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Enhanced site-selectivity in acylation reactions with substrate-optimized catalysts on solid supports†

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A concept for site selective acylation of poly-hydroxylated substrates is presented where polymer-supported catalysts are employed: catalytically active DMAP units were combined with a library of small molecule peptides attached to the solid phase with the goal to identify substrate-optimized catalysts through library screening. For selected examples, we demonstrate how the optimized catalysts can convert "their" substrate with a markedly enhanced site-selectivity, compared to only DMAP. Due to the solid support, product purification is significantly simplified, and the peptidic catalysts can be easily reused in multiple cycles while conserving its efficiency.

Enzymes are virtually perfect catalysts: they have a narrow scope that is paired with an outstanding specificity for the substrate and the chemical task they have been designed for following ages of evolution. Enzymes, therefore, are the major tools used by Nature to make site-selective reactions with complex multi-functionalized biomolecules possible.[1] It is remarkable that the natural strategy for the synthesis of densely functionalized biomolecules never relies on less economic pathways such as protecting group manipulations, in stark contrast to the *de novo*-synthesis methods developed by chemists where protecting group manipulations are still a necessary evil due to the lack of reactions with competitive selectivity.[2]

Gaining precise reactivity with predictable selectivity is a key challenge in contemporary synthetic chemistry, in particular, when the controlled modification of multiple-functionalized molecules is tackled. In the context of pursuing new methods for the site-selective modification of complex molecules,[3] chemists have compiled a reaction compendium that includes catalytic methods, for example, C–H bond oxidations[4] and alkylations,[5] the carbohydrate oxidation,[6] the organoboron-catalyzed functionalization of diols and carbohydrates,[7] and the base-catalyzed modification of *cis*-diols.[8,9] In many ways, these methods reflect the idea of achieving preferential reactivity of one group over another group through the catalyst recognition of a particular functional unit within the molecule.[10] In contrast, catalytic methods that exhibit selectivity for one substrate, rather than one functional unit, remained underdeveloped, even though this strategy is the closest to how enzymes work. The most commonly used concept to identify substrate-optimized catalysts is by mimicking natural evolution, *i.e.* the selection from diversity, in the laboratory through directed evolution of enzymes.[11a] Nevertheless, the fine-tuning of enzyme activity remains a great challenge, in particular with specific non-natural substrates.[11]

Motivated by the prospect of a synthetic access to substrate-specific catalysts that are, like enzymes, also site-selective within the substrate, we became inspired by the fascinating studies by Miller and co-workers demonstrating that low-molecular weight peptides are highly selective and readily tuned catalysts for a number of transformations.[12,13] In particular, the site-selectivities obtained with polyfunctional targets underline the potential of short peptidic sequences to create high degrees of both selectivity and substrate specificity, even in comparison to full grown proteins.[14] We started our own activities in the field with the idea to not use the peptide itself as the catalyst but to attach a catalytically active unit to the peptide core. It was expected that the catalytically active unit of the new system should still be accountable for catalysis while the peptidic chain may influence the selectivity, ultimately affording substrate-optimized catalysts. Following the lead that 4-(dimethylamino)pyridine (DMAP) is a widely used nucleophilic acylation catalyst,[15] the concept was tested first with the goal to discover DMAP-based acylation catalysts that could convert specific substrates with a significantly higher site-selectivity than one would achieve by using mere DMAP as the acylation catalyst. To this end, a library of small peptides containing the artificial amino acid **1** was screened for selected substrates, and it was demonstrated that the identification of optimized catalysts was indeed possible.[16] As exemplified by the benzoylation of polyol **2** providing **3b** (Scheme 1b), the substrates of interest were typically converted with a markedly enhanced site-selectivity, compared to the parent DMAP.

