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Combination of Perfluoroalkyl and Triazole Moieties: A New Recovery Strategy for TEMPO

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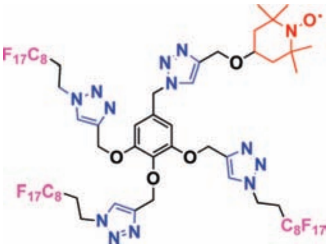
ABSTRACT



The attachment of multiple triazole moieties and perfluoroalkyl chains to TEMPO promotes emulsion formation in dichloromethane/water, giving a highly active and easily recoverable catalyst for the oxidation of alcohols.

The use of perfluorinated alkyl chains as tags has been broadly applied to impose fluorous properties onto a given molecule. Arguably the most important application of this strategy is to separate a perfluorinated compound from a complex reaction mixture by fluorous biphasic separations, for example, by extraction or retention of the tagged molecule with a perfluorinated solvent, fluorous silica, or perfluorinated polymers.[1] As this property provides an attractive method for catalyst recovery and recycling, perfluorinated tags have been attached to several metal-based catalysts[2] and organocatalysts.[3] Thus, homogeneous catalysis is achieved in an organic solvent due to the good solubility perfluorinated tagged compounds still have, but easy and selective recovery of the catalyst by a phase switch to a perfluorinated medium is possible.

A well-known alternative approach for the development of recyclable catalysts is their attachment to a polymeric support that is insoluble in the reaction medium, allowing its recovery by simple filtration. An inherent disadvantage of this strategy is the generally reduced reactivity of such modified catalysts due to the heterogeneous nature of the reaction.[4]

We report here the combination of multiple perfluoroalkyl chains and triazole moieties, leading to a new kind of building block that can be used for the tagging of TEMPO. The resulting reagent promotes the oxidation of alcohols to aldehydes in organic solvent/water mixtures with reaction

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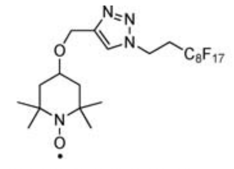
rates comparable to homogeneous TEMPO reagents, but can be easily recovered by liquid/emulsion filtration.



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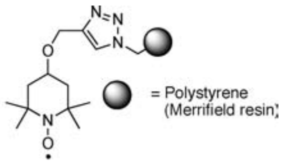

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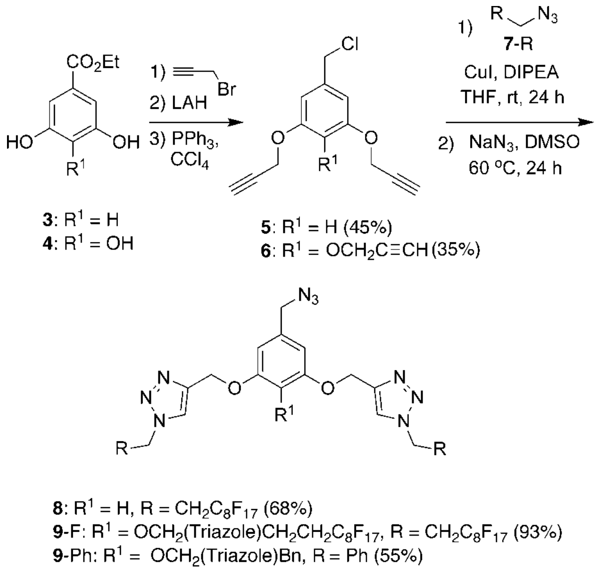
Based on our interest in developing immobilized reagents on organic and inorganic supports,[5] we recently utilized the copper-catalyzed[6] alkyne azide cycloaddition[7] (CuAAC) reaction as a versatile method for the ligation of TEMPO to polymers[8] such as **1**[9] or **2**.[10] In this context, we discovered that **1** showed low solubility in perfluorinated, but good solubility in organic solvents, and more strikingly, showed little affinity to fluorous but high affinity to conventional silica.[9]

To further investigate the combination of perfluorinated alkyl chains and triazole moieties, we attempted to synthesize azides **8** and **9**-F, which should be suitable building blocks for the attachment of catalysts and reagents modified by an alkynyl group.

