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PAPER

N-Heterocyclic carbene-catalyzed 1,3-dipolar cycloaddition reactions: a facile synthesis of 3,5-di- and 3,4,5-trisubstituted isoxazoles†

Shravankumar Kankala,[a] Ravinder Vadde*[a] and Chandra Sekhar Vasam*[b]

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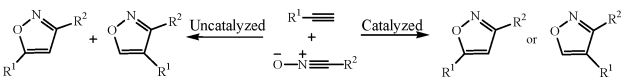
A first example of organo-*N*-heterocyclic carbene (NHC) catalyzed click-type fast 1,3-dipolar cycloaddition of nitrile oxides with alkynes was developed for the regioselective synthesis of 3,5-di- and 3,4,5-trisubstituted isoxazoles. Triethylamine (Et_3N) was employed as an effective base to generate both nitrile oxide and the organo-NHC catalyst *in situ*. This catalytic approach was used to attach a variety of substituents, including other biologically active fragments, onto the isoxazole ring to selectively design multinucleus structures. Further, we have also optimized the conditions for Cu(I)-free Sonogashira cross-coupling to obtain internal alkynes in high yields, which were subsequently used in cycloaddition. A catalytic cycle is proposed and the remarkable regiocontrol in the formation of isoxazoles was ascribed to a beneficial zwitterion intermediate developed by the interaction of the strongly nucleophilic organo-NHC catalyst with alkyne followed by nitrile oxide.

Introduction

An early study by Huisgen on 1,3-dipolar cycloaddition of azides and alkynes to obtain triazoles[1] has generated interest in exploring the usefulness of other dipoles.[2] Of particular interest, 1,3-dipolar cycloaddition of nitrile oxides (1,3-dipole) with alkynes (dienophile) has good synthetic value since it produces the biologically and technologically useful isoxazoles.[3] However, the development of a suitable catalyst is suggested to control the product regioselectivity and also to activate the inert alkyne dienophiles (Scheme 1).[3a–h]



Scheme 1 1,3-Dipolar cycloaddition of nitrile oxides with terminal alkynes.

1,3-Dipolar cycloaddition of nitrile oxides with terminal alkynes catalyzed by Cu(I) (click chemistry) and Ru(II) catalysts is well established to obtain regioselectively the 3,5-di- and 3,4-disubstituted isoxazoles, respectively.[3a–g] The Ru(II) catalysts were also used in the cycloaddition of internal alkynes to obtain sterically crowded 3,4,5-trisubstituted isoxazoles.[3a] However, no investigations using organocatalysts to accelerate the 1,3-dipolar cycloaddition have been reported. Considering the possible disproportionation by metal catalysts and the advantages found with organocatalysts in recent homogeneous catalysis,[4] we intend to develop an effective organocatalyst for 1,3-dipolar cycloaddition. Probably, a strong Lewis basic organocatalyst would be suitable to accelerate the reactivity of terminal/internal alkynes by forming an active zwitterion and thereby directing regioselective cycloaddition. The formation of zwitterions (alkenyl ion) in the stoichiometric/catalytic reactions of Lewis basic nucleophiles, including NHCs, with alkynes in some organic syntheses has already been reported.[5]

Within the context of Lewis base catalysis, *N*-heterocyclic carbenes (NHCs) are distinct Lewis base (nucleophilic) organocatalysts that have both σ basicity and π acidity characteristics.[6] Starting from the early investigations on thiamine-derived NHCs in benzoin,[6a] and later Stetter reactions,[6b] the mechanistic diversity of NHCs depending on their properties has led to the development of several unprecedented C–C and C–X (X = heteroatom) bond formations. Indeed the isolation of the first stable NHC by Arduengo in 1991[7] from imidazolium salts disclosed their tunable steric and electronic properties by varying the *N*-substituents on the imidazole ring. Further, the imidazolium salts, precursors to NHCs, are stable and easy to operate.

Herein we describe for the first time the usefulness of easily accessible nucleophilic organo-NHC catalysts in the click-type 1,3-dipolar cycloaddition of nitrile oxides with terminal and internal alkynes to produce regioselectively **(a)** 3,5-disubstituted and **(b)** sterically crowded 3,4,5-trisubstituted isoxazoles, respectively. Further, we also report the optimization of the conditions to obtain internal alkynes in high yields by a copper(I)-free Sonogashira cross-coupling which are required in cycloadditions.

[a]*Department of Chemistry, Kakatiya University, Warangal, India. E-mail: ravichemku@rediffmail.com; Fax: +91-870-2438800; Tel: +91-9390100594*

[b]*Department of Chemistry, Satavahana University, Karimnagar, India. E-mail: vasamcs@yahoo.co.in; Fax: +91-878-2255933; Tel: +91-9000285433*

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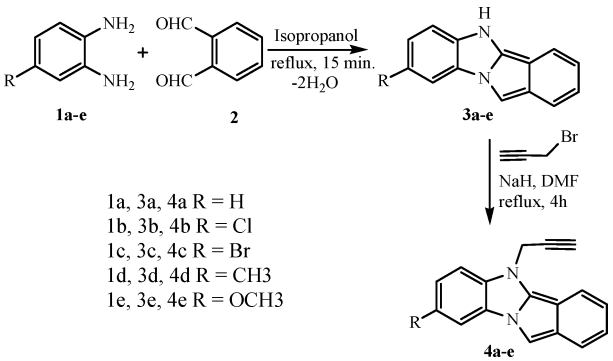
Results and discussion

