; Wang, J. C(sp)-C(sp^3) Bond Formation through Cu-Catalyzed Cross-Coupling of N-Tosylhydrazones and Trialkylsilylethynes. *J. Am. Chem. Soc.* **2012**, *134*, 5742−5745. (b) Ye, F.; Wang, C.; Ma, X.; Hossain, M. L.; Xia, Y.; Zhang, Y.; Wang, J. Synthesis of Terminal Allenes through Copper-Mediated Cross-Coupling of Ethyne with N-tosylhydrazones or α-Diazoesters. *J. Org. Chem.* **2015**, *80*, 647−652.

(9) Halcrow, M. A. Recent Advances in the Synthesis and Applications of 2,6-Dipyrazolylpyridine Derivatives and their Complexes. *New J. Chem.* **2014**, *38*, 1868−1882.

(10) Hansen, E. C.; Pedro, D. J.; Wotal, A. C.; Gower, N. J.; Nelson, J. D.; Caron, S.; Weix, D. J. New Ligands for Nickel Catalysis from Diverse Pharmaceutical Heterocycle Libraries. *Nat. Chem.* **2016**, *8*, 1126−1130.

(11) Izatt, R. M.; Izatt, S. R.; Bruening, R. L.; Izatt, N. E.; Moyer, B. A. Challenges to achievement of metal sustainability in our high-tech society. *Chem. Soc. Rev.* **2014**, *43*, 2451−2475.

(12) For a recent review see: Panak, P. J.; Geist, A. Complexation and Extraction of Trivalent Actinides and Lanthanides by TriazinylpyridineN-Donor Ligands. *Chem. Rev.* **2013**, *113*, 1199−1236.

(13) Kolarik, Z. Complexation and Separation of Lanthanides(III) and Actinides(III) by Heterocyclic N-Donors in Solutions. *Chem. Rev.* **2008**, *108*, 4208−4252.