The benzyl chlorides **5**[11] and **6** could be readily synthesized in a three-step procedure starting from commercially available benzoic acid esters **3** and **4**, respectively (Scheme 1). Ligation with azide **7**-R using catalytic amounts of CuI[12] followed by chloride azide exchange resulted in the target compounds **8** and **9** in high yields.

Scheme 1. Synthesis of Benzyl Azides with Multiple Triazole and Perfluoroalkyl Moieties



The fluorous tagged azides **8** or **9**-F were only slightly soluble in organic solvents, nevertheless, they smoothly underwent the CuAAC with **10** in high yields, again using catalytic amounts of CuI in THF (Scheme 2). **11** and **12** precipitated from the reaction mixture and could be conve-

Scheme 2. Synthesis of Novel TEMPO Reagents with Multiple Triazole and Perfluoroalkyl Moieties

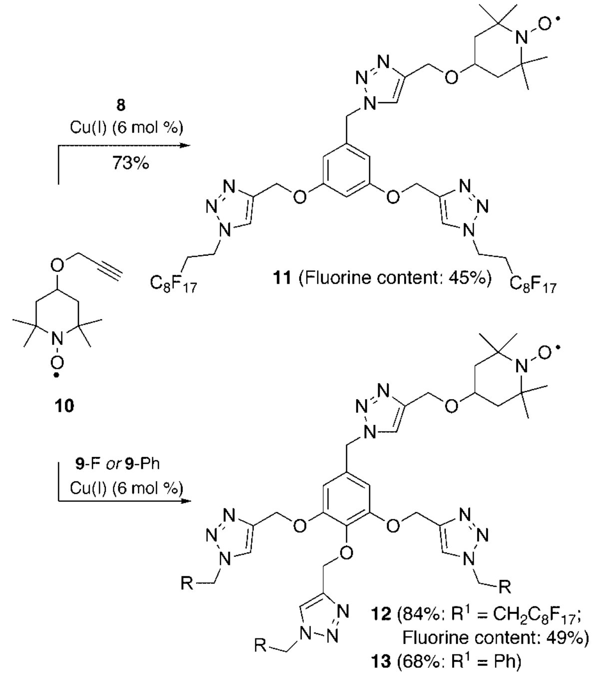


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Table 1. Oxidation of Alcohols with **11** and **12**[a]

entry	alcohol	catalyst	conversion[b] (%)	yield (%)	purity[b] (%)
1	4-bromobenzyl alcohol	**11**	>98	95	>98
2		**12**	>98	95	>98
3	4-methylbenzyl alcohol	**11**	>98	98	>98
4		**12**	>98	98	>98
5	1-octanol	**11**	>98	95	>97
6		**12**	>98	96	>96
7	1-decanol	**11**	>98	98	>96
8		**12**	>98	92	>95
9	cyclohexanol[c]	**11**	>98	92	>98
10		**12**	>98	91	>98

[a] Alcohol (1.0 mmol) in CH_2Cl_2 (2 mL), KBr (0.2 mmol), catalyst (1.0 mol %), NaOCl (0.8 mL, 1.1 mmol), $NaHCO_3$ (0.5 mmol), 0 °C. Reaction time 15 min. [b] Determined by ^1H NMR. [c] Reaction time 1 h.

niently isolated by simple filtration and purified from residual copper by washing with aqueous EDTA (0.1 M) solution. The absence of the typical azide band around 2100 cm^{-1} in the IR-spectrum further indicated that the products were obtained free from the starting materials **8** or **9**-F, respectively.

The new TEMPO derivatives **11** and **12** showed remarkable properties: They are largely insoluble in organic or fluorinated solvents (≤1 mg/10 mL CH_2Cl_2 or perfluoro(methylcyclohexane) at 25 °C) as well as in water; nevertheless, oxidation of alcohols using Anelli's conditions,[13] calling for KBr as the cocatalyst and NaOCl as the terminal oxidant, or using Minisci's conditions,[14] calling for Mn(II) and Co(II) nitrate as cocatalysts in acetic acid and oxygen as the terminal oxidant, proceeded with high yields and selectivity. Under both protocols, **12** could be recovered with high efficiency and subsequently reused as such without loss of activity.

