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Graphical Abstract

Organo-NHC catalyzed domino addition approach for the selective synthesis of 5-butynylisoxazoles and subsequent Sonogashira coupling

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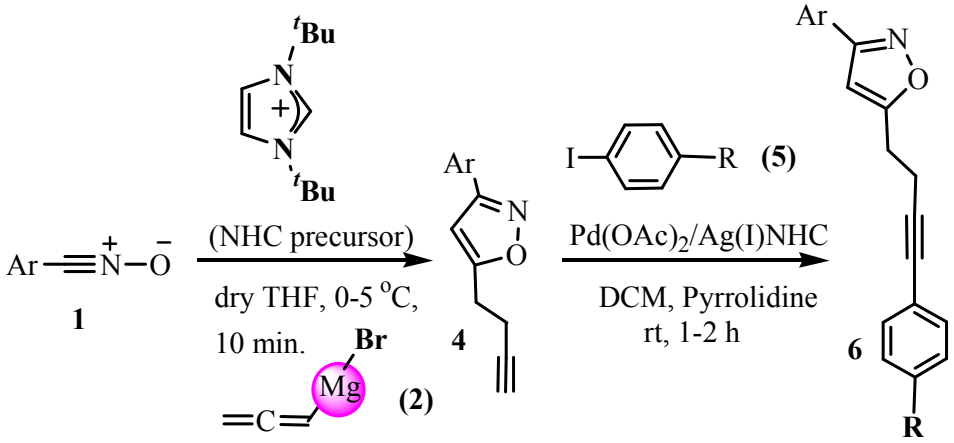
Organo-NHC catalysed domino addition of allenyl-MgBr to aryl nitrile oxides was developed to produce selectively the 5-butynylisoxazoles by minimising the unwanted protonation. Further, a Pd/Ag catalysed Sonogashira cross-coupling of 5-butynylisoxazoles was developed to produce selectively the internal alkynes by minimising the alkyne homo-coupling.



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ARTICLE TYPE

Organo-NHC catalyzed domino addition approach for the selective synthesis of 5-butynylisoxazoles and subsequent Sonogashira coupling

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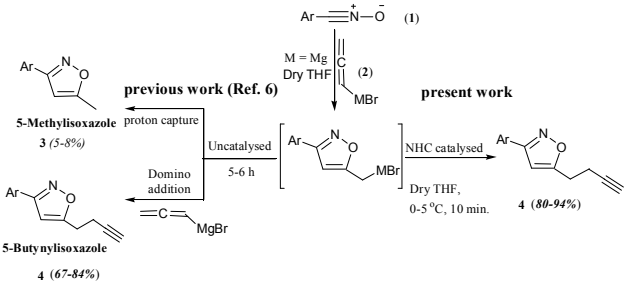
A nucleophilic organo *N*-heterocyclic carbene (NHC) catalysed click-type fast domino addition of allenyl-MgBr to aryl nitrile oxides to produce the 5-butynylisoxazoles with excellent selectivity and good yields is reported. The unwanted protanation and subsequent formation of 5-methylisoxazole byproducts is successfully supressed. Furthermore, a Pd/Ag catalysed protocol for Sonogashira cross-coupling of 5-butynylisoxazoles to obtain the corresponding internal alkynes with high selectivity and yields is developed by minimising the alkyne homo-coupling.

1. Introduction

The acid-base chemistry of Grignard reagents and imidazolium salt ionic liquids, the ability of Grignard reagents to deprotonate the imidazolium salts and the aptness of NHC-Grignard reagents in organic synthesis including nucleophilic addition is of significant interest for synthetic organic chemists.[1] Grignard reagents are more atom economical and user friendly as well as less expensive and easier to prepare,[2] although those are less functional group tolerant relative to zinc reagents.

