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Synthesis of 2- and 2,3-Substituted Pyrazolo[1,5-*a*]pyridines: Scope and Mechanistic Considerations of a Domino Direct Alkynylation and Cyclization of *N*-Iminopyridinium Ylides Using Alkenyl Bromides, Alkenyl Iodides, and Alkynes

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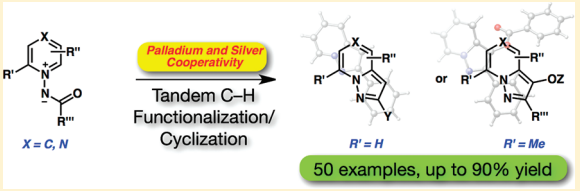
Supporting Information

ABSTRACT: Direct functionalization and tandem processes have both received considerable recent interest due to their cost and time efficiency. Herein we report the synthesis of difficult to obtain 2-substituted pyrazolo[1,5-*a*]pyridines through a tandem palladium-catalyzed/silver-mediated elimination/direct functionalization/cyclization reaction involving *N*-benzoyliminopyridinium ylides. As such, these biologically important molecules are prepared in an efficient, high-yielding manner, only requiring a two-step sequence from pyridine. Aryl-substituted alkenyl bromides and iodides are effective ylide coupling partners. Mechanistic studies led to the use of terminal alkynes, which extended the scope of the reaction to include alkyl substitution on the unsaturated reactive site. The optimization, scope, and mechanistic considerations of the process are discussed.



INTRODUCTION

Nitrogen-containing heterocycles are key components in a myriad of biologically active compounds.[1] Indeed, recent surveys have reported that greater than 90% of molecules currently under investigation by pharmaceutical companies contain nitrogen heterocycles, and of these, pyridine and pyridine derivatives constitute the most important family of compounds.[2] As such, there has been significant interest in developing efficient methods for the synthesis of these molecular architectures.

Pyrazolopyridines constitute an important class of pharmacologically active compounds and are often employed as indole isosteres due to their relatively high metabolic stability.[3] Notably, pyrazolo[1,5-*a*]pyridines (Figure 1), specifically when substituted in the 2-position, are known for their ability to act as dopamine D3 agonists and antagonists and are used in the treatment of psycho-stimulant addictions. Additionally the D3 receptor controls dopamine synthesis, release, and neuronal firing and is linked to the pathophysiology of Parkinson's disease as well as schizophrenia.[3] Other applications of pyrazolo[1,5-*a*]pyridines include an adenosine A1 receptor antagonist with potent diuretic activity as well as their use in the treatment of cardiac arrhythmias and for the diagnosis of ischemic heart diseases.[4] Finally, certain pyrazolo[1,5-*a*]pyridine derivatives have also been found to have superior reactivity than acyclovir and its prodrug valacyclovir as antiherpetic agents.[4]

Despite their clear importance, the synthesis of 2-substituted pyrazolo[1,5-*a*]pyridines (generalized as pyrazolopyridines) remains a challenge. The most common method for their preparation involves a [3 + 2] cycloaddition of a dipolarophile bearing an electron-withdrawing group onto an *N*-aminopyridinium salt (Scheme 1).[5] Typically, 2,3-disubstituted or 3-substituted pyrazolopyridines are obtained in moderate yields. Pyrazolopyridines bearing 2-substituents may be accesed via various intramolecular cyclizations, including displacements,[6] radical additions,[7] nitrene insertions,[8] and through rearrangements of pyridine derivatives bearing aziridine groups (Scheme 1).[5b,9] Several of these transformations are high yielding but require several synthetic steps for the synthesis of the reactive precursors, hampering the efficiency of the sequence.

Modern synthetic methodology often aims to emphasize molecular complexity while minimizing the number of synthetic steps required to achieve this. Processes whereby several bonds are made/broken in a single reaction vessel have garnered much attention.[10] These domino sequences are often atom economical and save considerable resources in both time and cost by reducing the number of operations required to reach a specific target. Concomitantly, the direct introduction of functionality via the functionalization of C−H bonds is a highly attractive synthetic strategy.[11] These processes are an opportunistic new class of C−C bond forming reactions, due in part to the ubiquity of C−H bonds in Nature. Consequently, these reactions have emerged as viable, efficient, and more environmentally friendly alternatives to classical cross-coupling reactions.[12] Combining

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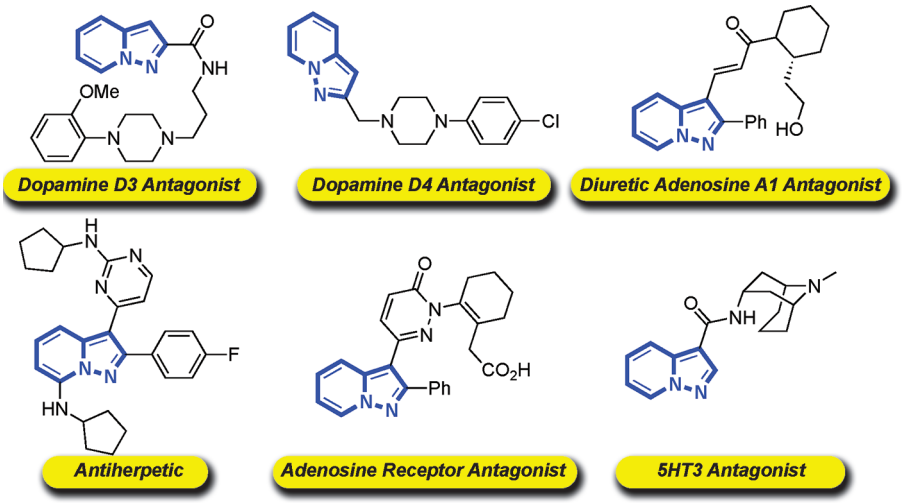
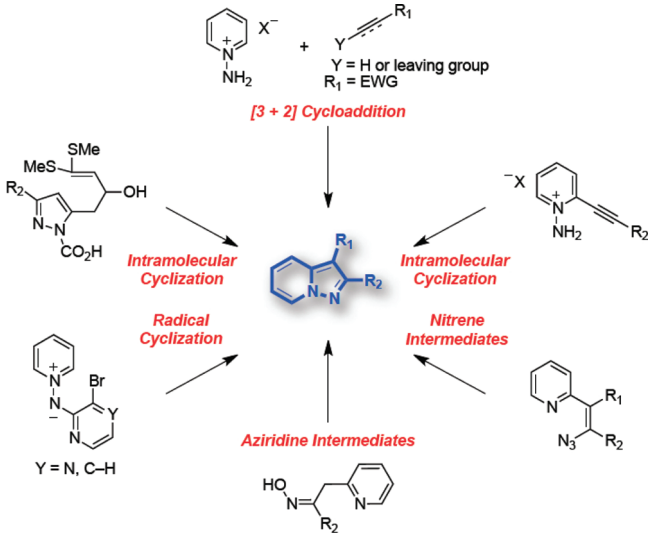
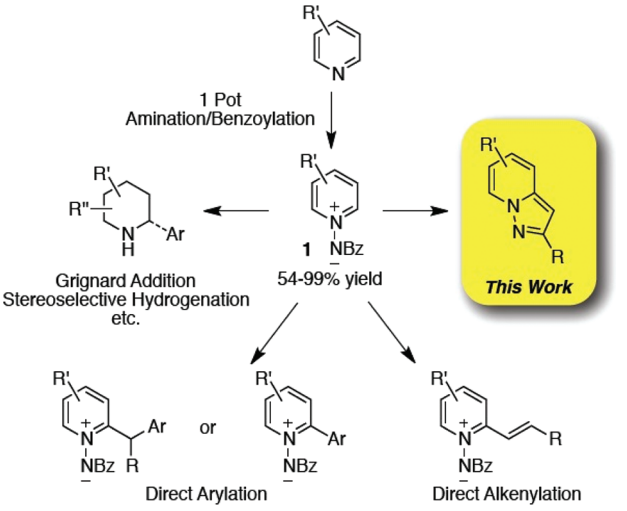


Figure 1. Various biologically active pyrazolo[1,5-*a*]pyridines.

Scheme 1. Previous Reported Methods for the Preparation of 2-Substituted Pyrazolo[1,5-*a*]pyridines



Scheme 2. Synthesis of Pyridine Derivatives and Direct Functionalization Reactions Employing *N*-Iminopyridinium Ylides



C−H activation with subsequent tandem reactions presents a highly desirable approach to molecular synthesis.

Recent examples of direct reactions on activated pyridines to generate 2-substituted pyridine and pyridine derivatives have clearly demonstrated the effectiveness of C−H derivatization over traditional cross-coupling methods, especially over using 2-metallopyridines in cross-coupling processes.[13] Our research program has been focused in developing novel methodologies aimed toward the preparation of various pyridine derivatives from *N*-iminopyridinium ylides (Scheme 2).[14] As part of this mandate we have recently demonstrated that *N*-iminopyridinium ylides are versatile substrates for both palladium- and copper-catalyzed direct functionalization reactions.[14d−f] These include both the direct and benzylic arylation of these ylides as well as a direct alkenylation reaction. *N*-Benzoyliminopyridinium ylide **1** is readily available on large scale in excellent yield through a one-pot amination/benzoylation of pyridine using *O*-(2,4-dinitrophenyl)hydroxylamine.[15] We recently disclosed preliminary results toward a divergent synthesis of pyrazolo[1,5-*a*]pyridines from *N*-iminopyridinium ylides and alkenyl iodides under palladium catalysis.[16] Herein we disclose further application of this transformation, expanding the scope of the alkenyl iodides, and we report the application of alkenyl bromides. Studies into the mechanism of the reaction are disclosed which suggest that alkynes are the true substrates, formed under the coupling conditions. The use of alkynes as the initial substrate further diversified the breadth of potential coupling partners. The scope of the reaction using alkynyl coupling partners is also explored. The process constitutes a direct alkynylation reaction in tandem with intramolecular ring closing to generate 2-substituted pyrazolo[1,5-*a*]pyridines in two steps from pyridine in good to excellent yields.

RESULTS AND DISCUSSION

Reaction Optimization. Pyrazolopyridine **4a** was first observed during the optimization of our previously reported direct

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Scheme 3. Effect of Altering the Base in the Direct Alkenylation Reaction

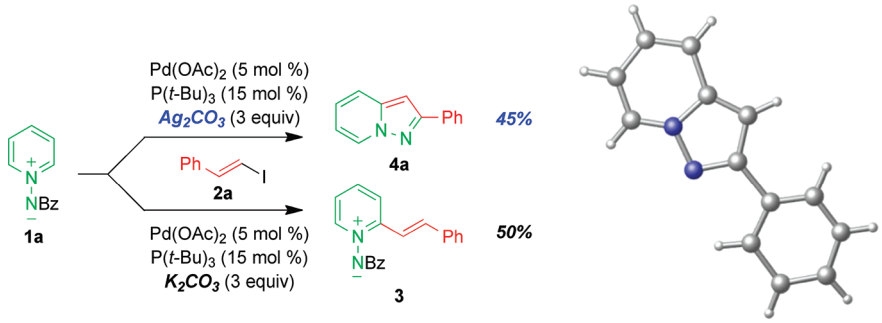
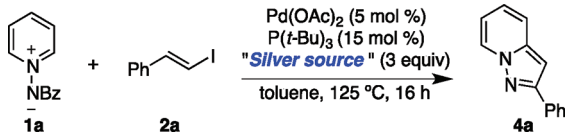


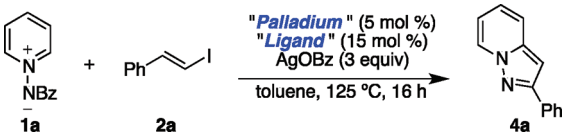
Table 1. Selected Screening of Silver Salts



entry[a]	silver source	yield[b] (%)
1−5	AgOTf, $AgSbF_4$, $AgBF_4$, $AgPF_6$, Ag_2SO_4	<5 (<5)[c]
6	AgTFA	<5 (16)[c]
7	AgOAc	13 (21)[c]
8	Ag_2CO_3	45 (50)[c]
9	AgOBz	51 (51)[c]

[a] 1.5 equiv of **1a** and 1 equiv of **2a** were used. [b] ^{1}H NMR yield determined using 1,3,5-trimethoxybenzene as an internal standard. [c] Number in parentheses indicates the yield observed with the inclusion of 2 equiv of K_2CO_3.

Table 2. Selected Screening of Palladium and Ligand Sources



entry[a]	palladium	ligand	yield[b] (%)
1	$Pd(dba)_2$	P(*t*-Bu)$_3$	31
2	$Pd(TFA)_2$	P(*t*-Bu)$_3$	40
3	PdI_2	P(*t*-Bu)$_3$	46
4	$Pd(OAc)_2$	P(*t*-Bu)$_3$	52
5	$PdBr_2$	P(*t*-Bu)$_3$	55
6	$PdBr_2$	P(Cy)$_3$	50
7	$PdBr_2$	P(2,4,6-MeOPh)$_3$	54
8	$PdBr_2$	PPh_3	59
9	$PdBr_2$	P(2-MePh)$_3$	60
10	$PdBr_2$	BINAP	61
11	$PdBr_2$	P(*n*-Bu)$_3$	62
12	$PdBr_2$	P(4-MeOPh)$_3$	63

[a] 1.5 equiv of **1a** and 1 equiv of **2a** were used. [b] ^{1}H NMR yield determined using 1,3,5-trimethoxybenzene as an internal standard.

alkenylation reaction (Scheme 3). Reacting ylide **1a** with (*E*)-(2-iodovinyl)benzene (**2a**) in the presence of $Pd(OAc)_2$ (5 mol %), P(*t*-Bu)$_3$ (15 mol %), and K_2CO_3 (3 equiv) gave the 2-alkenylated pyridinium **3** in moderate 50% yield. However, varying the base to Ag_2CO_3 (3 equiv) gave the 2-substituted pyrazolopyridine **4a** in 45% isolated yield along with an equal amount of benzoic acid.

Cognizant of the difficulties in preparing 2-substituted pyrazolopyridines, we proceeded to optimize the reaction conditions to furnish **4a**. The source of silver proved to be critical for the transformation to proceed (Table 1). Most silver reagents were incompatible for the reaction, even upon the inclusion of an additional external base (entries 1−5). Given the elegant work of Fagnou and Echavarren, while considering that a direct C−H functionalization may be a key step in the process, it was thought that the inclusion of an acetate/carbonate motif may be essential to promote a concerted metalation/deprotonation (CMD) of the pyridinium ylide.[17] Gratifyingly, AgTFA (entry 6), AgOAc (entry 7), and Ag_2CO_3 (entry 8) gave the product in increasing yields, indeed demonstrating the importance of this moiety in the transformation. In most cases, the inclusion of an ancillary carbonate source led to modest improvement in yields. Silver benzoate was determined to be the most favorable, in which case the introduction of an external base was not beneficial to the yield (entry 9). Varying the quantity of silver was deleterious, with the optimal loading being 3 equiv.

We next considered the palladium/ligand catalytic system (Table 2). All palladium sources examined promoted the reaction (entries 1−4); however, $PdBr_2$ offered the highest yield (entry 5). The reaction was remarkably insensitive to the ligand employed with a range of inexpensive phosphine reagents providing comparable levels of conversion to the desired heterocycle, displaying a high degree of versatility with regards to choice of cocatalyst (entries 5−12). However, P(4-MeOPh)$_3$ did give slightly improved results (entry 12) and thus was chosen for the remaining optimization. A ligand-to-palladium ratio of 3:1 provided the best results. It is noteworthy that palladium/ligand complexes such as Pd(*i*-Mes)-napquin dimer, $(PPh_3)_2Pd(OAc)_2$, and PEPPSI were also operative, albeit with lower yields.

The reaction was successful in all solvents examined (Table 3). Several polar, aromatic, and ethereal solvents were very well tolerated, further displaying a lack of reaction component sensitivity (entries 3−9). Though dimethoxyethane was found to give the best yield, 1,4-dioxane was ultimately chosen due to its lower volatility (entry 8).

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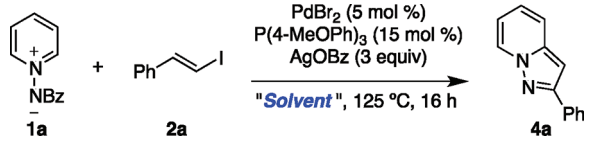
Table 3. Selected Reaction Solvent Screening



entry[a]	solvent	yield[b] (%)
1	dichloroethane	28
2	*N*,*N*-dimethylformamide	46
3	chlorobenzene	54
4	acetonitrile	62
5	toluene	63
6	tetrahydrofuran	64
7	*N*-methylpyrrolidinone	68
8	1,4-dioxane	69
9	dimethoxyethane	71

[a] 1.5 equiv of **1a** and 1 equiv of **2a** were used. [b] ^{1}H NMR yield determined using 1,3,5-trimethoxybenzene as an internal standard.

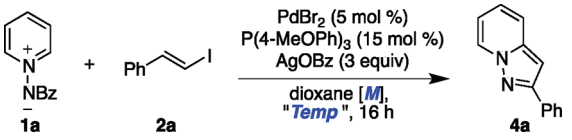
Among the final variables to be considered were the concentration of the reagents along with the reaction temperature and time (Table 4). The reaction performed better when an excess of the ylide relative to the iodide coupling partner was employed (entries 1−5). Using 2 equiv of the ylide increased the yield to 80% (entry 4). Further increasing the excess to 4 equiv provided only a marginal improvement (84%, entry 5), which did not justify the large excess. The optimal concentration was 0.2 M with respect to the iodide (entries 5−8). Reactivity was noted at temperatures as low as 95 °C (40% yield, entry 9), and a temperature of 125 °C provided the best results. It is interesting to note that increasing the temperature above this point gave poorer results (entry 13) because of the increase in degradation products. The time of the reaction was also considered, and 16 h was found to be necessary for increased levels of conversion.

