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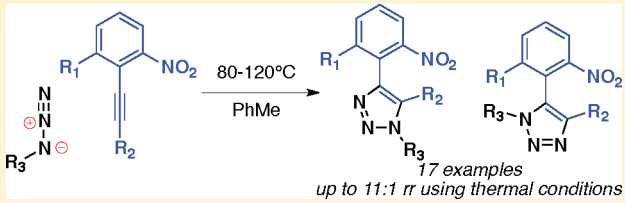
Synthesis and Computational Analysis of Densely Functionalized Triazoles Using *o*-Nitrophenylalkynes

Melissa L. McIntosh, Ryne C. Johnston, Ommidala Pattawong, Bradley O. Ashburn, Michael R. Naffziger, Paul Ha-Yeon Cheong,*[,†] and Rich G. Carter*

Department of Chemistry, Oregon State University, 153 Gilbert Hall, Corvallis, Oregon 97331, United States

Supporting Information

ABSTRACT: Dipolar cylcoadditions with azides using a series of *o*-nitrophenylethynes and disubstituted alkynes were studied experimentally and computationally. Density functional theory computations reveal the steric and electronic parameters that control the regioselectivity of these cycloadditions. Several new substrates were predicted that would either give enhanced regiocontrol or invert the regiochemical preference. Experimentally, the alkynes were screened in the [3 + 2] cycloaddition with benzyl azide. Of the 11 alkynes screened experimentally, the acetylenes containing halogen substitution directly on the alkyne provided the highest levels of regioselectivity. These haloalkynes were also shown to tolerate variation of the azide moiety with continued good levels of regioselectivity in most cases. Diverse functional groups can be incorporated through the cycloaddition process and their subsequent orthogonal modification was demonstrated.



INTRODUCTION

Dipolar cycloadditions have captured the attention of organic chemists since their discovery over 50 years ago by Robert Huisgen.[1] Advances in the field have provided wide-ranging access to heterocyclic natural products, pharmaceuticals and materials applications. While techniques for constructing these structures have been greatly expanded by transition-metal catalysis,[2] the search for alternate methods to increase the available substrate scope continue to be important in this area.

Much of the recent excitement in this field has focused on the development of copper-catalyzed dipolar cycloadditions [often referred to as "Click" chemistry or the copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC)] utilizing azides and alkynes. Alkyne/azide "Click" chemistry has become the gold standard for dipolar cycloadditions (Scheme 1, eq 1).[3] The broad utility of this process[4] can be found in the numerous applications in polymer chemistry, materials science,[5] pharmacology,[6] and chemical biology.[7] These transformations are generally limited to monosubstituted alkynes and provide excellent levels of chemical selectivity for the 1,4-triazole. In recent years, ruthenium-based catalysis has been shown to reverse the regioselecitivity to now favor the 1,5-triazole.[4,8] Strained alkynes have extended the reach of this chemistry to include disubstituted alkynes;[9] however, these examples are usually limited to strained cyclic alkynes or metal-catalyzed systems[10] and suffer from less than ideal regioselectivity (Scheme 1, eq 2). Despite these considerable advances in the field, control of regioselectivity in reactions involving disubstituted alkynes as well as the search for a nonmetal based solution remain challenges in this field.

Our laboratory has recently developed a Diels−Alder approach to construct highly substituted biaryl scaffolds (Scheme 2).[11] In this strategy, electron-deficient aryl (normally *o*-nitrophenyl) alkynes are used in cycloaddition/cycloreversion reactions with acyclic and cyclic dienes. This process has proven to be highly regioselective and allows efficient access to numerous classes of tetra-ortho-substituted biaryl compounds. The *o*-nitro moiety on the aromatic ring is likely critical to establishing the high regioselectivity and generality of this process. While the increased steric bulk of placing two ortho substituents on the aromatic ring of the aryl alkyne would appear to be disruptive to the construction of a highly congested system, the electron-withdrawing nature of the *o*-nitro moiety is able to override many steric effects, leading to the construction of >50 examples of tetra-ortho-substituted biaryl compounds **13** through this method to date.[11] Interestingly, placement of the nitro moiety in the para position relative to the alkyne is not beneficial to the chemical yield of the process.[11e] Our laboratory[11] and others[12] have hypothesized possible mechanistic pathways for this transformation, all of which involve the [2.2.2]-bicyclic intermediate **12**. Our original mechanism invoked a [4 + 2]-cycloaddition to generate bicycle **12**. Alternatively, we have observed under certain cases that intermediate **12** may also be obtained via a [2 + 2]-cycloaddition followed by [1,3]-shift to yield the same intermediate **12**.[11h] Through either path, [4 + 2]-cycloreversion extrudes an ethylene moiety and establishes aromaticity, which likely is the driving force for the biaryl formation.

Given the importance of the azide/alkyne dipolar cycloadditions coupled with the existing limitations in regioselective control present with disubstituted alkynes, an exploration of the

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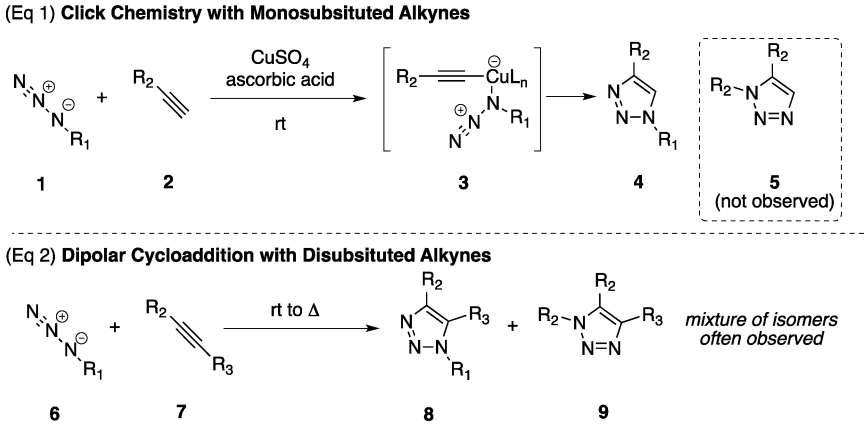
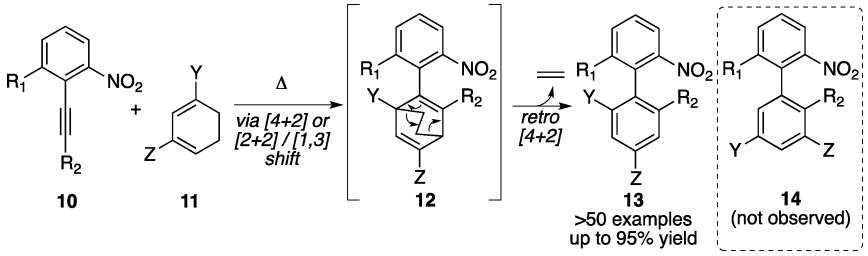
Scheme 1. Alkyne/Azide Dipolar Cycloadditions



Scheme 2. Diels–Alder Approach to Biaryls

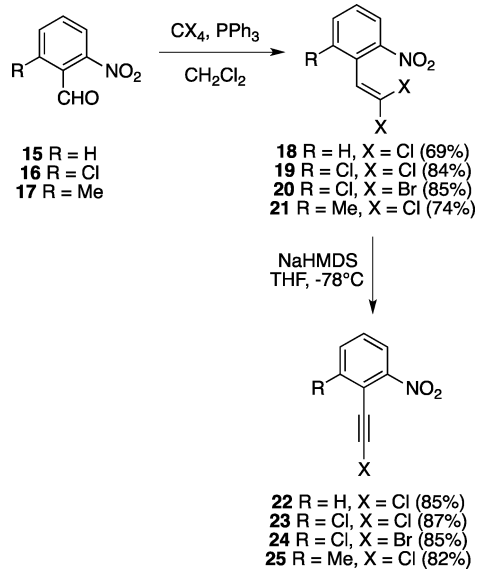


potential utility of our previously reported *o*-nitrophenylalkynes in dipolar cycloaddition processes might be warranted. Interestingly, despite the wealth of chemistry directed toward triazole synthesis, only limited publications have appeared utilizing *o*-nitrophenylalkynes as dipolarophiles.[13,14] Alternate dipolar cycloadditions toward these *o*-nitrophenyl heterocycles have also been disclosed.[15] The mechanism of the thermal dipolar cycloaddition between an azide and alkyne has been the subject of much discussion. In 1968, Firestone proposed a diradical mechanism for the azide/alkyne coupling[16] while Huisgen favored the concerted mechanism.[17] More recently, Houk reported the FMO analyses and underlying chemical principles that control the chemo- and regioselectivities of 1,3-dipolar cycloadditions.[18] In this article, we disclose the coupling of experiments with computations to understand and guide the regioselectivity of dipolar cycloadditions of azides and *o*-nitrophenylalkynes **10**.

RESULTS AND DISCUSSION

Our laboratory has synthesized a range of alkynes derived from our *o*-nitrophenylalkyne core to provide chemists with useful building blocks for rapid construction of biaryl templates.[11] In support of our continued effort in this direction, we wanted to expand the scope of *o*-nitrophenylalkyne substrates available for this reaction (Scheme 3). In particular, we were intrigued by the possibility of exploiting alkynyl halides as viable dipolarophiles. While we expressed some reservations about their potential stability due to the electron deficient aromatic ring, cycloaddition products derived from these alkynes would be potentially quite useful for further functionalization. It should be noted that iodoalkynes have recently been shown to be effective in a CuI/TTTA catalyst system for Click chemistry by Sharpless and Fokin;[19] however, we wished to expand the range of accessible substrates to include chloro- and bromo-

Scheme 3. Synthesis of Alkynyl Halides



containing alkynes. Fortunately, these alkynyl halides **22**–**25** were readily accessible via Corey–Fuchs olefination[20] of the known aldehydes **15**–**17**[11,21] followed by NaHMDS-mediated elimination of the dihalides **18**–**21**[22,23] in high yield. These alkynes were sufficiently stable for chromatographic purification and subsequent reaction; however, protection from light and storage at −30 °C improved their lifetime significantly. Not surprisingly, the chloroalkynes **22**,[24] **23**, and **25** were significantly more stable than the corresponding bromoalkyne **24**.

