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An Abnormal N-Heterocyclic Carbene–Copper(I) Complex in Click Chemistry

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Dedicated to Prof. K. N. Ganesh on the occasion of his 60th birthday.

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Abstract: Herein we report the synthesis of a copper(I) chloro complex using an abnormal N-heterocyclic carbene (*a*NHC) salt, 1,3-bis(2,6-diisopropylphenyl)-2,4-diphenylimidazolium. The CuCl(*a*NHC) complex efficiently catalyzed Huisgen 1,3-dipolar cycloaddition reactions (click reactions) of azides with alkynes to give 1,4-substituted 1,2,3-triazoles in excellent yields at room temperature within short reaction time under solvent-free conditions. The catalyst successfully activated benzyl azide and phenylacetylene under the low catalyst loading of 0.005 mol% resulting in a nearly quantitative yield of the product

Introduction

The isolation of normal N-heterocyclic carbenes (nNHCs) by Arduengo and co-workers^[1] more than two decades ago has led to numerous exciting discoveries in organometallic chemistry. The N-heterocyclic carbenes also have been used as nucleophiles for organocatalytic reactions efficiently catalyzing a number of organic transformations.^[2] The normal NHCs bind to the metal centre through the C-2 carbon atom (see

at room temperature with the high TON value of 19,800. The catalyst also exhibits high efficiency in the reaction between sterically hindered azides and alkynes under solvent-free conditions at room temperature. Furthermore, a number of internal alkynes was successfully tested in this copper-catalyzed cyclo-addition reaction for synthesis of 4,5-disubstituted triazoles.

Keywords: abnormal carbene; click reaction; copper(I) complex; internal alkynes; sterically hindered azides and alkynes

Scheme 1 for numbering). In 2001, Crabtree, Faller and co-workers first reported a new mode of NHC binding to a metal ion termed as the abnormal mode of metal binding of NHC through the C-4 centre on treatment of 2-pyridylmethylimidazolium salt with $IrH_5(PPh_3)_2$.^[3] It is now well established that the abnormal N-heterocyclic carbenes have excellent potential towards different catalytic reactions.^[4,5] However, the isolated abnormal carbenes have long been considered as transient species till the report by Bertrand



Scheme 1. Synthetic scheme leading to abnormal N-heterocyclic carbene copper(I) complex 1.

2982 Wiley Online Library

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and co-workers in 2009 when for the first time an abnormal N-heterocyclic carbene (aNHC) was isolated by chemically blocking the C-2 position and the isolated abnormal NHC was characterized by single crystal X-ray diffraction.^[6] This particular report led to the anticipation that the access to this type of abnormal NHC would lead to new cornerstones in the field of organometallic and organocatalysis.^[7] Metal coordinated aNHCs had earlier documented excellent potential to be utilized as catalysts, resulting the activation of unreactive bonds such as C-H, H-H and, in some cases, the aNHC coordinated metal complexes have outperformed the catalytic activity as compared to their normal NHC counterparts (nNHC).^[8] In this regard, earlier we had shown that the abnormal Nheterocyclic carbene [1,3-bis(2,6-diisopropylphenyl)-2,4-diphenyl-5-ylidene] can be used very efficiently in metal-free ring-opening polymerization of three different cyclic esters leading to the development of the best organocatalyst in terms of activity for ring-opening polymerization catalysis among any NHCs.^[2c] Recently, we have used the same aNHC to synthesize halobridged C-H activated palladium dimers for Suzuki-Miyaura cross-couplings of challenging aryl chloride substrates delivering excellent yields at room temperature under a very low-catalyst loading (0.005 mol%).^[5] Now with the present study, we report the synthesis and characterization of an aNHC coordinated copper(I) chloro complex 1 using 1,3bis(2,6-diisopropylphenyl)-2,4-diphenyl-imidazolium salt IA. Ther copmplex I is capable of transforming a range of versatile click reaction, also known as Huisgen 1,3-dipolar cycloadditions, under solvent-free condition. The Huisgen 1,3-dipolar cycloaddition^[9,10] originally introduced by Sharpless and co-workers in 2001,^[11] has been popularized as "click" reaction^[12] and very often applied to chemical synthesis, biology, and material sciences.^[13] The preparation of cyclic compounds from the click reaction and their application as ligands for transition metal chemistry have been reported by various research groups.^[14] However, the activation of sterically hindered azides and alkynes in click reactions has been limited under solvent-free conditions, which usually require elevated temperatures.^[12e] On the other hand, the synthesis of 4,5-disubstituted triazoles can be achieved by using internal alkyne substrates which usually require long time and thermal activation.^[12c,15-18] Thus the activation of sterically hindered azides and alkynes as well as the activation of internal alkynes through click reactions at room temperature under solvent-free conditions within short reaction times has remained among the great challenges in this area. In the present study, the catalyst 1 yielded the Huisgen 1,3-dipolar cycloaddition product, 1,4-substituted 1,2,3-triazoles in excellent yields at room temperature within very short reaction times. The catalysis went smoothly without requiring the use of any external hazardous organic solvent. The catalyst remained active in 10 successive catalytic cycles towards aliphatic as well as aromatic azide substrates. Furthermore, the catalyst successfully catalyzed the reaction between sterically hindered azides and alkynes at room temperature under solvent-free conditions. The synthesis of 4,5-disubstituted triazoles was also achieved by activating different internal alkynes using catalyst **1** within short reaction times.