DOI: 10.1021/acs.joc.9b02088
J. Org. Chem. XXXX, XXX, XXX−XXX

(14) (a) Lanham, W. B.; Runion, T. C. *PUREX Process For Plutonium and Uranium Recovery; USAEC Report ORNL-479*; Oak Ridge National Laboratory: Oak Ridge, TN, 1949. (b) Warf, J. C. Extraction of Cerium(IV) Nitrate by Butyl Phosphate. *J. Am. Chem. Soc.* **1949**, *71*, 3257−3258. (c) Batey, W. *Science and Practice of Liquid−Liquid Extraction*; Thompson, J. D., Ed.; Clarendon Press: Oxford, U.K., 1992; Vol. *2*, p 139.
(15) Madic, C.; Hudson, M. J.; Liljenzin, J.-O.; Glatz, J.-P.; Nannicini, R.; Facchini, A.; Kolarik, Z.; Odoj, R. Recent achievements in the development of partitioning processes of minor actinides from nuclear wastes obtained in the frame of the NEWPART European programme (1996-1999). *Prog. Nucl. Energy* **2002**, *40*, 523−526.
(16) Nash, K. L. The Chemistry of TALSPEAK: A Review of the Science. *Solvent Extr. Ion Exch.* **2015**, *33*, 1−55.
(17) Nash, K. L.; Nilsson, M. *Reprocessing and Recycling of Spent Nuclear Fuel*; Taylor, R., Ed.; Woodhead: Cambridge, U.K., 2015; pp 3−23.
(18) Kolarik, Z. Complexation and Separation of Lanthanides(III) and Actinides(III) by Heterocyclic N-Donors in Solutions. *Chem. Rev.* **2008**, *108*, 4208−4252.
(19) Chaudhuri, S.; Carrick, J. D. Synthetic Access to Functionalized Dipolarophiles of Lewis Basic Complexant Scaffolds through Sonogashira Cross-Coupling. *J. Org. Chem.* **2018**, *83*, 10261−10271.
(20) (a) Crespin, L.; Biancalana, L.; Morack, T.; Blakemore, D. C.; Ley, S. V. One-Pot Acid-Catalyzed Ring-Opening/Cyclization/Oxidation of Aziridines with N-Tosylhydrazones: Access to 1,2,4-Triazines. *Org. Lett.* **2017**, *19*, 1084−1087. (b) Fu, R.; Li, Z. Direct Synthesis of 2-Methylbenzofurans from Calcium Carbide and Salicylaldehyde p-Tosylhydrazones. *Org. Lett.* **2018**, *20*, 2342−2345. (c) Creary, X. Regioselectivity in the addition of singlet and triplet carbenes to 1,1-dimethylallene. A probe for carbene multiplicity. *J. Am. Chem. Soc.* **1980**, *102*, 1611−1618. (d) Gloss, G. L.; Moss, R. A. Carbenoid Formation of Arylcyclopropanes from Olefins, Benzal Bromides, and Organolithium Compounds and from Photolysis of Aryldiazomethanes. *J. Am. Chem. Soc.* **1964**, *86*, 4042−4053. (e) Sartorelli, A. C.; Agrawal, K. C.; Booth, B. A.; Pittman, J.; Bartholomew, D. G.; Broom, A. D. Antineoplastic and biochemical properties of arylsulfonylhydrazones of 2-formylpyridine N-oxide. *J. Med. Chem.* **1976**, *19*, 830−833.
(21) Supporting Information documents synthesis procedures and spectral data for accessing dipoles evaluated.
(22) Zora, M.; Kivrak, A.; Yazici, C. Synthesis of Pyrazoles via Electrophilic Cyclization. *J. Org. Chem.* **2011**, *76*, 6726−6742.
(23) Pérez-Aguilar, M. C.; Valdés, C. Regioselective One-Step Synthesis of Pyrazoles from Alkynes and N-Tosylhydrazones: [3+2] Dipolar Cycloaddition/[1,5] Sigmatropic Rearrangement Cascade. *Angew. Chem., Int. Ed.* **2013**, *52*, 7219−7223.
(24) Panda, S.; Maity, P.; Manna, D. Transition Metal, Azide, and Oxidant-Free Homo- and Heterocoupling of Ambiphilic Tosylhydrazones to the Regioselective Triazoles and Pyrazoles. *Org. Lett.* **2017**, *19*, 1534−1537.
(25) (a) Tai, S.; Dover, E. J.; Marchi, S. V.; Carrick, J. D. Pd-Catalyzed Diamination of 1,2,4-Triazinyl Complexant Scaffolds. *J. Org. Chem.* **2015**, *80*, 6275−6282. (b) Chin, A. L.; Carrick, J. D. Modular Approaches to Diversified Soft Lewis Basic Complexants through Suzuki-Miyaura Cross-Coupling of Bromoheteroarenes with Organotrifluoroborates. *J. Org. Chem.* **2016**, *81*, 1106−1115. (c) Cleveland, J. W.; Carrick, J. D. Pd-catalyzed Amination of Functionalized 6-bromo-pyridinyl-1,2,4-triazine Complexant Scaffolds. *Eur. J. Org. Chem.* **2017**, 3318−3327.