As a result, the optimal conditions for the tandem direct functionalization/cyclization reaction involved 1 equiv of the alkenyl iodide **2a**, 2 equiv of the pyridinium ylide **1a**, 3 equiv of AgOBz, 5 mol % of $PdBr_2$, 15 mol % of $P(4\text{-MeOPh})_3$, 0.2 M in 1,4-dioxane at 125 °C, providing the pyrazolopyridine **4a** in 78% isolated yield.

Reaction Scope: Alkenyl Halides. With an optimized set of conditions in hand, we were keen to investigate the scope of the reaction. We previously reported a convenient, high-yielding, and highly stereoselective method for the preparation of β-aryl vinyl halides using the anions of dihalomethanes.[18] With access to a wide range of functionalized styryl halides we first employed these reagents to challenge the current methodology.

The use of both *E*- and *Z*-β-styryl iodide successfully formed 2-phenylpyrazolopyridine **4a** (Table 5, entries 1 and 2), though the *E*-isomer afforded a higher yield. Styryl bromides were viable reacting partners, extending the breadth of potential pseudo-electrophile coupling partners. Interestingly, both β- and α-styryl bromide (**2c** and **2d**) furnished the same pyrazolopyridine product with the phenyl ring at the 2-position (entries 3 and 4). Unfortunately, styryl chlorides were inoperative (entry 5), presumably due to the inability of the reagent to undergo oxidative addition under the reaction conditions.[19] Pleasingly, using 0.5 equiv of bis-vinyl iodide **2f** gave the corresponding

Table 4. Selected Optimization of Reaction Conditions: Concentration, Stoichiometry, Temperature



entry	conc (M)	ylide/iodide	temp (°C)	yield[a] (%)
1	0.2	0.75/1.0	125	60
2	0.2	1.0/1.0	125	63
3	0.2	1.5/1.0	125	74
4	0.2	2.0/1.0	125	80
5	0.2	4.0/1.0	125	84
6	0.1	2.0/1.0	125	64
7	0.4	2.0/1.0	125	70
8	0.8	2.0/1.0	125	55
9	0.2	2.0/1.0	95	40
10	0.2	2.0/1.0	100	62
11	0.2	2.0/1.0	110	68
12	0.2	2.0/1.0	125	80 (78)[b]
13	0.2	2.0/1.0	135	69

[a] ^{1}H NMR yield determined using 1,3,5-trimethoxybenzene as an internal standard. [b] Isolated yield.

bis-pyrazolopyridine **4b** in 40% yield under unmodified conditions (entry 6). Electron-neutral substitution on the aromatic ring of the halide had little effect on the reaction (entries 7−10). Naphthyl as well as tolyl vinyl halides gave the desired products in moderate to good yield (entries 7−10). The presence of an *o*-methyl group gave only a slight decrease in yield, demonstrating little sensitivity toward steric hindrance. Electron-donating groups at the 2-, 3-, and 4-positions of the phenyl ring afforded the corresponding pyrazolopyridines in moderate to very good yield, with the (*E*)-β-aryl vinyl iodide bearing a benzyl ether proving to be the most reactive (entries 11−14). Concurrently we assessed electron-poor substrates (entries 15−18), and comparable yields were observed for arenes bearing nitrile and fluorine functionality. Styryl iodides bearing bromides or chlorides on the aryl component reacted in an extremely chemoselective fashion with no arylated byproduct observed (entries 18−21). These provide attractive scaffolds for further elaboration via cross-coupling reactions. However, substrates with aryl iodides provided complex mixtures of products.

We next varied the type of vinyl halide aiming to introduce vinyl or alkyl substituents onto the pyrazolopyridine core (Table 6). Iodo diene **2v** bearing a distal ester gave synthetically useful yields and provided a handle for a variety of potential functionalizations (entry 1). Simple alkyl-substituted vinyl halides (**2x**, **2y**) constituted a limitation of the methodology affording little or none of the desired products.[20] However sp^3 functionality could be introduced using cyclopropyl derivative **2w** in a good yield. We reason the viability of **2w** was due to the high s-character of the cyclopropane ring tuning the reactivity of the double bond.

Reaction Scope: Pyridinium Ylide Derivatives. Having demonstrated that a wide variety of alkenyl halides may be

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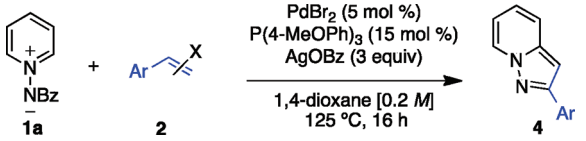
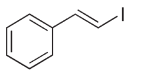
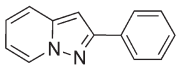
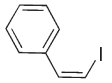
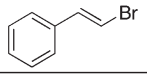
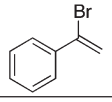
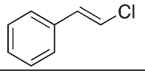
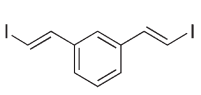
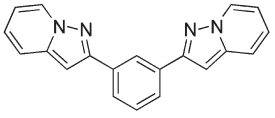
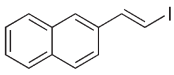
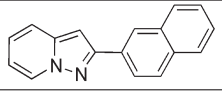
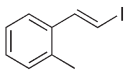
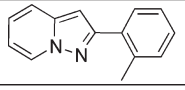
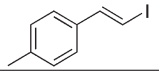
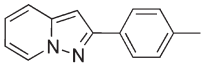
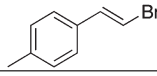
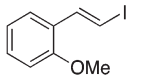
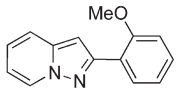
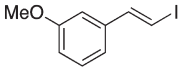
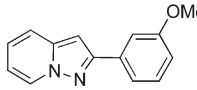
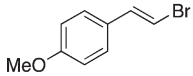
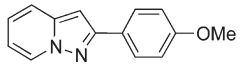
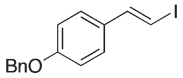
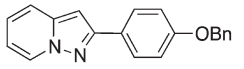
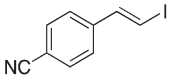
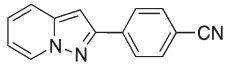
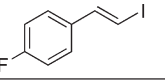
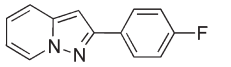
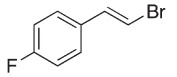
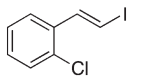
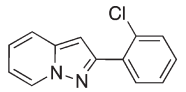
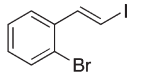
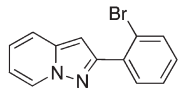
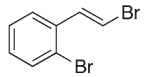
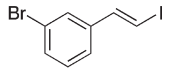
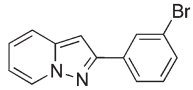
Table 5. Scope of (β)-Aryl Vinyl Halides



entry[a]	halide	product	yield (%)[b]
1	 **2a**	 **4a**	78
2	 **2b**		64
3	 **2c**		80
4	 **2d**		58
5	 **2e**		0
6[c]	 **2f**	 **4b**	40
7	 **2g**	 **4c**	61
8	 **2h**	 **4d**	70
9	 **2i**	 **4e**	79
10	 **2j**		76

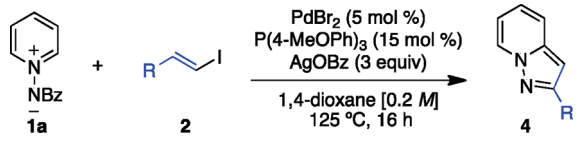
entry[a]	halide	product	yield (%)[b]
11	 **2k**	 **4f**	70
12	 **2l**	 **4g**	65
13	 **2m**	 **4h**	63
14	 **2n**	 **4i**	87
15	 **2o**	 **4j**	61
16	 **2p**	 **4k**	86
17	 **2q**		79
18	 **2r**	 **4l**	63
19	 **2s**	 **4m**	70
20	 **2t**		60
21	 **2u**	 **4n**	60

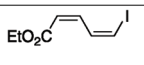
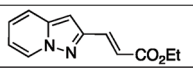
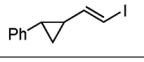
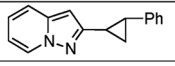
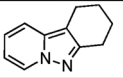
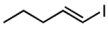
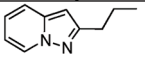
[a] 2.0 equiv of **1a** and 1 equiv of the halide were used. [b] Yield of isolated product. [c] 4 equiv of **1a** were used.

employed, we next considered substitution on the pyridinium moiety (Table 7). We were pleased to note that a nitrile at the 4-position of the heterocyclic ring had little effect on the reaction (entry 1). 3-Substituted pyridines bearing methyl and chloro substituents reacted in good yields (entries 2 and 3). In both cases, a slight preference was observed for reaction at the C−H in the less hindered 2-position. Both the isoquinolonium and quinolonium ylides were viable partners (entries 4, 5), with the

dx.doi.org/10.1021/jo201303x |J. Org. Chem. 2011, 76, 8243–8261

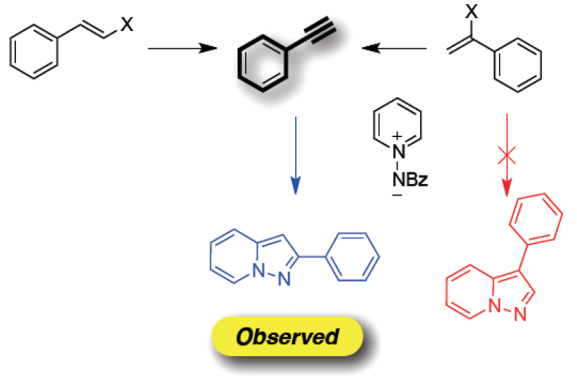
Table 6. Scope of Alternative Alkenyl Halides



entry[a]	halide	product	yield (%)[b]
1			49
	2v	**4o**	
2			62
	2w	**4p**	
3			0
	2x	**4q**	
4			0
	2y	**4r**	

[a] 1.5 equiv **1a** and 1 equiv of the halide were used. [b] Yield of isolated product.

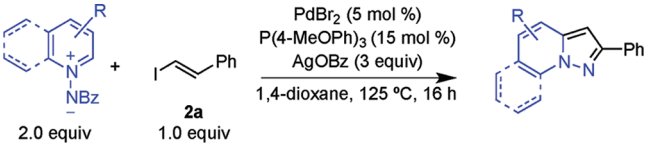
Scheme 4. Proposed Intermediate in the Synthesis of 2-Substituted Pyrazolopyridines

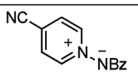
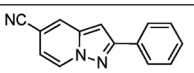
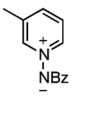
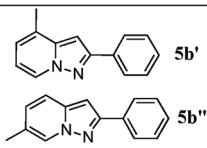
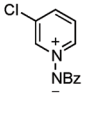
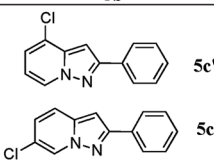
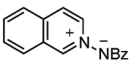
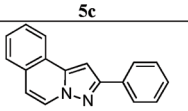
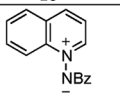
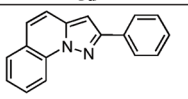
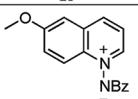
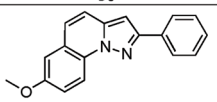
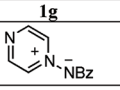
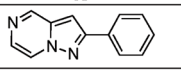


latter giving the pyrazolopyridine derivative in excellent yield. When the ylide derived from 6-methoxyquinoline was employed the yield decreased to 69% (entry 6), suggesting a possible effect of acidity at the 2-position of the ring in the transformation. Finally, pyrazine ylide **1h** furnished the desired 2-phenylpyrazolopyrazine in 69% yield (entry 7).

Mechanistic Investigations and Catalytic Cycle. Intriguingly, as noted in Table 5, both *E*-, *Z*-(β)-arylvinyl iodide and α-bromostyrene provided the same product, whereas the latter substrate was expected to provide the 3-substituted pyrazolo[1,5-*a*]pyridine (Scheme 4). We postulated that this could be the result of elimination of HBr from the vinyl bromide to provide phenylacetylene as a common reactive intermediate. To test this hypothesis, we first examined whether β-styryl iodide could be converted to phenyl acetylene under the reaction conditions in the absence of the pyridinium ylide (Table 8). When submitted to the full conditions, all of iodide **2a** was converted to the alkyne

Table 7. Scope of the Pyridinium in Coupling of Vinyl Halides



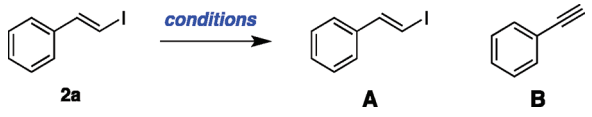
entry	ylide	product	yield (%)[a]
1			62
	1b	**5a**	
2		 **5b'** **5b"**	77 (3:1 **5b":5b')**
	1c	**5b**	
3		 **5c'** **5c"**	90 (3:1 **5c":5c')**
	1d	**5c**	
4			60
	1e	**5d**	
5			90
	1f	**5e**	
6			69
	1g	**5f**	
7			69
	1h	**5g**	

[a] Yield of isolated product.

(entry 1). When iodide **2a** was submitted to the conditions in the absence of silver benzoate, little of the iodide underwent elimination to the alkyne (entry 2). Likewise, when **2a** was mixed with the silver salt in the absence of palladium, the major product observed was indeed the recovered iodide (entry 3), indicating that the silver benzoate alone is insufficient to promote elimination. These results imply that the silver reagent is effective in dehalogenating the palladated alkene following oxidative addition by generating a highly reactive cationic palladium species that readily undergoes β-hydride elimination to form the alkyne (Scheme 5). Excess benzoate present in the reaction medium could deprotonate the palladium hydride, regenerating palladium(0) to resume the catalytic cycle.[21] In the absence of silver benzoate there is no driving force to coerce the elimination, and presumably the oxidative addition is reversible. Such a sequence would explain the decreased yields noted with the *Z*-alkenyl iodide, as rapid *syn* β-hydride elimination is

dx.doi.org/10.1021/jo201303x |*J. Org. Chem.* 2011, 76, 8243–8261

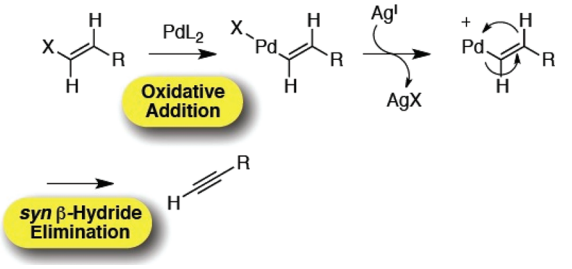
Table 8. Studies into the Fate of the Alkenyl Iodide under the Reaction Conditions



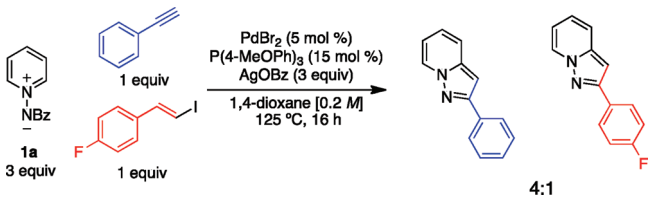
entry	conditions	product[a] (%)
1	iodide **2a** (1 equiv), $PdBr_2$ (5 mol %), $P(4\text{-MeOPh})_3$ (15 mol %), AgOBz (4 equiv), 1,4-dioxane (0.2 M), 125 °C, 16 h	**B** (>95)
2	iodide **2a** (1 equiv), $PdBr_2$ (5 mol %), $P(4\text{-MeOPh})_3$ (15 mol %), 1,4-dioxane (0.2 M), 125 °C, 16 h	**A** (84)
3	iodide **2a** (1 equiv), AgOBz (4 equiv), dioxane (0.2 M), 125 °C, 16 h	**A** (73)

[a] Yields of isolated product.

Scheme 5. Proposed Pathway to the Formation of Alkynes from Alkenyl Iodides



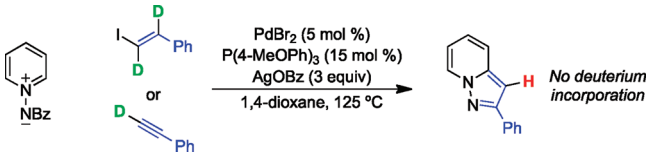
Scheme 6. Competition between 2p and Phenylacetylene



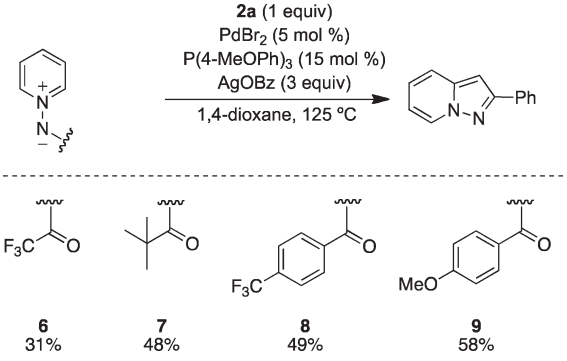
not possible. In addition, vinyl iodides bearing alkyl groups were nonoperative as the elimination to the alkyne was more difficult for these substrates.

Second, phenylacetylene was submitted instead of iodide **2a** under the standard conditions, and 2-phenylpyrazolopyridine was isolated in 56% yield (eq 1). The above results confirmed that the alkyne could be generated in situ and provided very strong evidence for the participation of an alkyne as a reaction intermediate when using vinyl halides. Following this positive result, a competition reaction was attempted between phenylacetylene and high-yielding 4-fluoro-β-styryl bromide **2p** (Scheme 6). The reaction displayed 4:1 selectivity toward the alkyne, suggesting that in the case of styryl halides, the reaction proceeds quickly once the alkyne is formed. Indeed, kinetic isotope effects of 1.7 and 1.5 were noted for **2a** and phenylacetylene, indicating that the C−H bond breaking event is not rate limiting and that the possible limiting step

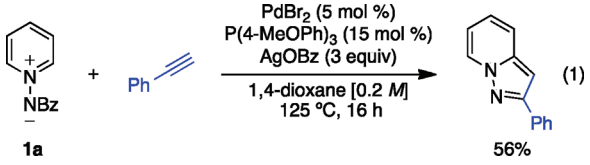
Scheme 7. Labeling Study in the Synthesis of 2-Substituted Pyrazolopyridines from Vinyl Iodides and Phenylacetylene



Scheme 8. Directing Group Effect on the Synthesis of Pyrazolopyridines



in the case of the alkenyl halides is the formation of the sp-hybrized intermediate.