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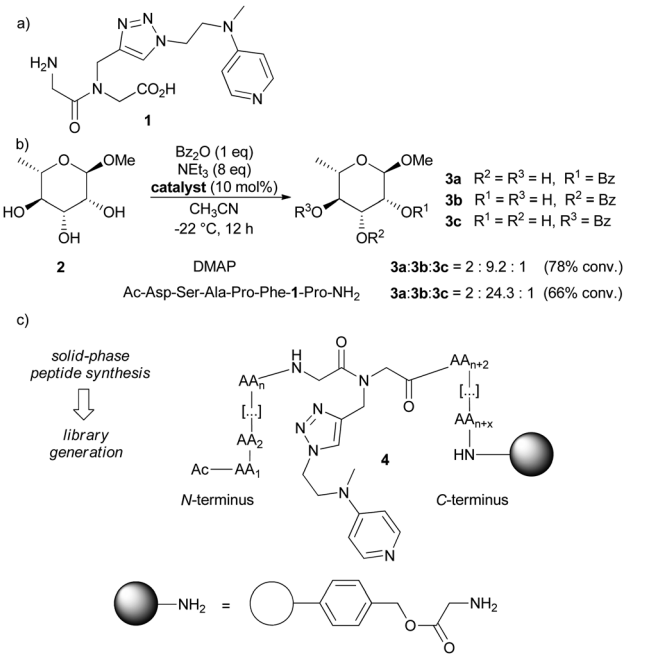
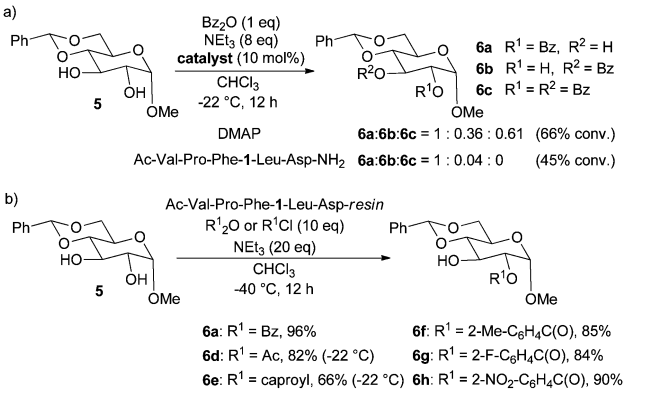


Scheme 1 General strategy for substrate-optimized catalysts: (a) artificial amino acid **1**, (b) substrate-optimized catalyst for the formation of **3b** from **2**,[16] (c) creation of a library of DMAP–peptide conjugates through Fmoc-SPPS on Boc-Gly Merrifield resin.

The strength of the concept was the ease of constructing the catalyst library through an automated solid-phase peptide synthesis using Fmoc-chemistry,[17] and one may attach any other catalytically active unit than DMAP to the peptide chain *via* alkyne–azide cycloaddition.[18] However, the use of relatively cost-intensive peptide catalysts with high molecular masses (in comparison to the substrates) was a constant issue, and product purification was problematic and time-consuming in most cases, in particular, when polar substrates were employed. The efficient reisolation of the peptides for further use was only possible with preparative HPLC; yet numerous careful attempts to reuse the catalysts failed.

We now report the advantages of polymer-supported DMAP–peptide conjugates **4** (Scheme 1c):[19,20] automated solid-phase synthesis on a Boc-glycine Merrifield resin provides a random library of catalytically active peptides still attached to the solid support where each member of the library owns the artificial amino acid **1** containing the DMAP unit (see the ESI† for further details). Of note, the peptide structures we generated possessed an acetyl group at the N-terminus, and the C-terminus was connected to the glycine-modified Merrifield resin. Activity screening with the solid-supported catalysts resulted in the direct identification of hits, and the substrate-optimized catalysts were easily separated from the reaction mixtures through simple washing and filtration, allowing for multiple reuse.

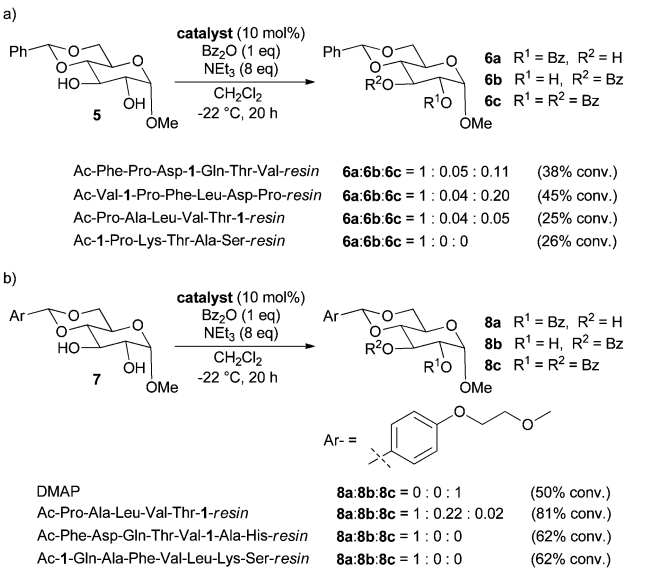
We began our studies with the optimization of the DMAP-catalyzed acylation of dihydroxylated substrate **5** with regard to the site-selectivity (Scheme 2). The benzoylation of glucose-derived diol **5** resulted in a poor selectivity with DMAP (**6a**:**6b** = 2.8:1), and substantial amounts of the dibenzoylated product were



