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Imidazole-Fused Enediynes by Selective C5–C4 Alkynylations of 4,5-Dibromoimidazoles

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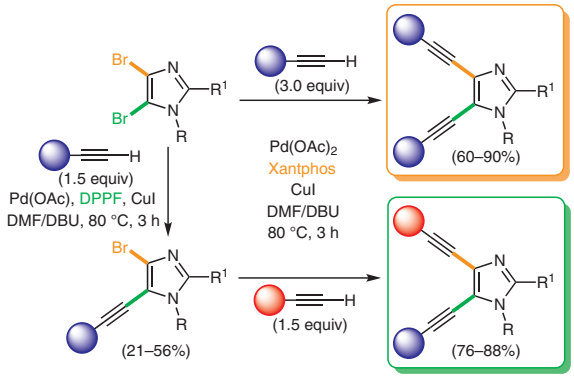

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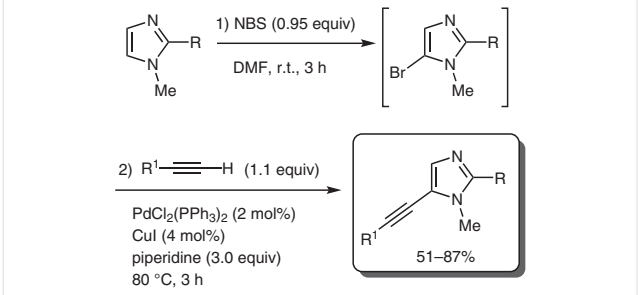
Abstract An efficient synthesis of symmetrical 1,2-disubstituted 4,5-dialkynylimidazoles by Sonogashira alkynylation of the corresponding 4,5-dibromo derivatives was developed. Moreover, through a careful tuning of the palladium ligand, unsymmetrical 1,2-disusbtituted 4,5-dialkynylimidazoles were also prepared through a regioselective C5 alkynylation of 4,5-dibromoimidazoles, followed by a second alkynylation involving the 4-bromo derivatives so obtained. This interesting class of imidazole-fused enediynes is also able to give thermal Bergman cycloaromatization (BC), as proved by DSC experiments.

Key words imidazoles, Sonogashira reaction, regioselectivity, enediynes, Bergman cyclization, palladium, copper, cross-coupling

Several naturally occurring acetylenes such as chalicheamicin and dynemicin display significant antitumor properties due to their ability to damage the DNA of cancer cells.[1] This biological activity has been attributed to the formation of 1,4-dehydrobenzene diradicals resulting from a thermal-induced Bergman cyclization[2] of an enediyne moiety, which is the common structural trait of this class of molecules.[1c,d,3] However, the strong anticancer activity displayed by enediynes is often overbalanced by several negative effects, such as high toxicity at therapeutic doses, that seriously impair their clinical use on humans.[1b] For this reason, the development of methods able to grant the access to new enediyne-containing molecular entities is an important synthetic target, aimed at obtaining analogues with improved pharmacological profiles.[1d,4]

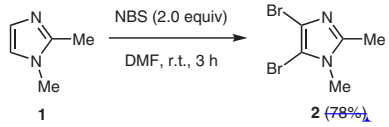
Despite the large number of studies devoted to the preparation of enediynes, to the best of our knowledge very few papers described the preparation of imidazole-fused enediynes,[5] regardless of the biological relevance of the imidazole nucleus itself.[6] In particular, symmetrical 4,5-dialkynylimidazoles were obtained by Sonogashira alkynylation[7] of the corresponding 4,5-diiodoimidazoles,[8] while the only preparation of unsymmetrical dialkynylimidazole derivatives was performed by sequential C2–C3 Sonogashira coupling involving 2-iodo-3-bromoimidazo[1,2-*a*]pyridine.[9]

Recently, we reported a synthetic protocol for the selective one-pot preparation of 2-substituted 5-alkynylimidazoles by regioselective C5 bromination with NBS, followed by Sonogashira alkynylation of the 5-bromoimidazole obtained in situ (Scheme 1).[10]



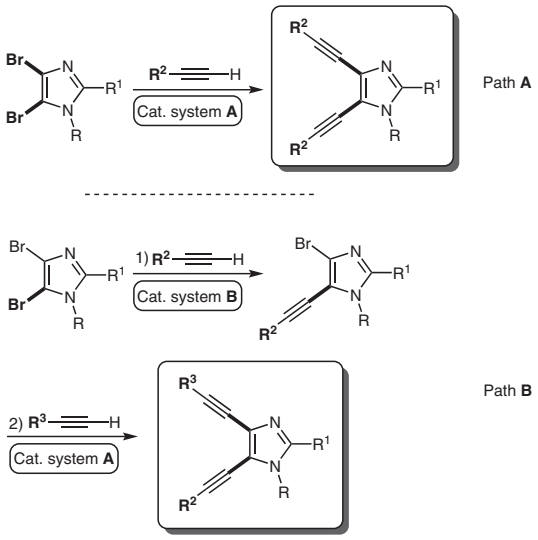
Scheme 1 Synthesis of 5-alkynylimidazoles by one-pot regioselective bromination and Sonogashira alkynylation[10]

During the optimization of the first step of the above reported protocol, we observed that 4,5-dibromo-1,2-dimethyl-1*H*-imidazole (**2**) may be easily obtained simply using 2.0 equivalents of NBS from commercially available 1,2-dimethyl-1*H*-imidazole (**1**), working in DMF at room temperature (Scheme 2). This convenient route to **2**, which represents a clean improvement over its previously reported preparation via bromination of **1** with molecular bromine,[11] encouraged us to start a study on the viability of using **2** as a precursor of imidazole-fused enediynes by sequential double Sonogashira alkynylations.[12]



Scheme 2 Synthesis of 4,5-dibromo-1,2-dimethyl-1*H*-imidazole (**2**)

Here we summarize the results of this study, which allowed us to find an efficient protocol for the double alkynylation of both the C–Br bonds of **2** to obtain symmetrical compounds featuring two identical alkynyl groups (Scheme 3, Path A). Moreover, through a careful tuning of the catalyst system, unsymmetrically substituted imidazoles were successfully obtained by sequential C5–C4 alkynylations (Scheme 3, Path B).



Scheme 3 Symmetrical imidazole-fused enediynes via synthetic Path A, and unsymmetrical analogues via synthetic Path B

At the beginning of our study, the same experimental conditions, which gave excellent results in the in situ Pd/Cu-catalyzed alkynylation of 5-bromo-1,2-dimethylimidazole (Scheme 1, step 2) were tried.[10] However, when 4,5-dibromo-1,2-dimethylimidazole (**2**) was reacted with 1.1 equivalents of phenylacetylene (**3a**) employing piperidine as the base, $Pd(PPh_3)_2Cl_2$ and CuI as the catalysts in DMF at 80 °C for 3 hours, a complex reaction mixture was obtained, and the main products resulted those deriving from alkyne homocouplings[12c] (data not shown).

Considering this negative result, which clearly proved the different chemical reactivity of 4,5-dibromoimidazole **2** when compared with the analogous 5-bromo derivative, we decided to verify the efficiency and the selectivity of a Sonogashira coupling involving equimolar amounts of **2** and **3a** chosen as model coupling partner, in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI.

Whereas performing sequential transition-metal-catalyzed carbon–carbon bond-forming reactions involving polyhalogenated substrates bearing different halogens is relatively easy, the achievement of the same regioselectivity using polyhalogenated derivatives containing two or more halogens of the same type may be a serious challenge.[13] However, when the electrophiles are polyhalogenated heteroarenes, the presence of the heteroatom(s) may induce a differentiation among the carbon–halogen bonds sufficient, after a judicious screening of the reaction system, to grant regioselective couplings by a kinetically determinant oxidative addition step.

As regards dibromoimidazole **2**, the 'normal' order of reactivity should be C5 > C4, considering the higher electrophilic character of the C–Br bond proximal to the pyrrole-like nitrogen atom in respect to the C–Br bond adjacent to the pyridine-like nitrogen ~~-like~~ atom. A similar reactivity (C5 > C4) was also observed in sequential Suzuki–Miyaura couplings involving polyhalogenated imidazoles and organoboron derivatives.[14] Hence, the selective formation of C5-alkynylimidazole **4a** from the coupling between equimolar amounts of **2** and **3a** was reasonably awaited or, on the contrary, an unselective C5,C4 double alkynylation to give the symmetrical imidazole-fused enediyne **5a** could be observed (Figure 1).