We also were interested in accessing alkyl, aryl disubstituted alkynes to probe in the cycloaddition process (Scheme 4). We initially intended to explore a standard alkylation strategy for

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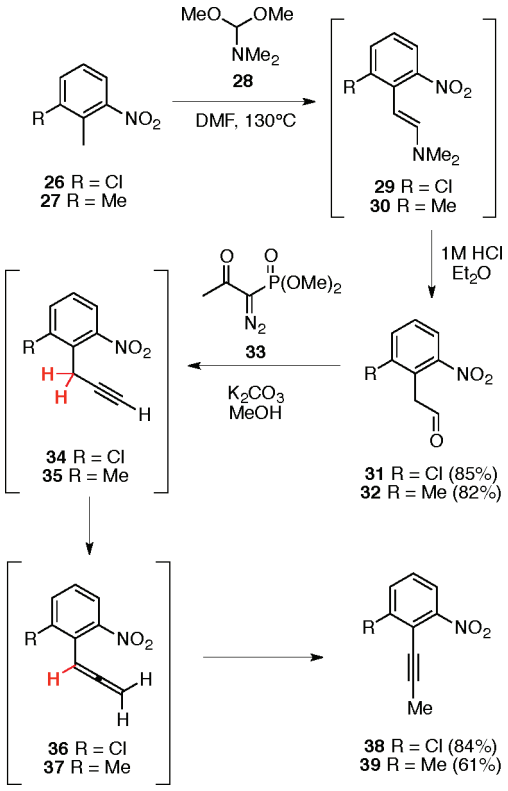
Scheme 4. Synthesis of Methylated Alkynes



incorporating a methyl moiety on the alkyne (e.g., LDA, THF; MeI). Unfortunately, this transformation proved unreliable, giving highly variable yields (0–65%). During this same period, we were exploring the possibility of alternate pathways to access this substitution pattern using the unconjugated aldehydes **31** and **32**. These aldehydes are accessible via divergence of our standard pathway for accessing aldehydes such as aldehyde **16**.[11b,25] Hydrolysis of the intermediate enamines **29**[26] and **30** provides a high-yielding route to aldehydes **31** and **32**. Treatment of these compounds with the Ohira–Bestmann reagent[27] **33** generated the desired methylated alkynes **38** and **39** in good yields. This transformation likely proceeds via initial formation of the unconjugated alkynes **34** and **35**, which undergo base-catalyzed isomerization first to allenes **36** and **37** and ultimately to aryl alkynes **38** and **39**. This strategy should provide a nice alternative to standard alkylations for accessing methyl, aryl disubstituted alkynes.

In parallel to this experimental work, we computationally explored the regioselectivities of the [3 + 2] dipolar cycloaddition process between azides and substituted alkynes as shown in Table 1. The computational predictions (column 5) were obtained from the relative energies of the 1,4- and 1,5-addition transition states at the B3LYP/6-311++G(2df,p)//B3LYP/6-31G(d) level of theory, as implemented in the Gaussian 09 suite of programs. To reduce the computational cost, benzyl groups were abbreviated to methyl.[28] The computed selectivities indicate that variations in R_1 result in negligible changes in selectivity; however, the regioselectivities vary greatly with the R_2 substituent. Select 1,3-dipolar cycloaddition transition states with R_1 = Cl are shown in Figure 1 to illustrate the steric and electronic control present in this system. In all cases, both the 1,4- and the 1,5-addition show the azide attack to occur perpendicular to the *o*-chloro-*o*-nitrophenyl group. In the parent compound series where R_2 = H, the 1,4-addition process is slightly preferred (**TS-I-1,4** more stable compared to **TS-I-1,5** by 0.3 kcal/mol). This poor selectivity reveals that the electron-withdrawing ability and the steric encumbrance of the *o*-chloro-*o*-nitrophenyl group are vanishingly small.

When the R_2 is a sterically encumbering group, such as a $SiMe_3$ (**TS-II** series), the steric interaction between the azidyl substituent and the *o*-chloro-*o*-nitrophenyl group dominates, favoring the 1,5-addition (**TS-II-1,5**) by 1.9 kcal/mol. Steric bulk alone, however, does not explain the selectivity, as is the case when R_2 = NMe_2. While NMe_2 and $SiMe_3$ are similar in size (*A* values of 2.1 and 2.5, respectively), the former gives exclusively the opposite 1,4-product by 6.3 kcal/mol. Similar to a nucleophilic enamine, the ynamine favors nucleophilic addition to the terminal electrophilic nitrogen of the azide (**TS-III-1,4**) over addition to the nucleophilic internal azidyl nitrogen in **TS-III-1,5**.

Some of the computed substrates were challenging to test experimentally. Prior attempts to make silyl-substituted alkynes derived from *o*-nitrophenylalkyne have proven challenging due to stability issues of the product (e.g., **44b**).[29] Hsung and co-workers have showcased the utility of ynamines in cycloaddition chemistry.[30] Unfortunately, attempts to synthesize ynamine-derived alkynes **43a–c** have also proven unsuccessful to date, likely due to the instability of the ynamine *o*-nitrophenyl species.

Our experimental investigation into the reactivity of the *o*-nitrophenylalkynes is illustrated in Table 2. In all cases, computational predictions were in good agreement with the experimentally observed regioselectivity. We initially screened in three categories: monosubstituted alkynes (entries a–c), disubstituted alkynes (entries d–g), and halogenated alkynes (entries h–k). Within the monosubstituted alkynes, we first screened the parent *o*-nitrophenylacetylene **40a** under thermal conditions. Interestingly, this thermal reaction has not been previously reported; however, Feringa and co-workers recently disclosed a phosphoramidite-accelerated copper-catalyzed version of this transformation, which provided the triazole in 62% yield as a single regioisomer.[14] The authors comment that significant differences in rate and chemical yield are observed with these reactions, with electron deficient alkynes such as **40a** providing the longest reactions times and lowest yields. Although entry a was observed to be high-yielding (84%), the regioselectivity was poor (entry a). As expected, more standard CuACC conditions ($CuSO_4$, ascorbic acid, and *t*-BuOH/H_2O (1:1), rt) provided a greatly improved regioselectivity. Similarly, the 2-chloro-6-nitrophenylacetylene (**40b**) provided only modest regiosiomeric control in the transformation (entry b). These thermal results are in stark contrast to the high regioselectivity we observed with these alkynes in a range of biaryl-forming cycloadditions.[11] Replacement of the halogen on the aromatic ring with a methyl group (alkyne **40c**) reduced the chemical reactivity to thermal cycloaddition, requiring 96 h to proceed with reasonable conversion (entry c). As seen with entry a, these monosubstituted alkynes are more effectively utilized (98% yield, single regioisomer) using standard Click conditions. Use of disubstituted alkynes **38–39** and **41–42** provided similar levels of regioselectivity to the monosubstituted alkynes under thermal conditions (entries d–g). Product **50e** was confirmed by X-ray crystallographic analysis. The most selective of this grouping was the ester alkyne **41** which provided 3.2:1 rr (**49f**:**50f**) as compared to computa-

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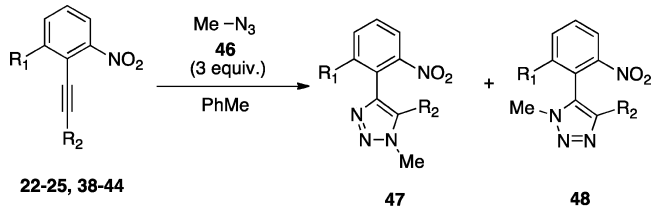
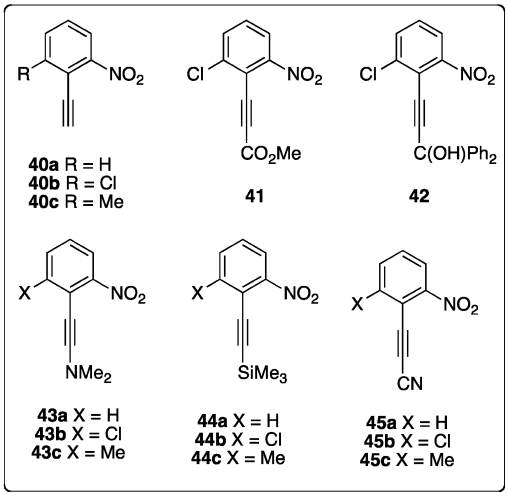
Table 1. Computational Scope of 1,3-Dipolar Cycloadditions





entry	alkyne	R_1	R_2	computed ratio (47:48)[a]
a	**40a**	H	H	3.9:1
b	**40b**	Cl	H	1.5:1
c	**40c**	Me	H	3.4:1
d	**39**	Me	Me	1:1.5
e	**38**	Cl	Me	1:1.6
f	**41**	Cl	CO_2Me	2.5:1
g	**42**	Cl	$C(OH)Ph_2$	1.9:1
h	**22**	H	Cl	9.5:1
i	**25**	Me	Cl	11:1
j	**23**	Cl	Cl	19:1
k	**24**	Cl	Br	12:1
l	**43a**	H	NMe_2	>100:1
m	**44a**	H	$SiMe_3$	1:17
n	**45a**	H	CN	7.0:1
o	**43b**	Me	NMe_2	>100:1
p	**44b**	Me	CN	5.3:1
q	**43c**	Cl	NMe_2	>100:1
r	**44c**	Cl	$SiMe_3$	1:14
s	**45c**	Cl	CN	14:1

[a]Relative energies of the 1,4- and 1,5-addition transition states at the B3LYP/6-311++G(2df,p)//B3LYP/6-31G(d) level of theory using Guassian 09.

tional predictions of 2.5:1 rr. Placement of an ester on the alkyne has proven to be a highly reactive and regioselective substrate **41**[11c] in our previous Diels–Alder reactions to form biaryl compounds. While this substrate **41** continued to prove reactive, the regioselectivity in the transformation was modest (3.2:1 rr, 92% overall yield). Interestingly, tertiary-alcohol-containing alkyne **42**, which had also proven highly selective in Diels–Alder processes, gave no selectivity (1:1 rr) in a sluggish reaction (45 h, 120 °C, 51% yield). We next turned to the previously unknown halogenated, disubstituted alkynes (entries h–k) derived from our *o*-nitrophenylalkyne core to provide chemists with useful building blocks for rapid construction of triazole templates. Computational analysis had indicated the increased regioselectivity was likely with these compounds. We were pleased to observe a noticeable increase in selectivity (5.7:1 rr) at 67% yield with the first halogenated alkyne **22**. The required 48 h, 120 °C conditions for reaction completion likely contributed to the reduced level of regioselectivity. Interestingly, replacement of the *o*-chloro moiety for a methyl group (entry i) provided similar regioselectivity. Use of our *o*-chloro-*o*-nitrophenylalkynes **23** and **24** proved to be more activated and nicely generated the cycloaddition product in high levels of regioselectivity (9:1 ratio) and chemical yield (64–72%) (entries j and k). On the basis of these results, it became clear that halogenated alkynes are advantageous for accessing high levels of regioselectivity in these systems.