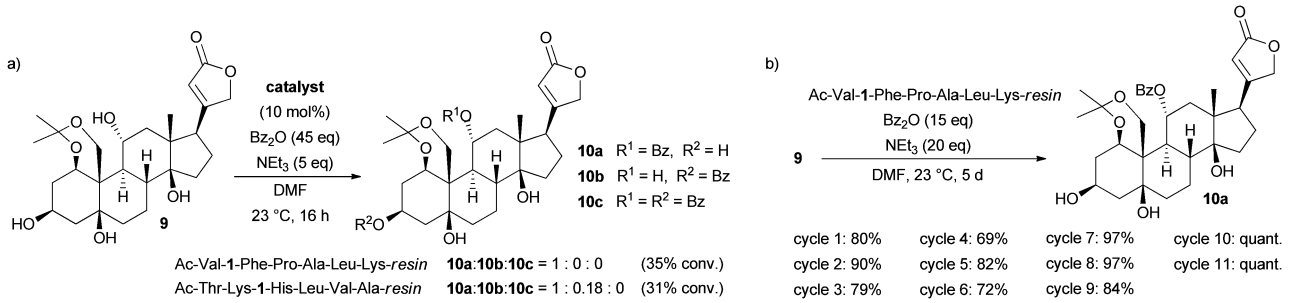
Scheme 2 The acylation of glucose-derived diol **5**: (a) substrate-optimized catalyst *vs.* DMAP,[16] (b) substrate-optimized on solid support.

also formed. We then found that a markedly higher selectivity (**6a**:**6b** = 28:1) can be obtained when employing 10 mol% of Ac-Val-Pro-Phe-**1**-Leu-Asp-NH_2, as an substrate-optimized but still homogeneous catalyst (Scheme 2a). The same peptidic sequence was a powerful catalyst when remaining attached at the solid phase: Ac-Val-Pro-Phe-**1**-Leu-Asp-resin (10 mol%) provided the monobenzoylated product **6a** in an excellent 96% isolated yield. A range of other acylations were also possible, and the esters **6d–h** were isolated in yields between 66 and 90%. Of primary importance, one catalyst was, upon filtration and washing, reused for all the reactions summarized in Scheme 2b.

We then questioned whether the site-selectivity with the solid supported catalyst might be simply due to the involvement of the resin, fully independent from the peptidic sequence bound to resin. However, screening of a small library of 21 catalysts on solid support unequivocally demonstrated that subtle changes in the catalyst structure influence the eventual selectivity: for example, the use of Ac-**1**-Pro-Lys-Thr-Ala-Ser-resin resulted only



Scheme 3 Optimization of the benzoylation of glucose-derived diols **5** and **7**.



Scheme 4 Optimization of the benzoylation of ouabagenin derivative **9**.

in the formation of the monobenzoylated sugar **6a** while mixtures with **6b** and **6c** were obtained through the use of other catalysts. When using DMAP under solution conditions for the benzoylation of diol **7**, a compound closely similar to **5** but with an additional ether group, we only obtained the dibenzoylated product **8c**, presumably due to the low solubility of the starting diol **7** under the reaction conditions, compared to an enhanced solubility of the mono- and dibenzoylated compounds **8** (Scheme 3b). On the other hand, the use of the supported catalysts allowed for the straightforward formation of the monobenzoylated compounds and underlines the hypothesis that the solid support is not an innocent bystander; instead, the resin may influence the substrate-specificity through, for example, polarity and diffusion effects. We optimized the benzoylation of diol **7** with the solid-supported catalysts and found that Ac-Phe-Asp-Gln-Thr-Val-**1**-Ala-His-resin and Ac-**1**-Gln-Ala-Phe-Val-Leu-Lys-Ser-resin performed equally well: the monobenzoylated compound **8a** was obtained as the exclusive product. This result highlights how fully unequal peptide sequences can afford the same selectivity effect while others (*e.g.*, Ac-Pro-Ala-Leu-Val-Thr-**1**-resin) are less effective and provide product mixtures.