The biologically imperative isoxazoles are key synthones and synthetic intermediates[3] and often used as masked β-diketones and β-aminoenones.[4] To construct isoxazole ring, the 1,3-dipolar cycloaddition between nitrile oxides and alkynes,[5] and domino addition between alkyne organometallics and nitrile oxides[6] have been reported. The selective synthesis of terminal alkyne-tagged isoxazole ring *via* nucleophilic addition would be an important aspect, which allows many subsequent side chain elaborations on isoxazole ring.

Previously Sampath et al. reported[6] the domino addition of allenyl-MgBr with nitrile oxide and observed the formation of mixture of 5-butynyl and 5-methylisoxazoles. It was described that during the second mole addition of allenyl-MgBr to Mg-cycloadduct, quenching of the reaction with aq. NH_4Cl lead to proton capture and directed the formation of 5-methylisoxazole as byproduct along with 5-butynylisoxazole (Scheme 1). Although, the above domino addition is an elegant concerted synthesis for 5-butynylisoxazole, the subsequent side-chain elloborations in one-pot are not possible due to the presence of 5-methylisoxazole byproduct. Since, the carbanion of Mg-cycloadduct is very reactive and functions as an extremely strong base, it captures the proton not only from water, but also from other possible sources during the domino additions and form the byproducts. In this respect, finding a solution to evade the unwanted protonation using Grignard reagents not only expands their scope in domino additions, but also in many other nucleophilic additions.



Scheme 1 Catalysed and uncatalysed domino addition of allenylmagnesium bromide to nitrile oxides.

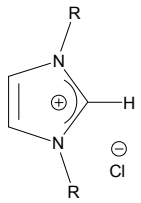
While organocatalysed domino reactions have emerged as important tools in organic synthesis, the usefulness of Lewis base nucleophilic NHCs as organo catalysts in domino reactions has received less attention.[7] It is also important to note that the NHCs and their precursors i.e. imidazolium salts are the good example for weak strong bronsted conjugate acid-base pair. Therefore, organo-NHCs are expected to mediate an efficient and fast non-concerted domino addition of Grignard reagents v*ia* forming NHC-Grignard adduct, that would minimise the unwanted protonation and byproduct formation. Our objective is to enhance the reactivity of Grignard reagents with a substoichiometric amount of a Lewis base NHCs, whereby the resulting NHC-Grignard complex induces high regioselectivity.

2. Results and Discussion

Herein we present a domino catalysed reaction by organo-NHCs during domino addition between allenyl-MgBr and nitrile oxide to produce the 5-butynylisoxazole selectively as a sole product without any 5-methylisoxazole formation. This accomplishment facilitated us to employ the as-synthesised 5-butynylisoxazoles directly for side chain elaboration (postsynthetic modifications) *via* Sonogashira cross-coupling to

obtain a variety of internal alkyne derivatives of 5-butynylisoxazole. Any postsynthetic modifications to alkyne function on isoxazole ring is problematic, when the ring is unmasked to β-diketones and β-aminoenones.

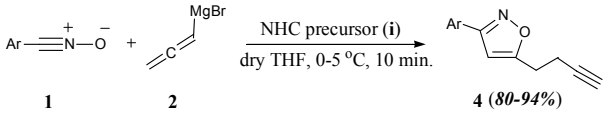
At first, we have investigated the domino addition between nitrile oxides (**1**) and allenyl-MgBr (**2**) without a catalyst to find out the exact source of proton that leads to formation of unwanted 5-methylisoxazole byproduct along with the target 5-butynylisoxazole. The reactants nitrile oxides (**1**) and allenyl-MgBr (**2**) were generated *in situ* using the established procedures.[8] Aq. NH_4Cl solution that used to quench the domino addition has been reported to be the probable source for proton to interact with Mg-cycloadduct.[6] During our experiments, we found that the Et_3NHCl present in nitrile oxide solution could also be a potential proton source (that formed by treating chloro-oxime with Et_3N organic base).The acidic pH of the solution was determined by simple litmus paper test. As the uncatalysed domino addition reaction needs ~5-6 h, the unwanted protonation of Mg-cycloadduct is possible to form the byproducts.[6]



R = **(i)** *tert*-butyl **(iv)** mesityl
(ii) *iso*-propyl **(v)** 4-chlorophenyl
(iii) cyclohexyl

Figure 1 NHC Precursors (imidazolium salts) used in the present study.

