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On-Resin Catalysis

A Resin-Bound Peptoid as a Recyclable Heterogeneous Catalyst for Oxidation Reactions

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Abstract: Reusable solid-grafted catalysts have environmental and economical advantages over soluble catalysts. Numerous catalysts, including peptides, were immobilized on solid supports to enable their recyclability. Nevertheless, the few catalytic peptoids – N-substituted glycine oligomers – reported to date were only used off-resin. The soluble peptoids **BT** and **DI**, a trimer and dimer having two catalytic side-chains, were developed as bio-inspired oxidation catalysts. **BT** has an additional structure-directing group, which enables intramolecular cooperativity between the two catalytic groups ("intra-peptoid" mode). Thus, it catalyzes the oxidation of primary alcohols with much higher efficiency than **DI**. Herein, we present resin-bound **BT** and **DI** (**TG-BT** and **TG-DI**) as the first insoluble and recyclable catalytic peptoids. We discovered that though **TG-BT** also operates through the intra-peptoid cooperativity mode, it is less efficient than **BT**, even after several cycles. On the other hand, **TG-DI** is far more active than **DI** and can be recycled several times to enable a much higher turn-over-number. Our studies revealed that **TG-DI** operates through an intra-resin cooperativity mode, and this enables its high activity compared with **DI**, **BT** and **TG-BT**.

Introduction

The continuous financial and environmental demands, particularly within the pharmaceutical industry, call for the use of highly efficient and benign procedures suitable for large-scale production with minimum waste. One approach for increasing catalysts efficiencies is to attach them to a solid support and use these in heterogeneous systems, such that the bound catalyst can be separated at the end of the reaction and recycled multiple times in subsequent catalytic reactions. In addition, catalysts grafted on solid support, which can be easily recovered and recycled, are desirable for achieving cleaner, cheaper and environmentally friendly processes. As a result, many immobilized organometallic catalysts and organocatalysts have been developed.[1,2] Several examples of resin-supported peptide catalysts were also reported; in these cases the peptides were synthesized via solid-phase methods and used on-resin in the reaction mixture.[3] The use of on-resin catalysts enable to avoid typical work-up and purification steps that are not only laborious but can also lead to product loss. In addition, compounds immobilized on a swellable solid support are solvated within the matrix of the resin; hence, they are expected to be more effectively solvated than the non-bound catalyst, overcoming the limitations of a reaction within a heterogeneous solution.[3b,3c]

Peptoids, N-substituted glycine oligomers,[4] are an important class of peptidomimetic foldamers,[5] with demonstrated utilities such as metal binding[6] and solution catalysis.[7] Peptoids can be efficiently generated on resin by a solid-phase method (the "submonomer method", Figure 1)[8] from various primary amines,[9] with high sequence specificity, and are chemically inert towards many catalytic transformations.

Based on these features, we have recently designed and developed a unique bio-inspired oxidation catalyst, **BT**, which incorporates two catalytic side-chains, phenanthroline-copper and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), and one non-catalytic benzyl group.[7b,7c] We showed that **BT**, combined with Cu^I and *N*-methyl imidazole (NMI) in an acetonitrile solution,

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Yekaterina (Katia) Stamatin was born in 1995 and studied Chemistry and Material Engineering at the Technion – Israel Institute of Technology. She graduated with honors in 2019. During her studies she joined the lab of Prof. Galia Maayan as an undergraduate researcher and studied peptoids as chelators for metal ions and as catalysts.

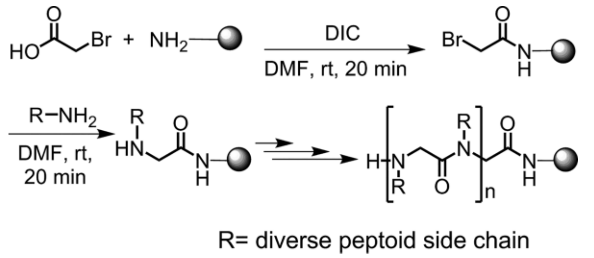

Figure 1. The two-steps solid-phase synthesis of peptoids in the "submonomer" method.

performs in the oxidation of benzylic, allylic and aliphatic primary alcohols with turn-over-frequency (TON) of up to 490 (at 0.1 mol-% catalyst). This TON is 16 times higher than the TON obtained when a mixture of the two catalytic groups, or the peptoid dimer (**DI**) that is lacking the non-catalytic group were used in the same reaction conditions. Our suggested explanation for the differences in reactivity is that the non-catalytic group constricts the spatial distance between the two catalytic groups leading to the creation of a catalytic pocket that performs via intramolecular cooperativity.[7c] We also demonstrated the higher catalytic activity of **BT** in the oxidative coupling of alcohols and amines for the production of various imines (TON up to 980 at 0.1 mol-% catalyst),[7b] compared with the reported catalytic system, in which the two catalytic groups were mixed in solution (TON up to 50).[10] Following this initial success we thought to further develop **BT** as a recyclable catalyst capable of performing on-resin in a heterogeneous system, and test whether it can perform with much higher TON in the oxidation of primary alcohols and the oxidative coupling of alcohols and amines.