(a) Organo-NHC-catalyzed regioselective synthesis of 3,5-disubstituted isoxazoles

We have employed some newly synthesized isoindole-derived terminal alkynes as partners to nitrile oxide in cycloaddition to derive multinucleus structures. These new terminal alkynes were obtained in a two step synthesis (Scheme 2). Firstly, the isoindoles (**3a–e**) were obtained by the condensation of *o*-phthaladehyde (OPA) **2** with *o*-phenylenediamines (OPDA) (**1a–e**) *via* the formation of a Schiff base. *N*-Propargylation of isoindoles (**3a–e**) gave terminal alkynes of isoindoles (**4a–e**). Previously, we have reported the application of OPA as a starting material to synthesize biologically useful quinazolines, macrocyclic Schiff bases and, in a recent contribution on organo-NHC-catalyzed benzoin condensation of OPA–chalcone, napthalenone-type metabolites.[6q,8] We now extend the work to obtain isoindole terminal alkynes for cycloaddition.

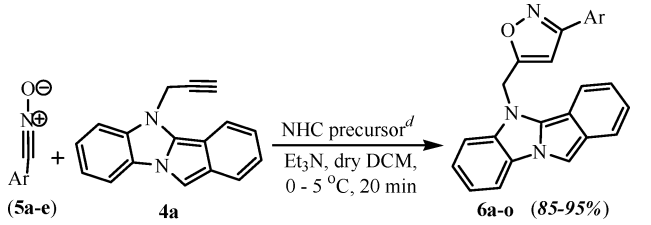


Scheme 2 Synthesis of isoindole terminal alkyne derivatives.

Optimization of conditions for the generation and stabilization of nitrile oxides is an important issue in cycloaddition. In our work, the nitrile oxides were generated *in situ* by the reaction of hydroximoyl chlorides with triethylamine base at 0–5 °C to limit the dimerisation to furoxans. The hydroximoyl chlorides were obtained by treating aldoximes with an equimolar amount of *N*-chlorosuccinimide in dimethyl formamide at room temperature.[9]

The stabilized nitrile oxides were then subjected to cycloaddition with isoindole-derived terminal alkynes under N_2 atmosphere. The details of the reaction and the results are summarized in Table 1. Firstly, the conditions for cycloaddition were optimized by using nitrile oxide (**5a**) and terminal alkyne (**4a**) as model substrates. The cycloaddition between **5a** and **4a** studied without a catalyst was sluggish (~30 h) and produced a mixture of two regioisomers of disubstituted (3,4- and 3,5-) isoxazole (entry 1, 54% yield of combined mixture in ~4 : 1 ratio). In this viewpoint, it was considered to use a nucleophilic organo-NHC catalyst to enhance the reactivity of the alkyne and thereby to improve the product regioselectivity. It is known that the lowest unoccupied orbital of alkynes (being low in energy) allows reactions with strong nucleophiles, but not directly with weak nucleophiles. We have considered the imidazolium salts (**i–vii**, Fig. 1) as organo-NHC catalyst precursors in this reaction, which were easily synthesized by a one pot method reported by Arduengo.[10] Our efforts began with the organo-NHC catalyst generated from salt (**i**) in the presence of mild triethylamine (Et_3N) base *via* the deprotonation of the C_2–H proton.

Table 1 Results of organo-NHC-catalyzed cycloaddition of terminal alkyne of isoindole (**4a**) with nitrile oxides (**5a–e**)[a]



Entry	Ar	Product	Time	Yield (%)[b]
1	4-$OMeC_6H_4$ (**5a**)	**6a**	30 h	54 (4 : 1)[c]
2	4-$OMeC_6H_4$ (**5a**)	**6a**	15 min	95
3	4-MeC_6H_4 (**5b**)	**6b**	18 min	92
4	2-$NO_2C_6H_4$ (**5c**)	**6c**	20 min	85
5	4-FC_6H_4 (**5d**)	**6d**	20 min	90
6	4-ClC_6H_4 (**5e**)	**6e**	20 min	92

[a] All products were characterized by NMR and mass spectral analysis. [b] Isolated yields after column chromatography. [c] Ratio of 3,5 and 3,4 isomers noted without catalyst. [d] Fig. 1 R = (i).

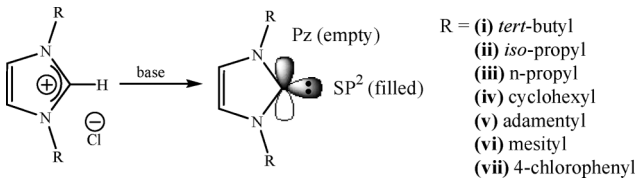


Fig. 1 NHC precursors (imidazolium salts) and NHCs.

Before the addition of nitrile oxide (**5a**), the reactivity/stability of alkyne (**4a**) was examined in the presence of organo-NHC catalyst of salt (**i**). There was no indication of possible homocoupling of alkyne. When the *in situ* generated nitrile oxide (**5a**) was added to alkyne (**4a**) in the presence of the above organo- NHC catalyst, the cycloaddition was accomplished quickly, within 15 min under the conditions mentioned in Table 1, and produced exclusively a single regioisomer of the corresponding 3,5-disubstituted isoxazole (**6a**) in good yields (Table 1, entry 2).

