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Direct Alkynylation of 3*H*-Imidazo[4,5-*b*]pyridines Using *gem*-Dibromoalkenes as Alkynes Source

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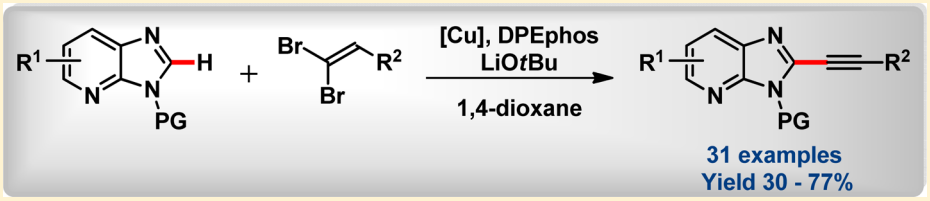
Supporting Information



ABSTRACT: C2 direct alkynylation of 3*H*-imidazo[4,5-*b*]pyridine derivatives is explored for the first time. Stable and readily available 1,1-dibromo-1-alkenes, electrophilic alkyne precursors, are used as coupling partners. The simple reaction conditions include an inexpensive copper catalyst ($CuBr{\cdot}SMe_2$ or $Cu(OAc)_2$), a phosphine ligand (DPEphos) and a base (LiO*t*Bu) in 1,4-dioxane at 120 °C. This C−H alkynylation method revealed to be compatible with a variety of substitutions on both coupling partners: heteroarenes and *gem*-dibromoalkenes. This protocol allows the straightforward synthesis of various 2-alkynyl-3*H*-imidazo[4,5-*b*]pyridines, a valuable scaffold in drug design.

INTRODUCTION

Transition-metal-catalyzed direct C−H functionalization has become a useful tool in modern organic chemistry, acknowledging today's need for complex molecules.[1] It allows access to a diversity of functional structures in an effective and straightforward manner. Nonetheless, heterocycles remain a challenge in organic synthesis due to their lack of reactivity and regioselectivity issues.[2] In fact, heteroarenes with strongly coordinating atoms, like nitrogen and sulfur, tend to poison the transition-metal catalyst or activate an undesired position. Despite these limitations, direct functionalization of heterocycles engages a wide part of the recent studies considering that it is commonly present in natural and synthetic compounds.[3] Many reports describe direct C−H arylations,[4] alkenylations[5] and alkylations[5a,6] of heterocyclic compounds. Compared to those, protocols for the direct alkynylation of an sp^2-hybridized heteroaryl carbon are still scarce. Indeed, the lack of reactivity of alkynes, more electron deficient than the corresponding alkenes, makes it harder to couple them with heteroarenes. As a consequence, terminal alkyne precursors have been developed to facilitate acetylene exchange.[7] Halogenoalkynes,[8] hypervalent alkynyliodoniums,[9] acetylenic sulfones,[10] copper acetylides,[11] and α,β-ynoic acids[12] allowed the generation of more activated alkyne moieties thus broadening the applications of direct alkynylation reactions to heterocycles. Among these alternatives, *gem*-dihaloalkenes emerged as more efficient coupling partners than the corresponding monohalogenated alkynes, along with being inexpensive and readily available.[13] Indeed, the two geminal halogen atoms on the alkenyl carbon enhance the reactivity for the oxidative addition of metal complexes, thus facilitating cross-coupling reactions.[14] All of the above alkyne precursors were used for the C−H alkynylation of indole, pyrrole, oxazole, and thiazole derivatives. To our knowledge, no direct C2 alkynylation method was described for the 3*H*-imidazo[4,5-*b*]pyridine scaffold, in which we were particularly interested as a part of a medicinal chemistry program. This heteroarene, a purine isostere, has been increasingly studied in drug design and development. For example, it can be found in candidates targeting cancer,[15] hypercholesterolemia,[16] infections,[17] and hypertension.[18]

From a chemical point of view, only one method has explored the synthesis of C2-alkynylated 3*H*-imidazo[4,5-*b*]pyridines (Scheme 1, eq 1).[19] It consisted of a copper-free Sonogashira coupling between C2-halogenated-3*H*-imidazo[4,5-*b*]pyridine and terminal alkynes. Nevertheless, this process was limited to *N*3-cyclopentyl-2-halogen-3*H*-imidazo[4,5-*b*]pyridines, and the authors did not mention the influence of other protecting groups on the coupling outcome. In this paper, we disclose our recent findings on the direct alkynylation of *N*3-protected-3*H*-imidazo-[4,5-*b*]pyridine derivatives using 1,1-dibromo-1-alkenes as alkyne precursors (Scheme 1, eq 2).

RESULTS AND DISCUSSION

We initiated our study by testing different *N*3-protected-6-bromo-3*H*-imidazo[4,5-*b*]pyridines in order to determine the most suitable protecting group for this coupling. For this purpose, the conditions previously developed in our group for the C−H alkynylation of azoles were applied (Table 1).[13a] It was clearly noticed that the *p*-methoxybenzyl (PMB) protection gave the best results for the desired alkynyl compounds. In fact,

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Scheme 1. Synthetic Pathways to C2-Alkynylated-3*H*-imidazo[4,5-*b*]pyridines

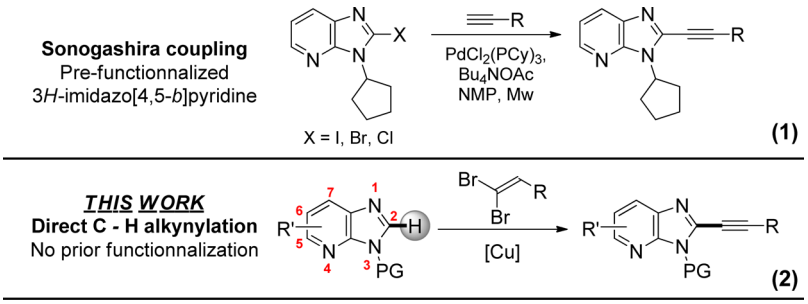
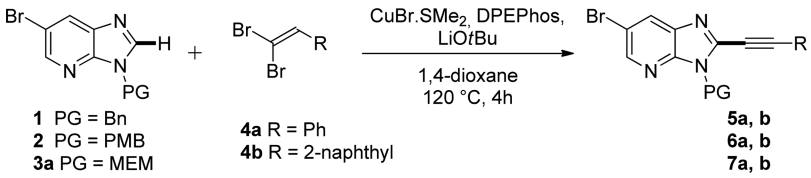


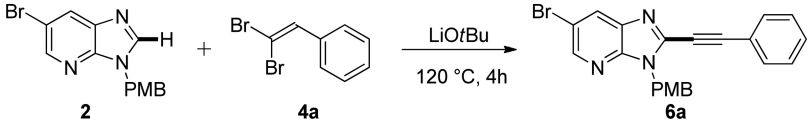
Table 1. Direct Alkynylation of Different *N*3-Protected-6-bromo-3*H*-imidazo[4,5-*b*]pyridines



R =	protecting group	yield[b]
Ph	Bn	**5a** 66%
	PMB	**6a** 65%
	MEM	**7a** 19%
2-naphthyl	Bn	**5b** 42%
	PMB	**6b** 60%
	MEM	**7b** 33%

[a]Unless otherwise noted, reaction conditions are *N*3-protected-6-bromo-3*H*-imidazo[4,5-*b*]pyridine (0.35 mmol), 1,1-dibromo-1-alkene (2 equiv), CuBr·SMe_2 (10 mol %), DPEphos (20 mol %), LiO*t*Bu (6 equiv), 1,4-dioxane (2 mL) at 120 °C for 4 h. [b]Isolated yields.

Table 2. Optimization of the Direct Coupling between 6-Bromo-3*H*-imidazo[4,5-*b*]pyridine 2 and (2,2-Dibromovinyl)benzene 4a



entry	catalyst	ligand	solvent	yield **6a**[b]
1	**CuBr·SMe_2**	**DPEphos**	**1,4-dioxane**	**65%**
2	CuI	DPEphos	1,4-dioxane	35%
3	$CuSO_4·5H_2O$	DPEphos	1,4-dioxane	31%
4	$Cu(OAc)_2$	DPEphos	1,4-dioxane	64%
5	$Pd(OAc)_2$	DPEphos	1,4-dioxane	0%
6	CuBr·SMe_2	XantPhos	1,4-dioxane	59%
7	CuBr·SMe_2	(±)Binap	1,4-dioxane	30%
8	CuBr·SMe_2	Dppp	1,4-dioxane	45%
9[c]	CuBr·SMe_2	DPEphos	1,4-dioxane	53%
10[d]	CuBr·SMe_2	DPEphos	1,4-dioxane	69%
11	CuBr·SMe_2	DPEphos	Toluene	25%
12	CuBr·SMe_2	DPEphos	PhF	traces
13[e]	CuBr·SMe_2	DPEphos	1,4-dioxane	49%

[a]Unless otherwise noted, reaction conditions are 6-bromo-3*H*-imidazo[4,5-*b*]pyridine **2** (0.35 mmol), (2,2-dibromovinyl)benzene **4a** (2 equiv), [Cu] (10 mol %), ligand (20 mol %), LiO*t*Bu (6 equiv), solvent (2 mL) at 120 °C for 4 h. [b]Isolated yields. [c]4 equiv of LiO*t*Bu was used. [d]8 equiv of LiO*t*Bu was used. [e]5 mol % of CuBr·SMe_2 and 10 mol % of DPEphos were used. DPEphos, bis[(diphenylphosphino)phenyl]ether; Dppp, 1,1-bis(diphenylphosphino)propane; XantPhos, 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene; Binap, (2,2′-bis(diphenylphosphino)-1,1′-binaphthyle.

coupling *N*3-benzyl- (Bn) and *N*3-PMB-3*H*-imidazo[4,5-*b*]-pyridine, respectively, with 1,1-dibromostyrene **4a** afforded **5a** and **6a** with similar yields. However, using **4b** as coupling partner gave **5b** in only 42% yield and **6b** in a good 60% yield. The 2-methoxyethoxymethyl ether (MEM) protecting group was the least effective providing **7a** and **7b** in 19 and 33% yield, respectively, under the standard conditions. Therefore, we decided to select PMB as a protecting group. Moreover, previous reports demonstrated that PMB-protected azoles can be easily deprotected under acidic conditions.[20]

Subsequently, we performed optimization studies using **2** and **4a** as benchmark partners (Table 2). The copper catalyst was first

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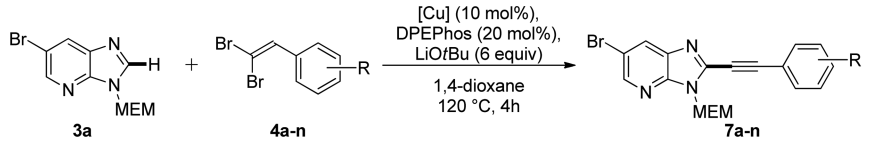
modified. While copper iodide (CuI) and copper sulfate ($CuSO_4$) afforded the desired product in low yields (entries 2−3), copper acetate ($Cu(OAc)_2$) gave **6a** in 64% yield similar to the initial copper bromide in dimethyl sulfide complex ($CuBr·SMe_2$) (entries 4 and 1, respectively). The use of palladium as the transition-metal catalyst led to no desired product **6a** (entry 5). Next, we turned our attention to the ligand effect. Several bidentate phosphines with similar steric and electronic effects as DPEphos were tested (XantPhos, Binap, Dppp) (entries 6−8), however, none of them gave better results. During our study, we noticed that the amount and the quality of the base played a crucial role in this coupling.[21] Compared to the initial 6 equiv used (entry 1), 4 equiv of LiO*t*Bu led to only 53% yield of isolated **6a** (entry 9), whereas 8 equiv afforded **6a** without a noticeable progress in the final outcome (entry 10). The solvent effect was also evaluated (entries 1, 11, 12), and 1,4-dioxane delivered **6a** in the highest 65% yield (entry 1).