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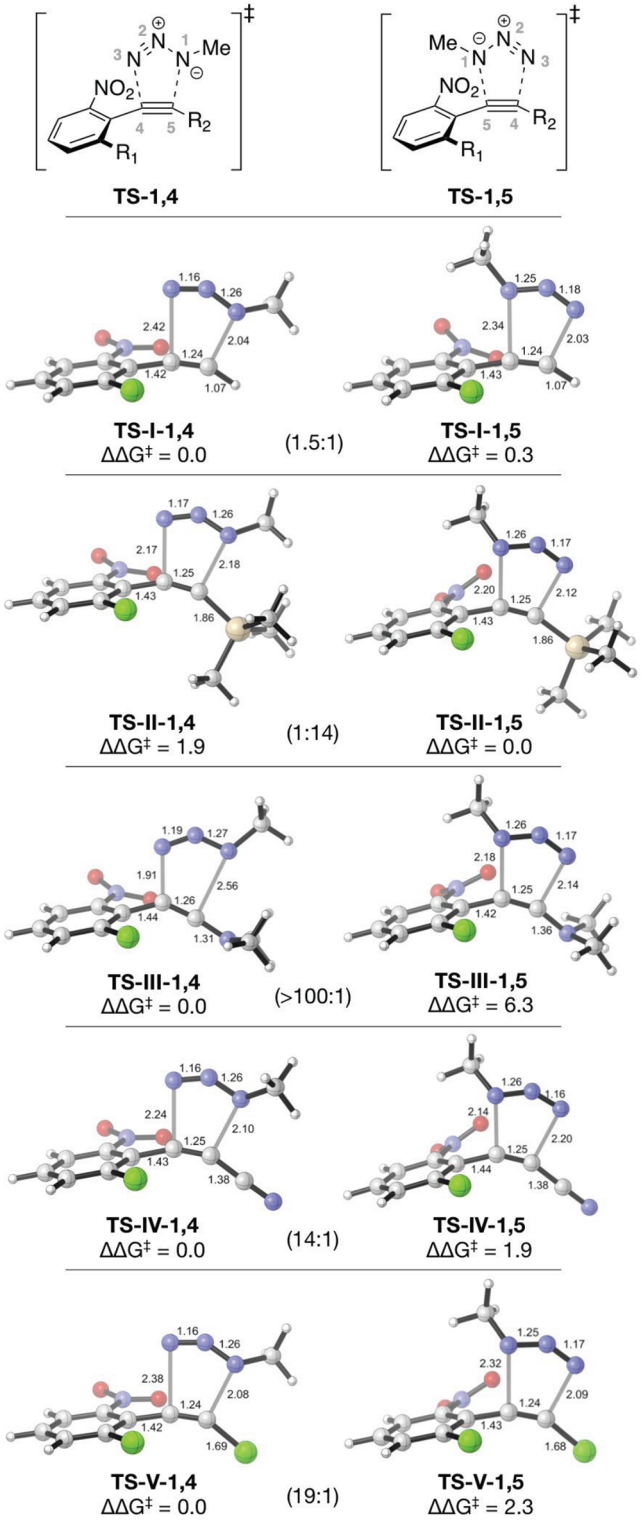

Figure 1. Computed transition states for 1,3-dipolar cycloadditions between various *o*-chloronitrophenylalkynes and methyl azide are shown. The B3LYP/6-311++G(2df,p)//B3LYP/6-31G(d) level of theory was used, and the computational predictions of regioselectivity are in good agreement with experiments (Table 2). Distances are in angstroms; relative free energies are in kcal/mol. Computationally predicted regiomeric ratios are in parentheses.

The halogenated alkynes proved to be our most regioselective while still experimentally accessible substrates for the dipolar cycloadditions. Consequently, we briefly explored the scope of this transformation using a collection of known azides (Table 3). Use of cinnamyl azide gave comparable levels of regioselectivity for the chloroalkyne **23** but reduced levels of regioselectivity with the bromoalkyne **24** (entries a–b). Aryl azides appeared to be problematic in the reaction as reduced regioselectivity and chemical yields were observed for both the bromo- and chloroalkynes. Finally, *tert*-butyl azidoacetate generated the corresponding triazoles in high regioselectivity, but in modest yield.

We also explored the Suzuki coupling capabilities of the synthesized heterocycles (Scheme 5). We have previously reported the utility of boroxines in cross-coupling protocols using the Organ's catalyst PEPPSI-IPr.[11g,31] For the more challenging ester containing substrate **49f**, we found Buchwald's Ph_2X-Phos ligand[32] to be superior to PEPPSI-IPr. The structure of **53** was confirmed by X-ray crystallographic analysis. It should be noted that while we employed commercial "phenylboronic acid" in this transformation, significant amounts of the boroxine could be observed by NMR in the unpurified reagent and no water was added to this transformation, again indicating that the boroxine may be the viable coupling component in the process. Further derivatization of the heterocyclic scaffold was also possible. Nitro reduction could be accomplished using Zn/HOAc to yield the lactam **54** in modest yield. We have previously observed the in situ formation of the lactam moiety on related biaryl systems.[11c] DIBAL-H reduction of the ester moiety could be accomplished to provide the alcohol **55**. Subsequent reduction of the nitro moiety revealed the amino alcohol **56**. Alternatively, the ester could be saponified to reveal the carboxylic acid **57** in excellent yield.

■ CONCLUSION

In summary, we have demonstrated the utility of substituted *o*-nitrophenylalkynes in dipolar cycloadditions on a range of substrates. The regioselectivity of the triazole dipolar cycloadditions was highly dependent on the nature of the dipolarophile. Density functional theory investigations revealed how various substitutions on the *o*-nitrophenylalkynes control the regioselectivity through a combination of steric and electronic effects. The synthesized scaffolds were converted into a range of derivatives to demonstrate the utility of the cycloaddition approach to densely functionalized heterocycles.

■ EXPERIMENTAL SECTION

Aldehyde 17. To a stirred solution of **27** (4.56 g, 4.00 mL, 30.17 mmol) in DMF (75 mL) was added *N*,*N*-dimethylformamide dimethyl acetal (DMF·DMA) (10.8 g, 12.0 mL, 90.3 mmol). After being heated at 140 °C for 72 h, the dark red solution was cooled to rt and added quickly to a rapidly stirred solution of $NaIO_4$ (21.04 g, 98.37 mmol) in H_2O (74 mL) and DMF (24 mL) at 0 °C. The reaction flask was washed with DMF (5 mL) at 0 °C and added to $NaIO_4$ mixture. The reaction was stirred at 0 °C for 2 h before being warmed to rt. The orange solution was filtered and rinsed with Et_2O (200 mL). The filtrate was then washed with H_2O (3 × 25 mL) and satd aq NaCl (3 × 25 mL). The dried (Na_2SO_4) extract was concentrated in vacuo to a dark red oil and purified via flash chromatography over silica gel; eluting with 10–30% Et_2O/hexanes gave known aldehyde **17**[21] (4.390 g, 26.58 mmol, 89%) as an orange solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.32 (s, 1H), 7.99 (dd, J = 1.5, 7.5 Hz, 1H), 7.65–7.50 (m, 2H), 2.45 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.4, 148.7, 139.2, 137.0, 131.9, 131.3, 121.9, 19.4 ppm.

Chloroacetylene 23. To a stirred solution of **16** (3.118 g, 16.80 mmol) and CH_2Cl_2 (170 mL) were added CCl_4 (3.98 g, 2.50 mL, 25.9

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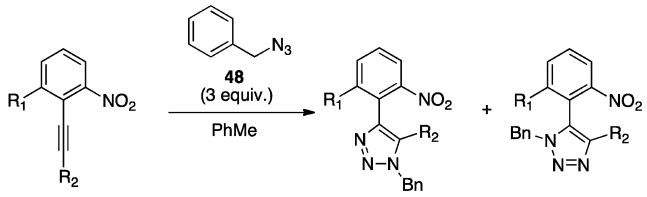
Table 2. Scope of Azide Dipolar Addition with *o*-Nitrophenyl Acetylenes

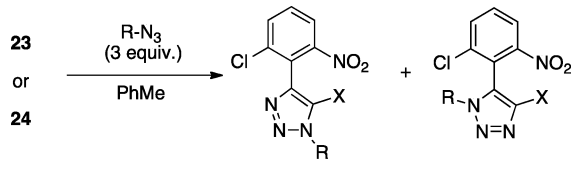


22-25, 38-42 49 50

entry	alkyne	R_1	R_2	time (h)	temp (°C)	overall yield (%)	experimental ratio (**49**:**50**)	computed ratio (**47**:**48**)
a	**40a**	H	H	48	80	84 (79)[a]	3.4:1 (1:0)[a]	3.9:1
b	**40b**	Cl	H	26	80	59	2:1	1.5:1
c	**40c**	Me	H	96	80	79 (98)[a]	2.3:1 (1:0)[a]	3.4:1
d	**39**	Me	Me	72	120	43	1:1	1:1.5
e	**38**	Cl	Me	24	120	65	2:1	1:1.6
f	**41**	Cl	CO_2Me	24	80	92	3.2:1	2.5:1
g	**42**	Cl	$C(OH)Ph_2$	45	120	51	1:1	1.9:1
h	**22**	H	Cl	24	120	66	5.7:1	9.5:1
i	**25**	Me	Cl	24	120	68	7:1	11:1
j	**23**	Cl	Cl	70	80	72	9:1	19:1
k	**24**	Cl	Br	72	80	64	9:1	12:1

[a]reaction conditions: $CuSO_4$, ascorbic acid, *t*-BuOH:H_2O (1:1), rt.

Table 3. Brief Exploration of Azide Scope in Cycloaddition



51 52

entry	alkyne	R	X	time (h)	temp (°C)	overall yield (%)	ratio (**51**:**52**)
a	**23**	(*E*)-PhCH=CHCH$_2$-	Cl	48	80	49	11:1
b	**24**	(*E*)-PhCH=CHCH$_2$-	Br	29	80	69	4:1
c	**23**	Ph	Cl	72	80	36	2:1
d	**24**	Ph	Br	53	120	24	1:1
e	**23**	*t*-BuO_2CCH$_2$-	Cl	48	80	37	9:1
f	**24**	*t*-BuO_2CCH$_2$-	Br	48	80	58	9:1

mmol) and PPh_3 (13.36 g, 50.93 mmol) at rt. After 30 h, the black solution was concentrated in vacuo until ca. 50 mL of mixture remained. The residue was then purified via flash chromatography over silica gel, eluting with 10−30% EtOAc/hexanes to give **19** (3.567 g) as an impure yellow oil.

To a stirred solution of impure **19** (3.567 g, 14.12 mmol) and THF (35.0 mL) was added NaHMDS (14.30 mL, 14.30 mmol, 1 M in THF) at −78 °C. After 1 h, the dark brown solution was quenched with satd aq NH_4Cl (20 mL), extracted with EtOAc (3 × 50 mL), and washed with satd aq NaCl (2 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by flash chromatography over silica gel, eluting with 20−50% EtOAc/hexanes to give **23** (2.954 g, 13.67 mmol, 97%) as a bright yellow crystalline solid: mp 93−94 °C; IR (thin film) 2217, 1526, 1338, 1118, 797, 750, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, J = 8.1, 1.2 Hz, 1H), 7.72 (dd, J = 8.1, 1.2 Hz, 1H), 7.43 (t, J = 8.2 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 139.5, 13.7, 128.9, 122.7, 117.3, 82.3, 61.8 ppm; HRMS (EI+) calcd for $C_8H_3NO_2Cl_2$ 214.9541, found 214.9539.

Bromoacetylene 24. To a stirred solution of **16** (2.628 g, 14.16 mmol), CH_2Cl_2 (94 mL), and CBr_4 (7.104 g, 21.42 mmol) at 0 °C, was added PPh_3 (11.23 g, 42.81 mmol, 0.4 M in CH_2Cl_2) via cannula over 5 min. After 15 h, the black solution was concentrated to ca. 60 mL and transferred to a flash column. Purification of the residue via flash chromatography over silica gel, eluting with 0−20% EtOAc/hexanes gave known **20**[23] (4.117 g) as a crude orange solid.

To a stirred solution of impure **20** (3.051 g, 8.937 mmol) and THF (22 mL) was added NaHMDS (9.00 mL, 9.00 mmol, 1 M in THF) at −78 °C via syringe over 5 min and allowed to slowly warm to 0 °C. After 2 h, the dark brown mixture was quenched with satd aq NH_4Cl (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic parts were washed with H_2O (2 × 10 mL) and satd aq NaCl (2 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo to a brown solid and purified via flash chromatography over silica gel, eluting with PhMe to give **24** (1.971 g, 7.567 mmol, 85%) as a yellow solid: mp 86−88 °C; IR (thin film) 2220, 1527, 1340, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J = 8.1, 1.2 Hz, 1H), 7.51 (dd, J = 8.1, 1.2, 1H), 7.37 (t, J = 8.2 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 139.6, 133.7, 128.9, 122.8, 117.7, 72.2, 65.3 ppm; HRMS (EI+) calcd for $C_8H_3NO_2ClBr$ 258.9036, found 258.9035.