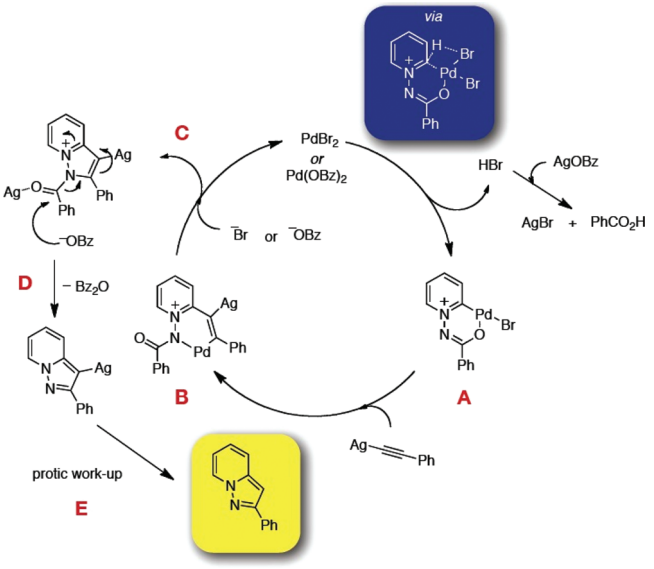


Next, a labeling study was undertaken to establish how the alkene might couple to the pyridinium ylide. Both deuterated (*E*)-β-styryl iodide and D-1-phenylacetylene were prepared and independently employed as substrates under the optimal reaction conditions (Scheme 7). No deuterium incorporation was observed in the final product with either substrate. This suggested that the actual reactive species involved in the C−H insertion may be fully eliminated and that the alkyne is deprotonated to form the silver acetylide.

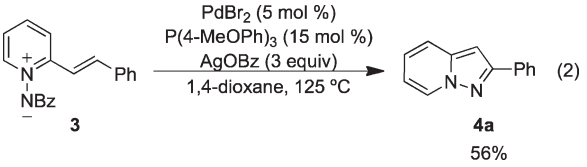
We next considered the coupling/cyclization sequence. The possibility of a formal [3 + 2] cyclization of the alkyne to the ylide was rapidly ruled out. First, precedent with analogous *N*-aminopyridinium salts indicates that the product of such a process would yield a 3-phenylpyrazolo[1,5-*a*]pyridine.[5] To lend weight toward this conclusion, the cyclization was attempted on the 2-vinylpyridinium ylide **3** accessed by our previously reported copper-catalyzed direct alkenylation reaction (eq 2).[14f] Indeed, when compound **3** was submitted to the complete reaction conditions, the 2-phenylpyrazolopyridine was isolated in 56% yield, suggesting that this could be a plausible intermediate, and importantly that coupling prior to cyclization is feasible. However, the reduced yield and the observation of unreacted ylide in the crude reaction mixture,[22] in addition to the fact that no alkenyl pyridine was ever observed during the reaction optimization, is consistent with an alternative mechanistic pathway via the alkyne. Interestingly, exclusion of either AgOBz or $PdBr_2$ led to no cyclization, implying that these reagents worked in concert to

dx.doi.org/10.1021/jo201303x |J. Org. Chem. 2011, 76, 8243–8261

Scheme 9. Proposed Catalytic Cycle



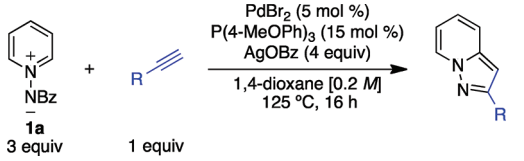
effect the transformation from **3**. Furthermore, the nature of the ylide group had a significant effect on yield (Scheme 8). While the benzoyl ylide **1a** proved to be most reactive, increasing the electron density of the ylide led to improved yields relative to when electron poor groups are present (**6** vs **7**, and **8** vs **9**). A reasonable explanation is the improved Lewis basicity of the carbonyl group, improving coordination to palladium and facilitating insertion of the palladium in the α-position of the heterocycle.

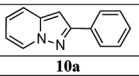
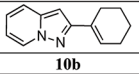
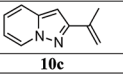
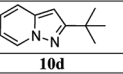
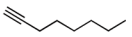
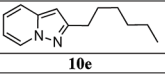
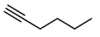
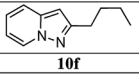
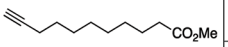
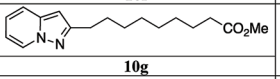
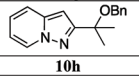
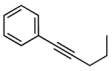
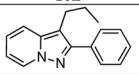


In our initial disclosure we proposed a catalytic cycle whereby a palladium-catalyzed direct alkenylation occurred followed by a silver-assisted cyclization.[16] Following the studies described here a revised cycle is proposed. First, $PdBr_2$ undergoes a directed insertion into the 2-position of the pyridinium ring (Scheme 9, A). This may happen via σ-bond metathesis,[17] generating HBr that can be buffered by the excess benzoate. The palladated ylide then may add across the silver acetylide giving the metallocycle **B**, analogous to Fujiwara-type alkynylation reactions.[23] The role of the silver may be to activate the triple bond.[24] It is possible that vinyl iodides bearing alkyl groups were nonoperative as the elimination to the alkyne is more difficult for these substrates. When it was demonstrated that the uncyclized 2-vinyl ylide could undergo the cyclization, similar Pd complexes had been reported, as has Pd-catalyzed conjugate addition of amines.[25] Reductive elimination (**C**) then gives the cyclic intermediate that rearomatizes through the expulsion of the benzoyl moiety (**D**). This may be assisted by the presence of Lewis acidic metal salts. Protonolysis of the C−Ag bond at C3 upon workup or from generated benzoic acids gives the observed product, explaining the lack or deuterium incorporation in the labeling studies (**E**).

Reaction Scope: Alkynes. As a result of the mechanistic studies, alkynes were identified as viable substrates for the reaction. We next considered the scope of these substrates cognizant that the

Table 9. Scope of Alkyne Coupling Partners



entry	alkyne	product	yield (%)[a]
1		 **10a**	76 (95)[b]
2		 **10b**	85
3		 **10c**	29
4		 **10d**	64
5		 **10e**	50
6		 **10f**	55
7		 **10g**	53
8		 **10h**	80
9		 **10i**	0

[a] Yields of isolated product. [b] Yield based on recovered starting material.

inclusion of alkynes may both increase the breadth of potential coupling partners and overcome some of the limitations of the vinyl halides. A short optimization sequence (Table S1, Supporting Information) improved the yield of the pyrazolopyridine from 56% to 76% by the inclusion of an extra 1 equiv of ylide and AgOBz. Here, the yield of pyrazolopyridine **4a** using phenylacetylene was comparable to that obtained with styryl iodide **2a** (76% vs 78%), providing a complementary set of reaction conditions. Most of the excess pyridinium ylide could be recovered furnishing a yield of 95% based on recovered starting material (Table 9, entry 1). It should also be noted that the reaction can be performed under microwave irradiation whereby 2-phenylpyrazolopyridine was obtained in 62% isolated yield after 30 min and 74% yield after 1 h at 125 °C. 1-Ethynylcyclohexene reacted to give the desired pyrazolopyridine in 85% yield (entry 2). The analogous 2-methyl-1-buten-3-yne only provided 29% of the product (entry 3), though the low yield may be attributed to the high volatility of the substrate. The use of alkynes permits the introduction of various 2-alkyl substituents with a variety of demands (entries 4−6). 3,3-Dimethyl-1-butyn, -1-octyne, and -1-hexyne all reacted in moderate yield, demonstrating the complimentarity of alkynes as substrates where alkyl substituted vinyl iodides were largely unreactive (Table 6). Methyl 10-undecynoate provided the product in 53% yield (entry 7), and protected alcohol was also operative (entry 8). Internal

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Table 10. Scope of the Pyridinium in the Synthesis of 2-Substituted Pyrazolopyridines from Alkynes

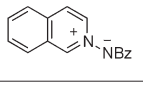
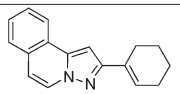
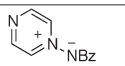
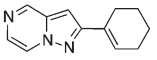
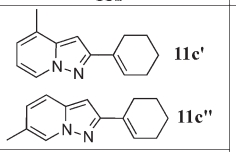
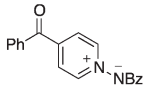
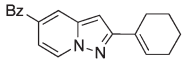
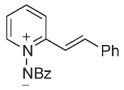
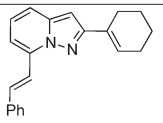
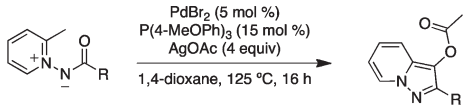
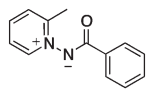
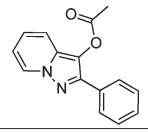
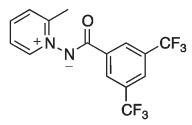
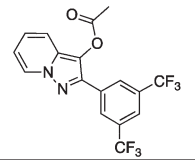
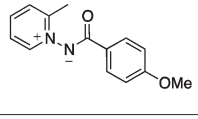
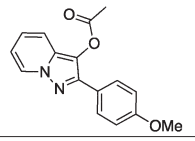
entry	ylide	product	yield (%)[a]
1			71
	1e	**11a**	
2			72
	1h	**11b**	
3		 **11c'** **11c"**	64 (3:1 **11c":11c'**)
	1c	**11c**	
4			45
	1i	**11d**	
5			21
	3	**11e**	

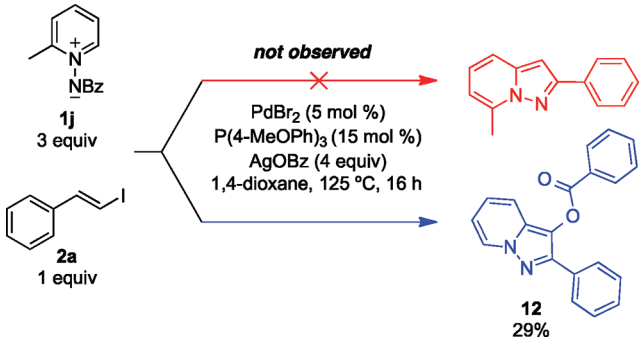
Table 11. Scope of 2,3-Disubstituted Pyrazolopyridines



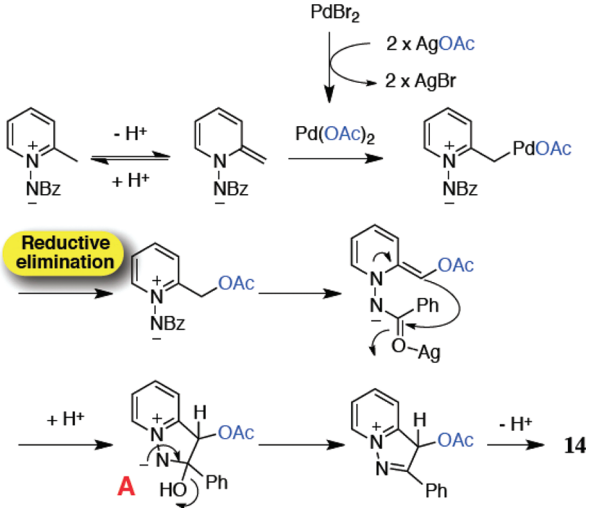
entry	pyridinium	product	yield (%)[a]
1			49
	13a	**14a**	
2			19
	13b	**14b**	
3			23
	13c	**14c**	

[a] Yields of isolated product.

Scheme 10. Synthesis of 2-Phenyl-3-acetylpyrazolopyridine



Scheme 11. Proposed Reaction Pathway in the Synthesis of 2,3-Disubstituted Pyrazolopyridines



alkynes remained inoperative, adding weight to the proposed requirement to form the silver acetylide.

The scope of the pyridinium ylide was investigated using 1-ethynylcyclohexene (Table 10). The isoquinolinium ylide reacted well, affording the product in 71% yield (entry 1), and the pyridazyl ylide **1h** also displayed similar reactivity (entry 2). As with the iodostyrene, substitution at the 3-position of the ylide gave the product in 64% yield as an inseparable 3:1 mixture favoring the least hindered adduct (entry 3). The 2-alkenyl ylide reacted in only 21% (entry 3), though competition with the intramolecular cyclization was noted.[26]

2-Picolonium Ylides. When the 2-picolonium ylide was applied in the reaction the anticipated methylated pyrazolopyridine was not observed. Instead the 2-phenyl, 3-acetyl pyrazolopyridine was isolated in 29% yield (Scheme 10). The structure of the product was confirmed through X-ray crystallography. The palladium catalyst and silver benzoate were both needed to effect the transformation, though **12** was still obtained without employing styryl iodide **2a**. Replacing AgOBz with AgOAc improved reaction yields to 49% (Table 11, entry 1), presumably due to the improved nucleophilicity of the acetate. Converting the benzoyl moiety to (3,5-trifluoromethyl)benzoyl or 4-methoxybenzoyl afforded the corresponding products in 19% and 22% yield (entries 2 and 3). To date, all efforts to improve the yields of these interesting 2,3-disubstituted products proved unsuccessful. The reaction is believed to proceed as illustrated in Scheme 11. With the large excess of acetate relative

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to palladium, it is likely that the metal undergoes ligand exchange to afford palladium acetate. The palladium(II) species then undergoes addition to the benzylic position of the picolonium ylide, presumably through an enamine intermediate due to the relative high acidity of the protons at that site, analogously to our previous report. With no electrophile present, and again due to the excess of acetate, reductive elimination occurs to give the acetoxy intermediate **A**.[27] An enamine intermediate can then be regenerated an undergo silver-promoted cyclization/condensation followed by rearomatization to give the observed product **14**.

CONCLUSION

In summary, we have presented novel, facile methods for the synthesis of 2-substituted pyrazolo[1,5-*a*]pyridines in two steps from pyridine. Previous methods to prepare these compounds either require multistep syntheses or require substitution on the 3-position of the product that would require further sequences for its removal. We solved these problems by developing an efficient cascade direct elimination/functionalization/cyclization process. As the two steps occur in tandem, the reaction is economical, and excess substrates employed can be recovered and reused. The scope of potential coupling partners tolerates a range of pyridinium species in conjunction with complementary vinyl iodides, bromides, and alkynes, which enable a wide range of groups to be installed onto the heterocyclic core. The flexibility of the reaction is likely due to the presence of a single reactive species, allowing chemists a wide choice of possible reagents in the preparation of these biologically relevant compounds.

EXPERIMENTAL SECTION

General Considerations. All reactions were run under anaerobic conditions (argon) with flame-dried glassware using standard techniques for manipulating air-sensitive compounds. Anhydrous solvents were obtained by filtration through drying columns or by distillation over sodium and calcium hydride. Flash column chromatography was performed using 230−400 mesh silica according to standard techniques. Nuclear magnetic resonance spectra were recorded either on 300 or 400 MHz spectrometers. Chemical shifts for ^{1}H NMR spectra are recorded in ppm from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ = 7.27 ppm). Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet and br = broad), coupling constant in Hz and integration. Chemical shifts for ^{13}C NMR spectra were recorded in ppm from tetramethylsilane using the central peak of deuterochloroform (77.36 ppm) as the internal standard. High-resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal. Combustion analyses were performed by the Laboratoire d'analyze élémentaire de l'Université de Montréal. Reagents: commercial reagents were used as supplied or purified by standard techniques where necessary.

General Procedure 1: Synthesis of Pyridinium Ylides. Pyridine derivative (1 equiv) and *O*-(2,4-dinitrophenyl)hydroxylamine (1.2 equiv) were added to H_2O/THF (1:1 mixture, 1.24 M). The reaction flask was sealed with a septum, and the resulting suspension was stirred at 40 °C for 16 h. During this period, the reaction mixture turned dark red. The reaction was poured into aqueous NaOH (2.5 N, 6 × vol) at room temperature and stirred for 5 min, and then acyl/aryl chloride (1.5 equiv) was added in one portion. After 5 h, the reaction was diluted with H_2O (5 × vol) and extracted with $CHCl_3$. The combined organic phases were washed with 2.5 N NaOH. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the *N*-iminobenzoylpyridinium ylide.

*N-Benzoyliminopyridinium Ylide (**1a**).* The title compound was prepared according to general procedure 1 using pyridine (1.24 mmol) and benzoyl chloride. Compound **1a** was isolated as a beige solid (236.0 mg, 96%). Characterization data was consistent with that reported in the literature:[15] mp 174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J = 5.9 Hz, 2H), 8.16 (d, J = 5.7 Hz, 2H), 7.87 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.0 Hz, 2H), 7.48−7.37 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 143.5, 137.4, 130.3, 128.1, 128.0, 126.1; IR (neat) 1548, 1465, 1332, 762, 710 cm^{-1}; HRMS calcd for $C_{12}H_{10}N_2O$ $[M]^+$ 198.0793, found 198.0798.