As a second case study, we chose the benzoylation of ouabagenin-derived acetonide **9**.[21] As summarized in Scheme 4, the optimization of this reaction was also successful: an excellent selectivity for the monobenzoylate compound **10a** was found when employing Ac-Val-**1**-Phe-Pro-Ala-Leu-Lys-resin. In the presence of Ac-Thr-Lys-**1**-His-Leu-Val-Ala-resin, for example, significant amounts of compound **10b** were generated. We then focused on the preparative scale benzoylation of the ouabagenin derivative **9**. Using the optimized catalyst Ac-Val-**1**-Phe-Pro-Ala-Leu-Lys-resin, the reaction was run until complete conversion with a large excess of both benzoic acid anhydride (15 equivalents) and triethylamine (20 equivalents) at room temperature in DMF. The desired product of the monobenzoylation, *i.e.* **10a**, was isolated in 80% yield; and after the reaction, the catalyst was entirely recovered. For a subsequent recycling study, the benzoylation of **9** was performed under the same reaction conditions as described above, except for the use of the recovered Ac-Val-**1**-Phe-Pro-Ala-Leu-Lys-resin catalyst. It was of utmost importance that the resin, after recovery through filtration, was carefully washed with CH_2Cl_2–MeOH (95/5) containing 3% triethylamine. Up to eleven successive runs were tested, and the product yield for each run was similar to that found for the first run, thus demonstrating the good reusability of the solid catalysts in the liquid phase.[22] We note that under these exact reaction conditions with DMAP, instead of the substrate-optimized catalyst, the dibenzoylated product **10c** was found to be the sole product of the reaction.

In summary, we have presented how acylation reactions catalyzed by solid-supported derivatives of DMAP can be optimized with the goal to achieve increased site-selectivity in the reactions. The catalysts consist of a catalytically active DMAP unit and vary in a peptide chain. The catalysts that were found to be optimal for a particular substrate can be recovered and reused while maintaining both their activity and selectivity; a library once created can be used for screening purposes in a continuous way. As a result, the use of the solid-supported catalysts is significantly more cost-effective than using the related DMAP–peptide conjugates not attached to the solid support.