Results and Discussion

The imidazolium salt, IA (Scheme 1) was employed for the current study as an aNHC precursor to prepare the copper complex. Complex 1 was prepared by treatment of the aNHC salt (IA) with potassium bis-(trimethylsilyl)amide and copper(I) chloride in THF. During the reaction, the colour of the reaction mixture changes from colourless to green. Analytically pure compound of 1 was obtained by recrystallization of the dried reaction mixture from a dichloromethane (DCM)/pentane mixture yielding light green coloured crystals of 1 in nearly 70% yield. The complex 1 was characterized by NMR spectroscopy, X-ray crystallography, and elemental analysis. The ¹H NMR spectrum of 1 featured the absence of the characteristic singlet at $\delta = 8.8$ ppm arising from C-5(H) of imidazolium salt, IA confirming the abnormal mode of copper binding. The ¹³C NMR spectrum revealed a singlet peak at $\delta = 159.4$ ppm assigned to the C-5 carbon resonance bound to the copper centre. This NMR chemical shift value is comparable to that reported with a copper carbene complex CuCl(TPh) (TPh=3methyl-1,4-diphenyl-1,2,3-triazol-5-ylidene) where a metal-bound carbon carbon appeared around $\delta =$ 161.3 ppm in the ¹³C NMR spectrum.^[12e] Finally, the molecular structure determined by the X-ray crystallographic study (see Figure 1) confirmed the atom connectivity of 1 as depicted in Scheme 1. Compound **1** crystallizes in the triclinic space group $P\overline{1}$. The geometry around the copper ion is linear exhibiting the abnormal mode of NHC binding in 1. The Cu-C and the Cu–Cl bond lengths were found to be 1.882(2) Å and 2.1031(10) Å, respectively. These values compare well with those observed [1.881(7) Å and 2.106(2) Å,for Cu–C and Cu–Cl, respectively] in a related NHC copper(I) complex, CuCl(IPr) [IPr=1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene].^[19] The C-Cu-Cl bond angle was determined as 173.65(6)° indicating a nearly linear geometry around the Cu(I) centre in complex 1. As a part of our ongoing interest to develop aNHC based homogeneous catalyst for different organic transformations,^[2c,5] we first evaluated the catalytic activity of aNHC copper(I) complex 1 for the click reaction of benzyl azide with phenylacetylene



Figure 1. Perspective ORTEP view of the molecular structure of **1**. Thermal ellipsoids are drawn with 50% probability. Hydrogen atoms and lattice held solvent molecule (dichloromethane) have been omitted for the sake of clarity. Selected bond lengths (in Å) and bond angles (°) for **1**: Cu1–C5, 1.882(2); Cu1–Cl1, 2.1031(10); C5–Cu1–Cl1, 173.65(6); N1–C5–Cu1, 128.31(14); C4–C5–Cu1, 127.05(15).

without adding any solvent. The reaction went on smoothly leading to quantitative conversion into product **4a** (Figure 2). The progress of the reaction



Figure 2. Plot of conversion [%] versus time (min) in the coupling of phenylacetylene (1.73 mmol) with benzyl azide (1.57 mmol) at 25 °C using catalyst **1** (1 mol%).

was monitored by ¹H NMR spectroscopy which reveals that within first 15 min, the reaction reaches to completion (Figure 2).