*4-Cyano-N-benzoyliminopyridinium Ylide (**1b**).* The title compound was prepared according to general procedure 1 using 4-cyanopyridine (1.24 mmol) and benzoyl chloride, but using a saturated aqueous $NaHCO_3$ solution instead of the aqueous NaOH solution. Compound **1b** was obtained as a beige solid (116.7 mg, 42%). Characterization data was consistent with that reported in the literature:[15] mp 184 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (d, J = 6.4 Hz, 2H), 8.15 (d, J = 7.3 Hz, 2H), 7.79 (d, J = 6.1 Hz, 2H), 7.49−7.40 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 142.4, 136.7, 131.3, 128.5 (2), 128.3, 117.2, 115.0; IR (neat) 3097, 3048, 2237, 1587, 1557, 1543, 1436, 1319, 1291, 1164, 704 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{13}H_9N_3O$ $[M + H]^+$ 224.1, found 224.1.

*3-Methyl-N-benzoyliminopyridinium Ylide (**1c**).* The title compound was prepared according to general procedure 1 using 3-picoline (1.24 mmol) and benzoyl chloride. Compound **1c** was obtained as a white solid (258.9 mg, 99%). Characterization data was consistent with that reported in the literature:[15] mp 142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.58 (d, J = 6.2 Hz,1H), 8.17−8.13 (m, 2H), 7.70 (d, J = 7.9 Hz, 1H), 7.54 (t, J = 6.5 Hz, 1H), 7.43−7.37 (m, 4H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 143.5, 140.8, 138.0, 137.4, 137.2, 130.3, 128.1, 128.0, 125.6, 18.7; IR (neat) 3055, 1592, 1548, 1334, 705 cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.49; H, 5.92; N, 13.02.

*3-Chloro-N-benzoyliminopyridinium Ylide (**1d**).* The title compound was prepared according to general procedure 1 using 3-chloropyridine (1.24 mmol) and benzoyl chloride. Compound **1d** was obtained as a beige solid (271.6 mg, 94%). Characterization data was consistent with that reported in the literature:[15] mp 129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s (br), 1H), 8.76 (d, J = 6.2 Hz, 1H), 8.13 (d, J = 6.4 Hz, 2H), 7.79 (d, J = 8.2 Hz, 1H), 7.51 (t, J = 6.6 Hz, 1H), 7.49−7.35 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 142.4, 141.0, 137.0, 136.3, 133.7, 130.5, 128.1, 128.0, 126.0; IR (neat) 3096, 1591, 1547, 1324, 711 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{12}H_9ClN_2O$ $[M + H]^+$ 233.0, found 233.0.

*N-Benzoyliminoisoquinolinium Ylide (**1e**).* The title compound was prepared according to general procedure 1 using isoquinoline (1.24 mmol) and benzoyl chloride, but adding benzoyl chloride first and letting it react for 30 min before addition of the aqueous NaOH solution. Compound **1e** was obtained as a beige solid (290.2 mg, 93%). Characterization data was consistent with that reported in the literature:[15] mp 174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 8.43 (d, J = 6.9 Hz, 1H), 8.23−8.20 (m, 2H), 8.08 (t, J = 8.3 Hz, 1H), 7.98 (t, J = 6.6 Hz, 1H), 7.91 (t, J = 7.3 Hz, 1H), 7.83 (t, J = 7.6 Hz, 1H), 7.46−7.42 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 145.2, 137.6, 136.5, 134.1, 133.5, 130.3, 130.1, 128.5, 128.1, 128.0, 126.9, 124.1; IR (neat) 3053, 1590, 1546, 1336, 1298, 908, 707 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{16}H_{13}N_2O$ $[M + H]^+$ 249.1, found 249.1.

*N-Benzoyliminoquinolinium Ylide (**1f**).* The title compound was prepared according to general procedure 1 using quinoline (1.24 mmol) and benzoyl chloride, but adding BzCl first and letting it react for 30 min before addition of the aqueous NaOH solution. Compound **1f** was

obtained as a beige solid (93%). Characterization data was consistent with that reported in the literature:[15] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (d, J = 5.9 Hz, 1H), 8.85 (d, J = 8.9 Hz, 1H), 8.45 (d, J = 8.4 Hz, 1H), 8.35−8.30 (m, 2H), 8.05 (d, J = 8.2 Hz, 1H), 7.94 (t, J = 7.3 Hz, 1H), 7.81 (t, J = 7.4 Hz, 1H), 7.73 (dd, J = 8.3, 5.9 Hz, 1H), 7.50−7.47 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 145.5, 139.5, 138.3, 137.5, 133.2, 130.1, 129.9, 129.2, 128.5, 128.1, 127.9, 120.3, 120.1; IR (neat) 3063, 1598, 1551, 1325, 1296, 714 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{16}H_{13}N_2O$ $[M + H]^+$ 249.1, found 249.1.

*6-Methoxy-N-benzoyliminoquinolinium Ylide (**1g**).* The title compound was prepared according to general procedure 1 using 6-methoxyquinoline (1.24 mmol) and benzoyl chloride, but adding BzCl first and letting it react for 30 min before addition of the aqueous NaOH solution. Compound **1g** was obtained as a beige solid (96%). Characterization data was consistent with that reported in the literature:[15] mp 129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (dd, J = 5.9, 1.3 Hz, 1H), 8.66 (d, J = 9.6 Hz, 1H), 8.32−8.25 (m, 3H), 7.59 (dd, J = 8.4, 5.9 Hz, 1H), 7.51−7.44 (m, 4H), 7.20 (d, J = 2.7 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 157.4, 144.3, 137.3, 135.6, 130.9, 130.0, 129.5, 128.5, 127.8, 125.7, 123.1, 120.1, 119.9, 56.5; IR (neat) 3088, 1566, 1553, 1330, 915, 722 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{17}H_{15}N_2O_2$ $[M + H]^+$ 279.31 m/z, observed 279.2 m/z.

*N-Benzoyliminopyrazinium Ylide (**1h**).* The title compound was prepared according to general procedure 1 using pyrazine (1.24 mmol) and benzoyl chloride. Compound **1h** was obtained as a beige solid (46%). Characterization data was consistent with that reported in the literature:[15] mp 121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (dd, J = 3.5, 1.4 Hz, 2H), 8.88 (dd, J = 3.5, 1.4 Hz, 2H), 8.19 (dd, J = 8.0, 1.3 Hz, 2H), 7.50−7.43 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 148.6, 136.6, 133.3, 131.4, 128.5, 128.3; IR (neat) 3060, 1607, 1590, 1557, 1424, 1315, 1283, 1184, 709 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{11}H_{10}N_3O$ $[M + H]^+$ 200.1, found 200.1.

*4-Benzoyl-N-benzoyliminopyridinium Ylide (**1i**).* The title compound was prepared according to general procedure 1 using 4-benzoylpyridine (1.24 mmol) and benzoyl chloride, but using a saturated aqueous $NaHCO_3$ solution instead of the aqueous NaOH solution. Compound **1i** was obtained as a beige solid (0.282 mg, 75%). Characterization data was consistent with that reported in the literature:[15] mp 179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, J = 7.1 Hz, 2H), 8.18 (dd, J = 7.6, 1.5 Hz, 2H), 7.92 (d, J = 7.1 Hz, 2H), 7.84−7.79 (m, 2H), 7.71 (t, J = 7.4 Hz, 1H), 7.57 (t, J = 7.8 Hz, 2H), 7.47−7.39 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 170.8, 142.9, 137.0, 135.2, 134.4, 132.9, 130.8, 130.2, 129.2, 128.3, 128.2, 126.0; IR (neat) 3106, 3080, 3049,1669, 1589, 1557, 1543, 1437, 1332, 1282, 1171, 713, 696 cm^{-1}; LRMS (APCI, Pos) calcd for $C_{19}H_{15}N_2O_2$ $[M + H]^+$ 303.1, found 303.1.

*N-Trifluoroacetyliminopyridinium Ylide (**6**).* Pyridine (1.24 mmol) and *O*-(2,4-dinitrophenyl) hydroxylamine (1.34 mmol) were mixed in MeCN (1 mL). The reaction vessel was sealed, and the reaction was stirred at 40 °C for 24 h. The reaction was concentrated, and the resulting residue was triturated in three times with Et_2O (10 mL). The resulting solid was filtered and dried under vacuum to afford the *N*-aminopyridinium salt (336 mg, 98% yield). The *N*-aminopyridinium salt (0.812 mmol) was suspended in dichloromethane (5 mL). To this was added K_2CO_3 (4.72 mmol) followed by trifluoroacetic anhydride (0.974 mmol). The resulting mixture was stirred for 15 h at room temperature, after which the solid was filtered. Concentration of the filtrate yielded **6** as a white solid (150 mg, 97% yield): mp 99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (d, J = 5.9 Hz, 2H), 8.10 (t, J = 7.7 Hz, 1H), 7.81 (t, J = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0 (q, J = 34 Hz), 160.1, 142.5, 138.6, 126.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.7; IR (neat) 3043, 1640, 1613, 1478, 1205, 1179, 1133, 771 cm^{-1}; HRMS Calcd for $C_7H_6F_3N_2O$ $[M + H]^+$ 191.04267, found 191.05622.

*N-Trimethylacetyliminopyridinium Ylide (**7**).* Pyridine (8.68 mmol) and *O*-(2,4-dinitrophenyl)hydroxylamine (9.38 mmol) were mixed in MeCN (15 mL). The reaction vessel was sealed, and the reaction was stirred at 40 °C for 24 h. The reaction was concentrated, and the resulting residue was triturated in three times with Et_2O (100 mL). The resulting solid was filtered and dried under vacuum to afford the *N*-aminopyridinium salt (2.23 g, 98% yield). The salt (2.00 g, 15.0 mmol) was dissolved in 10% aq NaOH (80 mL, 200.0 mmol) after which pivaloyl chloride (9.3 mL, 75.0 mmol) was added dropwise over 45 min. The solution was stirred for 20 h at room temperature, after which saturated aq NaCl was added. Extraction with CH_2Cl_2 (5 × 100 mL), drying with Na_2SO_4, and removal of the solvent under reduced pressure afforded **7** (2.67 g, 99% yield) as an off-white solid: mp 66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 5.1 Hz, 2H), 7.70 (t, J = 7.8 Hz, 1H), 7.44 (t, J = 7.0 Hz, 2H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.4, 143.4, 136.6, 125.6, 38.2, 28.2; IR (neat) 2955, 1556, 1392, 1213, 770, 680 cm^{-1}; LRMS (APCI, pos) calcd for $C_{10}H_{15}N_2O$ $[M + H]^+$ 179.1, found 179.1.

*N-(4-Trifluoromethylbenzoyl)iminopyridinium Ylide (**8**).* The title compound was prepared according to general procedure 1 using pyridine (1.24 mmol) and 4-(trifluoromethyl)benzoyl chloride. Compound **8** was obtained as a yellow solid (267.3 mg, 81%): mp 165−170 °C: R_f = 0.63 (CH_2Cl_2/MeOH, 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82−8.80 (m, 2H), 8.25 (d, J = 8.1 Hz, 2H), 7.97−7.91 (m, 1H), 7.68 (app dd, J = 14.3, 7.5 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 144.1, 141.6, 138.1, 132.5 (q, J = 32.1 Hz), 129.2, 127.0, 125.6 (q, J = 3.7 Hz), 125.1 (q, J = 272.1 Hz); IR (neat) 3114, 3074, 1820, 1595, 1558, 1321, 1067 cm^{-1}; HRMS calcd for $C_{13}H_{10}F_3N_2O$ $(M + H)^+$ 267.07397, found 267.07486.

*N-(4-Methoxybenzoyl)iminopyridinium Ylide (**9**).* The title compound was prepared according to general procedure 1 using pyridine (1.24 mmol) and 4-(methoxy)benzoyl chloride. Compound **9** was obtained as a yellow oil (144.9 mg, 51%): R_f = 0.46 (CH_2Cl_2/MeOH, 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (m, 2H), 8.09 (m, 2H), 7.82 (m, 1H), 7.57 (m, 2H), 6.89 (m, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 157.1, 147.0, 143.3, 136.7, 127.0, 123.6, 115.1, 56.3; IR (neat) 3130, 3038, 2837, 1648, 1505, 1468, 1284, 1179 cm^{-1}; HRMS calcd for $C_{13}H_{13}N_2O_2$ $(M + H)^+$ 229.09267, found 229.09337.

*2-Methyl-N-benzoyliminopyridinium Ylide (**13a**).* The title compound was prepared according to general procedure 1 using picoline (1.24 mmol) and benzoyl chloride. Compound **13a** was isolated as a white solid (98% yield). Characterization data was consistent with that reported in the literature:[15] mp 111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 6.2 Hz, 1H), 8.19−8.15 (m, 2H), 7.80 (dt, J = 7.7, 1.3 Hz, 1H), 7.56 (d, J = 7.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.43−7.38 (m, 3H), 2.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 154.3, 145.4, 137.8, 137.6, 130.5, 128.5, 128.4, 128.2, 128.1, 124.0, 19.9; IR (neat) 3054, 1593, 1553, 1491, 1330, 773, 707 cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.41; H, 6.09; N, 13.08.

*2-Methyl-N-(3,5-trifluoromethylbenzoyl)iminopyridinium Ylide (**13b**).* The title compound was prepared according to general procedure 1 using picoline (1.24 mmol) and 3,5-(trifluoromethyl)benzoyl chloride (1.84 mmol). Compound **13b** was isolated as a white solid (77% yield): R_f = 0.43 (CH_2Cl_2/MeOH, 95/5); mp 102−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 2H), 8.62 (d, J = 6.3 Hz, 1H), 7.97−7.93 (m, 2H), 7.69−7.67 (m, 1H), 7.63−7.59 (m, 1H), 2.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 153.7, 144.5, 139.6, 138.1, 131.0 (q, J = 33 Hz), 128.3, 127.9, 123.8, 123.45 (q, J = 272.7 Hz), 123.4 (sept, J = 3.8 Hz), 19.3; IR (neat) 3100, 2928, 1630, 1593, 1282, 1113, 905, 736; HRMS calcd for $C_{15}H_{11}F_6N_2O$ $(M + H)^+$ 349.07862, found 349.07701.

*2-Methyl-N-(4-methoxybenzoyl)iminopyridinium Ylide (**13c**).* The title compound was prepared according to general procedure 1 using picoline (1.24 mmol) and 4-methoxybenzoyl chloride. Compound **13c** was obtained as yellow oil (308.5 mg, 51%): R_f = 0.43 (CH_2Cl_2/MeOH, 9/1);

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63−8.61 (m, 1H), 8.16−8.12 (m, 2H), 7.86 (td, J = 7.8, 1.4 Hz, 1H), 7.61−7.59 (m, 1H), 7.55−7.50 (m, 1H), 6.95−6.92 (m, 2H), 3.86 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 162. 1, 154.9, 146.0, 138.0, 130.4, 128.4, 124.4, 113.9, 56.3, 20.4; IR (neat) 3391, 3072, 2962, 1590, 1540, 1342, 1247, 1027 cm^{-1}; HRMS calcd for $C_{14}H_{15}N_2O_2$ $(M + H)^+$ 243.11280, found 243.11377.

General Procedure 2: Synthesis of (*E*)-β-Aryl Vinyl Iodides from Benzyl Bromides and CH_2I_2. *Method A.* A solution of CH_2I_2 (483 mL, 6.0 mmol) in THF (1.5 mL) was added dropwise to a solution of NaHMDS (2.20 g, 12.0 mmol) in THF (8 mL) and ether (8 mL) at −78 °C (dry ice/acetone bath) in the dark. After 20 min, a solution of the benzyl bromide substrate (4.0 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred for 90 min and then removed from the cold bath to warm to rt. After 30 min, DBU (0.597 mL, 4.0 mmol) was added dropwise and the solution stirred for 1 h before ether (50 mL) was added. The mixture was filtered through a plug of Celite/silica (approximately 3 cm Celite over 3 cm silica) and the solvent removed under reduced pressure. The residue was purified by flash chromatography to provide the pure vinyl iodide.

Method B. A solution of CH_2I_2 (644 mL, 8.0 mmol) in THF (1.9 mL) was added dropwise to a solution of LiHMDS (1.34 g, 8.0 mmol) in THF (8 mL) and ether (8 mL) at −78 °C (dry ice/acetone bath) in the dark. After 20 min, a solution of the benzyl bromide substrate (4.0 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred at −78 °C and allowed to warm to rt slowly over 16 h. After this time, DBU (1.19 mL, 8.0 mmol) was added dropwise and the solution stirred for 1 h before ether (50 mL) was added. The mixture was filtered through a plug of Celite/silica (approximately 3 cm Celite over 3 cm silica) and the solvent removed under reduced pressure. The residue was purified by flash chromatography to provide the vinyl iodide. Where necessary, residual CH_2I_2 following flash chromatography was removed under high vacuum.

*(E)-(2-Iodovinyl)benzene (**2a**).* Prepared according to general procedure 2 (method A) starting from benzyl bromide (684 mg, 4.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded **2a** as a yellow oil (849 mg, 92%, 98:2 E/Z). Characterization data was consistent with that reported in the literature:[18b] R_f = 0.65 (hexanes, 100%); ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.44 (d, J = 14.9 Hz, 1H), 7.38−7.27 (m, 5H), 6.84 (dd, J = 14.9, 1.8 Hz, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 145.0, 137.6, 128.7, 128.4, 126.0, 76.7; IR (neat) 3059, 3021, 1595, 1494, 1444, 1210, 1169, 1070, 945, 726, 688 cm^{-1}.

*(Z)-1-Iodo-2-phenylethene (**2b**).* Iodomethylenetriphenylphosphorane (0.550 g, 1.0 mmol, 1.2 equiv) was added to a flame-dried flask with stir bar. The flask was sealed with a septum, purged with argon, and suspended in THF (2.3 mL). NaHMDS (1 mL of a 1 M solution) was added slowly, and the resulting solution was cooled to −60 °C. HMPA (0.3 mL) was added, and the solution was cooled further to −78 °C. Benzaldehyde (0.082 mL, 0.8 mmol, 1 equiv) was added, and the mixture was stirred at −78 °C for 1 min and then allowed to warm to rt over 35 min. Et_2O (20 mL) was added, and the mixture was filtered over Celite. Purification by chromatography yielded **2b** as a yellow liquid (0.132 g, 72%). Characterization data was consistent with that reported in the literature:[18b] R_f = 0.72 (hexanes, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.60 (m, 2H), 7.39−7.34 (m, 3H), 7.30 (d, J = 8.5 Hz, 1H), 6.56 (d, J = 8.5 Hz, 1H).

