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Efficient Synthesis of *tert*-Butyl 2,4-Dialkynylated and 2-Alkynylated-4-arylated-1*H*-imidazole-1-carboxylate *via* Regioselective Sonogashira Cross-coupling Reaction

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Abstract: An efficient regioselective cross-coupling reactions of *tert*-butyl 2,4-dibrominated-5-methyl-1*H*-imidazole-1-carboxylate is reported under simple and mild conditions. This new synthetic route selectively gave an easy access to 2,4-dialkynylated and 2-alkynylated-4-arylated-1*H*-imidazole-1-carboxylate in good to excellent yields.

Introduction

Transition metal-catalyzed reactions are of major importance in organic synthesis field[1,2] and have attracted considerable attention from researchers in recent years.[3] Particularly, the Sonogashira cross-coupling reaction,[4] which involves a palladium catalyzed sp^2-sp coupling between aryl/alkenyl halides or triflates and terminal alkynes in the presence or absence of a copper(I) cocatalyst, is one of the most important and versatile synthetic transformations for the preparation of aryl-alkynes and conjugated enynes. These interesting classes of synthetic intermediates[5] are present in numerous natural products.[6] Furthermore, the Sonogashira reaction has also found many applications in pharmaceuticals and organic materials.[7-9]
Alkynylation of mono-halogenated heterocyclic compounds using Sonogashira-type cross-coupling has been extensively studied in the literature.[10] Particularly and thanks to their functionalization capacity, halogenoimidazoles have been used as precursors in palladium-catalyzed cross coupling reactions to generate several imidazole derivatives exhibiting various biological activities.[11] For example, the imidazole core substituted with an alkynyl group such as 4-ethynylimidazole (**A**) has been described as anti-inflammatory and cytoprotective agent.[12] Moreover, alkynylated imidazoles are also known to be potent inhibitors of EGFR tyrosine kinase (**B**),[13] p38α Kinase (**C**), [14] and also act as inhibitors of mGluR5 (**D**)[15] and BCR-ABL (**E**)[16] (Figure 1). Although the metallo-catalyzed reactivity of monohalogenated imidazoles has been extensively investigated,[17] only a few methods have been developed for the selective cross-coupling of dihalogenated ones leading to unsymmetrical difunctionalization products.[11c,18]

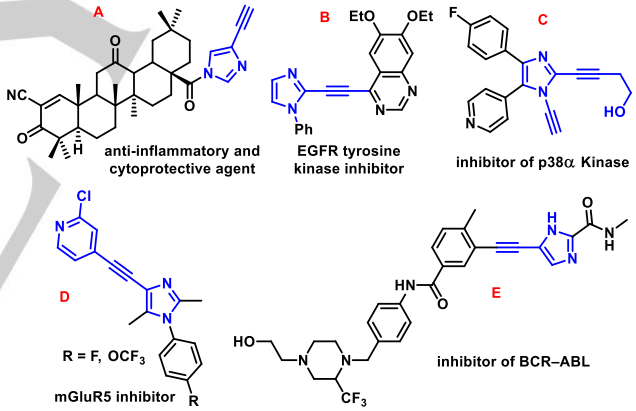
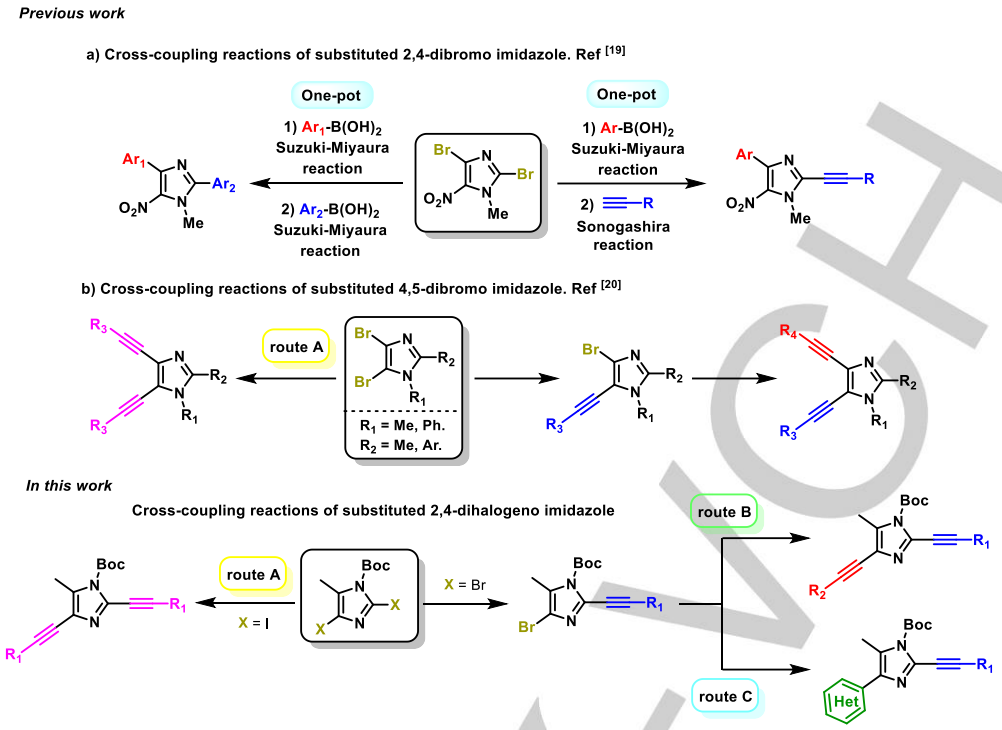


Figure 1. Some biologically active alkynylated imidazoles.

In 2017, Vanelle *et al*.[19] reported the regioselective bis-Suzuki-Miyaura or Suzuki-Miyaura/Sonogashira reaction starting from 2,4-dibromo-1-methyl-5-nitro-1*H*-imidazole. The regioselectivity of the cross-coupling reaction at C-4 was controled by the presence of the nitro group at C-5, acting as a directing group and significantly increasing the electrophilic properties of the C-4, offering to this position a strong reactivity towards palladium-catalyzed cross-coupling reactions. Likewise, an efficient synthesis of 1,2-disubstituted 4,5-dialkynylimidazoles by bis-Sonogashira alkynylation of the corresponding 4,5-dibromo imidazole derivatives was developed by Bellina *et al*.[20] This two-step synthesis of unsymmetrical imidazole-fused enediynes was performed using $PdCl_2(MeCN)_2$ as catalyst, CuI as co-catalyst in presence of Xantphos as ligand. However, few examples of this selective functionalization of vicinal dibromides have been described in low to moderate yields during the monoalkynylation reaction.

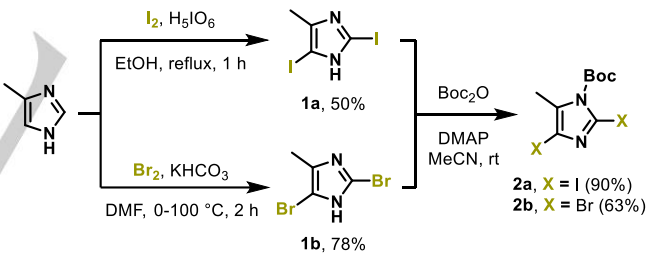


Scheme 1. Convergent approach to selective bis-alkynylation or alkynylation/arylation of dihalogenated imidazole derivatives.

The reported syntheses show the need of versatile strategies to prepare imidazoles containing multiple substitutions. To the best of our knowledge, the selective alkynylation of 2,4-dihalogenated-1*H*-imidazole derivatives involving Sonogashira cross-coupling has never been reported, to date. Thus, the development of a general synthetic method applicable for the selective functionalization of imidazole heterocycle remains, therefore, essential to increase molecular diversity.[21] Continuing our investigations on the functionalization of nitrogen heterocycles and in order to provide a new access to polysubstituted imidazole derivatives,[22] we report herein a regioselective Sonogashira cross-coupling between *tert*-butyl 2,4-dibromo-5-methyl-1*H*-imidazole-1-carboxylate **2b** and various alkynes. The first Sonogashira cross coupling occurred selectively at C-2 leading to the formation of 2-alkynylated-4-bromo-5-methyl-1*H*-imidazole-1-carboxylates which underwent a second Sonogashira or Suzuki-Miyaura cross-coupling reactions, giving thus access to a small library of unsymmetrical 2,4-disubstituted imidazole derivatives (Scheme 1).

Results and Discussion

Our first investigations to achieve a selective alkynylation were focused on the preparation of *tert*-butyl 2,4-dihalogeno-5-methyl-1*H*-imidazole-1-carboxylates **2a-b** which were then used as starting materials under Sonogashira cross-coupling conditions. Thus, the dihalogenoimidazoles **2a-b** were synthesized from commercially available 4-methylimidazole, following well-known procedures,[23,24] in two sequential steps as shown in scheme 2. While the diiodination of 4-methylimidazole was performed with iodine and periodic acid in ethanol refluxing, its dibromination was carried out in the presence of bromine and $KHCO_3$ in DMF at 100 °C. Unprotected 2,4-dihalogenoimidazoles **1a** and **1b** were then reacted with Boc_2O and DMAP in acetonitrile, leading to new *tert*-butyl 2,4-diiodo and 2,4-dibromo-5-methyl imidazoles **2a-b** in 90% and 63% yields, respectively (Scheme 2).



Scheme 2. Synthesis of *tert*-butyl 2,4-dihalogeno-5-methyl-1*H*-imidazole-1-carboxylates **2a-b**.

The molecular structure of the new compound **2b** was unambiguously confirmed by X-ray crystal analysis as depicted in Figure 2.[25]

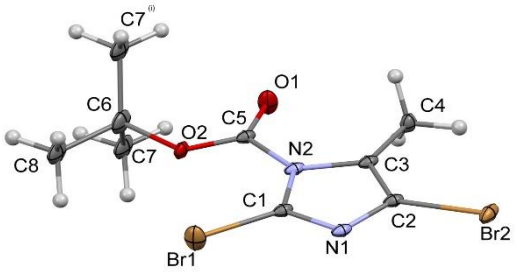
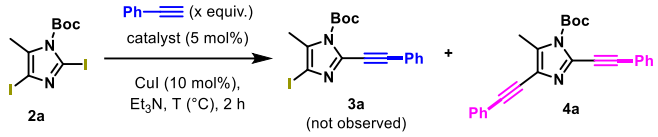


Figure 2. X-ray single-crystal structure of compound **2b**.

First, we examined the coupling reaction of 2,4-diiodoimidazole **2a** with phenylacetylene using 5 mol% of catalyst, 10 mol% of CuI as co-catalyst in the presence of an excess of triethylamine as base, and varying the amount of alkyne, the temperature and the reaction time. The results are summarized in Table 1.

Table 1. Optimization of Sonogashira cross-coupling conditions between **2a** and phenylacetylene.