As a control experiment, we also carried out the catalytic reaction maintaining identical reaction conditions using CuCl as catalyst (loading 1 mol%) under solvent-free conditions with benzyl azide and phenylacetylene as substrates. Even after 60 min, CuCl produced only a trace amount of 4a (less than 5%), an observation also noted in earlier studies.^[12e,g] Furthermore, we investigated the scope of the reaction by carrying out reactions of benzyl azide and 4-bromobenzyl azide with a variety of alkynes using 1 mol% of **1** as catalyst under solvent-free conditions and the results of the catalytic reactions are summarized in Table 1. The reactions were carried out at room temperature in the absence of any solvent with a catalyst loading of 1.0 mol%. Also a few representative substrates were cyclized using the low catalyst loading of 0.1 mol% resulting in nearly quantitative yields under solvent-free conditions which led to the products 4a (60 min, 99%), **40** (3 h, 91%) and **4s** (7 h, 90%) requiring longer times as compared with the 1 mol% catalyst loading conditions. During the catalysis under solvent free condition, the initial liquid reaction mixture solidifies after the consumption of substrates (see the Supporting Information, video clips). Analytically pure product was isolated as a solid material after initial work-up with dichloromethane/water. The results presented in Table 1 establish that the catalyst 1 is very active in the click reaction. It successfully works for both electron-rich as well as electron-poor alkynes. Also the catalyst has sufficient functional group tolerance as indicated in the case of products (4c, 4d, 4g, 4h, 4o, 4r, 4s, 4t, 4u, 4x, 4y, 4z, 4aa, 4ab, 4ac and 4ae; Table 1). Cycloadditions with phenylacetylene as well as with electron-deficient fluoro-substituted phenylacetylene proceeded smoothly to give the corresponding 1,2,3-triazoles in almost quantitative yield in a short period of time (4a, 4d, 4e, and 4h; Table 1 within 30 min). The reactions are comparatively slow (reaction completion time 45 min to 2 h) for electron-rich alkynes such as alkyl-substituted alkynes, and trimethylsilylacetylene (4i, 4j, 4k, 4l, 4m, 4n, 4o, 4p, 4v and 4w; Table 1). Functional groups such as hydroxy, amine, amide, ester, acid and different halides were tolerated (4r, 4s, 4t, 4, 4x, 4y, 4z, 4aa, 4ab, 4ac and 4ae; Table 1), during the reaction requiring relatively longer reaction times (2-5 h). Our catalyst also survives 2-ethynylpyridine in the reaction medium to afford the corresponding triazole product (4ad, Table 1) after 3 h at room temperature. We then investigated the scope of this catalytic system to activate electron-rich as well as electron-poor alkynes in the presence of aryl azides instead of aliphatic azides. Results are presented in Table 2. All reactions proceeded smoothly to completion within short reaction

	R ¹	+ R ² cataly	$r^2 \longrightarrow R^2$		
	2	no so 3	olvent, 25 °C	4 N N	
Entry	Azide	Alkyne	Product	Time	Yield ^[b] [%]
	R ¹	R ²			
1	$\mathbf{R}^1 - \mathbf{H}$	$\mathbf{R}^2 - \mathbf{H}$	49	20 min	00
2	$\mathbf{R}^{1} - \mathbf{H}$	R = H $R^2 - Me$	-7a 4b	20 min	08
2	$\mathbf{R}^{-\mathbf{H}}$	$R^2 = OMe$	40 4c	20 min	98
4	$\mathbf{R}^{-\mathbf{H}}$	$R^2 - F$	4C 4d	5 min	98
5	$\mathbf{R}^{1}-\mathbf{Br}$	R = I $R^2 - H$	4u 4e	30 min	98
6	$\mathbf{R}^{1}-\mathbf{Br}$	$R^2 - Me$	40 4f	40 min	97
7	$R^{1}=Br$	$R^2 = OMe$	41 40	30 min	98
8	$\mathbf{R}^{1} = \mathbf{B}\mathbf{r}$	$R^2 = F$	46 4h	10 min	98
0	K – Di		711	10 11111	20
9	$R^1 = H$	n=2	4 i	45 min	98
10	$R^1 = H$	n=4	4i	45 min	98
11	$R^1 = H$	n=6	-j 4k	45 min	98
12	$R^1 = Br$	n = 2	41	10 mm	98
13	$R^1 = Br$	n=4	4m	1 h	98
14	$R^1 = Br$	n=6	4n	1 h	98
		×			
15	$\mathbf{R}^1 - \mathbf{H}$	X-Si	40	45 min	97
15	$\mathbf{R}^{-\mathbf{H}}$	X = SI X = C	40 4n		97
10	$\mathbf{R}^{1} = \mathbf{B}\mathbf{r}$	X = C X = C	4p 4a	2 h 3 h	96
17	K – Di	OH	тү	5 11	20
		R ³			
18	$R^1 = H$	$R^3 = H$	4 r	2 h	96
19	$R^1 = H$	$R^3 = Me$	4 s	2 h	96
20	$\mathbf{R}^{1} = \mathbf{B}\mathbf{r}$	$R^3 = H$	4t	3 h	96
21	$\mathbf{R}^1 = \mathbf{B}\mathbf{r}$	$R^3 = Me$	4 u	3 h	96
22	$R^1 = H$	~	4v	45 min	99
23	$R^1 = Br$		4w	1 h	97
20		\mathbb{R}^3			
24	$\mathbf{R}^1 = \mathbf{H}$	$R^3 = Cl$	4 x	5 h	75 ^[c]
25	$R^1 = H$	$R^3 = Br$	4y	5 h	73 ^[c]
26	$\mathbf{R}^{1} = \mathbf{H}$	$R^3 = NH_2$	4z	4 h	98 ^[d]
		O L			
		R ³			
27	$R^1 = H$	$R^3 = NH_2$	4 aa	2 h	93