*1,3-Bis-((E)-2-iodovinyl)benzene (**2f**).* Prepared according to general procedure 2, method A.

*(E)-2-(2-Iodovinyl)naphthalene (**2g**).* Prepared according to general procedure 2 (method A) starting from 2-(bromomethyl)napthylene (884 mg, 4.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded **2g** as a yellow solid (782 mg, 70%, 98:2 E/Z). Characterization data was consistent with that reported in the literature:[18b] R_f = 0.53 (hexanes, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81−7.75 (m, 3H), 7.65 (s, 1H), 7.56 (d, J = 14.9 Hz, 1H), 7.46 (m, 3H), 6.94 (d, J = 14.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 135.0, 133.3, 133.1, 128.4, 128.2, 127.7, 126.6, 126.4, 126.2, 122.7, 77.0; IR (neat) 3049, 1599, 1585, 1507, 1433, 1293, 1216, 952, 765, 735 cm^{-1}.

*(E)-1-(2-Iodovinyl)-2-methylbenzene (**2h**).* Prepared according to general procedure 2 (method A) starting from 2-methylbenzyl bromide (740 mg, 4.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded **2h** as an off-white solid (879 mg, 90%, 99:1 E/Z). Characterization data was consistent with that reported in the literature:[18b] R_f = 0.63 (hexanes, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J = 14.7 Hz, 1H), 7.32−7.11 (m, 4H), 6.68 (d, J = 14.7 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 136.9, 134.7, 130.3, 128.2, 126.2, 125.6, 77.7, 19.7; IR (neat) 3055, 3017, 2921, 1587, 1562, 1479, 1457, 1379, 1280, 1190, 947, 740 cm^{-1}.

*(E)-1-(2-Iodovinyl)-4-methylbenzene (**2i**).* Prepared according to general procedure 2 (method A) starting from 4-methylbenzyl bromide (740 mg, 4.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded **2i** as an off-white solid (906 mg, 93%, 99:1 $E/$). Characterization data was consistent with that reported in the literature:[18b] R_f = 0.54 (hexanes, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 14.9 Hz, 1H), 7.21−7.13 (m, 4H), 6.75 (d, J = 14.9 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 138.2, 134.9, 129.3, 125.8, 75.4, 21.3; IR (neat) 3053, 3029, 2915, 2859, 1608, 1591, 1561, 1509, 1379, 1280, 1189, 1172, 958, 765 cm^{-1}.

*(E)-1-(2-Iodovinyl)-2-methoxybenzene (**2k**).* Prepared according to general procedure 2 (method B) starting from 2-methoxybenzyl bromide (804 mg, 4.0 mmol). Purification by flash chromatography (hexanes/Et_2O, 95/5) afforded **2k** as a yellow oil (784 mg, 75%, 98:2 $E/$). Characterization data was consistent with that reported in the literature:[14f] R_f = 0.68 (Et_2O/hexanes, 5/95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 14.9 Hz, 1H), 7.29 (t, J = 7.7 Hz, 2H), 6.97−6.88 (m, 3H), 3.88 (s, 3H).

*(E)-1-(2-Iodovinyl)-3-methoxybenzene (**2l**).* Prepared according to a modification of general procedure 2 (method A) starting from 3-methoxybenzyl bromide (834 mg, 4.1 mmol) and employing excess DBU (900 μL, 6.0 mmol). Purification by flash chromatography (hexanes/Et_2O, 95/5) afforded **2l** as a yellow oil (1.038 g, 95%, 99:1 E/Z). Characterization data was consistent with that reported in the literature:[18b] R_f = 0.70 (hexanes/Et_2O, 95/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 14.9 Hz, 1H), 7.27 (t, J = 7.9 Hz, 1H), 6.93−6.85 (m, 4H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 144.7, 138.8, 129.6, 118.5, 113.9, 111.2, 77.1, 55.2; IR (neat) 3057, 2999, 1596, 1572, 1490, 1428, 1313, 1284, 1261, 1152, 1048, 944, 757, 684 cm^{-1}; HRMS calcd for C_9H_9IO $[M + H]^+$ 259.9693, found 259.9691.

*(E)-1-(2-Iodovinyl)-4-benzyloxybenzene (**2n**).* Prepared according to a modification of general procedure 2 (method B) starting from 1-(benzyloxy)-4-(bromomethyl)benzene (1.11 g, 4.0 mmol) and employing excess DBU (1.8 mL, 12.0 mmol). Purification by flash chromatography (hexanes/Et_2O, 99/1) afforded **2n** as an off-white solid (1.02 g, 76%, 99:1 E/Z). Characterization data was consistent with that reported in the literature:[18b] R_f = 0.18 (hexanes/Et_2O, 99/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.32 (m, 6H), 7.24−7.19 (m, 2H), 6.94−6.90 (m, 2H), 6.62 (d, J = 14.9 Hz, 1H), 5.05 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 144.2, 136.6, 130.9, 128.6, 128.0, 127.44, 127.26, 115.0, 73.8, 70.0; IR (neat) 3054, 2932, 2868, 1600, 1508, 1454, 1377, 1281, 1181, 947, 836, 768, 747, 735 cm^{-1}; HRMS calcd for $C_{15}H_{13}IOAg$ $[M + Ag]^+$ 442.9057, found 442.9063.

*(E)-4-(2-Iodovinyl)benzonitrile (**2o**).* Prepared according to general procedure 2 (method B) starting from 4-(bromomethyl)benzonitrile 756 mg, 4.0 mmol). Purification by flash chromatography (hexanes/Et_2O, 9/1) afforded **2o** as a pale yellow solid (843 mg, 51%, 99:1 E/Z). Characterization data was consistent with that reported in the literature:[18b] R_f = 0.34 (hexanes/Et_2O 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−7.56 (m, 2H), 7.40 (d, J = 15.0 Hz, 1H), 7.35−7.33 (m, 2H),

7.06 (d, J = 15.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 141.4, 132.5, 126.3, 118.5, 111.5, 81.7; IR (neat) 3242, 3048, 2221, 1601, 1407, 1173, 937, 771 cm^{-1}; HRMS calcd for C_9H_6INAg $[M + Ag]^+$ 361.8590, found 361.8596.

*(E)-1-Fluoro-4-(2-iodovinyl)benzene (**2p**).* Prepared according to general procedure 2 (method A) starting from 4-fluorobenzyl bromide (756 mg, 4.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded **2p** as a yellow solid (843 mg, 85%, 98:2 E/Z). Characterization data was consistent with that reported in the literature:[18b] R_f = 0.66 (hexanes, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 14.9 Hz, 1H), 7.27−7.22 (m, 2H), 7.02−6.95 (m, 2H), 6.73 (dd, J = 14.9, 0.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (d, J = 249 Hz), 143.7, 133.9 (d, J = 3 Hz), 127.6 (d, J = 8 Hz), 115.7 (d, J = 22 Hz), 76.1 (d, 2.5 Hz); IR (neat) 3056, 1598, 1578, 1505, 1230, 1172, 1157, 949, 837, 769 cm^{-1}; HRMS calcd for C_8H_6FI $[M]^+$ 247.9493, found 247.9493.

*(E)-1-Chloro-2-(2-iodovinyl)benzene (**2r**).* Prepared according to general procedure 2 (method A) starting from 2-chlorobenzyl bromide (823 mg, 4.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded **2r** as a yellow oil (816 mg, 78%, 98:2 E/Z). Characterization data was consistent with that reported in the literature:[18b] R_f = 0.75 (hexanes, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 14.9 Hz, 1H), 7.42−7.33 (m, 2H), 7.26−7.21 (m, 2H), 6.90 (d, J = 14.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 135.6, 132.0, 129.9, 129.2, 126.9, 126.7, 79.6; IR (neat) 3057, 1590, 1466, 1438, 1274, 1180, 1051, 946, 747 cm^{-1}; HRMS calcd for C_8H_6ClI $[M]^+$ 263.9197, found 263.9200.

*(E)-1-Bromo-2-(2-iodovinyl)benzene (**2s**).* Prepared according to general procedure 2 (method B) starting from 2-bromobenzyl bromide (1.0 g, 4.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded **2s** as a yellow oil (1.09 g, 87%, 98:2 E/Z). Characterization data was consistent with that reported in the literature:[18b] R_f = 0.48 (hexanes, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 14.8 Hz, 1H), 7.55 (dd, J = 7.9, 1.3 Hz, 1H), 7.40 (dd, J = 7.9, 1.7 Hz, 1H), 7.30−7.26 (m, 1H), 7.16 (td, J = 7.7, 1.7 Hz, 1H), 6.86 (d, J = 14.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 137.5, 132.9, 129.5, 127.6, 127.0, 122.3, 79.9; IR (neat) 3056, 1587, 1461, 1027, 945, 743 cm^{-1}.

*(E)-1-Bromo-3-(2-iodovinyl)benzene (**2u**).* Prepared according to general procedure 2 (method B) starting from 3-bromobenzyl bromide (1.0 g, 4.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded **2u** as a yellow oil (1.08 g, 87%, 98:2 E/Z). Characterization data was consistent with that reported in the literature:[18b] R_f = 0.56 (hexanes, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.37 (m, 2H), 7.33 (d, J = 14.9 Hz, 1H), 7.20−7.14 (m, 2H), 6.87 (d, J = 14.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 139.4, 131.1, 130.1, 128.8, 124.5, 122.8, 78.7; IR (neat) 3056, 1590, 1557, 1474, 1209, 1071, 942, 755 cm^{-1}.

*Ethyl (2E,4Z)-5-Iodopenta-2,4-dienoate (**2v**).* To a solution of ethyl (*Z*)-β-iodoacrylate (5.0 mL, 39 mmol, 1 equiv) in CH_2Cl_2 (90 mL) at −78 °C was added DIBAL (43 mmol, 1.1 equiv) over 10 min. After being stirred for 5 min, the reaction was quenched with MeOH (7.0 mL), followed by aqueous sodium potassium tartrate (200 mL). Following warming to room temperature, Et_2O (100 mL) was added, and the mixture was stirred for 1 h and then further diluted with Et_2O and water (50 mL). The organic layer was separated, and the aqueous phase was extracted with Et_2O (4 × 80 mL). The combined organic extracts were washed with brine, dried with K_2CO_3, and concentrated to give the crude aldehyde. Separately, trimethyl phosphonoacetate (8.20 mL, 41 mmol, 1.1 equiv) in THF (80 mL) was cooled to −78 °C. To this solution was added *n*-BuLi (1.7 M in hexanes, 41 mmol, 1.1 equiv), and the solution was stirred for 30 min. The previously prepared aldehyde in THF (40 mL) was then added via cannula. The reaction mixture was allowed to warm to rt over 2 h and then stirred at rt for 1 h after which Et_2O/water (50/50, 100 mL) was added. The organic layer was separated, and the aqueous phase was extracted 4× with Et_2O. The combined organic extracts were washed with brine, dried with Mg_2SO_4, concentrated, and purified via column chromatography (petroleum ether/EtOAc, 95/5) to give **2v** as a yellow liquid (9:1 E/Z). Characterization data was consistent with that reported in the literature:[14f] R_f = 0.41 (petroleum ether/EtOAc, 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (ddd, J = 15.2, 10.3, 0.9 Hz, 1H), 6.90 (ddd, J = 11.2, 7.7, 0.8 Hz, 1H), 6.82 (ddd, J = 7.9, 0.8, 0.8 Hz, 1H), 6.10 (ddd, J = 15.2, 0.7, 0.7 Hz, 1H), 4.23 (q, J = 7.3 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H).

*(E)-(2-(2-Iodovinyl)cyclopropyl)benzene (**2w**).* A stirred solution of DME (7.7 mL, 74.5 mmol, 2 equiv) in CH_2Cl_2 (170 mL) was cooled to −15 °C. $ZnEt_2$ (7.6 mL, 74.5 mmol, 2 equiv) was added dropwise while the temperature of the solution was maintained below −14 °C. CH_2I_2 (12.0 mL, 149.0 mmol, 4 equiv) was added dropwise, maintaining the reaction temperature below −6 °C. After the mixture was stirred for 10 min, a solution of cinnamyl alcohol (5.0 g, 37.3 mmol, 1 equiv) in CH_2Cl_2 (30 mL) was added dropwise, keeping the reaction temperature below −5 °C. The reaction was allowed to stir and warm to room temperature over 16 h after which time saturated NH_4Cl solution (50 mL) was added followed by aqueous HCl (10%, 100 mL). The mixture was diluted with Et_2O (300 mL), and then the organic layer was separated, washed with Na_2SO_3, $NaHCO_3$, and saturated NaCl solutions, dried over $MgSO_4$, and concentrated. The crude cyclopropane was purified with column chromatography (30% EtOAc/hexanes). To remove residual unreacted cinnamyl alcohol following chromatography, the product was dissolved in actone/water (1:1, 184 mL), and then NMO (6.5 g, 55 mmol, 1.5 equiv) and OsO_4 (0.061 M in *t*-BuOH, 15 mL, 2.5 mol %) were added. The reaction was stirred in the dark for 16 h and then diluted with Et_2O and washed with Na_2SO_3 (100 mL). The organic layer was removed, and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with $NaHCO_3$ (100 mL) and brine, dried over $MgSO_4$, and purified by column chromatography (hexanes/EtOAc, 7/3) to give *trans*-2-phenylcyclopropylmethanol (3.85 g, 26 mmol, 70%).

PCC (1.02 g, 4.8 mmol, 1.1 equiv) was added to a solution of *trans*-2-phenylcyclopropylmethanol (0.630 g, 4.2 mmol, 1 equiv) in CH_2Cl_2 (25 mL). The solution was stirred for 14 h and filtered through silica and Celite (hexanes/EtOAc, 7/3) to afford the cyclopropyl aldehyde (0.513 g, 3.6 mmol, 88%).

$CrCl_2$ (3.10 g, 25.2 mmol, 7 equiv) was dissolved in THF (20 mL) and the mixture cooled to 0 °C. The previously prepared cyclopropyl aldehyde (0.513 g, 3.6 mmol, 1 equiv) and iodoform (2.83 g, 7.2 mmol, 2 equiv) were dissolved in THF (15 mL). The aldehyde/iodoform solution was added to the $CrCl_2$ solution at 0 °C via syringe, and the mixture was allowed to stir for 3 h. Water (100 mL) was added, and the organic layer was separated. The aqueous phase was extracted with Et_2O (3 × 100 mL), and the combined organic layers were dried with Na_2SO_4, concentrated, and purified by column chromatography (hexanes, 100%) to afford the title compound **2w** as a colorless oil (0.608 g, 61%, 7.5:1 E/Z). Characterization data was consistent with that reported in the literature:[14f] R_f = 0.55 (hexanes, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (t, J = 7.3 Hz, 2H), 7.20 (d, J = 7.3 Hz, 1H), 7.09 (d, J = 7.3 Hz, 2H), 6.20 (dd, J = 14.4, 8.8 Hz, 1H), 6.04 (d, J = 14.4 Hz, 1H), 2.03 (m, 1H), 1.74 (m, 1H), 1.29 (m, 1H), 1.18 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 141.3, 128.4, 125.9, 125.7, 71.8, 29.5, 24.7, 16.1; IR (neat) 3025, 1604, 1495, 1458, 1277, 1199, 1180, 1127, 1073, 942 cm^{-1}; GCMS calcd for $C_{11}H_{11}I$ 269.99, found 270.01.

*1-Iodocyclohexene (**2x**).* Cyclohexanone (5.2 mL, 50 mmol, 1 equiv) was added dropwise over 5−10 min to hydrazine monohydrate (15 mL, 310 mmol, 6 equiv) with vigorous stirring. A white precipitate formed, and the reaction mixture was refluxed at 150 °C for 2 h. The mixture was cooled to room temperature, and then water (100 mL) was added. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried with Na_2SO_4, and concentrated to give the crude hydrazone. Tetramethylguanidine (37 mL, 300 mmol, 6 equiv) in THF (55 mL) was added to iodine (14 g, 300 mmol, 6 equiv)

in THF (80 mL). The resulting solution was added via cannula to the crude hydrazone (2.8 g) in THF (25 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight, refluxed for 2 h at 85 °C, and then cooled to room temperature. The organic layer was washed with aqueous HCl (1 M, 100 mL) and saturated NaCl solution. The aqueous layer was extracted with Et_2O (2 × 100 mL), dried with $MgSO_4$, concentrated, and purified via column chromatography (hexanes, 100%) to give **2x** as a colorless oil (0.970 g, 20% over two steps). Characterization data was consistent with that reported in the literature:[28] R_f = 0.8 (hexanes, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (m, 1H), 2.51 (m, 2H), 2.10 (m, 2H), 1.60−1.70 (m, 4H).

*1-Iodopentene (**2y**).* To a flame-dried round-bottomed flask were added pentyne (4.2 mL, 42.6 mmol, 1.0 equiv) and hexanes (50 mL). The solution was cooled to −78 °C after which DIBAL (9.5 mL, 53.3 mmol, 1.3 equiv) was added over 30 min. The reaction temperature was warmed to rt overnight and then cooled to −78 °C. Iodine (13.8 g, 54.3 mmol, 1.3 equiv) was dissolved in THF (50 mL) and added via syringe. The solution was allowed to stir at −78 °C for 30 min and allowed to stir at rt for 1 h. The solution was poured onto 100 mL of iced 1 M HCl, and an additional 100 mL 1 M HCl was added. The organic layer was separated, and the aqueous phase was extracted with 3 × 100 mL of pentane. The organic layers were combined, washed with satd $NaHCO_3$ solution (2 × 100 mL), satd $Na_2S_2O_3$ solution (2 × 100 mL), and satd NaCl solution (2 × 100 mL), and then dried with $MgSO_4$. Filtration through a pad of silca and concentration afforded **2y** as a clear liquid (1.92 g, 9:1 *E*/*Z*, 25%). Characterization data was consistent with that previously reported in the literature:[29] R_f = 0.81 (hexanes, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (dt, J = 14.5, 1.5 Hz, 1H), 5.96 (dt, J = 14.5, 1.5 Hz, 1H), 2.03 (m, 2H), 1.43 (s, J = 7.5 Hz, 2H), 0.91 (t, J = 7.5 Hz, 3H).