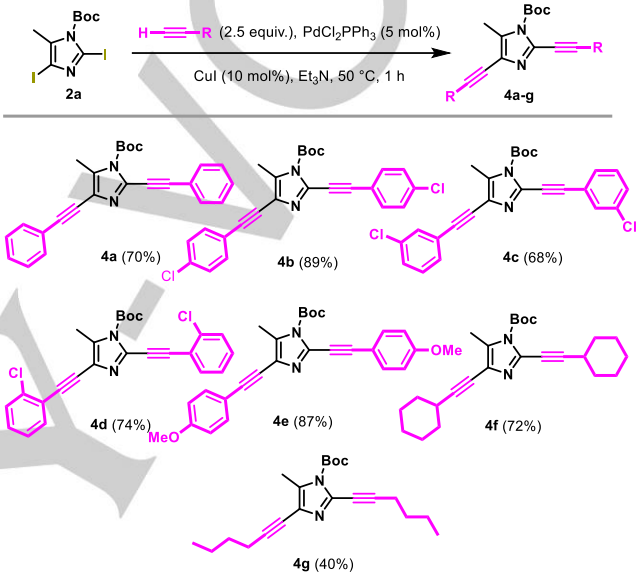
Entry	T(°C)	Alkyne (equiv.)	Catalyst	Conversion (%)[a]	**4a**[b]
1	25	1.05	$Pd_2(dba)_3$	42	21
2	25	1.05	$Pd(PPh_3)_4$	31	17
3	50	1.05	$Pd(PPh_3)_4$	47	26
4	25	1.05	$PdCl_2(MeCN)_2$	47	22
5	25	1.05	$PdCl_2(PPh_3)_2$	50	27
6	50	1.05	$PdCl_2(PPh_3)_2$	50	31
7	50	2.1	$PdCl_2(PPh_3)_2$	89	49[c]
8	25	2.5	$PdCl_2(PPh_3)_2$	70	41
9	**50**	**2.5**	**$PdCl_2(PPh_3)_2$**	**100**	**70**[c]
10	50	2.5	$PdCl_2(PPh_3)_2$	50	42[d]

[a] The conversion was determined from the crude ^{1}H NMR spectrum. [b] Yield of isolated product **4a** after column chromatography. [c] The reaction was carried out in 1h. [d] The reaction was carried out with 2.5 mol% of $PdCl_2(PPh_3)_2$ and 5 mol% of CuI during 5h.

According to all the results obtained during this study, it was found that whatever the reaction conditions used (choice of catalyst, amount of alkyne, temperature and reaction time), the monoalkynylation product **3a** was never formed. Sonogashira cross-coupling reaction between 2,4-diiodoimidazole **2a** and phenylacetylene led to the formation of dialkynylated product **4a**, given the equal reactivity of positions C-2 and C-4 in these reaction conditions, presumably due to the high reactivity of the C-I bond towards the insertion of palladium during the oxidative addition step.

After screening the various conditions, the use of phenylacetylene (2.5 equiv.), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%) in triethylamine at 50 °C proved to be the most appropriate choice for obtaining dialkynylated product **4a** in good yield (Table 1, entry 9). Employing $Pd_2(dba)_3$, $Pd(PPh_3)_4$ or $PdCl_2(MeCN)_2$ instead of $PdCl_2(PPh_3)_2$ decreased significantly the yield of product **4a** (Table 1, entries 1-4). Likewise, the dialkynylation reaction was less efficient when the cross-coupling was performed at room temperature (Table 1, entries 5 and 8). Despite the use of 2.1 equivalents of alkyne under the best reaction conditions (Table 1, entry 7), the conversion of compound **2a** was not complete and the yield of isolated bis-coupling product **4a** did not exceed 49%. This result proved that an excess of alkynes (2.5 equiv.) was therefore required, probably because of the formation of the undesired homocoupling product. Reducing the amount of catalyst (2.5 mol% of $PdCl_2(PPh_3)_2$) and co-catalyst (5 mol% of CuI) resulted in an incomplete conversion rate of compound **2a**, (Table 1, entry 10).

After establishing the best conditions to perform the bis-alkynylation of **2a** (Table 1, entry 9), we extended this coupling to synthesize a small library of 1,5-disubstituted 2,4-bis-alkynylated imidazole **4a-g.** Various alkynes were used to explore the scope of this reaction and the results obtained are summarized in Scheme 3.



Scheme 3. Synthesis of 1,5-disubstituted-2,4-bis-alkynylated imidazoles **4** by Sonogashira coupling reaction.

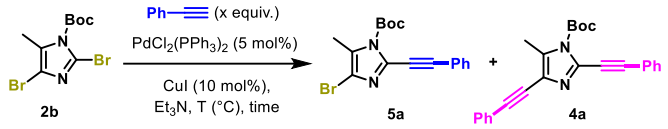
As shown in Scheme 3, terminal alkynes containing an alkyl or an aryl group were properly coupled with **2a**, giving access to 2,4-dialkynylated products **4a-g** in moderate to good yields. Under our optimized conditions, numerous substituents were tolerated on the terminal alkynes. A terminal alkyne bearing an electron-donating group such as a methoxy group in *para* position on the aromatic ring was easily coupled with **2a,** providing the corresponding product **4e** in 87% yield. Likewise, terminal alkynes with an halide substituent on the benzene ring, such as chlorine in position *para*, *meta* or *ortho* were found to be effective and compatible with this coupling reaction, affording the expected products **4b** (89%), **4c** (68%) and **4d** (74%), respectively. Note that the *ortho* position of chlorine on the aromatic ring was less efficient than the *para* position which could be explained by steric hindrance. Overall, the coupling reactions were not affected either by the presence of the electron-donating or electron-withdrawing group on the aromatic ring. Aliphatic alkynes such as 1-hexyne and ethynylcyclohexane also provided the desired products **4g** and **4f** in 40% and 72% yields, respectively. The unselective Sonogashira coupling observed starting from the diiodine compound **2a** led us to consider an innovative alternative strategy to control the selectivity of this reaction.

Selective Sonogashira coupling reactions

In order to carry out these dialkynylation reactions selectively at C-2 and C-4 positions of imidazole **2**, we decided to study the reactivity of *tert*-butyl 2,4-dibromo-5-methyl-1*H*-imidazole-1-carboxylate **2b** using the conditions previously optimized during the dialkynylation of **2a**.

The results of the various attempts for cross-coupling between **2b** and phenylacetylene are illustrated in Table 2.

Table 2. Optimization of the regioselective Sonogashira coupling between **2b** and phenylacetylene.



Entry	T(°C)	Alkyne (equiv.)	Time (h)	Conversion (%)[a]	Yield (%)[b]	
					5a	**4a**
1	25	1.1	6	50	40	0
2	50	1.1	6	80	70	0
3	25	1.5	12	65	50	0
4	**50**	**1.5**	**1**	**100**	**88**	**0**
5	90	1.1	6	100	47	41
6	90	2.5	6	100	32	53
7	50	1.5	1	100	70[c]	0

[a] The conversion was determined from the crude ^{1}H NMR spectrum.
[b] Yields of isolated products **5a** and **4a** after column chromatography.
[c] The reaction was carried out with 2.5 mol% of $PdCl_2(PPh_3)_2$ and 5 mol% of CuI.

We began our study by using $PdCl_2(PPh_3)_2$ (5 mol%) and CuI (10 mol%) in the presence of a slight excess of alkyne (1.1 equiv.) at room temperature for 6 hours. The reaction afforded the monoalkynylated product **5a** in 40% yield, along with unreactive starting material **2b** (Table 2, entry 1). Interestingly, under the same reaction conditions and by increasing the temperature to 50 °C, the yield of the desired product **5a** increased to 70% although the reaction remained incomplete (Table 2, entry 2). No significant improvement in the result of this cross-coupling was observed when the reaction was carried out at room temperature, using an excess of alkyne (1.5 equiv.) (Table 2, entry 3). Gratifyingly, by heating the reaction at 50 °C, the starting material was completely consumed after only 1 hour, and the isolated yield of monoalkynylated product **5a** was improved to 88% (Table 2, entry 4). Noteworthy, no trace of the dialkynylation product **4a** was observed, indicating the high regioselectivity of Sonogashira cross-coupling at C-2 position of **2b**. Reducing the loading of $PdCl_2(PPh_3)_2$ (2.5 mol%) and CuI (5 mol%), the starting material **2b** was completely consumed but significantly affected the reaction yield, providing compound **5a** in only 70% yield (Table 2, entry 7). Performing the reaction at 90 °C and whatever the amount of alkyne used, this coupling reaction was not selective since a significant amount of the dialkynylated product **4a** was formed (Table 2, entries 5-6). This result proved the importance of the temperature to achieve this coupling in a totally selective manner. To confirm the molecular structure of the monoalkynylated product **5a**, an X-ray crystal analysis was performed as shown in Figure 3.[26]

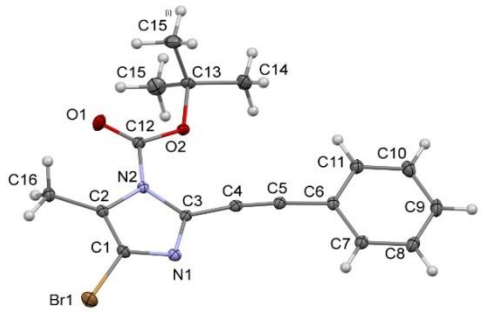
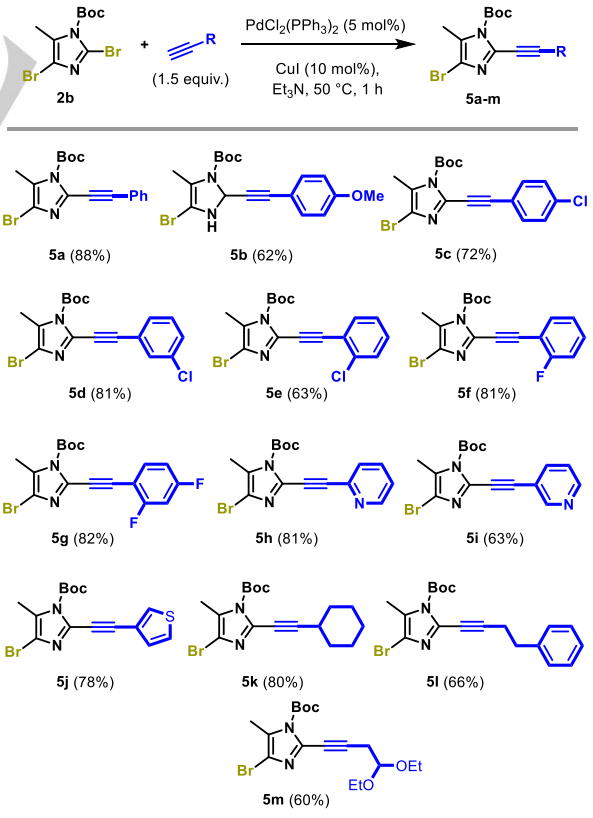


Figure 3. X-ray single-crystal structure of compound **5a**.

The regioselectivity observed in the Sonogashira coupling reaction starting from dibromoimidazole **2b** is undoubtedly favored by the more electrophilic properties of the brominated C-2 carbon.[27]

After establishing the best conditions to carry out the Sonogashira coupling selectively at C-2 (Table 2, entry 4), we examined the scope and limitations of this selective alkynylation of **2b** using several terminal alkynes. In all cases, the cross-coupling reaction selectively provided the C2-alkynylated products **5a-m** in good to excellent yields. The obtained results are summarized in Scheme 4.