Oxidations of alcohols were carried out at 0 °C in the presence of 1 mol % of catalyst and 1.1 equiv of NaOCl (Table 1-3). Under these conditions, most alcohols were quantitatively oxidized within 15 min, with the exception of the more challenging cyclohexanol, which was smoothly oxidized within 1 h. In all cases, the purity of the isolated carbonyl derivatives was >95%.

Table 2. Activity Comparison of Heterogeneous (**2**, **12**) and Homogeneous (TEMPO, **1**, **13**) TEMPO Catalysts in the Anelli Oxidation of 4-Methylbenzyl Alcohol[a]

entry	catalyst (mol %)	time (min)	yield[b] (%)	TON	TOF (h^{-1})
1	TEMPO (0.2)	40	≥98	500	≥750
2	TEMPO (0.2)	15	60	300	1200
3	**1** (0.2)	40	≥98	500	≥750
4	**2** (2.5)	15	68	29	116
5	**2** (0.2)	40	58	300	450
6	**12** (1.0)	15	≥98	100	≥400
7	**12** (0.2)	40	97	500	≥750
8	**12** (0.2)	15	74	370	1480
9	**13** (0.2)	40	96	500	≥750

[a] Alcohol (25 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL), KBr (0.2 equiv), TEMPO catalyst, NaOCl (1.1 equiv, 20 mL), $NaHCO_3$ (0.5 equiv), 0 °C. [b] Purity >98% in all cases.

Table 3. Oxidation of 4-Methylbenzyl Alcohol with TEMPO **12**. Recovery and Recycling Experiment[a]

run	conversion[b] (%)	yield (%)	purity[b] (%)
1	>98	98	>98
2	>98	99	>98
3	>98	97	>98
4	>98	92	>98

[a] Alcohol (2.5 mmol), CH_2Cl_2 (5 mL), KBr (0.5 mmol), **12** (1.0 mol %,), NaOCl (2.0 mL, 2.8 mmol), $NaHCO_3$ (1.3 mmol), 0 °C. Reaction time 15 min. **12** was recovered by filtration and reused after washing once with water and twice with CH_2Cl_2. [b] Determined by ^1H NMR.

Notably, the activity of **12** (Table 2, entries 6−8) in the oxidation of 4-methylbenzylalcohol on a 25 mmol scale in CH_2Cl_2/water is about four times higher than polystyrene supported TEMPO **2** (entries 4−5) and at least comparable to that of TEMPO or fluorous tagged TEMPO **1** (entries 1−3), both being soluble in the solvent system employed for the reaction.

However, **12** can be recovered in a highly efficient manner by simple filtration of the reaction mixture through a standard sintered glass funnel (16−40 μm pore size) and reused without further purification. For example, the oxidation of 4-methylbenzyl alcohol to the corresponding aldehyde was carried out in four runs in 92−98% yield with no observable loss of activity using an initial amount of 1 mol % of catalyst **12** (Table 3). Analysis of the filtrates by NMR gave no indication that **12** or fragments thereof due to degradation were present. Moreover, the catalytic activity of the filtrates for alcohol oxidations under the reaction conditions was in the limits of the known[13,15] background reaction in the absence of any catalyst (see Supporting Information). In contrast, **11**, although also insoluble but apparently more highly dispersed in CH_2Cl_2/water, was not held back by a sintered glass funnel as described above for **12**. Therefore, its recovery by filtration was not possible, but could be readily achieved by chromatography due to its high affinity to silica in a similar way as already noticed for **1**.[9] For practical purposes, **12** therefore seems to be the catalyst of choice.

