

Supported Catalysis

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Molecular Engineering of Trifunctional Supported Catalysts for the Aerobic Oxidation of Alcohols

Antony E. Fernandes,* Olivier Riant, Klavs F. Jensen, and Alain M. Jonas*

Abstract: We describe a simple and general method for the preparation and molecular engineering of supported trifunctional catalysts and their application in the representative Cu/TEMPO/NMI-catalyzed aerobic oxidation of benzyl alcohol. The methodology allows in one single step to immobilize, with precise control of surface composition, both pyta, Cu^I, TEMPO, and NMI sites on azide-functionalized silica particles. To optimize the performance of the heterogeneous trifunctional catalysts, synergistic interactions are finely engineered through modulating the degree of freedom of the imidazole site as well as tuning the relative surface composition, leading to catalysts with an activity significantly superior to the corresponding homogeneous catalytic system.

The development of multifunctional heterogeneous catalysts based on homogeneous catalytic systems has recently emerged as a promising field for advancing modern and sustainable chemistry.^[1] This family of catalysts is crucial for reactions requiring multiple active components (such as metal, ligand, base, and other cofactors), and can prove particularly advantageous for performing cascade of reactions^[2] within a single and recyclable material incorporating a complete cocktail of the required active ingredients.^[3] The careful positioning of these individual functions on a solid support can also provide ways for improving activity^[4] and selectivity^[5] by tailoring synergistic interactions, in a way reminiscent of enzymatic catalysis. This requires precise control of the relative concentrations^[6] and the dynamic interactions^[7] between the immobilized partners.

However, it remains challenging to transfer such complex systems from homogeneous catalysis to the realm of heterogeneous catalysis, because this requires synthetic efforts commensurate with the number of active molecules to immobilize, often necessitating orthogonal and sequential approaches.^[8] Therefore, general and robust strategies for rapidly accessing such multifunctional catalysts need to be developed.

Herein, we demonstrate the easy and rational heterogenization of a complex trifunctional catalytic system of considerable practical importance,^[9] leading to performances significantly superior to the corresponding homogeneous case while benefiting from the well-known advantages of supported catalysis. Most importantly, our methodology allows not only to quantitatively tune the surface composition of the catalyst, but also to adjust the degree of freedom of the catalytic components for increased activity.

We recently reported^[10] on a versatile methodology for the preparation of bifunctional supported molecular catalysts based on simultaneously reacting couples of alkynylated partners to an azide-functionalized mesoporous silica platform using the copper-catalyzed azide-alkyne cycloaddition (CuAAC)^[11] reaction. Notably, we demonstrated that the surface composition faithfully reflected the relative proportion of each ingredient in the grafting solution. This strategy was initially applied to the Cu^I/2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)-catalyzed aerobic oxidation of alcohols,^[9a,12] and allowed the precision preparation of bifunctional supported catalysts displaying an activity superior to that of their monofunctional equivalent as a result of binary synergistic interactions.^[10]

From our previous study,^[10] we envisioned that incorporating *N*-methylimidazole (NMI) sites (NMI is known to accelerate the Cu/TEMPO-catalyzed aerobic oxidation of alcohols by decreasing the Cu^{II}/Cu^I reduction potential)^[12a,b] would improve the catalytic performances of our binary supported Cu/TEMPO catalysts. Accordingly, preliminary results indeed suggested that adding free NMI to the binary supported Cu/TEMPO catalyst could lead to a substantial acceleration. This guided us to the preparation of supported trifunctional catalysts that incorporate pyridyltriazole (pyta),^[5c,13] Cu^I, TEMPO, and NMI sites (Scheme 1).