The functionalization of copper-bipyridine (CuBipy) with polymer resins was already reported, showing that solid-supported CuBipy can catalyze the aerobic oxidation of primary benzylic alcohols in a heterogeneous system.[11] In this system, however, only Bipy was supported, while the nitroxyl catalyst operated in solution. Moreover, the supported catalysts were used at 5 mol-% loading and therefore the TON even after seven runs was less than 140.

Results and Discussion

In our previous work, **BT** and **DI** were synthesized on a Rink-amide resin. However, literature reports both on solid-supported CuBipy catalysts and on resin-bound peptide catalysts, suggest that the use of TentaGel (polyethylene glycol–polystyrene) resin leads to the best catalytic results.[11,12] We therefore decided to prepare the two peptoids on TentaGel resin. The two peptoids were also prepared on rink amine resin to be used as control catalysts. The peptoids were synthesized manually according to the "submonomer" method and only a small sample was cleaved from the resin for analysis. The peptoids were characterized by Reverse Phase High Performance Liquid Chromatography (RP-HPLC) and mass spectrometry (MS), and their purity was determined by HPLC to be 93 % for **BT** and 86 % for **DI**. The un-cleaved peptoids **TG-BT** and **TG-DI** (Figure 2A) were used on-resin in two oxidation reactions; benzyl alcohol oxidation and the oxidative coupling of benzyl alcohol and various amines for the formation of imines (Figure 2B and Figure 2C).

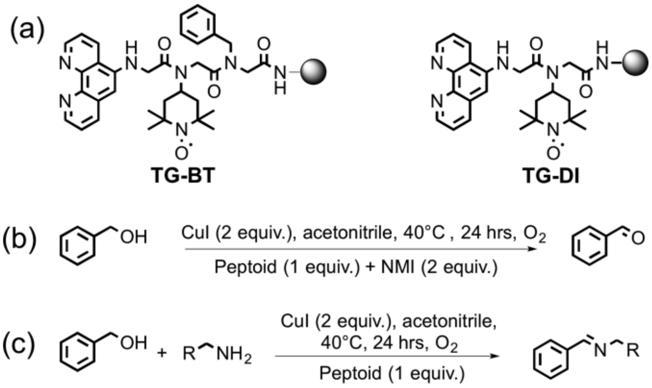

Figure 2. (a) The sequence of the catalysts used in this study. (b) The two reactions, benzyl alcohol oxidation and oxidative coupling of benzyl alcohol and various amines,that were attempted to be catalyzed by on-resin peptoids.

In order to explore the reactivity of **TG-BT** as a catalyst in the heterogeneous oxidation of primary alcohols, it was suspended in acetonitrile and subjected to the same reaction conditions that worked well in the homogeneous system.[7c] Thus, it was treated with Cu^I and NMI and this solution was stirred for one hour in room temperature, in order to create the Cu-peptoid complex. Thereafter benzyl alcohol was added, the reaction vessel was sealed under oxygen atmosphere and the reaction mixture was stirred for 24 hours prior to its analysis by Gas Chromatography (GC). Initially, 0.5 mol-% of **TG-BT** were used, just as in the previous homogeneous reaction, but only 54 % conversion to the aldehyde were obtained (Table 1, entry 1). As the use of Cu^I only, even at 2 mol-%,[13] did not yield any product, we have increased the peptoid loading to 1 mol-% and the Cu^I loading to 2 mol-%, but this did not lead to an increase in the obtained aldehyde (Table 1, entries 2–3). Only when the temperature was increased to 40 °C, we could obtain an increase in product formation to 88 % conversion (Table 1, entry 4). Notably, using **TG-DI** and Cu^I in the same amounts and reaction conditions led to full conversion. Decreasing the amount of **TG-DI** to 0.5 mol-%, however, resulted in a decrease

Table 1. Catalyst optimization studies in the oxidation of benzyl alcohol.[a]