Table 1. Solvent-free route to triazoles by click chemistry using 1 as catalyst and aliphatic azide as substrate.^[a]

times and the triazoles **6a–61** were isolated in excellent yield with high purity after simple work-up with dichloromethane/water (see Experimental Section). Table 2 showcases that in the presence of catalyst **1**, phenyl azides react and yield the triazole products (**6a**, **6b**, **6i** and **6j**; Table 2) in very short reaction times. The reactions are comparatively slow for sterically crowded azides such as 2,6-dimethylazide (6c, 6d, 6e and 6k; Table 2) and mesityl azide (6f, 6g, 6h and 6l; Table 2) substrates. Encouraged by these results, we attempted reactions of sterically hindered alkynes with sterically hindered azides using catalyst 1. The results are shown in Scheme 2. Generally for such challenging sterically hindered substrates, one

Table 1. (Continued)

Entry	Azide	Alkyne	Product	Time	Yield ^[b] [%]
28 29	$ \begin{array}{c} \mathbf{R}^1 \!=\! \mathbf{H} \\ \mathbf{R}^1 \!=\! \mathbf{H} \end{array} $	$R^3 = OMe$ $R^3 = OH$	4ab 4ac	15 min 15 min	97 83
		N =			
30	$R^1 = H$	<u></u> −− <u></u> {NH ₂	4ad	3 h	96
31	$\mathbf{R}^1 \!=\! \mathbf{H}$		4ae	5 h	93 ^[c]

^[a] Reaction conditions: azide (1.57 mmol), alkyne (1.73 mmol), catalyst 1 (1.0 mol%), 25 °C.

^[b] Isolated yield after initial work-up with dichloromethane/water.

^[c] Reaction temperature was 70 °C.

^[d] Reaction was carried out in presence of water at 25 °C for 4 h. The resulting compound precipitates from water and the compound was dissolved in mixture of cold (0 °C) ethanol and few drops of concentrated HCl (12M) to isolate **4z**·HCl.

needs *t*-BuOH/water and a stoichiometric amount of $CuSO_4$ /sodium ascorbate to prepare the triazole **9a** by the reaction of mesitylacetylene with mesityl azide employing Sharpless conditions.^[11]

In the present study, the reaction using 1 mol% of **1** as catalyst took 5 h at room temperature under solvent-free conditions to yield **9a** in 95% yield, and 24 h at room temperature under solvent-free conditions to

yield **9b** in 78% yield. The high activity of catalyst **1** in the Huisgen cycloaddition prompted us to test its reactivity with more challenging internal alkyne substrates.

Although several copper catalysts are being used regularly to carry out click reactions using the terminal alkynes but only few studies have been reported for the activation of internal alkynes leading to the

D2

Table 2. Solvent-free route to triazoles by click chemistry using 1 as catalyst and aryl azide as substrate.^[a]