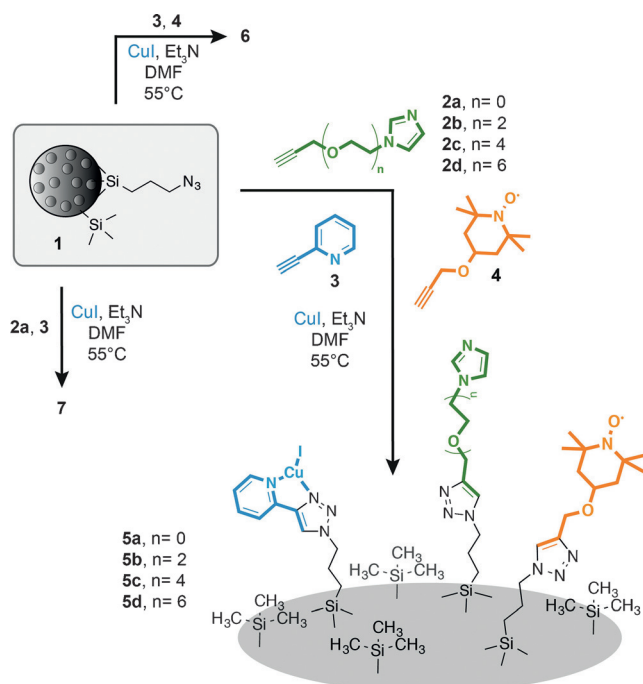
Meanwhile, we surmised that another advantage could result from using CuAAC chemistry by considering the Cu^I catalyst (CuI) used during the grafting step as an inherent component of the final catalytic system; thus, reducing the immobilization procedure to a single step from readily accessible azide-functionalized mesoporous silica **1** (Scheme 1).

Based on the surface area and the amount of grafted azide in **1** (270 m² g⁻¹, 0.26 mmol g⁻¹), we calculated that an average distance of ~1.3 nm separates each functionalizable site. To tune the ability of the additional imidazole site to reach this distance, and thus to act cooperatively, imidazole derivatives **2a-d** (Scheme 1), bearing oligo(ethylene oxide) spacers of various lengths, were synthesized (see the Supporting Information). The statistical theory of chain molecules allowed us to compute the probability to have the imidazole at a specific

[*] Dr. A. E. Fernandes, Prof. O. Riant, Prof. A. M. Jonas
Institute of Condensed Matter and Nanosciences
Université Catholique de Louvain
Louvain-la-Neuve, 1348 (Belgium)
E-mail: antony.fernandes@uclouvain.be
alain.jonas@uclouvain.be

Dr. A. E. Fernandes, Prof. K. F. Jensen
Department of Chemical Engineering
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)

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Scheme 1. Preparation of supported bifunctional and trifunctional catalysts in one step from azide-functionalized mesoporous silica **1**.

location depending on the spacer length (Supporting Information); the maximal probability to be 1.3 nm away from the grafting site being attained with an hexaethylene glycol spacer (Figure S2).

Trifunctional catalysts **5a–d** were thus prepared using a 2:1:3 mixture of **2a–d/3/4**^[14] (NMI being generally used in a 2-fold excess vs. Cu; 1:3 being the optimal pyta/TEMPO proportions obtained with the bifunctional supported catalysts)^[10] in one step from silica platform **1**, ensuring in each case an equimolar CuI loading with respect to 2-ethynylpyridine **3** (Scheme 1). The catalysts were characterized by FT-IR, XPS, ICP-AES, and N₂-physisorption (Supporting Information). Namely, FT-IR showed in each case the disappearance of the characteristic azide band at ~2100 cm⁻¹, while XPS analysis confirmed the appearance of Cu^I signals. As expected, the Cu concentration, as determined by ICP AES analysis, was found to be nearly the same for each catalyst (~0.050 mmol g⁻¹; Supporting Information). Similarly, bifunctional supported catalysts **6** and **7** were prepared from a 1:3 mixture of **3/4** and a 2:1 mixture of **2a/3**, respectively (Scheme 1).

Catalysts **5a–d**, **6**, and **7** were evaluated in the benchmark aerobic oxidation of benzyl alcohol to benzaldehyde in toluene at 80 °C under O₂ bubbling (5.5 mL min⁻¹; Figure 1 a).

