A new solvent system for efficient synthesis of 1,2,3-triazoles

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Abstract—The use of CH_2Cl_2 as a co-solvent with H_2O in the copper(I)-catalyzed 1,3-dipolar cycloaddition of organic azides and alkynes increased reaction rates and provided the corresponding 1,2,3-triazoles in excellent yields compared to other organic co-solvent systems. Moreover, we applied this discovery to prepare the functional multivalent compound in an excellent yield.
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The copper(I)-catalyzed 1,3-dipolar cycloaddition of organic azides and alkynes[1] resulting in the formation of 1,2,3-triazoles has become an increasingly attractive area because it is a highly efficient process in bond formations among diverse building blocks for chemical synthesis,[2] bioconjugation,[3] materials and surface science,[4] and combinatorial chemistry.[5] In addition, a number of compounds containing 1,2,3-triazoles have shown a broad spectrum of biological activities such as antibacterial,[6] herbicidal, and fungicidal,[7] antiallergic,[8] and anti-HIV.[9]

In general, the copper(I)-catalyzed 1,3-dipolar cycloaddition is known as a mild reaction that does not require much specific precautions. It usually proceeds to completion in 6–36 h at ambient temperature in water with a variety of organic co-solvents, such as *tert*-butanol, ethanol, DMSO, THF, or CH_3CN. However, it is still of interest to develop more efficient cycloaddition methods, since reactions that involve the azides or alkynes having the low reactivity require long reaction times and give low yields. A few papers recently reported that the addition of ligand, a copper(I) stabilizer, enhanced the catalytic activity of copper(I), improved reaction yields, and reduced reaction times.[10]

Interestingly, in recent days we discovered that 1,2,3-triazole **3** could be successfully prepared when we used CH_2Cl_2 as organic co-solvent in the ligand-free copper(I) catalyzed 1,3-dipolar cycloaddtion. Although

CH_2Cl_2 has been employed as solvent in the ligand-mediated copper(I) catalyzed 1,3-dipolar cycloaddtion, it was used for organic ligand which accelerated the reaction rate, not as a co-solvent.[10a] Herein, we report our successful application of CH_2Cl_2 as the co-solvent in ligand-free reaction.

Initially, compound **3** was supposed to be easily synthesized by treating azide **1** with the terminal alkyne **2** in H_2O/EtOH (entry 1 in Table 1). However, the reaction did not proceed at all. Then, the reactions were carried out in different organic co-solvents such as CH_3CN (entries 2 and 3), DMSO (entry 4), THF (entry 5), and *t*-BuOH (entry 6), but they all failed. Surprisingly, the addition of CH_2Cl_2 to H_2O/*t*-BuOH mixture drove the reaction to proceed, and the desired product **3** was isolated in 60% yield in 24 h (entry 7). More surprisingly, the reaction was completed in 2 h when it was run in CH_2Cl_2/H_2O as the solvent system, and gave product **3** in 96% yield (entry 8).

Next, the generality of this solvent system in the copper(I)-catalyzed 1,3-dipolar cycloaddition was investigated. A variety of organic azides and alkynes were treated with $CuSO_4 \cdot 5H_2O$ (5 mol %) and sodium ascorbate (15 mol %) in CH_2Cl_2/H_2O (1/1). All substrates investigated gave 1,2,3-triazoles in excellent yields (Table 2). In order to show the efficiency of CH_2Cl_2/H_2O solvent system, the same reactions were also performed in *t*-BuOH/H_2O (2/1), which is one of the most popular solvent systems used for the click reaction. The reaction of phenylacetylene (**4**) and benzyl azide (**9**) in CH_2Cl_2/H_2O afforded 1,2,3-triazole **16** in 97% yield after 7 h,[11] whereas the same reaction in *t*-BuOH/H_2O furnished