	$R^1 \longrightarrow N_3 + R^2 \longrightarrow \frac{\text{catalyst 1 (1 mol\%)}}{\text{no solvent, 25 °C}} \qquad R^3 \longrightarrow N_N^{\prime} N$					
	5 ^{R°}	3		6		
Entry	Azide	Alkyne	Product	Time	Yield ^[b] [%]	
	R^3 R^1 R^1 R^2	R4				
1 2	$R^{1} = R^{2} = R^{3} = H$ $R^{1} = R^{2} = R^{3} = H$	$R^4 = H$ $R^4 = Me$	6a 6b	10 min 15 min	98 98	
3	$R^1 = R^2 = Me, R^3 = H$	$R^4 = H$	6c	6 h	94	
4	$R^1 = R^2 = Me, R^3 = H$	$R^4 = Me$	6d	7 h	95	
5	$R^1 = R^2 = Me, R^3 = H$	$R^4 = F$	6e	7 h	93	
6	$\mathbf{R}^1 = \mathbf{R}^2 = \mathbf{R}^3 = \mathbf{M}\mathbf{e}$	$R^4 = H$	6f	5 h	95	
7	$R^1 = R^2 = R^3 = Me$	$R^4 = Me$	6g	6 h	91	
8	$R^1 = R^2 = R^3 = Me$	$R^4 = F$	6ĥ	6 h	92	
9	$R^1 = R^2 = R^3 = H$	OH	6i	1 h	95	
10	\mathbf{P}^1 \mathbf{P}^2 \mathbf{P}^3 \mathbf{H}	<i>"</i> /	6	1 h	04	
10	$\mathbf{K} = \mathbf{K} = \mathbf{K} = \mathbf{\Pi}$ $\mathbf{P}^1 - \mathbf{P}^2 - \mathbf{M}_{\mathbf{P}} \mathbf{P}^3 - \mathbf{U}$		uj 61z	1 II 0 h	9 4 01	
12	R = R = MC, R = R $R^{1} - R^{2} - R^{3} - Me$		UK 61	911 8 h	91 02	
12	$\mathbf{X} = \mathbf{X} = \mathbf{X} = \mathbf{W}\mathbf{U}$		UI UI	0 11	14	

^[a] Reaction conditions: azide (1.57 mmol), alkyne (1.73 mmol), catalyst 1 (1.0 mol%), 25 °C.

^[b] Isolated yield after initial work-up with dichloromethane/water.



Scheme 2. Reaction of sterically hindered alkynes with sterically hindered azides to form triazoles in the presence of 1 as a catalyst. *Reaction conditions:* azide (1.57 mmol), alkyne (1.73 mmol), catalyst 1 (1.0 mol%), 25 °C.

4,5-substituted triazole.^[12c,15-18] In a preliminary experiment, we noticed that the treatment of dimethyl acetylenedicarboxylate or diethyl acetylenedicarboxylate with phenyl or benzyl azide in the presence of 1 mol% catalyst 1 yields the corresponding triazole (12a, 12b, and 12c, Scheme 3) in good yield within short reaction times under solvent-free conditions at room temperature. We next carried out the reaction using less activated alkyne substrates (diphenylacetylene, 3-hexyne, 1-phenyl-1-butyne) with 1 mol% of 1 as catalyst. The triazoles (12d, 12e, and 12f, Scheme 3) were formed in fair to good yields after heating at 70°C. The reaction using diphenylacetylene was complete within 5 h but for other two internal alkyne substrates, we needed 24 h to obtain good yields. In the case of unsymmetrical internal alkynes, we obtained a mixture of two isomers in 2:1 ratio (**12g** and **12g'** as well as **12h** and **12h'**).

We observed no decomposition of the catalysts or precipitation of metallic copper during all the reactions using 1 as catalyst. The stability of the catalytically active species was subjected to further investigation by performing the *in situ* recycling experiments. One of the major problems in homogeneous catalysis is the inability for recycling the catalysts as they are inseparable from the reaction mixture. Earlier attempts by Fukuzawa, Li, Sarkar and co-workers have shown that the activity of copper(I) NHC catalysts in click reactions gradually decreases as the number of catalytic cycles increases and beyond six cycles the catalysts were not tested.^[12d-f] Herein, we checked the longevity of the catalyst 1 by performing several catalytic runs into the same reaction pot to check whether the catalyst remains live^[5,20] for several catalytic cycles. We performed 10 successive catalytic runs by using 1 mol% of catalyst loading and two different sets of substrates such as benzyl azide and phenylacetylene as well as phenyl azide and phenylacetylene. The catalytic reaction was continued for 10 successive

catalytic cycles without adding any extra catalysts (see Experimental Section), however, after each catalytic cycle, a fresh batch of substrates was added. The result of this experiment indicated a sustained activity of catalyst **1** for 10 successive cycles (see the Supporting Information for details). Furthermore, we have



Scheme 3. Reaction of azides with internal alkynes to form 4,5-disubstituted triazoles in the presence of **1** as catalyst. *Reaction conditions:* azide (1.57 mmol), alkyne (1.73 mmol), catalyst **1** (1.0 mol%).