Scheme 4. Scope of the regioselective Sonogashira coupling of **2b** with various alkynes.

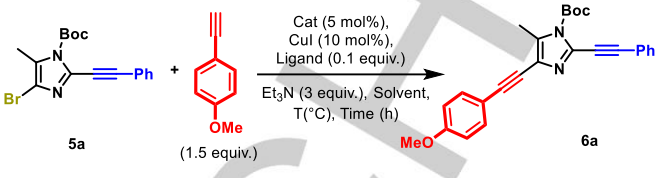
As shown in Scheme 4, alkynes substituted by alkyl, aryl and heteroaryl groups were efficiently coupled selectively with the dibrominated compound **2b**, producing the C-2 monoalkynylated products **5a-m** in good to excellent yields. Notably, phenylacetylene and phenylacetylene bearing an electron-donating group, such as a methoxy group in *para* position were easily coupled with **2b** providing the corresponding products **5a** (88%) and **5b** (62%), respectively. Aromatic terminal alkynes substituted by electron-withdrawing groups such as chlorine in *para*, *meta* or *ortho* position were also successfully introduced at C-2 position of **2b** in yields ranging from 63% and 81%. However, phenylacetylene with the chlorine at *ortho* position seemed to provide a less efficient result probably because of steric hindrance. Likewise, the presence of one or two fluorine atoms on the benzene ring of phenylacetylene was effective and compatible with this coupling reaction conditions, yielding the monoalkynylated products **5f** (81%) and **5g** (82%), respectively. These results show that the nature and the number of halogens carried by the benzene ring of the alkyne do not significantly affect the efficiency of this reaction of C2-alkynylation of **2b**. Unfortunately, the use of a terminal alkyne with a strong attractor group on the aromatic ring such as 4-nitrophenylacetylene was inconclusive, since no trace of the coupling product was observed and the starting material was fully recovered. In addition, aliphatic alkynes such as ethynylcyclohexane and 4-phenylbutynyl were coupled with **2b** affording the expected products **5k** (80%) and **5l** (66%), respectively. Homopropargylic acetal was also compatible with the Sonogashira conditions, providing the desired product **5m** in 60% yield. Importantly, the use of heteroarylboronic acids such as 2-pyridinyl, 3-pyridinyl and 3-thienyl was very effective, giving respectively **5h** (81%), **5i** (63%) and **5j** (78%), allowing thus easy diversification into potentially important heterocyclic structures. The resulting imidazole bromides **5** could then be used to modify the C-4 position through other cross-coupling reactions.

C-4- Sonogashira coupling reaction

Having successfully developed the selective C2-alkynylation of imidazole **2b**, we next focused on the alkynylation of *tert*-butyl 2-alkynylated 4-bromo-5-methyl-1*H*-imidazole-1-carboxylates **5** at C-4 position. The reaction between C2-alkynylated imidazole **5a** and 4-methoxyphenylacetylene was chosen as a model to perform the C4-alkynylation. Unlike the coupling reaction of bromine at C-2 position, the reactivity of bromine at C-4 position seems to be tricky since the use of previuosly optimized alkynylation conditions at C-2 position proved unsatisfactory (Table 3, entry 1). After 72 hours of stirring at 50 °C, the analysis of the crude ^{1}H-NMR spectrum showed 70% of the dialkynylated product **6a** accompanied with 30% of unreactive starting material **5a**. A similar result was obtained when the reaction was heated at 120 °C in a sealed tube (Table 3, entry 2). In order to perform this C4-alkynylation of **5a** more efficiently, other reaction conditions have been attempted. The obtained results are shown in Table 3.

As shown in Table 3, the use of $PdCl_2(PPh_3)_2$ (5 mol%) as a catalyst in triethylamine and heating in a sealed tube at 50 °C or 120 °C, resulted in a mixture of the expected product **6a** along with the starting material **5a** in a 70/30 ratio, respectively (Table 3, entries 1-2). Using a polar aprotic solvent such as DMF at 80 °C gave only decomposition of starting materiel **5a** (Table 3, entry 3). Replacing DMF with THF, only 20% of starting material **5a** was converted to the desired product **6a** (Table 3, entry 4).

Table 3. Optimization of the C4-alkynylation reaction of **5a**.

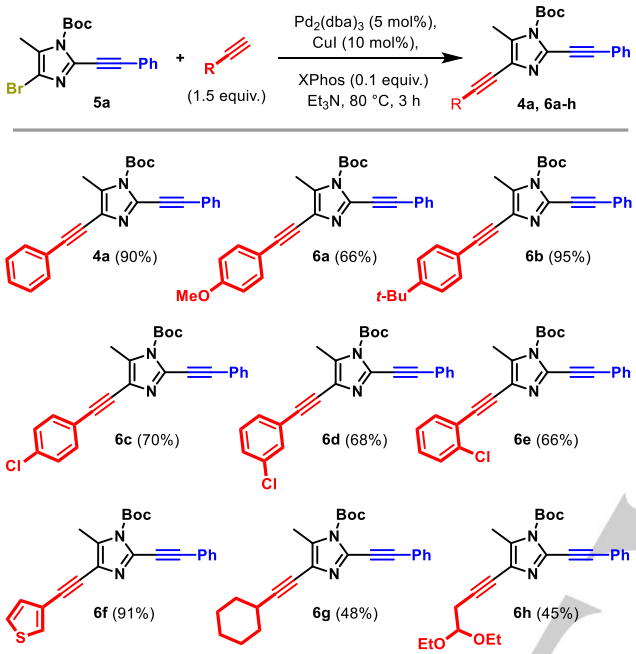


Entry	Solvent	Catalyst	Ligand	T (°C)	Time (h)	**6a/5a**[a]
1	Et_3N	$PdCl_2(PPh_3)_2$	--	50	72	70/30
2	Et_3N	$PdCl_2(PPh_3)_2$	--	120	72	70/30
3	DMF	$PdCl_2(PPh_3)_2$	--	80	1	0/0[b]
4	THF	$PdCl_2(PPh_3)_2$	--	80	72	20/80
5	THF	$PdCl_2(PPh_3)_2$	PPh_3	80	72	32/68
6	THF	$PdCl_2(PPh_3)_2$	PPh_3	80	3	35/65[c]
7	THF	$PdCl_2(PPh_3)_2$	PPh_3	120	72	52/48
8	THF	$PdCl_2(PPh_3)_2$	PPh_3	120	3	40/60[c]
9	Et_3N	$PdCl_2(PPh_3)_2$	$AsPh_3$	120	72	59/41
10	Et_3N	$PdCl_2(PPh_3)_2$	XPhos	120	72	85/15 (34%)[d]
11	Et_3N	$PdCl_2(MeCN)_2$	XPhos	120	72	05/95
12	Et_3N	$Pd_2(dba)_3$	XPhos	120	3	100/0 (63%)[d]
13	**Et_3N**	**$Pd_2(dba)_3$**	**XPhos**	**80**	**3**	**100/0 (66%)**[d]
14	Et_3N	$Pd_2(dba)_3$	XPhos	50	3	90/10
15	Et_3N	$Pd_2(dba)_3$	--	80	3	15/85

[a] The ratio of mixture (**6a/5a**) was calculated from the crude ^{1}H NMR spectrum.
[b] A decomposed product was observed.
[c] The reaction was carried out under microwave irradiation for 3 hours.
[d] Yield of isolated product **6a** after column chromatography.

Adding PPh_3 (10 mol%), as a ligand in the presence of $PdCl_2(PPh_3)_2$ (5 mol%) as a catalyst, improved slightly the ratio **6a/5a** (Table 3, entries 5 and 7). Likewise, changing the conventional thermal heating by microwave irradiation at 80 °C or 120 °C has no significant effect on the conversion (Table 3, entries 6 and 8). Using the same catalyst and varying the ligand ($AsPh_3$ or XPhos) in triethylamine at 120 °C, the reaction was still not complete and the isolated yield of **6a** did not exceed 34% (Table 3, entries 9-10). Under the same reaction conditions, replacing $PdCl_2(PPh_3)_2$ by $PdCl_2(MeCN)_2$ was unsuccessful (Table 3, entry 11). Interestingly, when the coupling reaction was performed using $Pd_2(dba)_3$/XPhos tandem as catalyst in triethylamine at 120 °C, the starting material was completely consumed after 3 hours, and the yield of the C4-alkynylated product **6a** was improved to 63% (Table 3, entry 12). Decreasing the temperature to 80 °C, the yield of the C4-alkynylation product **6a** reached 66% (Table 3, entry 13). Performing the reaction at 50 °C gave only partial conversion, confirming the

importance of heating at 80 °C to obtain a full conversion (Table 3, entry 14). When the reaction was conducted without ligand, the C4-alkynylation was inefficient, since only 15% of **5a** was converted into the expected product **6a** (Table 3, entry 15), indicating the crucial role of the ligand for the efficiency of this C4-alkynylation reaction. Having established the optimized conditions for Sonogashira cross-coupling at C-4 [alkyne (1.5 equiv.), $Pd_2(dba)_3$ (5 mol%), XPhos (10 mol%) in triethylamine at 80 °C for 3 h] (Table 3, entry 13), we extended this coupling to a series of commercially available alkynes (Scheme 5).



Scheme 5. Synthesis of unsymmetrical *tert*-butyl 2,4-dialkynylated-5-methyl-1*H*-imidazole-1-carboxylates **6a-h**.

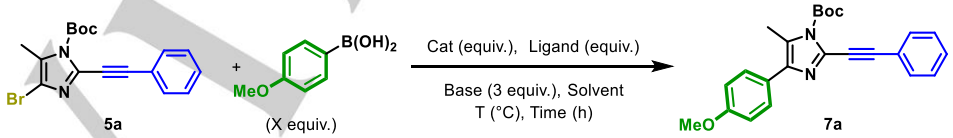
As shown in Scheme 5, the C4-alkynylation of compound **5a** was carried out successfully leading to the C2,C4-dialkynylation products **4a** and **6a-h** in yields ranging from 45% and 95%. Phenylacetylene and phenylacetylene substituted with an electon-donating group, such as methoxy or *tert*-butyl at the *para* position of the benzene ring were successfully introduced, yielding **4a** (90%), **6a** (66%) and **6b** (95%), respectively. Likewise, the use of phenylacetylene bearing an electron-withdrawing group such as chlorine at the *para*, *meta* or *ortho* position provided the expected products **6c-e** in 70%, 68% and 66% yields, respectively. The position of chlorine on the aromatic ring has no significant effect on the efficiency of the Sonogashira coupling. Interestingly, this alkynylation reaction conditions were compatible with heteroaromatic alkynes such as 3-ethynylthiophene giving access to the desired product **6e** in 91% yield. Moreover, the C4-alkynylation conducted with aliphatic alkynes seems to be less efficient, since ethynylcyclohexane and homopropargylic acetal provided the expected products **6g** and **6h** in moderate 48% and 45% yields, respectively.