Notes and references

1 (*a*) M. Reetz, *J. Am. Chem. Soc.*, 2013, **135**, 12480; (*b*) R. Breslow, *Artificial Enzymes*, Wiley-VCH, Weinheim, 2005; (*c*) C. M. Clouthierab and J. N. Pelletier, *Chem. Soc. Rev.*, 2012, **41**, 1585.
2 I. S. Young and P. S. Baran, *Nat. Chem.*, 2009, **1**, 193.
3 (*a*) X. Zhu and R. R. Schmidt, *Angew. Chem., Int. Ed.*, 2009, **48**, 1900; (*b*) D. Lee and M. S. Taylor, *Synthesis*, 2012, 3421.
4 M. C. White, *Synlett*, 2012, 2746.
5 J. L. Jeffrey, J. A. Terrett and D. W. C. MacMillan, *Science*, 2015, **349**, 1532.
6 (*a*) M. Jäger and A. J. Minnaard, *Chem. Commun.*, 2016, **52**, 656; (*b*) P. A. Jordan and S. J. Miller, *Angew. Chem., Int. Ed.*, 2012, **51**, 2907; (*c*) K. Chung and R. M. Waymouth, *ACS Catal.*, 2016, **6**, 4653; (*d*) N. N. H. M. Eisink, J. Lohse, M. D. Witte and A. J. Minnaard, *Org. Biomol. Chem.*, 2016, **14**, 4859.
7 (*a*) M. S. Taylor, *Acc. Chem. Res.*, 2015, **48**, 295; (*b*) M. G. Chudzinski, Y. Chi and M. S. Taylor, *Aust. J. Chem.*, 2011, **64**, 1466; (*c*) D. Lee and M. S. Taylor, *Org. Biomol. Chem.*, 2013, **11**, 5409; (*d*) E. Dimitrijević and M. S. Taylor, *Chem. Sci.*, 2013, **4**, 3298; (*e*) D. Lee and M. S. Taylor, *J. Am. Chem. Soc.*, 2011, **133**, 3724; (*f*) K. Tanveer, K. Jarrah and M. S. Taylor, *Org. Lett.*, 2015, **17**, 3482; (*g*) G. E. Garrett, K. Tanveer and M. S. Taylor, *J. Org. Chem.*, 2017, **82**, 1085.
8 (*a*) Z. X. Giustra and K. L. Tan, *Chem. Commun.*, 2013, **49**, 4370; (*b*) Y. Lu, C. Hou, J. Ren, X. Xin, H. Xu, Y. Pei, H. Dong and Z. Pei, *Molecules*, 2016, **21**, 641; (*c*) A. D. Worthy, X. Sun and K. L. Tan, *J. Am. Chem. Soc.*, 2012, **134**, 7321; (*d*) X. Sun, H. Lee and K. L. Tan, *Nat. Chem.*, 2013, **5**, 790.
9 (*a*) K. Sakurai, T. Takeshita, M. Hiraizumi and R. Yamada, *Org. Lett.*, 2014, **16**, 6318; (*b*) Y. Ueda, W. Muramatsu, K. Mishiro, T. Furuta and T. Kawabata, *J. Org. Chem.*, 2009, **74**, 8802; (*c*) B. Ren, M. Rahm, X. Zhang, Y. Zhou and H. Dong, *J. Org. Chem.*, 2014, **79**, 8134; (*d*) I.-H. Chen, K. G. M. Kou, D. N. Le, C. M. Rathbun and V. M. Dong, *Chem. – Eur. J.*, 2014, **20**, 5013; (*e*) C. L. Allen and S. J. Miller, *Org. Lett.*, 2013, **15**, 6178; (*f*) F. Iwasaki, T. Maki, O. Onomura, W. Nakashima and Y. Matsumura, *J. Org. Chem.*, 2000, **65**, 996; (*g*) Y. Demizu, Y. Kubo, H. Myoshi, T. Maki, Y. Matsumura, N. Moriyama and O. Onomura, *Org. Lett.*, 2008, **10**, 5075; (*h*) W. Muramatsu and

Y. Takemoto, *J. Org. Chem.*, 2013, **78**, 2336; (*i*) Y. X. Zhou, O. Ramström and H. Dong, *Chem. Commun.*, 2012, **48**, 5370; (*j*) T. Takeichi, M. Kuriyama and O. Onomura, *Tetrahedron Lett.*, 2011, **52**, 6646; (*k*) B. Ren, O. Ramström, Q. Zhang, J. Ge and H. Dong, *Chem. – Eur. J.*, 2016, **22**, 2481.

10 (*a*) E. Kattnig and M. Albert, *Org. Lett.*, 2004, **6**, 945; (*b*) T. Kawabata, W. Muramatsu, T. Nishio, T. Shibata and H. Schedel, *J. Am. Chem. Soc.*, 2007, **129**, 12890; (*c*) G. Hu and A. Vasella, *Helv. Chim. Acta*, 2002, **85**, 4369; (*d*) E. Mensah, N. Camasso, W. Kaplan and P. Nagorny, *Angew. Chem., Int. Ed.*, 2013, **52**, 12932; (*e*) E. V. Evtushenko, *Carbohydr. Res.*, 2012, **359**, 111; (*f*) G. Wang, J.-R. Ella-Menye, M. St. Martin, H. Yang and K. Williams, *Org. Lett.*, 2008, **10**, 4203; (*g*) H. Takeuchi, K. Mishiro, Y. Ueda, Y. Fujimori, T. Furuta and T. Kawabata, *Angew. Chem., Int. Ed.*, 2015, **54**, 6177.

11 (*a*) M. T. Reetz, *J. Org. Chem.*, 2009, **74**, 5767; (*b*) G. A. Strohmeier, H. Pichler, O. May and M. Gruber-Khadjawi, *Chem. Rev.*, 2011, **111**, 4141.