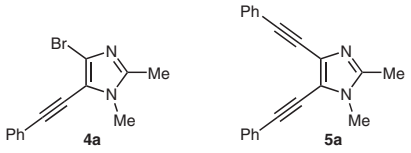
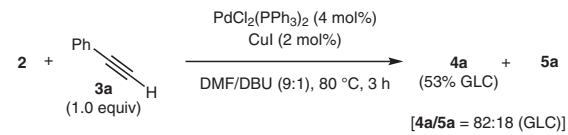


Figure 1 Chemical structures of imidazoles **4a** and **5a**

We initially examined the impact of the base/solvent system on the outcome of the alkynylation (Table S1, Supporting Information), and we found that the best results in terms of yield and selectivity were obtained when the coupling was carried out in a 9:1 (v:v) mixture of DMF and DBU at 80 °C for 3 hours, in the presence of 4 mol% $PdCl_2(PPh_3)_2$ and 2 mol% CuI (Table S1, entry 8). Under these experimental conditions, C5-alkynylated imidazole **4a** was obtained in 53% GLC yield and in 82:18 molar ratio with the corresponding symmetrical enediyne **5a** (Scheme 4).



Scheme 4 $PdCl_2(PPh_3)_2$-mediated selective alkynylation of **2** with **3a**

It is known that the stereoelectronic features of the palladium ligand may have a significant impact on regioselective couplings involving heteroarene bearing two or more

halogens of the same type, due to its influence on the oxidative addition which clearly represents, in these cases, the selectivity-determining step of the whole catalytic cycle.[13a,14b] Hence, encouraged by the positive result summarized in Scheme 4, we evaluated the influence of the nature of the palladium ligand on our model reaction (Table 1). In order to allow a fast comparison between different ligands, $PdCl_2(MeCN)_2$ was chosen as a convenient palladium precatalyst for this further screening instead of $PdCl_2(PPh_3)_2$, while all the other reaction parameters were left unaltered in respect to those summarized in Scheme 4. It is relevant to note that at the end of all the reactions phenylacetylene (**3a**) was never detected in the reaction mixture, probably due to its partial transformation into high molecular weight oligomers, which are common by-products in copper-catalyzed alkynylations.[12c] Considering also the fact that under the adopted experimental conditions no degradation of **2** was noticed, the overall yield of **4a** + **5a** may be reasonably adopted as a measure of the efficiency of the catalyst system.

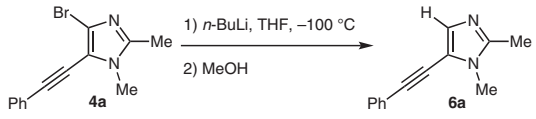
From the results reported in Table 1, it emerged that the use of PPh_3 gave a very similar reaction outcome than that obtained with $Pd(PPh_3)_2Cl_2$ (Table 1, entries 1 and 2). On the contrary, P(2-furyl)$_3$ taken as an example of soft ligand gave a lower conversion even if it showed a better selectivity (entry 3). In order to rise the conversion of **2**, 1.5 equivalents of **3a** were then employed (entry 4). As expected, a higher conversion of **2** into **4a** and **5a** was observed, but the use of an excess of **3a** lowered the **4a**:**5a** ratio from 93:7 to 78:22 (entries 3 and 4). Even worse, the hard PCy_3 ligand displayed poorer selectivity and yield (entry 5).

The activity of a series of bidentate phosphines was then evaluated (Table 1, entries 6–9). As can be seen from Table 1, these species generally improved the conversion of **2** into alkynylimidazoles **4a** and **5a**, apart from DPPE (entry 6). In particular, 1,1-bisdiphenylphosphinoferrocene (DPPF) was found to show a good selectivity, leading to the monoalkynylated product **4a** in 59% GLC yield, and to **5a** in 18% GLC yield (entry 9). The conversion of the alkyne into products was thus almost quantitative (95%). However, compound **4a** was isolated chemically pure in only 28% yield, due to difficulties in the separation from unreacted dibromoimidazole **2**. To confirm the C5 regioselectivity of the alkynylation using DPPF as the ligand, an unambiguously chemical assignment of the position of the alkynyl moiety of bromoimidazole **4a** was set up (Scheme 5). In detail, **4a** was debrominated through a metal/halogen exchange with BuLi at –100 °C, followed by protonolysis with MeOH (Scheme 5). The ^{1}H NMR spectrum of the resulting debrominated imidazole was compared with the spectrum of an authentic sample of 1,2-dimethyl-5-(phenylethynyl)-1*H*-imidazole (**6a**), previously prepared by us through the one-pot C-5 bromination/alkynylation reaction on 1,2-dimethyl-1*H*- imidazole (Scheme 1).[10]

Table 1 Ligand Screening for the Sonogashira Coupling Involving **2** and **3a**[a]

Entry	Pd ligand	Product Yield (%)[b]		**4a**:**5a**
		4a	**5a**	
1[c]	–	53	12	82:18
2	PPh_3	51	16	76:24
3	P(2-furyl)$_3$	38	3	93:7
4[d]	P(2-furyl)$_3$	40	11	78:22
5	PCy_3	17	15	53:47
6	DPPE	15	4	79:21
7	DPPB	54	19	74:26
8	DPEphos	50	18	74:26
9	DPPF	59 (28)	18	77:23
10[d]	**DPPF**	**47 (42)**	**41**	**53:47**
11	Xantphos	26	38	41:59
12[e]	**Xantphos**	**0**	**100 (90)**	**0:100**

[a] Unless otherwise stated, the reactions were carried out using **2** (1 mmol), **3a** (1 mmol), $PdCl_2(MeCN)_2$ (4 mol%), CuI (2 mol%), and Pd ligand (8 mol% if monodentate, 4 mol% if bidentate), in a 9:1 mixture (v:v) of DMF and DBU (5 mL) for 3 h at 80 °C (oil bath temperature).
[b] GLC yield. In parentheses, isolated yield.
[c] $PdCl_2(PPh_3)_2$ (4 mol%) was employed as the catalyst precursor.
[d] Reaction carried out using 1.5 mmol of **3a**.
[e] Reaction carried out using 3.0 mmol of **3a**.



Scheme 5 Selective debromination of imidazole **4a**

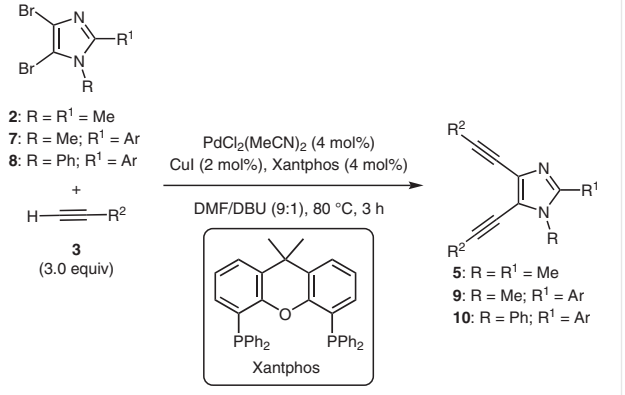
Since the use of DPPF as the palladium ligand led to the highest chromatographic yield in the monoalkynylated imidazole **4a**, once again 1.5 equivalents of **3a** were employed to rise the conversion of **2** (Table 1, entry 10). As already observed when P(2-furyl)$_3$ was used as the palladium ligand, a higher conversion of **2** into **4a** and **5a** was observed, but the recorded increase in overall GLC yield was negatively counterbalanced by a lowering in the **4a**:**5a** ratio from 77:23 to 53:47 (entries 9 and 10). Despite a lower GLC yield, **4a** was isolated in 42% yield from the crude reaction mixture due the fact that the separation of the monalkynylated product **4a** from the dialkynylated product **5a** resulted easier than its separation from dibromoimidazole **2**.

After recording that the trend of activity of the in situ formed catalytic system with bidentate phosphines parallels the increasing of the bite angle,[15] the effect of 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), which displays a bite angle of 108°, was attempted (Table 1, entry 11). As a result, the use of Xantphos lowered the kinetic discrimination between the two C–Br bonds of **2**, allowing in this case to observe a slight prevalence (59:41) of

the dialkynylated product **5a** with respect to the monoalkynylimidazole **4a**. Imidazole **5a** was recovered from the crude reaction mixture in 38% yield, along with **4a** (26%). The conversion of this reaction, with respect to the alkyne **3a**, was thus quantitative. The latter trial was finally repeated with 3.0 equivalents of **3a**, resulting in a quantitative conversion into the dialkynylated product **5a**, which was isolated in a satisfactory 90% yield (entry 12).

In summary, the regioselective coupling of **2** with 1.5 equivalents of **3a** in the presence of 4 mol% $PdCl_2(MeCN)_2$, 4 mol% DPPF, 2 mol% CuI, at 80 °C for 3 hours in a 9:1 mixture of DMF and DBU allowed us to isolate the pure monoalkynylated imidazole **4a** in 42% yield (Table 1, entry 10). On the other hand, the symmetrical imidazole-fused enediyne **5a** was obtained in 90% isolated yield simply replacing DPPF with Xantphos and doubling the amount of **3a** (entry 12).