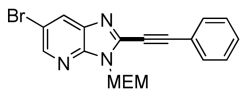
Finally, when decreasing the catalyst loading to 5 mol % of copper, **6a** was obtained in a lower yield (entry 13). The optimal conditions for the C−H direct alkynylation of 3*H*-imidazo[4,5-*b*]pyridines with *gem*-dibromoalkenes turned out to be $CuBr·SMe_2$ (10 mol %), DPEphos (20 mol %) ,and LiO*t*Bu (6 equiv) in 1,4-dioxane at 120 °C.

Meanwhile, we were interested in generating *N*3-unprotected imidazo[4,5-*b*]pyridines. Therefore, deprotection of *N*3-PMB alkyne **6a** was performed under acidic conditions. Unfortunately, the desired deprotected compound could not be isolated even though different acids were tested (hydrochloric, sulfuric, and trifluoroacetic acids). Degradation of compound **6a** was observed with the formation of unidentified byproducts. For this reason, we turned our attention to MEM as a protecting group. The direct alkynylation conditions developed in Table 2 led to the formation of compound **7a** in only 19% yield (Scheme 2). When $Cu(OAc)_2$ was used as catalyst instead of $CuBr·SMe_2$, the isolated yield of **7a** was increased to 46%. The same improvement was noted for compound **7b** isolated in 77% yield. The optimized conditions were subsequently applied to a variety of 1,1-dibromo-1-alkenes **4a−n** (Scheme 2). Electron-rich and electron-deficient *gem*-dibromo

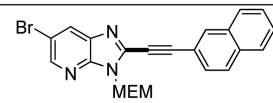
Scheme 2. Direct Alkynylation between *N*3-MEM-6-bromo-3*H*-imidazo[4,5-*b*]pyridine 3a and Various Dibromoalkenes[a,b]



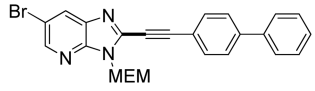
7a 19 % / 46 % [c]



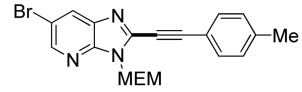
7b 33 % / 77 % [c]



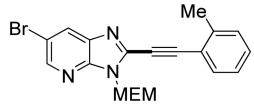
7c 44 %



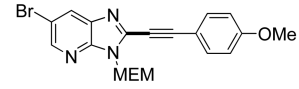
7d 53 %



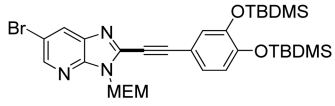
7e 60 %



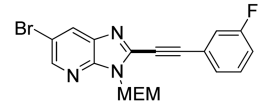
7f 52 %



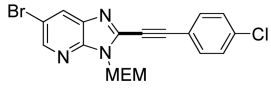
7g 55 %



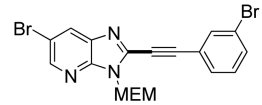
7h 36 %



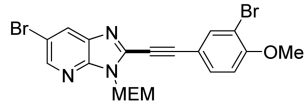
7i 54 %



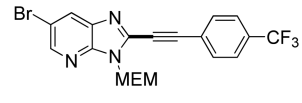
7j 51 %



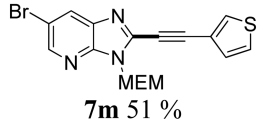
7k 47 %



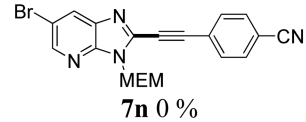
7l 31 %



7m 51 %



7n 0 %



[a]Unless otherwise noted, reaction conditions are 6-bromo-3*H*-imidazo[4,5-*b*]pyridine **3a** (0.35 mmol), (2,2-dibromovinyl)benzene **4** (2 equiv), $CuBr·SMe_2$ (10 mol %), DPEphos (20 mol %), LiO*t*Bu (6 equiv), 1,4-dioxane (2 mL) at 120 °C for 4 h. [b]Average isolated yield after two runs. [c]$Cu(OAc)_2$ (10 mol %) was used as copper catalyst.

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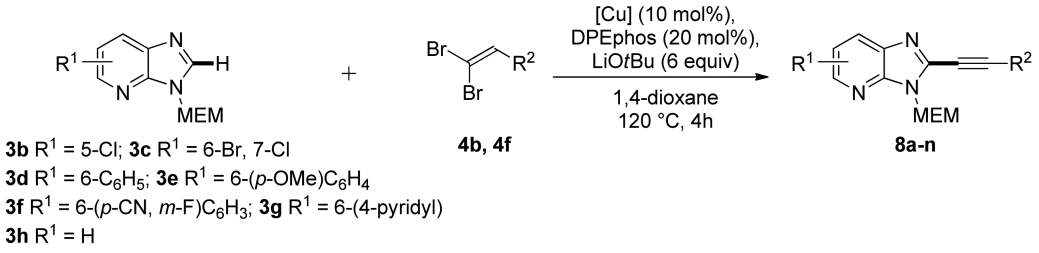
olefins reacted with 6-bromo-3*H*-imidazo[4,5-*b*]pyridine **3a** to provide C2-alkynyl-3*H*-imidazo[4,5-*b*]pyridines in moderate to good yields. 4-Phenyl-dibromostyrene gave the coupling product **7c** in only 44% yield. Electron-rich dibromoalkenes (Me, OMe, and OTBDMS substitutions) allowed better results furnishing alkynes **7d**−**g** between 53 and 60% isolated yields. Sterically hindered dibromoalkenes were also compatible with the optimized conditions, and product **7e** was isolated in a 60% yield. Compound **7h** with *m*-fluorine substituted benzene was obtained with only 36% yield. We were pleased to notice that halogen substitutions on the *gem*-dibromoalkenes were also tolerated, enabling further functionalizations. Indeed, *p*-chloro and *m*-bromo alkenes reacted successfully with 3*H*-imidazo[4,5-*b*]pyridine **3a** and afforded the corresponding coupling products **7i**−**k** in moderate yields. Electron-withdrawing trifluoromethyl moiety decreased the reactivity of the dibromoalkene, and compound **7l** was isolated in only 31% yield. Alkyne **7m**, resulting from the C−H alkynylation of **3a** with 3-(2,2-dibromoethenyl)-thiophene, was obtained in 51% yield. Unfortunately, the copper-catalyzed alkynylation conditions were not compatible with a nitrile functional group. Alkyl *gem*-dibromoalkenes were not reactive, and starting material **3a** was mainly recovered. It must be mentioned that CuBr·SMe$_2$ and Cu(OAc)$_2$ gave the same isolated yields for compounds **7d**, **7f**, **7h**, and **7l**, and CuBr·SMe$_2$ gave better results for compounds **7i**, **7k**, and **7m**.[22]

Next, the effect of a variety of substitutions on the 3*H*-imidazo[4,5-*b*]pyridine scaffold was evaluated (Scheme 3). When bromine atom at position 6 was replaced by chlorine atom at position 5, a drop in the reaction yields was observed (**8a** versus **7b**, **8b** versus **7f**).When chlorine atom was inserted at position 7 along with bromine at position 6, compound **8c** was isolated with a good 60% yield, while *gem*-dibromoalkene with an electron-donating methoxy substitution afforded **8d** in just 39% yield. Next, 6-aryl-imidazo[4,5-*b*]pyridine **3d**−**f** reacted well with 2-naphthyl-1,1-dibromoethenyl giving alkynes **8e**, **8g**, and **8i** in moderate to good yields. However, *p*-methoxy-1,1-dibromostyrene was less reactive toward the C2 alkynylation of 6-aryl-3*H*-imidazo[4,5-*b*]pyridine since compounds **8f**, **8h**, and **8j** were obtained in 30, 30, and 35% yields, respectively. Substitution with electron-deficient 4-pyridyl heterocycle on C6 of the

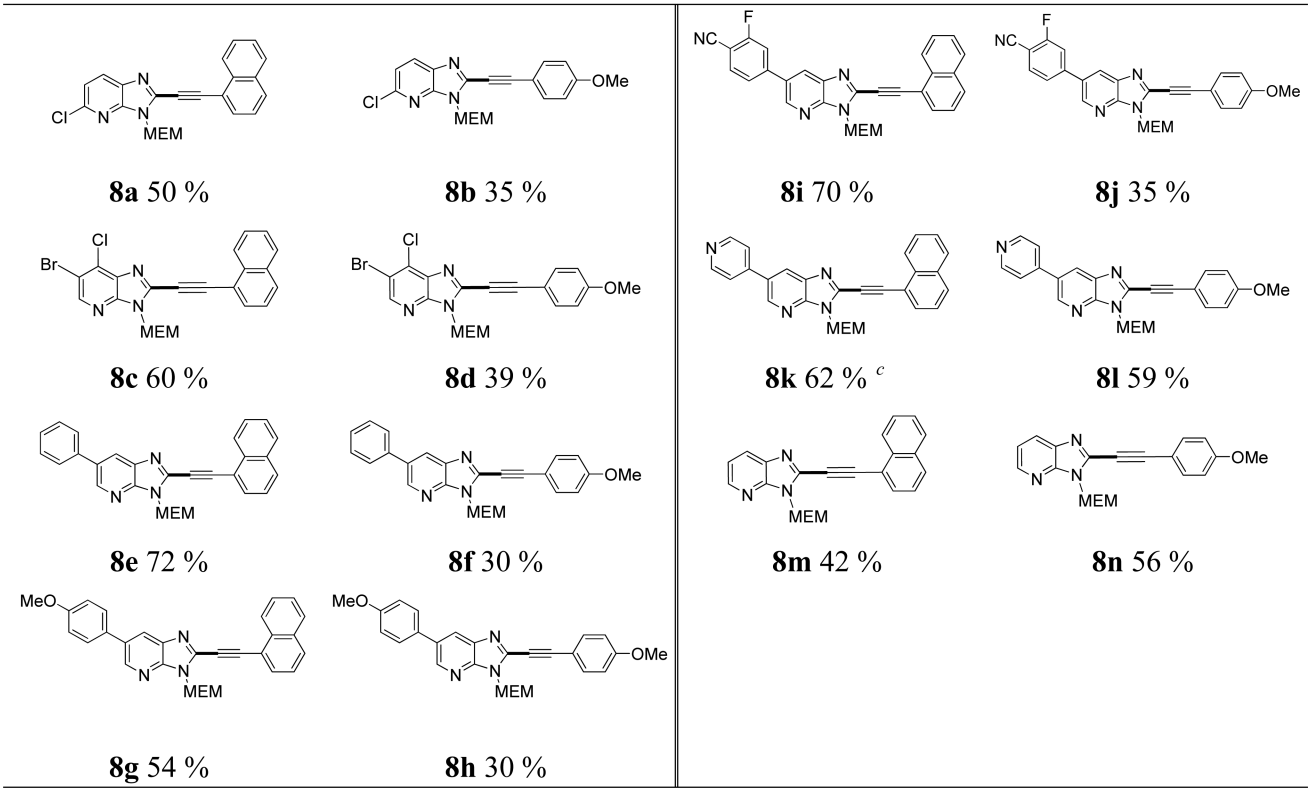
Scheme 3. Direct Alkynylation between Various *N*3-MEM-3*H*-imidazo[4,5-*b*]- pyridines 3 and Dibromoalkenes 4[a,b]



3b R^1 = 5-Cl; **3c** R^1 = 6-Br, 7-Cl
3d R^1 = 6-C_6H_5; **3e** R^1 = 6-(*p*-OMe)C_6H_4
3f R^1 = 6-(*p*-CN, *m*-F)C_6H_3; **3g** R^1 = 6-(4-pyridyl)
3h R^1 = H

4b, 4f

8a-n



8a 50 %
8b 35 %
8i 70 %
8j 35 %
8c 60 %
8d 39 %
8k 62 % [c]
8l 59 %
8e 72 %
8f 30 %
8m 42 %
8n 56 %
8g 54 %
8h 30 %

[a]Unless otherwise noted, reaction conditions are 3*H*-imidazo[4,5-*b*]pyridine **3** (0.35 mmol), (2,2-dibromovinyl)benzene **4** (2 equiv), CuBr·SMe$_2$ (10 mol %), DPEphos (20 mol %), LiO*t*Bu (6 equiv), 1,4-dioxane (2 mL) at 120 °C for 4 h. [b]Average isolated yield after 2 runs. [c]Cu(OAc)$_2$ (10 mol %) was used as copper catalyst.