C4-Suzuki-Miyaura coupling reaction

Having successfully developed the selective C2,C4-dialkynylation of 2,4-dibrominated imidazole **2b** and in order to introduce more molecular diversity, we decided then to study the reactivity of bromine at C-4 through Suzuki-Miyaura cross-coupling.[28] Different conditions were tried to react the monoalkynylated product **5a** with 4-methoxyphenylboronic acid (Table 4).

Initial optimization of the Suzuki-Miyaura coupling reaction between **5a** and *p*-methoxyphenylboronic acid was performed using $PdCl_2(PPh_3)_2$ (5 mol%) as a catalyst and Na_2CO_3 (3 equiv.) as base in dioxane/H_2O (4/1) at 90 °C (Table 1, entry 1).[29] The analysis of the crude ^{1}H-NMR spectrum showed the formation of a complex mixture. Replacing $PdCl_2(PPh_3)_2$ by the $Pd(OAc)_2$ (5 mol%)/PPh_3 (10 mol%) tandem in a mixture of DME/EtOH/H_2O (3/1/1) at 65 °C under microwave irradiation did not improve the result (Table 4, entry 2).[19] Fortunately, the use of $Pd_2(dba)_3$ (5 mol%)/XPhos (10 mol%) as a catalyst system and potassium phosphate as a base in a mixture of toluene/water (5/0.5) at 110 °C afforded the formation of the expected product **7a** in 60% isolated yield (Table 4, entry 3).[30] Gratifyingly, under the same conditions and increasing the amount of boronic acid (2 equiv.), the starting material was completely consumed after 2 hours, and the arylated product **7a** was obtained in 85% yield (Table 4, entry 4).

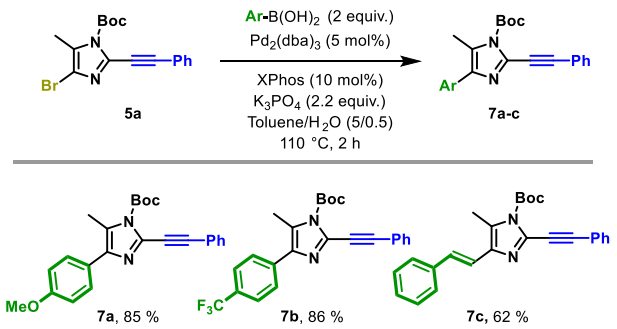
Table 4. Optimizations of Suzuki-Miyaura cross-coupling conditions between **5a** and *p*-methoxy phenylboronic acid.



Entry	Ar-B(OH)$_2$ (equiv.)	Solvent	Catalyst (equiv.)	Base	Ligand	T (°C)	Time (h)	**7a/5a**
1	1.5	Dioxane/H_2O (4/1)	$PdCl_2(PPh_3)_2$ (0.1)	Na_2CO_3	--	90	1	n.d[b]
2	1.5	DME/EtOH/H_2O (3/1/1)	$Pd(OAc)_2$ (0.05)	Na_2CO_3	PPh_3	65	1[c]	n.d[b]
3	1.5	Toluene/H_2O (5/0.5)	Pd2(dba)$_3$ (0.05)	K_3PO_4	XPhos	110	24	80/20 (60%)[a]
4	**2**	**Toluene/H_2O (5/0.5)**	**$Pd_2(dba)_3$ (0.05)**	**K_3PO_4**	**XPhos**	**110**	**2**	**100/0 (85%)[a]**

[a] Yield of isolated product **7a**.
[b] A complex mixture of products is formed.
[c] Reaction carried out under microwave irradiation.

Having the optimized reaction conditions, some boronic acids were coupled with **5a** and the results obtained are shown in Scheme 6. These reactions proceeded smoothly to give efficient access to new 2-alkynylated 4-arylated imidazoles **7a-c** in good to excellent yields (Scheme 6).



Scheme 6. Selective synthesis of C2-alkynylated/C4-arylated imidazoles **7**.

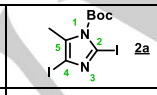
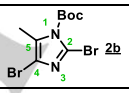
Arylboronic acid bearing an electron-rich group such as methoxy in *para* position was efficiently coupled to give the C4-arylated product **7a** in 85% yield. *p*-Trifluoromethyphenylboronic acid containing an electron-withdrawing group was also tolerated, providing the desired product **7b** in 86% yield. No difference in the efficiency of this coupling was observed depending on the nature of the substituent on the aromatic ring. In addition, these conditions were successfully applied to (*E*)-styrylboronic acid, affording the expected product **7c** in 62% yield with retention of the double bond configuration.

The reactions described in this present work constitute an efficient and suitable approach for the synthesis of various 2,4-dialkynylated and 2-alkynylated-4-arylated-5-methyl-1*H*-imidazole-1-carboxylates.

Computational study

To depict experimental results made herein, the reactivity of C-X bonds was firstly estimated thanks to the determination of their BDE. As reported in Table 5, BDEs of C-Br bonds are always higher than C-I highlighting that less energy (e.g. a difference of 10 kcal.mol^{-1}) is requested to dissociate the iodine as expected.[31]

Table 5. Bond length (Å) and bond energies BDE (kcal/mol) of compounds **2a** and **2b**.

Compoud Structure	 **2a**	 **2b**
C-X Bond length (Å)	C_2-I = 2.091 C_4-I = 2.088	C_2-Br = 1.869 C_4-Br = 1.875
C-X bond energies BDE (kcal/mol)	C_2-I (BDE) = 73.5 C_4-I (BDE) = 78.2	C_2-Br (BDE) = 84,6 C_4-Br (BDE) = 89.9

Furthermore, in each case, a lowest C-X BDE at C-2 position is observed (i.e. C_2-I = 73.5 kcal.mol^{-1} and C_2-Br = 84.6 kcal.mol^{-1}) revealing that this postion seems to be more reactive than the C-4 position, which is 4-5 kcal.mol^{-1} higher. However, such a difference could not fully explain why a regioselectivity is solely observed in the Sonogashira coupling reaction using the 2,4-dibromoimidazole **2b** and not with the 2,4-diiodoimidazole **2a**.

To further evaluate this difference on their regioselectivity, relative free energies for the possible pathways in the oxidative addition of **2a** or **2b** with (PMe_3)Pd(0) were then determined in triethylamine as shown in Figures 4 and 5.

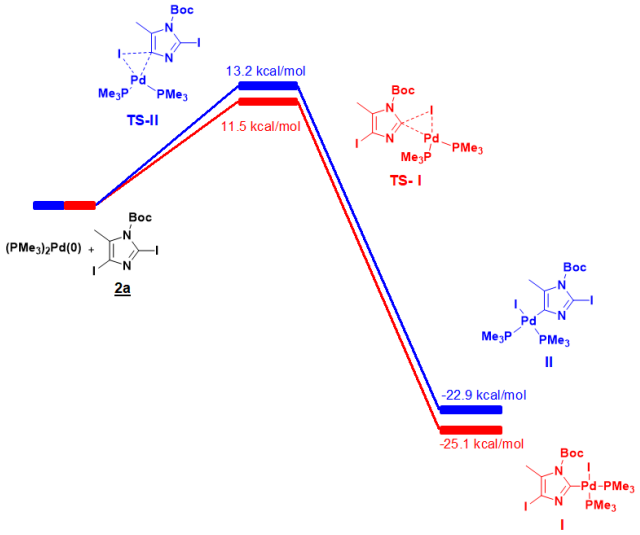


Figure 4. Energy profiles of compound **2a** with (PMe_3)$_2$Pd(0) in the oxidative addition pathways.

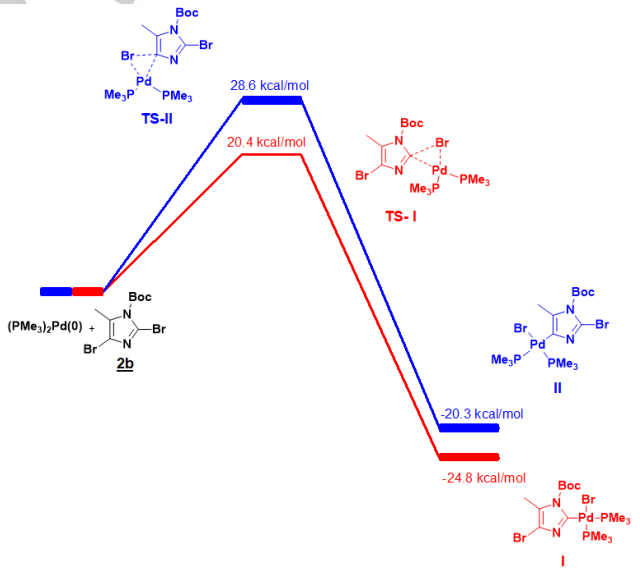


Figure 5. Energy profiles of compound **2b** with (PMe_3)$_2$Pd(0) in the oxidative addition pathways**.**

In each case, TS on C-2 (TS-I) and C-4 (TS-II) positions and corresponding palladium(2)-intermediates (I and II) were computed. Wathever the halogen selected, ΔG values of TS-I and intermediates I are always lower than those for TS-II and intermediates II, demonstrating that this oxidative addition is both kinetically and thermodynamically more favorable in position-2 than position-4. Furthermore, differences on ΔG values between each TS of a given halogen, clearly indicate that lower energies are requested to react both positions C-2 and C-4 of the **2a** (e.g. 10-15 kcal.mol^{-1} lower) than **2b**. More interestingly, in the case of the 2,4-diiodoimidazole **2a** a small difference, of 1.7 kcal.mol^{-1}, is observed between, ΔG values of TS-I and TS-II. Such a difference could explain, why no regioselectivity is observed using the 2,4-diiodoimidazole **2a**. This observation is obviously not the same using the 2,4-

dibromoimidazole **2b**, as a difference of 8.2 kcal.mol^{-1} is observed between TS-I and TS-II, with a reactivity in favor of intermediate-I. This relatively large difference on their TS energy barrier agrees with the experimental results and provides some insights on the origin of the regioselectivity of **2b** in favor of the C-2 position.

Conclusion

In conclusion, we have demonstrated that the choice of halogen atom and catalytic system could play a crucial role to control the chemical reactivity of both halogen atoms at C-2 and C-4 positions of imidazole core. Thus, our optimized conditions allowed to discriminate between two bromine atoms of *tert*-butyl 2,4-dibromo-5-methyl-1*H*-imidazole-1-carboxylate **2b** using an efficient successive Sonogashira cross-coupling reactions, which were carried out regioselectively at C-2 and then at C-4, in good to excellent yields. In addition, this strategy was extended to selectively perform a double C2-alkynylation/C4-arylation sequence giving access to a new variety of disubstituted imidazoles.

The methodology developed represents an efficient approach to introduce a diverse and controlled functionalization at C-2 and C-4 positions of imidazole, opening the way to the possibility of constructing a new chemical library of variously substituted imidazole derivatives. The potential for expanding the application of this selective Sonogashira cross-coupling reaction to synthesize other new heterocycle compounds having a biological interest is underway in our laboratory.