With these two protocols in hands, we then evaluated their scope starting from the synthesis of symmetrically substituted 4,5-dialkynylimidazoles **5**, **9**, and **10** from the corresponding 4,5-dibromoimidazoles **2**, **7**, and **8** according to the experimental conditions reported in Table 1, entry 12 (Scheme 6).



Scheme 6 Synthesis of symmetrical imidazole-fused enediynes **5**, **9**, and **10**

As it can be seen from Table 2, where the results obtained in the preparation of compounds **5**, **9**, and **10** are summarized, Sonogashira reactions involving **2** and electron-rich arylalkynes proceeded easily and in excellent yields. In fact, when 4-ethynylanisole (**3b**) was employed as the alkyne, the corresponding dialkynylated product **5b** was isolated in 80% yield (Table 2, entry 2). On the contrary, the use of the typical electron-poor alkyne **5c** gave the required symmetrical enediyne **5c** in a lower 60% yield (entry 3). The reaction proceeded well even when an aliphatic alkyne was employed. In fact, the symmetrical enediyne **5d** resulting from the coupling involving **2** and dodec-1-yne (**3d**) was obtained in 77% isolated yield (entry 4).

Table 2 Synthesis of Symmetrical Imidazole-Fused Enediynes **5**, **9**, and **10**[a]

Entry	4,5-Dibromoimidazole			Alkyne		Product	
		R	R^1	**3**	R^2		Yield (%)[b]
1	**2**	Me	Me	**3a**	Ph	**5a**	90
2	**2**	Me	Me	**3b**	4-$MeOC_6H_4$	**5b**	80
3	**2**	Me	Me	**3c**	4-$CO_2EtC_6H_4$	**5c**	60
4	**2**	Me	Me	**3d**	*n*-$C_{10}H_{21}$	**5d**	77
5	**2**	Me	Me	**3e**	$HO(CH_2)_4$	**5e**	72
6	**7a**	Me	4-$CO_2EtC_6H_4$	**3b**	4-$MeOC_6H_4$	**9a**	79
7	**7b**	Me	4-$MeSO_2C_6H_4$	**3b**	4-$MeOC_6H_4$	**9b**	88
8	**7c**	Me	4-MeC_6H_4	**3a**	Ph	**9c**	72
9	**7c**	Me	4-MeC_6H_4	**3b**	4-$MeOC_6H_4$	**9d**	73
10	**8a**	Ph	4-$MeOC_6H_4$	**3a**	Ph	**10a**	75

[a] The reactions were carried out using dibromoimidazole **2**, **7**, or **8** (1 mmol), **3** (3.0 mmol), $PdCl_2(MeCN)_2$ (4 mol%), CuI (2 mol%), and Xantphos (4 mol%) in a 9:1 mixture (v:v) of DMF and DBU (5 mL) for 3 h at 80 °C (oil bath temperature).
[b] Isolated yield.

Free hydroxyl group were well tolerated, as demonstrated by using hex-5-yn-1-ol (**3e**). The desired enediyne **5e** was in fact isolated in 72% yield (Table 2, entry 5).

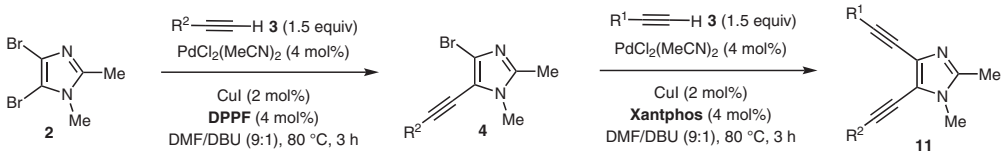
The precatalyst systems $PdCl_2(MeCN)_2$/Xantphos resulted also very efficient in promoting the alkynylation of 2-aryl-4,5-dibromo-1-methylimidazoles **7a–d**. To our delight, the required enediynes **9a–d** were in fact isolated in 72–88% yields (Table 2, entries 6–9). Interestingly, the symmetrical enediyne **10a** was also obtained in 75% yield by reaction of a typical 1,2-diaryl-4,5-dibromoimidazole, **8a**, with phenylacetylene (**3a**) (entry 10).

Having secured the synthesis of symmetrical enediynes, our attention was devoted towards the preparation of unsymmetrical enediynes **11**. Considering the results ob-

Table 3 Synthesis of 5-Alkynyl-4-bromoimidazoles **4** by Regioselective C5 Alkynylation of 4,5-Dibromoimidazole **2**[a]

Entry	Alkyne		Product		
	3	R	**4**	**4**/**5**	Yield (%)[b]
1	**a**	Ph	**a**	53/47	42
2	**b**	4-$MeOC_6H_4$	**b**	81/19	51
3	**c**	4-$CO_2EtC_6H_4$	**c**	100/0	21[c]
4	**d**	*n*-$C_{10}H_{21}$	**d**	68/32	46
5	**e**	4-hydroxybutyl	**e**	92/8	56

[a] The reactions were carried out using **2** (1 mmol), **3** (1.5 mmol), $PdCl_2(MeCN)_2$ (4 mol%), CuI (2 mol%), and DPPF (4 mol%, in a 9:1 mixture (v:v) of DMF and DBU (5 mL) for 3 h at 80 °C (oil bath temperature). Unless otherwise stated, the complete conversion of **2** was observed.
[b] Isolated yield.
[c] By GLC and GC-MS analyses of the crude reaction mixture a **2**/**4c** molar ratio of 53/47 was determined.



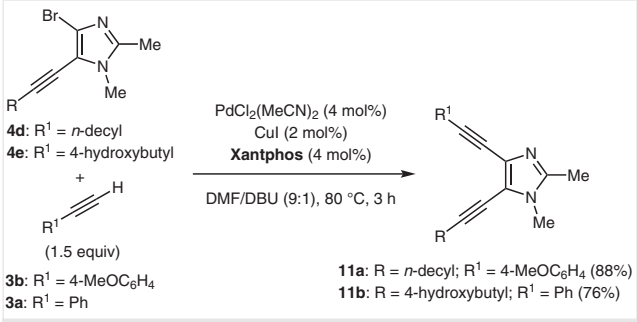
Scheme 7 Two-step synthesis of unsymmetrical imidazole-fused enediynes **11**

tained using Xantphos as the palladium ligand, we decided to perform the first, regioselective, alkynylation using DPPF as the ligand according to the reaction conditions of Table 1, entry 10 (Scheme 7 and Table 3). Thus, the resulting 5-alkynyl-4-bromoimidazoles **4** were reacted with a different alkyne, using Xantphos as the ligand (Scheme 7).

As can be seen from Table 3, where the results of the regioselective C5-alkynylation of **2** are reported, the use of DPPF as the palladium ligand enabled the regioselective C5-alkynylation without the necessity of employing substrates bearing two different halogen atoms, such as the case reported by Gueffier and co-workers in 2017 working on 2,3-dihalogenoimidazo[1,2-*a*]pyridines.[9] The required 5-alkynyl-4-bromoimidazoles **4** were recovered in reasonable yields after 3 hours at 80 °C from mixtures containing also variable amounts of the corresponding dialkynylimidazole derivatives **5** (Table 3).

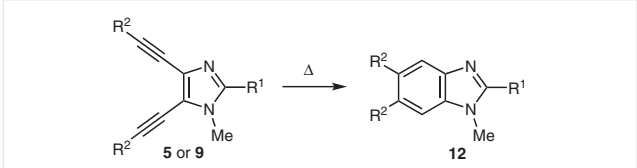
In detail, when the coupling was performed using arylalkynes such as phenylacetylene (**3a**) or 4-ethynylanisole (**3b**), a complete conversion of dibromide **2** was noticed, and the desired monoalkynylated products **4a** and **4b** were obtained in 42% and 51% isolated yields, respectively (Table 3, entries 1, 2). A similar chemical yield (46%) was observed when dodec-1-yne (**2d**) was employed in the reaction with **2**, (entry 4). The hydroxy group of hex-5-yn-1-ol (**3e**) was well tolerated (entry 5), giving rise also to the highest **4**/**5** GLC ratio (92/8). In contrast, when ethyl 4-ethynylbenzoate (**3c**) was employed as a typical electron-poor arylalkyne, we experienced an incomplete conversion of **2**, and a poor 21% isolated yield of bromoenyne **4c**. This low yield was attributed to the tendency of such an alkyne, in the presence of a less effective catalytic system, to be involved in competitive homocoupling reactions. In fact, it has been recently demonstrated that Cu-promoted Glaser–Hay-type alkyne homocouplings, such as those involved in the by-product formation under Sonogashira conditions,[12c] are faster when more acidic alkynes are involved.[16]

The preparation of unsymmetrical enediynes **11** was completed by reacting 5-alkynyl-4-bromoimidazoles **4d** and **4e**, taken as examples, under the reaction conditions of Table 1, entry 12. In particular, when compound **4d** was coupled with 1.5 equivalents of 4-ethynylanisole (**3b**), the reaction provided the desired compound **11a** in 88% isolated yield (Scheme 8), proving once again the efficacy of the precatalyst system based on Xantphos for the alkynylation of bromoimidazoles. A similar yield (76%) was obtained when imidazole **4e** was reacted with phenylacetylene (**3a**), providing the desired unsymmetrical enediyne **11b** (Scheme 8).