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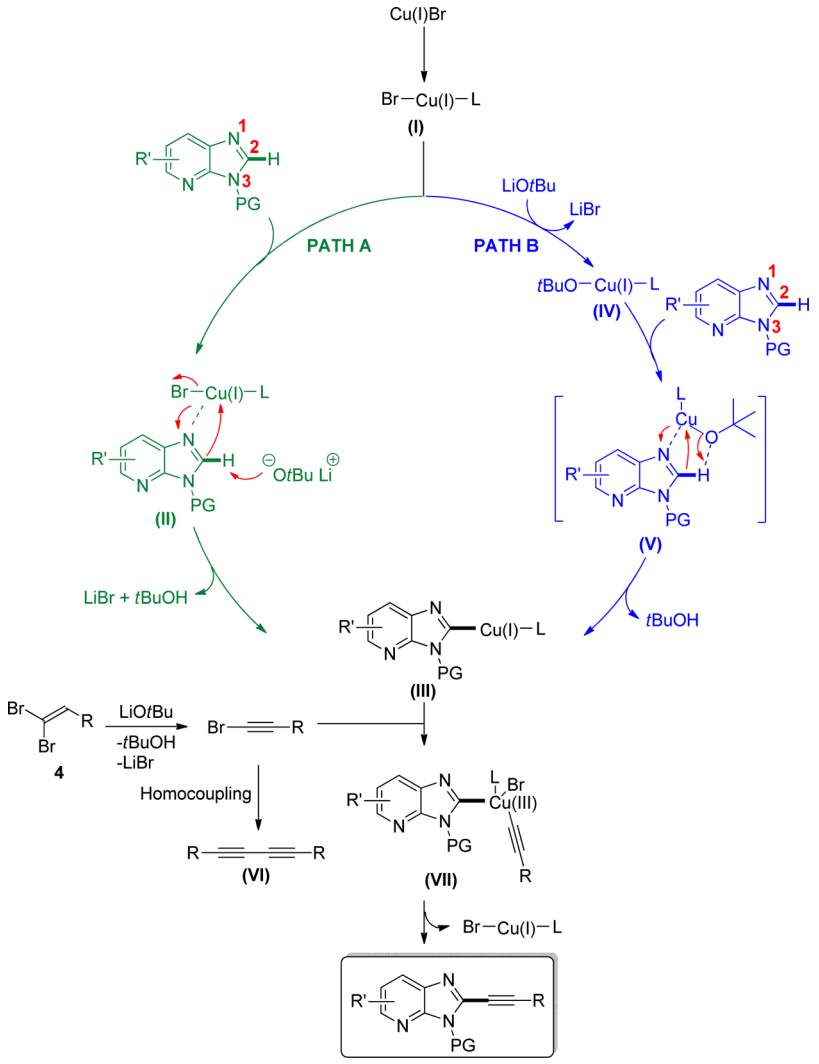
Scheme 4. Proposed Mechanism for the Direct Alkynylation of 3*H*-Imidazo[4,5-*b*]pyridines



3*H*-imidazo[4,5-*b*]pyridine **3g** led to alkynes **8k** and **8l** in satisfying yields. Finally, nonsubstituted 3*H*-imidazo[4,5-*b*]-pyridine **3h** afforded the coupling products **8m** and **8n** in moderate yields. As a conclusion, the nature of the substituents on the 3*H*-imidazo[4,5-*b*]pyridine derivatives and on the *gem*-dibromoalkenes plays a crucial role on the C2 direct alkynylation outcome.

From a mechanistic point of view, two possible pathways can be envisioned for the direct alkynylation of 3*H*-imidazo[4,5-*b*]-pyridines (Scheme 4). In pathway A, the sequence starts with the coordination of the copper complex **I** to the nitrogen adjacent to the activable C−H bond of the 3*H*-imidazo[4,5-*b*]pyridine (*N*1) leading to intermediate **II**. A previous report by Fairlamb et al. demonstrated the crucial role of *N*1 in purine nucleosides toward transition-metal coordination.[23] This metal coordination enhances the acidity and therefore the reactivity of the C2−H bond of the heterocycle, as described by Gorelsky.[24] Indeed, when our optimized conditions were applied to *N*3-protected indole and 7-azaindole, no coupling products were isolated.[25]

In the next step, deprotonation in the presence of a base and rearrangement lead to 2-cuprio-3*H*-imidazo[4,5-*b*]pyridine **III**.[13a] The latter can also be obtained according to pathway B. A ligand exchange between complex **I** and the base furnishes alkoxide complex **IV** as proposed by Hartwig et al.[26] Internal deprotonation of 3*H*-imidazo[4,5-*b*]pyridine via intermediate **V** forms copper complex **III**. Meanwhile, dehydrobromination of the dibromoalkene **4** leads to the corresponding bromoalkyne which can form diyne **VI** by homocoupling. When *N*3-PMB-3*H*-imidazo[4,5-*b*]pyridine **2** reacted with phenylethynyl bromide, product **6a** was obtained in 60% yield following the reaction conditions described in Table 1. This observation along with the formation of diyne **VI** as the main side product in this direct alkynylation reaction confirm the dehydrobromination of dibromoalkene **4**. An oxidative addition of bromoalkyne onto complex **III** results in a four coordinated copper(III) intermediate **VII**. A subsequent reductive elimination step generates the coupling product with the regeneration of the catalytic system. Both of the proposed pathways require a large excess of base (6 equiv) for the deprotonation step of the 3*H*-imidazo[4,5-*b*]pyridine as well as for the dehydrobromination step of the dibromoalkene.

Finally, some of the *N*3-MEM-6-bromo-2-alkynyl-3*H*-imidazo[4,5-*b*]pyridines **7** were deprotected under acidic conditions. Even though obtained in moderate yields, we succeeded in synthesizing *N*3-unprotected 2-alkynyl-imidazo[4,5-*b*]pyridines **9** as illustrated in Scheme 5.

In summary, a copper-catalyzed direct C2−H alkynylation of 3*H*-imidazo[4,5-*b*]pyridines has been developed for the first time. To this end, readily available *gem*-dibromoalkenes were

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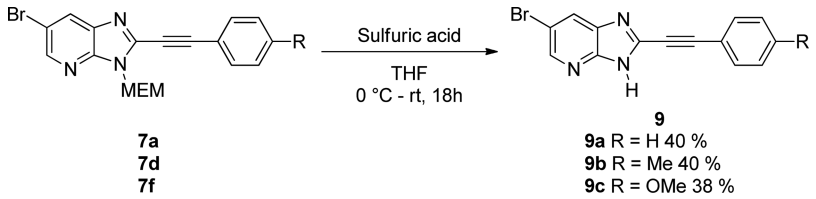
Scheme 5. Deprotection of *N*3-MEM-3*H*-imidazo[4,5-*b*]pyridine derivatives



7a
7d
7f

9
9a R = H 40 %
9b R = Me 40 %
9c R = OMe 38 %

used as electrophilic alkynylating reagents. The optimized reaction conditions were compatible with different substituents and protecting groups on the 3*H*-imidazo[4,5-*b*]pyridine. At the same time, a wide variety of electron-rich and electron-deficient dibromoalkenes reacted successfully with the 3*H*-imidazo[4,5-*b*]pyridine moiety. This procedure expands the scope of direct alkynylation reactions and represents an original method for the functionalization of the 3*H*-imidazo[4,5-*b*]pyridine scaffold, recently explored in medicinal chemistry.

EXPERIMENTAL SECTION

General Remarks. Commercially available reagents and solvents were used without further purification. Depending on the supplier and the batch used, LiO*t*Bu had to be repurified by sublimation. Yields refer to isolated and purified products. Reactions were monitored by thin-layer chromatography (TLC) carried out on 60F-254 silica gel plates and visualized under UV light at 254 and 365 nm. Column chromatography was performed on a Combiflash Companion using prepacked silica 60 columns. Chemical shifts (δ) of ^{1}H and ^{13}C NMR are reported in ppm, and residual nondeuterated solvents were used as references. Multiplicities are designated by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quadruplet, bs = broad singlet, m = multiplet. Melting points were measured with a Stuart SMP30. High-resolution mass spectra (HRMS) were measured by a TOF spectrometer, using electrospray ionization (ESI) or atmospheric pressure photoionization (APPI) method.

Typical Procedure A for the Synthesis of Variously Substituted 3*H*-Imidazo[4,5-*b*]pyridines. To a mixture of substituted 2,3-diaminopyridine (1 equiv) in trimethylorthoformate was added dropwise a concentrated solution of HCl (35%) (2 equiv). The reaction was stirred overnight at room temperature. Subsequently, the reaction mixture was dissolved in H_2O, neutralized by addition of a 3 M NaOH aqueous solution and extracted with AcOEt. The combined organic layers were dried with anhydrous $MgSO_4$ and filtered. Evaporation of the solvent under reduced pressure allowed the desired products with no further purification.

