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Effects of a Flexible Alkyl Chain on a Ligand for CuAAC Reaction

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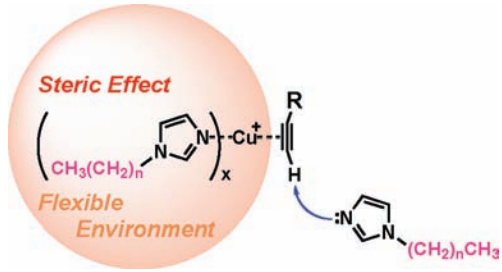
ABSTRACT



Imidazole derivatives substituted by a normal alkyl group are shown to be efficient as a ligand for the copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC) reaction. An alkyl chain on the imidazole ligands shows an efficient steric effect and benefits the reaction. Such functionalities of an alkyl chain allow a rapid CuAAC reaction of even a bulky alkyne, which has been difficult to perform under conventional conditions.

An alkyl chain is a part of many amphiphiles or other organic materials and plays an important role in determining their properties.[1] Although it ordinarily has an extended form with all *anti* configurations as its stable shape, it can readily change its conformation in a host molecule to an unusual one, such as coiled, folded, or U-shaped, to adjust its volume to the cavity size.[2] However, such a flexible nature of an alkyl chain has rarely been noted as a special functionality for synthetic reagents.[3,4] In addition, a normal alkyl group with a variety of conformations may have an appreciable steric effect. On the basis of such a viewpoint, we sought to utilize the latent functionalities of a normal alkyl group in the design of a ligand for a transition metal catalyst. Herein we describe the efficiency of imidazoles carrying a long alkyl chain[5,6] as a ligand for the copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC) reaction.[7]

The CuAAC reaction[7] has been a representative of click chemistry[8] that has been utilized in various areas,[9] and there are a few examples where the reaction was accelerated by a ligand.[10−12] Polydentate ligands, such as tris(benzyltria-

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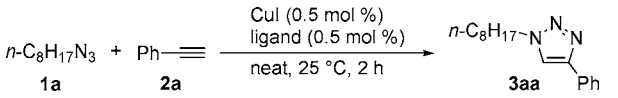
zolylmethyl)amine (TBTA),[10a,b] are well-balanced to stabilize Cu(I) and to accelerate the reaction.[10] Monodentate ligands with rigid backbones, such as an NHC (ICy or SIMes) or a phosphoramidite, were also shown to have a high accelerating effect.[11] These previous instances suggest that bulky ligands are desirable for an efficient catalyst. Indeed, during our initial investigations of the CuAAC reaction between 1-azidooctane (**1a**) and phenylacetylene (**2a**) under the conditions in Table 1, bulky 1-(1-adamantyl)imidazole (**4b**) was shown to be excellent as a ligand and much more efficient than 1-methylimidazole (**4a**) (Table 1, entries 1−8). 1,2-Dimethylimidazole (**5**) and 1,4-dimethylimidazole (**6**) also gave **3aa** in higher yields than the case of **4a**, but they are not up to **4b** (Table 1, entries 9 and 10).[6d] We then investigated the efficiency of imidazoles substituted by a normal alkyl group in hopes of finding its steric effect. As expected, they proved to be effective, and especially 1-decylimidazole (**4d**) showed as good a result as **4b** (Table 1, entries 11 and 12).[13] With **4d**, we also replaced CuI by some other Cu sources, and CuI was shown to be the best among them (Table 2).

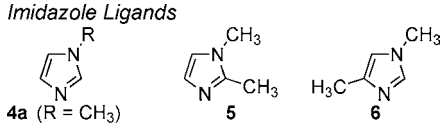
Table 1. CuAAC Reaction between 1-Azidooctane (**1a**) and Phenylacetylene (**2a**) with Various Ligands[a]



entry	ligand	yield (%)[b]
1	none	4
2	Et_3N	15
3	n-Bu_3N	37
4	EtN^iPr_2	18
5	2,6-lutidine	6
6	DMAP[d]	29
7	**4a** (R = CH_3)	35
8	**4b** (R = 1-ad[e])	99
9	**5**	61
10	**6**	51
11	**4c** (R = n-C_4H_9)	63
12	**4d** (R = n-$C_{10}H_{21}$)	96[c]

[a] Reactions were run using **1a** (1.0 mmol), **2a** (1.05 mmol), CuI (0.005 mmol), and a ligand (0.005 mmol). [b] Determined by ^{1}H NMR. [c] Isolated yield. [d] DMAP = *N*,*N*-dimethyl-4-aminopyridine. [e] ad = adamantyl.