2987

performed the kinetic experiments using benzyl azide and phenylacetylene substrates for each of the 10 successive catalytic cycles. From this measurement, it can be observed that 20 min is enough to obtain quantitative conversion of the substrates into the product for the first six catalytic cycles, however, for the 7th-10th catalytic cycles, the reaction becomes slow requiring 40 min to obtain similar conversion (see the Supporting Information). This result also encouraged us to check the longevity of the catalyst in the case of click reactions between sterically hindered alkynes with sterically hindered azides. We performed 5 successive catalytic runs by using 1 mol% of catalyst 1 to activate mesitylacetylene and mesityl azide under solvent-free conditions at room temperature. The result demonstrates that the catalyst 1 stays active for 5 catalytic cycles towards cyclization of mesitylacetylene and mesityl azide (see the Supporting information). This sustained catalytic activity in consecutive catalytic runs prompted us to check the catalyst's ability to execute the click reaction under lower catalyst loading. The lower catalyst loading test was performed using benzyl azide and phenylacetylene as substrates under solvent-free conditions at room temperature (Table 3). The result in Table 3 indicates that the catalyst 1 is active for coupling of benzyl azide and phenylacetylene with a catalyst loading as low as 0.005 mol% resulting in a nearly quantitative yield of the product at room temperature which leads to a high TON value of 19,800 (Table 3). Also we have been able to scale-up the reaction at room temperature as well as at 0°C. The reaction was carried out using 50 mg (0.078 mmol) of catalyst 1, phenylacetylene (1.2 mL, 10.73 mmol), and benzyl azide (1.3 mL, 9.76 mmol) at 0 °C under solvent-free conditions which required a longer time (3 h) as compared to that required (20 min) for the similar scale reaction at room temperature.

Table 3. Click reactions of benzyl azide and phenylacetylene using catalyst 1 at different loadings.^[a]

2a	N ₃ + Ph────	catalyst 1		Ph N_N N 1a
Entry	Catalyst [mol%]	Time [min]	Yield ^[b] [%]	TON
1	0.50	30	99	198
2	0.25	45	99	396
3	0.10	60	99	990
4	0.01	180	99	9900
5	0.005	240	99	19800

^[a] *Reaction conditions:* azide (1.57 mmol), alkyne (1.73 mmol), catalyst **1** (1.0 mol%), 25 °C.

^[b] Isolated yield after initial work-up with dichloromethane/ water.

To compare the activity of the present catalyst with those reported in literature, it may be noted that there have been few reports of copper catalysts to tolerate a variety of functional groups.^[10e,12i-m] The catalytic results presented by catalyst 1 (Table 1, Table 2, Scheme 2, and Scheme 3), we can conclude that the present catalyst is a versatile one which can survive a range of functional groups and can activate sterically hindered substrates as well as it can activate internal alkynes. For example, Fukuzawa and co-workers have demonstrated that the catalytic reaction using 3 mol% copper(I) 1,2,3-triazol-5-ylidene complex gave 9a in 71% yield within 30 min at 100°C under neat conditions and yielded 9b in 63% yield in 18 h at 100 °C under solvent-free conditions.^[12e] In the present study, the reaction using only $1 \mod 1$ as catalyst took 5 h at room temperature under solvent-free conditions to afford 9a in 95% yield, and 24 h at room temperature under solvent-free condition to afford 9b in 78% yield, respectively. This result clearly supports that the present catalyst is more active than earlier reported^[12e,n,o] catalysts in cyclizing the sterically hindered challenging substrates at ambient temperature. Furthermore, Nolan and co-workers have earlier shown that the reaction using 5 mol% [(SIMes)CuBr] [SIMes = N, N'-bis(2, 4, 6-trimethylphenyl)-4, 5-dihydroimidazol-2-vlidene] catalyst for 48 h at 70°C under neat conditions gave 12e in 80% yield.^[12c] In the present study, we used a lower loading of catalyst 1 (1 mol%) to obtain a similar yield of 12e (80%) at 70°C under solvent-free conditions in a faster way (in 24 h).

Conclusions

In summary, we have developed a versatile and highly efficient catalytic system bearing the abnormal N-heterocyclic carbene for the Huisgen 1,3-dipolar cycloaddition of azides and alkynes at room temperature. This catalysis can be performed under solvent-free conditions to get a variety of pure triazoles in good to excellent yields within short reaction times. Electronrich, electron-deficient and different functionalized alkynes and aliphatic as well as aromatic azides were successfully used by this catalytic protocol resulting in nearly quantitative yield. The catalyst exhibits its activity at very low catalyst loadings of up to 0.005 mol% at room temperature resulting in a high TON value of 19,800. The catalyst can successfully catalyze the reaction between sterically hindered azides and sterically hindered alkynes under solventfree conditions at ambient temperature. Furthermore, the catalyst exhibits efficacy for the more challenging internal alkyne substrates demonstrating its utility in click chemistry for versatile substrates.