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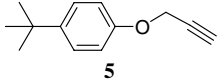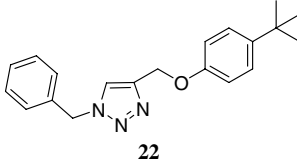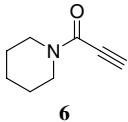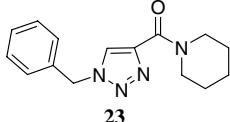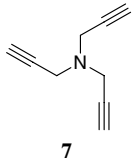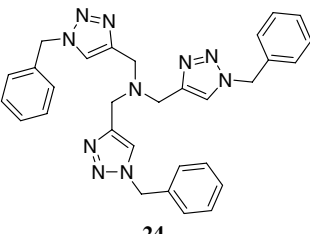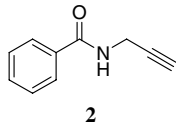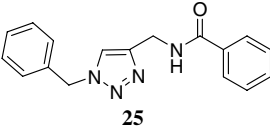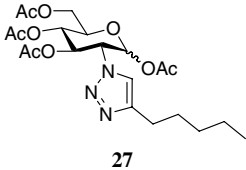
Table 1. The copper(I)-catalyzed synthesis of 1,2,3-triazole **3** in various solvent systems[a]
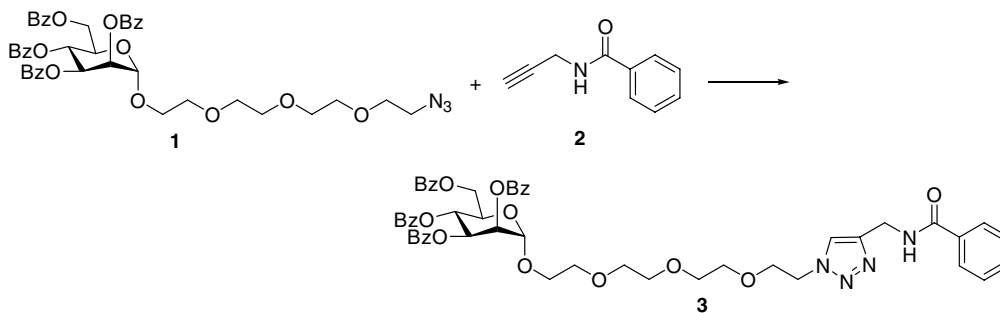
Entry	CuSO$_4$·5H$_2$O (mol %)	Sodium ascorbate (mol %)	Solvent	Temperature	Time (h)	3, Yield[b] (%)
1	5	25	H$_2$O/EtOH (2:1)	rt	24	None
2	5	25	H$_2$O/CH$_3$CN (2:1)	rt	24	None
3	10	30	H$_2$O/CH$_3$CN (1:1)	rt	24	None
4	10	30	H$_2$O/DMSO/CH$_3$CN (1:2:2)	rt	24	None
5	10	30	H$_2$O/CH$_3$CN/THF (1:2:2)	rt	24	None
6	20	40	H$_2$O/t-BuOH (2:1)	rt	24	None
7	5	15	H$_2$O/t-BuOH/CH$_2$Cl$_2$ (1:2:1)	rt	24	60
8	5	15	H$_2$O/CH$_2$Cl$_2$ (1:1)	rt	2	96

[a] Reaction condition: **1** (1 equiv), **2** (1.1 equiv), solution concentration (0.05 M).
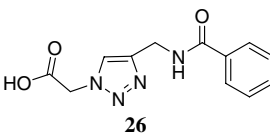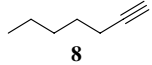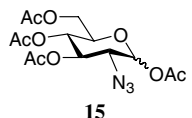[b] Isolated yields.

Table 2. Effect of the use of CH$_2$Cl$_2$ in the copper(I)-catalyzed 1,3-dipolar cycloaddition

Entry	Alkyne	Azide	Product	Method[a]	Time (h)	Yield[b] (%)
1	**4**	**9**	**16**	A B	7 24	97 83
2	**4**	**10**	**17**	A B	2 24	99 96
3	**4**	**11**	**18**	A B	5 24	99 92
4	**4**	**12**	**19**	A B	2 24	85 37
5	**4**	**13**	**20**	A B	1 24	94 80
6	**4**	**14**	**21**	A B	3 3	95 93

Table 2 (*continued*)

| Entry	Alkyne	Azide	Product	Method[a]	Time (h)	Yield[b] (%)
7	**5**	**9**	**22**	A B	5 24	99 93
8	**6**	**9**	**23**	A B	2 24	99 98
9	**7**	**9**	**24**	A B	12 24	98 93
10	**2**	**9**	**25**	A B	1.5 24	93 89
11	**2**	**13**	**26**	A B	11 24	99 98
12	**8**	**15**	**27**	A B	6 24	94 34

[a] Method A: CH_2Cl_2/H_2O (1/1), rt. Method B: *t*-BuOH/H_2O (2/1), rt.
[b] Isolated yields.