The trend in catalytic activity with the trifunctional catalysts linearly followed the probability to have the imidazole end of the linker at a point located 1.3 nm away from its grafting point on the substrate (Figure 1 b). The hexaethylene glycol spacer gives the best results among the probed spacer lengths (as predicted in Figure S2), with a ~3.5-fold improvement of the initial turnover frequency (TOF) compared to **5a** bearing no ethylene oxide spacer (Figure 1 c,

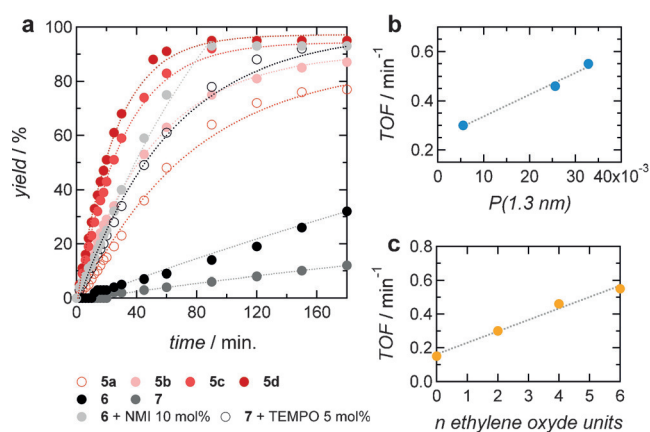


Figure 1. a) Catalytic activity of **5a–d**, **6**, and **7** in the aerobic oxidation of benzyl alcohol. b) Initial TOF plotted versus the calculated probability for the imidazole site to reach another site located 1.3 nm away from the grafting point of the linker. c) Initial TOF as a function of the number of ethylene oxide units *n* on the NMI site. Conditions: BrOH (0.26 mmol) in toluene (0.2 M), O₂ bubbling (5.5 mL min⁻¹), 80 °C. Reactions were performed using a 5 mol % loading in Cu. Yields were determined by GC analysis using dodecane as the internal standard.

Table 1: Values of initial turnover frequencies (TOFs).

Catalyst	TOF [× 10 ⁻² min ⁻¹] ^[a]
5a	14.8
5b	30.0
5c	46.4
5d	55.1
6	3.1
7	1.3
6 + NMI	25.4
7 + TEMPO	22.7
5a + NMI	56.9
5d + NMI	68.0
5d + TEMPO	52.4
5d ^[b]	94.4
8 ^[b]	74.0
5d ^[b] + TEMPO	90.7
5d ^[b] + NMI	102.0
8 ^[b] + TEMPO	80.4
8 ^[b] + NMI	102.9
NMI/9-Cu/TEMPO (2:1:3)	11.7
NMI/9-Cu/TEMPO (2:1:1)	11.9
NMI/9-Cu/TEMPO (2:1:0)	6.8
NMI/9-Cu/TEMPO (0:1:1)	–

[a] Initial TOFs were obtained by fitting the corresponding experimental data at low conversions with a linear function passing through the origin (Supporting Information) and are calculated with respect to Cu (5 mol %). [b] Catalyst prepared from a new batch of **1** (see in the text).

Table 1). Interestingly, bifunctional catalysts **6** and **7** performed particularly slowly, giving, respectively, 32 % and 12 % of the aldehyde product after 3 hours of reaction. In parallel, when combining the binary supported systems **6** or **7** with homogeneous NMI or TEMPO, respectively, the activity raised to the one of **5a–d** (Figure 1); however, the corresponding initial TOFs only reached less than 50 % of those obtained with catalyst **5d** (Table 1).

Altogether, this clearly demonstrates the importance of the NMI site and the beneficial synergistic effects in trifunctional catalysts **5a–d**, which is in agreement with the recently postulated mechanisms for the Cu/TEMPO/NMI-catalyzed aerobic oxidation of alcohols.^[9c, 12b, 15] Although the mechanism is still debated, it was recently demonstrated that the reaction path involves the formation of an initiating (bipy)-(NMI)Cu adduct that combines with TEMPO species. Therefore, both bipyridine, Cu, NMI, and TEMPO are essential for the reaction to proceed efficiently.

To verify whether the degree of freedom of the oligo(ethylene oxide) spacer in **5d** was indeed optimal, we performed a series of tests adding homogeneous NMI to the reaction mixture (Figure 2).