Chloroacetylene 22. To a stirred solution of **15** (4.584 g, 30.33 mmol) and CH_2Cl_2 (500 mL), was added CCl_4 (8.61 g, 5.40 mL, 56.0 mmol), and PPh_3 (23.94 g, 91.27 mmol) at rt. After 6 h, the black solution was concentrated in vacuo until ca. 100 mL of mixture remained. The residue was then purified via flash chromatography over silica gel, eluting with 10−30% EtOAc/hexanes to give known **18**[22] (4.567 g, 20.95 mmol, 69%) as a crude yellow solid.

To a stirred solution of impure **18** (4.567 g, 20.95 mmol) and THF (50 mL) was added NaHMDS (21.0 mL, 21.0 mmol, 1 M in THF) at −78 °C over 10 min. After 1 h, the reaction was warmed to 0 °C and quenched with satd aq NH_4Cl (50 mL). The solution was diluted with

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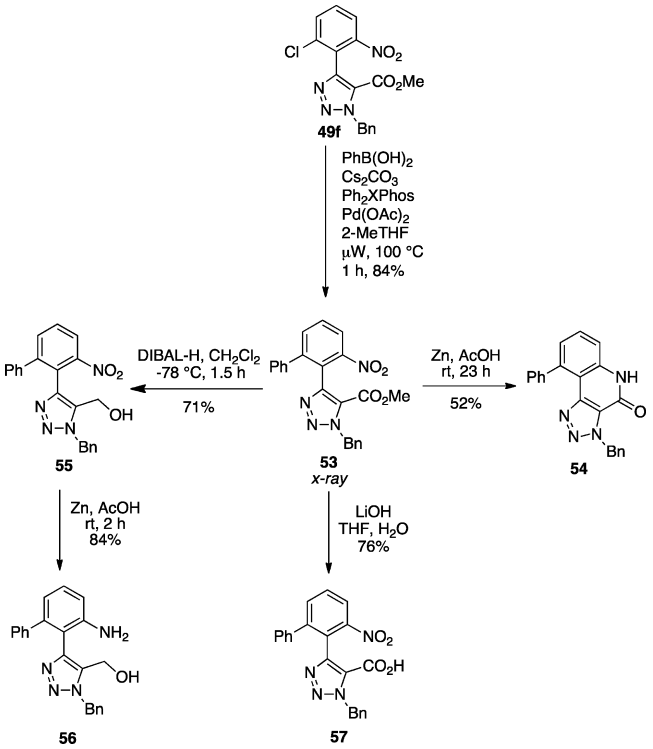
Scheme 5. Derivatization of Triazoles



H_2O, extracted with Et_2O (3 × 50 mL), and washed with satd aq NaCl (1 × 100 mL) and brine (2 × 50 mL). The dried ($MgSO_4$) extract was concentrated in vacuo to give known **22**[24] (3.218 g, 17.82 mmol, 85%) as a beige solid: mp 79−81 °C; IR (neat) 3103, 2845, 2220, 1569, 1519, 1341, 786, 742 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.08 (dd, J = 1.0, 8.3 Hz, 1H), 7.68 (dd, J = 1.2, 7.8 Hz, 1H), 7.61 (td, J = 1.3, 7.6 Hz, 1H), 7.51 (td, J = 1.5, 7.4 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 135.3, 132.9, 129.0, 124.8, 117.7, 76.3, 64.8 ppm; HRMS (CI+) calcd for $C_8H_5ClNO_2$ (M + H) 182.0009, found 182.0005.

Chloroacetylene 25. To a stirred solution of **17** (5.828 g, 33.29 mmol) and CH_2Cl_2 (350 mL) were added CCl_4 (8.29 g, 5.20 mL, 52.93 mmol) and PPh_3 (27.77 g, 105.9 mmol) at rt. After 30 h, the black solution was concentrated in vacuo until ca. 100 mL of mixture remained. The residue was then purified via flash chromatography over silica gel, eluting with 0−10% EtOAc/hexanes to give impure **21** (6.038 g) as a yellow oil.

To a stirred solution of impure **21** (3.316 g, 14.29 mmol) and THF (36.0 mL) was added NaHMDS (15.0 mL, 15.0 mmol, 1 M in THF) at −78 °C over 10 min turning from an orange to darks brown solution. After 1 h, the reaction was warmed to 0 °C and quenched with satd aq NH_4Cl (50 mL). After 5 min, the orange-brown solution was extracted with Et_2O (3 × 50 mL) and washed with satd aq NaCl (2 × 20 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified via flash chromatography over silica, eluting with 35% hexanes/PhMe to give **25** (2.372 g, 12.13 mmol, 85%) as a yellow solid: mp 93−94 °C; IR (thin film) 2213, 1526, 1456, 1381, 802, 740, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.2, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.37 (t, J = 8.0, 1H), 2.55 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 144.2, 133.9, 128.2, 122.0, 116.9, 80.3, 63.4, 21.2 ppm; HRMS (CI+) calcd for $C_9H_7NO_2Cl$ (M + H) 196.0165, found 196.0154.

Enamine 29. To a stirred solution of **26** (3.855 g, 22.46 mmol) in DMF (50 mL) was added *N,N*-dimethylformamide dimethyl acetal (DMF·DMA) (8.07 g, 9.00 mL, 67.75 mmol). After heating at 140 °C for 16 h, the dark red solution was cooled to rt, diluted with Et_2O (200 mL), and washed with HCl (2 × 50 mL, 10% v/v), sat aq $NaHCO_3$ (2 × 50 mL), and sat aq NaCl (2 × 5 mL). The dried (Na_2SO_4) extract was concentrated in vacuo to give **29** (4.940 g, 111.0 mmol, 97%) as a red oil: IR (thin film) 3081, 2847, 2808, 1634, 1585, 1524, 1378, 1101, 952, 866, 835, 774, 752, 723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 - 7.32 (m, 2H), 6.97 (t, J = 7.8 Hz, 1H), 6.70 (d, J = 13.8 Hz, 1H), 5.10 (d, J = 13.8 Hz, 1H), 2.86 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 145.5, 133.0, 132.1, 131.9, 123.1, 122.1, 86.9, 39.3 ppm; HRMS (EI+) calcd for $C_{10}H_{11}N_2O_2Cl$ 226.0509, found 226.0508.

2-(2′-Chloro-6′-nitrophenyl)acetaldehyde (31). A 2-L, single-necked, round-bottomed flask, equipped with a powder funnel and magnetic stirring bar, was charged with DMF (1 L) and 2-chloro-6-nitrotoluene **26** (69.74 g, 406.5 mmol, 1 equiv). *N,N*-Dimethylformamide dimethyl acetal (162 mL, 1.22 mol, 3 equiv) was added via syringe to the yellow solution. The powder funnel was replaced by a Fredrichs condenser, and the mixture was brought to 135 °C in a silicon oil bath over 2 h. The reaction was covered with aluminum foil to aid heating. After 18 h, the reaction evolved to a brick red solution and showed complete conversion via TLC. The mixture was cooled to room temperature over 2 h and then carefully poured over 2 min into a rapidly, mechanically stirred, ice-cooled solution of satd aq $NaHCO_3$ (500 mL) and Et_2O (500 mL) in a 2-L Erlenmeyer flask. After 15 min, the solution was transferred to a separatory funnel and allowed to settle for 15 min. A 1-L portion of the mixture was collected in an Erlenmeyer flask, and the remaining solution in the separatory funnel was washed with 5% aq $NaHCO_3$ (4 × 300 mL). The ethereal partition was collected and set aside. The previously collected 1-L portion was transferred to a separatory funnel and extracted with ether (3 × 400 mL) via separatory funnel. The ethereal partitions were combined and concentrated via rotary evaporation (38 °C, 28 mmHg) to give enamine **29**[26] as a dark red liquid.[33]

A 2-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer, yellow poly cap, and powder funnel, was immersed in an ice-cold water bath, charged with the red enamine **29** oil, and diluted with Et_2O (300 mL). To the solution was added 1 M HCl (300 mL), and the powder funnel was replaced by a 90° gas inlet adapter open to the air. The mixture was allowed to warm to rt over 2.5 h with *vigorous* stirring. The biphasic solution was transferred to a 2-L separatory funnel, and the ethereal partition was collected. The aqueous partition was acidified to pH = 1 with 3 M HCl and was extracted with MTBE (2 × 200 mL). The ethereal partitions were combined and washed with 10% aq $NaHCO_3$ (2 × 50 mL), H_2O (100 mL), and brine (2 × 50 mL), dried over Na_2SO_4, filtered, and concentrated via rotary evaporation (38 °C, 28 mmHg) and then under high vacuum (50 °C, 0.50 mmHg) to provide aldehyde **31** as a red oil (69.34 g 347.4 mmol, 85%): IR (thin film) 3432, 2844, 2733, 1731, 158, 1351, 1109, 1019, 876, 802, 730, 667 cm^{-1}; 1H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.97 (dd, J = 8.4, 1.2 Hz, 1H), 7.74 (dd, J = 8.4, 1.2 Hz, 1H), 7.46 (t, J = 8.4, 1H), 4.31 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 150.8, 137.1, 134.3, 129.0, 126.8, 123.5, 44.5 ppm; HRMS (EI+) calcd for $C_8H_7NO_3Cl$ (M^+) 200.0114, found 200.0117.

Aldehyde 32. To a stirred solution containing **27** (5.26 g, 6.00 mL, 34.8 mmol) and DMF (80 mL) was added *N,N*-dimethylformamide dimethyl acetal (14.0 mL, 12.6 g, 105.7 mmol) was added via syringe to the yellow solution and heated to 140 °C. After 24 h, the reaction evolved to a brick red solution, cooled to room temperature, quenched with aq $NaHCO_3$ (200 mL, 5% w/v), and extracted with Et_2O (3 × 150 mL). The ethereal partition were combined and concentrated in vacuo to give enamine **30** as a dark red liquid (ca. 200 mL).

To a mechanically stirred solution of the dark red enamine **30** and Et_2O (250 mL), was added aq HCl (250 mL, 10% v/v). After 2.5 h of *vigorous* stirring, the biphasic solution was extracted with Et_2O (3 × 100 mL). The ethereal partitions were combined and washed with aq $NaHCO_3$ (2 × 100 mL, 10% w/v) and sat aq NaCl (2 × 100 mL). The dried (Na_2SO_4) extract was concentrated in vacuo to provide crude **32** as a red oil. Purification via flash chromatography over silica gel, eluting with PhMe, gave known **32**[34] (5.121 g, 28.58 mmol, 82%) as a dark orange oil: IR (thin film) 3430, 2842, 2732, 1724, 1610, 1524, 1348, 935, 803, 731, 672 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.86 (t, J = 0.9 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.51 (d, J = 7.4 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 4.02 (s, 2H), 2.38 (s, 3H) ppm; ^{13}C

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NMR (75 MHz, $CDCl_3$) δ 196.8, 150.5, 140.3, 135.1, 128.0, 126.5, 122.7, 43.9, 20.4 ppm; HRMS (CI+) calcd for $C_9H_{10}NO_3$ (M^+) 180.0661, found 180.0666.