16 in 83% yield after 24 h (entry 1). This result clearly indicates that the reaction rate in CH_2Cl_2/H_2O has increased significantly compared to that in *t*-BuOH/H_2O. The click reaction of **4** with azides **10**, **11**, **12**, and **13** also showed the increased reaction rates in CH_2Cl_2/H_2O (entries 2–5), except for the reaction with azidoacetic acid (**14**), which provided **21** in excellent yields in both solvent systems (entry 6). Next, the click reactions of azide **9** were performed with propargyl ether **5** (entry 7), acetylenic amide **6**[12] (entry 8), tripropargylamine (**7**) (entry 9), and propargyl amide **2** (entry 10). All reactions provided the desired 1,2,3-triazoles **22**, **23**, **24**,[10b] and **25** in excellent yields. In particular, in the case of acetylenic amide **6**, which is known for its low reactivity toward 1,3-dipolar cycloaddition with azides,[12] the click reaction gave **23** in a quantitative yield after only 2 h. The reaction of alkyne **8** with sugar azide **15** in CH_2Cl_2/H_2O afforded the 1,2,3-triazole **27** in 94% yield after 6 h, whereas the reaction in *t*-BuOH/H_2O gave **27** in 34% yield after 24 h. Clearly, the new solvent

system, CH_2Cl_2/H_2O, increased the yield of the formation of the 1,2,3-triazoles and reduced the reaction times. Although the reason was not elucidated exactly, it is considered that the high solubility of the substrates in CH_2Cl_2 makes the reaction faster.