The aforementioned optimized conditions for cycloaddition were then extended to different nitrile oxides (**5b–e**) with various electronic properties. It has been noted that all these reactions catalyzed by organo-NHC of salt (**i**) were highly regioselective towards the 3,5-disubstituted isoxazoles (Table 1). In fact, these catalytic reactions were found to proceed almost instantaneously (during the first minute), although an approximate time of 15–20 min was used. However, a small decrease in yields of isoxazoles (Table 1, entry 4) could be caused by the presence of an *ortho*-nitro group on the nitrile oxide exerting an *ortho* effect. Although Table 1 describes the results obtained with only organo-NHC catalyst of salt (**i**), the organo-NHC catalysts of salts **ii–vii** can also perform equally well to produce only 3,5-disubstituted isoxazoles.

After these efforts, we also studied the catalytic cycloaddition of terminal alkynes (**4b–e**) with nitrile oxides (**5a–c**) and noticed the formation of only 3,5-disubstituted isoxazoles as a sole product in high yields (see ESI†).

The catalytic conditions optimized in the above 1,3-dipolar cycloadditions by organo-NHC catalysts for the regioselective synthesis of 3,5-disubstituted isoxazoles are comparable or relatively better than those of copper-catalyzed[3b–i] and microwave-induced 1,3-dipolar cycloadditions[11] in terms of the ranges of the isoxazole yields and reactions times. These are also more facile than other catalytic methods[12] for the synthesis of 3,5-disubstituted isoxazoles such as (i) base-catalyzed cycloaddition of primary nitro compounds with terminal alkynes; (ii) palladium-catalyzed four-component coupling of a terminal alkyne, hydrazine, carbon monoxide and aryl iodide; (iii) gold-catalyzed cycloisomerization of α,β-acetylenic oximes; (iv) gold-catalyzed transformation of the cross-dehydrogenative coupling product of nitrones and terminal alkynes; (v) silver-catalyzed cyclization of alkynyl oxime ethers.

Regarding the characterization, the formation of 3,5-disubstituted isoxazoles (**6a–q**) was conformed by ^{1}H and ^{13}C NMR and mass spectroscopies (experimental and ESI†). The absence of ^{1}H NMR signals of terminal alkyne at δ = ~2.10, and emergence of a new signal at δ = ~6.20 corresponding to the 4th C–H proton of isoxazole provides good support for the cycloaddition forming 3,5-disubstituted isoxazoles. The same features are reflected in the ^{13}C NMR spectra, where the signal belonging to the terminal carbon of alkyne disappeared and a new signal belonging to the 4th C–H ring carbon appeared at δ = ~99 after cycloaddition.

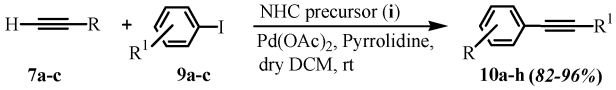
Further control experiments were performed by submitting a 1 : 1 mixture of alkynes (**4a**) and (**4b**) to the cycloaddition with nitrile oxide (**5a**) to ensure the involvement of the NHC catalyst in the cycloaddition path. It was found that under identical reaction conditions, again only the corresponding 3,5-disubstituted isoxazoles (**6a**) and (**6f**) were formed (91% of combined mixture in ~1 : 1.2 ratios). There was no evidence for side reactions such as homocoupling or cross-coupling of alkynes. This result clearly indicates the decisive role of the NHC catalyst in the cycloadditions.

(b) Organo-NHC-catalyzed regioselective synthesis of sterically crowded 3,4,5-trisubstituted isoxazoles

To elaborate on the scope of the organo-NHC-catalyzed cycloadditions, we have also organized the regioselective synthesis of some sterically crowded 3,4,5-trisubstituted isoxazoles by employing some pre-synthesized internal alkynes as partners to nitrile oxides. Since the nucleophilic organo-NHC catalyst can interact with both terminal and internal alkyne functions in the same fashion, we have undertaken this study. It is noticeable that the Sharpless copper catalyst is not suitable for the cycloaddition of internal alkynes.

First, we gave attention to optimizing the conditions for synthesis of internal alkynes by Pd(II)-catalyzed Sonogashira cross-coupling of terminal alkynes with aryl iodides in the presence of an amine base. According to the original report on Sonogashira coupling,[13] the Pd(II) catalyst needs the support of a Cu(I) co-catalyst. However, recent investigations recommended the Cu(I)-free Sonogashira coupling to prevent the possible oxidative dimerization of terminal alkynes by Cu(I).[14] Since NHCs have also been recognized as strong σ-donating ligands, the metal–NHC complexes have become popular catalysts to process certain organic transformations, specifically cross-coupling and metathesis.[15]

Table 2 Results of Pd(II)–NHC-catalyzed synthesis of internal alkynes (**10a–h**)[a]



7a-c **9a-c** **10a-h (82-96%)**

Entry	R	R^1	Product	Yield (%)[b]
1	C_6H_5 (**7a**)	4-Me (**9a**)	**10a**	96
2	C_4H_9 (**7b**)	**9a**	**10b**	92
3	HOC_2H_4 (**7c**)	**9a**	**10c**	95
4	**7a**	4-$OMeC_6H_4$ (**9b**)	**10d**	82
5	**7b**	**9b**	**10e**	90
6	**7c**	**9b**	**10f**	92
7	**7a**	2-$NO_2C_6H_4$ (**9c**)	**10g**	85
8	**7b**	**9c**	**10h**	94

[a] All products were characterized by IR, NMR and mass spectral analysis. [b] Isolated yields after column chromatography.