Experimental Section

General methods and materials

All reactions were carried out under argon atmosphere. Reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates, and all compounds were visualized by UV irradiation (longwave at 365 nm or shortwave at 254 nm). All column chromatography was performed with silica gel 60 (230 – 400.13 mesh, 0.040 – 0.063 mm). Absolute Ethanol, 1,4-dioxane and toluene were purchased from commercial suppliers and were used without further distillation. Triethylamine was distilled from calcium hydride. THF was distilled from sodium and benzophenone. The purity of all final compounds was verified by ^{1}H and ^{13}C NMR analysis, HRMS and melting point. NMR spectra were obtained at 300 MHz for ^{1}H and 75 MHz for ^{13}C with Bruker® 300 MHz NMR spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$ as the internal standard (^{1}H NMR: $CDCl_3$ at 7.28 ppm; ^{13}C NMR: $CDCl_3$ at 77.04 ppm) or were recorded using tetramethylsilane (TMS) in the solvent of DMSO-d_6 as the internal standard (^{1}H NMR: DMSO at 2.50 ppm; ^{13}C NMR: DMSO at 40.0 ppm). Coupling constants *J* are reported in hertz. All the NMR spectra were processed in MestReNova. Electrospray ionization mass spectrometry experiments (HRMS) were obtained on a hybrid tandem quadrupole/time-offlight (Q-TOF) instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source (Micromass, Manshester, U.K.) operated in positive mode. Melting points (m.p. [°C]) of samples were measured using open capillary tubes.

All ab-initio and DFT calculations were performed using the Turbomole 7.4 program.[32] HF and RI-B3LYP-D3 level of theory were used to fully optimize the reactants, intermediates and transition states (TS) in gas phase. The TZVP basis set was used for H, C, N, O, Br and I atoms,[33] while the LanL2DZ basis set and its effective-core potential were used for the Pd atom.[34] Single point and frequency calculations were then carried out to confirm 3D structure reached for each transition state (with one imaginary frequency) or minimum (no imaginary frequency). The bond dissociation energy (BDE) calculations were also run by following methodology reported in the literature.[31] Furthermore, solvent effects (triethylamine) were also included using COSMO solvation model by carrying single-point solvent calculations on the optimized geometries in gas phase. Energy profiles reported in Figures 4 and 5 highlight relative free energy, DG, changes by reacting compounds **2a** or **2b** with $(PMe_3)_2Pd(0)$ in triethylamine. Here, a PMe_3 ligand was used to model the larger PPh_3 ligand, as frequently reported in the literature.[35] Cartesian coordinates of all the calculated structures are available in the ESI.

Synthesis and characterization of 2,5-diiodo-4-methylimidazol (1a):

Compound **1a** was prepared according to the literature procedure.[23] To a stirred solution of 4(5)-methylimidazole (5g, 60.9 mmol) in anhydrous ethanol (25 mL) at room temperature was added H_5IO_6 (2.47 g, 10.84 mmol) and finely powdered I_2 (6.65 g, 26.19 mmol). The reaction mixture was stirred at 60 °C for 45 min under argon atmosphere. The mixture was then cooled to room temperature and mixture was poured into stirred ice-water (175 g) containing prior dissolved Na_2SO_3 (8.7 g). The solid formed is filtered and washed several time with water and ethanol. The solid crude product was purified by column chromatography on silica gel (P.E/AcOEt : 8/2). White solid (12.2 g, 60% Yield); M.p. = 176 °C; (petroleum ether/EtOAc : 8 / 2). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.77 (s, 1H), 2.11 (s, 3H).

Synthesis and characterization of 2,5-dibromo-4-methylimidazol (1b):[24]

Based on a literature procedure, Bromine (13.9 mL, 244 mmol, 2 equiv.) was added dropwise to a solution of 4(5)-methylimidazole (10 g, 121 mmol) and potassium hydrogencarbonate (24.5 g, 244 mmol, 2 equiv.) in anhydrous *N*,*N*-dimethylformamide (100 mL) at 0 °C under argon. After warming to room temperature, the reaction mixture was stirred for 0.5 h and heated at 100 °C for 4 h. After cooling, the reaction mixture was poured into a saturated aqueous solution of $Na_2S_2O_3$ and the solid formed is filtered and washed several time with water affording compound **1b** (11.3 g, 78 %) as a white solid. M.p. 207 °C (*Litt*.[24] M.p. 189–191 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 13.0 (s, 1 H), 2.09 (s, 3 H).

Typical procedure for the synthesis of 2,4-dihalogenated *tert*-butyl 5-methyl-1*H*-imidazole-1-carboxylate 2:

To a stirred solution of dihalogenated imidazole **1** (1.0 equiv., 5 g) in dry MeCN (25 mL) was added DMAP (0.12 equiv.) and Boc_2O (1.2 equiv.). The reaction mixture was stirred at room temperature for 4 hours under argon atmosphere. The solvent was removed in vacuo and the resulting residue was dissolved in ethyl acetate. Saturated sodium chloride solution was added and the phases were separated. The combined organic phases were dried under $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel to give pure 2,4-dihalogenated *tert*-butyl 5-methyl-1*H*-imidazole-1-carboxylates **2a-b**.

***tert*-Butyl 2,4-diiodo-5-methyl-1*H*-imidazole-1-carboxylate (2a):**

Column chromatography on silica-gel (petroleum ether/EtOAc, 9:1) followed by recrystallization from Et_2O afforded compound **2a** as white solid (5.85 g, 90 % yield). M.p. 82 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 1.68 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.5, 135.4, 89.1, 87.6, 84.6, 27.9, 14.5. IR (cm^{-1}): υ 2931, 2858, 2228, 1762, 1287, 1135. HRMS (ESI): *m/z* calcd. For $C_9H_{13}I_2N_2O_2$ $[M + H]^+$ 434.9066, Found: 434.9064.

***tert*-Butyl 2,4-dibromo-5-methyl-1*H*-imidazole-1-carboxylate (2b):**

Column chromatography on silica-gel (petroleum ether/EtOAc, 9:1) followed by recrystallization from Et_2O afforded compound **2b** as white solid (4.47 g, 63 % yield). M.p. 73 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 1.66 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 146.3, 129.5, 116.6, 116.2, 87.5, 27.8, 12.7. IR (cm^{-1}): υ 2933, 2855, 2224, 1761, 1292, 1127.

HRMS (ESI): *m/z* calcd. for $C_9H_{13}Br_2N_2O_2$ [M + H]$^+$ 338.9344, Found: 338.9342.

General procedure for the synthesis of *tert*-butyl 5-methyl-2,4-dialkynyl-1*H*-imidazole-1-carboxylate 4:
Triethylamine (8 mL) was added to a solid mixture containing *tert*-butyl 2,4-diiodo-5-methyl-1*H*-imidazole-1-carboxylate **2a** (300 mg, 0.88 mmol), $Pd(PPh_3)_2Cl_2$ (50 mg, 0.071 mmol) and CuI (17 mg, 0.088 mmol). The resulting mixture was stirred under an argon atmosphere. Solution of Alkyne (2.2 mmol, 2.5 equiv.) in 2 mL of Et_3N was added dropwise to the first solution and the reaction mixture was heated at 50 °C for 1h. After cooling to room temperature, the mixture was concentrated under vacuum giving a brown solid. The solid was suspended in ethyl acetate (200 mL) and washed with 1M HCl solution (15 mL), water (15 mL) and a saturated NaCl solution (15 mL). The crude product was purified by column chromatography using a mixture of petroleum ether/EtOAc as eluent to give pure *tert*-butyl 5-methyl-2,4-dialkynyl-1*H*-imidazole-1-carboxylate **4**.

***tert*-Butyl 5-methyl-2,4-bis(phenylethynyl)-1*H*-imidazole-1-carboxylate (4a):**
Column chromatography on silica-gel (petroleum ether/EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **4a** as beige solid (140 mg, 70% yield). M.p. 134 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.54 (m, 4H), 7.40-7.34 (m, 6H), 2.59 (s, 3H), 1.68 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 133.7 (2C), 131.9 (2C), 131.1, 131.5, 129.2, 128.5 (2C), 128.3 (3C), 124.5, 122.9, 121.9, 92.2, 92.0, 86.5, 81.6, 80.2, 28.0 (3C), 12.9. IR (cm^{-1}): υ 3061, 2978, 2926, 2222, 1762, 1599, 1318, 1125. HRMS (ESI): *m/z* calcd. for $C_{25}H_{23}N_2O_2$ [M + H]$^+$: 383.1760, Found: 383.1758.

***tert*-Butyl 2,4-bis[(4-chlorophenyl)ethynyl]-5-methyl-1*H*-imidazole-1-carboxylate (4b):**
Column chromatography on silica-gel (petroleum ether/EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **4b** as yellow solid (277 mg, 89% yield). M.p. 154 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 2.58 (s, 3H), 1.67 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 135.5, 134.4, 134.0, 133.7, 133.1 (2C), 132.7 (2C), 128.9 (2C), 128.7 (2C), 124.3, 121.4, 120.3, 91.2, 91.0, 86.7, 82.5, 81.0, 28.0 (3C), 13.0. IR (cm^{-1}): υ 3067, 2975, 2926, 2221, 1759, 1317, 1127. HRMS (ESI): *m/z* calcd. for $C_{25}H_{21}Cl_2N_2O_2$ [M + H]$^+$: 451.0980, Found: 451.0979.

***tert*-Butyl 2,4-bis[(3-chlorophenyl)ethynyl]-5-methyl-1*H*-imidazole-1-carboxylate (4c):**
Column chromatography on silica-gel (petroleum ether/EtOAc, 9.8:0.2) afforded compound **4c** as yellow oil (211 mg, 68% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56-7.28 (m, 8H), 2.59 (s, 3H), 1.68 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 134.4, 134.3, 134.2, 131.6, 131.2, 130.8, 130.0, 129.8, 129.7, 129.6, 129.5, 128.6, 124.6, 124.2, 123.5, 90.8, 90.7, 86.8, 82.7, 81.1, 28.0 (3C), 13.0. IR (cm^{-1}): υ 3065, 2979, 2928, 2218, 1757, 1591, 1320, 1129. HRMS (ESI): *m/z* calcd. for $C_{25}H_{21}Cl_2N_2O_2$ [M + H]$^+$: 451.0980, Found: 451.0980.

***tert*-Butyl 2,4-bis[(2-chlorophenyl)ethynyl]-5-methyl-1*H*-imidazole-1-carboxylate (4d):**
Column chromatography on silica-gel (petroleum ether/EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **4d** as yellow solid (230 mg, 74% yield). M.p. 107 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63-7.51 (m, 2H), 7.47-7.42 (m, 2H), 7.36-7.25 (m, 4H), 2.64 (s, 3H), 1.66 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 136.3, 135.5, 134.9, 133.8, 133.2, 130.9, 130.3, 129.5, 129.3, 129.2, 126.6, 126.5, 124.4, 122.9, 122.0, 88.9, 88.9, 86.9, 86.8, 84.5, 27.9 (3C), 12.9. IR (cm^{-1}): υ 3062, 2974, 2932, 2211, 1752, 1589, 1325, 1130. HRMS (ESI): *m/z* calcd. for $C_{25}H_{21}Cl_2N_2O_2$ [M + H]$^+$: 451.0980, Found: 451.0978.