Scheme 8 Synthesis of unsymmetrical enediynes **11a** and **11b**

Finally, the ability of some imidazole-fused enediynes to be involved in thermal Bergman cyclization (Scheme 9) was evaluated by differential scanning calorimetry (DSC). The use of this experimental method to study the behavior of enediynes under reaction conditions that favor the cyclization has been already reported,[5] and it seems to us a practical method to perform a comparison among the reactivity of enediyne analogues.



Scheme 9 Benzimidazole **12** via thermal Bergman cyclization involving enediynes **5** or **9**

In particular, 1,2-dimethylimidazoles **5a–d** and 2-aryl-1-methylimidazoles **9a–c** were selected for this study. The onset temperature of the exothermic peak observed in the DSC thermogram of each enediyne, which represents the temperature at which the Bergman cyclization occurs, is reported in Table 4. No exothermic peaks were recorded during a second scanning of the samples (see the thermograms in Supporting Information), which confirmed that an irreversible process has taken place.[17]

A quick analysis of the data outlined in Table 4 clearly reveals the influence of the substituents at both the triple bonds and the imidazole ring. As regards enediynes **5**, while

Table 4 Bergman Cyclization Temperature (t_{BC}) of Selected Imidazole-Fused Enediyne **5** or **9**

Enediyne **5** or **9**			Product	
	R^1	R^2	**12**	t_{BC} (°C)[a]
5a	Me	Ph	**a**	302
5b	Me	4-$MeOC_6H_4$	**b**	280
5c	Me	4-$CO_2EtC_6H_4$	**c**	264
5d	Me	*n*-$C_{10}H_{21}$	**d**	284
9a	4-$CO_2EtC_6H_4$	4-$MeOC_6H_4$	**e**	319
9b	4-$MeSO_2C_6H_4$	4-$MeOC_6H_4$	**f**	302
9c	4-MeC_6H_4	Ph	**g**	312

[a] The onset temperature of the exothermic peak is reported.

the higher reactivity of **5c** when compared with the analogous **5a** and **5b** is expected due to the reported positive effect on Bergman cyclization exerted by electron-withdrawing substituents on the triple bond(s),[18] the fact that **5a** resulted less reactive than **5b**, which bears the strong electron-donor methoxyphenyl moiety, is quite unpredicted. We noticed also that the presence of an aryl substituent on the C2 position of the imidazole ring, either electron-deficient (for enediynes **9a** and **9b**) or mildly electron-rich (for enediyne **9c**) led to a sharp decrease in reactivity. The onset BC temperatures recorded for these three enediynes resulted in fact 20–30 °C higher than that observed for the corresponding 2-methylimidazole-fused enediynes **5b** and **5a**, respectively. It has been proposed that the percentage of double-bond character of an enediyne double bond could be involved in the efficiency of Bergman cyclization[19] but, in the literature, there is no clear evidence of this parameter or on the distance between the two alkynyl moieties[20] when acyclic enediynes are involved.[21]

In conclusion, we have demonstrated that playing with palladium ligands may be a good way to enhance the chemical difference between vicinal bromine atoms on imidazoles, allowing a regioselective oxidative addition of Pd(0) species and, consequently, making the catalytic cycle to start. Not only the best ligand in terms of selectivity is useful, but also the worst one, because its employment opens the way towards unselective, but not for this reason useless, multiple alkynylation protocols. We proved also that the imidazole-fused enediynes so prepared are able to undergo Bergman cycloaromatization, and studies on the practical application of this reaction to the preparation of polysubstituted benzoazoles and on the observed reactivity are in progress.

Melting points were recorded on a hot-stage microscope (Reichert Thermovar). Precoated silica gel PET foils (Sigma-Aldrich) were used for TLC analyses. GLC analyses were performed on a Dani GC 1000 instrument equipped with a PTV injector and recorded with a Dani DDS 1000 data station. Three types of capillary columns were used: an Agilent J & W HP-5ms column (30 m × 0.25 mm i.d. × 0.25 µm), an Agilent J & W DB-5 column (30 m × 0.25 mm i.d. × 1 µm) and an Alltech AT-35 FSOT column (30 m × 0.25 mm i.d. × 0.25 µm). EI-MS spectra were recorded at 70 eV by GLC-MS, performed on an Agilent 6890N gas-chromatograph interfaced with an Agilent 5973N mass detector. The ESI spectra were acquired on a Acquity QDa Water spectrometer (Temperature Probe: 600 °C; ESI capillary voltage 1.5 V; Cone voltage 15 V; mass range 200–1000) coupled with a Acquity HUPLC Water (Phase A 95/5 H_2O/MeCN + 0.1% formic acid, Phase B 5/95 H_2O/MeCN + 0.1% formic acid; Column Acquity UPLC 2.1 × 100 mm, BEH C18, 1.7 µm; Flow 0.6 mL/min). Elementar analyses were acquired with an Elementar Vario Micro Cube in CHNS mode. ^{1}H NMR spectra were recorded on a Varian Gemini 200 or on a Buker 400 MHz spectrometer using TMS as an internal standard. Standard notations were used in order to report NMR spectra. The ^{13}C NMR spectra were recorded at 50 or 100 MHz, using Varian Gemini or Bruker instrument, respectively, and the spectra were referred to the signal of the solvent. Differential Scanning Calorimetry (DSC) thermograms were recorded under N_2 atmosphere by a Mettler Toledo DSC 922e Module Stare apparatus equipped with a liquid N_2 cooling system. The DSC experiments were carried out with 2.8–3.4 mg of samples using crucibles with pierced caps under a N_2 atmosphere at a heating/cooling rate of 20 °C × min^{-1} from a temperature of 20 °C up to 395 °C, followed by cooling to 20 °C and heating to 395 °C for the second time. Unless otherwise stated, all the reactions were performed under a positive atmosphere of argon by standard syringe, cannula, and septa techniques. DMF was dried by distillation at reduced pressure over CaH_2. THF was dried by distillation over $LiAlH_4$. 1-Methyl-1*H*-imidazole, 1,2-dimethyl-1*H*-imidazole (**1**), and hex-5-yn-1-ol (**3e**) were purified by distillation at reduced pressure. Phenylacetylene (**3a**), dodec-1-yne (**3d**), 4-ethynylanisole (**3b**), Et_3N, *i*-Pr_2NEt, tributylamine, 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and piperidine were purified by distillation at reduced pressure over CaH_2. 4-Bromoanisole and ethyl 4-bromobenzoate were degassed just before their use. NBS was purified by crystallization. Ethyl 4-(4,5-dibromo-1-methyl-1*H*-imidazol-2-yl)benzoate, 4,5-dibromo-2-[4-(methylsulfonyl)phenyl]-methyl-1*H*-imidazole, 4,5-dibromo-1-methyl-2-(4-methylphenyl)-1*H*-imidazole, and 4,5-dibromo-2-(4-methoxyphenyl)-1-phenyl-1*H*-imidazole were synthesized according to literature procedure previously developed by us.[22] All the other commercially available reagents and solvents were used as received.

4,5-Dibromo-1,2-dimethyl-1*H*-imidazole (2)

A modification of a literature procedure for the synthesis of the title compound was adopted.[23] A solution of 1,2-dimethyl-1*H*-imidazole (**1**; 1.33 mL, 1.44 g, 15 mmol) and NBS (5.34 g, 30 mmol) in EtOAc or DMF (75 mL) was stirred overnight in the open air and in the dark at r.t. The clear orange-yellowish solution thus obtained was washed with a 10% aq NaOH (2 × 50 mL), 10% aq Na_2SO_3 (2 × 50 mL), H_2O (50 mL), and brine (50 mL). The aqueous phases were back-extracted with EtOAc (50 mL) and the combined organic phases were dried (Na_2SO_4). The solvent was removed under reduced pressure, affording the title compound as a colorless solid; yield: 2.83 g (74%); ■■*78% in Scheme 2, check!*■■mp 86–88 °C (Lit.[24] mp 88–90 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.54 (s, 3 H), 2.40 (s, 3 H).