Propyne 38. To a stirred solution of **31** (5.412 g, 27.11 mmol) and MeOH (385 mL) were added K_2CO_3 (7.635 g, 55.24 mmol) and **33**[27] (6.253 g, 32.55) dropwise via syringe at rt. After 4 h, the dark red mixture was quenched with pH 7 buffer (350 mL), concentrated in vacuo, and filtered. The orange solid was washed with H_2O (20 mL), dissolved in EtOAc (100 mL), and washed with satd aq NaCl (2 × 15 mL). The dried ($MgSO_4$) extract was concentrated in vacuo to give **38** (4.467 g, 22.84 mmol, 84%) as an orange solid: mp 100−102 °C; IR (thin film) 3086, 2249, 2208, 1519, 1346, 881, 809, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, J = 8.1, 1.0 Hz, 1H), 7.64 (dd, J = 8.1, 1.0 Hz, 1H), 7.32 (t, J = 8.2 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 138.6, 133.2, 127.7, 122.4, 118.8, 101.5, 71.8, 5.0; HRMS (EI+) calcd for $C_9H_6NO_2Cl$ (M^+) 195.0087, found 195.0088.

Propyne 39. To a stirred solution of **32** (4.786 g, 26.71 mmol) and MeOH (480 mL) were added K_2CO_3 (7.322 g, 52.98 mmol) and **33**[27] (6.208 g, 32.31 mmol) dropwise via syringe at rt. After 15 h, the dark red mixture was quenched with pH 7 buffer (480 mL), concentrated in vacuo, and filtered. The orange solid was washed with H_2O (20 mL), dissolved in EtOAc (100 mL), and washed with satd aq NaCl (2 × 25 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified via flash chromatography over silica gel, eluting with 0−15% EtOAc/hexanes to give **39** (2.845 g, 16.34 mmol, 61%) as an orange solid: mp 42−44 °C; IR (thin film) 2251, 2208, 1607, 1528, 804, 743, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.12 (t, J = 7.9 Hz, 1H), 2.48 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 143.2, 133.3, 127.0, 121.3, 118.1, 99.12, 73.3, 20.9, 4.5; HRMS (EI+) calcd for $C_{10}H_9NO_2$ (M^+) 175.0633, found 175.0633.

Acetylene 40c. To a stirred solution of **17** (1.655 g, 10.00 mmol), K_2CO_3 (3.620 g, 26.20 mmol), and MeOH (140 mL) was added diazophosphonate **33**[27] (2.350 g, 12.23 mmol) slowly, at rt, in ca. 0.2 mL portions over 1 h. After 3 h, the solution was quenched with pH 7 buffer (200 mL) and concentrated in vacuo to remove the MeOH and give crude **40c** as an orange solid (1.387 g). The solid was filtered, and the mother liquor was diluted with EtOAc (150 mL) and washed with satd aq NaCl (2 × 50 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by flash chromatography over silica gel, eluting with 1% EtOAc/hexanes, to give crude **40c** (138.5 mg). The crude material isolated from recrystallization and column chromatography were combined and recrystallized with hexane to give **40c** as a pale yellow solid (1.422 g, 8.823 mmol, 88%): mp 58−59 °C; IR (thin film) 3284, 2108, 1529, 1349, 797, 778, 736, 645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 3.75 (s, 1H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 144.2, 133.8, 128.5, 121.8, 116.7, 89.7, 76.7, 21.2; HRMS (EI+) calcd for $C_9H_7NO_2$ (M^+) 161.0477, found 161.0467.

Triazole 49a and 50a. To a pressure vessel containing **40a** (73.5 mg, 0.500 mmol) were added PhMe (1 mL) and azide **48** (199.5 mg, 1.5 mmol) sequentially at rt. The reaction mixture was sealed under Ar and heated to 80 °C. After 48 h, the crude mixture was cooled to rt, concentrated in vacuo, and purified via flash chromatography over silica gel, eluting with 20−40% EtOAc/hexanes to give sequentially **49a** (91.5 mg, 327 μmol, 65%) as a white solid followed by **50a** (26.1 mg, 93.2 μmol, 19%) as a pale yellow solid. NMR analysis of the crude mixture indicated the ratio to be 2.7:1 rr (**49a**:**50a**). Major regioisomer **49a**:[14] mp 103−105 °C; IR (neat) 1528, 1359 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.74 (s, 1H), 7.67 (t, J = 7.7 Hz, 1H), 7.50 (t, J = 7.7 Hz, 1H), 7.38−7.41 (m, 3H), 7.33 (d, J = 6.5 Hz, 2H), 5.61 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 142.4 134.3, 132.5, 131.1, 129.2, 128.94, 128.89, 128.0, 124.7, 124.0, 122.9, 54.3 ppm; HRMS (ES+) calcd for $C_{15}H_{13}N_4O_2$ (M + H) 281.1039, found 281.1029. Minor regioisomer **50a**: mp 73−75 °C; IR (neat) 1528, 1350 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 7.9 Hz, 1H), 7.66 (s, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.55 (t, J = 7.3 Hz, 1H), 7.18−7.24 (m, 3H), 7.01 (d, J = 7.7 Hz, 1H), 6.94 (d, J = 6.8 Hz, 2H), 5.43 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 134.4, 133.9, 133.2, 133.10, 133.08, 131.0, 128.7, 128.4, 127.8, 124.9, 122.2, 52.8 ppm; HRMS (ES+) calcd for $C_{15}H_{13}N_4O_2$ (M + H) 281.1039, found 281.1029.

Triazole 49a. To a stirred solution of **40a** (73.5 mg, 500 μmol) and H_2O/*t*-BuOH (3.00 mL, 1:1) was added ascorbic acid (14.5 mg, 82.5 μmol), $Cu_2SO_4{\cdot}5H_2O$ (6.5 mg, 26 μmol) and azide **48** (199.5 mg, 1.5 mmol) sequentially at rt. After 19 h, the mixture was filtered and washed with hexanes to give the sole regioisomer **49a**[14] (110.1 mg, 393 μmol, 79%) as a beige solid.

Triazoles 49b and 50b. To a pressure vessel containing **40b**[11a,b] (45.6 mg, 0.251 mmol) were added PhMe (500 μL) and azide **48** (100 mg, 750 μmol) at rt. The reaction mixture was sealed under Ar and heated to 80 °C. After 26 h, the crude mixture was cooled to rt, filtered through Celite eluting with 100% EtOAc and concentrated in vacuo to give an inseparable mixture of regioisomers (46.6 mg, 0.148 mmol, 59%, 2:1 rr (**49b**:**50b**)): mp 174−175 °C; IR (thin film) 3077, 2879, 1527, 1362, 1229, 1089, 760, 729 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.95 (d, J = 8.2 Hz, 1H of minor), 7.80 (dd, J = 8.1, 1.2 Hz, 1H of major), 7.75 (s, 1H of major), 7.72 (dd, J = 8.1, 1.2 Hz, 1H of major), 7.71 (d, J = 8.2 Hz, 1H of minor), 7.69 (s, 1H of minor), 7.61 (t, J = 8.2 Hz, 1H of minor), 7.49 (t, J = 8.1 Hz, 1H of major), 7.45−7.35 (m, 3H of major), 7.35−7.25 (m, 2H of major), 7.25 (t, J = 7.3 Hz, 1H of minor), 7.20 (t, J = 7.5 Hz, 2H of minor), 7.03 (d, J = 7.5 Hz, 2H of minor), 5.67 (s, 2H of major), 5.45 (dd, J = 15.0 Hz, 2H of minor) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 151.4, 139.6, 135.9, 134.4, 134.1, 133.4, 131.6, 129.9, 129.2, 128.8, 128.7, 128.6, 128.3, 127.8, 124.5, 124.2, 123.1, 122.6, 54.3, 53.4; HRMS (EI+) calcd for $C_{15}H_{11}N_4O_2Cl$ (M + H) 314.0570, found 314.0581.

Triazoles 49c and 50c. To a pressure vessel containing **40c** (39.9 mg, 0.248 mmol) were added PhMe (500 μL) and azide **48** (133 mg, 1 mmol) at rt. The reaction mixture was sealed under Ar and heated to 80 °C. After 96 h, the crude mixture was cooled to rt and concentrated in vacuo to give an inseparable mixture of regioisomers (70.2 mg, 0.197 mmol, 79%, 2.3:1 rr (**49c**:**50c**)). Regioisomer mixture: mp 152−153 °C; IR (neat) 3077, 1529, 1362, 807 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.94 (d, J = Hz, 1H of minor), 7.70 (d, J = 7.8 Hz, 1H of major), 7.60 (s, 1H of minor), 5.64 (s, 2H of major), 7.56 (t, J = 7.9 Hz, 1H of minor), 7.52 (d, J = 7.5 Hz, 1H of minor), 7.59−7.18 (m, 8H of major), 7.21 (t, J = 7.5 Hz, 2H of minor), 7.00 (d, J = 7.4 Hz, 2H of minor), 5.65 (d, 1H of minor), 5.13 (d, J = 15.0 Hz, 1H of minor), 2.26 (s, 3H of major); ^{13}C NMR (175 MHz, $CDCl_3$) δ 150.8, 149.7, 142.1, 141.5, 140.7, 134.8, 134.6, 134.1, 133.8, 133.7, 131.4, 130.7, 129.2, 129.1, 128.8, 128.7, 128.6, 128.5, 127.8, 124.4, 123.2, 122.3, 121.4, 121.1, 54.2, 53.0, 20.7, 19.6 ppm; HRMS (ES+) calcd for $C_{16}H_{15}N_4O_2$ (M + H) 295.1195, found 295.1208.

Triazole 49c. To a stirred solution of **40c** (111.6 mg, 692.3 μmol) and H_2O/*t*-BuOH (3.00 mL, 1:1) were added ascorbic acid (20.1 mg, 114 μmol), $Cu_2SO_4{\cdot}5H_2O$ (9.0 mg, 36 μmol), and azide **48** (293.4 mg, 2.196 mmol) sequentially at rt. Upon addition of azide **48** a white ppt formed. After 12 h, the mixture was filtered and washed with hexanes to give the sole regioisomer **49c** (199.6 mg, 678.3 μmol, 98%) as a pure white solid.

Triazole 49d and Triazole 50d. To a pressure vessel containing **37** (69.2 mg, 390.5 μmol) were added PhMe (800 μL) and azide **48** (174.3 mg, 1.309 mmol) at rt. The reaction mixture was sealed under Ar and heated to 120 °C. After 72 h, the reaction was cooled to rt, concentrated in vacuo, and purified via flash chromatography over silica gel, eluting with 20−40% EtOAc/Hexanes to give an inseparable mixture of regioisomers (50.3 mg, 168 μmol, 43%, 1:1 rr (**49d**:**50d**)) as a yellow oil. Regioisomer mixture: IR (neat) 1529, 1496, 1455, 1353, 1016, 914, 804, 754, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.58−7.47 (m, 2H), 7.46−7.39 (m, 2H), 7.38−7.27 (m, 3H), 7.26−7.09 (m, 5H), 6.92 (d, J = 7.3 Hz, 2H), 5.56 (s, 2H), 5.49 (d, J = 14.9 Hz, 1H), 5.05 (d, J = 14.9 Hz, 1H), 2.15 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H), 1.50 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 149.8, 142.5, 142.1, 141.5, 140.2, 134.8, 134.7, 134.3, 134.0, 132.0, 130.7, 129.4, 129.1, 128.6, 128.6, 128.5, 128.3, 128.3, 126.7, 124.9, 122.2, 121.7, 121.0,

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53.2, 52.0, 20.2, 19.1, 10.2, 8.2 ppm; HRMS (EI+) calcd for $C_{17}H_{16}N_4O_2$ (M^+) 308.1273, found 308.1288.