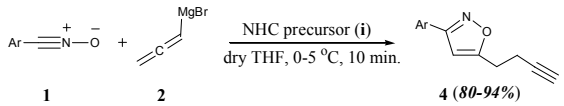
Recently we have reported the organo-NHC catalysed alkyne-nitrile oxide 1,3-dipolar cycloaddition for the regioselective synthesis of 3,5-disubstituted isoxazoles.[5] Based on the above observations, we assessed the scope of Lewis base nucleophilic organo-NHC catalysts (Figure 1) in domino addition. Interestingly, we found that the use of organo-NHC catalyst (1,3-Di-*tert*-butylimidazolin-2-ylidene(**i**)) facilitated the domino addition very fast (<10 min.). The reaction mixture turned colourless to green precipitate. Quenching of the reaction with aq.NH_4Cl, gave 5-butynylisoxazoles (**4**) selectively in high yields without any 5-methylisoxazole (Scheme 2), indicating the protonation either by Et_3NHCl or quenching agent aq.NH_4Cl during domino addition was successfully minimised. The role of Et_3NHCl as possible source for proton in other synthetic reactions was also reported previously.[9]



Scheme 2 Organo-NHC catalysed selective synthesis of 5-butynylisoxazole by domino addition.

The reduced reaction time (<10 min) in the catalysed reaction relative to the uncatalysed process (~6h) has enhanced the product selectivity. Although Table 1 illustrates the results obtained with only oragno-NHC catalyst of salt (**i**), the organo-NHC catalysts of salts **ii-v** (Figure 1) can also perform equally well to produce selectively the 5-butynylisoxazole (ESI). It is an evidence for the high efficacy of orgao-NHC catalysts in domino addition. The pure 5-butynylisoxazole product was characterised by NMR and mass spectroscopic techniques (ESI).

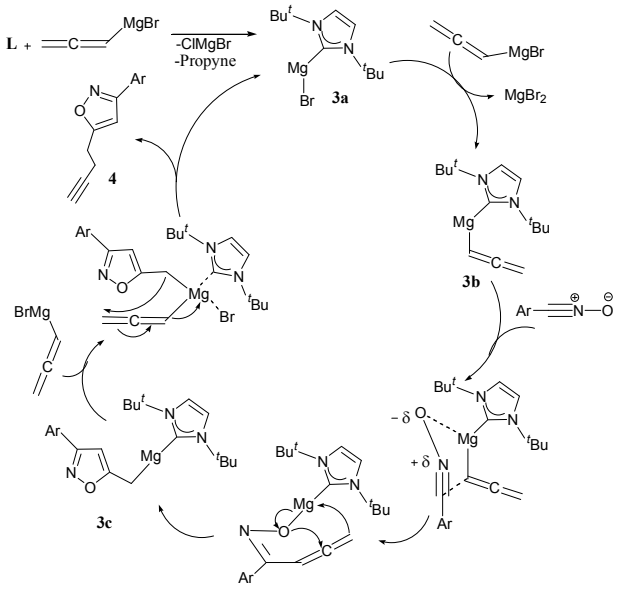
Table 1 Results of organo-NHC catalysed synthesis of 5-butynylisoxazole.[a]