(26) Doak, B. C.; Scanlon, J. J.; Simpson, J. S. Synthesis of Unsymmetrical 1,1′-Disubstituted Bis(1,2,3-triazole)s using Monosilylbutadiynes. *Org. Lett.* **2011**, *13*, 527−539.
(27) Harigae, R.; Moriyama, K.; Togo, H. Preparation of 3,5-Disubstituted Pyrazoles and Isoxazoles from Terminal Alkynes, Aldehydes, Hydrazines, and Hydroxylamine. *J. Org. Chem.* **2014**, *79*, 2049−2058.
(28) Full dissemination of the X-ray crystallographic data for **2** and **3** can be found in the Supporting Information.
(29) Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.
(30) (a) Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B* **1988**, *37*, 785−789.
(31) Godbout, N.; Salahub, D. R.; Andzelm, J.; Wimmer, E. Optimization of Gaussian-type Basis Sets for Local Spin Density Functional Calculations. Part I. Boron through Neon, Optimization Technique and Validation. *Can. J. Chem.* **1992**, *70*, 560−571.
(32) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; et al. *Gaussian 16*, Revision A.03; Gaussian, Inc.: Wallingford CT, 2016.
(33) Additional orbital diagrams shown in the Supporting Information.
(34) (a) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. NMR Chemical Shifts of Trace Impurities: Common Laboratory Solvents, Organics, and Gases in Deuterated Solvents Relevant to the Organometallic Chemist. *Organometallics* **2010**, *29*, 2176−2179. (b) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. NMR Chemical Shifts of Common Laboratory Solvents as Trace Impurities. *J. Org. Chem.* **1997**, *62*, 7512−7515.
(35) (a) Creary, X. Regioselectivity in the addition of singlet and triplet carbenes to 1,1-dimethylallene. A probe for carbene multiplicity. *J. Am. Chem. Soc.* **1980**, *102*, 1611−1618. (b) Gloss, G. L.; Moss, R. A. Carbenoid Formation of Arylcyclopropanes from Olefins, Benzal Bromides, and Organolithium Compounds and from Photolysis of Aryldiazomethanes. *J. Am. Chem. Soc.* **1964**, *86*, 4042−4053.
(36) Sartorelli, A. C.; Agrawal, K. C.; Booth, B. A.; Pittman, J.; Bartholomew, D. G.; Broom, A. D. Antineoplastic and Biochemical Properties of Arylsulfonylhydrazones of 2-Formylpyridine N-Oxide. *J. Med. Chem.* **1976**, *19*, 830−833.
(37) Panda, S.; Pradhan, N.; Manna, D. Ring-Opening of Indoles: An Unconventional Route for the Transformation of Indoles to 1H-Pyrazoles Using Lewis Acid. *ACS Comb. Sci.* **2018**, *20*, 573−578.
(38) Pérez-Aguilar, M. C.; Valdés, C. Regioselective One-Step Synthesis of Pyrazoles from Alkynes and N-Tosylhydrazones: [3+2] Dipolar Cycloaddition/[1,5] Sigmatropic Rearrangement Cascade. *Angew. Chem., Int. Ed.* **2013**, *52*, 7219−7223.
(39) Zhang, Z.; Zhou, Q.; Ye, F.; Xia, Y.; Wu, G.; Hossain, M. L.; Zhang, Y.; Wang, J. Copper(I)-Catalyzed Three-Component Coupling of N-Tosylhydrazones, Alkynes and Azides: Synthesis of Trisubstituted 1,2,3-Triazoles. *Adv. Synth. Catal.* **2015**, *357*, 2277−2286.
(40) (a) Butler, R. N.; Hanniffy, J. M.; Stephens, J. C.; Burke, L. A. A Ceric Ammonium Nitrate N-Dearylation of *N*-*p*-Anisylazoles Applied to Pyrazole, Triazole, Tetrazole, and Pentazole Rings: Release of Parent Azoles. Generation of Unstable Pentazole, HN5/N5$^-$, in Solution. *J. Org. Chem.* **2008**, *73*, 1354−1364. (b) Yang, Y.; Hu, Z.-L.; Li, R.-H.; Chen, Y.-H.; Zhan, Z.-P. Pyrazole Synthesis via a Cascade Sonogashira Coupling/Cyclization of N-propargyl Sulfonylhydrazones. *Org. Biomol. Chem.* **2018**, *16*, 197−201. (c) Lei, X.; Lin, G.-Q.; Liu, P.; Xu, Q.-Q.; Dong, C. A Complementary Approach to 3,5-Substituted Pyrazoles with Tosyl-hydrazones and Terminal Alkynes Mediated by TfOH. *Synlett* **2012**, *23*, 2087−2092.

DOI: 10.1021/acs.joc.9b02088
J. Org. Chem. XXXX, XXX, XXX−XXX