Triazole 49e and Triazole 50e. To a pressure vessel containing **36** (316.2 mg, 1.909 mmol) were added PhMe (2.00 mL) and azide **48** (1.066 mg, 8.006 mmol) at rt. The reaction mixture was sealed under Ar and heated to 120 °C. After 24 h, the reaction was cooled to rt, concentrated in vacuo, and purified via flash chromatography over silica gel, eluting with 20−40% EtOAc/hexanes to give an inseparable mixture of regioisomers (405.4 mg, 1.233 mmol, 65%, 2:1 rr (**49e**:**50e**)) as a yellow oil. Regioisomer mixture: IR (neat) 1733, 1533, 1455, 1437, 1359, 1122, 883, 806, 728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, J = 8.1, 1.3 Hz, 1H of minor), 7.90 (dd, J = 8.1, 1.2 Hz, 1H of major), 7.76 (dd, J = 8.1, 1.2 Hz, 1H of major), 7.69 (dd, J = 8.1, 1.3 Hz, 1H of minor), 7.59 (t, J = 8.1 Hz, 1H of minor), 7.55 (t, J = 8.1 Hz, 1H of major), 7.48−7.34 (m, 3H of major/minor), 7.24−7.14 (m, 2H of major/minor), 6.99−6.94 (m, 1H of minor), 5.40 (d, J = 12.7 Hz, 1H of minor), 5.62 (s, 2H of major), 5.32 (d, J = 12.7 Hz, 1H of minor), 2.16 (s, 3H of minor), 2.12 (s, 3H of major) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 138.7, 137.9, 134.6, 134.2, 133.6, 132.8, 132.6, 131.5, 130.4, 129.1, 128.6, 128.4, 128.34, 128.31, 128.1, 126.7, 125.2, 123.1, 122.7, 52.1, 53.5, 10.3, 8.5 ppm; HRMS (EI+) calcd for $C_{16}H_{13}N_4O_2Cl$ (M^+) 328.0727, found 328.0723.

Triazole 49f and 50f. To a pressure vessel containing **41** (220 mg, 917 μmol) were added PhMe (2 mL) and azide **48** (366 mg, 2.75 mmol) sequentially at rt. The reaction mixture was sealed under Ar and heated to 80 °C. After 24 h, the crude mixture was cooled to rt, concentrated in vacuo, and purified via flash chromatography over silica gel, eluting with 30−40% EtOAc/hexanes to give sequentially **49f** (240.9 mg, 646 μmol, 70% yield) as an orange oil followed by **50f** (74.4 mg, 199 μmol, 22%) as a white solid. NMR analysis of the crude mixture indicated the ratio to be 3.2:1 rr (**49f**:**50f**). Major regioisomer **49f**: IR (neat) 1731, 1536, 1479, 1347, 1260, 1212, 1158, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 0.6, 8.3 Hz, 1H), 7.79 (dd, J = 0.6, 8.1 Hz, 1H), 7.61 (t, J = 8.2 Hz, 1H), 7.33−7.38 (m, 3H), 7.29 (d, J = 6.4 Hz, 2H), 6.02 (s, 2H), 3.66 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 150.2, 144.4, 137.0, 135.0, 134.2, 130.6, 128.9, 128.4, 127.3, 125.9, 125.6, 123.0, 54.3, 52.6 ppm; HRMS (EI+) calcd for $C_{17}H_{13}N_4O_4Cl$ (M^+) 372.0625, found 372.0637. Minor regioisomer **50f**: mp 125−129 °C; IR (neat) 1733, 1536, 1474, 1355, 1209, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, J = 1.0, 8.2 Hz, 1H), 7.76 (dd, J = 1.0, 8.0 Hz, 1H), 7.65 (t, J = 8.2 Hz, 1H), 7.24−7.27 (m, 1H), 7.20 (t, J = 7.3 Hz, 2H), 7.02 (d, J = 7.4 Hz, 2H), 5.52 (d, J = 15.0 Hz, 1H), 5.39 (d, J = 14.9 Hz, 1H), 3.82 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 149.0, 137.6, 136.8, 135.1, 134.7, 132.4, 131.9, 128.9, 128.7, 128.5, 123.6, 121.7, 53.9, 52.2 ppm; HRMS (EI+) calcd for $C_{17}H_{13}N_4O_4Cl$ (M^+) 372.0625, found 372.0621.

Triazole 49g and 50g. To a pressure vessel containing **42** (10 mg, 27.5 μmol) were added PhMe (60 μL) and azide **48** (11 mg, 82.5 μmol) sequentially at rt. The reaction mixture was sealed under Ar and heated to 120 °C. After 45 h, the crude mixture was cooled to rt, concentrated in vacuo, and purified via flash chromatography over silica gel, eluting with 0−40% EtOAc/hexanes to give a mixture of regioisomers (7.0 mg, 2.00 μmol, 51%, 1:1 rr (**49g**:**50g**)). Analytical samples of the individual isomers could be obtained by preparative thin-layer chromatography over silica gel, eluting with 30% EtOAc/hexanes to give sequentially **50g** then **49g**. Regioisomer **49g**: IR (neat) 3286, 2919, 1531, 1447, 1346, 1025, 737 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.76 (dd, J = 1.0, 8.3 Hz, 1H), 7.45 (dd, J = 1.0, 8.0 Hz, 1H), 7.31 (m, 4H), 7.27 (m, 3H), 7.15 (m, 4H), 7.11 (m, 2H), 7.07 (m, 3H) 5.41 (s, 2H), 3.04 (s, 1H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 149.1, 142.9, 142.6, 140.0, 138.1, 137.7, 135.5, 134.0, 129.5, 128.7, 128.23, 128.16, 128.13, 128.07, 127.9, 127.5, 126.5, 126.2, 123.1, 53.8 ppm; HRMS (ES+) calcd for $C_{27}H_{19}ClN_4NaO_3$ (M + Na) 505.1043, found 505.1047. Regioisomer **50g**: IR (neat) 3401, 3062, 2925, 1724, 1532, 1448, 1347, 758 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.16 (dd, J = 1.0, 8.3 Hz, 1H), 7.46 (dd, J = 1.1, 8.0 Hz, 1H), 7.37 (t, J = 8.2 Hz, 1H), 7.24 (m, 3H), 7.18 (t, J = 7.7 Hz, 1H), 7.13 (m, 4H), 6.98 (d, J = 7.6 Hz, 1H), 5.36 (d, J = 15.0 Hz, 1H), 5.24 (d, J = 14.9 Hz, 1H), 3.29 (s, 1H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 150.0, 149.1, 144.73, 144.68, 137.6, 134.0, 133.0, 130.8, 128.8, 128.64, 128.56, 128.5, 127.8, 127.7, 127.5, 127.4, 127.2, 123.3, 123.2, 53.5 ppm; HRMS (ES+) calcd for $C_{27}H_{19}ClN_4NaO_3$ (M + Na) 505.1043, found 505.1047.

Triazole 49h and 50h. To a pressure vessel containing **22** (90.5 mg, 0.500 mmol) were added PhMe (1 mL) and azide **48** (199.5 mg, 1.5 mmol) sequentially at rt. The reaction mixture was sealed under Ar and heated to 120 °C. After 24 h, the crude mixture was cooled to rt, concentrated in vacuo, and purified via flash chromatography over silica gel, eluting with 10−30% EtOAc/hexanes to give sequentially **49h** (87.9 mg, 280 μmol, 56%) as an orange oil followed by **50h** (16 mg, 50.9 μmol, 10%) as a pale yellow solid. NMR analysis of the crude mixture indicated the ratio to be 5.7:1 rr (**49h**:**50h**). Major regioisomer **49h**: IR (neat) 1533, 1352 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.1 Hz, 1H), 7.70−7.72 (m, 2H), 7.61 (t, J = 7.3 Hz, 1H), 7.35 (m, 5H), 5.61 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 139.9, 133.6, 133.0, 132.2, 130.0, 129.1, 128.8, 128.7, 127.7, 124.9, 124.1, 123.7, 52.4 ppm; HRMS (ES+) calcd for $C_{15}H_{12}N_4O_2Cl$ (M + H) 315.0649, found 315.0649. Minor regioisomer **50h**: mp 100−102 °C; IR (neat) 1528, 1346, 1284 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.1 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.20−7.25 (m, 3H), 7.02 (d, J = 7.5 Hz, 1H), 6.96 (d, J = 7.2, 2H), 5.60 (d, J = 15.1 Hz, 1H), 5.23 (d, J = 15.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 134.8, 133.6, 133.5, 133.1, 131.6, 130.0, 128.8, 128.7, 127.9, 125.4, 120.4, 54.2 ppm; HRMS (EI+) calcd for $C_{15}H_{11}N_4O_2Cl$ (M^+) 314.0571, found 314.0567.

Triazole 49i and Triazole 50i. To a pressure vessel containing **25** (639.2 mg, 3.268 mmol) were added PhMe (6.00 mL) and azide **48** (1.531 mg, 11.50 mmol) at rt. The reaction mixture was heated to 120 °C. After 24 h, the reaction was cooled to rt, concentrated in vacuo, and purified via flash chromatography over silica gel, eluting with 20−40% EtOAc/Hexanes to give an inseparable mixture of regioisomers (733.6 mg, 2.23 mmol, 68%, 7:1 rr (**49i**:**50i**)) as a yellow oil. Regioisomer mixture: IR (neat) 1534, 1459, 1369 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.1 Hz, 1H for minor), 7.90 (d, J = 8.0 Hz, 1H for major), 7.61−7.59 (m, 1H for minor), 7.58 (d, J = 8.0 Hz, 1H for major), 7.51 (t, J = 8.0 Hz, 1H for major), 7.48 (d, J = 8.1 Hz, 1H for minor), 7.44−7.32 (m, 3H for major/minor), 7.31−7.25 (m, 2H for major), 7.19 (t, J = 7.2 Hz, 2H for minor), 6.96 (d, J = 7.4 Hz, 2H for minor), 5.89 (d, J = 14.8 Hz, 1H for minor), 5.65 (s, 2H for major), 5.09 (d, J = 14.8 Hz, 1H for minor), 2.24 (s, 3H for major), 1.59 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 149.1, 142.4, 141.5, 139.1, 135.4, 134.8, 133.8, 133.0, 131.4, 130.0, 129.1, 128.9, 128.8, 128.6, 128.5, 127.3, 124.6, 122.8, 122.8, 122.3, 119.0, 54.4, 52.3, 20.1, 19.1 ppm; HRMS (CI+) calcd for $C_{16}H_{14}N_4O_2Cl$ (M^+) 329.0805, found 329.0791.