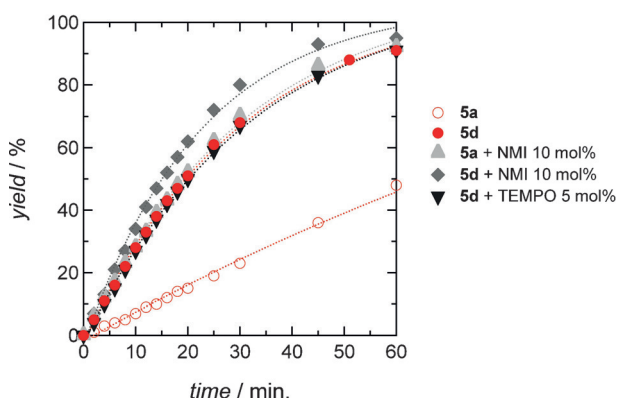


Figure 2. Catalytic activity of **5a** and **5d** in the aerobic oxidation of benzyl alcohol in presence of additional free NMI and TEMPO. Conditions: BnOH (0.26 mmol) in toluene (0.2 M), O₂ bubbling (5.5 mL min⁻¹), 80 °C. Reactions were performed using a 5 mol % loading in Cu. Yields were determined by GC analysis using dodecane as the internal standard.

Only a slight improvement could be observed when combining **5d** and free NMI (initial TOF increasing by ~20 %), whereas when using **5a**/NMI, the TOFs reached what could be obtained with **5d** only (Table 1). This confirmed that the hexaethylene glycol spacer is of proper length to ensure maximal freedom while keeping the imidazole site close to the catalyst surface. Similarly, no difference could be noted when using **5d** or **5d**/TEMPO (Figure 2 and Table 1).

Next, we were wondering whether it could be possible to increase the specific activity of **5d**, that is, the activity per mass unit of catalyst. Following our experimental procedure and earliest results,^[10] the surface concentration of Cu in our multifunctional catalysts is directly controlled by the fraction of **3** used in the grafting solution. Thus, increasing this proportion would result in having more Cu sites on the surface and, in principle, would require less silica catalyst to achieve similar activity.

Accordingly, **8** was prepared by reacting a 2:1:1 mixture of **2d/3/4** with a new batch of silica **1** (252 m² g⁻¹, 0.29 mmol g⁻¹) using our procedure (Scheme 1). To ensure reliable comparison, **5d** was also prepared from this same batch of silica. Trifunctional catalyst **8** (see the Supporting Information for full characterization details) showed a ~50 % increase in its

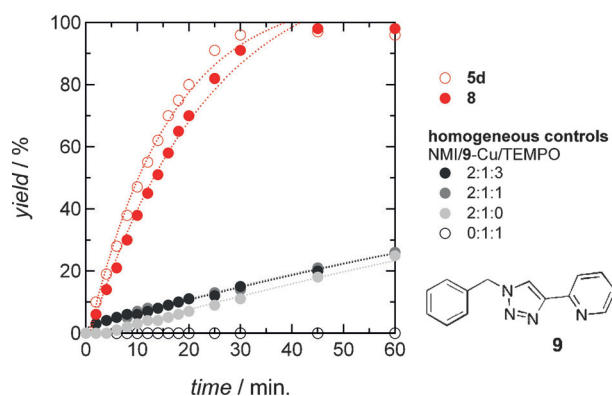


Figure 3. Catalytic activity of **5d** and **8** in the aerobic oxidation of benzyl alcohol and comparison with homogeneous controls. Conditions: BnOH (0.26 mmol) in toluene (0.2 M), O₂ bubbling (5.5 mL min⁻¹), 80 °C. Reactions were performed using a 5 mol % loading in Cu. Homogeneous control experiments correspond to CuI (5 mol %), **9** (5 mol %), TEMPO, and NMI. Yields were determined by GC analysis using dodecane as the internal standard.

Cu content (0.079 mmol g⁻¹) compared to the new **5d** (0.054 mmol g⁻¹), resulting in ~30 % less catalyst being needed to achieve a 5 mol % Cu loading vs. benzyl alcohol in the catalytic tests (Figure 3).

Remarkably, **8** performed only slightly slower than **5d** (initial TOF being inferior by ~20 %), with both catalysts yielding complete transformation of benzyl alcohol to benzaldehyde in less than 45 minutes (Figure 3 and Table 1).

Grafting density and surface area are important parameters because they directly impact the average distance between each site. This explains the difference of activity between **5d** prepared from the two different batches of azide-functionalized silica **1** (Table 1).