***tert*-Butyl 2,4-bis[(4-methoxyphenyl)ethynyl]-5-methyl-1*H*-imidazole-1-carboxylate (4e):**
Column chromatography on silica-gel (petroleum ether/EtOAc, 9:1) followed by recrystallization from Et_2O afforded compound **4e** as beige solid (266 mg, 87% yield). M.p. 153 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 9.0 Hz, 2H), 7.49 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.57 (s, 3H), 1.67 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 159.7, 147.2, 133.5 (2C), 133.0 (2C), 132.9, 131.3, 124.5, 115.1, 114.2 (2C), 114.0 (3C), 92.5, 91.9, 86.3, 80.3, 79.1, 55.5, 55.3, 28.0 (3C), 12.9. IR (cm^{-1}): υ 3058, 2970, 2933, 2216, 1745, 1602, 1570, 1248, 1128. HRMS (ESI): *m/z* calcd. for $C_{27}H_{27}N_2O_4$ [M + H]$^+$: 443.1971, Found: 443.1968.

***tert*-Butyl 2,4-bis(cyclohexylethynyl)-5-methyl-1*H*-imidazole-1-carboxylate (4f):**
Column chromatography on silica-gel (petroleum ether/EtOAc, 9.8:0.2) afforded compound **4f** as yellow oil (196 mg, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60 (quint, *J* = 5.7 Hz, 2H), 2.43 (s, 3H), 1.92-1.82 (m, 4H), 1.80-1.68 (m, 4H), 1.64 (s, 9H), 1.61-1.47 (m, 6H), 1.41-1.27 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 131.6, 131.0, 124.2, 97.7, 96.8, 85.8, 72.6, 71.7, 32.5 (2C), 32.0 (2C), 29.8, 29.6, 27.9 (3C), 25.9, 25.7, 24.8 (2C), 24.8 (2C), 12.6. IR (cm^{-1}): υ 2929, 2855, 2228, 1751, 1143. HRMS (ESI): *m/z* calcd. for $C_{25}H_{35}N_2O_2$ [M + H]$^+$: 395.2699, Found: 395.2698.

***tert*-Butyl 2,4-di(hex-1-ynyl)-5-methyl-1*H*-imidazole-1-carboxylate (4g):**
Column chromatography on silica-gel (petroleum ether/EtOAc, 9.8:0.2) afforded compound **4g** as yellow oil (93 mg, 40% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H), 2.46-2.39 (m, 4H), 1.64 (s, 9H), 1.62-1.44 (m, 8H), 0.94 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.3, 131.7, 130.9, 124.1, 94.0, 92.8, 85.7, 72.7, 71.8, 30.6, 30.1, 27.8 (3C), 22.0, 21.9, 19.2, 19.1, 13.6, 13.5, 12.6. IR (cm-1): u 2932, 2858, 2223, 1750, 1140. HRMS (ESI): *m/z* calcd. for $C_{21}H_{31}N_2O_2$ [M + H]$^+$: 343.2386, Found: 343.2384.

General procedure for the synthesis of *tert*-butyl 4-bromo-2-alkynyl-5-methyl-1*H*-imidazole-1-carboxylate 5:
To an oven-dried schlenk tube, *tert*-butyl 2,4-dibromo-5-methyl-1*H*-imidazole-1-carboxylate **2b** (300 mg, 0.88 mmol), $Pd(PPh_3)_2Cl_2$ (50 mg, 0.071 mmol) and CuI (17 mg, 0.088 mmol) were added to triethylamine (8 mL). Solution of Alkyne (1.33 mmol, 1.5 equiv.) in 2 mL of Et_3N was added dropwise to the first solution and the resulting mixture was bubbled with in-house argon for 5 min. The reaction was stirred at 50 °C for 1h. The progress of the reaction was monitored by TLC. After cooling to room temperature, the mixture was concentrated under vacuum. The solid formed was suspended in ethyl acetate (200 mL) and washed with 1M HCl solution (15 mL), a saturated NaCl solution (15 mL) and water (15 mL). The crude product was purified by column chromatography using a mixture of petroleum ether/EtOAc as eluent to give pure *tert*-butyl-2-alkynyl-5-methyl-1*H*-imidazole-1-carboxylate **5**.

***tert*-Butyl 4-bromo-5-methyl-2-(phenylethynyl)-1*H*-imidazole-1-carboxylate (5a):**
Column chromatography on silica-gel (petroleum ether/EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **5a** as white solid (278 mg, 87% yield). M.p. 140 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59-7.55 (m, 2H), 7.40-7.34 (m, 3H), 2.44 (s, 3H), 1.66 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 131.9 (2C), 130.7, 129.3, 128.5, 127.7 (2C), 121.8, 117.7, 92.9, 86.7, 79.7, 27.9 (3C), 12.5. IR (cm^{-1}): υ 2984, 2928, 2212, 1755, 1562, 1293, 1133. HRMS (ESI): *m/z* calcd. for $C_{17}H_{18}BrN_2O_2$ [M + H]$^+$: 361.0552**,** Found: 361.0545.

***tert*-Butyl 4-bromo-2-[(4-methoxyphenyl)ethynyl]-5-methyl-2,3-dihydro-1*H*-imidazole-1-carboxylate (5b):**
Column chromatography on silica-gel (petroleum ether/EtOAc, **9:1**) followed by recrystallization from Et_2O afforded compound **5b** as beige solid (178 mg, 62% yield). M.p. 113 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ

7.51 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 2.43 (s, 3H), 1.65 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 146.8, 133.5 (2C), 131.1, 127.9, 117.5, 114.2 (2C), 113.8, 93.2, 86.6, 78.7, 55.3, 27.9 (3C), 12.5. IR (cm^{-1}): υ 2988, 2930, 2208, 1758, 1601, 1291, 1133. HRMS (ESI): *m/z* calcd. for $C_{18}H_{20}BrN_2O_3$ $[M + H]^+$**:** 391.0657, Found: 391.0653.

***tert*-Butyl 4-bromo-2-[(4-chlorophenyl)ethynyl]-5-methyl-1*H*-imidazole-1-carboxylate (5c):**

Column chromatography on silica-gel (petroleum ether/EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **5c** as yellow solid (218 mg, 63% yield)**.** M.p**.** 145 **°C.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.45 (m, 2H), 7.38-7.32 (m, 2H), 2.43 (s, 3H), 1.65 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 135.5, 133.7 (2C), 133.0, 128.9 (2C), 127.9, 120.3, 117.8, 91.7, 86.8, 80.6, 27.9 (3C), 12.6. IR (cm^{-1}): υ 2974, 2930, 1758, 1555, 1298, 1129. HRMS (ESI): *m/z* calcd. for $C_{17}H_{17}BrClN_2O_2$ $[M + H]^+$**:** 395.0162, Found: 395.0159.

***tert*-Butyl 4-bromo-2-[(3-chlorophenyl)ethynyl]-5-methyl-1*H*-imidazole-1-carboxylate (5d):**

Column chromatography on silica-gel (petroleum ether/EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **5d** as yellow solid (281 mg, 81% yield)**.** M.p. 146 **°C.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (t, *J* = 1.5 Hz, 1H), 7.45 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.40-7.36 (m, 1H), 7.34-7.31 (m, 1H), 2.44 (s, 3H), 1.66 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 134.4, 131.6, 130.3, 130.0, 129.8, 129.6, 128.0, 123.5, 117.9, 91.3, 86.9, 80.8, 27.9 (3C), 12.6. IR (cm^{-1}): υ 2979, 2928, 1759, 1589, 1560, 1293, 1135. HRMS (ESI): *m/z* calcd. for $C_{17}H_{17}BrClN_2O_2$ $[M + H]^+$**:** 395.0162, Found: 395.0158.

***tert*-Butyl 4-bromo-2-[(2-chlorophenyl)ethynyl]-5-methyl-1*H*-imidazole-1-carboxylate (5e):**

Column chromatography on silica-gel (petroleum ether/EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **5e** as yellow solid (250 mg, 63% yield). M.p. 102 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.59 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.51 (td, *J* = 7.5, 1.8 Hz, 1H), 7.45 (td, *J* = 7.5, *J* = 1.5 Hz, 1H), 2.44 (s, 3H), 1.66 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 136.3, 133.7, 130.3 (2C), 129.5, 128.0, 126.6, 121.9, 117.9, 89.5, 86.9, 84.1, 27.8 (3C), 12.6. IR (cm^{-1}): υ 3067, 2979, 2929, 1762, 1553, 1297, 1131. HRMS (ESI): *m/z* calcd. for $C_{17}H_{17}BrClN_2O_2$ $[M + H]^+$**:** 395.0162, Found: 395.0157.

***tert*-Butyl 4-bromo-2-[(2-fluorophenyl)ethynyl]-5-methyl-1*H*-imidazole-1-carboxylate (5f):**

Column chromatography on silica-gel (petroleum ether/EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **5f** as yellow solid (200 mg, 81% yield). M.p. 102 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (td, *J* = 7.5, 1.8 Hz, 1H), 7.42-7.35 (m, 1H), 7.19-7.09 (m, 2H), 2.44 (s, 3H), 1.64 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8 (d, *J* = 252.0 Hz), 146.7, 133.8, 131.1 (d, *J* = 7.5 Hz), 130.2, 128.0, 124.2 (d, *J* = 3.7 Hz), 117.8, 115.7 (d, *J* = 21.0 Hz), 110.5 (d, *J* = 15.7 Hz), 87.1, 86.4, 84.3 (d, *J* = 3.0 Hz), 27.8 (3C), 12.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.1. IR (cm^{-1}): υ 2982, 2931, 1760, 1610, 1562, 1295, 1136. HRMS (ESI): *m/z* calcd. for $C_{17}H_{17}BrFN_2O_2$ $[M + H]^+$**:** 379.0457, Found: 379.0453.

***tert*-Butyl 4-bromo-2-[(2,4-difluorophenyl)ethynyl]-5-methyl-1*H*-imidazole-1-carboxylate (5g):**

Column chromatography on silica-gel (petroleum ether/EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **5g** as yellow solid (251 mg, 82% yield). M.p. 142 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59-7.51 (m, 1H,), 6.95-6.86 (m, 2H), 2.44 (s, 3H), 1.64 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (dd, *J* = 252.7, 11.3 Hz),163.2 (dd, *J* = 255.0, 12.7 Hz), 146.6, 134.8 (dd, *J* = 9.7, 2.3 Hz), 130.1, 128.1, 117.8, 112.0 (dd, *J* = 21.7, 3.7 Hz), 106.9 (dd, *J* = 15.7, 4.5 Hz), 104.5 (dd, *J* = 25.5, 24.0 Hz), 87.1, 85.4 (d, J = 1.5 Hz), 84.1 (dd, *J* = 3.0, 2.2 Hz), 27.8 (3C), 12.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ -103.7 (d, *J* = 8.46 Hz), -104.8 (d, *J* = 8.46 Hz). IR (cm^{-1}): υ 3068, 2977, 2933, 1758, 1611, 1587, 1553, 1300, 1132. HRMS (ESI): *m/z* calcd. for $C_{17}H_{16}BrF_2N_2O_2$ $[M + H]^+$**:** 397.0363, Found: 397.0360.