Triazole 49j and Triazole 50j. To a pressure vessel containing **23** (54.2 mg, 253 μmol) were added PhMe (500 μL) and azide **48** (100 mg, 750 μmol) at rt. The reaction mixture was sealed under Ar and heated to 80 °C. After 70 h, the reaction was cooled to rt, concentrated in vacuo, and purified via flash chromatography over silica gel, eluting with 0−30% EtOAc/hexanes to give a mixture of regioisomers (63.3 mg, 181 μmol, 72%, 9:1 (**49j**:**50j**)) as a yellow solid. Analytical samples of the individual isomers could be obtained by preparative thin layer chromatography over silica gel, eluting with 30% EtOAc/Hexanes to give sequentially **49j** then **50j**. Major regioisomer **49j**: IR (neat) 1608, 1533, 1355, 1226, 991, 883, 808, 759, 727, 704 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.99 (d, J = 8.2 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.61 (t, J = 8.1 Hz, 1H), 7.42 (t, J = 7.2 Hz, 2H), 7.37 (t, J = 7.2 Hz, 1H), 7.29 (d, J = 7.1 Hz, 2H), 5.66 (s, 2H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 151.0, 137.5, 134.1, 133.7, 131.1, 129.1, 128.6, 127.2, 125.5, 123.2, 123.1, 52.4 ppm; HRMS (ES+) calcd for $C_{15}H_{11}N_4O_2Cl_2$ (M + H) 349.0259, found 349.0270. Minor regioisomer **50j**: IR (neat) 3090, 2920, 1533, 1345, 1285, 804, 745 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.07 (dd, J = 1.1, 8.3 Hz, 1H), 7.75 (dd, J = 1.2, 8.1 Hz, 1H), 7.66 (t, J = 8.2 Hz, 1H), 7.26 (t, J = 7.5 Hz, 2H), 7.19 (t, J = 7.8 Hz, 1H), 7.00 (d, J = 7.1 Hz, 2H), 5.44 (d, J = 14.9, 1H), 5.40 (d, J = 14.9, 1H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 149.6, 138.0, 134.7, 132.5, 132.3, 129.2, 128.9, 128.8, 128.4, 127.8, 123.6, 120.0 ppm; HRMS (ES+) calcd for $C_{15}H_{11}N_4O_2Cl_2$ (M + H) 349.0259, found 349.0245.

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Triazole 49k and Triazole 50k. To a pressure vessel containing **24** (21 mg, 80.7 μmol) were added PhMe (160 μL) and azide **48** (32 mg, 240 μmol) at rt. The reaction mixture was sealed under Ar and heated to 80 °C. After 72 h, the reaction was cooled to rt, concentrated in vacuo, and purified via flash chromatography over silica gel, eluting with 0−40% EtOAc/hexanes to give a mixture of regioisomers (20.2 mg, 51.6 μmol, 64%, 9:1 (**49k**:**50k**)) as a red-orange solid. Analytical samples of the individual isomers could be obtained by preparative thin layer chromatography over silica gel, eluting with 30% EtOAc/Hexanes to give sequentially **49k** then **50k**. Major regioisomer **49k**: mp 126−128 °C; IR (neat) 3088, 3034, 2924, 1533, 1455, 1353, 988, 759 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.42−7.38 (m, 3H), 7.27 (m, 2H), 5.70 (s, 2H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 150.9, 140.8, 137.6, 134.1, 133.9, 131.0, 129.1, 128.6, 127.2, 123.8, 123.1, 112.2, 53.2 ppm; HRMS (ES+) calcd for $C_{15}H_{11}N_4O_2ClBr$ (M + H) 392.9754, found 392.9770. Minor regioisomer **50k**: IR (neat) 3096, 2922, 1532, 1455, 1347, 1263, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.66 (t, *J* = 8.1 Hz, 1H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 2H), 7.01 (d, *J* = 7.6 Hz, 2H), 5.46 (d, *J* = 15.0 Hz, 1H) 5.42 (d, *J* = 15.2 Hz, 1H) ppm; HRMS (ES+) calcd for $C_{15}H_{11}N_4O_2ClBr$ (M + H) 392.9754, found 392.9753.

Triazole 51a and 52a. To a pressure vessel containing **23** (17.8 mg, 83.2 μmol) were added PhMe (190 μL) and azide (45.8 mg, 288 μmol) sequentially at rt. The reaction mixture was sealed under Ar and heated to 80 °C. After 48 h, the crude mixture was cooled to rt, concentrated in vacuo, and purified via flash chromatography over silica gel, eluting with 0−30% EtOAc/hexanes to give a mixture of regioisomers (15.2 mg, 40.5 μmol, 49%, 11:1 rr (**51a**:**52a**)). Analytical samples of the individual isomers could be obtained by preparative thin layer chromatography over silica gel, eluting with 30% EtOAc/hexanes to give sequentially **51a** then **52a**. Major regioisomer **51a**: IR (neat) 3083, 3028, 2926, 1533, 1449, 1355, 1266, 966, 760 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.40 (tt, *J* = 5.8, 15.8 Hz, 1H), 5.24 (d, *J* = 5.6 Hz, 2H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 151.1, 137.5, 137.4, 135.5, 134.7, 134.1, 131.1, 128.7, 128.5, 126.8, 125.3, 123.3, 123.1, 120.7, 50.7 ppm; HRMS (ES+) calcd for $C_{17}H_{13}N_4O_2Cl_2$ (M + H) 375.0416, found 375.0410. Minor regioisomer **52a**: IR (neat) 2921, 2849, 1533, 1450, 1348, 1046, 733 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.63 (t, *J* = 8.2 Hz, 1H), 7.30−7.28 (m, 3H), 7.19 (d, *J* = 5.8 Hz, 2H), 6.28 (d, *J* = 15.3 Hz, 1H), 6.21 (m, 1H), 5.06 (qd, *J* = 5.8, 14.6 Hz, 2H) ppm; HRMS (ES+) calcd for $C_{17}H_{13}N_4O_2Cl_2$ (M + H) 375.0416, found 375.0397.

Triazole 51b and 52b. To a pressure vessel containing **24** (21.0 mg, 80.7 μmol) were added PhMe (160 μL) and azide (39.3 mg, 247 μmol) sequentially at rt. The reaction mixture was sealed under Ar and heated to 80 °C. After 29 h, the crude mixture was cooled to rt, concentrated in vacuo, and purified via flash chromatography over silica gel, eluting with 0−40% EtOAc/hexanes to give a mixture of regioisomers (22.3 mg, 53.1 μmol, 69%, 4:1 rr (**51b**:**52b**)). Analytical samples of the individual isomers could be obtained by preparative thin layer chromatography over silica gel, eluting with 30% EtOAc/hexanes to give sequentially **51b** then **52b**. Major regioisomer **51b**: mp 133−136 °C; IR (neat) 3083, 3028, 2925, 1532, 1449, 1355, 1222, 760, 737 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 1.0, 8.2 Hz, 1H), 7.81 (dd, *J* = 1.0, 8.1 Hz, 1H), 7.61 (t, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 6.53 (d, *J* = 15.9 Hz, 1H), 6.40 (tt, *J* = 5.7, 15.9 Hz, 1H), 5.28 (d, *J* = 5.7 Hz, 2H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 151.0, 140.6, 137.6, 135.6, 134.7, 134.1, 131.0, 128.7, 128.4, 126.8, 123.8, 123.1, 120.9, 112.0, 51.6 ppm; HRMS (ES+) calcd for $C_{17}H_{13}BrClN_4O_2$ (M + H) 418.9910, found 418.9930. Minor regioisomer **52b**: IR (neat) 2919, 2851, 1532, 1449, 1351, 1263, 732 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.78 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.28 (m, 3H), 7.19 (dd, *J* = 1.4, 7.3 Hz, 2H), 6.29 (d, *J* = 15.9 Hz, 1H), 6.40 (tt, *J* = 5.7, 15.9 Hz, 1H), 5.28 (d, *J* = 5.7 Hz, 2H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 150.0, 137.8, 135.9, 135.2, 134.7, 132.2, 130.0, 128.6, 126.6, 123.6, 121.7, 120.7, 120.3, 53.1 ppm; HRMS (ES+) calcd for $C_{17}H_{13}BrClN_4O_2$ (M + H) 418.9910, found 418.9916.

Triazole 51c and 52c. To a pressure vessel containing **23** (19 mg, 88.8 μmol) were added PhMe (190 μL) and azide (33 mg, 277 μmol) sequentially at rt. The reaction mixture was sealed under Ar and heated to 80 °C. After 72 h, the crude mixture was cooled to rt, concentrated in vacuo, and purified via flash chromatography over silica gel, eluting with 0−40% EtOAc/hexanes to give a mixture of regioisomers (11.5 mg, 34.3 μmol, 36%, 2:1 rr (**51c**:**52c**)). Analytical samples of the individual isomers could be obtained by preparative thin layer chromatography over silica gel, eluting with 30% EtOAc/hexanes to give sequentially **51c** then **52c**. Major regioisomer **51c**: IR (neat) 3082, 2919, 1533, 1501, 1351, 1242, 983, 760, 746 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 1.0, 8.3 Hz, 1H), 7.85 (dd, *J* = 1.1, 8.1 Hz, 1H), 7.73 (m, 2 H), 7.63 (m, 4H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 151.1, 137.8, 137.6, 134.9, 134.2, 131.2, 130.2, 129.6, 125.6, 125.4, 125.0, 123.1 ppm; HRMS (ES+) calcd for $C_{14}H_9Cl_2N_4O_2$ (M + H) 335.0103, found 335.0110. Minor regioisomer **52c**: IR (neat) 3084, 2924, 2854, 1717, 1537, 1498, 1348, 1307, 1262, 1098, 994, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 1.0, 8.3 Hz, 1H), 7.81 (dd, *J* = 1.0, 8.1 Hz, 1H), 7.68 (t, *J* = 8.2 Hz, 2H), 7.43 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 137.8, 136.2, 135.3, 135.0, 132.4, 130.0, 129.9, 127.7, 124.0, 123.8, 120.7, 120.4 ppm; HRMS (ES+) calcd for $C_{14}H_9Cl_2N_4O_2$ (M + H) 335.0103, found 335.0098.

Triazole 51d and 52d. To a pressure vessel containing **24** (19.8 mg, 76.1 μmol) were added PhMe (160 μL) and azide (29.1 mg, 244 μmol) sequentially at rt. The reaction mixture was sealed under Ar and heated to 80 °C. After 53 h, the crude mixture was cooled to rt, concentrated in vacuo, and purified via flash chromatography over silica gel, eluting with 0−40% EtOAc/hexanes to give a mixture of regioisomers (mg, μmol, 24%, 1:1 rr (**51d**:**52d**)). Analytical samples of the individual isomers could be obtained by preparative thin layer chromatography over silica gel, eluting with 30% EtOAc/hexanes to give sequentially **51d** then **52d**. Major regioisomer **51d**: IR (neat) 2920, 1533, 1499, 1350, 808, 759, 745 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 2 H), 7.65 (t, *J* = 8.3 Hz, 1 H), 7.64 (m, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 151.0, 141.0, 137.7, 135.6, 134.2, 131.1, 130.3, 129.5, 125.5, 123.7, 123.1, 112.2 ppm; HRMS (ES+) calcd for $C_{14}H_9BrClN_4O_2$ (M + H) 378.9597, found 378.9612. Minor regioisomer **52d**: IR (neat) 3083, 2922, 2851, 1535, 1497, 1347, 1292, 1092, 992, 758 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.68 (t, *J* = 8.2 Hz, 1 H), 7.45 (m, 4 H), 7.28 (m, 1H) ppm; HRMS (ES+) calcd for $C_{14}H_9BrClN_4O_2$ (M + H) 378.9597, found 378.9587.