*Preparation of 3-Benzyl-6-bromo-3H-imidazo[4,5-b]pyridine (**1**).* 6-bromo-3*H*-imidazo[4,5-*b*]pyridine **a** was prepared following procedure A with commercially available 2,3-diamino-5-bromopyridine (12.00 g, 63.82 mmol) in trimethylorthoformate (200 mL) to give **a** (12.00 g, 95%) as a dark gray solid; mp: 223−225 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.47 (s, 1H), 8.41 (d, J = 1.6 Hz, 1H), 8.27 (d, J = 1.2 Hz, 1H); MS (ES+) m/z (%): 198.0 (100) $[M + H]^+$. Spectroscopic data were in agreement with those reported in the literature.[27]

To a mixture of compound **a** (6.00 g, 30.30 mmol) in dry DMF (80 mL) at 0 °C under argon atmosphere was added NaH (a 60% dispersion in mineral oil) (1.33 g, 33.33 mmol, 1.1 equiv) portionwise. The mixture was left stirring at 0 °C for 30 min under argon inlet, then benzyl bromide (5.70 g, 33.33 mmol, 1.1 equiv) was added dropwise. The reaction mixture was then allowed to warm up to room temperature and stirred under argon atmosphere overnight. Subsequently, the DMF was evaporated under reduced pressure, and the resulting residue was taken in H_2O and extracted with AcOEt. The combined organic layers were dried on $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/AcOEt 80/20) to give **1** as a beige solid (3.40 g, 39%); mp: 106−108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.47 (d, J = 1.7 Hz, 1H), 8.21 (d, J = 1.6 Hz, 1H), 8.02 (s, 1H), 7.41−7.26 (m, 5H), 5.44 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 145.8, 145.5, 145.2, 136.5, 135.5, 130.5, 129.2, 128.6, 127.9, 114.2, 47.4; MS (ES+) m/z (%): 288.0 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{13}H_{11}N_3Br$ 288.0136; found 288.0150.

*Preparation of 6-Bromo-3-(p-methoxybenzyl)-3H-imidazo[4,5-b]pyridine (**2**).* To a mixture of the 6-bromo-3*H*-imidazo[4,5-*b*]pyridine **a** (4.00 g, 20.20 mmol) in dry DMF (58 mL) at 0 °C under argon atmosphere was added NaH (60% dispersion in mineral oil) (0.90 g, 22.20 mmol, 1.1 equiv) portionwise. The mixture was left stirring at 0 °C for 30 min under argon atmosphere, then *p*-methoxybenzyl bromide (0.90 g, 22.20 mmol, 1.1 equiv) was added dropwise. The reaction mixture was then allowed to warm up to room temperature and stirred under argon atmosphere overnight. Subsequently, the DMF was evaporated under reduced pressure, and the resulting residue was taken in H_2O and extracted with AcOEt. The combined organic layers were dried on $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/AcOEt 70/30) to give **2** as a green solid (2.50 g, 39%); mp: 102−104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.47 (d, J = 1.8 Hz, 1H), 8.20 (d, J = 1.8 Hz, 1H), 7.99 (s, 1H), 7.26 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.37 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.7, 145.7, 145.2, 144.9, 136.5, 130.4, 129.4, 127.4, 114.4, 114.0, 55.3, 46.9; MS (ES+) m/z (%): 318.0 (100) $[M + H]^+$, 359.0 (10) $[M + CH_3CN + H]^+$; HRMS (ESI) calcd for $C_{14}H_{13}N_3OBr$ 318.0242; found 318.0237.

Typical Procedure B for the Protection of 3*H*-Imidazo[4,5-*b*]pyridines with MEMCl. To a solution of 3*H*-imidazo[4,5-*b*]pyridine (1 equiv) in dry toluene was added triethylamine (1.5 equiv). The reaction was stirred at 0 °C for 30 min. A solution of 2-methoxyethoxymethyl chloride (MEMCl) (2 equiv) in toluene was added to the mixture via a dropping funnel over a period of 1 h at 0 °C. The reaction mixture was then heated to reflux (110 °C) overnight. The solvent was evaporated under reduced pressure, and the residue purified by column chromatography (cyclohexane/AcOEt) to give the *N*3-protected-3*H*-imidazo[4,5-*b*]pyridine.

*Preparation of 6-Bromo-3-((2-methoxyethoxy)methyl)-3H-imidazo[4,5-b]pyridine (**3a**).* The reaction was carried out following procedure B and starting from 6-bromo-3*H*-imidazo[4,5-*b*]pyridine **a** (3.00 g, 15.15 mmol), MEMCl (3.77 g, 30.30 mmol) and triethylamine (3.16 mL) in 250 mL toluene to give **3a** (1.68 g, 40%) as an orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.46 (d, J = 1.0 Hz, 1H), 8.22 (t, J = 3.0 Hz, 2H), 5.73 (s, 2H), 3.74−3.64 (m, 2H), 3.55−3.47 (m, 2H), 3.34 (s, 3H); MS (ES+) m/z (%): 286.0 (100) $[M + H]^+$. Spectroscopic data were in agreement with those reported in the literature.[28]

*Preparation of 5-Chloro-3-((2-methoxyethoxy)methyl)-3H-imidazo[4,5-b]pyridine (**3b**).* 5-Chloro-3*H*-imidazo[4,5-*b*]pyridine **b** was prepared following procedure A from commercially available 2,3-diamino-6-chloropyridine (8.55 g, 59.55 mmol) in trimethylorthoformate (195 mL) to give **b** (9.00 g, 98%) as a gray solid; mp: 224−226 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.50 (s, 1H), 8.07 (d, J = 8.3 Hz, 1H), 7.29 (d, J = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 151.6, 145.2, 143.7, 128.4, 126.1, 117.6; MS (ES+) m/z (%): 154.0 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_6H_5N_3Cl$ 154.0172; found 154.0172.

Compound **3b** was prepared following procedure A starting from 5-chloro-3*H*-imidazo[4,5-*b*]pyridine **b** (3.00 g, 19.54 mmol), MEMCl (4.87 g, 39.07 mmol) and triethylamine (4.07 mL) in 300 mL toluene to give **3b** (2.70 g, 57%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$)

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δ (ppm) 8.22 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 8.3 Hz, 1H), 5.73 (s, 2H), 3.75−3.70 (m, 2H), 3.55−3.49 (m, 2H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 146.1, 145.9, 144.4, 133.7, 130.1, 118.9, 72.7, 71.2, 68.7, 58.7; MS (ES+) m/z (%): 242.1 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{10}H_{13}N_3O_2Cl$ 242.0696; found 242.0691.

*Preparation of 6-Bromo-7-chloro-3-((2-methoxyethoxy)methyl)-3H-imidazo[4,5-b]pyridine (**3c**).* 6-Bromo-7-chloro-3*H*-imidazo[4,5-*b*]pyridine **c** was prepared starting from 6-bromo-3*H*-imidazo[4,5-*b*]pyridine **a**. Compound **a** (3.00 g, 15.15 mmol) in AcOH (18 mL) was added to *m*-chloroperbenzoic acid (7.47 g, 30.30 mmol, 2 equiv). The reaction mixture was stirred at room temperature for 3 days and then filtered on a sintered glass disk to allow a first fraction of 6-bromo-3*H*-imidazo[4,5-*b*]pyridine 4-oxide. The filtrate was concentrated under reduced pressure, taken in AcOEt, and filtered again to allow a second fraction of the *N*-oxide. Both fractions of 6-bromo-3*H*-imidazo[4,5-*b*]pyridine 4-oxide were taken in AcOEt, and the resulting suspension was refluxed for 1 h. Subsequent filtration on sintered glass disk furnished 6-bromo-3*H*-imidazo[4,5-*b*]pyridine 4-oxide with no trace of benzoic acid. The solid was distributed into microwave tubes in 250 mg portions, and $POCl_3$ (1.5 mL) was added in each tube. The reaction mixture was heated under microwave irradiation at 80 °C for 10 min. Subsequently, the crude materials were poured on ice and neutralized with a 3 M NaOH aqueous solution, and the aqueous layer was extracted with AcOEt. The combined organic layers were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting product **c** (1.43 g, 40%), a beige solid, is an inseparable mixture of two regiosiomers: 7-chloro and 5-chloro- imidazo[4,5-*b*]pyridine in 85/15 ratio, respectively; mp: 199−201 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.54 (bs, 1H), 8.57 (s, 2H), 8.50 (s, 0.3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 146.6, 145.8, 145.5, 142.3, 133.7, 133.2, 132.3, 130.4, 128.8, 127.8, 113.1, 111.1; MS (ES+) m/z (%): 231.9 (100) $[M + H]^+$, 273.0 (20) $[M + CH_3CN + H]^+$; HRMS (ESI) calcd for $C_6H_4N_3ClBr$ 231.9277; found 231.9287.

Compound **3c** was prepared following procedure A starting from 6-bromo-7-chloro-3*H*-imidazo[4,5-*b*]pyridine **c** (1.85 g, 7.94 mmol), MEMCl (1.98 g, 15.88 mmol), and triethylamine (1.66 mL) in 150 mL toluene to give **3c** (1.62 g, 64%) as a yellow solid; mp: 72−74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.36 (s, 1H), 8.15 (s, 1H), 5.61 (s, 2H), 3.66−3.52 (m, 2H), 3.44−3.35 (m, 2H), 3.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 147.0, 146.4, 145.5, 135.3, 134.5, 115.5, 73.5, 71.7, 69.3, 59.2; MS (ES+) m/z (%): 322.0 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{10}H_{12}N_3O_2ClBr$ 319.9801; found 319.9803.

*Preparation of 3-((2-Methoxyethoxy)methyl)-3H-imidazo[4,5-b]pyridine (**3h**).* 3*H*-imidazo[4,5-*b*]pyridine **d** was prepared following procedure A with commercially available pyridine-2,3-diamine (2.00 g, 18.33 mmol) in trimethylorthoformate (60 mL) to give **d** (1.63 g, 74%) as a dark red solid; mp: 150−152 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.43 (s, 1H), 8.34 (d, J = 4.5 Hz, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.22 (dd, J = 4.5, 7.9 Hz, 1H). Spectroscopic data were in agreement with those reported in the literature.[27]

Compound **3h** was prepared following procedure A starting from 3*H*-imidazo[4,5-*b*]pyridine **d** (0.60 g, 5.04 mmol), MEMCl (1.25 g, 10.07 mmol) and triethylamine (1.05 mL) in 80 mL toluene to give **3h** (0.63 g, 60%) as an yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.07 (dd, J = 4.8, 0.9 Hz, 1H), 7.98 (s, 1H), 7.74 (dd, J = 8.0, 0.9 Hz, 1H), 6.91 (dd, J = 8.0, 4.8 Hz, 1H), 5.43 (s, 2H), 3.41−3.38 (m, 2H), 3.17−3.14 (m, 2H), 2.98 (s, 3H). Spectroscopic data were in agreement with those reported in the literature.[28]

Typical Procedure C for the Suzuki Coupling of 6-Bromo-3-((2-methoxyethoxy)methyl)-3*H*-imidazo[4,5-*b*]pyridine. In a round-bottom flask and under argon inlet, to a solution of 6-bromo-3-((2-methoxyethoxy)methyl)-3*H*-imidazo[4,5-*b*]pyridine (3.50 mmol, 1 equiv) in 1,4-dioxane (6 mL) were added $PdCl_2$(dppf) (0.35 mmol, 0.1 equiv) and an aqueous solution of Cs_2CO_3 (2M) (13.98 mmol, 4 equiv). Then, the boronic acid (10.48 mmol, 3 equiv) was slowly added. The reaction mixture was stirred at 100 °C for 12 h. The mixture was extracted with AcOEt (3×), and the organic layers dried with $MgSO_4$. Purification by flash column chromatography (cyclohexane/AcOEt 80/20) afforded the desired products.