***tert*-Butyl 4-bromo-5-methyl-2-(pyridin-2-ylethynyl)-1*H*-imidazole-1-carboxylate (5h):**

Column chromatography on silica-gel (petroleum ether/EtOAc, 8:2) followed by recrystallization from Et_2O afforded compound **5h** as yellow solid (181 mg, 81% yield). M.p. 123 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, *J* = 4.2 Hz, 1H), 7.71 (td, *J* = 7.5, 1.8 Hz, 1H), 7.09 (dt, *J* = 6.9, 1.2 Hz, 1H), 7.32-7.27 (m, 1H), 2.45 (s, 3H), 1.68 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 146.5, 142.3, 136.1, 130.0, 128.4, 127.9, 123.5, 117.9, 91.6, 87.4, 78.9, 27.9 (3C), 12.5. IR (cm^{-1}): υ 3054, 2971, 2926, 2221, 1763, 1577, 1551, 1300, 1134. HRMS (ESI): *m/z* calcd. for $C_{16}H_{17}BrN_3O_2$ $[M + H]^+$**:** 362.0504, Found: 362.0498.

***tert*-Butyl 4-bromo-5-methyl-2-(pyridin-3-ylethynyl)-1*H*-imidazole-1-carboxylate (5i):**

Column chromatography on silica-gel (petroleum ether/EtOAc, 8:2) followed by recrystallization from Et_2O afforded compound **5i** as beige solid (200 mg, 63% yield). M.p. 119 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.80 (d, *J* = 1.2 Hz, 1H), 8.61 (dd, *J* = 5.1, 1.8 Hz, 1H), 7.86 (dt, *J* = 8.1, 1.8 Hz, 1H), 7.33 (ddd, *J* = 8.1, 5.1, 1.2 Hz, 1H), 2.45 (s, 3H), 1.66 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.3, 149.5, 146.5, 138.8, 130.1, 128.2, 123.2, 119.1, 118.0, 89.4, 87.0, 82.9, 27.9 (3C), 12.6. IR (cm^{-1}): υ 3063, 2974, 2929, 1760, 1560, 1289, 1132. HRMS (ESI): *m/z* calcd. for $C_{16}H_{17}BrN_3O_2$ $[M + H]^+$**:** 362.0504, Found: 362.0499.

***tert*-Butyl 4-bromo-5-methyl-2-(thiophen-3-ylethynyl)-1*H*-imidazole-1-carboxylate (5j):**

Column chromatography on silica-gel (petroleum ether/EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **5j** as yellow solid (251 mg, 78% yield). M.p. 142 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 3.0, 0.7 Hz, 1H), 7.33 (dd, *J* = 4.8, 3.0 Hz, 1H), 7.22 (dd, *J* = 4.8, 0.9 Hz, 1H), 2.43 (s, 3H), 1.66 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 130.7, 130.5, 129.7, 127.7, 125.8, 120.9, 117.7, 88.3, 86.7, 79.4, 27.9 (3C), 12.5. IR (cm^{-1}): υ 3065, 2990, 2927, 2213, 1754, 1561, 1295, 1130. HRMS (ESI): *m/z* calcd. for $C_{15}H_{16}BrN_2O_2S$ $[M + H]^+$**:** 367.0116, Found: 367.0289.

***tert*-Butyl 4-bromo-2-(cyclohexylethynyl)-5-methyl-1*H*-imidazole-1-carboxylate (5k):**

Column chromatography on silica-gel (petroleum ether/EtOAc, 9.8:0.2) afforded compound **5k** as yellow oil (259 mg, 80% yield). M.p. 142 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60 (quint, *J* = 5.7 Hz, 1H), 2.37 (s, 3H), 1.92-1.87 (m, 2H), 1.82-1.72 (m, 2H), 1.65 (s, 9H), 1.62-1.51 (m, 3H), 1.34-1.27 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 126.3, 116.8, 98.3, 86.3, 77.2, 71.2, 39.5, 32.0, 29.9, 27.9 (3C), 25.7, 24.9, 23.0, 12.4. IR (cm^{-1}): υ 2929, 2855, 2232, 1760, 1289, 1137. HRMS (ESI): *m/z* calcd. for $C_{17}H_{24}BrN_2O_2$ $[M + H]^+$**:** 367.1021, Found: 367.1016.

***tert*-Butyl 4-bromo-5-methyl-2-(4-phenylbut-1-yn-1-yl)-1*H*-imidazole-1-carboxylate (5l):**

Column chromatography on silica-gel (petroleum ether/EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **5l** as yellow solid (225 mg, 66% yield). M.p**.** 69 **°C.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.23 (m, 5H), 2.96 (t, *J* = 7.8 Hz, 2H), 2.73 (t, *J* = 7.8 Hz, 2H), 2.39 (s, 3H), 1.59 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 140.2, 130.9, 128.5 (2C), 128.4 (2C), 127.0, 126.5, 117.1, 94.1, 86.3, 71.9, 34.4, 27.8 (3C), 21.9, 12.5. IR (cm^{-1}):υ 2981, 2931, 2235, 1756, 1580, 1295, 1133. HRMS (ESI): *m/z* calcd. for $C_{19}H_{22}BrN_2O_2$ $[M + H]^+$**:** 389.0865, Found: 389.0859.

***tert*-Butyl 4-bromo-2-(4,4-diethoxybut-1-yn-1-yl)-5-methyl-1*H*-imidazole-1-carboxylate (5m):**

Column chromatography on silica-gel (petroleum ether/EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **5m** as yellow oil (197 mg, 60%yield)**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (t, *J* = 5.7 Hz, 1H), 3.75-3.57 (m, 4H), 2.78 (d, *J* = 5.7 Hz, 2H), 2.39 (s, 3H), 1.65 (s, 9H), 1.24 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 138.7, 127.1, 117.0, 100.6, 90.3, 86.4, 72.5, 62.3 (2C), 27.8 (3C), 26.3, 15.2 (2C), 12.4. IR (cm^{-1}): υ 2980, 2910, 2877, 2243, 1749, 1283, 1132. HRMS (ESI): *m/z* calcd. for $C_{17}H_{26}BrN_2O_4$ $[M + H]^+$**:** 401.1076, Found: 401.1076.

General procedure for the synthesis of *tert*-butyl 2,4-dialkynyl 5-methyl-1*H*-imidazole-1-carboxylates 4a and 6:

To an oven-dried schlenk tube equipped with a stir bar, *tert*-butyl 4-bromo-5-methyl-2-(phenylethynyl)-1*H*-imidazole-1-carboxylate **5a** (300 mg, 0.83 mmol), $Pd_2(dba)_3$ (38.0 mg, 0.042 mmol), CuI (16 mg, 0.083 mmol) and Xphos (40 mg, 0.08 mmol) were added to triethylamine (8 mL). The mixture sparged with argon for 15 min while being stirred at room temperature. Solution of alkyne Alkyne (1.5 mmol, 1.5 equiv.) in 2 mL of Et_3N was then added to the reaction vessel and the reaction mixture was allowed to stir at 80 °C for 3 h. After cooling to room temperature, the mixture was concentrated under vacuum. The solid formed was suspended in ethyl acetate (200 mL) and washed with 1% HCl (15 mL), a saturated NaCl solution (15 mL) and water (15 mL). The crude product was purified by column chromatography using a mixture of petroleum ether/EtOAc as eluent to give pure *tert*-butyl 2,4-dialkynyl 5-methyl-1*H*-imidazole-1-carboxylates **4a** and **6**.

***tert*-Butyl 4-[(4-methoxyphenyl)ethynyl]-5-methyl-2-(phenylethynyl)-1*H*-imidazole-1-carboxylate (6a):**

Column chromatography on silica-gel (petroleum ether/EtOAc, 9:1) followed by recrystallization from Et_2O afforded compound **6a** as yellow solid (226 mg, 66% yield). M.p. 122 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.57 (m, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.41-7.36 (m, 3H), 7.33 (d, *J* = 8.7 Hz, 2H), 2.58 (s, 3H), 1.68 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 147.1, 133.2 (2C), 133.0 (2C), 131.9, 131.0, 129.2, 128.4 (2C), 124.8, 122.0, 115.1, 114.0 (2C), 92.1, 92.0, 86.4, 80.3, 80.2, 55.3, 28.0 (3C), 12.8. IR (cm^{-1}): υ 3063, 2981, 2929, 2835, 2214, 1750, 1603, 1327, 1127. HRMS (ESI): *m/z* calcd. for $C_{26}H_{25}N_2O_3$ $[M + H]^+$**:** 413.1865, Found: 413.1860.

***tert*-Butyl 4-[(4-(*tert*-butyl)phenyl)ethynyl]-5-methyl-2-(phenylethynyl)-1*H*-imidazole-1-carboxylate (6b):**

Column chromatography on silica-gel (petroleum ether /EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **6b** as white solid (345 mg, 95% yield). M.p. 143 **°**C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.57 (m, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.41-7.36 (m, 5H), 2.58 (s, 3H), 1.68 (s, 9H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 147.1, 133.5, 131.9 (2C), 131.3 (2C), 129.2, 129.0, 128.4 (2C), 125.3 (2C), 124.7, 122.0, 119.9, 92.2, 92.1, 86.4, 80.9, 80.3, 34.7, 31.2 (3C), 28.0 (3C), 12.8. IR (cm^{-1}): υ 3065, 2962, 2867, 2223, 1745, 1568, 1329, 1128. HRMS (ESI): *m/z* calcd. for $C_{29}H_{31}N_2O_2$ $[M + H]^+$**:** 439.2386, Found: 439.2382.

***tert*-Butyl 4-[(4-chlorophenyl)ethynyl]-5-methyl-2-(phenylethynyl)-1*H*-imidazole-1-carboxylate (6c):**

Column chromatography on silica-gel (petroleum ether /EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **6c** as white solid (242 mg, 70% yield). M.p. 169 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.57 (m, 2H), 7.47 (d, *J* = 8.7 Hz, 9H), 7.41-7.36 (m, 3H), 7.33 (d, *J* = 8.7 Hz, 2H), 2.58 (s, 3H), 1.68 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 134.3, 133.9, 132.7 (2C), 131.9 (2C), 129.3, 129.2, 128.6 (2C), 128.4 (2C), 124.2, 121.9, 121.4, 92.3, 90.9, 86.6, 82.7, 80.1, 27.9 (3C), 12.8. IR (cm^{-1}): υ 3065, 2981, 2929, 2220, 1748, 1592, 1323, 1125. . HRMS (ESI): *m/z* calcd. for $C_{25}H_{22}ClN_2O_2$ $[M + H]^+$**:** 417.1370, Found: 417.1366.

***tert*-Butyl 4-[(3-chlorophenyl)ethynyl]-5-methyl-2-(phenylethynyl)-1*H*-imidazole-1-carboxylate (6d):**

Column chromatography on silica-gel (petroleum ether /EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **6d** as white solid (200 mg, 68% yield)**.** M.p. 128 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.58 (m, 3H), 7.46-7.38 (m, 4H), 7.28-7.25 (m, 2H), 2.64 (3H), 1.68 (9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 135.5, 134.7, 133.1, 131.9 (2C), 131.3, 129.2 (2C), 128.5 (2C), 126.5, 124.2, 123.0, 121.9, 92.4, 88.9, 86.9, 86.6, 80.1, 28.0 (3C), 12.8. IR (cm^{-1}): υ 3069, 2975, 2930, 2221, 1761, 1593, 1281, 1127. HRMS (ESI): *m/z* calcd. for $C_{25}H_{22}ClN_2O_2$ $[M + H]^+$**:** 417.1370, Found: 417.1365.