Imidazole Ligands

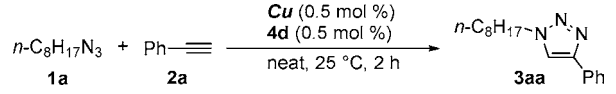


4a (R = CH_3)
4b (R = 1-ad)
4c (R = n-C_4H_9)
4d (R = n-$C_{10}H_{21}$)

5

6

Table 2. CuAAC Reaction with 1-Decylimidazole (**4d**) and Various Cu Sources[a]

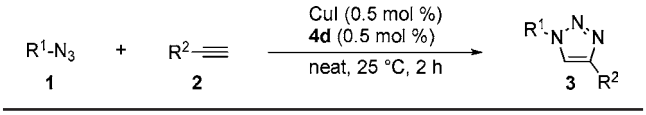


entry	Cu	yield (%)[b]
1	CuI	96
2	CuBr	63
3	CuCl	38
4	CuCN	54
5	$Cu(CH_3CN)_4PF_6$	31
6	$CuSO_4$ with Na ascorbate[c]	34

[a] Reactions were run using **1a** (1.0 mmol), **2a** (1.05 mmol), a Cu salt (0.005 mmol), and **4d** (0.005 mmol). [b] Determined by ^{1}H NMR. [c] 0.025 mmol (2.5 mol %) of Na ascorbate was used.

We then applied the condition with 0.5 mol % of CuI and 0.5 mol % of **4d** to some other azides and alkynes (Table 3).

Table 3. CuAAC Reaction with 1-Decylimidazole (**4d**)[a]



entry	R^1	R^2	**3**	yield (%)[b]
1	$PhCH_2$ (**1b**)	Ph (**2a**)	**13ba**	99
2	p-$CH_3OC_6H_4CH_2$ (**1c**)	Ph (**2a**)	**3ca**	99
3	p-$CF_3C_6H_4CH_2$ (**1d**)	Ph (**2a**)	**3da**	99
4	t-$BuOCOCH_2$ (**1e**)	Ph (**2a**)	**3ea**	97
5	cyclohexyl (**1f**)	Ph (**2a**)	**3fa**	99
6	$PhCH_2$ (**1b**)	p-$CH_3OC_6H_4$ (**2b**)	**3bb**	99
7	$PhCH_2$ (**1b**)	p-$CF_3C_6H_4$ (**2c**)	**3bc**	99
8	$PhCH_2$ (**1b**)	CH_3OCO (**2d**)	**3bd**	97
9	$PhCH_2$ (**1b**)	n-C_8H_{17} (**2e**)	**3be**	99

[a] Reactions were run using **1** (1.0 mmol), **2** (1.05 mmol), CuI (0.005 mmol), and **4d** (0.005 mmol). [b] Isolated yields.

Reactions with various substrates afforded excellent yields. Azides with benzyl groups (**1b**, **1c**, **1d**), an ester group (**1e**),

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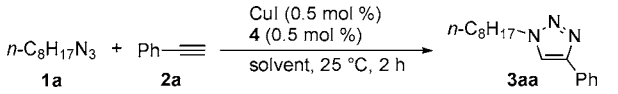
and a cyclohexyl group (**1f**) showed rapid reactions (Table 3, entries 1−5). Acetylenes with phenyl groups (**2b**, **2c**), an ester group (**2d**), and a primary alkyl group (**2e**) were also applicable (Table 3, entries 6−9).