*3-((2-Methoxyethoxy)methyl)-6-phenyl-3H-imidazo[4,5-b]pyridine (**3d**).* Following procedure C afforded **3d** (0.65 g, 66%) as a green solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.64 (d, J = 1.4 Hz, 1H), 8.38−8.12 (m, 2H), 7.60 (m, 2H), 7.47 (m, 2H), 7.39 (m, 1H), 5.77 (s, 2H), 3.78−3.67 (m, 2H), 3.55−3.47 (m, 2H), 3.34 (s, 3H); MS (ES+) m/z (%): 284.1 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{16}H_{18}N_3O_2$ 284.1399; found 284.1400. Spectroscopic data were in agreement with those reported in the literature.[28]

*3-((2-Methoxyethoxy)methyl)-6-(4-methoxyphenyl)-3H-imidazo-[4,5-b]pyridine (**3e**).* Following procedure C afforded **3e** (1.07 g, 98%) as a green solid; mp: 68−70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.58 (d, J = 1.9 Hz, 1H), 8.23 (s, 1H), 8.18 (d, J = 1.9 Hz, 1H), 7.51 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 5.74 (s, 2H), 3.83 (s, 3H), 3.75−3.68 (m, 2H), 3.53−3.46 (m, 2H), 3.32 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ (ppm) 159.4, 146.2, 144.8, 144.0, 135.2, 132.7, 131.0, 128.6, 126.0, 114.6, 73.0, 71.6, 68.9, 59.1, 55.4; MS (ES+) m/z (%): 314.2 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{17}H_{20}N_3O_3$ 314.1505; found 314.1509.

*2-Fluoro-4-(3-((2-methoxyethoxy)methyl)-3H-imidazo[4,5-b]-pyridin-6-yl)benzonitrile (**3f**).* Following procedure C afforded **3f** (0.91 g, 80%) as a brown solid; mp: 173−175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.65 (s, 1H), 8.41 (s, 1H), 8.28 (s, 1H), 7.75 (t, J = 7.2 Hz, 1H), 7.50 (dd, J = 13.4, 9.3 Hz, 2H), 5.81 (s, 2H), 3.79−3.70 (m, 2H), 3.57−3.50 (m, 2H), 3.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 163.6 (d, $^1J_{C-F}$ = 259.6 Hz), 146.0, 145.9, 144.1, 134.2, 130.2, 126.6, 123.9 (d, $^4J_{C-F}$ = 3.3 Hz), 115.5, 115.2, 113.9, 100.6, 100.4, 73.4, 71.7, 69.3, 59.2; MS (ES+) m/z (%): 327.1 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{17}H_{16}N_4O_2F$ 327.1257; found 327.1255.

*3-((2-Methoxyethoxy)methyl)-6-(pyridine-4-yl)-3H-imidazo[4,5-b]pyridine (**3g**).* In a sealed tube and under argon inlet, $Pd(PPh_3)_4$ (300 mg, 0.26 mmol, 0.1 equiv) was added to a solution of 6-bromo-3-((2-methoxyethoxy)methyl)-3*H*-imidazo[4,5-*b*]pyridine (744 mg, 2.60 mmol) in a mixture of 1,4-dioxane/H_2O 4/1 (15 mL), followed by K_2CO_3 (1.08 g, 7.80 mmol, 3equiv) and the boronic acid (639 mg, 5.20 mmol, 2 equiv). The reaction mixture was stirred at 110 °C for 12 h. After cooling to room temperature, the mixture was extracted with AcOEt (3×), and the organic layers dried with $MgSO_4$. Purification by flash column chromatography (dichloromethane/EtOH 95/5) afforded **3g** as a beige solid (600 mg, 80%); mp: 53−55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.73−8.72 (m, 3H), 8.32 (d, J = 2.0 Hz, 1H), 8.30 (s, 1H), 7.56 (d, J = 6.1 Hz, 2H), 5.80 (s, 2H), 3.79−3.68 (m, 2H), 3.59−3.45 (m, 2H), 3.35 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ (ppm) 150.2, 147.5, 145.8, 145.5, 143.6, 135.2, 129.6, 126.3, 121.7, 72.9, 71.4, 68.8, 58.9; MS (ES+) m/z (%): 285.1 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{15}H_{17}N_4O_2$ 285.1352; found 285.1353.

Typical Procedure for the Synthesis of 1,1-Dibromoalkenes (4). 1,1-Dibromoalkenes were synthesized according to the Ramirez procedure starting from commercially available aldehydes.[29] The typical procedure for their preparation follows, presenting 2-bromo-4-(2,2-dibromovinyl)-1-methoxybenzene as an example.[30]

*2-Bromo-4-(2,2-dibromovinyl)-1-methoxybenzene (**4k**).* In a round-bottom flask and under argon inlet, a solution of PPh_3 (10.98 g, 41.85 mmol, 3 equiv) in dichloromethane (30 mL) was slowly added via a dropping funnel to a solution of 3-bromo-4-methoxybenzaldehyde (3.00 g, 13.95 mmol) and carbon tetrabromide (6.94 g, 20.93 mmol, 1.5 equiv) in dichloromethane (100 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure. Purification by flash column chromatography (cyclohexane) afforded dibromoalkene **4k**, a yellow solid (1.80 g, 35%); mp: 58−60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.76 (d, J = 2.1 Hz, 1H), 7.47 (dd, J = 8.6, 2.1 Hz, 1H), 7.34 (s, 1H), 6.87 (d, J = 8.6 Hz, 1H), 3.90 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ (ppm) 155.7, 134.8, 133.0, 128.8, 128.8, 111.4, 111.3, 88.8, 56.2; HRMS (APPI) calcd for $C_9H_7Br_3O$ 367.8046; found 367.8038.

Compounds **4a**,[31] **4b**,[31] **4c**,[32] **4d**,[31] **4e**,[33] **4f**,[33] **4g**,[34] **4h**,[35] **4i**,[33] **4j**,[32] **4l**,[36] **4m**,[37] and **4n**[32] showed satisfactory spectroscopic data in agreement with those reported in the literature.

Typical Procedure D for the Direct Alkynylation between 3*H*-Imidazo[4,5-*B*]pyridines and 1,1-Dibromoalkenes. In a round-bottom flask, *N*3-protected-3*H*-imidazo[4,5-*b*]pyridine (1 equiv),

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copper catalyst (0.1 equiv), DPEPhos (0.2 equiv), and 1,4-dioxane (2 mL) were mixed under argon inlet for 5 min at room temperature. LiO*t*Bu (6 equiv) was then added, the reaction mixture was stirred for 1 min, and 1,1-dibromoalkene (2 equiv) was added. The mixture was stirred at 110 °C for 4 h. The crude reaction mixture was allowed to cool to room temperature. AcOEt was added to the mixture, which was filtered through Celite. The solvents were evaporated under reduced pressure. Purification by flash column chromatography (cyclohexane/AcOEt 95/5) afforded the desired alkynes. It should be noticed that the direct alkynylation reaction was performed in a sealed tube for compounds **5a**, **5b**, **6a**, **6b**, **7a**, **7d**, **7e**, **7f**, **7m**, **8g**, and **8j** which gave better results than if performed in a flask.

*3-Benzyl-6-bromo-2-(phenylethynyl)-3H-imidazo[4,5-b]pyridine (**5a**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **1** (100 mg, 0.35 mmol) and CuBr·SMe_2 (7.13 mg, 0.04 mmol) as the copper catalyst in a sealed tube afforded **5a** (90 mg, 66%) as a brown solid after flash chromatography, followed by recrystallization in cyclohexane; mp: 127−129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.48 (s, 1H), 8.17 (s, 1H), 7.59 (d, J = 6.9 Hz, 2H), 7.50−7.37 (m, 5H), 7.30 (d, J = 6.7 Hz, 3H), 5.60 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 146.3, 145.6, 139.5, 136.4, 135.9, 132.3, 130.4, 129.9, 129.0, 128.8, 128.3, 128.1, 120.6, 114.8, 97.2, 78.7, 47.2; MS (ES+) m/z (%): 390.0 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{15}N_3Br$ 388.0449; found 388.0454.

*3-Benzyl-6-bromo-2-(naphthalen-2-ylethynyl)-3H-imidazo[4,5-b]pyridine (**5b**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **1** (100 mg, 0.35 mmol) and CuBr·SMe_2 (7.13 mg, 0.04 mmol) as the copper catalyst in a sealed tube afforded **5b** (64 mg, 42%) as a yellow solid after flash chromatography, followed by recrystallization in cyclohexane; mp: 202−204 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.49 (s, 1H), 8.18 (s, 1H), 8.12 (s, 1H), 7.85 (d, J = 7.5 Hz, 3H), 7.57 (t, J = 8.5 Hz, 3H), 7.46 (d, J = 6.7 Hz, 2H), 7.33 (d, J = 7.2 Hz, 3H), 5.64 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 146.3, 145.6, 136.5, 136.0, 133.7, 133.2, 132.8, 129.9, 129.0, 128.6, 128.4, 128.2, 128.1, 128.0, 127.9, 127.9, 127.2, 117.8, 114.9, 97.7, 79.0, 47.2; MS (ES+) m/z (%): 440.1 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{25}H_{17}N_3Br$ 438.0606; found 438.0608.

*6-Bromo-3-(4-methoxybenzyl)-2-(phenylethynyl)-3H-imidazo-[4,5-b]pyridine (**6a**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **2** (100 mg, 0.31 mmol) and CuBr·SMe_2 (6.46 mg, 0.03 mmol) as the copper catalyst in a sealed tube afforded **6a** (84 mg, 65%) as a brown solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 176−178 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.48 (s, 1H), 8.16 (s, 1H), 7.64−7.62 (m, 2H), 7.55−7.29 (m, 5H), 6.85−6.82 (m, 2H), 5.54 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.6, 146.2, 136.4, 134.3, 132.3, 130.4, 130.2, 129.8, 129.7, 128.8, 128.1, 120.7, 114.8, 114.2, 97.1, 78.9, 55.4, 46.7; MS (ES+) m/z (%): 420.1 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{17}N_3OBr$ 418.0555; found 418.0563.

*6-Bromo-3-(4-methoxybenzyl)-2-(naphthalen-2-ylethynyl)-3H-imidazo[4,5-b]-pyridine (**6b**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **2** (100 mg, 0.31 mmol) and CuBr·SMe_2 (6.46 mg, 0.03 mmol) as the copper catalyst in a sealed tube afforded **6b** (87 mg, 60%) as a white solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 154−156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.48 (d, J = 1.9 Hz, 1H), 8.15 (s, 1H), 8.14 (s, 1H), 7.85 (dd, J = 8.7, 2.8 Hz, 3H), 7.62 (dd, J = 7.5, 0.9 Hz, 1H), 7.55 (t, J = 4.5 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.56 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.6, 146.2, 145.5, 139.4, 136.5, 133.7, 133.1, 132.8, 129.8, 129.7, 128.6, 128.2, 128.0, 127.9, 127.2, 117.8, 114.8, 114.3, 97.6, 79.1, 55.4, 46.7; MS (ES+) m/z (%): 470.1 (35) $[M + H]^+$; HRMS (ESI) calcd for $C_{26}H_{19}N_3OBr$ 468.0711; found 468.0726.