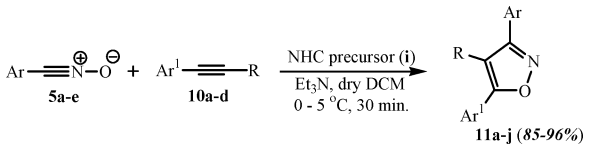
In this respect, the Pd(II)–NHC catalyst generated *in situ* (see the Experimental) has catalyzed the Cu(I)-free Sonogashira coupling of some specific terminal alkynes (**7a–c**) with aryl iodides (**9a–c**) in the presence of pyrrolidine base (milder than even Et_3N) and provided excellent yields of the corresponding internal alkynes (**10a–h**) at room temperature (Table 2). The Sonogashira coupling of this work is very tolerant of other functional groups on terminal alkynes (**7b** and **c**) as indicated by spectral analysis.

Among the various pre-synthesized internal alkynes (**10a–h**), we have chosen internal alkynes (**10a–d**), designed with specific electronic and steric properties, to conduct cycloaddition with nitrile oxides (**5a–e**). Two sets of control cycloaddition experiments were planned with or without organo-NHC catalyst. In the absence of catalyst, the cycloaddition of nitrile oxide (**5a**) studied with the internal alkynes (**10a**) and (**10c**) was very slow, but the former reaction (**10a** with **5a**) yielded a single regioisomer (Table 3, entry 1) and the latter one (**10c** with **5a**) yielded a mixture of two regioisomers of trisubstituted isoxazole (Table 3, entry 7) due to steric factors. This observation reveals the necessity of a catalyst to improve not only the yields of isoxazole but also to control the regioselectivity for steric reasons.

In view of the above information, organo-NHC catalyst of salt (**i**) (Fig. 1) was brought into the cycloaddition of the substrates listed in Table 3. To our delight, the catalytic cycloaddition reactions of internal alkynes (**10a–d**) also occurred instantaneously, similarly to those terminal alkynes, upon mixing with nitrile oxides (**5a–e**) under simple stirring at 0–5 °C for a period of 30 min, and produced selectively 3,4,5-trisubstituted isoxazoles (**11a–j**) in good yields (Table 3) by diminishing the steric factors. The result of a control experiment is also provided (entry 13). It is now clear that NHC catalysts are involved in the cycloaddition.

We noticed that the results and conditions depicted in Table 3 for the organo-NHC-catalyzed regioselective synthesis of 3,4,5-trisubstituted isoxazoles are found to be comparable or relatively better than the previous reports,[3a,h,i,16] including (i) Ru(II)-catalyzed cycloaddition of nitrile oxide with internal alkynes; (ii) sequential 1,3-dipolar cycloaddition and cross-coupling of silicon adducts; (iii) base-catalyzed cycloaddition of primary nitro compounds with internal alkynes; (iv) palladium-catalyzed cross-coupling of 4-iodo-substituted 2,5-dihydroisoxazoles and isoxazoles; (v) Sonogashira coupling of acid chlorides with terminal alkynes,

Table 3 Results of organo-NHC-catalyzed cycloaddition of internal alkynes (**10a–d**) and nitrile oxides (**5a–e**)[a]

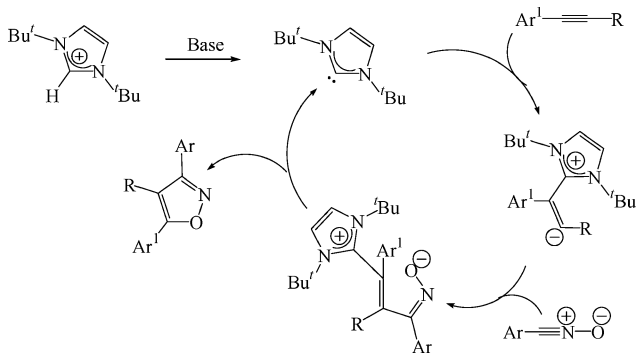


Entry	Internal alkyne (Ar^1, R)	Nitrile oxide (Ar)	Product	Yield (%)[b]
1	Ph—≡—C_6H_4(4-Me) (**10a**)	4-$OMeC_6H_4$ (**5a**)	**11a**	24[c]
2	Ph—≡—C_6H_4(4-Me) (**10a**)	4-$OMeC_6H_4$ (**5a**)	**11a**	96
3	**10a**	2-$NO_2C_6H_4$ (**5c**)	**11b**	85
4	**10a**	4-FC_6H_4 (**5d**)	**11c**	90
5	C_4H_9—≡—C_6H_4(4-Me) (**10b**)	4-MeC_6H_4 (**5b**)	**11d**	92
6	**10b**	4-ClC_6H_4 (**5e**)	**11e**	90
7	HOC_2H_4—≡—C_6H_4(4-Me) (**10c**)	**5a**	**11f**	32 (8 : 2)[c]
8	**10c**	**5a**	**11f**	94
9	**10c**	**5b**	**11g**	90
10	Ph—≡—C_6H_4(4-OMe) (**10d**)	**5a**	**11h**	92
11	**10d**	**5b**	**11i**	92
12	**10d**	**5c**	**11j**	85
13	**10d** + **10c**	**5a**	**11f** + **11h**	86[d]

[a] All products were characterized by IR, NMR and mass spectral analysis. [b] Isolated yields after column chromatography. [c] Without NHC catalyst. [d] Control experiment (**11f** = 46% + **11h** = 40%)

followed by 1,3-dipolar cycloaddition with nitrile oxide under dielectric heating; (vi) gold-catalyzed domino reaction of alkynyl oxime ethers.