Experimental Section

Experimental Materials and Instrumentation

All manipulations were performed under a dry and oxygenfree atmosphere (argon) using standard Schlenk techniques or inside a glovebox maintained at below 0.1 ppm of O₂ and H₂O levels, utilizing oven-dried (130°C) glassware after evacuation while hot prior to use. All solvents were distilled from Na/benzophenone prior to use. All other chemicals were purchased from Sigma-Aldrich and used as received. The HR-MS data were obtained using a Q-Tof Micromass, Waters instrument. Elemental analyses were performed in a Perkin-Elmer 2400, Series II, CHNS/O analyser. The melting point was measured in a sealed glass tube on a Büchi B-540 melting point apparatus. Analytical TLC was performed on a Merck 60 F254 silica gel plate (0.25 mm thickness). NMR spectra were recorded on a JEOL ECS 400 MHz spectrometer and on a Bruker Avance III 500 MHz spectrometer. All chemical shifts were reported in ppm using tetramethylsilane as a reference. Chemical shifts (δ) downfield from the reference standard were assigned positive values. Abnormal N-heterocyclic carbene salt 1,3bis(2,6-diisopropylphenyl)-2,4-diphenyl-imidazolium salt (IA, Scheme 1) was prepared starting from N,N'-bis(2,6- diisopropylphenyl)benzamidine^[21] following a modified literature protocol^[6] Benzyl azide, 4-bromobenzyl azide, phenyl azide, 2,6-dimethylphenyl azide, mesityl azide, 2,6-diisopropylphenyl azide, 1-ethynyl-2,6- diisopropylbenzene and mesitylacetylene were prepared according to literature procedures.[12n,14c,22]

Synthesis of Complex 1

Under an argon atmosphere, THF (10 mL) was added at -78°C to a mixture of 1,3-bis(2,6-diisopropylphenyl)-2,4-diphenylimidazolium salt IA (308 mg, 0.50 mmol), copper(I) chloride (50 mg, 0.5 mmol) and potassium bis(trimethylsilyl)amide (200 mg, 1 mmol). After 30 min at ~ -78 °C, the mixture was warmed to room temperature and stirred for 12 h. Solvent was evaporated under reduced pressure and the residue was extracted with dichloromethane $(3 \times 20 \text{ mL})$. The analytically pure light green title compound was obtained by recrystallization from CH₂Cl₂/pentane. yield: 224 mg (0.35 mmol, 70%); mp 231–233 °C. ¹H NMR (500 MHz, $CDCl_{3}$, 25 °C, TMS): $\delta = 7.49-7.40$ (m, 4 H), 7.21– 7.18 (m, 8H), 7.05 (t, J = 8 Hz, 2H), 6.85 (d, J = 7.5 Hz, 2H), 2.68–2.63 (m, 2H), 2.58–2.54 (m, 2H), 1.41 (d, J=7 Hz, 6H), 0.95 (d, J=7 Hz, 6H), 0.80 (t, J=6.8 Hz, 12H); ¹³C NMR (125 MHz, 25 °C, TMS): $\delta = 159.4$, 144.9, 144.5, 144.4, 141.6, 135.7, 131.1, 130.9, 130.5, 130.4, 130.3, 129.4, 129, 128.2, 128.1, 127.9, 125.2, 124.5, 123.5, 28.8, 28.6, 25.8, 23.7, 23.4, 22.5; HR-MS: m/z = 639.256, calcd. for $C_{39}H_{45}ClCuN_2$ [M+H]⁺: 639.258; elemental analysis: calcd. for C₃₉H₄₄ClCuN₂: C 73.22, H 6.93, N 4.38; found: C 72.80, H 6.88, N 4.17.

X-ray Crystallographic Details

The single-crystal X-ray diffraction data of the crystal were collected on a Bruker Kappa APEX-II CCD DUO diffractometer at 100(2) K using graphite-monochromated Mo K α radiation (λ =0.71073 Å). Multiscan absorption correction

was applied. The lattice parameters were determined from least-squares analysis, and reflection data were integrated using the program SHELXTL.^[23] The crystal structure was solved by direct method using SHELXS-97 and refined by full-matrix least-squares refinement on F^2 with anisotropic displacement parameters for non-H atoms using SHELXL-97.^[24] CCDC 881468 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif (see also the Supporting Information).