EI-MS: *m*/*z* (%) = 256 (48), 254 (100), 252 (52), 175 (74), 173 (82), 134 (55), 132 (61), 94 (17), 82 (14), 80 (14), 52 (16).

The physical and spectral properties of this compound were in agreement with those reported in the literature.[24,25]

Ethyl 4-(4,5-Dibromo-1-methyl-1*H*-imidazol-2-yl)benzoate (7a)

NBS (356 mg, 2 mmol) was added to a solution of ethyl 4-(1-methyl-1*H*-imidazol-2-yl)benzoate (230 mg, 1 mmol) in DMF (5 mL) and the resulting suspension was stirred at r.t. for 48 h. The resulting reaction mixture was diluted with EtOAc (100 mL), washed with 10% aq NaOH (2 × 50 mL), 10% aq Na_2SO_3 (2 × 50 mL), H_2O (50 mL), and brine (50 mL). The aqueous phases were back-extracted with EtOAc (50 mL) and the combined organic phases were dried (Na_2SO_4). The solvent was removed under reduced pressure, affording the title compound as an orange solid; yield: 360 mg (93%); mp 123–125 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.13 (m, 2 H), 7.67 (m, 2 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 3.74 (s, 3 H), 1.42 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 165.9, 147.4, 133.4, 131.3, 130.0 (2 C), 128.5 (2 C), 117.3, 106.8, 61.4, 35.0, 14.5.

EI-MS: *m*/*z* (%) = 390 (50), 389 (18), 388 (100), 386 (52), 209 (20), 307 (20), 268 (53), 266 (54), 134 (19), 132 (22).

Anal. Calcd for $C_{13}H_{12}Br_2N_2O_2$: C, 40.24; H, 3.12; N, 7.22. Found: C, 40.30; H, 3.11; N, 7.52.

4,5-Dibromo-2-[4-(methylsulfonyl)phenyl]methyl-1*H*-imidazole (7b)

NBS (356 mg, 2 mmol) was added to a solution of 1-methyl-2-(4-methylsulfonyl)phenyl-1*H*-imidazole (236 mg, 1 mmol) in DMF (5 mL) and the resulting reaction mixture was stirred in the dark at r.t. for 48 h. The mixture was then diluted with EtOAc (100 mL) and washed with 10% aq NaOH (2 × 50 mL), 10% aq Na_2SO_3 (2 × 50 mL), H_2O (50 mL), and brine (50 mL). The aqueous phases were back-extracted with EtOAc (50 mL) and the combined organic phases were dried (Na_2SO_4). The solvent was removed under reduced pressure, affording the title compound as a colorless solid; yield: 378 mg (96%); mp 197–199 °C.

H NMR (200 MHz, $CDCl_3$): δ = 8.04 (m, 2 H), 7.82 (m, 2 H), 3.77 (s, 3 H), 3.09 (s, 3 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 146.2, 141.0, 134.5, 129.3 (2 C), 127.8 (2 C), 117.6, 107.4,44.5, 35.0.

EI-MS: *m*/*z* (%) = 396 (53), 395 (17), 394 (100), 392 (50), 315 (25), 313 (23), 274 (40), 272 (36), 134 (21), 132 (22).

Anal. Calcd for $C_{11}H_{10}Br_2N_2O_2S$: C, 33.53; H 2.56; N, 7.1; S, 8.14. Found: C, 33.50; H, 2.58; N, 7.15; S, 7.98..

4,5-Dibromo-1-methyl-2-(4-methylphenyl)-1*H*-imidazole (7c)

NBS (2.48 g, 13.9 mmol) was added to a solution of 1-methyl-2-(4-methylphenyl)-1*H*-imidazole (1.20 g, 6.98 mmol) in DMF (35 mL). The resulting suspension was stirred for 46 h at r.t. in the dark. EtOAc (500 mL) was added to the reaction mixture and the organic layer was washed with 10 aq NaOH (2 × 250 mL). The organic phase was washed with 5% aq Na_2SO_3 (2 × 250 mL), then with H_2O (3 × 200 mL), and finally with brine (300 mL). The aqueous phases were extracted with EtOAc (120 mL). The organic phases were combined, dried (Na_2SO_4), and the solvent was removed under reduced pressure affording the title compound as a colorless solid; yield: 1.84 g (80%); mp 96–98 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.39 (m, 2 H), 7.19 (m, 2 H), 3.61 (s, 3 H), 2.33 (s, 3 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 148.6, 139.8, 129.4, 128.6, 126.5, 116.4, 105.4, 34.7, 21.5.

EI-MS: *m*/*z* (%) = 332 (49), 330 (100), 328 (53), 251 (36), 249 (37), 210 (62), 208 (64), 132 (9), 103 (9).

Anal. Calcd for $C_{11}H_{10}Br_2N_2$: C, 40.03; H, 3.05; N, 8.49. Found: C, 40.29; H, 3.11; N, 8.71.

4,5-Dibromo-2-(4-methoxyphenyl)-1-phenyl-1*H*-imidazole (8a)

NBS (356 mg, 2 mmol) was added to a solution of 2-(4-methoxyphenyl)-1-phenyl-1*H*-imidazole (250 mg, 1 mmol) in DMF (5 mL) and the resulting reaction mixture was stirred in the dark at r.t. for 24 h. The mixture was then diluted with EtOAc (100 mL) and washed with 10% aq NaOH (2 × 50 mL), 10% aq Na_2SO_3 (2 × 50 mL), H_2O (50 mL), and brine (50 mL). The aqueous phases were back-extracted with EtOAc (50 mL) and the combined organic phases were dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (95:5, toluene/EtOAc). The title compound was obtained as a pale organge solid; yield: 220 mg (54%); mp 135–137 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (m, 3 H), 7.21 (m, 4 H), 6.70 (m, 2 H), 3.71 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 148.3, 136.7, 129.7 (2 C), 129.6 (2 C), 128.2 (2 C), 121.7, 117.8, 113.7 (2 C), 105.9, 55.2.

ESI-MS: *m*/*z* = 408 $[M + H]^{+1}$.

Anal. Calcd for $C_{16}H_{12}Br_2N_2$: C,47.09; H, 2.96; N, 6.86. Found: C, 46.90; H, 3.00; N, 6.60.

Procedure for the Screening of the Reaction Conditions for the Pd- and Cu-Promoted Alkynylation of 4,5-Dibromo-1,2-dimethyl-1*H*-imidazole (2) with Phenylacetylene (3a)

A mixture of 4,5-dibromo-1,2-dimethyl-1*H*-imidazole (**2**; 0.25 g, 1.0 mmol), phenylacetylene (**3a**; 0.11 mL, 0.10 g, 1 mmol), Pd catalyst (10 mg, 0.04 mmol), CuI (3 mg, 0.02 mmol), Pd ligand (0.08 mmol if monodentate, 0.04 mmol if bidentate) in the selected solvent(s) (5 mL) was stirred under argon for 3 h at the temperature reported in Table 1 and Table S1. After cooling to r.t., the crude reaction mixture was diluted with EtOAc, and sat. aq NH_4Cl (100 mL) was added. The resulting mixture was stirred in the open air for 0.5 h and then extracted with EtOAc. The organic extract was washed with H_2O (3 × 25 mL) and brine (25 mL), biphenyl was added as internal standard, and the resulting mixture was analyzed by GLC and GC/MS. Table 1 and Table S1 summarize the results of this screening.

Symmetrical 1,2-Disubstituted 4,5-Dialkynyl-1*H*-imidazoles 5, 9, and 10; General Procedure

A solution of 4,5-dibromo-1,2-disubstituted-1*H*-imidazole **2**, **7a–e**, or **8a** (1 mmol) or 5-alkynyl-4-bromo-1,2-dimethyl-1*H*-imidazole, alkyne **3** (3 mmol or 1.5 mmol), $Pd(MeCN)_2Cl_2$ (10 mg, 0.04 mmol, 4 mol%), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (26 mg, 0.04 mmol, 4 mol%), and CuI (3 mg, 0.02 mmol, 2 mol%) in DMF (4.5 mL) and DBU (0.5 mL) was stirred at 80 °C for 3 h. The reaction mixture was then diluted with EtOAc (100 mL) and sat. aq NH_4Cl (100 mL) was added. The resulting mixture was stirred in the open air for 0.5 h and then extracted with EtOAc. The combined organic extractswere washed with H_2O (3 × 25 mL) and brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel. This procedure was employed to prepare 1,2-dimethylimidazole-fused enediynes **5a–e**, 2-aryl-1-methylimidazole-fused enediynes **9a–d**, and 1,2-diarylimidazole-fused enediyne **10a** (Table 2).