Triazole 51e and 52e. To a pressure vessel containing **23** (19.9 mg, 93.0 μmol) were added PhMe (190 μL) and azide (46.8 mg, 298 μmol) sequentially at rt. The reaction mixture was sealed under Ar and heated to 80 °C. After 48 h, the crude mixture was cooled to rt, concentrated in vacuo, and purified via flash chromatography over silica gel, eluting with 0−40% EtOAc/hexanes to give a mixture of regioisomers (12.8 mg, 34.3 μmol, 37%, 9:1 rr (**51e**:**52e**)). Analytical samples of the individual isomers could be obtained by preparative thin layer chromatography over silica gel, eluting with 30% EtOAc/hexanes to give sequentially **51e** then **52e**. Major regioisomer **51e**: mp 95−97 °C; IR (neat) 3086, 2982, 2932, 1747, 1536, 1354, 1238, 1156, 993, 760 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 1.1, 8.2 Hz, 1H), 7.82 (dd, *J* = 1.2, 8.1 Hz, 1H), 7.63 (t, *J* = 8.2 Hz, 1H), 5.14 (s, 2H), 1.52 (s, 9H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 163.7, 151.0, 137.6, 137.2, 134.1, 131.1, 126.2, 123.0, 84.4, 50.3, 27.9 ppm; HRMS (ES+) calcd for $C_{14}H_{15}Cl_2N_4O_4$ (M + H) 373.0470, found 373.0472. Minor regioisomer **52e**: IR (neat) 2923, 2852, 1748, 1538, 1369, 1239, 1156, 757 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 1.0, 8.3 Hz, 1H), 7.90 (dd, *J* = 1.1, 8.1 Hz, 1H), 7.76 (t, *J* = 8.3 Hz, 1H), 4.91 (d, *J* = 17.3 Hz, 1H), 4.81 (d, *J* = 17.3 Hz, 1H), 1.28 (s, 9H) ppm; HRMS (ES+) calcd for $C_{14}H_{15}Cl_2N_4O_4$ (M + H) 373.0470, found 373.0487.

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Triazole 51f and 52f. To a pressure vessel containing **24** (26.1 mg, 100 μmol) were added PhMe (200 μL) and azide (47.2 mg, 300 μmol) sequentially at rt. The reaction mixture was sealed under Ar and heated to 80 °C. After 48 h, the crude mixture was cooled to rt, concentrated in vacuo, and purified via flash chromatography over silica gel, eluting with 0−35% EtOAc/hexanes to give a mixture of regioisomers (24.5 mg, 58.7 μmol, 58%, 9:1 rr (**51f**:**52f**)). Analytical samples of the individual isomers could be obtained by preparative thin layer chromatography over silica gel, eluting with 30% EtOAc/hexanes to give sequentially **51f** then **52f**. Major regioisomer **51f**: mp 140−142 °C; IR (neat) 3084, 2981, 2934, 1748, 1534, 1455, 1370, 1236, 990, 760 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.01 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 8.2 Hz, 1H), 5.17 (d, J = 18.2 Hz, 2H), 1.51 (s, 9H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.8, 151.0, 140.5, 137.6, 134.1, 131.1, 123.6, 123.0, 113.0, 84.3, 51.2, 27.9 ppm; HRMS (ES+) calcd for $C_{14}H_{15}BrClN_4O_4$ (M + H) 416.9965, found 416.9977. Minor regioisomer **52f**: IR (neat) 3087, 2982, 2929, 1748, 1537, 1353, 1238, 1156, 858, 758, 744 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.18 (dd, J = 1.0, 8.3 Hz, 1H), 7.90 (dd, J = 1.0, 8.1 Hz, 1H), 7.75 (t, J = 8.3 Hz, 1H), 4.92 (d, J = 17.2 Hz, 1H), 4.83 (d, J = 17.2 Hz, 1H), 1.40 (s, 9H) ppm; HRMS (ES+) calcd for $C_{14}H_{15}BrClN_4O_4$ (M + H) 416.9965, found 416.9973.

Triazole 53. To a microwave vessel containing **46f** (25 mg, 80 μmol) were added sequentially $PhB(OH)_2$ (45.6 mg, 240 μmol), Cs_2CO_3 (79.9 mg, 240 μmol), Ph_2XPhos (7.4 mg, 16 μmol), $Pd(OAc)_2$ (1.8 mg, 8 μmol), and 2-MeTHF (400 μL). The solution was sealed under argon and heated to 100 °C in a microwave. After 1 h, the mixture was filtered over a pad of Celite, eluting with Et_2O, and concentrated in vacuo. The residue was purified by flash chromatography over silica gel, eluting 0−30% EtOAc/hexanes, to give **53** (27.8 mg, 67 μmol, 84%) as a pale yellow solid: mp 110−113 °C; IR (neat) 3062, 3034, 2955, 1732, 1540, 1479, 1355, 1266, 1218, 1105, 820, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, J = Hz, 1H), 7.69 (m, 2H), 7.30 (m, 3H), 7.21 (t, J = 7.30 Hz, 1H), 7.16 (t, J = 7.36 Hz, 2H), 6.99 (m, 4H), 5.84 (q, J = 14.81, 34.16 Hz, 2H), 3.57 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 149.6, 146.1, 145.4, 138.7, 135.2, 134.4, 129.8, 129.1, 128.7, 128.1, 128.0, 127.6, 126.9, 125.7, 124.6, 123.4, 54.0, 52.3 ppm; HRMS (EI+) calcd for $C_{23}H_{18}N_4O_4$ (M^+) 414.1328, found 414.1331.

Lactam 54. To a flask containing triazole **53** (25.3 mg, 61 μmol) stirring in glacial acetic acid (240 μL) at rt was added Zn dust (12.1 mg, 185 μmol). After 20 h, a second portion of Zn dust (16.8 mg, 0.257 mmol) was added. After 3 h, the reaction was quenched with satd aq $NaHCO_3$ (15 mL). The reaction mixture was diluted with EtOAc (15 mL), and the organic layer was washed with satd aq$NaHCO_3$ (15 mL), DI water (15 mL), and satd aq NaCl (15 mL). The organic layer was then dried over $MgSO_4$ and concentrated in vacuo. The pink solid was purified by trituration with EtOAc to give **54** (11.0 mg, 31 μmol, 52%) as a white solid: mp 257−258 °C; IR (neat) 3060, 2923, 1695, 1664, 1675, 1558, 1373, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.62 (s, 1H), 7.57 (m, 3H), 7.51 (m, 5H), 7.40 (m, 1H), 7.32 (m, 8H), 6.12 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 147.7, 140.4, 140.2, 136.6, 135.2, 129.5, 128.9, 128.8, 128.6, 128.0, 127.9, 126.7, 123.6, 115.4, 112.6, 53.4 ppm; HRMS (ES +) calcd for $C_{22}H_{17}N_4O$ (M + H) 353.1402, found 353.1385.

Alcohol 55. To a flask containing triazole **53** (25 mg, 60 μmol) stirring in DCM (600 μL) at −78 °C was added DIBAL-H (180 mL, 18 μmol). After 1.5 h, the mixture was warmed to 0 °C and the reaction quenched with Rochelle's salt. The reaction mixture was diluted with DCM (10 mL), and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organics were washed with brine (2 × 10 mL), dried over $MgSO_4$,and concentrated in vacuo. The solid was purified by flash chromatography over silica gel, eluting 0−30% EtOAc/hexanes, to give **55** (16.5 mg, 43 μmol, 71%) as a beige solid: mp 148−150 °C; IR (neat) 3315, 3063, 2927, 1532, 1359, 732, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, J = 7.55. 1.81 Hz, 1H), 7.69 (m, 2H), 7.31 (m, 6H), 7.14 (dd, J = 7.91, 1.54 Hz, 2H), 7.01 (m, 2H) 5.58 (s, 2H), 4.02 (m, 2H), 0.49 (t, J = 7.00 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 144.5, 140.5, 138.8, 134.7, 133.8, 133.2, 130.0, 129.5, 128.9, 128.5, 128.2, 128.0, 126.9, 123.6, 123.5, 52.7, 52.4 ppm; HRMS (CI+) calcd for $C_{22}H_{19}N_4O_3$ (M + H) 387.1457, found 387.1455.

Amino Alcohol 56. To a flask containing triazole **55** (10.9 mg, 28 μmol) stirring in glacial acetic acid (120 μL) at rt was added Zn dust (5.5 mg, 84 μmol). After 2 h, the reaction was quenched with satd aq $NaHCO_3$ (3 mL). The reaction mixture was diluted with EtOAc (5 mL), and the organic layer was washed with satd aq $NaHCO_3$ (3 mL) and DI water (3 mL). The aqueous layer was extracted with EtOAc (5 mL). The organic layer was washed with satd aq NaCl (5 mL). The organic layer was then dried over $MgSO_4$ and concentrated in vacuo. The solid was purified by flash chromatography over silica gel, eluting 0−100% EtOAc/hexanes, to give **56** (8.4 mg, 24 μmol, 84%) as a pale yellow solid: IR (neat) 3361, 1616, 1462, 1004, 761, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.12 (overlapping m, 13H), 7.12 (d, J = 7.5 Hz, 1H), 6.87 (d, J = 8.03 Hz, 1H), 5.54 (d, J = 8.59 Hz, 2H), 4.32 (bs, 2H), 3.98 (d, J = 13.83 Hz, 1H), 3.77 (d, J = 13.78, 1H), 0.53 (bs, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 143.0, 142.4, 141.4, 134.8, 132.9, 130.0, 129.8, 128.8, 128.3, 128.2, 127.5, 126.9, 120.2, 115.5, 114.0, 52.9, 52.4 ppm; HRMS (CI+) calcd for $C_{22}H_{21}N_4O$ (M + H) 357.1715, found 357.1716.

Carboxylic Acid 57. To a vial containing triazole **53** (88 mg, 212 μmol) stirring in EtOH (1 mL) was added $LiOH·H_2O$ (36 mg, 848 μmol) at rt. After 9 h, the reaction was quenched with aq HCl (3 mL, 6 N) and concentrated in vacuo. The reaction solid was taken up in EtOAc (5 mL) and DI water (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL). The organic layer was washed with brine (2 × 5 mL), dried over $MgSO_4$, and concentrated in vacuo. The solid was purified by flash chromatography over silica gel, eluting 0−10% MeOH/DCM, to give **57** (64.7 mg, 161 μmol, 76%) as a white solid: IR (neat) 3381, 2924, 1607, 1530, 1497, 1356, 764 cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 8.10 (m, 1H), 7.2 (d, J = 5.2 Hz, 2H), 7.14−7.27 (m, 8H), 6.96 (m, 2H), 6.08 (d, J = 14.8 Hz, 1H), 5.81 (d, J = 14.8 Hz, 1H) 4.88 (s, 1H) ppm; ^{13}C NMR (100 MHz, MeOD) δ 152.0, 145.5, 139.2, 136.5, 134.2, 129.3, 129.0, 128.2, 127.5, 127.3, 127.0, 126.5, 125.1, 122.8, 121.9, 52.7 ppm; HRMS (TOF+) calcd for $C_{22}H_{16}N_4NaO_4$ (M + Na) 423.1069, found 423.1064.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C spectra for all new compounds are provided. X-ray crystallographic data (CIF) for compounds **50e** and **53** are also provided. Cartesian coordinates, energies, and additional computational informational are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: paulc@science.oregonstate.edu; rich.carter@oregonstate.edu.

†Corresponding author for computational work.

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