General Procedure for the [3+2] Cycloaddition of Azides and Terminal Alkynes

Alkyne (1.73 mmol), azide (1.57 mmol), and catalyst **1** (10 mg, 1 mol%) were loaded in a 25-mL Schlenk flask. The reaction mixture was stirred at room temperature. After an appropriate period of time, the reaction was quenched by dissolving the reaction mixture in dichloromethane (10 mL). Subsequently, a simple aqueous work-up was carried out by adding 10 mL of water, and the organic layer was extracted with dichloromethane. The water layer was washed twice by adding two 5 mL portions of dichloromethane. The white solid was dried under high vacuum for 12 h which evaporated the excess volatile alkyne substrate yielding NMR pure isolated product. In case of non-volatile alkyne substrates, the excess alkynes were removed by column chromatographic separation. All reported yields are isolated yields and are average of at least two runs.

General Procedure for the [3+2] Cycloaddition of Sterically Hindered Azides and Sterically Hindered Alkynes

Alkyne (1.73 mmol), azide (1.57 mmol), and catalyst **1** (10 mg, 1 mol%) were loaded in a 25-mL Schlenk flask. The reaction mixture was stirred at room temperature. After an appropriate period of time, the reaction was quenched by dissolving the reaction mixture in dichloromethane (10 mL). Subsequently, a simple aqueous work-up was carried out by adding 10 mL of water, and the organic layer was extracted with dichloromethane. The water layer was washed twice by adding two 5 mL portions of dichloromethane. The crude product was purified by flash chromatography on silica gel yielding NMR pure isolated product. All reported yields are isolated yields and are average of at least two runs.

General Procedure for the [3+2] Cycloaddition of Azides and Internal Alkynes

Alkyne (1.73 mmol), azide (1.57 mmol), and catalyst 1 (10 mg, 1 mol%) were loaded in a 25-mL Schlenk flask. The reaction was allowed to proceed at room temperature or at 70 °C. After an appropriate period of time, the reaction was quenched by dissolving the reaction mixture in dichloromethane (10 mL). Subsequently, a simple aqueous work-up was carried out by adding 10 mL of water, and the organic layer was extracted with dichloromethane. The water layer was washed twice by adding two 5 mL portions of dichloromethane. The crude product was purified by flash chromatography on silica gel yielding NMR pure isolated product.

All reported yields are isolated yields and are average of at least two runs.

Procedure for Catalyst Longevity Experiment between Benzyl Azide and Phenylacetylene

In a Schlenk flask, the compound 1 (10 mg, 1 mol%), phenylacetylene (1.73 mmol) and benzyl azide (1.57 mmol) were taken and stirred at 25 °C. The reaction mixture was monitored by ¹H NMR spectroscopy by taking aliquots of the reaction mixture after 40 min intervals and the reaction was stopped when the consumption of substrates was complete. During this period, a solid product was formed. Again a fresh batch of liquid substrates phenylacetylene (1.73 mmol) and benzyl azide (1.57 mmol) was added for the next catalytic cycle without adding any further catalyst into the reaction vessel. This procedure was repeated for a total of ten consecutive catalytic runs.

Procedure for Catalyst Longevity Experiment between Phenyl Azide and Phenylacetylene

In a Schlenk flask, the compound **1** (10 mg, 1 mol%), phenylacetylene (1.73 mmol) and phenyl azide (1.57 mmol) were taken and stirred at 25 °C. The reaction mixture was monitored by ¹H NMR spectroscopy by taking aliquots of the reaction mixture after 30 min intervals and the reaction was stopped when the consumption of substrates was complete. During this period, a solid product was formed. Again a fresh batch of liquid substrates phenylacetylene (1.73 mmol) and phenyl azide (1.57 mmol) was added for the next catalytic cycle without adding any further catalyst into the reaction vessel. This procedure was repeated for a total of ten consecutive catalytic runs.

Procedure for Catalyst Longevity Experiment between Mesityl Azide and Mesitylacetylene

In a Schlenk flask, the compound **1** (10 mg, 1 mol%), mesitylacetylene (1.73 mmol) and mesityl azide (1.57 mmol) were taken and stirred at 25 °C. The reaction mixture was monitored by ¹H NMR spectroscopy by taking aliquots of the reaction mixture after each 9 h interval and the reaction was stopped when the consumption of substrates was complete. During this period, a solid product was formed. Again a fresh batch of liquid substrates mesitylacetylene (1.73 mmol) and mesityl azide (1.57 mmol) was added for the next catalytic cycle without adding any further catalyst in to the reaction vessel. This procedure was repeated for a total of five consecutive catalytic runs.

Rate of Conversion

A round-bottom flask was charged with compound **1** (10 mg, 1 mol%), phenylacetylene (1.73 mmol), and benzyl azide (1.57 mmol) at 25 °C. The reaction mixture was monitored by ¹H NMR spectroscopy after taking aliquots of the reaction mixture after each 2 min interval and the reaction was stopped when the substrate consumption was complete.

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