1,2-Dimethyl-4,5-bis(phenylethynyl)-1*H*-imidazole (5a) (Table 2, entry 1)

The crude reaction product obtained by Pd- and Cu-mediated alkynylation of 4,5-dibromo-1,2-dimethyl-1*H*-imidazole (**2**) with phenylacetylene (**3a**) was purified by flash chromatography on silica gel with a mixture of EtOAc and toluene (60:40) as eluent to give **5a** as a yellow solid; yield: 266 mg (90%); mp 126–127 °C. GLC analysis showed that **5a** had chemical purity higher than 98%.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.55 (m, 4 H), 7.30 (m, 6 H), 3.54 (s, 3 H), 2.35 (s, 3 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 146.1, 131.3 (2 C), 131.1 (2 C), 128.6, 128.3 (2 C), 128.1 (2 C), 128.0, 127.0, 123.2, 122.3, 119.8, 99.2, 92.2, 83.0, 77.3, 31.4, 13.5.

EI-MS: *m*/*z* (%) = 297 (23), 296 (100), 214 (12), 213 (20), 218 (16).

Anal. Calcd for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N,9.45. Found: C, 84.80; H, 5.73; N, 9.47.

4,5-Bis[(4-methoxyphenyl)ethynyl]-1,2-dimethyl-1*H*-imidazole (5b) (Table 2, entry 2)

The crude reaction product obtained by Pd- and Cu-mediated alkynylation of 4,5-dibromo-1,2- dimethyl-1*H*-imidazole (**2**) with 4-ethynylanisole (**3b**) was purified by flash chromatography on silica gel with EtOAc as eluent to give **5b** as a yellow solid; yield: 285 mg (80%); mp 143–144 °C. GLC analysis showed that **5b** had chemical purity higher than 98%.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.46 (m, 4 H), 6.84 (m, 4 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.53 (s, 3 H), 2.35 (s, 3 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 159.7, 159.3, 145.7, 132.7 (4 C), 126.7, 119.7, 115.3, 114.4, 113.9 (2 C), 113.8 (2 C), 99.0, 91.8, 81.7, 76.1, 55.2, 55.1, 31.3, 13.4.

EI-MS: *m*/*z* (%) = 357 (26), 356 (100), 341 (30), 259 (5), 178 (15).

Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.30; H, 5.70; N, 7.91.

Diethyl 4,4′-[(1,2-Dimethyl-1*H*-imidazole-4,5-diyl)]bis(ethyne-2,1-diyl)dibenzoate (5c) (Table 2, entry 3)

The crude reaction product obtained by Pd- and Cu-mediated alkynylation of 4,5-dibromo-1,2-dimethyl-1*H*-imidazole (**2**) with ethyl 4-ethynylbenzoate (**3c**) was purified by flash chromatography on silica gel with EtOAc as eluent to give **5c** as a yellow solid; yield: 264 mg (60%); mp 165–167 °C. GLC analysis showed that **5c** had chemical purity higher than 98%.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.04 (m, 4 H), 7.60 (m, 4 H), 4.40 (q, *J* = 7.0 Hz, 2 H), 4.38 (q, *J* = 7.0 Hz, 2 H), 3.65 (s, 3 H), 2.41 (s, 3 H), 1.41 (t, *J* = 7.0 Hz, 3 H), 1.40 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 166.0, 165.6, 131.2 (4 C), 131.0 (4 C), 130.2, 129.7, 129.4 (4 C), 129.3 (4 C), 127.7, 126.8, 99.1, 92.0, 85.7, 80.0, 61.3, 61.2, 31.7, 14.4, 13.7.

EI-MS: *m*/*z* (%) = 442 (7), 441 (32), 440 (100), 412 (7), 384 (8).

Anal. Calcd for $C_{27}H_{24}N_2O_4$: C, 73.62; H, 5.49; N, 6.36. Found: C, 73.40 H, 5.40; N, 6.55.

4,5-Bis(dodec-1-yn-1-yl)-1,2-dimethyl-1*H*-imidazole (5d) (Table 2, entry 4)

The crude reaction product obtained by Pd- and Cu-mediated alkynylation of 4,5-dibromo-1,2-dimethyl-1*H*-imidazole (**2**) with dodec-1-yne (**3d**) was purified by flash chromatography on silica gel with a mixture of EtOAc and toluene (50:50) as eluent to give **5d** as a beige solid; yield: 326 mg (77%); mp 50–51 °C. GLC analysis showed that **5d** had chemical purity higher than 98%.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.47 (s, 3 H), 2.48 (t, *J* = 7.0 Hz, 2 H), 2.41 (t, *J* = 7.0 Hz, 2 H), 2.30 (s, 3 H), 1.46 (m, 32 H), 0.88 (m, 6 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 144.4, 126.5, 119.4, 99.7, 92.3, 73.8, 68.9, 31.9 (2 C), 31.1, 29.6 (2 C), 29.4 (2 C), 29.3 (2 C), 29.2, 29.0, 28.8, 28.7, 28.6, 28.5, 22.7 (2 C), 19.8, 19.6, 14.1 (2 C), 13.4.

EI-MS: *m*/*z* (%) = 424 (91), 353 (46), 339 (54), 325 (31), 299 (100), 213 (44), 199 (43), 185 (44).

Anal. Calcd for $C_{29}H_{48}N_2$: C, 82.01; H, 11.39; N, 6.60. Found: C, 81.80; H, 11.30; N, 6.56.

6,6′-(1,2-Dimethyl-1*H*-imidazol-4,5-diyl)bis(hex-5-yn-1-ol) (5e) (Table 2, entry 5)

The crude reaction product obtained by Pd- and Cu-mediated alkynylation of 4,5-dibromo-1,2- dimethyl-1*H*-imidazole (**2**) with hex-5-yn-1-ol (**3e**) was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and MeOH (97:3) as eluent to give **5e** as a beige solid; yield: 207 mg (72%); mp 88–89 °C. GLC analysis showed that **5e** had chemical purity higher than 98%.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.78 (br s, 2 H), 3.65 (m, 4 H), 3.46 (s, 3 H), 2.53 (m, 2 H), 2.45 (m, 2 H), 2.30 (s, 3 H), 1.70 (m, 6 H), 1.26 (m, 2 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 144.7, 126.2, 119.6, 99.9, 92.6, 74.0, 69.0, 61.7, 61.7, 31.9, 31.3, 29.7, 25.0, 25.1, 19.7, 19.4, 13.3.

EI-MS: *m*/*z* (%) = 288 (53), 243 (48), 231 (100), 201 (37), 199 (34), 185 (49), 174 (43), 173 (62), 172 (62), 159 (41).

Anal. Calcd for $C_{17}H_{24}N_2O$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.55; H, 8.40; N, 9.76.

Ethyl4-{4,5-Bis[(4-methoxyphenyl)ethynyl]-1-methyl-1*H*-imidazol-2-yl}benzoate (9a) (Table 2, entry 6)

The crude product obtained by Pd- and Cu-mediated alkynylation of ethyl 4-(4,5-dibromo-1-methyl-1*H*-imidazol-2-yl)benzoate (**7a**) with 4-ethynylanisole (**3b**) was triturated with a mixture of toluene and EtOAc (90:10) to afford the title compound **9a** as a yellow solid; yield: 387 mg (79%); mp 128–130 °C. GLC analysis showed that **9a** had chemical purity higher than 98%.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.13 (m, 2 H), 7.79 (m, 2 H), 7.51 (m, 2 H), 7.49 (m, 2 H), 6.89 (m, 2 H), 6.86 (m, 2 H), 4.40 (q, *J* = 7.0 Hz, 2 H), 3.82 (s, 3 H), 3.81 (s, 6 H), 1.41 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 1656.0, 160.1, 159.6, 146.9, 133.7, 133.14 (2 C), 133.08 (2 C), 130.8, 129.8, 128.7 (2 C), 128.5 (2 C), 122.3, 115.3, 114.4, 114.2 (2 C), 114.0 (2 C), 100.5, 92.8, 81.3, 76.0, 61.3, 55.5, 55.4, 33.7, 14.5.

Anal. Calcd for $C_{31}H_{26}N_2O_4$: C, 75.90; H, 5.34; N, 5.71. Found: C, 75.80; H, 5.40; N, 5.75.