Entry	Ar	Products	Yield (%)[b]
1	4-$OMeC_6H_4$ (**1a**)	**4a**	84
2	4-MeC_6H_4 (**1b**)	**4b**	85
3	2-$NO_2C_6H_4$ (**1c**)	**4c**	91
4	2-$NO_2C_6H_4$ (**1c**)	**4c**	81 (12)[c]
5	4-ClC_6H_4 (**1d**)	**4d**	89
6	C_6H_5 (**1e**)	**4e**	90
7	4-$NO_2C_6H_4$ (**1f**)	**4f**	94
8	4-FC_6H_4 (**1g**)	**4g**	86
9	2,3-di$OMeC_6H_3$ (**1h**)	**4h**	87
10	2-naphthyl (**1i**)	**4i**	92
11	4-CNC_6H_4 (**1j**)	**4j**	90
12	3-Br-4-$OMeC_6H_3$ (**1k**)	**4k**	88
13	4-OHC_6H_4 (**1l**)	**4l**	90

[a]All products were characterised by $^1H/^{13}C$ NMR, mass spectral analysis. [b]Determined by GC. [c]The yield in the parenthesis is for 5-methylisoxazoles were isolated in 12 % yields without organo-NHC catalyst.

Based on the success of the title reaction, to further explore the robustness of the protocol, a series of nitrile oxides (**1a-l**) were subjected for domino addition with allenyl-MgBr in the presence of organo-NHC catalyst. All of these investigated domino additions were accomplished fast producing their corresponding 5-butynylisoxazoles (**4a-l**) selectively in high yields (Scheme 2, table 1).



Scheme 3 A plausible mechanism of organo-NHC catalysed domino addition between allenyl-MgBr and nitrile oxide and selective formation of 5-butynylisoxazole.

Taking into consideration the known the acid-base chemistry of interaction between Grignard reagents and imidazolium salts, a probable mechanism is postulated for the reaction as depicted in Scheme 3. It would be reasonable to propose that an organo-NHC generated during the catalytic cycle will stabilize the transient species and acts as charge carrier. Based on this hypothesis Scheme 3 will provide the possible sequential steps to complete the catalytic cycle.

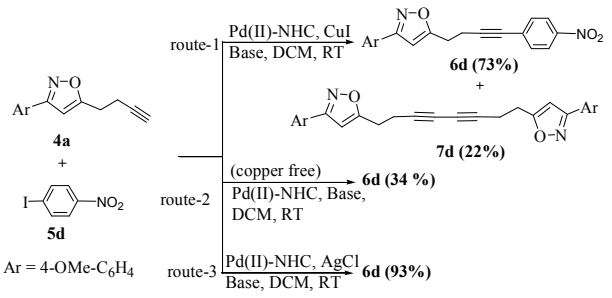
As illustrated in scheme 3, the formation of 5-butynylisoxazoles could occur in a non-concerted catalytic intermolecular domino addition fashion. Lewis base activation of Grignard reagents by NHCs has been reported.[10] The reactions of imidazolium salt with 2 moles of allenyl-MgBr will form the NHC-Mg-allenyl intermediate (**3b**) *via* the deprotonation of imidazolium salt[1b] and the interaction of (**3b)** with nitrile oxide leads to (**3c)** *via* 3+2 cycloaddition through a pseudo-envelop conformation, which explains the regioselective formation of 3,5-disubstituted isoxazole-Mg-NHC (**3c**). The domino addition of second mole of allenyl-MgBr to the intermediate (**3c**) leads to the selective formation of final product, 5-butynylisoxazole(**4**).

Side chain elaborations on 5-butynylisoxazole *via Sonogashira cross-coupling*

Initially, the Sonogashira cross-coupling of 5-butynylisoxazole (**4a)** and nitro substituted aryl iodide (**5d**) was chosen as a model reaction in dichloromethane (DCM) and the reaction progress *via* three different catalytic routes was monitored to minimise the possible alkyne homo-coupling.

1. Pd/Cu catalysed Sonogashira cross-coupling (route 1)
2. Cu-free Pd catalysed Sonogashira cross-coupling (route 2)
3. Pd/Ag catalysed Sonogashira cross-coupling (route 3)

The details of the reaction conditions, catalyst composition and products are illustrated in Scheme 4. Instead of commercial Pd(II)salt source, NHC-ligand bound Pd(II) was used as catalysts to improve the catalytic performance in all three routes.