*6-Bromo-3-((2-methoxyethoxy)methyl)-2-(phenylethynyl)-3H-imidazo[4,5-b]pyridine (**7a**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3a** (100 mg, 0.35 mmol) and $Cu(OAc)_2$ (6.35 mg, 0.04 mmol) as the copper catalyst in a sealed tube afforded **7a** (62 mg, 46% versus 19% with CuBr·SMe_2) as an orange solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 70−72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.48 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 7.70−7.61 (m, 2H), 7.50−7.36 (m, 3H), 5.87 (s, 2H), 3.82−3.75 (m, 2H), 3.55−3.49 (m, 2H), 3.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 146.5, 145.8, 139.9, 136.3, 132.5, 130.5, 130.0, 128.8, 120.5, 115.2, 97.2, 78.1, 72.9, 71.6, 69.5, 59.2; MS (ES+) m/z (%): 386.1 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{17}N_3O_2Br$ 386.0504; found 386.0511.

*6-Bromo-3-((2-methoxyethoxy)methyl)-2-(naphtalen-2-ylethynyl)-3H-imidazo[4,5-b]- pyridine (**7b**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3a** (100 mg, 0.35 mmol) and $Cu(OAc)_2$ (6.35 mg, 0.04 mmol) as the copper catalyst afforded **7b** (118 mg, 77% versus 33% with CuBr·SMe_2) as a white solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 117−119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.48 (d, J = 2.0 Hz, 1H), 8.21−8.17 (m, 2H), 7.87−7.84 (m, 3H), 7.65 (dd, J = 8.5, 1.5 Hz, 1H), 7.57−7.54 (m, 2H), 5.91 (s, 2H), 3.88−3.76 (m, 2H), 3.59−3.47 (m, 2H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 146.5, 145.8, 140.0, 136.4, 133.8, 133.4, 132.8, 130.0, 128.6, 128.2, 128.0, 128.0, 127.9, 127.2, 117.7, 115.2, 97.8, 78.4, 72.9, 71.6, 69.5, 59.2; MS (ES+) m/z (%): 438.1 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{19}N_3O_2Br$ 436.0661; found 436.0662.

*2-([1,1′-Biphenyl]-4-ylethynyl)-6-bromo-3-((2-methoxyethoxy)-methyl)-3H-imidazo-[4,5-b]pyridine (**7c**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3a** (100 mg, 0.35 mmol) and CuBr·SMe_2 (6.46 mg, 0.04 mmol) as the copper catalyst afforded **7c** (71 mg, 44%) as a yellowish solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 139−141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.48 (s, 1H), 8.17 (s, 1H), 7.78−7.56 (m, 6H), 7.53−7.37 (m, 3H), 5.88 (s, 2H), 3.82−3.79 (m, 2H), 3.54−3.52 (m, 2H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 146.4, 145.7, 143.1, 139.8, 139.8, 136.3, 132.8, 129.9, 129.0, 128.1, 127.3, 127.1, 119.2, 115.1, 97.2, 78.7, 72.8, 71.5, 69.4, 59.1; MS (ES+) m/z (%): 464.1 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{24}H_{21}N_3O_2Br$ 462.0817; found 462.0818.

*6-Bromo-3-((2-methoxyethoxy)methyl)-2-(p-tolylethynyl)-3H-imidazo[4,5-b]pyridine (**7d**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3a** (100 mg, 0.35 mmol) and CuBr·SMe_2 (6.46 mg, 0.04 mmol) as the copper catalyst in a sealed tube afforded **7d** (74 mg, 53% versus 48% with $Cu(OAc)_2$) as a light yellow solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 89−91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.44 (d, J = 1.9 Hz, 1H), 8.13 (d, J = 1.9 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 5.84 (s, 2H), 3.78−3.75 (m, 2H), 3.58−3.42 (m, 2H), 3.32 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 146.2, 145.7, 141.0, 140.1, 136.3, 132.3, 129.8, 129.5, 117.4, 115.1, 97.7, 77.6, 72.8, 71.5, 69.4, 59.2, 21.8; MS (ES+) m/z (%): 402.1 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{19}N_3O_2Br$ 400.0661; found 400.0657.

*6-Bromo-3-((2-methoxyethoxy)methyl)-2-(o-tolylethynyl)-3H-imidazo[4,5-b]pyridine (**7e**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3a** (100 mg, 0.35 mmol) and CuBr·SMe_2 (6.46 mg, 0.04 mmol) as the copper catalyst in a sealed tube afforded **7e** (84 mg, 60%) as a brown solid after flash chromatography; mp: 64−66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.45 (s, 1H), 8.14 (s, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.38−7.12 (m, 3H), 5.84 (s, 2H), 3.81−3.69 (m, 2H), 3.53−3.43 (m, 2H), 3.30 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 146.4, 141.6, 136.4, 133.0, 130.5, 130.2, 130.0, 130.0, 128.8, 126.0, 120.4, 115.2, 96.4, 81.8, 72.8, 71.5, 69.4, 59.2, 21.0; MS (ES+) m/z (%): 400.1 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{19}N_3O_2Br$ 400.0661; found 400.0652.

*6-Bromo-3-((2-methoxyethoxy)methyl)-2-((4-methoxyphenyl)-ethynyl)-3H-imidazo-[4,5-b]pyridine (**7f**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3a** (100 mg, 0.35 mmol) and CuBr·SMe_2 (6.46 mg, 0.04 mmol) as the copper catalyst in a sealed tube afforded **7f** (76 mg, 52% versus 53% with

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$Cu(OAc)_2$) as a yellow solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 137−139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.44 (d, J = 1.8 Hz, 1H), 8.13 (d, J = 1.8 Hz, 1H), 7.57 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 5.84 (s, 2H), 3.83 (s, 3H), 3.80−3.75 (m, 2H), 3.53−3.48 (m, 2H), 3.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 161.3, 146.1, 145.8, 136.4, 134.1, 130.1, 129.8, 115.0, 114.5, 112.4, 97.8, 77.3, 72.8, 71.5, 69.4, 59.2, 55.5; MS (ES+) m/z (%): 416.1 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{19}N_3O_3Br$ 416.0610; found 416.0609.

*2-((3,4-Bis((tert-butyldimethylsilyl)-oxy)phenyl)ethynyl)-6-bromo-3-((2-methoxy- ethoxy)methyl)-3H-imidazo[4,5-b]pyridine (**7g**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3a** (100 mg, 0.35 mmol) and CuBr·SMe_2 (6.46 mg, 0.04 mmol) as the copper catalyst afforded **7g** (124 mg, 55%) as a beige solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 95−97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.46 (d, J = 1.4 Hz, 1H), 8.15 (d, J = 1.3 Hz, 1H), 7.15 (dd, J = 8.2, 2.0 Hz, 1H), 7.11 (d, J = 1.9 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 5.85 (s, 2H), 3.82−3.75 (m, 2H), 3.54−3.48 (m, 2H), 3.33 (s, 3H), 1.00 (s, 9H), 0.99 (s, 9H), 0.23 (s, 6H), 0.22 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 149.9, 147.1, 146.1, 145.7, 140.3, 136.3, 129.7, 126.5, 124.7, 121.3, 115.0, 112.9, 97.8, 72.7, 71.5, 69.4, 59.1, 25.9, 18.5, 18.4, - 4.0, - 4.3; MS (ES+) m/z (%): 648.2 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{30}H_{45}N_3O_4BrSi_2$ 646.2132; found 646.2120.

*6-Bromo-2-((3-fluorophenyl)ethynyl)-3-((2-methoxyethoxy)-methyl)-3H-imidazo[4,5-b]pyridine (**7h**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3a** (100 mg, 0.35 mmol) and CuBr·SMe_2 (6.46 mg, 0.04 mmol) as the copper catalyst afforded **7h** (51 mg, 36% versus 32% with $Cu(OAc)_2$) as a brown solid after flash chromatography; mp: 71−73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.47 (d, J = 1.8 Hz, 1H), 8.16 (d, J = 1.8 Hz, 1H), 7.47−7.29 (m, 3H), 7.14 (d, J = 7.2 Hz, 1H), 5.85 (s, 2H), 3.78−3.75 (m, 2H), 3.52−3.49 (m, 2H), 3.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 162.4 (d, $^1J_{C-F}$ = 248.1 Hz), 146.7, 145.7, 139.4, 136.2, 130.5 (d, $^3J_{C-F}$ = 8.5 Hz), 130.2, 128.4 (d, $^4J_{C-F}$ = 3.2 Hz), 122.3 (d, $^3J_{C-F}$ = 9.4 Hz), 119.2 (d, $^2J_{C-F}$ = 23.5 Hz), 117.9 (d, $^2J_{C-F}$ = 21.2 Hz), 115.3, 95.5 (d, $^4J_{C-F}$ = 3.4 Hz), 78.7, 72.8, 71.6, 69.5, 59.2; MS (ES+) m/z (%): 406.0 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{16}N_3O_2FBr$ 404.0410; found 404.0405.

*6-Bromo-2-((4-chlorophenyl)ethynyl)-3-((2-methoxyethoxy)-methyl)-3H-imidazo[4,5-b]pyridine (**7i**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3a** (100 mg, 0.35 mmol) and CuBr·SMe_2 (6.46 mg, 0.04 mmol) as the copper catalyst afforded **7i** (80 mg, 54% versus 37% with $Cu(OAc)_2$) as a yellowish solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 118−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.46 (d, J = 1.5 Hz, 1H), 8.14 (d, J = 1.6 Hz, 1H), 7.56 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 5.83 (s, 2H), 3.85−3.71 (m, 2H), 3.59−3.44 (m, 2H), 3.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 146.5, 145.7, 136.7, 136.2, 133.5, 130.0, 129.2, 118.9, 115.2, 95.8, 78.9, 72.7, 71.5, 69.4, 59.1; MS (ES+) m/z (%): 422.0 (100) $[M + H]^+$; HRMS calcd for $C_{18}H_{16}N_3O_2ClBr$ 420.0114; found 420.0114.

*6-Bromo-2-((3-bromophenyl)ethynyl)-3-((2-methoxyethoxy)-methyl)-3H-imidazo[4,5-b]pyridine (**7j**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3a** (100 mg, 0.35 mmol) and CuBr·SMe_2 (6.46 mg, 0.04 mmol) as the copper catalyst afforded **7j** (83 mg, 51%) as a white solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 91−93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.49 (s, 1H), 8.18 (s, 1H), 7.79 (s, 1H), 7.58 (d, J = 7.5 Hz, 2H), 7.37−7.17 (m, 1H), 5.87 (s, 2H), 3.87−3.70 (m, 2H), 3.61−3.45 (m, 2H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 146.7, 145.7, 136.2, 134.9, 133.5, 130.9, 130.2, 130.1, 122.5, 122.4, 115.2, 95.2, 79.1, 72.8, 71.6, 69.4, 59.2; MS (ES+) m/z (%): 466.0 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{16}N_3O_2Br_2$ 463.9609; found 463.9602.

*6-Bromo-2-((3-bromo-4-methoxyphenyl)-ethynyl)-3-((2-methoxyethoxy)methyl)-3H-imidazo[4,5-b]pyridine (**7k**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3a** (100 mg, 0.35 mmol) and CuBr·SMe_2 (6.46 mg, 0.04 mmol) as the copper catalyst afforded **7k** (81 mg, 47% versus 21% with $Cu(OAc)_2$) as a yellow solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 136−138 °C;^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.45 (d, J = 2.0 Hz, 1H), 8.14 (d, J = 2.0 Hz, 1H), 7.82 (d, J = 2.0 Hz, 1H), 7.57 (dd, J = 8.6, 2.0 Hz, 1H), 6.90 (d, J = 8.6 Hz, 1H), 5.83 (s, 2H), 3.93 (s, 3H), 3.78−3.75 (m, 2H), 3.53−3.50 (m, 2H), 3.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 157.7, 146.4, 145.8, 139.8, 137.0, 136.3, 133.2, 130.0, 115.2, 113.8, 111.9, 111.8, 95.9, 78.1, 72.8, 71.6, 69.4, 59.2, 56.5; MS (ES+) m/z (%): 496.0 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{18}N_3O_3Br_2$ 493.9715; found 493.9719.