Entry	Peptoid	mol-% peptoid	mol-% Cu^I	Conversion[b]
1[c]	**TG-BT**	0.5	0.5	54
2[c]	None	–	2	< 5
3[c]	**TG-BT**	1	2	54
4	**TG-BT**	1	2	88
5	**TG-DI**	**1**	**2**	**> 99**
6	**TG-DI**	0.5	2	46
7	**RA-BT**	1	2	17
8	**RA-DI**	1	2	5

[a] Reactions were performed in acetonitrile (1 mL) at 40 °C and under oxygen atmosphere, with 3.3 µmol catalyst, 6.6 µmol CuI, 6.6 µmol NMI and 330 µmol benzyl alcohol for 24 hours. [b] Conversions were determined by gas chromatography. [c] Reaction was done at room temperature (about 20 °C).

in product formation to 46 %. Moreover, the use of **BT** or **DI** on rink amine resin (**RA-BT** and **RA-DI**) led to only a small conversion of the alcohol to the aldehyde (Table 1, entries 7–8). Overall, our results suggest that the best peptoid to catalyze this reaction on resin is **TG-DI** in 1 mol-% under oxygen atmosphere at 40 °C. This observation is both remarkable and surprising: (a) because in the homogeneous system **BT** was shown to be a much better catalyst than **DI** and this was rationalized by the intramolecular cooperativity between TEMPO and Cu-phenanthroline (CuPhen), which was only possible within **BT**, and (b) because in the homogeneous system we obtained only 34 % conversion when **DI** was used as a catalyst (at 1 mol-%), while in the heterogeneous system full conversion is obtained.

According to Table 1, changing the amount of **TG-BT** did not effect the conversion in the reaction, while changing the amount of **TG-DI** did. This observation is consistent with our previous results in the homogeneous system suggesting that the cooperativity between TEMPO and CuPhen is intramolecular in the case of **TG-BT** and intermolecular in the case of **TG-DI**. Here, just like in the homogeneous system, the term “intramolecular cooperativity” refers to the cooperativity between TEMPO and CuPhen groups that are located within the same peptoid (“intra-peptoid”, Figure 3). Notably, this cooperativity mode might be less effective when the peptoid is resin-bound than when its unbound (steric effects). However, while in the homogeneous system the term “intermolecular cooperativity” refers to cooperativity between TEMPO and CuPhen groups that are not located within the same peptoid but rather within two separate peptoids in the solution (“inter-peptoid”), here “intermolecular cooperativity” can refer to either the cooperativity between TEMPO and CuPhen groups that are located within two separate peptoids bound to the same resin bead (“intra-resin”, Figure 3) or two separate peptoids bound to two different resin beads (“inter-resin”, Figure 3). If the reaction with **TG-DI** takes place either intra-resin or both intra-resin and inter-resin, while the reaction with **TG-BT** occurs only intra-peptoid, this can explain the better conversions obtained with **TG-DI** compared to the results obtained when either **TG-BT** or **DI** (that operates in solution only via the inter-peptoid cooperativity mode), are used as catalysts.

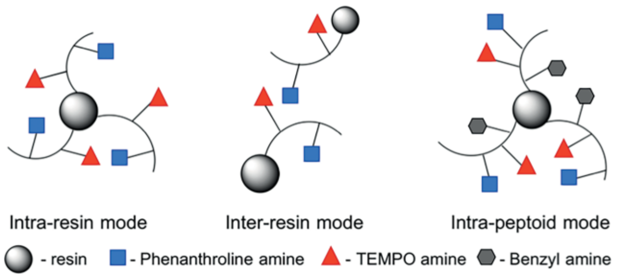

Figure 3. The three different cooperativity modes suggested for the catalytic activity of **TG-DI** (intra-resin and inter-resin) and of **TG-BT** (intra-peptoid).