The efficiency of the catalyst for click chemistry should stay relatively constant in a wide range of reaction media.[8] As shown in Table 4, **4d** was also useful in the reactions

Table 4. CuAAC Reaction Using 1-Decylimidazole (**4d**) and 1-Methylimidazole (**4a**) with Various Solvents[a]



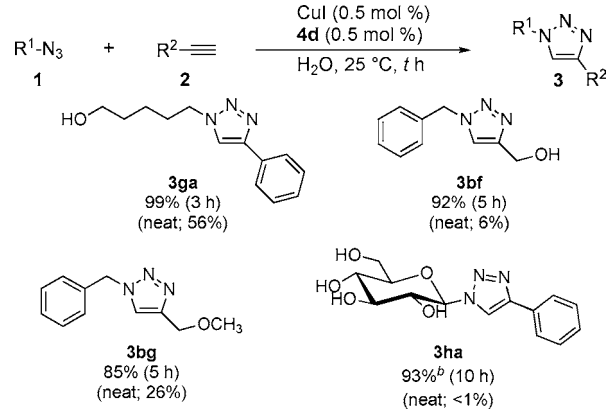
		yield (%)[b]	
entry	solvent	with **4d**	with **4a**
11	hexane	71	2
2	$CHCl_3$	85	46
3	CH_2Cl_2	99	99
4	DMSO	53	23
5	CH_3CN	85	82
6	CH_3OH	26	7
7	*t*-BuOH	40	10
8	H_2O	97	34

[a] Reactions were run using **1a** (1.0 mmol), **2a** (1.05 mmol), CuI (0.005 mmol), **4** (0.005 mmol), and a solvent (0.5 mL). [b] Determined by ^1H NMR.

using a variety of solvents, and the effect of the long alkyl chain on **4d** was observed in almost solvents. **4d** was much more effective than **4a** in hexane (Table 4, entry 1), and the efficiency of **4d** was also seen in $CHCl_3$ and DMSO (Table 4, entries 2 and 4). In CH_2Cl_2 or CH_3CN, **4d** and **4a** gave similarly good results (Table 4, entries 3 and 5).[14,15] Although alcoholic solvents retarded the reaction, the accelerating effect of **4d** was still available (Table 4, entries 6 and 7). In addition, **4d** maintained the activity even in the presence of water, and its large accelerating effect was observed (Table 4, entry 8).[16]

Such a broad utility of the ligand expands the scope of substrates. For example, although the substrates having a hydroxyl group (**1g**, **2f**) showed a significant inhibition of the reaction under the neat condition, we could perform their reactions efficiently in the presence of water, which may interrupt the coordination of a hydroxyl group to a Cu catalyst (Scheme 1, **3ga** and **3bf**). A similar enhancement by water was also seen in the reaction of methyl propargyl ether (**2g**) (Scheme 1, **3bg**), and even the glucosyl azide

Scheme 1. CuAAC Reaction in the Presence of Water[a]

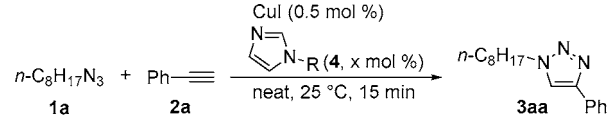


[a] Reactions were run using **1** (1.0 mmol), **2** (1.05 mmol), CuI (0.005 mmol), **4d** (0.005 mmol), and H_2O (0.5 mL). [b] Run in the presence of H_2O (0.1 mL) and *t*-BuOH (0.4 mL).

without any protection of hydroxyl groups (**1h**) could also be used for the reaction by using a mixture of water and *t*-BuOH as a solvent (Scheme 1, **3ha**).[10h,17]

We further investigated the reaction between **1a** and **2a** with various amounts of imidazole derivatives in a shorter reaction time (Scheme 2).[18] As a result, the use of more than

Scheme 2. CuAAC Reaction between 1-Azidooctane (**1a**) and Phenylacetylene (**2a**) with Various Amounts of 1-Decylimidazole (**4d**) and 1-Hexadecylimidazole (**4e**)



x (mol %)	**4d** (R = *n*-$C_{10}H_{21}$)	**4e** (R = *n*-$C_{16}H_{33}$)
0.5	47%	22%
1.0	40%	**90%**
1.5	**91%**	**99%**
2.0	**99%**	**99%**

1.5 mol % of **4d** brought about a further acceleration, and the reaction using 2.0 mol % of **4d** proceeded to completion within only 15 min. Furthermore, with 1-hexadecylimidazole (**4e**), carrying an even longer alkyl chain, only 1.0 mol % was enough to gain a similar acceleration. The additional drastic acceleration can be attributed to the effect of free imidazole molecules not coordinating to a Cu catalyst and working as a base to deprotonate from a terminal alkyne in forming a copper-acetylide intermediate.[7a,14] The longer alkyl chain probably has a larger steric effect to repulse the multiple coordination of **4e**, and released **4e** might work as a base.