Finally, based on the results obtained in our work concerning the regioselective synthesis of both 3,5-di- and 3,4,5-trisubstiututed isoxazoles including control experiments, a plausible mechanism has been deduced (Scheme 3). The formation of isoxazoles could occur in a domino fashion in cycloaddition. According to Scheme 3, the organo-NHC catalyst will interact first with the alkyne (terminal/internal) and form a zwitterion. The formation of a zwitterion in the catalytic/stoichiometric reaction of nucleophiles including NHCs and alkynes has already been already established.[5] The reactive zwitterionic species will now interact with nitrile oxide through nucleophilic attack and form another zwitterion *via* C–C bond formation, which finally undergoes C–O heterocyclization to produce regioselectively the corresponding isoxazoles.



Scheme 3 A plausible mechanism for the formation of 3,5-di- and 3,4,5-trisubstituted isoxazoles.

Conclusions

A facile catalytic approach to synthesize regioselectively both 3,5-di- and 3,4,5-trisubstiututed isoxazoles in high yields was developed by the nucleophilic organo-NHC-catalyzed 1,3-dipolar cycloaddition of nitrile oxide with alkynes. To our knowledge, this is the first effort established with an organocatalyst to process the cycloaddition of both terminal and internal alkynes. Most importantly, the NHC catalyst precursors used in this work are easy to synthesize and operate. Specifically, the multinucleus structures like isoindole linked disubstituted isoxazoles and sterically crowded trisubstituted isoxazoles can be accessed easily selectively by this method, which could be useful in biology and material science. Our method could be an efficient alternative to Sharpless copper catalyst and Fokin Ru(II) catalyst in the 1,3-dipolar cycloaddition of nitrile oxide with alkynes. Depending on the choice of starting materials, this is also an alternative to other existing catalytic methods.[12a,b,16] There have been some reports on catalyst-free 1,3-dipolar cycloadditions of nitrile oxide to alkyne[17] or alkene,[18] but these appear to be applicable for specific examples.

Further, we have also disclosed that the combination of Pd(II)–NHC catalyst and mild pyrrolidine base works well in Cu(I)-free Sonogashira coupling to obtain internal alkynes in high yields. We are currently working on the development of cycloaddition reactions under non-inert conditions using air stable Ag(I)–NHCs as precursors to provide free organo-NHC catalysts in solution. The Ag(I)–NHCs were obtained by Lin's Ag_2O method.[15f] Lewis basic nucleophiles such as *N*-oxides, phosphines, quaternary ammonium salts and tertiary amines are also worthwhile to be considered in cycloaddition, which will certainly explore new catalytic paths. Since alkynes, nitro compounds and aldehydes, and NHCs in the form of thiamine, are also available in nature, our efforts may also be useful to connect Nature's chemical reactions.

Experimental section

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 240 C apparatus. ^1H and ^{13}C NMR spectra were recorded with a Mercuryplus 400 spectrometer (operating at 400 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 using a Shimadzu QP5050A quadrupole-based mass spectrometer. IR spectra were recorded with a Perkin-Elmer 881 spectrometer.

General procedure for the synthesis of 3,5-disubstituted isoxazoles (6a–q). To terminal alkynes **4a–e** (1 mmol) and NHC precursor (**i**) (5 mol%) in dry DCM (5 ml) under nitrogen atmosphere was added Et_3N (5 mol%). The mixture was stirred for 10 min. The reaction mixture was cooled to 0–5 °C and added dropwise to a solution of benzonitrile oxide **5a–e** (1 mmol), generated *in situ* by the treatment of triethylamine (1.2 mmol) with the corresponding

chlorooximes (1 mmol) in dry DCM (10 ml) over a period of 2 min while maintaining the temperature between 0–5 °C. The reaction mass was allowed to attain room temperature and stirring was continued for 20 min. After conversion was complete, the mixture was quenched by addition of saturated solution of NH_4Cl (2 ml) and diluting with dichloromethane (40 ml). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 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 (**6a–q**).

5-(3-(4-Methoxyphenyl)isoxazol-5-ylmethyl)-5*H* benzo(4,5)imidazo(2,1a)isoindole (6a). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 3.84 (s, 3H), 4.56 (s, 2H), 6.38 (s, 1H), 6.94–7.28 (m, 13H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 56.24, 58.30, 99.06, 109.22, 112.10, 113.42, 117.11, 118.76, 120.95, 124.05, 125.62, 128.22, 128.62, 128.85, 135.52, 150.62, 157.85, 162.44 ppm. MS (EI, 70 eV): *m*/*z* (%) = 394 [M + H]$^+$. **EA** calcd (%) for $C_{25}H_{19}N_3O_2$ (393.15): calcd. C 76.32, H 4.87, N 10.68; found C 76.30, H 4.85, N 10.65.