To probe this point and to suggest a catalytic mode of operation in the heterogeneous system, we performed three experiments. First, in order to check whether an inter-resin mode is possible with **TG-DI**, two additional on-resin peptoid dimers were synthesized: **TG-DT**, which includes the TEMPO group and benzylamine, and **TG-DP** incorporating the phenanthroline group and benzylamine. Using these two peptoids for the oxidation of benzyl alcohol at the same reaction conditions described in Table 1, entries 5 and 6, we discovered that each peptoid alone could not catalyze this reaction. However, if the two peptoids are used together, catalytic intermolecular cooperativity is possible. Thus, by using 0.5 or 1 mol-% TG-**DT** together with 0.5 or 1 mol-% TG-**DP**, respectively, the conversion from alcohol to aldehyde was 88 % and > 99 %, respectively. The high conversions suggest that the inter-resin mode is feasible. An additional experiment, where different concentrations of **TG-DI** were used to catalyze benzyl alcohol oxidation, indicates that the reaction conversion is highly dependent on the concentration of the catalyst, supporting an inter-resin mode of activity (Figure 4a). To test whether the intra-resin mode is also possible when using **TG-DI** as a catalyst, we wished to vary to amount of **DI** oligomers on the resin and see if the conversion is changing accordingly. Therefore, we have synthesized six batches of **TG-DI** such that in each batch different concentrations of amines were used in the relevant synthetic steps. These six types of **TG-DI** catalyst were used in the oxidation of benzyl alcohol in the same reaction conditions as described in Table 1, entry 5. The results show a clear dependence of the alcohol conversion on the amount of peptoid catalyst bound to the resin (Figure 4b), suggesting that there is an intermolecular catalytic cooperativity in the intra-resin mode. The highest conversion of about 97 % was obtained when 1 M amines where used in the synthesis suggesting that these synthetic conditions produce the optimal amount of peptoids on one resin bead. At lower concentrations, there was a decrease in the alcohol conversion, suggesting that there are lower interactions between peptoids on more diluted resin beads, and thus supporting the activity of the catalyst via the intra-resin cooperativity mode. At higher concentrations, there was also a decrease in the conversion, indicating that the presence of too many peptoid oligomers on one resin bead is not desirable for the activity of this catalyst. Overall, these results suggest that **TG-DI** operates in both the inter-resin and intra-resin cooperativity modes, which can explain its higher activity, compare to **TG-BT** and **DI**.

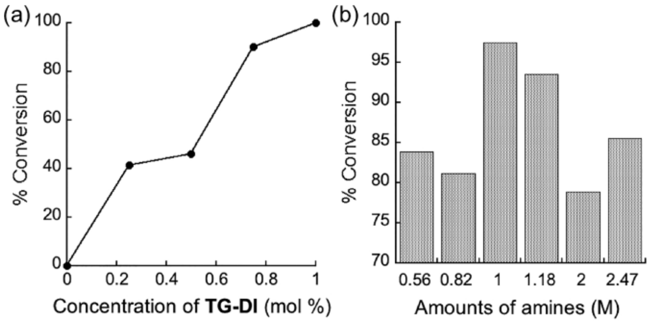

Figure 4. (a) Conversion of benzyl alcohol to benzaldehyde as a function of the concentration of the catalyst. (b) Conversion of benzyl alcohol to benzaldehyde as a function of the amounts of incorporated amines within **TG-DI**. All the reactions were performed in acetonitrile (1 mL) at 40 °C and under oxygen atmosphere, with 3.3 µmol catalyst, 6.6 µmol CuI, 6.6 µmol NMI and 330 µmol benzyl alcohol for 24 hours. Benzaldehyde conversions were determined by gas chromatography (GC).

In order to evaluate the progress of the reaction with time and to determine the time needed to obtain full conversion, we have repeated the reaction from Table 1, entry 5 and analyzed by GC a sample from the solution every several hours. The results showed a gradual and rather linear increase in alcohol conversion, and full conversion was achieved already after 17 hours (Figure S11). Finally, we wished to explore whether the catalyst **TG-DI** can be re-used, as its recyclability will enable to obtain an overall TON higher than that achieved in one catalytic reaction. We note here that the bound peptoid can only be cleaved from the resin in highly acidic conditions, meaning it cannot be cleaved from the resin in the catalytic conditions applied during the oxidation reaction, and thus leaching of the catalyst was not observed. In addition, as the resin is not swelled in acetonitrile, the resin-bound catalyst is precipitated at the end of the reaction, when the stirring is stopped. Therefore, **TG-DI** could be simply separated from the solution of the reaction mixture at the end of the reaction and re-used in a subsequent identical oxidation reaction. Accordingly, after repeating the reaction described in Table 1, entry 5, the solvent was decanted, the resin-bound catalyst was washed three times with acetonitrile, which was decanted each time, and used again in an identical reaction. The conversion of the alcohol in the second cycle was about 90 % and the catalyst was separated, washed and used again for four more consecutive cycles. A rather constant decrease in the alcohol conversion was observed in each cycle reaching a conversion of about 5 % in the fifth cycle (Figure S13). The overall TON for the oxidation reaction of benzyl alcohol using **TG-DI** at 1 mol-% was 296 – about 10 times higher than the TON obtained when 1 mol-% **DI** was used as a catalyst in the homogeneous reaction. With these results we have demonstrated for the first time the recyclability of a peptoid catalyst in a heterogeneous catalytic system.