General Procedure 3: Synthesis of (*E*)-β-Aryl Vinyl Bromides from Benzyl Bromides and CH_2Br_2. Dibromomethane (281 μL, 4 mmol) was added dropwise to a solution of NaHMDS (550 mg, 3.0 mmol) in THF (2 mL) and ether (2 mL) at −78 °C (dry ice/acetone bath) in the dark. After 20 min, a solution of the benzyl bromide substrate (1.0 mmol) in THF (1 mL) was added dropwise. The reaction mixture was maintained at −78 °C for at least 3 h, stirring was continued at −78 °C, and then the mixture was allowed to warm to rt slowly over 16 h. Ether (50 mL) was added, and then the mixture was filtered through a plug of Celite/silica (approximately 3 cm Celite over 3 cm silica) and the solvent removed under reduced pressure. The residue was purified by flash chromatography to provide the vinyl bromide.

*(E)-(2-Bromovinyl)benzene (**2c**).* Prepared according to general procedure 3 starting from benzyl bromide (171 mg, 1.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded **2c** as a colorless oil (127 mg, 69%, 99:1 *E*/). Characterization data was consistent with that reported in the literature:[18b] R_f = 0.60 (hexanes, 100%); ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.37−7.29 (m, 5H), 7.12 (d, J = 14.0 Hz, 1H), 6.78 (d, J = 14.0 Hz, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 137.1, 135.9, 128.8, 128.2, 126.1, 106.5; IR (neat) 3074, 3024, 1607, 1445, 730 cm^{-1}.

*(E)-1-(2-Bromovinyl)-4-methylbenzene (**2j**).* Prepared according to general procedure 3 for vinyl bromides starting from 4-methylbenzyl bromide (186 mg, 1.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded **2j** as a white solid (179 mg, 91%, >99:1 *E*/*Z*). Characterization data was consistent with that previously reported in the literature:[18b] R_f = 0.59 (hexanes, 100%); ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.24−7.12 (m, 4H), 7.08 (d, J = 14.0 Hz, 1H), 6.71 (d, J = 14.0 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 138.1, 136.9, 133.1, 129.4, 125.9, 105.4, 21.2; IR (neat) 3070, 2914, 1602, 1509, 1226, 1194, 949, 907, 825, 769, 725 cm^{-1}.

*(E)-1-(2-Bromovinyl)-4-methoxybenzene (**2m**).* Prepared according to the general procedure for vinyl bromides starting from 4-methoxybenzyl bromide (201 mg, 1.0 mmol). Purification by flash chromatography (hexanes/Et_2O, 95/5) afforded **2m** as a white solid (153 mg, 72%, >99:1 *E*:*Z*). Characterization data was consistent with that reported in the literature:[18b] R_f = 0.46 (hexanes/Et_2O, 95/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24−7.20 (m, 2H), 7.02 (d, J = 13.9 Hz, 1H), 6.85−6.82 (m, 2H), 6.59 (d, J = 13.9 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 136.4, 128.6, 127.2, 114.1, 103.9, 55.2; IR (neat) 3067, 2932, 2837, 1605, 1510, 1460, 1254, 1177, 1028, 776 cm^{-1}.

*(E)-1-Fluoro-4-(2-bromovinyl)benzene (**2q**).* Prepared according to the general procedure for vinyl bromides starting from 4-fluorobenzyl bromide (189 mg, 1.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded **2q** as a colorless oil (159 mg, 79%, >99:1 *E*/*Z*). Characterization data was consistent with that reported in the literature:[18b] R_f = 0.53 (hexanes, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.22 (m, 2H), 7.07−6.97 (m, 3H), 6.67 (dd, J = 14.0, 0.4 Hz, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 162.6 (d, J = 248 Hz), 136.0, 132.1 (d, J = 3 Hz), 127.7 (d, J = 8 Hz), 115.8 (d, J = 22 Hz), 106.9 (d, 2.5 Hz); IR (neat) 3056, 1590, 1557, 1474, 1421, 1209, 1071, 942, 755 cm^{-1}.

*(E)-1-Bromo-2-(2-bromovinyl)benzene (**2t**).* Prepared according to the general procedure for vinyl bromides starting from 2-bromobenzyl bromide (250 mg, 1.0 mmol). Purification by flash chromatography (hexanes, 100%) afforded **2t** as a colorless oil (175 mg, 67%, >99:1 *E*/*Z*). Characterization data was consistent with that reported in the literature:[18b] R_f = 0.56 (hexanes, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.52 (m, 1H), 7.42 (d, J = 13.9 Hz, 1H), 7.38−7.35 (m, 1H), 7.28−7.23 (m, 1H), 7.16−7.11 (m, 1H), 6.74 (d, J = 13.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2, 135.9, 133.1, 129.6, 127.6, 127.1, 122.7, 109.2; IR (neat) 3069, 1603, 1463, 1435, 1219, 1020, 931, 740 cm^{-1}

*(E)-(2-Chlorovinyl)benzene (**2e**).* Chloroiodomethane (109 μL, 1.5 mmol) was added dropwise to a solution of NaHMDS (550 mg, 3.0 mmol) in THF (2 mL) and ether (2 mL) at −78 °C (dry ice/acetone bath) in the dark. After 20 min, a solution of the benzyl bromide (171 mg, 1.0 mmol) in THF (1 mL) was added dropwise. The reaction mixture was stirred at −78 °C, and then the mixture was allowed to warm to rt slowly over 16 h. Ether (50 mL) was added, the mixture was filtered through a plug of Celite/silica (approximately 3 cm Celite over 3 cm silica), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes, 100%) to provide **2e** as a colorless oil (123 mg, 89%, 97:3 *E*/*Z*. Characterization data was consistent with that reported in the literature:[18b] R_f = 0.60 (hexanes, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.26 (m, 5H), 6.86 (d, J = 13.7 Hz, 1H), 6.66 (dd, J = 13.7, 0.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 133.2, 128.7, 128.1, 126.1, 118.7; IR (neat) 3076, 3025, 1607, 1573, 1497, 1446, 1245, 1073, 936, 737, 691 cm^{-1}.

General Procedure 4: Synthesis of 2-Substituted Pyrazolo-[1,5-*a*]pyridines from Vinyl Halides. To a 3 mL conical microwave vial equipped with a spin vane was added pyridinium ylide (1.0 mmol, 2 equiv). In a glovebox were added *p*-tris(methoxyphenyl)phosphine (0.15 equiv), palladium bromide (0.05 equiv), and silver benzoate (1.5 mmol, 3 equiv), and the microwave vial was crimped shut. The alkenyl iodide derivative (0.5 mmol, 1 equiv) was dissolved in 1,4-dioxane (0.5 mL) and added via syringe. The syringe was rinsed three times with 0.5 mL of dioxane to reach a final volume of 2 mL. The solution was heated to 125 °C with fast stirring. Within 5 min, a color change was observed. The mixture was stirred for 16 h and then cooled to room temperature. Dichloromethane was added, and the precipitate was filtered through a cotton plug and washed with dichloromethane. Saturated sodium bicarbonate was added, and the organic phase was extracted with dichloromethane (3 × 50 mL). The solution was dried with Na_2SO_4, concentrated under reduced pressure, and purified via column chromatography to afford the title compounds.

*2-Phenylpyrazolo[1,5-a]pyridine (**4a**).* The title compound was prepared according to general procedure 4 using 0.5 mmol of (*E*)-(2-iodovinyl)benzene. Purification by column chromatography (CH_2Cl_2/hexanes, 95/5) afforded **4a** as a light yellow powder (75.3 mg, 78%).

Characterization data was consistent with that reported in the literature:[16] R_f = 0.79 (CH_2Cl_2, 100%); mp 110−113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 6.9 Hz, 1H), 7.97 (d, J = 7.5 Hz, 2H), 7.54−7.34 (m, 3H), 7.08 (t, J = 7.8 Hz, 1H), 6.80 (s, 1H), 6.73 (t, J = 6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 142.5, 134.2, 129.4, 129.3, 129.2, 124.2, 122.3, 118.7, 112.7, 94.4; IR (neat) 3086, 1630, 1508, 1467, 1327, 763, 688 cm^{-1}; HRMS calcd for $C_{13}H_{11}N_2$ $[M + H]^+$ 195.09167, found 195.09088.

*1,3-Di(pyrazolo[1,5-a]pyridin-2-yl)benzene (**4b**).* The title compound was prepared according to General Procedure 4 using 0.244 mmol of **2f**. Purification by column chromatography (toluene/EtOAc, 6/4) afforded **4b** as a light yellow oil in (75.3 mg, 40%): R_f = 0.80 (toluene/EtOAc, 6/4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58−8.57 (m, 1H), 8.54 (dd, J = 7.0, 1.0 Hz 2H), 8.00 (dd, J = 7.7, 1.7 Hz 2H), 7.59−7.54 (m, 3H), 7.15−7.11 (m, 2H), 6.93−6.92 (s, 2H), 6.79−6.75 (dt, J = 6.9, 1.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 141.2, 133.4, 128.9, 128.2, 126.1, 124.3, 123.0, 117.6, 111.4, 93.6; IR (neat) 3077, 2975, 1634, 1256, 770 cm^{-1}; HRMS calcd for $C_{20}H_{15}N_4$ $[M + H]^+$ 311.12912, found 311.12912.

*2-(Naphthalen-2-yl)pyrazolo[1,5-a]pyridine (**4c**).* The title compound was prepared according to general procedure 4 using 0.5 mmol of **2g**. Purification by column chromatography (hexanes/CH_2Cl_2, 1:1) afforded **4c** as a light yellow/orange powder (75.6 mg, 61%): R_f = 0.79 (CH_2Cl_2, 100%); mp 61 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, J = 7.0 Hz, 1H), 8.49 (s, 1H), 8.13 (dd, J = 8.5, 1.4 Hz, 1H), 7.95 (dd, J = 8.8, 3.6 Hz, 2H), 7.90−7.87 (m, 1H), 7.55−7.48 (m, 3H), 7.09 (m, 1H), 6.93 (s, 1H), 6.75 (t, J = 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 142.5, 134.2, 129.4, 129.2, 124.2, 118.7, 112.7, 94.4; IR (neat) 3104, 3051, 2918, 1632, 1506, 1497, 1327, 1254, 1141, 827, 777 cm^{-1}; HRMS calcd for $C_{17}H_{13}N_2$ $[M + H]^+$ 245.10732, found 245.10732.

*2-(2-Methylphenyl)pyrazolo[1,5-a]pyridine (**4d**).* The title compound was prepared according to general procedure 4 using 0.5 mmol of **2h**. Purification by column chromatography (CH_2Cl_2, 100%) afforded **4d** as a light beige powder (73.3 mg, 70%). Characterization data was consistent with that reported in the literature:[16] R_f = 0.27 (CH_2Cl_2, 100%); mp 59−63 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.52 (d, J = 6.9 Hz, 1H), 7.75−7.67 (m, 1H), 7.55 (d, J = 9.6 Hz, 1H), 7.30 (s, 3H), 7.12 (t, J = 6.8 Hz 1H), 6. 75 (m, 1H), 6.65 (s, 1H); 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 154.9, 141.8, 137.4, 134.0, 131.8, 130.8, 129.3, 129.2, 126.8, 124.3, 118.7, 112.4, 97.8, 22.2; IR (neat) 1720, 1631, 1507, 1459, 1328, 759, 724 cm^{-1}; HRMS calcd for $C_{14}H_{13}N_2$ $[M + H]^+$ 209.10732, found 209.10685.

*2-(4-Methylphenyl)pyrazolo[1,5-a]pyridine (**4e**).* The title compound was prepared according to general procedure 4 using 0.5 mmol of **2i**. Purification by column chromatography (CH_2Cl_2, 100%) afforded **4e** as a light beige powder in (82.5 mg, 79%). Characterization data was consistent with that reported in the literature:[16] R_f = 0.23 (CH_2Cl_2/hexanes, 9/1); mp 117−118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.49 (d J = 6.9 Hz, 1H), 7.90 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 9.3 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.08 (t, J = 8.0 Hz 1H), 6.77 (s, 1H), 6.72 (t, J = 6.9 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 154.5, 142.6, 139.4, 131.4, 130.3, 129.2, 127.8, 124.4, 118.5, 112.2, 94.7, 22.3; IR (neat) 1632, 1513, 1472, 1424, 1328, 1250, 827, 774, 744 cm^{-1}; HRMS calcd for $C_{14}H_{13}N_2$ $[M + H]^+$ 209.10732, found 209.10644.

*2-(2-Methoxyphenyl)pyrazolo[1,5-a]pyridine (**4f**).* The title compound was prepared according to general procedure 4 using using 0.5 mmol of **2k**. Purification by column chromatography (CH_2Cl_2, 100%) afforded **4f** as a light beige powder in (78.9 mg, 70%): R_f = 0.27 (CH_2Cl_2/hexanes, 9/1); mp 55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 7.0 Hz, 1H), 8.11 (dd, J = 7.7, 1.5 Hz, 1H), 7.53 (d, J = 8.9 Hz, 1H), 7.40−7.34 (m, 1H), 7.12−7.03 (m, 4H), 6.72 (t, J = 6.8 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 146.8, 130.5, 130.46, 130.41, 129.2, 124.1, 122.6, 121.8, 118.9, 112.6, 112.2, 99.0, 56.4; IR (neat) 3005, 2934, 1633, 1582, 1519, 1478, 1328, 1272, 11244, 1024, 753 cm^{-1}; HRMS calcd for $C_{14}H_{13}N_2O$ $[M + H]^+$ 225.1022, found 225.1015.

*2-(3-Methoxyphenyl)pyrazolo[1,5-a]pyridine (**4g**).* The title compound was prepared according to general procedure 4 using 0.5 mmol of **2l**. Purification by column chromatography (CH_2Cl_2, 100%) afforded **4g** as a yellow powder (73.4 mg, 65%). Characterization data was consistent with that reported in the literature:[16] R_f = 0.23 (CH_2Cl_2, 100%); mp 43−45 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, J = 6.9 Hz, 1H), 7.58−7.52 (m, 2H), 7.49 (d, J = 9.0 Hz, 1H), 7.36 (t, J = 8.3 Hz, 1H), 7.06 (t, J = 6.9 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H); 6.79 (s, 1H), 6.71 (t, J = 6.9 Hz, 1H), 3.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 154.2, 142.3, 135.6, 130.6, 129.4, 123.7, 119.9, 118.7, 115.1, 112.6, 112.4, 94.8, 56.0; IR (neat) 2833, 1603, 1583, 1520, 1470, 1245, 1158, 1041, 768, 737 cm^{-1}; HRMS calcd for $C_{14}H_{13}N_2O$ $[M + H]^+$ 225.10224, found 225.10151.

*2-(4-Methoxyphenyl)pyrazolo[1,5-a]pyridine (**4h**).* The title compound was prepared according to General Procedure 4 using 0.5 mmol of **2m**. Purification by column chromatography (CH_2Cl_2, 100%) afforded **4h** as a yellow powder (72.4 mg, 63%): R_f = 0.23 (CH_2Cl_2, 100%); mp 100−101 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J = 6.9 Hz, 1H), 7.93−7.88 (m, 2H), 7.47 (d, J = 8.9 Hz, 1H), 7.09−6.97 (m, 3H), 6.72−6.67 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 154.3, 142.5, 129.3, 128.6, 126.8, 124.2, 118.5, 115.0, 112.2, 93.9, 56.2; IR (neat) 3076, 2954, 1631, 1514, 1243, 1178, 842, 771 cm^{-1}; HRMS calcd for $C_{14}H_{13}N_2O$ $[M + H]^+$ 225.10224, found 225.10223.

*2-[4-(Benzyloxy)phenyl]pyrazolo[1,5-a]pyridine (**4i**).* The title compound was prepared according to General Procedure 4 using 0.5 mmol of **2n**. Purification by column chromatography (CH_2Cl_2, 100%) afforded **4i** as a light yellow powder (131 mg, 87%). Characterization data was consistent with that reported in the literature:[16] R_f = 0.24 (CH_2Cl_2, 100%); mp 164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 6.9 Hz, 1H), 7.92 (d, J = 9.0 Hz, 2H), 7.50−7.31 (m, 6H), 7.10−7.04 (m, 3H), 6.73−6.67 (m, 2H), 5.13 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 154.4, 142.5, 137.9, 129.5, 129.3, 128.8, 128.6, 128.4, 127.1, 124.3, 118.6, 115.9, 112.2, 93.9, 71.0; IR (neat) 3031, 1612, 1451, 1250, 836, 725 cm^{-1}; HRMS calcd for $C_{20}H_{17}N_2O$ $[M + H]^+$ 301.13354, found 301.13310.

*4-Pyrazolo[1,5-a]pyridin-2-ylbenzonitrile (**4j**).* The title compound was prepared according to general procedure 4 using 0.5 mmol of **2o**. Purification by column chromatography (CH_2Cl_2/hexanes, 9/1) afforded **4j** as a yellow powder (67 mg, 61%). Characterization data was consistent with that reported in the literature:[16] R_f = 0.63 (CH_2Cl_2, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, J = 6.9 Hz, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 9.3 Hz, 1H), 7.13 (t, J = 7.9 Hz, 1H), 6.84 (s, 1H), 6.80 (t, J = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 142.7, 138.7, 133.2, 129.6, 127.7, 124.6, 119.9, 119.1, 113.4, 112.5, 95.3; IR (neat) 3032, 2223, 1632, 1505, 1427, 842, 753 cm^{-1}; HRMS calcd for $C_{14}H_{10}N_3$ $[M + H]^+$ 220.08692, found 220.08626.