While adding homogeneous TEMPO to **8** did not bring significant improvements, adding free NMI led to a substantial ~40 % increase in the initial TOF, whereas only a ~10 % increase is observed with **5d** prepared from the same batch of **1** (Table 1 and Supporting Information). Altogether, this suggests that the distribution of the active sites in **8** is less optimal than in **5d**, but still allows achieving better activity per mass unit of catalyst (~15 % based on initial TOFs). A maximal turnover number (TON) of 228 and initial TOF of 0.95 min⁻¹ could be obtained with **8** based on Cu (Supporting Information).

Notably, our trifunctional catalysts all performed much faster than homogeneous control experiments carried out with pyridyl-triazole ligand **9**^[16] (Figure 3), CuI, NMI, and TEMPO (Figure 3 and Table 1), emphasizing the beneficial synergistic effects of concentrating each catalytic partner in close proximity on the silica supports. Remarkably, it appeared that when performing the homogeneous tests with **9** instead of the usual bipyridine ligand, the reaction works with or without TEMPO (Figure 3 and Supporting Information). This is obviously not the case with our heterogeneous catalysts: the bifunctional pyta-Cu/NMI supported catalyst **7** is the least active, and good activity is restored upon adding homogeneous TEMPO to **7** (Figure 1). Further studies are

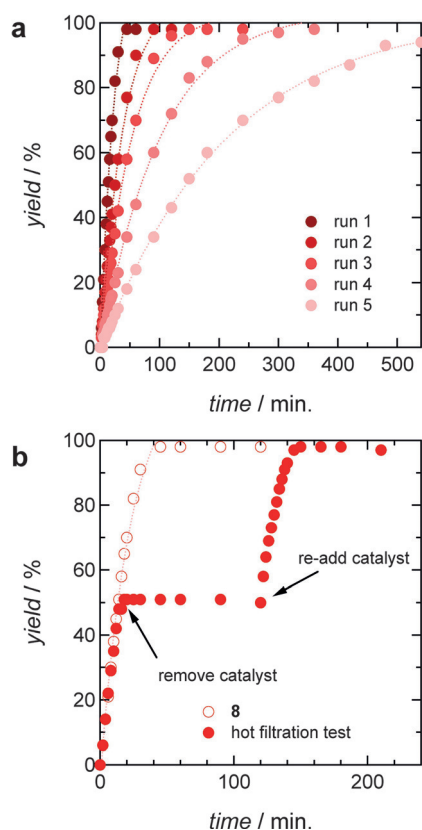


Figure 4. a) Recycling and b) hot filtration experiments with catalyst **8** in the aerobic oxidation of benzyl alcohol. Conditions: BnOH (0.26 mmol) in toluene (0.2 M), O₂ bubbling (5.5 mL min⁻¹), 80 °C. Reactions were performed using a 5 mol% loading in Cu. Yields were determined by GC analysis using dodecane as the internal standard.

underway to explore the use of pyridyl-triazole ligands in homogeneous Cu-catalyzed aerobic oxidation reactions.

Finally, the recycling of **8** was investigated in the model aerobic oxidation of benzyl alcohol (Figure 4a). Catalyst **8** could be easily recovered and reused following simple filtration and rinsing, still giving quantitative conversions after 5 runs, albeit with increased reaction time (corresponding to a total TON of ~97). ICP-AES analysis of the used catalysts indicated a minor Cu loss of 1% after 1 run and 4% after 5 runs (Supporting Information). A hot filtration test (Figure 4b) demonstrated that activity totally stopped upon removing the catalyst, whereas it could be recovered upon re-addition of **8** to the reaction mixture.

In conclusion, we have demonstrated a simple and general approach to the preparation of supported trifunctional catalysts and their rational molecular engineering. The fine-tuning of the linker length on the imidazole site together with the optimization of surface composition allowed the development of efficient and recyclable catalysts for the heterogeneous Cu/TEMPO/NMI-catalyzed aerobic oxidation of benzyl alcohol. We anticipate that the straightforward and modular strategy presented here will provide a powerful tool to the rapid preparation, screening, and rational engineering of supported multifunctional catalysts.