The high activity of **12** can be most likely attributed to its behavior to act like a surfactant by forming an emulsion between the organic and aqueous phase, suggesting a detergent effect that enhances catalysis (Figure 1).[16] The combination of multiple polar triazole and perfluoroalkyl

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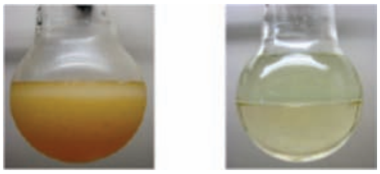

Figure 1. Reaction mixture containing **12** (left; Table 2, entry 7) or **13** (right; Table 2, entry 9).

chains seems to be decisive for this property since both, **1** or **13**, the latter being analogous to **12** but having the perfluoroalkyl chains replaced by benzyl groups, are readily soluble in dichloromethane. Those display similar activities as **12** (Table 2, entries 3 and 9) but cannot be recovered by simple filtration from the reaction mixture.

Alternatively, the TEMPO derivative **12** was investigated under Minisci's conditions, using Mn(II)- and Co(II)-nitrate as cocatalysts in acetic acid oxygen as the terminal oxidant.[14] Under these conditions benzylic alcohols were oxidized within 2−4 h, while 1-octanol, cyclohexyl alcohol and cinnamyl alcohol required 7−20 h (Table 4) to reach conversions ≥90%.

Table 4. Aerobic Oxidation of Alcohols with TEMPO **12**[a]

entry	alcohol	time (h)	conversion[b] (%)	yield (%)
1	benzyl alcohol	2	90	89
2	4-methylbenzyl alcohol	2	>98	98
3	4-methoxybenzyl alcohol	3	>98	96
4	4-bromobenzyl alcohol	3	95	92
5	cinnamyl alcohol	20	>98	90
6	cyclohexyl alcohol	12	>98	93
7[c]	1-octanol	7	90	82
8	thiophen-2-yl-methanol	4	>98	91

[a] Alcohol (1.0 mmol) in AcOH (1 mL), $Mn(NO_3)_2{\cdot}4H_2O$ (2.0 mol %), $Co(NO_3)_2 \cdot 6\, H_2O$ (2.0 mol %), **12** (1.0 mol %,), oxygen atmosphere, 40 °C. [b] Determined by ^1H NMR. [c] 5.0 mol % of catalyst used.

In contrast to unmodified TEMPO, **12** can be also recovered by simple filtration of the reaction mixture through a standard sintered glass funnel (see above) and reused without further purification. For example, the oxidation of 4-methylbenzyl alcohol to the corresponding aldehyde was carried out in three runs in 96−98% yield with consistent catalytic activity (Table 5).

Again, the activity of **12** (Table 6) in the oxidation of 4-methyl benzyl alcohol is about three to four times higher than polystyrene supported TEMPO **2** and only slightly reduced to that of unmodified TEMPO.

Table 5. Oxidation of 4-Methylbenzyl Alcohol with TEMPO **12**. Recovery and Recycling Experiment[a]

run	conversion[b] (%)	yield (%)	purity[b] (%)
1	>98	98	>98
2	>98	99	>98
3	97	96	>98

[a] Alcohol (3.0 mmol) in AcOH (3 mL), for conditions see Table 4, reaction time = 2 h. **12** was recovered by filtration and reused after washing once with water and twice with CH_2Cl_2. [b] Determined by ^1H NMR.

Table 6. Activity Comparison of Heterogeneous (**2**, **12**) and Homogeneous TEMPO Catalysts in the Aerobic Oxidation of 4-Methylbenzyl Alcohol[a]

catalyst	conversion[b] (%)	yield (%)
TEMPO	97	92
2	26	25
12	84	82

[a] For conditions, see Table 4, reaction time = 1 h. [b] Determined by ^1H NMR.

In conclusion, we have developed a new TEMPO derivative that retains the activity of homogeneous TEMPO catalysts for the oxidation of alcohols, but nevertheless allows recovery by simple filtration. The fluorous/triazole building blocks developed here should also be suitable for other catalysts and reagents that are carried out in aqueous/organic two-phase media, which is under investigation in our laboratories.

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Supporting Information Available: Experimental procedures and characterization data for compounds **8**, **9**, **11**, **12**, and **13**; details on catalyzes performed and catalyst recovery. This material is avaliable free of charge via the Internet at http://pubs.acs.org.

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