*2-(4-Fluorophenyl)pyrazolo[1,5-a]pyridine (**4k**).* The title compound was prepared according to general procedure 4 using 0.5 mmol of **2p**. Purification by column chromatography (CH_2Cl_2/hexanes, 95/5) afforded **4k** as a beige powder (96.4 mg, 86%). Characterization data was consistent with that reported in the literature:[16] R_f = 0.79 (CH_2Cl_2, 100%); mp 145−147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, J = 6.3 Hz, 1H), 7.95−7.90 (m, 2H), 7.48 (d, J = 8.4 Hz, 1H), 7.18−7.02 (m, 3H), 6.75−6.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (d, J = 247.2 Hz), 153.5, 142.5, 130.3 (d, J = 3.3 Hz), 129.3, 129.0 (d, J = 9.1 Hz), 124.4, 118.7, 116.5 (d, J = 21.7 Hz), 112.6, 94.3; IR (neat) 1630, 1599, 1512, 1473, 1429, 1213, 772, 745 cm^{-1}; HRMS calcd for $C_{13}H_{10}FN_2$ $[M + H]^+$ 213.08225, found 213.08138.

*2-(2-Chlorophenyl)pyrazolo[1,5-a]pyridine (**4l**).* The title compound was prepared according to general procedure 4 using 0.5 mmol of **2r**. Purification by column chromatography CH_2Cl_2/hexanes, 95/5)

afforded **4l** as a yellow powder (72.4 mg, 63%). Characterization data was consistent with that reported in the literature:[16] R_f = 0.79 (CH_2Cl_2, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 7.2 Hz, 1H), 7.97 (d, J = 6.9 Hz, 1H), 7.58−7.49 (m, 2H), 7.39−7.27 (m, 2H), 7.11 (t, J = 7.8 Hz 1H), 7.04 (s, 1H); 6.76 (t, J = 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 141.5, 133.6, 133.1, 132.3, 131.2, 130.2, 129.3, 127.8, 124.2, 119.1, 112.9, 99.0; IR (neat) 3031, 1634, 1518, 1462, 1333, 1048, 724 cm^{-1}; HRMS calcd for $C_{13}H_{10}ClN_2$ $[M + H]^+$ 229.0527, found 229.05273.

2-(2-Bromophenyl)pyrazolo[1,5-a]pyridine (***4m***). The title compound was prepared according to general procedure 4 using 0.5 mmol of **2s**. Purification by column chromatography (CH_2Cl_2, 100%) afforded **4m** as a yellow-brown powder (96.0 mg, 70%). Characterization data was consistent with that reported in the literature:[16] R_f = 0.39 (CH_2Cl_2/hexanes, 9/1); mp 45−46 °C; ^{1}H NMR (300 MHz, $CDCl_3$,) δ 8.51 (d, J = 6.9 Hz, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.27 (t, J = 8.1 Hz, 1H), 7.14 (t, J = 8.1 Hz, 1H), 6.99 (s, 1H), 6.78 (t, J = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 141.5, 135.4, 134.5, 132.7, 130.5, 129.3, 128.3, 124.2, 123.3, 119.0, 112.8, 98.8. IR (neat) 3055, 1633, 1519, 1458, 1330, 1024, 755, 737, 726 cm^{-1}; HRMS calcd for $C_{13}H_{10}BrN_2$ $[M + H]^+$ 273.00219, found 273.00219.

2-(3-Bromophenyl)pyrazolo[1,5-a]pyridine (***4n***). The title compound was prepared according to General Procedure 4 using 0.5 mmol of **2u**. Purification by column chromatography (hexanes/EtOAc, 1:1) afforded **4n** as a yellow-brown powder (81.5 mg, 60%): R_f = 0.63 (CH_2Cl_2/hexanes, 9/1); mp 126 °C; ^{1}H NMR (300 MHz, $CDCl_3$,) δ 8.46 (d, J = 7.0 Hz, 1H), 8.14 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.52−7.48 (m, 2H), 7.31 (t, J = 7.9 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 6.76−6.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 142.5, 136.2, 132.1, 131.1, 130.2, 129.3, 125.8, 124.5, 123.8, 118.9, 113.0, 94.8; IR (neat) 3045, 1633, 1519, 1465, 1330, 1068, 772, cm^{-1}. HRMS calcd for $C_{13}H_{10}BrN_2$ $[M + H]^+$ 273.00219, found 273.00234.

(E)-Ethyl 2-(Pyrazolo[1,5-a]pyridin-2-yl)acrylate (***4o***). The title compound was prepared according to general procedure 4 using 0.4 mmol of **2v**. Purification by column chromatography (CH_2Cl_2/hexanes, 9/1) afforded **4o** a light brown oil (42.1 mg, 49% yield). Characterization data was consistent with that reported in the literature:[16] R_f = 0.26 (CH_2Cl_2/hexanes, 95/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, J = 7.1 Hz, 1H), 7.79 (d, J = 16.1 Hz, 1H), 7.50 (d, J = 8.9 Hz, 1H), 7.12 (d, J = 7.0 Hz, 1H), 6.78 (t, J = 6.9 Hz, 1H), 6.67 (m, 2H), 4.28 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 150.3, 142.1, 137.2, 129.3, 124.6, 122.1, 119.2, 113.7, 97.4, 61.4, 15.1; IR (neat) 2980, 1711, 1650, 1634, 1299, 1269, 1173, 1034, 979 cm^{-1}; HRMS calcd for $C_{12}H_{13}N_2O_2$ $[M + H]^+$ 217.09715, found 217.09671.

2-(2-Phenylcyclopropyl)pyrazolo[1,5-a]pyridine (***4p***). The title compound was prepared according to General Procedure 4 using 0.5 mmol of **2w**. Purification by column chromatography (CH_2Cl_2/hexanes, 9/1) afforded **4p** as a light brown powder (73 mg, 62%). Characterization data was consistent with that reported in the literature:[16] R_f = 0.26 (CH_2Cl_2/hexanes, 95/5); mp 53−55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.371 (d, J = 7.5 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.34−7.29 (m, 2H), 7.22−7.17 (m, 3H), 7.04 (t, J = 7.8 Hz, 1H), 6.65 (t, J = 6.9 Hz, 1H), 6.28 (s, 1H), 2.49−2.36 (m, 2H), 1.69−1.62 (m, 1H), 1.55−1.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 143.0, 142.0, 129.2, 129.0, 126.7, 126.6, 124.1, 118.1, 111.7, 94.4, 28.4, 22.6, 19.3. IR (neat) 3027, 1724, 1632, 1520, 1493, 745, 695 cm^{-1}; HRMS calcd for $C_{16}H_{15}N_2$ $[M + H]^+$ 235.12297, found 235.12373.

2-Phenylpyrazolo[1,5-a]pyridine-5-carbonitrile (***5a***). The title compound was prepared according to general procedure 4 using 1.0 mmol of **1b**. Purification by column chromatography (CH_2Cl_2/hexanes, 95/5) affored **5a** as a yellow powder (67.4 mg, 62%). Characterization data was consistent with that reported in the literature:[16] R_f = 0.76 (CH_2Cl_2, 100%); mp 186−189 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 7.2 Hz, 1H), 7.96−7.92 (m, 3H), 7.50−7.38 (m, 3H), 7.69 (s, 1H), 6.83 (d, J = 7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 140.8, 132.7, 130.2, 130.1, 129.8, 127.5, 125.3, 118.4, 112.5, 107.7, 97.7; IR (neat) 3048, 2229, 1523, 1476, 1455, 1431, 1258, 753, 718 cm^{-1}; HRMS calcd for $C_{14}H_{10}N_3$ $[M + H]^+$ 220.08692, found 220.08705.

3/6-Methyl-2-phenylpyrazolo[1,5-a]pyridine (***5b***). The title compound was prepared according to general procedure 4 using 1.0 mmol of **1c**. Purification by column chromatography (CH_2Cl_2/hexanes, 9/1) afforded **5b** a beige powder (45 mg, 77%, inseparable mixture of products). Characterization data was consistent with that reported in the literature:[16] R_f = 0.43 (CH_2Cl_2, 100%); mp 121−129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.98 (d, J = 7.5 Hz, 2H), 7.52−7.34 (m, 4H), 6.94 (d, J = 8.4 Hz, 1H), 6.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 143.7, 141.2, 134.4, 129.6, 129.0, 127.4, 123.2, 122.4, 118.0, 112.7, 94.1, 93.5, 18.8; IR (neat) 1507, 1438, 1318, 1027, 809, 761, 691 cm^{-1}; HRMS calcd for $C_{14}H_{13}N_2$ $[M + H]^+$ 209.10732, found 209.10685.

3/6-Chloro-2-phenylpyrazolo[1,5-a]pyridine (***5c***). The title compound was prepared according to general procedure 4 using 1.0 mmol of **1d**. Purification by column chromatography (CH_2Cl_2/hexanes, 9/1) afforded **5c** as a beige powder (45 mg, 77%): R_f = 0.43 (CH_2Cl_2, 100%); mp 121−129 °C; ^{1}H NMR (major, 300 MHz, $CDCl_3$) δ 9.42 (m, 1H), 9.22−9.20 (m, 2H), 8.15 (m, 4H), 8.10−8.04 (m, 7H), 7.70−7.65 (m, 3H), 7.58−7.46 (m, 18H), 7.08−6.99 (m, 6H); ^{13}C NMR (major, 75 MHz, $CDCl_3$) δ 154.7, 141.6, 133.5, 129.7, 127.9, 127.4, 124.6, 123.4, 111.9, 94.9; IR (neat) 3069, 3030, 1630, 1533, 745 cm^{-1}; HRMS calcd for $C_{13}H_{10}ClN_2$ $[M + H]^+$ 229.05270, found 229.05282.

2-Phenylpyrazolo[1,5-a]isoquinoline (***5d***). The title compound was prepared according to General Procedure 4 using 1.0 mmol of **1e**. Purification by chromatography (CH_2Cl_2/hexanes, 9/1) afforded **5d** as a beige powder (73.7 mg, 60%). Characterization data was consistent with that reported in the literature:[16] R_f = 0.84 (CH_2Cl_2, 100%); mp 117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 6.9 Hz, 1H), 8.12 (d, J = 7.8 Hz, 1H), 8.03 (d, J = 6.3 Hz, 2H), 7.65 (d, J = 8.1 Hz, 1H), 7.62−7.47 (m, 4H), 7.44−7.37 (m, 1H), 7.29 (s, 1H), 6.98 (d, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 140.7, 134.0, 129.7, 129.2, 128.8, 128.5, 128.1, 127.2, 125.3, 124.6, 113.0, 95.4. IR (neat) 1537, 1460, 1360, 792, 756, 695 cm^{-1}; HRMS calcd for $C_{17}H_{13}N_2$ $[M + H]^+$ 245.10732, found 245.1067.

2-Phenylpyrazolo[1,5-a]quinoline (***5e***). The title compound was prepared according to General Procedure 4 using 1.0 mmol of **1f**. Purification by column chromatography (CH_2Cl_2/hexanes, 9/1) afforded **5e** a yellow powder (110.2 mg, 90%). Characterization data was consistent with that reported in the literature:[16] R_f = 0.81 (CH_2Cl_2, 100%); mp 92−95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, J = 8.7 Hz, 1H), 8.07 (d, J = 8.1 Hz, 2H), 7.75 (m, 2H), 7.52−7.37 (m, 4H), 6.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 140.4, 135.8, 134.4, 130.2, 129.6, 129.2, 129.1, 128.2, 125.5, 124.0, 117.5, 116.4, 97.6; IR (neat) 1732, 1603, 1454, 1392, 1812, 743, 679 cm^{-1}; HRMS calcd for $C_{17}H_{13}N_2$ $[M + H]^+$ 245.10732, found 245.10727.

7-Methoxy-2-phenylpyrazolo[1,5-a]quinoline (***5f***). The title compound was prepared according to general procedure 4 using 0.3244 mmol of **1g**. Purification by chromatography (CH_2Cl_2/hexanes, 1:1) afforded **5f** as a yellow powder (30.3 mg, 69%): R_f = 0.65 (CH_2Cl_2/hexanes, 1:1); mp 98−100 C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 9.1 Hz, 1H), 8.06 (d, J = 7.7 Hz, 2H), 7.45 (m, 3H), 7.35−7.27 (m, 3H), 7.15 (m, 1H), 6.88 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 153.2, 139.4. 134.4. 130.6, 129.5, 129.0, 127.1, 125.0, 119.3, 117.94, 117.93, 110.2, 97.2, 56.5; IR (neat) 3372, 2935, 1728, 1619, 1563, 1167, 760 cm^{-1}; HRMS calcd for $C_{18}H_{15}N_2O$ $[M + H]^+$ 275.11789, found 275.11824.

2-Phenylpyrazolo[1,5-a]pyrazine (***5g***). The title compound was prepared according to General Procedure 4 using 0.5 mmol of **1h**. Purification by column chromatography (CH_2Cl_2/hexanes, 9/1) afforded **5g** as a white powder (81.5 mg, 60%): R_f = 0.63 (CH_2Cl_2/hexanes, 1:1);

mp 142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.39 (d, J = 4.7 Hz, 1H), 7.98 (d, J = 7.4 Hz, 2H), 7.86 (d, J = 4.7 Hz, 1H), 7.51−7.39 (m, 3H), 7.05 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 145.3, 138.0, 133.0, 130.1, 129.9, 129.8, 129.4, 128.2, 127.5, 122.5, 96.1. IR (neat) 3127, 3020, 1527, 1469, 1421, 1331, 1233, 1080 cm^{-1}; HRMS calcd for $C_{12}H_{10}N_3$ $[M + H]^+$ 196.08692, found 196.08726.

*2-(E)-Styryl-N-benzoyliminopyridinium Ylide (**3**).* To a microwave vial with a stir bar was added the **1a** (0.6 mmol, 1.5 equiv), $CuBr_2$ (0.04 mmol, 10 mol %), and crushed dry K_2CO_3 (0.8 mmol, 2 equiv). The vial was then sealed with a septum and purged with argon for 5 min. To a separate vial was added **2a** (0.4 mmol, 1 equiv). The iodide was diluted in PhCl (0.5 mL) and added to the reaction vessel via syringe. The vial and syringe were then rinsed three times with PhCl (0.5 mL) bringing the total reaction volume to 2 mL. The reaction was stirred vigorously for 16 h at 125 °C. Following cooling, 2 mL of CH_2Cl_2/MeOH (9:1) was added, and the solution was filtered though a silica/Celite pad. The pad was then rinsed with 15 mL of CH_2Cl_2/MeOH (9:1). The combined solution was concentrated and the crude mixture was purified via column chromatography (CH_2Cl_2/MeOH, 95/5) to afford **3** as a cream-colored solid (98.2 mg, 81%). Characterization data was consistent with that reported in the literature:[14f] R_f = 0.26 (CH_2Cl_2/MeOH, 95/5); mp 199−201 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J = 6.9 Hz, 1H), 8.25 (d, J = 7.0 H, 2H), 7.99 (d, J = 8.2 Hz, 1H), 7.85 (t, J = 8.2 H, 1H), 7.78 (d, J = 16.6 Hz, 1H), 7.52−7.41 (m, 7H), 7.36−7.34 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 146.2, 140.3, 137.7, 136.0, 131.0, 130.9, 129.8, 129.3, 129.0, 128.8, 128.7, 128.4, 124.1, 124.0, 119.4; IR (neat) 3054, 1612, 1590, 1552, 1483, 1173, 965 cm^{-1}; HRMS calcd for $C_{20}H_{17}N_2O$ $(M + H)^+$ 301.13354, found 301.13502.

General Procedure 5: Synthesis of 2-Substituted Pyrazolo-[1,5-*a*]pyridines from Alkynes. To a 3 mL conical microwave vial equipped with a spin vane was added pyridinium ylide (1.5 mmol, 3 equiv). In a glovebox were added P(4-MeOPh)$_3$ (0.15 equiv), $PdBr_2$ (0.05 equiv), and AgOBz (2.0 mmol, 4 equiv), and the microwave vial was crimped shut. The alkyne derivative (0.5 mmol, 1 equiv) was dissolved in 1,4-dioxane (0.5 mL) and added via syringe. The syringe was rinsed three times with 0.5 mL of dioxane to reach a final volume of 2 mL. The solution was heated to 125 °C with fast stirring. Within 5 min, a color change was observed. The mixture was stirred for 16 h and then cooled to room temperature. Dichloromethane was added, and the precipitate was filtered on a cotton plug and washed with CH_2Cl_2. Saturated Na_2CO_3 was added, and the organic phase was extracted with CH_2Cl_2. The solution was dried with Na_2SO_4 and concentrated under reduced pressure and purified via column chromatography to afford the title compounds.

*2-Cyclohexenylpyrazolo[1,5-a]pyridine (**10b**).* The title compound was prepared according to general procedure 5 using 0.5 mmol of the alkyne. Purfication by column chromatography (CH_2Cl_2/hexanes, 1/1) afforded **10b** as a light brown powder (84.2 mg, 85%): R_f = 0.43 (CH_2Cl_2/hexanes, 1/1); mp 44−45 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, J = 7.0 Hz, 1H), 7.42 (d, J = 9 Hz, 1H), 7.00−6.95 (m, 1H), 6.63−6.52 (m, 2H), 6.44 (s, 1H), 2.52−2.60 (m, 2H), 2.21−2.20 (m, 2H), 1.81−1.63 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 140.9, 130.2, 128.2, 126.6, 122.9, 117.4, 110.9, 92.4, 26.1, 25.5, 22.6, 22.1; IR (neat) 3075, 2922, 2854, 1629, 1516, 1488, 1327, 1252, 1138, 918, 767 cm^{-1}; HRMS calcd for $C_{13}H_{15}N_2$ $[M + H]^+$ 199.12297, found 199.12269.