Encouraged by these results we wished to test the catalytic capability and recyclability of **TG-DI** in the oxidative coupling of alcohols and amines to form imines.[7b] Initially, benzyl alcohol and benzylamine (in the same concentration as benzyl alcohol) were used as substrates and the reaction was carried out in the same conditions described in Table 1, entry 5 (1 mol-% catalyst), but without NMI, which is not needed in this reaction.[7b] These conditions lead to > 99 % conversion. Decreasing the catalyst loading to 0.5 mol-% or to 0.2 mol-% still yielded > 99 % conversion. At 0.1 mol-% catalyst the conversion was still high (96 %), but lowering it further led to lower conversion (e.g., at 0.05 mol-% the conversion was 85 %). The highest TON obtained in this reaction using **TG-DI** as a catalyst was therefore 960, similar to the TON obtained when BT was used as a catalyst in the homogeneous system (980) but, notably, about 20 times higher than the TON obtained when **DI** was used as a catalyst in the homogeneous system (< 5 % conversion and TON < 50 in the oxidative coupling of benzyl alcohol and benzylamine at 0.1 mol-% catalyst). This result is remarkable for a heterogeneous system and can be explained by the observation that at the range of 0.1–1 mol-% catalyst, the conversion to imines is not dependent on the concentration of the catalyst, suggesting that it operates only via the intra-resin mode.

The oxidative coupling of benzyl alcohol and benzylamine, using 0.1 mol-% **TG-DI** was repeated and a sample from the solution was analyzed by GC every several hours. The results showed a sharp increase in imine conversion to about 80 % in 8 hours but full conversion was only achieved after 22 hours (Figure S12). Recycling of **TG-DI** (0.1 mol-%) was done following the same procedure that was used in the oxidation of alcohols (see above). After the second cycle the conversion was 83 %, and this was decreased further to 53 % after the third cycle. The catalyst was recycled four more times and the conversion decreased gradually to about 20 % in the last cycle (Figure S14). Additional cycles yielded even lower conversions. The overall TON after 8 cycles was therefore 2762, almost 3 times higher and about 60 times higher than the highest TON obtained when **BT** or **DI**, respectively, were used in the homogeneous system.

Finally, the scope of the oxidative coupling reaction using 0.1 mol-% **TG-DI**, 1 equiv. of benzyl alcohol and 1.1 equiv. of an amine (see SI for details) was evaluated. The results, depicted in Figure 5, show that the highest conversions (> 95 %) were obtained with benzyl-containing aromatic amines, while with (S)-(–)-1-(1-Naphthyl)ethylamine the conversion is lower (86 %), suggesting that the size of the aromatic group effects the reaction. As expected, the conversions of the less reactive aliphatic amines were also lower, but still comparable to these obtained when **BT** was used as a homogeneous catalyst.[7b]

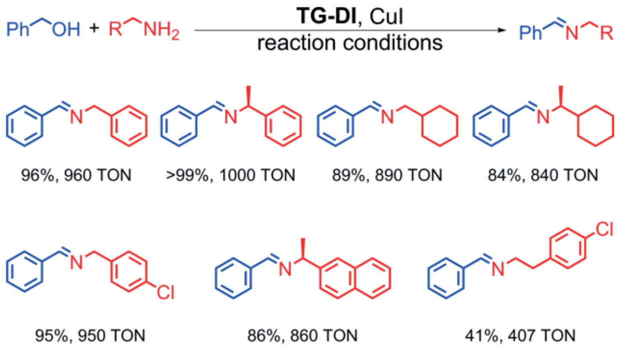

Figure 5. Substrate scope in the oxidative coupling of benzyl alcohol with various amines. Reactions were performed in acetonitrile (1 mL) at 40 °C with 3.3 mmol alcohol, 3.6 mmol amine, 0.1 mol-% **TG-DI** and 0.2 mol-% CuI under oxygen atmosphere for 24 h. Conversions were determined by GC.