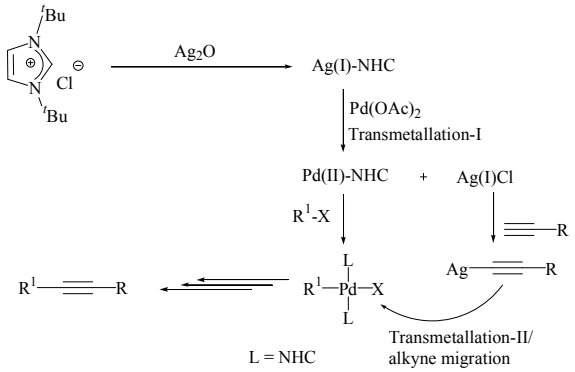


Scheme 4 Optimisation of Sonogashira cross-coupling between alkyne (**4a**) and aryl iodide (**5d**).

The Pd/Cu catalysed Sonogashira coupling conducted between the alkyne (**4a**) and nitro substituted aryl iodide (**5d**) yielded cross-coupled and homo-coupled products (Scheme 4). The role of copper as catalyst for alkyne homo-coupling side reaction (Hay/Glaser-type) during Sonogashira cross-coupling was described in some previous works.[11] A copper free Pd-catalysed Sonogashira coupling (Scheme 4, catalytic route 2) conducted using the same substrates i.e. (**4a**) and (**5d**) gave single cross-coupled product, but the reaction was very slow and yields were poor (~34 %).

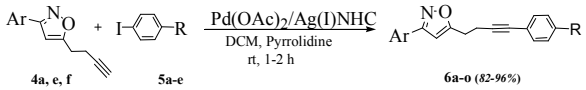
Literature reports the use of Ag(I) and Au(I) salts/complexes also as co-catalysts with palladium to act as transmetallation agents.[12] We explored with scope of Pd with Ag as co-catalyst for Sonogashira cross-coupling of 5-butynylisoxazole (Scheme 4, catalytic route 3) to reap the benefits of Ag(I) and Pd(II) properties. At this juncture, we attempted to combine the well-known transmetallation chemistry[13] between Ag(I)-NHCs and Pd(II) with Sonogashira cross-coupling to introduce Ag(I) as co-catalyst.

Generally, the Pd(II)-NHC catalysts for cross-coupling can be generated in two ways, either by (**i**) direct metallation of Pd(II) source with imidazolium salt or by (**ii**) transmetallation of carbene from Ag(I)-NHCs to Pd(II) source.[13] In this work, for the catalytic route 3 of Scheme 4, the Pd(II)-NHC catalyst was generated *in situ* from Ag(I)-NHCs *via* carbene transfer/transmetallation as shown in Scheme 5. This process usually accompanies Ag(I)Cl byproduct.[13]



Scheme 5 Methodology for Pd/Ag catalysed Sonogashira coupling developed in this work *via* double transmetallation reactions of Ag(I).

The reaction of Ag(I)Cl with terminal acetylenes to form Ag-acetylides intermediates those are useful in organic synthesis was also reported previously.[12b, 14] In this respect, we found that the Ag(I)Cl byproduct of Scheme 5 could be useful to design the Pd/Ag co-catalysed Sonogashira coupling of catalytic route 3 of Scheme 4 without any additional/external Ag(I)-halide. This strategy makes the catalytic route 3 of Scheme 4 more atom-economic with no need for addition of any external Ag(I) co-catalyst.