*2-(Prop-1-en-2-yl)pyrazolo[1,5-a]pyridine (**10c**).* The title compound was prepared according to general procedure 5 using 0.5 mmol of the alkyne. Purification by column chromatography (CH_2Cl_2/hexanes, 7/3) gave **10c** as a light brown oil (22.7 mg, 29%): R_f = 0.63 (CH_2Cl_2/hexanes, 7/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, J = 7.0, 0.9 Hz, 1H), 7.46 (d, J = 8.9 Hz, 1H), 7.08−7.04 (m, 1H), 6.70 (td, J = 6.9, 1.2 Hz, 1H), 6.59 (s, 1H), 5.78 (s, 1H), 5.23 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 141.9, 137.7, 129.2, 124.1, 118.6, 114.7, 112.3, 94.5, 21.4; IR (neat) 3085, 2972, 1631, 1518, 1245, 1014, 893, 734 cm^{-1}; HRMS calcd for $C_{10}H_{11}N_2$ $[M + H]^+$ 159.09167, found 159.09142.

*2-tert-Butylpyrazolo[1,5-a]pyridine (**10d**).* The title compound was prepared according to general procedure 5 using 0.5 mmol of the alkyne. Purfication by column chromatography (CH_2Cl_2/hexanes, 95/5) afforded **10d** as a light brown oil (55.3 mg, 64%): R_f = 0.75 (CH_2Cl_2, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 7.0 Hz, 1H), 7.42 (d, J = 8.9 Hz, 1H), 7.04−7.00 (m, 1H), 6.65 (t, J = 6.8, Hz, 1H), 6.35 (s, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 140.4, 128.0, 122.5, 117.1, 110.3, 92.5, 32.0, 30.4; IR (neat) 3078, 2958, 2864, 1632, 1519, 1492, 1327, 1236, 770 cm^{-1}; HRMS calcd for $C_{11}H_{15}N_2$ $[M + H]^+$ 175.12297, found 175.12277.

*2-Hexylpyrazolo[1,5-a]pyridine (**10e**).* The title compound was prepared according to general procedure 5 using 0.5 mmol of the alkyne. Purification by column chromatography (CH_2Cl_2/hexanes, 95/5) afforded **10e** as a light brown oil (39.3 mg, 50%): R_f = 0.73 (CH_2Cl_2, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, J = 7.0 Hz, 1H), 7.41 (d, J = 8.9 Hz, 1H), 7.04 (t, J = 7.8 Hz, 1H), 6.65 (t, J = 6.9 Hz, 1H), 6.29 (s, 1H), 2.82 (m, 2H), 1.74 (q, J = 7.6 Hz, 2H), 1.41−1.31 (m, 6H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 141.8, 129.0, 123.9, 118.2, 111.5, 95.9, 32.5, 30.6, 30.0, 29.5, 23.5, 14.9; IR (neat) 3081, 2925, 2855, 1634, 1520, 1488, 1328, 1253, 1142, 1021, 765 cm^{-1}; HRMS calcd for $C_{13}H_{19}N_2$ $[M + H]^+$ 203.15428, found 203.15410.

*2-Butylpyrazolo[1,5-a]pyridine (**10f**).* The title compound was prepared according to General Procedure 5 using 0.366 mmol of the alkyne. The product was purified by column chromatography (CH_2Cl_2/hexanes, 95/5) to give a light brown oil (34.9 mg, 55%): R_f = 0.69 (CH_2Cl_2, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 7.0 Hz, 1H), 7.41 (dd, J = 8.9, 0.8 Hz, 1H), 7.04 (d, J = 7.3 Hz, 1H), 6.65 (t, J = 6.9 Hz, 1H), 6.29 (s, 1H), 2.83 (t, J = 7.7 Hz, 2H), 1.75 (quintet, J = 7.5 Hz, 2H), 1.43 (sextet, J = 7.4 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 141.8, 129.0, 123.9, 118.2, 111.5, 95.9, 32.8, 29.1, 23.4, 14.8; IR (neat) 3072, 2955, 1635, 1520, 1474, 1329, 1254, 1238, 1144, 1023, 767 cm^{-1}; HRMS calcd for $C_{11}H_{15}N_2$ $[M + H]^+$ 175.12297, found 175.12282.

*Methyl 9-(Pyrazolo[1,5-a]pyridin-2-yl)nonanoate (**10g**).* The title compound was prepared according to general procedure 5 using 0.475 mmol of the alkyne. Purification by column chromatography (CH_2Cl_2, 100%) afforded **10g** as a yellow oil (75.9 mg, 54%): R_f = 0.63 (CH_2Cl_2, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (dd, J = 7.0, 0.9 Hz, 1H), 7.42 (dt, J = 8.9, 1.1 Hz, 1H), 7.04 (ddd, J = 8.9, 6.7, 1.1 Hz, 1H), 6.65 (td, J = 6.9, 1.3 Hz, 1H), 6.28 (s, 1H), 3.67 (s, 3H), 2.81 (t, J = 7.7 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.77−1.70 (m, 2H), 1.67−1.60 (m, 2H), 1.42−1.31 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 157.3, 141.8, 129.0, 123.9, 118.2, 111.5, 95.9, 52.3, 35.0, 30.6, 30.2, 30.1, 30.0, 29.9, 29.4, 25.8; IR (neat) 2926, 2853, 1734, 1634, 1520, 1435, 1253, 1024, 737 cm^{-1}; HRMS calcd for $C_{17}H_{24}N_2NaO_2$ $[M + Na]^+$ 311.17354, found 311.173.

*2-(2-(Benzyloxy)propan-2-yl)pyrazolo[1,5-a]pyridine (**10h**).* The title compound was prepared according to general procedure 5 using 0.258 mmol of the alkyne. Purification by column chromatography (CH_2Cl_2, 100%) afforded **10h** as a yellow oil (55.0 mg, 80%): R_f = 0.63 (CH_2Cl_2, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (dt, J = 7.0, 0.9 Hz, 1H), 7.49 (dt, J = 8.9, 1.1 Hz, 1H), 7.37−7.25 (m, 5H), 7.08 (ddd, J = 8.9, 6.7, 1.1 Hz, 1H), 6.71 (td, J = 6.9, 1.3 Hz, 1H), 6.58 (d, J = 0.8 Hz, 1H), 4.37 (s, 2H), 1.78 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 141.9, 140.3, 129.4, 129.1, 128.3, 128.0, 124.1, 118.8, 112.1, 95.2, 75.6, 66.4, 28.5; IR (neat) 3029, 2978, 2932, 2862, 1634, 1520, 1328, 1156, 1057, 776; HRMS calcd for $C_{17}H_{19}N_2O$ $[M + H]^+$ 267.14906, found 267.14919.

*2-Cyclohexenylpyrazolo[5,1-a]isoquinoline (**11a**).* The title compound was prepared according to general procedure 5 using ylide **1c** and 0.25 mmol of the alkyne. Purification by column chromatography

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(CH_2Cl_2, 100%) afforded **11a** as a yellow powder (44.5 mg, 72%): R_f = 0.83 (CH_2Cl_2, 100%); mp 87−88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 7.4 Hz, 1H), 8.08−8.06 (m, 1H), 7.71−7.68 (m, 1H), 7.55 (m, 2H), 7.01 (s, 1H), 6.92 (d, J = 7.4 Hz, 1H), 6.60 (m, 1H), 2.63−2.59 (m, 2H), 2.32−2.26 (m, 2H), 1.88−1.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 139.9, 131.2, 129.7, 128.6, 128.3, 128.0, 127.4, 127.2, 125.3, 124.5, 112.2, 94.3, 27.0, 26.5, 23.5, 23.1; IR (neat) 2924, 2856, 1634, 1537, 1477, 1368, 1033, 754 cm^{-1}; HRMS calcd for $C_{17}H_{17}N_2$ $[M + H]^+$ 249.13862, found 249.13856.

*2-Cyclohexenylpyrazolo[1,5-a]pyrazine (**11b**).* The title compound was prepared according to general procedure 5 using ylide **1f** and 0.242 mmol of the alkyne. Purification by column chromatography (CH_2Cl_2, 100%) afforded **11b** as a yellow oil (34.7 mg, 72%): R_f = 0.52 (CH_2Cl_2, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (dd, J = 8.4, 0.5 Hz, 1H), 7.74−7.72 (m, 1H), 7.65 (m, 1H), 7.43−7.35 (m, 3H), 6.66−6.63 (m, 1H), 6.61 (s, 1H), 2.67−2.63 (m, 2H), 2.33−2.27 (m, 2H), 1.89−1.82 (m, 2H), 1.78−1.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 130.0, 129.0, 127.2, 125.2, 117.4, 116.3, 95.4, 27.1, 26.5, 23.6, 23.2; IR (neat) 2928, 2856, 1613, 1482, 1386, 1033, 805, 739 cm−1; HRMS calcd for $C_{17}H_{17}N_2$ $[M + H]^+$ 249.13949, found 249.13862.

*2-Cyclohexenyl-6- and -4-methylpyrazolo[1,5-a]pyridine (**11c**).* The title compound was prepared according to general procedure 5 using ylide **1g** and 0.25 mmol of the alkyne. Purification by column chromatography (CH_2Cl_2, 100%) afforded **11c** as an inseparable 4:1 mixture toward the least hindered product (44.5 mg, 72% combined): R_f = 0.83 (CH_2Cl_2, 100%); mp: 46−47 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28−8.25 (m), 8.20 (s, 1H), 7.33 (d, J = 9.0 Hz, 1H), 6.89 (d, J = 9.1 Hz, 1H), 6.59−6.55 (m, 1H), 6.44 (m, 1H), 3.71 (s, 1H), 2.56−2.51 (m, 3H), 2.43 (s, 1H), 2.30−2.21 (m, 6H), 1.84−1.66 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 155.8, 142.9, 140.4, 131.3, 128.1, 127.3, 127.1, 127.0, 126.9, 126.8, 122.7, 121.6, 117.1, 112.0, 92.9, 92.2, 67.9, 54.3, 27.1, 26.5, 23.0, 23.1, 19.1, 18.9; IR (neat) 2922, 1642, 1517, 1485, 1435, 1319, 1054, 797 cm^{-1}; HRMS calcd for $C_{14}H_{17}N_2$ $[M + H]^+$ 213.13862, found 213.13841.

*(2-Cyclohexenylpyrazolo[1,5-a]pyridin-5-yl)(phenyl)methanone (**11d**).* The title compound was prepared according to general procedure 5 using ylide **1i** and 0.241 mmol of the alkyne. Purification by column chromatography (CH_2Cl_2, 100%) afforded **11d** as a yellow oil (32.8 mg, 45%): R_f = 0.59 (CH_2Cl_2, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (dd, J = 7.2, 0.8 Hz, 1H), 7.90 (dd, J = 1.7, 0.8 Hz, 1H), 7.86−7.83 (m, 2H), 7.67−7.63 (m, 1H), 7.56−7.52 (m, 2H), 7.23 (dd, J = 7.2, 1.9 Hz, 1H), 6.70 (s, 1H), 6.65−6.62 (m, 1H), 2.59−2.54 (m, 2H), 2.31−2.26 (m, 2H), 1.87−1.81 (m, 2H), 1.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 157.6, 140.3, 138.0, 133.5, 132.7, 130.8, 130.6, 129.3, 129.1, 128.4, 122.6, 111.5, 96.7, 27.0, 26.56, 23.4, 23.0; IR (neat) 2927, 1652, 1516, 1319, 1258, 1112, 736, 710; HRMS calcd for $C_{20}H_{18}N_2NaO$ $[M + Na]^+$ 325.13133, found 325.13113.

*(E)-2-Cyclohexenyl-7-styrylpyrazolo[1,5-a]pyridine (**11e**).* The title compound was prepared according to general procedure 5 using ylide **3** and 0.25 mmol of the alkyne. Purification by column chromatography (CH_2Cl_2, 100%) afforded **11e** as a yellow powder (13.9 mg, 21%): R_f = 0.73 (CH_2Cl_2, 100%); mp 95−98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 2H), 7.64−7.60 (m, 2H), 7.41−7.36 (m, 3H), 7.33−7.27 (m, 1H), 7.08−7.03 (m, 1H), 6.97−6.94 (m, 1H), 6.68−6.63 (m, 1H), 6.53 (s, 1H), 2.63−2.56 (m, 2H), 2.30−2.22 (m, 2H), 1.84−1.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 141.8, 137.3, 136.9, 133.9, 130.5, 128.6, 128.3, 127.1, 126.4, 122.7, 120.1, 115.9, 109.3, 92.8, 26.1, 25.6, 22.6, 22.2; IR (neat) 3057, 2924, 1632, 1522, 1305, 1260, 1080, 782, 717 cm^{-1}; HRMS calcd for $C_{21}H_{21}N_2$ $[M + H]^+$ 301.16993, found 301.16961.

*2-Phenylpyrazolo[1,5-a]pyridin-3-yl Benzoate (**12**).* Prepared according to general procedure 4 using ylide **13a** and 0.5 mmol of **2a**. Purification by column chromatography (CH_2Cl_2, 100%) afforded **12** as a tan powder (42.4 mg, 29%): R_f = 0.61 (CH_2Cl_2, 100%); mp 86−88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J = 7.0 Hz, 1H), 8.31 (d, J = 7.8 Hz, 2H), 7.98 (d, J = 7.7 Hz, 2H), 7.73−7.68 (m, 1H), 7.58 (t, J = 7.7 Hz, 2H), 7.46−7.34 (m, 4H), 7.12 (m, 1H), 6.79 (t, J = 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 144.4, 134.8, 134.2, 132.4, 131.3, 129.7, 129.65, 129.57, 129.4, 128.2, 124.0, 122.9, 117.3, 117.2, 113.0; IR (neat) 3061, 1741. 1639, 1526, 1474, 1237, 1087, 1022, 741 cm^{-1}; HRMS calcd for $C_{20}H_{15}N_2O_2$ $[M + H]^+$ 315.11242, found 315.1128.

*2-Phenylpyrazolo[1,5-a]pyridin-3-yl Acetate (**14a**).* Prepared according to general procedure 4 using 0.5 mmol of ylide **13a** in the absence of iodide and alkyne. Purification by column chromatography (CH_2Cl_2, 100%) afforded **14a** as a tan powder (61.8 mg, 49%): R_f = 0.63 (CH_2Cl_2, 100%); mp 66−67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 7.0 Hz, 1H), 7.95−7.92 (m, 2H), 7.51−7.45 (m, 2H), 7.43−7.37 (m, 1H), 7.32 (d, J = 9.0 Hz, 1H), 7.10 (ddd, J = 8.9, 6.7, 0.7 Hz, 1H), 6.75 (td, J = 6.9, 1.3 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 144.2, 134.0, 132.4, 129.5, 129.4, 128.2, 124.0, 122.9, 117.0, 112.9; IR (neat) 3041, 2932, 1762, 1638, 1472, 1348, 1190, 1077, 740 cm^{-1}; HRMS calcd for $C_{15}H_{13}N_2O_2$ $[M + H]^+$ 253.09712, found 253.09715.

*2-(3,5-(Trifluoromethyl)phenyl)pyrazolo[1,5-a]pyridin-3-yl Acetate (**14b**).* Prepared according to general procedure 4 using 0.5 mmol of ylide **13b** in absence of iodide and alkyne. Purification by column chromatography (CH_2Cl_2, 100%) afforded **14b** as a beige oil (31.8 mg, 19%): R_f = 0.67 (CH_2Cl_2, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 2H), 8.41 (dd, J = 7.1, 1.0 Hz, 1H), 7.90 (s, 1H), 7.40 (dt, J = 9.0, 1.2 Hz, 1H), 7.19 (ddd, J = 9.0, 6.7, 1.0 Hz, 1H), 6.87 (td, J = 6.9, 1.3 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 140.1, 134.6, 134.3, 133.1, 132.6, 129.4, 127.8 (m), 124.6, 124.0 (q, J = 272.8 Hz), 122.0 (m), 117.4, 114.0, 21.4; IR (neat) 3047, 1764, 1360, 1282, 1172, 1121, 896, 747 cm^{-1}; HRMS calcd for $C_{17}H_{10}F_6N_2NaO_2$ $[M + Na]^+$ 411.05446, found 411.05387.

*2-(4-Methoxyphenyl)pyrazolo[1,5-a]pyridin-3-yl Acetate (**14c**).* Prepared according to general procedure 4 using 0.206 mmol of ylide **13c** in the absence of iodide and alkyne. Purification by column chromatography (CH_2Cl_2, 100%) afforded **14c** as a beige oil (13.2 mg, 23%): R_f = 0.61 (CH_2Cl_2, 100%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (dt, J = 7.0, 1.0 Hz, 1H), 7.89−7.84 (m, 2H), 7.31−7.27 (m, 1H), 7.09 (ddd, J = 9.0, 6.7, 1.0 Hz, 1H), 7.03−6.98 (m, 2H), 6.73 (td, J = 6.9, 1.4 Hz, 1H), 3.87 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 160.7, 160.7, 144.1, 134.0, 129.4, 129.3, 124.9, 123.9, 122.4, 116.7, 115.0, 112.6, 56.1, 21.6; IR (neat) 2935, 1763, 1612, 1481, 1247, 1174, 1029, 836, 742 cm^{-1}; HRMS calcd for $C_{16}H_{14}N_2NaO_3$ $[M + Na]^+$ 305.091, found 305.08966.

■ ASSOCIATED CONTENT

Supporting Information. Table S1, ^{1}H and ^{13}C NMR spectra for new compounds, and X-ray data for compounds **4a** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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