Conclusions

In this work we report an important advance in foldamers chemistry – the finding that catalytic peptoids that are synthesized on solid support (resin) can be also used on-resin. Thus, they can perform as effective and recyclable catalysts in the oxidation of benzyl alcohol and in the oxidative coupling of benzyl alcohol with various amines to form imines; the later with an overall TON of about 3000, three times higher or even 60 times (!) higher than the TON obtained using **BT** or **DI**, respectively, as off-resin catalysts. We have previously demonstrated that **BT** can catalyze the oxidation of primary alcohols and the oxidative coupling of alcohols and amines with a TON 20 times higher than a mixture of the two catalytic groups, or the peptoid **DI** in the same reaction conditions. We therefore suggested that **BT** catalyzes the reactions via an intra-peptoid cooperativity mode that enables its high efficiency. In the present work, we have synthesized **BT** and **DI** on TentaGel resin and tested the performance of resin-bound **BT** (**TG-BT**) and **DI** (**TG-DI**) as heterogeneous and recyclable catalysts in the same oxidation transformations. We discovered that although both peptoids can be used as on-resin recyclable catalysts, **TG-DI** is a much better catalyst than **TG-BT**. To understand this result, we have changed the amount of peptoid on the resin or the concentration of the catalyst in solution, and tested a mixture of two control peptoid dimers, **TG-DP** and **TG-DT**, bearing a benzyl group and either a phenanthroline or TEMPO group, respectively. The results from these experiments showed that **TG-DI** catalyzes the oxidation of benzyl alcohol in an intra-resin cooperative mode, which we suggest that due to steric considerations in the heterogeneous system, is superior to the intra-peptoid cooperativity. Although there are several examples of soluble catalytic peptoids, the use of on-resin peptoid catalysts enable not only to recycle them and obtain higher TON, but also to avoid typical work-up and purification steps that are laborious, expensive and can lead to product loss. As such, this work represents an important progress in the construction of peptoids and other peptidomimetic oligomers as efficient and recyclable on-resin catalysts towards applications in energy and pharmaceuticals related research.

Experimental Section

Catalysis Experiments: A typical heterogeneous catalytic oxidation of benzyl alcohol was performed as following: the peptoid on different resins (1 mol-%, 3.3 µmol) and CuI (6.6 µmol, 2 equiv.) were placed in a dry vial, which was then capped with a septum under nitrogen environment. Dry acetonitrile (0.3 mL) was added, and the mixture was stirred for 2 minutes at room temperature following by the addition of *N*-methylimidazole (6.6 µmol, 2 equiv.). The vial was opened to room atmosphere and additional acetonitrile (0.7 mL) was added. The mixture was stirred for 1 hour at room temperature to enable peptoid-metal complex formation. After 1 hour, benzyl alcohol (330 µmol) was added, and a small oxygen balloon at atmospheric pressure attached to a needle was inserted via the septum. The mixture was allowed to stir at about 40 °C for 24 hr before it was cooled down and analyzed by GC. A typical heterogeneous catalytic synthesis of imines was performed as following: the peptoid on Tentagel resin (0.1 mol-%, 0.33 µmol) and CuI (0.66 µmol, 2 equiv.) were placed in a dry vial, which was then capped with a septum under nitrogen environment. Dry acetonitrile (0.3 mL) was added, and the mixture was stirred for 2 minutes at room temperature before benzylamine (363 µmol) was added. The vial was opened to room atmosphere and additional acetonitrile (0.4 mL) was added. The solvent was stirred for 1 hour at room temperature, to enable peptoid-metal complex formation. After 1 hour, the alcohol (330 µmol) was added, and a small oxygen balloon at atmospheric pressure attached to a needle was inserted via the septum. The mixture was allowed to stir at about 40 °C for 24 hr before it was cooled down and analyzed by GC.

Recycling Experiments: Recycling of the catalyst was done after receiving high conversions (> 99 %). The solvent was decanted and the resin-bound catalyst was washed three times with 2 mL of acetonitrile. After three washes, the resin was left with small amount of solvent.

Acknowledgments

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Keywords: Heterogeneous catalysis · Peptoids · Alcohol oxidation · Oxidative coupling · On-resin recycling

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[13] Cu^{I} is added as a solid and therefore we preferred to use 2 mol-% in order to avoid the error in weighting a very small amount.

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On-Resin Catalysis

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A Resin-Bound Peptoid as a Recyclable Heterogeneous Catalyst for Oxidation Reactions

Catalytic peptoids that are synthesized on solid support (resin) can be also used on-resin. Thus, they can perform as effective and recyclable catalysts in the oxidation of benzyl alcohol and in the oxidative coupling of benzyl alcohol with various amines to form imines in an overall turn-over number (TON) of up to 60 times higher than the TON obtained when the catalyst was used off-resin.

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