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- [1] a) J. M. Notestein, A. Katz, *Chem. Eur. J.* **2006**, 12, 3954–3965; b) F.-X. Felpin, E. Fouquet, *ChemSusChem* **2008**, 1, 718–724; c) J.-K. Lee, M. Kung, H. Kung, *Top. Catal.* **2008**, 49, 136–144; d) K. Motokura, M. Tada, Y. Iwasawa, *Chem. Asian J.* **2008**, 3, 1230–1236; e) E. L. Margelefsky, R. K. Zeidan, M. E. Davis, *Chem. Soc. Rev.* **2008**, 37, 1118–1126; f) S. Shylesh, W. R. Thiel, *ChemCatChem* **2011**, 3, 278–287; g) C. Yu, J. He, *Chem. Commun.* **2012**, 48, 4933–4940; h) N. A. Brunelli, C. W. Jones, *J. Catal.* **2013**, 308, 60–72; i) U. Díaz, D. Brunel, A. Corma, *Chem. Soc. Rev.* **2013**, 42, 4083–4097; j) M. J. Climent, A. Corma, S. Iborra, M. J. Sabater, *ACS Catal.* **2014**, 4, 870–891; k) K. Motokura, *ChemCatChem* **2014**, 6, 3067–3068.
- [2] a) N. R. Shiju, A. H. Alberts, S. Khalid, D. R. Brown, G. Rothenberg, *Angew. Chem. Int. Ed.* **2011**, 50, 9615–9619; *Angew. Chem.* **2011**, 123, 9789–9793; b) T. L. Lohr, T. J. Marks, *Nat. Chem.* **2015**, 7, 477–482.
- [3] I. Wheeldon, S. D. Minter, S. Banta, S. C. Barton, P. Atanassov, M. Sigman, *Nat. Chem.* **2016**, 8, 299–309.
- [4] a) S. Huh, H.-T. Chen, J. W. Wiench, M. Pruski, V. S. Y. Lin, *Angew. Chem. Int. Ed.* **2005**, 44, 1826–1830; *Angew. Chem.* **2005**, 117, 1860–1864; b) R. K. Zeidan, S.-J. Hwang, M. E. Davis, *Angew. Chem. Int. Ed.* **2006**, 45, 6332–6335; *Angew. Chem.* **2006**, 118, 6480–6483; c) K. K. Sharma, T. Asefa, *Angew. Chem. Int. Ed.* **2007**, 46, 2879–2882; *Angew. Chem.* **2007**, 119, 2937–2940; d) K. Motokura, M. Tada, Y. Iwasawa, *Angew. Chem. Int. Ed.* **2008**, 47, 9230–9235; *Angew. Chem.* **2008**, 120, 9370–9375; e) K. K. Sharma, R. P. Buckley, T. Asefa, *Langmuir* **2008**, 24, 14306–14320; f) S. Shylesh, A. Wagner, A. Seifert, S. Ernst, W. R. Thiel, *Chem. Eur. J.* **2009**, 15, 7052–7062; g) S. Shylesh, A. Wagner, A. Seifert, S. Ernst, W. R. Thiel, *Angew. Chem. Int. Ed.* **2010**, 49, 184–187; *Angew. Chem.* **2010**, 122, 188–191; h) K. K. Sharma, A. V. Biradar, S. Das, T. Asefa, *Eur. J. Inorg. Chem.* **2011**, 3174–3182; i) H. Noda, K. Motokura, A. Miyaji, T. Baba, *Angew. Chem. Int. Ed.* **2012**, 51, 8017–8020; *Angew. Chem.* **2012**, 124, 8141–8144; j) H. Noda, K. Motokura, A. Miyaji, T. Baba, *Adv. Synth. Catal.* **2013**, 355, 973–980; k) K. Motokura, Y. Ito, H. Noda, A. Miyaji, S. Yamaguchi, T. Baba, *ChemPlusChem* **2014**, 79, 1053–1058; l) H. Noda, K. Motokura, W.-J. Chun, A. Miyaji, S. Yamaguchi, T. Baba, *Catal. Sci. Technol.* **2015**, 5, 2714–2727; m) Q. Zhao, Y. Zhu, Z. Sun, Y. Li, G. Zhang, F. Zhang, X. Fan, *J. Mater. Chem. A* **2015**, 3, 2609–2616.
- [5] a) S. Huh, H.-T. Chen, J. W. Wiench, M. Pruski, V. S. Y. Lin, *J. Am. Chem. Soc.* **2004**, 126, 1010–1011; b) E. L. Margelefsky, A. Bendjériou, R. K. Zeidan, V. Dufaud, M. E. Davis, *J. Am. Chem. Soc.* **2008**, 130, 13442–13449; c) C. C. Paluti, E. S. Gawalt, *J. Catal.* **2010**, 275, 149–157; d) W. Xiao, R. Jin, T. Cheng, D. Xia, H. Yao, F. Gao, B. Deng, G. Liu, *Chem. Commun.* **2012**, 48,