(13) In this case, the steric effect of the alkyl chain might keep the reactivity of copper-acetylide intermediates; otherwise, copper acetylide species are known to become an inactive polymeric form; see: Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313.

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(15) It was reported that CH_3CN could be an efficient ligand for CuAAC reactions; see ref 14.

(16) As for the reaction in the presence of water, further investigations corresponding to Table 1 were also performed. See Supporting Information for details, Table S1.

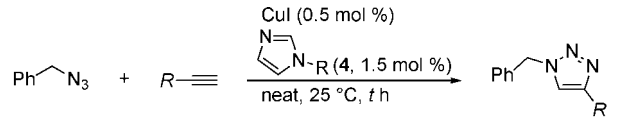
(17) See Supporting Information for more details, Scheme S1.

(18) Similar investigations were also performed with **4a** and **4b**. See Supporting Information for details, Scheme S2.

The imidazole ligands with a long alkyl chain in particular were efficient for the reactions of bulky alkynes. A bulky alkyne is a relatively unfavorable substrate in the CuAAC reaction under mild conditions. Actually the reactions of *tert*-butylacetylene (**2h**) or cyclohexylacetylene (**2i**) with **1b** under the condition using 0.5 mol % of **4d** as in Table 3 resulted in low yields (6% and 0%, respectively),[19] and previous research also suggests that such reactions should be performed under harsher conditions.[10f,20] This may be caused by the difficulty of a bulky alkyne to form a stable π-complex due to its steric hindrance, which would lead to a higher pK_a of its terminal proton than in the other cases;[14] thus a base catalyst would be required for a rapid reaction. However, the use of a large amount of a small amine will saturate the coordination spaces of a Cu catalyst and suppress the catalytic activity.[5b,10a] Meanwhile, with 1.5 mol % of **4d** or **4e**, carrying a long alkyl chain, the reaction of even **2h** could be performed smoothly to give **3bh** in high yields, and the use of the same amount of **4a** or even **4b** was less efficient (Scheme 3). Besides, more noteworthy is that in the case of **2i**, only **4e** gave a prominent result (Scheme 3). These results suggest that the steric effect of **4e** might leave a free imidazole acting as a base while keeping a coordinatively unsaturated Cu catalyst.[21] In addition, the fact that the rigid backbone of **4b** also disturbed the reaction despite its sufficient steric effect indicates that the flexible alkyl chain must be present to create a favorable environment around a Cu center, even for a bulky substrate.[22]

In summary, we have showed the efficiency of *N*-alkylimidazoles as a ligand to achieve a rapid CuAAC reaction. The alkyl chain gave an efficient steric effect, and imidazoles worked not only as a ligand but also as a base. Furthermore, the flexible alkyl chain could provide a favorable environment around a Cu center for a variety of substrates. These results suggest a new concept for an efficient ligand of transition metal catalysis. Further studies on the detailed clarification of the role of the alkyl chain and the application of this methodology to the other catalytic processes are currently underway in our laboratory.

Scheme 3. CuAAC Reaction of Acetylenes with Bulky Substituents



1b

2h (*R* = *t*-Bu)
2i (*R* = cyclohexyl)

3bh (*R* = *t*-Bu)
3bi (*R* = cyclohexyl)

2 (*t* h)	**4a** (R = CH_3)	**4d** (R = *n*-$C_{10}H_{21}$)	**4e** (R = *n*-$C_{16}H_{33}$)	**4b** (R = 1-ad)
2h (3 h)	4%	**99%**	**93%**	79%
2i (2 h)	<1%	18%	**92%**	4%

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Supporting Information Available: Experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) The use of CH_3CN or CH_2Cl_2 as a solvent was also not effective for those reactions. See Supporting Information for details, Scheme S3.

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