4,5-Bis[(4-methoxyphenyl)ethynyl]-1-methyl-2-[4-(methylsulfonyl)phenyl]-1*H*-imidazole (9b) (Table 2, entry 7)

The reaction product obtained by Pd- and Cu-mediated alkynylation of 4,5-dibromo-1-methyl-2-(4-methylsulfonyl)phenyl-1*H*-imidazole (**7b**) with 4-ethynylanisole (**3b**) was triturated with a mixture of toluene and EtOAc (50:50) affording the title compound **9b** as a yellow solid; yield: 436 mg (88%); mp 179–180 °C. GLC analysis showed that **9b** had chemical purity higher than 98%.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.01 (m, 2 H), 7.92 (m, 2 H), 7.49 (m, 4 H), 6.90 (m, 2 H), 6.87 (m, 2 H), 3.83 (s, 6 H), 3.81 (s, 3 H), 3.07 (s, 3 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 160.2, 159.7, 145.7, 140.6, 134.7, 133.1 (4 C), 129.4 (2 C), 128.8, 127.7 (2 C), 122.8, 115.0, 114.2 (2 C), 114.1, 114.0 (2 C), 100.9, 93.0, 81.0, 75.7, 55.5, 55.4, 44.5, 33.8.

Anal. Calcd for $C_{29}H_{24}N_2O_4S$: C, 70.14; H, 4.87; N, 5.64. Found: C, 69.98; H, 4.88; N, 5.50.

1-Methyl-2-(4-methylphenyl)-4,5-bis(phenylethynyl)-1*H*-imidazole (9c) (Table 2, entry 8)

The crude product obtained by Pd- and Cu-mediated alkynylation of 4,5-dibromo-1-methyl-2-(4-methylphenyl)-1*H*-imidazole (**7c**) with phenylacetylene (**3a**) was purified by flash chromatography on silica gel with a mixture of toluene and EtOAc (94:6) as eluent. The chromatographic fractions containing the product were collected and concentrated, affording **9c** as a pale-yellow solid; yield: 268 mg (72%); mp 176–179 °C. GLC analysis showed that **9c** had chemical purity higher than 98%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (m, 6 H), 7.32 (m, 8 H), 3.80 (s, 3 H), 2.42 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 139.5, 131.63,131.4, 129.4, 128.8, 128.7, 128.5, 128.5, 128.3, 128.2, 126.7, 123.3, 122.5, 121.6, 100.1, 92.6, 82.9, 77.5, 33.4, 21.4.

EI-MS: *m*/*z* (%) = 373 (28), 372 (100), 213 (15), 204 (10), 186 (7).

Anal. Calcd for $C_{27}H_{20}N_2$: C, 87.07; H, 5.41; N, 7.52. Found: C, 87.15; H, 5.25; N, 7.38.

4,5-Bis[(4-methoxyphenyl)ethynyl]-1-methyl-2(4-methylphenyl)-1*H*-imidazole (9d) (Table 2, entry 9)

The crude product obtained by Pd- and Cu-mediated alkynylation of 4,5-dibromo-1-methyl-2-(4-methylphenyl)-1*H*-imidazole (**7c**) with 4-ethynylanisole (**3b**) was purified by flash chromatography on silica gel with a mixture of toluene and EtOAc (93:7) as eluent. The chromatographic fractions containing the product were collected and concentrated to afford **9d** as a pale-yellow solid; yield: 315 mg (73%); mp 162–164 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (m, 2 H), 7.49 (m, 4 H), 7.24 (m, 2 H), 6.86 (m, 4 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.73 (s, 3 H), 2.38 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 159.6, 148.3, 139.3, 133.1 (2 C), 133.0 (2 C), 129.3 (2 C), 128.7 (2 C), 128.3, 127.0, 121.5, 115.6, 114.7, 114.2 (2 C), 114.0 (2 C), 99.9, 92.4, 81.8, 76.4, 55.4, 55.3, 33.4, 21.4.

ESI-MS: *m*/*z* = 433 $[M + H]^+$.

Anal. Calcd for $C_{29}H_{24}N_2O_2$: C, 80.53; H, 5.59; N, 6.48. Found: C, 80.79; H, 5.40; N, 6.50.

2-(4-Methoxyphenyl)-1-phenyl-4,5-bis(phenylethynyl)-1*H*-imidazole (10a) (Table 2, entry 10)

The crude product obtained by Pd- and Cu-mediated alkynylation of 4,5-dibromo-1-phenyl-2-(4-methoxylphenyl)-1*H*-imidazole (**8a**) with phenylacetylene (**3a**) was purified by flash chromatography on silica gel with a mixture of toluene and EtOAc (95:5) as eluent. The chromatographic fractions containing the product were collected and concentrated, affording **10** as a colorless solid; yield: 337 mg (75%); mp 185–187 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (m, 2 H), 7.61 (m, 2 H), 7.48 (m, 3 H), 7.36 (m, 8 H), 7.29 (m, 3 H), 6.76 (m, 2 H), 3.77 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 147.7, 136.9, 131.7 (2 C), 131.1 (2 C), 130.2 (2 C), 129.4 (2 C), 129.0, 128.9, 128.6, 128.4 (2 C), 128.3 (3), 127.7 (2 C), 123.3, 122.6, 122.2, 121.8, 113.7 (2C), 99.9, 93.2, 82.8, 78.0, 55.2.

ESI-MS: *m*/*z* = 451 $[M + H]^+$.

Anal. Calcd for$C_{32}H_{22}N_2O$: C, 85.31; H, 4.92; N, 6.22. Found: C, 85.40; H, 4.77; N, 6.26

5-Alkynyl-4-bromo-1,2-dimethyl-1*H*-imidazoles 4; General Procedure

A solution of 4,5-dibromo-1,2-dimethyl-1*H*-imidazole (**2**; 254 mg, 1 mmol), alkyne **3** (1.5 mmol), $Pd(MeCN)_2Cl_2$ (10 mg, 0.04 mmol, 4 mol%), 1,1′-bis(diphenylphosphino)ferrocene (22 mg, 0.04 mmol, 4 mol%), and CuI (3 mg, 0.02 mmol, 2 mol%) in DMF (4.5 mL) and DBU (0.5 mL) was stirred at 80 °C for 3h. The reaction mixture was then diluted with EtOAc (100 mL) and sat. aq NH_4Cl (100 mL) was added. The resulting mixture was stirred in the open air for 0.5 h and then extracted with EtOAc. The combined organic extracts were washed with H_2O (3 × 25 mL) and brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel. This procedure was employed to prepare compounds **4a**–**e** (Table 3).

4-Bromo-1,2-dimethyl-5-(phenylethynyl)-1*H*-imidazole (4a) (Table 3, entry 1)

The crude reaction product obtained by C-5 Pd- and Cu-mediated alkynylation of 4,5-dibromo-1,2-dimethyl-1*H*-imidazole (**2**) with phenylacetylene (**3a**) was purified by flash chromatography on silica gel with a mixture of toluene and EtOAc (60:40) as eluent to give **4a** as a beige solid; yield: 116 mg (42%); mp 117–121 °C. GLC analysis showed that **4a** had chemical purity higher than 98%.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.52 (m, 2 H), 7.35 (m, 3 H), 3.59 (s, 1 H), 2.37 (s, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 145.8, 131.3 (2 C), 128.7, 128.4 (2 C), 122.4, 119.2, 115.7, 98.7, 76.4, 32.0, 13.7.

EI-MS: *m*/*z* (%) = 277 (14), 276 (96), 275 (25), 274 (100), 273 (10), 142 (20), 139 (11), 128 (30), 127 (26), 56 (12).

Anal. Calcd for $C_{13}H_{11}BrN_2$: C, 56.75; H, 4.03; N, 10.18. Found: C, 57.01; H, 4.06; N, 10.25.

4-Bromo-5-[(4-methoxyphenyl)ethynyl]-1,2-dimethyl-1*H*-imidazole (4b) (Table 3, entry 2)

The crude reaction product obtained by C-5 Pd- and Cu-mediated alkynylation of 4,5-dibromo-1,2-dimethyl-1*H*-imidazole (**2**) with 4-ethynylanisole (**3b**) was purified by flash chromatography on silica gel with a mixture of toluene and EtOAc (60:40) as eluent to give **4b** as a beige solid; yield: 155 mg (51%); mp 107–111 °C. GLC analysis showed that **4b** had chemical purity higher than 98%.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.46 (m, 2 H), 6.86 (m, 2 H), 3.83 (s, 3 H), 3.58 (s, 3 H), 2.37 (s, 3 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 160.0, 145.5, 133.0 (2 C), 118.6, 115.9, 114.4, 114.1 (2 C), 98.6, 75.2, 55.4, 32.0, 13.7.

EI-MS: *m*/*z* (%) = 307 (16), 306 (98), 305 (18), 304 (100), 291 (61), 290 91 (10), 289 (64), 261 (10), 114 (10), 56 (16).