5a R = Me
5b R = OMe
5c R = H
5d R = NO_2
5e R = COMe
4a Ar = 4-OMeC_6H_4
4e Ar = C_6H_5
4f Ar = 4-$NO_2C_6H_4$

6a Ar = 4-OMeC_6H_4, **R** = Me
6b Ar = 4-OMeC_6H_4, **R** = OMe
6c Ar = 4-OMeC_6H_4, **R** = H
6d Ar = 4-OMeC_6H_4, **R** = NO_2
6e Ar = 4-OMeC_6H_4, **R** = COMe
6f Ar = C_6H_5, **R** = Me
6g Ar = C_6H_5, **R** = OMe
6h Ar = C_6H_5, **R** = H

6i Ar = C_6H_5, **R** = NO_2
6j Ar = C_6H_5, **R** = COMe
6k Ar = 4-$NO_2C_6H_4$, **R** = Me
6l Ar = 4-$NO_2C_6H_4$, **R** = OMe
6m Ar = 4-$NO_2C_6H_4$, **R** = H
6n Ar = 4-$NO_2C_6H_4$, **R** = NO_2
6o Ar = 4-$NO_2C_6H_4$, **R** = COMe

Scheme 6 Pd/Ag catalysed Sonogashira coupling of 5-butynylisoxazoles with aryl iodides.

In this context, we noticed that a combination of *in situ* generated Pd(II)-NHC and Ag(I)Cl as catalysts worked well to accomplish a fast Sonogashira coupling between (**4a**) and (**5d**) to produce the corresponding internal alkyne derivative (**6d**) selectively and minimising the formation of unwanted homo-coupled products. (Scheme 4, catalytic route 3). The effect of different bases and solvents in Sonogashira coupling between (**4a**) and (**5d**) was also investigated (ESI). The use of pyrrolidine is found to be advantageous over the other bases (ESI). The details of the spectral analysis of these products are given in ESI.

The latitude of Pd/Ag catalysed Sonogashira coupling protocol was extended to other aryl halides. The details of the reactants and corresponding product yields are summarised in Table 2. In less than 2 h all the reaction could be accomplished with good to excellent yields (Table 2). No homo-coupling was detected in any of these reactions. Nevertheless, the aryl halides bearing electron withdrawing groups provided slightly better yields of internal alkynes as compared to those with electron donating substituents concurring with earlier reports.[15]

Table 2 Pd(II)-NHC Catalysed Sonogashira cross coupling reaction of 5-butynylisoxazole with aryl iodides.[a]

Entry	Ar	R	Product	Yield (%)[b]
1	4-OMeC_6H_5 (**4a**)	Me (5a)	6a	84
2	**4a**	OMe (5b)	**6b**	82
3	**4a**	H (5c)	**6c**	90
4	**4a**	NO_2 (5d)	**6d**	93
5	**4a**	COMe (5e)	**6e**	94
6	C_6H_5 (**4e**)	5a	6f	82
7	**4e**	**5b**	**6g**	82
8	**4e**	**5c**	**6h**	88
9	**4e**	**5d**	**6i**	91
10	**4e**	**5e**	**6j**	90
11	4-$NO_2C_6H_5$ (**4f**)	5a	6k	89
12	**4f**	**5b**	**6l**	90
13	**4f**	**5c**	**6m**	90
14	**4f**	**5d**	**6n**	96
15	**4f**	**5e**	**6o**	94

[a]All products were characterised by IR, $^1H/^{13}C$ NMR and mass spectral analysis.
[b]GC yields after 2 hour.

3. Conclusions

We have developed a nucleophilic organo-NHC catalysed domino addition of allenyl-MgBr with nitrile oxide to obtain selectively as a sole product by avoiding the protonation side reaction. While the previously reported uncatalysed domino addition and the product formation was attributed to an SN^i reaction involving a Schlenk equilibrium, the present catalytic work discloses a non-concerted organo-NHC mediated reaction mechanism for domino addition.