The application of the new reaction condition to synthesize a multivalent ligand was next explored. The initial attempt to carry out the click reaction of azide-functionalized sugar **13** and alkyne-functionalized trivalent core compound **28** did not work in either CH_2Cl_2/H_2O or *t*-BuOH/H_2O even after 24 h (Scheme 1), whereas the reaction of **13** with **4** afforded the 1,2,3-triazole **20** in excellent yield (entry 5 in Table 2). Although it was not clear why the reaction of **13** with **28** did not work, this was easily overcome by using azide-functionalized sugar **29** in place of **13**. The reaction proceeded successfully in CH_2Cl_2/H_2O in 1 h to give the trivalent compound **30** in 96% yield, whereas the reaction in *t*-BuOH/H_2O gave **30** in 29% yield even after 24 h.
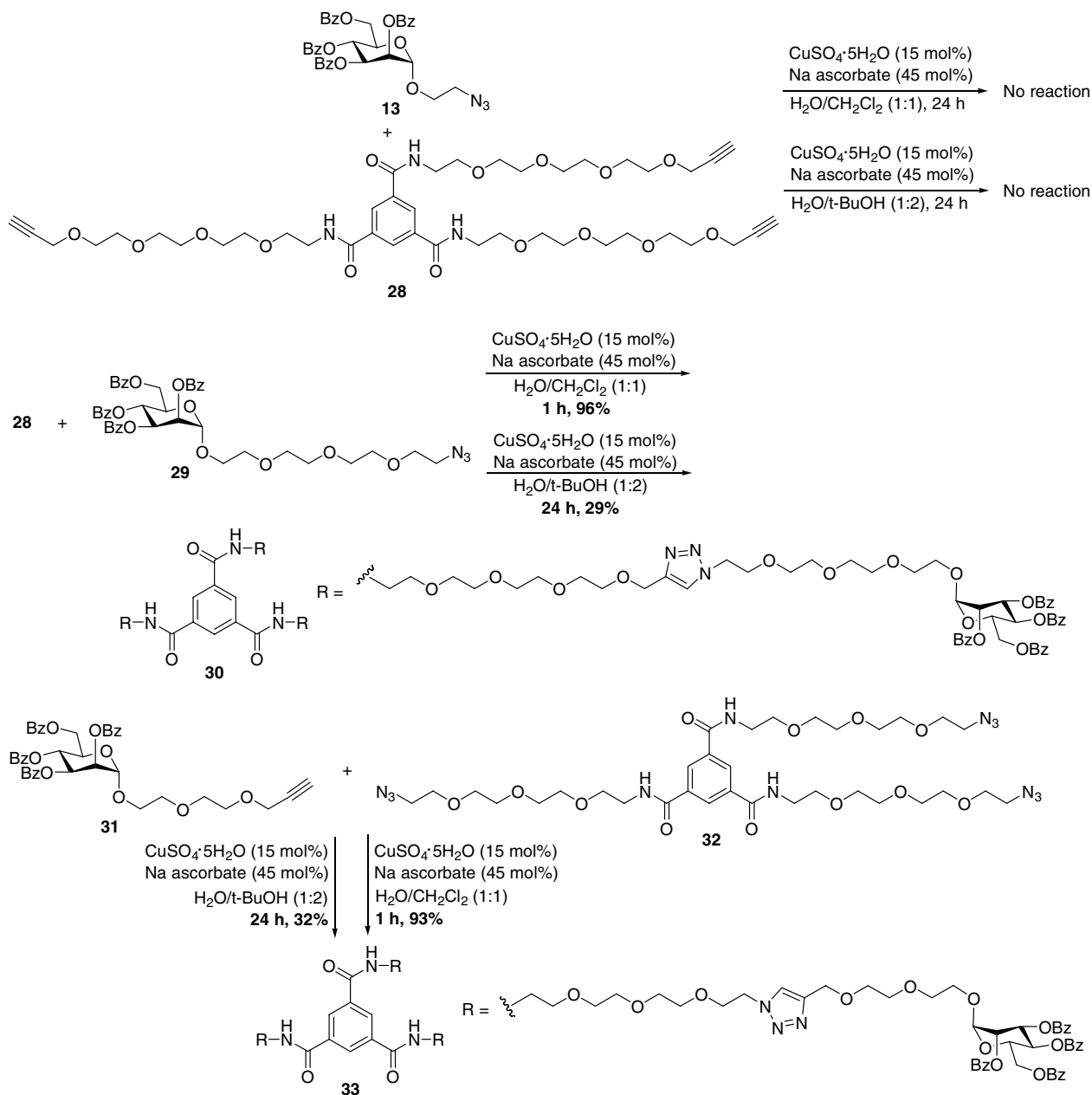
Scheme 1.

Conversely, the reaction of the alkyne-functionalized sugar **31** and azide-functionalized trivalent core compound **32** in CH$_2$Cl$_2$/H$_2$O also afforded **33** in 93% yield after 1 h, compared to 32% yield after 24 h in t-BuOH/H$_2$O.

In conclusion, we have found that the use of CH$_2$Cl$_2$ as a co-solvent with H$_2$O in the copper(I)-catalyzed 1,3-dipolar cycloaddition of organic azides and alkynes significantly increases the reaction rates in comparison to other organic co-solvent systems. This reaction condition eliminates the need of ligands and simplifies the reaction protocol. Moreover, we have shown that this solvent system is generally applicable to cycloaddition reactions involving various azides and alkynes, and tolerates a number of different functional groups. Finally, the synthesis of the multivalent compounds **30** and **33** was done efficiently in excellent yields using this solvent

system, demonstrating the synthetic application to structurally complex molecules.

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11. Typical procedure of click reaction for **16**: To a solution of phenylacetylene (**4**, 100 mg, 0.75 mmol) and benzyl azide (**9**, 80 mg, 0.83 mmol) in CH_2Cl_2 (0.7 mL) and H_2O (0.7 mL) were added $CuSO_4 \cdot 5H_2O$ (9.3 mg, 0.04 mmol) and sodium ascorbate (22 mg, 0.11 mmol). The resulting solution was stirred for 7 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and H_2O (5 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to give 1,2,3-triazole **16** (170 mg, 97%) as a white solid.

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