***tert*-Butyl 4-[(2-chlorophenyl)ethynyl]-5-methyl-2-(phenylethynyl)-1*H*-imidazole-1-carboxylate (6e):**

Column chromatography on silica-gel (petroleum ether /EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **6e** as yellow oil (228 mg, 66% yield)**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ. 7.61-7.58 (m, 3H), 7.46-7.38 (m, 4H), 7.28-7.25 (m, 2H), 2.64 (s, 3H), 1.68 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 134.2 (2C), 131.9 (2C), 131.3, 129.6 (2C), 129.3, 128.6, 128.5 (2C), 124.7, 124.0, 121.9, 92.3, 90.6, 86.6, 82.9, 80.1, 28.0 (3C), 12.8. IR (cm^{-1}): υ 3062, 2976, 2929, 2219, 1759, 1593, 1568, 1323, 1129. HRMS (ESI): *m/z* calcd. for $C_{25}H_{22}ClN_2O_2$ $[M + H]^+$**:** 417.1370, Found: 417.1365.

***tert*-Butyl 5-methyl-2-(phenylethynyl)-4-(thiophen-3-ylethynyl)-1*H*-imidazole-1-carboxylate (6f):**

Column chromatography on silica-gel (petroleum ether /EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **6f** as beige solid (293 mg, 91% yield). M.p. 122 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.56 (m, 2H), 7.54 (dd, *J* = 3.0, 0.9 Hz, 1H), 7.41-7.36 (m, 3H), 7.30 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.21 (dd, *J* = 5.1, 0.9 Hz, 1H), 2.57 (s, 3H), 1.67 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 133.5, 131.9 (2C), 131.1, 129.8, 129.2, 128.8, 128.4 (2C), 125.3, 124.4, 122.0, 121.9, 92.2, 87.2, 86.5, 81.1, 80.2, 28.0 (3C), 12.8. IR (cm^{-1}): υ 3107, 2975, 2928, 2219, 1758, 1589, 1307, 1124. HRMS (ESI): *m/z* calcd. for $C_{23}H_{21}N_2O_2S$ $[M + H]^+$**:** 389.1324, Found: 389.1316.

***tert*-Butyl 4-(cyclohexylethynyl)-5-methyl-2-(phenylethynyl)-1*H*-imidazole-1-carboxylate (6g):**

Column chromatography on silica-gel (petroleum ether /EtOAc, 9.8:0.2) afforded compound **6g** as yellow oil (129 mg, 48% yield)**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.55 (m, 2H), 7.38-7.35 (m, 3H), 2.63 (quint, *J* = 5.4 Hz, 1H), 2.49 (s, 3H), 1.91-1.87 (m, 2H), 1.78-1.72 (m, 3H), 1.66 (s, 9H),1.63-1.51 (m, 2H), 0.9-0.85 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 143.2, 132.5, 131.8 (2C), 130.5, 129.1, 128.4 (2C), 125.0, 122.0, 97.1, 91.9, 86.2, 80.4, 72.6, 32.5, 29.6, 27.9 (3C), 25.9, 24.8, 12.6. IR (cm^{-1}): υ 3055, 2927, 2854, 2222, 1747, 1572, 1324, 1140. HRMS (ESI): *m/z* calcd. for $C_{25}H_{29}N_2O_2$ $[M + H]^+$**:** 389.2229, Found: 389.2224.

***tert*-Butyl 4-(4,4-diethoxybut-1-ynyl)-5-methyl-2-(phenylethynyl)-1*H*-imidazole-1-carboxylate (6h):**

Column chromatography on silica-gel (petroleum ether /EtOAc, 9:1) afforded compound **6h** as yellow oil (130 mg, 45% yield)**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.8, 3.3 Hz, 2H), 7.39-7.36 (m, 3H), 4.76 (t, *J* = 5.7 Hz, 1H), 3.74 (q, *J* = 7.2 Hz, 2H), 3.62 (q, *J* = 7.2 Hz, 2H), 2.79 (d, *J* = 5.7 Hz, 2H), 2.50 (s, 3H),1.66 (s, 9H), 1.25 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 133.2, 131.8 (2C), 130.6, 129.1, 128.4 (2C), 124.6, 122.0, 101.0, 91.9, 88.3, 86.3, 80.3, 74.1, 62.0, 27.9 (3C), 26.0, 15.2, 12.6. IR (cm^{-1}): υ 3063, 2977, 2927, 2223, 1755, 1590, 1320, 1129.. HRMS (ESI): *m/z* calcd. for $C_{25}H_{31}N_2O_4$ $[M + H]^+$: 423.2284, Found: 423.2278.

General procedure for the Synthesis of *tert*-butyl 4-aryl-5-methyl-2-(phenylethynyl)-1*H*-imidazole-1-carboxylate 7:

An oven-dried 15 mL sealed-tube flask, which was equipped with a stir bar, was charged with *tert*-butyl 4-bromo-5-methyl-2-(phenylethynyl)-1*H*-imidazole-1-carboxylate **5a** (100 mg, 0.28 mmol, 1.0 equiv.), boronic acid (0.42 mmol, 2.0 equiv.) $Pd_2(dba)_3$ (13.0 mg, 0.014 mmol), Xphos (13.2 mg, 0.028 mmol) and K_3PO_4 (118 mg, 0.55 mmol, 2 equiv.). A solution of toluene (4.0 mL) and deionized water (0.4 mL) was then added and the reaction mixture was stirred at 110 °C for 2 hours under argon atmosphere. Once cooled to room temperature, the mixture was concentrated under vacuum. The solid formed was suspended in ethyl acetate (200 mL) and washed with saturated NH_4Cl solution (15 mL) and water (15 mL). The combined organic layers were dried with $MgSO_4$. The crude material was purified by column chromatography using a mixture of petroleum ether/EtOAc as eluent to give pure *tert*-butyl 4-aryl-5-methyl-2-(phenylethynyl)-1*H*-imidazole-1-carboxylate **7**.

***tert*-Butyl 4-(4-methoxyphenyl)-5-methyl-2-(phenylethynyl)-1*H*-imidazole-1-carboxylate (7a):**

Column chromatography on silica-gel (petroleum ether /EtOAc, 9.5:0.5) afforded compound **7a** as yellow oil (93 mg, 85 **%** yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.55 (m, 4H), 7.40-7.36 (m, 3H), 6.97 (d, *J* = 9.0 Hz, 2H), 3.86 (s, 3H), 2.57 (s, 3H), 1.68 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 147.8, 140.0, 131.9 (2C), 129.4 (2C), 129.0, 128.4 (2C), 126.0, 124.8, 122.2, 116.3, 113.8 (2C), 92.1, 85.9, 80.7, 55.3, 28.0 (3C), 12.7. IR (cm^{-1}): υ 3062, 2960, 2924, 2851, 2220, 1751, 1612, 1325, 1116. HRMS (ESI): *m/z* calcd. for $C_{24}H_{25}N_2O_3$ $[M + H]^+$**:** 389.1865, Found: 389.1864.

***tert*-Butyl 5-methyl-2-(phenylethynyl)-4-[4-(trifluoromethyl)phenyl]-1*H*-imidazole-1-carboxylate (7b):**

Column chromatography on silica-gel (petroleum ether /EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **7b** as white solid (103 mg, 86% yield). M.p. 118 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.63-7.59 (m, 2H), 7.43-7.38 (m, 3H), 2.62 (s, 3H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 143.3, 138.8, 137.1, 131.9 (2 C), 130.5, 129.3 (q, *J* = 32.5 Hz), 129.0, 128.4 (2C), 128.2 (2 C), 126.6, 125.5, 125.3 (q, *J* = 3.8 Hz), 122.3 (q, *J* = 272.0 Hz), 92.4, 86.3, 80.2, 28.0 (3 C), 12.7. ^{19}F NMR (282 MHz, CDCl3): δ -62.46. IR (cm^{-1}): υ 3058, 2987, 2931, 1756, 1618, 1589, 1316, 1110. HRMS (ESI): *m/z* calcd. for $C_{24}H_{22}F_3N_2O_2$ $[M + H]^+$**:** 427.1633, Found: 427.1629.

***tert*-Butyl (*E*)-5-methyl-2-(phenylethynyl)-4-styryl-1*H*-imidazole-1-carboxylate (7c):**

Column chromatography on silica-gel (petroleum ether /EtOAc, 9.8:0.2) followed by recrystallization from Et_2O afforded compound **7c** as yellow solid (67 mg, 62**%** yield). M.p. 130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (dd, *J* = 7.5, 3.3 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.48 (d, *J* = 15.6 Hz, 1H), 7.40-7.36 (m, 3H), 7.35 (d, *J* = 7.8 Hz, 2H), 7.25 (t, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 15.6 Hz, 1H), 2.54 (s, 3H), 1.67 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.6, 137.8, 137.5, 131.9 (2C), 131.3, 129.4, 129.1, 128.6 (2C), 128.4 (2C), 127.4, 126.7, 126.4 (2C), 122.1, 117.0, 92.4, 86.0, 80.5, 28.0 (3C), 11.5. IR (cm^{-1}): υ 3057, 2981, 2928, 1749, 1596, 1326, 1128. HRMS (ESI): *m/z* calcd. for $C_{25}H_{25}N_2O_2$ $[M + H]^+$**:** 385.1916, Found: 385.1910.

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[26] CCDC 2078587 [for compound **5a**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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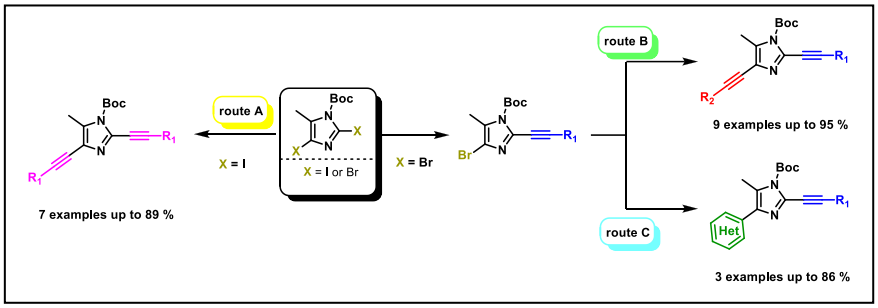

Insert text for Table of Contents here. An efficient and suitable selective Sonogashira cross-coupling reaction, to access unknown 2,4-dialkynylated and 2-alkynylated-4-arylated-5-methyl-1*H*-imidazole-1-carboxylates has been developed..

Institute and/or researcher Twitter usernames: Dr. Badr Jismy, Dr. Abdelkarim El Qami, Dr. Johan Jacquemin, Dr. Regis Guillot, Dr. Abdellatif Tikad, Prof. Mohamed Abarbri*