5-(3-(4-Methylphenyl)isoxazol-5-ylmethyl)-5*H*-benzo(4,5)imidazo(2,1a)isoindole (6b). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.36 (s, 3H), 4.56 (s, 2H), 6.36 (s, 1H), 6.94–7.18 (m, 13H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 23.56, 58.32, 99.06, 109.22, 112.10, 113.42, 117.24, 118.72, 120.95, 124.05, 125.62, 128.22, 128.62, 128.85, 135.52, 150.62, 157.85, 162.44 ppm. MS (EI, 70 eV): *m*/*z* (%) = 378 [M + H]$^+$. EA calcd (%) for $C_{25}H_{19}N_3O$ (377.15): calcd. C 79.55, H 5.07, N 11.13; found C 79.52, H 5.05, N 11.10.

5-(3-(2-Nitrophenyl)-isoxazol-5-ylmethyl)-5*H*-benzo(4,5)imidazo(2,1a)isoindole (6c). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 4.56 (s, 2H), 6.36 (s, 1H), 6.96-7.48 (m, 13H, Ar-H) ppm. MS (EI, 70 eV): *m*/*z* (%) = 409 [M + H]$^+$. EA calcd (%) for $C_{24}H_{16}N_4O_3$ (408.12): calcd. C 70.58, H 3.95, N 13.72; found C 70.56, H 3.93, N 13.70.

General procedure for Sonogashira cross-coupling. In a typical procedure, a suspension of $Pd(OAc)_2$ (0.03 mmol) and NHC precursor (**i**) (0.06 mmol) was dissolved in DCM (2 ml). Then, the indicated amount of the above dichloromethane solution was added to a mixture of aryl iodides (1 mmol), phenyl acetylenes (1.2 mmol), pyrrolidine (3 mmol) and DCM (5 ml). Then, the mixture was stirred at room temperature for 2 h to give desired internal alkyne 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 products (**10a–h**).

4-Methyldiphenylacetylene (10a). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.52 (s, 3H), 7.10–7.24 (m, 2H, Ar-H), 7.41–7.50 (m, 3H, Ar-H), 7.60–7.68 (m, 4H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 21.69, 88.90, 89.74, 114.2, 115.6, 123.8, 128.2, 128.5, 131.7, 133.3, 159.9 ppm. IR (KBr): = 3045, 2214, 2038, 1607, 1595, 1168, 1025, 834, 754, 694 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 193 [M + H]$^+$. EA calcd (%) for $C_{15}H_{12}$ (192.04): calcd. C 93.71, H 6.29; found C 93.65, H 6.26.

Butyl-4-methylphenylacetylene (10b). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.92 (t, 3H, *J* = 7.3 Hz), 1.28–1.62 (m, 4H), 2.24 (s, 3H), 2.42 (t, 2H, *J* = 6.9 Hz), 6.94 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.24 (d, 2H, *J* = 8.0 Hz, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.82, 19.26, 21.54, 22.19, 31.14, 82.80, 86.22, 120.71, 129.41, 131.94, 138.35 ppm. IR (KBr): = 3140, 3022, 2925, 2140, 1355, 1177, 830 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 173 [M + H]$^+$. EA calcd (%) for $C_{13}H_{16}$ (172.10): calcd. C 90.64, H 9.36; found C 90.32, H 9.26.

4-(4-Methylphenyl)-3-butyn-1-ol (10c). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.23 (s, 3H), 2.62 (t, 2H, *J* = 6.5 Hz), 2.68 (br s, 1H), 3.72 (t, 2H, *J* = 6.5 Hz), 6.95 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.20 (d, 2H, *J* = 8.0 Hz, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 21.82, 24.12, 61.50, 82.82, 86.24, 120.75, 129.44, 131.92, 138.30 ppm. IR (KBr): = 3416, 3046, 2925, 2140, 1355, 1177, 830 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 161 [M + H]$^+$. EA calcd (%) for $C_{11}H_{12}O$ (160.03): calcd. C 82.46, H 7.55; found C 82.44, H 7.54.

4-Methoxydiphenylacetylene (10d). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.82 (s, 3H), 6.88–6.90 (m, 2H, Ar-H), 7.35–7.42 (m, 3H, Ar-H), 7.55–7.62 (m, 4H, Ar-H) ppm. IR (KBr): = 3014, 2216, 2029, 1607, 1595, 1273, 1102, 834, 754, 691 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 209 [M + H]$^+$. EA calcd (%) for $C_{15}H_{12}O$ (208.10): calcd. C 86.51, H 5.81; found C 86.49, H 5.78.

Butyl-4-methoxyphenylacetylene (10e). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.92 (t, 3H, *J* = 7.3 Hz), 1.28–1.62 (m, 4H), 2.4 (t, 2H, *J* = 6.9 Hz), 3.82 (s, 3H), 6.92 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.24 (d, 2H, *J* = 8.0 Hz, Ar-H) ppm. IR (KBr): = 3140, 3022, 2925, 2140, 1355, 1170, 1050, 830 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 189 [M + H]$^+$. EA calcd (%) for $C_{13}H_{16}O$ (188.03): calcd. C 82.94, H 8.57; found C 82.92, H 8.46.

4-(4-Methoxyphenyl)-3-butyn-1-ol (10f). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.62 (t, 2H, *J* = 6.5 Hz), 2.74 (br s, 1H), 3.72 (t, 2H, *J* = 6.5 Hz), 3.82 (s, 3H), 6.92 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.24 (d, 2H, *J* = 8.0 Hz, Ar-H) ppm. IR (KBr): = 3416, 3046, 2925, 2140, 1355, 1170, 1050, 830 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 177 [M + H]$^+$. EA calcd (%) for $C_{11}H_{12}O_2$ (176.06): calcd. C 74.98, H 6.86; found C 74.96, H 6.84.