12 (*a*) S. J. Miller, *Acc. Chem. Res.*, 2004, **37**, 601; (*b*) S. J. Miller, G. T. Copeland, N. Papaioannou, T. E. Horstmann and E. M. Ruel, *J. Am. Chem. Soc.*, 1998, **120**, 1629; (*c*) G. T. Copeland and S. J. Miller, *J. Am. Chem. Soc.*, 2001, **123**, 6496; (*d*) B. R. Sculimbrene, A. J. Morgan and S. J. Miller, *J. Am. Chem. Soc.*, 2002, **124**, 11653; (*e*) C. T. Mbofana and S. J. Miller, *J. Am. Chem. Soc.*, 2014, **136**, 3285; (*f*) K. W. Fiori, A. L. A. Puchlopek and S. J. Miller, *Nat. Chem.*, 2009, **1**, 630; (*g*) E. A. C. Davie, S. M. Mennen, Y. Xu and S. J. Miller, *Chem. Rev.*, 2007, **107**, 5759.

13 (*a*) Y. Koshi, E. Nakata, M. Miyagawa, S. Tsukiji, T. Ogawa and I. Hamachi, *J. Am. Chem. Soc.*, 2008, **130**, 245; (*b*) Y. Zhao, J. Rodrigo, A. H. Hoveyda and M. L. Snapper, *Nature*, 2006, **443**, 67; (*c*) K. Ishihara, Y. Kosugi, S. Umemura and A. Sakakura, *Org. Lett.*, 2008, **10**, 3191; (*d*) M. Matsumoto, S. J. Lee, M. L. Waters and M. R. Gagné, *J. Am. Chem. Soc.*, 2014, **136**, 15817; (*e*) M. Wiesner, J. D. Revell and H. Wennemers, *Angew. Chem., Int. Ed.*, 2008, **47**, 1871; (*f*) C. E. Müller, D. Zell, R. Hrdina, R. C. Wende, L. Wanka, S. M. M. Schuler and P. R. Schreiner, *J. Org. Chem.*, 2013, **78**, 8465; (*g*) R. C. Wende, A. Seitz, D. Niedek, S. M. M. Schuler, C. Hofmann, J. Becker and P. R. Schreiner, *Angew. Chem., Int. Ed.*, 2016, **55**, 2719.

14 (*a*) M. Sanchez-Roselló, A. L. A. Puchlopek, A. J. Morgan and S. J. Miller, *J. Org. Chem.*, 2008, **73**, 1774; (*b*) K. S. Griswold and S. J. Miller, *Tetrahedron*, 2003, **59**, 8869; (*c*) C. A. Lewis and S. J. Miller, *Angew. Chem., Int. Ed.*, 2006, **45**, 5616; (*d*) P. A. Lichtor and S. J. Miller, *Nat. Chem.*, 2012, **4**, 990; (*e*) T. P. Pathak and S. J. Miller, *J. Am. Chem. Soc.*, 2012, **134**, 6120; (*f*) C. A. Lewis, K. E. Longcore, S. J. Miller and P. A. Wender, *J. Am. Chem. Soc.*, 2009, **72**, 1864.

15 (*a*) W. Steglich and G. Höfle, *Angew. Chem.*, 1969, **81**, 1001; (*b*) G. Höfle, W. Steglich and H. Vorbrüggen, *Angew. Chem.*, 1978, **90**, 602; (*c*) M. R. Heinrich, H. S. Klisa, H. Mayr, W. Steglich and H. Zipse, *Angew. Chem.*, 2003, **115**, 4975.

16 F. Huber and S. F. Kirsch, *Chem. – Eur. J.*, 2016, **22**, 5914.

17 (*a*) G. B. Fields and R. L. Noble, *Int. J. Pept. Protein Res.*, 1990, **35**, 161; (*b*) L. A. Carpino and G. Y. Han, *J. Org. Chem.*, 1972, **37**, 3404.

18 (*a*) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596; (*b*) C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057.

19 (*a*) S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer and S. J. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3815; (*b*) A. Kirschning, H. Monenschein and R. Wittenberg, *Angew. Chem., Int. Ed.*, 2001, **40**, 650.

20 (*a*) S. J. Shuttleworth, M. Allin and P. K. Sharma, *Synthesis*, 1997, 1217; (*b*) C. A. McNamara, M. J. Dixon and M. Bradley, *Chem. Rev.*, 2002, **102**, 3275.

21 M. S. Reddy, H. Zhang, S. Phoenix and P. Deslongchamps, *Chem. – Asian J.*, 2009, **4**, 725.

22 I. Sádaba, M. L. Granados, A. Riisager and E. Taarning, *Green Chem.*, 2015, **17**, 4133.