- 11898–11900; e) A. T. Dickschat, F. Behrends, S. Surmiak, M. Weiß, H. Eckert, A. Studer, *Chem. Commun.* **2013**, 49, 2195–2197; f) L. Deiana, L. Ghisu, S. Afewerki, O. Verho, E. V. Johnston, N. Hedin, Z. Bacsik, A. Córdova, *Adv. Synth. Catal.* **2014**, 356, 2485–2492.
- [6] a) A. Puglisi, R. Annunziata, M. Benaglia, F. Cozzi, A. Gervasini, V. Bertacche, M. C. Sala, *Adv. Synth. Catal.* **2009**, 351, 219–229; b) C.-H. Tsai, H.-T. Chen, S. M. Althaus, K. Mao, T. Kobayashi, M. Pruski, V. S. Y. Lin, *ACS Catal.* **2011**, 1, 729–732; c) N. A. Brunelli, K. Venkatasubbaiah, C. W. Jones, *Chem. Mater.* **2012**, 24, 2433–2442.
- [7] a) N. A. Brunelli, S. A. Didas, K. Venkatasubbaiah, C. W. Jones, *J. Am. Chem. Soc.* **2012**, 134, 13950–13953; b) S. Shylesh, D. Hanna, J. Gomes, S. Krishna, C. G. Canlas, M. Head-Gordon, A. T. Bell, *ChemCatChem* **2014**, 6, 1283–1290.
- [8] a) A. T. Dickschat, F. Behrends, M. Bühner, J. Ren, M. Weiß, H. Eckert, A. Studer, *Chem. Eur. J.* **2012**, 18, 16689–16697; b) A. T. Dickschat, S. Surmiak, A. Studer, *Synlett* **2013**, 24, 1523–1528.
- [9] a) J. M. Hoover, J. E. Steves, S. S. Stahl, *Nat. Protoc.* **2012**, 7, 1161–1166; b) B. L. Ryland, S. S. Stahl, *Angew. Chem. Int. Ed.* **2014**, 53, 8824–8838; *Angew. Chem.* **2014**, 126, 8968–8983; c) J. Rabeah, U. Bentrup, R. Stöber, A. Brückner, *Angew. Chem. Int. Ed.* **2015**, 54, 11791–11794; *Angew. Chem.* **2015**, 127, 11957–11960.
- [10] A. E. Fernandes, O. Riant, A. M. Jonas, K. F. Jensen, *RSC Adv.* **2016**, 6, 36602–36605.
- [11] A. E. Fernandes, A. M. Jonas, O. Riant, *Tetrahedron* **2014**, 70, 1709–1731.
- [12] a) J. M. Hoover, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, 133, 16901–16910; b) J. M. Hoover, B. L. Ryland, S. S. Stahl, *J. Am. Chem. Soc.* **2013**, 135, 2357–2367; c) J. M. Hoover, B. L. Ryland, S. S. Stahl, *ACS Catal.* **2013**, 3, 2599–2605.
- [13] a) G. Zhang, Y. Wang, X. Wen, C. Ding, Y. Li, *Chem. Commun.* **2012**, 48, 2979–2981; b) D. Wang, D. Denux, J. Ruiz, D. Astruc, *Adv. Synth. Catal.* **2013**, 355, 129–142.
- [14] A. Gheorghe, A. Matsuno, O. Reiser, *Adv. Synth. Catal.* **2006**, 348, 1016–1020.
- [15] B. L. Ryland, S. D. McCann, T. C. Brunold, S. S. Stahl, *J. Am. Chem. Soc.* **2014**, 136, 12166–12173.
- [16] J. D. Crowley, P. H. Bandeen, L. R. Hanton, *Polyhedron* **2010**, 29, 70–83.

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