2-Nitrodiphenylacetylene (10g). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.28–7.34 (m, 3H, Ar-H), 7.55–7.61 (m, 3H, Ar-H), 7.74–7.82 (m, 2H, Ar-H) 8.24 (d, 1H, Ar-H) ppm. IR (KBr): = 3100, 3040, 2934, 2048, 1607, 1533, 1236, 1105, 831, 768, 735 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 224 [M + H]$^+$. EA calcd (%) for $C_{14}H_9NO_2$ (223.02): calcd. C 75.33, H 4.06, N 6.27; found C 75.31, H 4.04, N 6.24.

Butyl-2-nitrophenylacetylene (10h). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.92 (t, 3 H, *J* = 7.3 Hz), 1.58–1.64 (m, 4H), 2.42 (t, 2 H, *J* = 6.9 Hz), 7.64–7.82 (m, 3H, Ar-H) 8.21 (d, 1H, Ar-H) ppm. IR (KBr): = 3040, 2934, 2150, 1607, 1533, 1345, 758 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 204 [M + H]$^+$. EA calcd (%) for $C_{12}H_{13}NO_2$ (203.06): calcd. C 70.92, H 6.45, N 6.89; found C 70.86, H 6.41, N 6.88.

General procedure for the synthesis of 3,4,5-trisubstituted isoxazoles. To internal alkynes (1 mmol) and NHC precursor (**i**) (5 mol%) in dry DCM (5 ml) under nitrogen atmosphere was added Et_3N (5 mol%). The mixture was stirred for 10 min. The

reaction mixture was cooled to 0–5 °C and added dropwise to a solution of benzonitrile oxide (1 mmol), generated *in situ* by the treatment of triethylamine (1.2 mmol) with the corresponding chlorooxime (1 mmol) in dry DCM (15 ml) over a period of 2 min while maintaining the temperature between 0–5 °C. The reaction mass was allowed to attain room temperature and stirring was continued for 30 min. After conversion was complete, the mixture was quenched by addition of saturated solution of NH_4Cl (2 ml) and diluting with dichloromethane (40 ml). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 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 (**11a–j**).

3-(4-Methoxyphenyl)-5-(4-methylphenyl)-4-phenylisoxazole (11a). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.32 (s, 3 H), 3.84 (s, 3H), 6.81–6.86 (m, 2H, Ar-H), 7.12–7.20 (m, 2H, Ar-H), 7.31–7.53 (m, 7H, Ar-H), 7.60–7.68 (m, 2H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 21.84, 54.16, 108.62, 115.23, 121.04, 126.24, 127.53, 127.62, 127.89, 129.42, 130.88, 137.26, 157.20, 159.24, 160.47 ppm. IR (KBr): = 3008, 2844, 1604, 1508, 1428, 1258, 1105, 1063, 942, 838, 742, 736, 684 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 364 [M + Na]$^+$. EA calcd (%) for $C_{23}H_{19}NO_2$ (341.14): calcd. C 80.92, H 5.61, N 4.10; found C 80.90, H 5.58, N 4.09.

5-(4-Methylphenyl)-3-(2-nitrophenyl)-4-phenylisoxazole (11b). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.32 (s, 3 H), 7.12–7.19 (m, 2H, Ar-H), 7.31–7.53 (m, 8H, Ar-H), 7.61–7.70 (m, 2H, Ar-H), 8.32 (m, 1 H, Ar-H) ppm. IR (KBr): = 3100, 3080, 2922, 1942, 1508, 1428, 1245, 1063, 932, 836, 786, 736, 680 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 379 [M + Na]$^+$. EA calcd (%) for $C_{22}H_{16}N_2O_3$ (356.12): calcd. C 74.15, H 4.53, N 7.86; found C 74.13, H 4.50, N 7.85.

3-(4-Fluorophenyl)-5-(4-methylphenyl)-4-phenylisoxazole (11c). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.32 (s, 3 H), 6.93–7.02 (m, 2H, Ar-H), 7.12–7.20 (m, 2H, Ar-H), 7.31–7.53 (m, 7H, Ar-H), 7.63–7.70 (m, 2H, Ar-H) ppm. IR (KBr): = 3008, 2854, 1602, 1508, 1428, 1245, 1063, 942, 838, 788, 736, 680 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 352 [M + Na]$^+$. EA calcd (%) for $C_{22}H_{16}FNO$ (329.10): calcd. C 80.23, H 4.90, N 4.25; found C 80.21, H 4.89, N 4.22.

4-Butyl-3,5-di(4-methylphenyl)isoxazole (11d). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.92 (t, 3H, *J* = 7.5 Hz), 1.41–1.63 (m, 4H), 2.42 (t, 2H, *J* = 7.2 Hz), 2.32 (s, 6H), 6.94–7.01 (m, 2H, Ar-H), 7.24–7.31 (m, 2H, Ar-H), 7.44–7.52 (m, 4H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.26, 21.34, 21.96, 25.22, 29.14, 31.22, 112.26, 125.43, 126.63, 127.42, 129.34, 130.04, 136.48, 139.48, 159.16, 161.34 ppm. IR (KBr): = 2932, 1638, 1527, 1428, 1245, 1258, 1184, 1126, 1063, 932, 902, 838, 786, 736 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 328 [M + Na]$^+$. EA calcd (%) for $C_{21}H_{23}NO$ (305.12): calcd. C 82.58, H 7.59, N 4.59; found C 82.56, H 7.58, N 4.55.