*6-Bromo-3-((2-methoxyethoxy)methyl)-2-((4-(trifluoromethyl)-phenyl)ethynyl)-3H-imidazo[4,5-b]pyridine (**7l**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3a** (100 mg, 0.35 mmol) and CuBr·SMe_2 (6.46 mg, 0.04 mmol) as the copper catalyst afforded **7l** (48 mg, 31% versus 28% with $Cu(OAc)_2$) as a white solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 121−123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.50 (d, J = 1.8 Hz, 1H), 8.19 (d, J = 1.8 Hz, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H), 5.88 (s, 2H), 3.80−3.77 (m, 2H), 3.53−3.51 (m, 2H), 3.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 146.9, 145.7, 139.2, 136.3, 132.7, 132.0 (q, $^2J_{C-F3}$ = 32.3 Hz), 130.3, 125.8 (q, $^3J_{C-F3}$ = 3.7 Hz), 124.3 (d, $^4J_{C-F3}$ = 0.9 Hz), 123.7 (q, $^1J_{C-F3}$ = 270.8 Hz), 115.4, 95.1, 80.0, 72.9, 71.6, 69.6, 59.2; MS (ES+) m/z (%): 454.0 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{16}N_3O_2F_3Br$ 454.0378; found 454.0375.

*6-Bromo-3-((2-methoxyethoxy)methyl)-2-(thiophen-3-ylethynyl)-3H-imidazo[4,5-b]- pyridine (**7m**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3a** (100 mg, 0.35 mmol) and CuBr·SMe_2 (6.46 mg, 0.04 mmol) as the copper catalyst in a sealed tube afforded **7m** (70 mg, 51% versus 42% with $Cu(OAc)_2$) as a beige solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 99−101 °C;^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.47 (d, J = 1.8 Hz, 1H), 8.16 (d, J = 1.8 Hz, 1H), 7.82−7.74 (m, 1H), 7.37 (dd, J = 5.0, 3.0 Hz, 1H), 7.32−7.26 (m, 1H), 5.85 (s, 2H), 3.81−3.78 (m, 2H), 3.54−3.51 (m, 2H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 146.4, 145.7, 139.9, 136.3, 132.4, 129.9, 126.3, 119.7, 115.1, 92.6, 77.9, 72.8, 71.5, 69.5, 59.2; MS (ES+) m/z (%): 394.0 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{16}H_{15}N_3O_2SBr$ 392.0068; found 392.0060.

*5-Chloro-3-((2-methoxyethoxy)methyl)-2-(naphtalen-2-ylethynyl)-3H-imidazo[4,5-b]pyridine (**8a**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3b** (100 mg, 0.41 mmol) and CuBr·SMe_2 (8.51 mg, 0.04 mmol) as the copper catalyst afforded **8a** (80 mg, 50%) as a brown solid after flash chromatography; mp: 121−123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.19 (s, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.85 (d, J = 8.3 Hz, 3H), 7.64 (d, J = 8.5 Hz, 1H), 7.60−7.48 (m, 2H), 7.29 (d, J = 8.3 Hz, 1H), 5.89 (s, 2H), 3.85−3.82 (m, 2H), 3.57−3.54 (m, 2H), 3.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 147.3, 134.3, 134.1, 133.7, 133.3, 132.8, 130.0, 128.6, 128.2, 128.0, 127.9, 127.1, 120.1, 117.8, 97.5, 78.5, 72.8, 71.6, 69.5, 59.2; MS (ES+) m/z (%): 392.1 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{19}N_3O_2Cl$392.1166; found 392.1168.

*5-Chloro-3-((2-methoxyethoxy)methyl)-2-((4-methoxyphenyl)-ethynyl)-3H-imidazo-[4,5-b]pyridine (**8b**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3b** (100 mg, 0.41 mmol) and CuBr·SMe_2 (8.51 mg, 0.04 mmol) as the copper catalyst afforded **8b** (53 mg, 35%) as a brown solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 114−116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.96 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 8.7 Hz, 2H), 7.29 (s, 1H), 6.92 (d, J = 8.7 Hz, 2H), 5.84 (s, 2H), 3.85 (s, 3H), 3.83−3.77 (m, 2H), 3.58−3.48 (m, 2H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 161.2, 147.0, 134.2, 134.1, 130.9, 129.8, 120.4, 119.9, 114.4, 112.5, 97.5, 77.3, 72.7, 71.5, 69.5, 59.2, 55.5; MS (ES+) m/z (%): 372.1 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{19}N_3O_3Cl$ 372.1115; found 372.1102.

*6-Bromo-7-chloro-3-((2-methoxyethoxy)-methyl)-2-(naphtalen-2-ylethynyl)-3H-imidazo[4,5-b]pyridine (**8c**).* The reaction carried out

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following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3c** (100 mg, 0.31 mmol) and CuBr·SMe_2 (6.41 mg, 0.03 mmol) as the copper catalyst afforded **8c** (88 mg, 60%) as a yellow solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 138−140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.52 (s, 1H), 8.18 (s, 1H), 7.84 (d, J = 7.6 Hz, 3H), 7.63 (d, J = 8.4 Hz, 1H), 7.59−7.48 (m, 2H), 5.89 (s, 2H), 3.85−3.78 (m, 2H), 3.56−3.50 (m, 2H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 147.4, 146.0, 139.9, 134.4, 134.3, 133.7, 133.4, 132.6, 128.5, 128.1, 127.9, 127.8, 127.1, 117.4, 115.9, 98.3, 78.1, 73.2, 71.5, 69.6, 59.2; MS (ES+) m/z (%): 472.0 (100) $[M + H]^+$;HRMS (ESI) calcd for $C_{22}H_{18}N_3O_2ClBr$ 470.0271; found 470.0273.

*6-Bromo-7-chloro-3-((2-methoxyethoxy)-methyl)-2-((4-methoxyphenyl)ethynyl)-3H-imidazo[4,5-b]pyridine (**8d**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3c** (100 mg, 0.31 mmol) and CuBr·SMe_2 (6.41 mg, 0.03 mmol) as the copper catalyst afforded **8d** (55 mg, 39%) as a brown solid after flash chromatography; mp: 117−119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.52 (s, 1H), 7.58 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 5.85 (s, 2H), 3.85 (s, 3H), 3.80−3.77 (m, 2H), 3.56−3.46 (m, 2H), 3.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 161.4, 147.2, 146.1, 140.3, 134.4, 134.2, 134.2, 115.8, 114.5, 112.1, 98.5, 77.1, 73.1, 71.5, 69.5, 59.2, 55.5; MS (ES+) m/z (%): 452.0 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{18}N_3O_3ClBr$ 450.0220; found 450.0229.

*3-((2-Methoxyethoxy)methyl)-2-(naphtalen-2-ylethynyl)-6-phenyl-3H-imidazo[4,5-b]pyridine (**8e**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3d** (100 mg, 0.35 mmol) and CuBr·SMe_2 (7.26 mg, 0.04 mmol) as the copper catalyst afforded **8e** (109 mg, 72%) as a brown solid after flash chromatography; mp: 127−129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.69 (d, J = 1.8 Hz, 1H), 8.21 (s, 2H), 7.92−7.80 (m, 3H), 7.73−7.59 (m, 3H), 7.59−7.45 (m, 4H), 7.40 (t, J = 7.3 Hz, 1H), 5.96 (s, 2H), 3.92−3.84 (m, 2H), 3.62−3.53 (m, 2H), 3.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 146.6, 145.2, 139.4, 138.5, 135.5, 133.7, 133.7, 133.2, 132.8, 129.2, 128.5, 128.2, 128.0, 128.0, 127.8, 127.6, 127.1, 126.0, 117.9, 97.2, 78.8, 72.8, 71.6, 69.4, 59.2; MS (ES+) m/z (%): 434.2 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{28}H_{24}N_3O_2$ 434.1869; found 434.1863.

*3-((2-Methoxyethoxy)methyl)-2-((4-methoxyphenyl)ethynyl)-6-phenyl-3H-imidazo-[4,5-b]pyridine (**8f**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3d** (100 mg, 0.35 mmol) and CuBr·SMe_2 (7.26 mg, 0.04 mmol) as the copper catalyst afforded **8f** (43 mg, 30%) as a brown solid after flash chromatography; mp: 97−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.67 (s, 1H), 8.19 (s, 1H), 7.62 (dd, J = 7.8, 4.8 Hz, 4H), 7.50 (t, J = 7.4 Hz, 2H), 7.41 (dd, J = 8.3, 6.3 Hz, 1H), 6.94 (d, J = 8.8 Hz, 2H), 5.93 (s, 2H), 3.91−3.80 (m, 5H), 3.56−3.53 (m, 2H), 3.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 161.2, 146.6, 144.9, 139.7, 138.6, 135.4, 134.1, 133.6, 129.2, 127.8, 127.6, 125.8, 114.4, 112.6, 97.3, 72.7, 71.6, 69.3, 59.2, 55.5; MS (ES+) m/z (%): 414.2 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{25}H_{24}N_3O_3$ 414.1818; found 414.1802.

*3-((2-Methoxyethoxy)methyl)-6-((4-methoxyphenyl)-2-(naphtalen-2-ylethynyl)-3H-imidazo[4,5-b]pyridine (**8g**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3e** (100 mg, 0.32 mmol) and CuBr·SMe_2 (6.56 mg, 0.03 mmol) as the copper catalyst in a sealed tube afforded **8g** (80 mg, 54%) as a yellow solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 160−162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.65 (d, J = 1.9 Hz, 1H), 8.21 (s, 1H), 8.15 (d, J = 1.9 Hz, 1H), 7.86 (d, J = 8.4 Hz, 3H), 7.66 (d, J = 9.8 Hz, 1H), 7.55 (dd, J = 9.1, 3.7 Hz, 4H), 7.03 (d, J = 8.7 Hz, 2H), 5.95 (s, 2H), 3.88−3.85 (m, 5H), 3.57−3.54 (m, 2H), 3.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.6, 146.2, 145.0, 139.2, 135.5, 133.7, 133.5, 133.2, 132.8, 131.0, 128.7, 128.5, 128.2, 128.1, 128.0, 127.8, 127.1, 125.5, 118.0, 114.7, 97.1, 78.8, 72.8, 71.6, 69.3, 59.2, 55.5; MS (ES+) m/z (%): 464.2 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{29}H_{26}N_3O_3$ 464.1974; found 464.1953.

*3-((2-Methoxyethoxy)methyl)-6-((4-methoxyphenyl)-2-((4-methoxyphenyl)ethynyl)-3H-imidazo[4,5-b]pyridine (**8h**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3e** (100 mg, 0.32 mmol) and CuBr·SMe_2 (6.56 mg, 0.03 mmol) as the copper catalyst afforded **8h** (43 mg, 30%) as a brown solid after flash chromatography; mp: 87−89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.62 (s, 1H), 8.13 (s, 1H), 7.61−7.53 (m, 4H), 7.02 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 5.90 (s, 2H), 3.85−3.81 (m, 8H), 3.58−3.48 (m, 2H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 161.2, 159.5, 144.7, 135.5, 134.1, 133.4, 132.2, 131.0, 128.7, 125.3, 114.6, 114.4, 113.7, 112.7, 97.2, 72.7, 71.6, 69.3, 59.2, 55.5, 55.5; MS (ES+) m/z (%): 444.2 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{26}H_{26}N_3O_4$ 444.1923; found 444.1925.