Anal. Calcd for $C_{14}H_{13}BrN_2O$: C, 55.10; H, 4.29; N, 9.18. Found: C, 55.11; H, 4.38; N, 9.19

Ethyl 4-[(4-Bromo-1,2-dimethyl-1*H*-imidazol-5-yl)ethynyl]benzoate (4c) (Table 3, entry 3)

The crude reaction product obtained by C-5 Pd- and Cu-mediated alkynylation of 4,5-dibromo-1,2-dimethyl-1*H*-imidazole (**2**) with ethyl 4-ethynylbenzoate (**3c**) was purified by flash chromatography on silica gel with a mixture of Et_2O and EtOAc (95:5) as eluent to give **4c** as a colorless solid; yield: 73 g (21%); mp 130–131 °C. GLC analysis showed that **4c** had chemical purity higher than 98%.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.03 (m, 2 H), 7.57 (m, 2 H), 4.39 (q, *J* = 7.3 Hz, 2 H), 3.63 (s, 3 H), 2.41 (s, 3 H), 1.41 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 165.9, 146.3, 131.4 (2 C), 130.2, 129.6 (2 C), 126.9, 120.3, 115.4, 98.3, 79.6, 61.3, 32.1, 14.5, 13.7.

EI-MS: *m*/*z* (%) = 349 (17), 348 (99), 347, (19), 346 (100), 320 (35), 319 (10), 318 (36), 303 (15), 301 (15), 56 (16).

Anal. Calcd for $C_{16}H_{15}BrN_2O_2$: C, 55.35; H, 4.35; N, 8.07. Found: C, 55.40; H, 3.99; N, 8.09.

4-Bromo-5-(dodec-1-yn-1-yl)-1,2-dimethyl-1*H*-imidazole (4d) (Table 3, entry 4)

The crude reaction product obtained by C-5 Pd- and Cu-mediated alkynylation of 4,5-dibromo-1,2-dimethyl-1H-imidazole (**2**) with dodec-1-yne (**3d**) was purified by flash chromatography on silica gel with a mixture of toluene and EtOAc (40:60) as eluent to give **4d** as a colorless solid; yield: 156 mg (46%); mp 75–76 °C. GLC analysis showed that **4d** had chemical purity higher than 98%.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.51 (s, 3 H), 2.48 (t, *J* = 7.0 Hz, 2 H), 2.34 (s, 3 H), 1.63 (qt, *J* = 7.0 Hz, 2 H), 1.46 (m, 2 H), 1.27 (m, 12 H), 0.88 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 144.6, 117.6, 116.1, 100.2, 68.0, 31.9, 31.7, 29.6, 29.5, 29.3, 29.1, 28.8, 28.6, 22.7, 19.8, 14.3, 13.5.

EI-MS: *m*/*z* (%) = 340 (38), 338 (39), 259 (100), 215 (38), 213 (80), 211 (46), 147 (36), 134 (82).

Anal. Calcd for $C_{17}H_{27}BrN_2$: C, 60.18; H, 8.02; N, 8.26. Found: C, 60.20; H, 8.15; N, 8.27

6-(4-Bromo-1,2-dimethyl-1*H*-imidazol-5-yl)hex-5-yn-1-ol (4e) (Table 3, entry 5)

The crude reaction product obtained by C-5 Pd- and Cu-mediated alkynylation of 4,5-dibromo-1,2-dimethyl-1*H*-imidazole (**2**) with hex-5-yn-1-ol (**3e**) was purified by flash chromatography on silica gel with a mixture of toluene and EtOAc (4:6) as eluent to give **4e** as a yellow solid; yield: 152 mg (56%); mp 94–96 °C. GLC analysis showed that **4e** had chemical purity higher than 98%.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.73 (t, *J* = 5.9 Hz, 2 H), 3.51 (s, 3 H), 3.02 (br s, 1 H), 2.53 (t, *J* = 6.6 Hz, 2 H), 2.34 (s, 3 H), 1.74 (m, 4 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 114.9, 117.4, 116.0, 99.9, 68.2, 61.8, 31.9, 31.8, 25.0, 19.6, 13.5.

EI-MS: *m*/*z* (%) = 272 (51), 270 (51), 213 (100), 211 (78), 189 (46), 187 (43), 174 (35), 173 (44), 147 (50), 134 (98), 56 (45).

Anal. Calcd for $C_{11}H_{15}BrN_2O$: C, 48.72; H, 5.58; N, 10.33. Found: C, 48.75; H, 5.38; N, 10.35.

5-(Dodec-1-yn-1-yl)-4-[(4-methoxyphenyl)ethynyl]-1,2-dimethyl-1*H*-imidazole (11a)

A mixture of 4-bromo-5-(dodec-1-yn-1-yl)-1,2-dimethyl-1*H*-imidazole (**4d**; 0.08 g, 0.25 mmol), 4-ethynylanisole (**3b**; 55 µL, 0.05 g, 0.38 mmol), $Pd(MeCN)_2Cl_2$ (4 mg, 0.016 mmol, 4 mol%), Xantphos (10 mg, 0.016 mmol, 4 mol%), and CuI (1.4 mg, 0.008 mmol, 2 mol%) in DMF (2.25 mL) and DBU (0.25 mL) was stirred at 80 °C for 3 h. The reaction mixture was then diluted with EtOAc (50 mL) and sat. aq NH_4Cl (50 mL) was added. The resulting mixture was stirred in the open air for 0.5 h and then extracted with EtOAc. The combined organic extracts were washed with H_2O (3 × 10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with a mixture of hexane and EtOAc (4:6) as eluent to give **11a** as a red liquid; yield: 0.086 g (88%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.46 (m, 2 H), 6.84 (m, 2 H), 3.80 (s, 3 H), 3.52 (s, 3 H), 2.52 (t, *J* = 6.8 Hz, 2 H), 2.36 (s, 3 H), 1.64 (qt, *J* = 6.8 Hz, 2 H), 1.48 (m, 2 H), 1.25 (m, 12 H), 0.87 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 159.4, 145.1, 133.0 (2 C), 126.2, 120.1, 115.7, 113.7 (2 C), 100.7, 91.5, 81.6, 69.0, 55.3, 32.0, 31.4, 29.75, 29.69, 29.5, 29.3, 29.0, 28.7, 22.8, 20.0, 14.3, 13.6.

EI-MS: *m*/*z* (%) = 391 (28), 390 (100), 319 (11), 305 (27), 291 (15), 265 (15), 263 (20), 250 (14).

Anal. Calcd for $C_{26}H_{34}N_2O$: C, 79.96; H, 8.77; N, 7.17. Found: C, 80.01; H, 8.78; N, 7.00.

6-[1,2-Dimethyl-4-(phenylethynyl)-1*H*-imidazol-5-yl]hex-5-yn-1-ol (11b)

A mixture of 6-(4-bromo-1,2-dimethyl-1*H*-imidazol-5-yl)hex-5-yn-1-ol (**4e**; 0.11 g, 0.4 mmol), phenylacetylene (**3a**; 65 µL, 0.06 g, 0.6 mmol), $Pd(MeCN)_2Cl_2$ (4 mg, 0.016 mmol, 4 mol%), Xantphos (10 mg, 0.016 mmol, 4 mol%), and CuI (1.4 mg, 0.008 mmol, 2 mol%) in DMF (2.25 mL) and DBU (0.25 mL) was stirred at 80 °C for 3 h. The reaction mixture was then diluted with EtOAc (50 mL) and sat. aq NH_4Cl (50 mL) was added. The resulting mixture was stirred in the open air for 0.5 h and then extracted with EtOAc. The combined organic extracts were washed with H_2O (3 × 10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with a mixture of toluene and EtOAc (40:60) as eluent to give **11b** as a beige solid; yield: 0.083 g (76%); mp 114–116 °C. GLC analysis showed that **11b** had chemical purity higher than 98%.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.50 (m, 2 H), 7.29 (m, 3 H), 3.69 (t, *J* = 5.9 Hz, 2 H), 3.45 (s, 3 H), 2.54 (t, *J* = 6.4 Hz, 2 H), 2.32 (s, 3 H), 1.75 (m, 4 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 145.2, 131.2 (2 C), 128.1 (2 C), 127.9, 125.3, 123.1, 120.5, 100.6, 91.7, 82.9, 68.7, 61.5, 31.8, 31.3, 24.9, 19.6, 13.3.

EI-MS: *m*/*z* (%) = 293 (22), 292 (100), 291 (25), 235 (75), 233 (47), 165 (20).

Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 78.01; H, 6.95; N, 9.65.

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Supporting Information

Supporting information (Table S1, copies of NMR spectra for compounds **4a–e**, **5a–e**, **9a–d**, **10a**, and DSC thermograms for compounds

5a–d and **9a–c**) for this article is available online at https://doi.org/10.1055/s-0037-1610666.

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