The above approach enabled us to perform side-chain elaboration directly on as-synthesised 5-butynylisoxazole *via* Sonogashira cross-coupling without the interference of 5-methylisoxazole. A new Pd/Ag catalysed system, which is much efficient and atom-economic than Pd/Cu catalysed and coppper free Pd-catalysed systems is developed for the Sonogashira cross-coupling of 5-butynylisoxazole to give the corresponding internal alkynes as sole products in high yields, by suppressing the alkyne homo-coupling side reaction. Thus, the internal alkynes of 5-butynylisoxazoles act as useful starting materials to access 1,3-dicarbonyl compounds *via* hydrolysis of isoxazole ring of internal alkynes. We have also demonstrated that the benefit of Ag(I)Cl, a byproduct of the Transmetallation-I (Scheme 5), as a co-catalyst for the subsequent Sonogashira coupling of 5-butynylisoxazoles (Transmetallation-II, Scheme 5), which again highlights the atom efficiency of our Pd/Ag catalysed Sonogashira coupling protocol.

4. Experimental Section

4. 1. General

All commercially available reagents were used without further purification. Reaction solvents were dried by standard methods before use. Purity of the compounds was checked by TLC using Merck 60F254 silica gel plates. Elemental analyses were obtained with an Elemental Analyser Perkin-Elmer 240C apparatus. IR spectra were recorded with a Perkin-Elmer 881 spectrometer. ^1H and ^{13}C NMR spectra were recorded with a Mercuryplus 400 spectrometer (operating at400 MHz for ^1H and 100.58 MHz for ^{13}C); chemical shifts were referenced to TMS. EI (electron impact) mass spectra (at an ionising voltage of 70 eV) were obtained usinga Shimadzu QP5050A quadrupole-based mass spectrometer.

4.2. General procedure for the synthesis of 5-butynylisoxazoles (4a-l). To a suspension of magnesium turnings (8 mmol, 8 equiv) in anhydrous tetrahydrofuran (20 mL) added mercury(II) chloride (5 mg, 1% w/w of propargyl bromide) and propargyl bromide (80 wt % solution in toluene, 6 mmol, 6 equiv) in small portions slowly to generate a cloudy pale yellow solution of allenylmagnesium bromide. This was cooled to 0-5 ºC and added with NHC precursor (1,3-Di-*tert*-butylimidazolium chloride (**i**)) (2 mmol). To this, a solution of *in situ* generated benzonitrile oxide (1 mmol), was added by maintaining the temperature between 0-5 ºC under stirring. The reaction mass was allowed to stir for 5 minutes at room temperature. After this conversion, the mixture is quenched by addition of saturated solution of NH_4Cl (2 mL) and diluted with dichloromethane (20 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (anhydrous Na_2SO_4) and evaporated under reduced pressure to afford a crude product which was subjected to column chromatography (silica gel, 60-120 mesh, eluent; n-hexane/EtOAc gradient) to afford pure products (**4a-l**).

4.3. General procedure for Sonogashira cross-coupling. In a typical procedure, to a suspension of $Pd(OAc)_2$ (0.03 mmol) and Ag(I)-NHC (NHC = 1,3-Di-*tert*-butylimidazolin-2-ylidene (**i**)) (0.03 mmol) was dissolved in DCM (10 mL). Then, the indicated amount of above dichloromethane solution was added to a mixture of aryl iodides (1 mmol), 5-butynylisoxazoles (1.2 mmol), pyrrolidine (3 mmol, 3 equiv), and DCM (15 mL). Then, the mixture was stirred at room temperature for 2 h to form the

desired coupled products. Complete consumption of starting material was judged by TLC and GC analysis. After, the mixture was filtered and evaporated, the residue was purified by column chromatography (silica gel, 60-120 mesh, eluent; n-hexane/EtOAc (8:2) gradient) to afford the desired coupled product (**6a-o**).

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Notes and references

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† Electronic Supplementary Information (ESI) available: The spectral data of 5-butynylisoxazoles (**4a-l)** and their internal alkynes **(6a-o)**. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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