*2-Fluoro-4-(3-((2-methoxyethoxy)-methyl)-2-(naphtalen-2-ylethynyl)-3H-imidazo-[4,5-b]pyridin-6-yl)benzonitrile (**8i**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3f** (100 mg, 0.31 mmol) and CuBr·SMe_2 (6.30 mg, 0.03 mmol) as the copper catalyst afforded **8i** (103 mg, 70%) as a brown solid after flash chromatography; mp: 170−172 °C; ^{1}HNMR (300 MHz, $CDCl_3$) δ (ppm) 8.61 (s, 1H), 8.16 (s, 1H), 8.14 (s, 1H), 7.81 (d, J = 7.2 Hz, 3H), 7.67 (t, J = 7.2 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.53−7.40 (m, 4H), 5.91 (s, 2H), 3.94−3.76 (m, 2H), 3.64−3.48 (m, 2H), 3.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 163.4 (d, $^1J_{C-F}$ = 259.3 Hz), 147.6, 145.8 (d, $^3J_{C-F}$ = 8.1 Hz), 144.6, 140.1, 135.3, 134.0, 133.6, 133.2, 132.6, 130.3 (d, $^4J_{C-F}$ = 1.8 Hz), 128.5, 128.1, 127.9, 127.9, 127.8, 127.1, 125.9, 123.6(d, $^4J_{C-F}$ = 3.2 Hz), 117.5, 115.0 (d, $^2J_{C-F}$ = 20.4 Hz), 113.9, 100.2 (d, $^2J_{C-F}$ = 15.6 Hz), 97.8, 78.3, 72.8, 71.5, 69.4, 59.1; MS (ES+) m/z (%): 477.2 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{29}H_{22}N_4O_2F$ 477.1727; found 477.1703.

*2-Fluoro-4-(3-((2-methoxyethoxy)-methyl)-2-((4-methoxyphenyl)ethynyl)-3H-imidazo[4,5-b]pyridin-6-yl)benzonitrile (**8j**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3f** (100 mg, 0.31 mmol) and CuBr·SMe_2 (6.30 mg, 0.03 mmol) as the copper catalyst in a sealed tube afforded **8j** (50 mg, 35%) as a brown solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 150−152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.64 (s, 1H), 8.19 (s, 1H), 7.75 (t, J = 7.2 Hz, 1H), 7.62 (d, J = 8.1 Hz, 2H), 7.54−7.47 (m, 2H), 6.94 (d, J = 8.1 Hz, 2H), 5.93 (s, 2H), 3.87−3.82 (m, 5H), 3.56−3.53 (m, 2H), 3.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 163.6 (d, $^1J_{C-F}$ = 259.5 Hz), 161.4, 146.1, 146.0, 144.4, 134.2, 130.4, 125.9,123.8 (d, $^4J_{C-F}$ = 3.2 Hz), 115.4, 115.1, 114.5, 114.0, 112.3, 100.5, 100.3, 98.1, 77.4, 72.9, 71.6, 69.5, 59.2, 55.6; MS (ES+) m/z (%): 457.2 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{26}H_{22}N_4O_3F$ 457.1676; found 457.1666.

*3-((2-Methoxyethoxy)methyl)-2-(naphthalen-2-ylethynyl)-6-(pyridin-4-yl)-3H-imidazo[4,5-b]pyridine (**8k**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3g** (100 mg, 0.35 mmol) and $Cu(OAc)_2$ (6.39 mg, 0.04 mmol) as the copper catalyst afforded **8k** (94 mg, 62%) as a beige solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 117−119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.22 (s, 1H), 7.86 (d, J = 6.7 Hz, 3H), 7.70−7.61 (m, 3H), 7.60−7.51 (m, 2H), 7.39 (s, 2H), 7.17−7.07 (m, 2H), 5.98 (s, 2H), 3.86 (s, 2H), 3.56 (s, 2H), 3.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 158.7, 133.9, 133.7, 133.5, 133.1, 132.6, 132.0, 131.8, 128.4, 128.0, 127.8, 127.8, 127.8, 127.0, 123.6, 120.0, 117.5, 97.5, 78.5, 72.8, 71.4, 69.3, 59.1; MS (ES+) m/z (%): 435.2 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{27}H_{23}N_4O_2$ 435.1821; found 435.1819.

*3-((2-Methoxyethoxy)methyl)-2-((4-methoxyphenyl)ethynyl)-6-(pyridin-4-yl)-3H-imidazo[4,5-b]pyridine (**8l**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3g** (100 mg, 0.35 mmol) and CuBr·SMe_2 (7.23 mg, 0.04 mmol) as the copper catalyst afforded **8l** (86 mg, 59%) as a yellow solid after flash chromatography, followed by recrystallization in a mixture of cyclohexane/dichloromethane; mp: 125−127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.70 (s, 1H), 8.26 (s, 1H), 7.84−7.44 (m, 6H), 6.93 (d, J = 8.6 Hz, 2H), 5.92 (s, 2H), 3.85−3.81 (m, 5H), 3.59−3.48 (m, 2H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 161.3, 158.9, 144.4, 135.6, 134.2, 133.9, 132.2, 128.5, 125.7, 123.9, 120.2, 114.5, 112.5, 97.8, 72.8, 71.6, 69.4, 59.2, 55.6; MS (ES+) m/z (%): 415.2 (100)

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$[M + H]^+$; HRMS (ESI) calcd for $C_{24}H_{23}N_4O_3$ 415.1770; found 415.1757.

*3-((2-Methoxyethoxy)methyl)-2-(naphthalen-2-ylethynyl)-3H-imidazo[4,5-b]pyridine (**8m**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3h** (100 mg, 0.48 mmol) and CuBr·SMe_2 (9.92 mg, 0.05 mmol) as the copper catalyst afforded **8m** (72 mg, 42%) as a brown solid after flash chromatography; mp: 65−67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.45 (d, J = 4.5 Hz, 1H), 8.19 (s, 1H), 8.06 (d, J = 7.9 Hz, 1H), 7.85 (d, J = 8.4 Hz, 3H), 7.65 (d, J = 8.5 Hz, 1H), 7.58−7.49 (m, 2H), 7.31−7.27 (m, 1H), 5.94 (s, 2H), 3.85−3.82 (m, 2H), 3.55−3.52 (m, 2H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 145.8, 135.3, 133.7, 133.2, 132.8, 128.5, 128.2, 128.0, 128.0, 127.8, 127.8, 127.1, 119.6, 118.0, 97.0, 78.7, 72.7, 71.6, 69.3, 59.2; MS (ES+) m/z (%): 358.2 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{20}N_3O_2$ 358.1556; found 358.1551.

*3-((2-Methoxyethoxy)methyl)-2-((4-methoxyphenyl)ethynyl)-3H-imidazo[4,5-b]- pyridine (**8n**).* The reaction carried out following procedure D starting from 3*H*-imidazo[4,5-*b*]pyridine **3h** (100 mg, 0.48 mmol) and CuBr·SMe_2 (9.92 mg, 0.05 mmol) as the copper catalyst afforded **8n** (91 mg, 56%) as a brown solid after flash chromatography; mp: 79−81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.37 (dd, J = 4.8, 1.2 Hz, 1H), 7.96 (dd, J = 7.8, 1.2 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.21 (dd, J = 8.0, 4.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 5.83 (s, 2H), 3.85−3.67 (m, 5H), 3.48−3.47 (m, 2H), 3.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 161.0, 147.0, 145.4, 139.0, 135.2, 133.9, 127.5, 119.4, 114.3, 112.5, 96.9, 77.5, 72.5, 71.5, 69.1, 59.0, 55.4; MS (ES+) m/z (%): 338.2 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{20}N_3O_3$ 338.1505; found 338.1507.

Typical Procedure E for the Deprotection of N3-MEM-3H-imidazo[4,5-b]pyridines. In a round-bottom flask and under argon inlet, sulfuric acid (130 equiv) was added dropwise to a solution of *N*3-MEM-3*H*-imidazo[4,5-*b*]pyridine (1 equiv) in THF (2 mL) at 0 °C. The mixture was stirred overnight at room temperature. After neutralization of the crude reaction mixture with a saturated solution of $NaHCO_3$, the precipitate was filtered and washed several times with dichloromethane. The desired products were obtained without any further purification.

*6-Bromo-2-(phenylethynyl)-3H-imidazo[4,5-b]pyridine (**9a**).* The reaction carried out following procedure E starting from C2-alkynylated 3*H*-imidazo[4,5-*b*]pyridine **7a** (95 mg, 0.25 mmol) afforded **9a** (30 mg, 40%) as a beige solid; mp: 220−222 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 14.02 (bs, 1H), 8.50 (s, 1H), 8.32 (s, 1H), 7.69 (d, J = 7.0 Hz, 2H), 7.57−7.49 (m, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 146.4, 145.5, 137.7, 131.9, 130.4, 129.1, 128.9, 119.9, 92.7, 80.0; MS (ES+) m/z (%): 298 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{14}H_9N_3Br$ 297.9980; found 297.9990.

*6-Bromo-2-(p-tolylethynyl)-3H-imidazo[4,5-b]pyridine (**9b**).* The reaction carried out following procedure E starting from C2-alkynylated 3*H*-imidazo[4,5-*b*]pyridine **7d** (130 mg, 0.32 mmol) afforded **9b** (41 mg, 40%) as a beige solid; mp: 226−228 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.1 (d, J = 0.9 Hz, 1H), 7.80 (d, J = 0.9 Hz, 1H), 7.45 (d, J = 7.9 Hz, 2H), 7.25 (d, J = 7.9 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 158.0, 148.7, 140.0, 139.3, 138.2, 131.2, 129.4, 123.9, 119.7, 109.1, 88.5, 85.6, 21.0; MS (ES+) m/z (%): 312 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{15}H_{11}N_3Br$ 312.014; found 312.0136.

*6-Bromo-2-((4-methoxyphenyl)ethynyl)-3H-imidazo[4,5-b]-pyridine (**9c**).* The reaction carried out following procedure E starting from C2-alkynylated 3*H*-imidazo[4,5-*b*]pyridine **7f** (50 mg, 0.12 mmol) afforded **9c** (15 mg, 38%) as a brown solid; mp: 160−162 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.43 (s, 1H), 8.23 (s, 1H), 7.61 (d, J = 7.2 Hz, 2H), 7.06 (d, J = 7.2 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 160.6, 150.1, 144.6, 139.3, 133.6, 125.8, 114.7, 113.1, 112.0, 92.4, 79.9, 55.4; MS (ES+) m/z (%): 328 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{15}H_{11}N_3OBr$ 328.0085; found 328.0086.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00406.

^{1}H and ^{13}C spectra copies of the nonreported starting materials **1**, **2**, **3** and **4k** along with alkynes **5**, **6**, **7**, **8**, and **9** (PDF)

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Notes

The authors declare no competing financial interest.

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