4-Butyl-3-(4-chlorophenyl)-5-(4-methylphenyl)isoxazole (11e). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.92 (t, 3H, *J* = 7.5 Hz), 1.41–1.63 (m, 4H), 2.42 (t, 2H, *J* = 7.2 Hz), 2.32 (s, 3H), 6.94–7.01 (m, 2H, Ar-H), 7.24–7.31 (m, 4H, Ar-H), 7.44–7.52 (m, 2H, Ar-H) ppm. IR (KBr): = 2938, 1642, 1527, 1428, 1245, 1258, 1176, 1126, 1062, 934, 902, 838, 788, 736 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 348 [M + Na]$^+$. EA calcd (%) for $C_{20}H_{20}ClNO$ (325.08): calcd. C 73.72, H 6.19, N 4.30; found C 73.70, H 6.16, N 4.28.

2-(3-(4-Methoxyphenyl)-5-(4-methylphenyl)-4-isoxazolyl)-1-ethanol (11f). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.32 (s, 3H), 2.52 (t, 2H, *J* = 6.9 Hz), 3.84 (s, 3H), 3.91 (t, 2H, *J* = 6.9 Hz), 4.25 (s, 1H), 6.92–7.01 (m, 2H, Ar-H), 7.28–7.32 (m, 2H, Ar-H), 7.44–7.52 (m, 4H, Ar-H) ppm. ^{13}C NMR (100 MHz, CDCl3, 25 °C): δ = 21.52, 24.22, 56.20, 64.08, 110.82, 115.63, 121.53, 127.41, 128.32, 129.25, 129.96, 138.47, 161.84, 162.28, 165.04 ppm. IR (KBr): = 3422, 2934, 1612, 1527, 1441, 1298, 1258, 1176, 1116, 1062, 948, 902, 838, 788, 736 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 332 [M + Na]$^+$. EA calcd (%) for $C_{19}H_{19}NO_3$ (309.07): calcd. C 73.77, H 6.19, N 4.53; found C 73.75, H 6.14, N 4.49.

2-(3,5-di(4-Methylphenyl)-4-isoxazolyl)-1-ethanol (11g). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.32 (s, 6H), 2.52 (t, 2H, *J* = 6.9 Hz), 3.91 (t, 2H, *J* = 6.9 Hz), 4.25 (s, 1H), 6.92–7.01 (m, 2H, Ar-H), 7.28–7.32 (m, 2H, Ar-H), 7.44–7.52 (m, 4H, Ar-H) ppm. IR (KBr): = 3428, 2934, 1612, 1527, 1441, 1276, 1241, 1176, 1116, 1062, 948, 902, 838, 788, 736 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 316 [M + Na]$^+$. EA calcd (%) for $C_{19}H_{19}NO_2$ (293.10): calcd. C 77.79, H 6.53, N 4.77; found C 77.78, H 6.50, N 4.76.

3,5-di(4-Methoxyphenyl)-4-phenylisoxazole (11h). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.85 (s, 6H), 6.84–6.92 (m, 4H, Ar-H), 7.46–7.58 (m, 7H, Ar-H), 7.64–7.72 (m, 2H, Ar-H) ppm. IR (KBr): = 3005, 2942, 2826, 1614, 1508, 1428, 1275, 1107, 1084, 942, 838, 742, 734, 680 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 380 [M + Na]$^+$. EA calcd (%) for $C_{23}H_{19}NO_3$ (357.10): calcd. C 77.29, H 5.36, N 3.92; found C 77.28, H 5.33, N 3.90.

5-(4-Methoxyphenyl)-3-(4-methylphenyl)-4-phenylisoxazole (11i). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.34 (s, 3 H), 3.85 (s, 3H), 6.81–6.86 (m, 2H, Ar-H), 7.12–7.20 (m, 2H, Ar-H), 7.31–7.53 (m, 7H, Ar-H), 7.65–7.70 (m, 2H, Ar-H) ppm. IR (KBr): = 3005, 2942, 1614, 1508, 1428, 1275, 1107, 1084, 942, 838, 742, 734, 680 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 364 [M + Na]$^+$. EA calcd (%) for $C_{23}H_{19}NO_2$ (341.02): calcd. C 80.92, H 5.61, N 4.10; found C 80.90, H 5.60, N 4.09.

5-(4-Methoxyphenyl)-3-(2-nitrophenyl)-4-phenylisoxazole (11j). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.85 (s, 3H), 7.12–7.20 (m, 2H, Ar-H), 7.31–7.53 (m, 8H, Ar-H), 7.64–7.70 (m, 2H, Ar-H), 8.32 (m, 1H, Ar-H) ppm. IR (KBr): = 3100, 3045, 2904, 1613, 1508, 1428, 1275, 1063, 932, 838, 786, 736, 680 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 395 [M + Na]$^+$. EA calcd (%) for $C_{22}H_{16}N_2O_4$ (372.02): calcd. C 70.96, H 4.33, N 7.52; found C 70.94, H 4.32, N 7.51.

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