

## Organocatalysis

Prebiotically Plausible Organocatalysts Enabling a Selective Photoredox  $\alpha$ -Alkylation of Aldehydes on the Early EarthAnna C. Closs<sup>+, [a, b]</sup> Elina Fuks<sup>+, [a]</sup> Maximilian Bechtel,<sup>[a]</sup> and Oliver Trapp<sup>\*, [a, b]</sup>*In memoriam of Prof. Dr. Dr. h.c. mult. Rolf Huisgen 1920–2020.*

**Abstract:** Organocatalysis is a powerful approach to extend and (enantio-) selectively modify molecular structures. Adapting this concept to the Early Earth scenario offers a promising solution to explain their evolution into a complex homochiral world. Herein, we present a class of imidazolidine-4-thione organocatalysts, easily accessible from simple molecules available on an Early Earth under highly plausible prebiotic reaction conditions. These imidazolidine-4-thiones are readily formed from mixtures of aldehydes or ketones in presence of ammonia, cyanides and hydrogen sulfide in high selectivity and distinct preference for individual compounds of the resulting catalyst library. These organocatalysts enable the enantioselective  $\alpha$ -alkylation of aldehydes under prebiotic conditions and show activities that correlate with the selectivity of their formation. Furthermore, the crystallization of single catalysts as conglomerates opens the pathway for symmetry breaking.

One of the fundamental questions of the origin of life is how the complex organic structures of our biosystem with a diversity of functionalities have emerged from a simple prebiotic feedstock. Numerous pathways have been reported explaining the possible formation of sugars,<sup>[1]</sup> amino acids,<sup>[2]</sup> nucleobases<sup>[3]</sup> and RNA/DNA nucleosides,<sup>[4]</sup> however, the emergence of a distinct property of living matter remains unsolved, namely symmetry breaking leading to homochirality.

Besides addressing this mystery on its own with circular polarized light in space<sup>[5]</sup> or parity violation,<sup>[6]</sup> prebiotic organocatalysis might have played a key role in the simultaneous generation of molecular complexity at the very beginning of fundamental processes leading to (bio-)molecules. Prebiotic organocatalysis not only provides the ability of inducing enantioselectivity but also enables the formation of larger molecules with a broad variety of functionalities. In contrast to metal-based catalysis, it further tolerates the presence of water, ubiquitous on the Early Earth. In this context, amino acids<sup>[7]</sup> and short peptides<sup>[8]</sup> were extensively studied. Most of these transformations are limited to specific organic transformations and are thus not able to create the molecular diversity we find today. Proline shows the highest catalytic activity and can be applied in aldol-type condensations<sup>[9]</sup> as well as Mannich<sup>[10]</sup> and Michael<sup>[11]</sup> reactions, but its existence in meteorites or experiments mimicking prebiotic scenarios is scarcely detected.<sup>[12]</sup> So far, an enormously important reaction, the  $\alpha$ -alkylation of aldehydes, has not been feasible under prebiotic conditions at all. This carbon–carbon bond-forming transformation would elongate small carbonyl compounds, that can be traced back to extraterrestrial material or obtained in presence of electric discharges,<sup>[2b, 13]</sup> not only broadening the pool of prebiotic accessible molecular structures but also increasing the insolubility in water, much needed for compartmentalization by micelle or lipid layer formation. Proven extremely challenging for many years,<sup>[14]</sup> in modern chemistry the intermolecular  $\alpha$ -alkylation is dominated by photoredox organocatalysis. This includes transformations using transition metal-based photocatalysts<sup>[15]</sup> and metal-free dyes.<sup>[16]</sup> Melchiorre's group elegantly demonstrated the photoactivity of enamines when excited directly or in colored electron-donor-acceptor complexes without the addition of external chromophores.<sup>[17]</sup>


In the course of our studies in prebiotic chemistry, we discovered a straightforward access to a class of organocatalysts, that enables the intermolecular  $\alpha$ -alkylation of aldehydes under plausible conditions on the Early Earth (reducing conditions, water, volcanic activity). (Scheme 1).


Based on the structures of established organocatalysts, we considered cyclic secondary amines with modular incorporation of sterically demanding residues to be promising prebiotic analogues. By a retrosynthetic analysis of potential structures, we identified imidazolidine-4-thiones **1**, which are intermediates in the formation of activated  $\alpha$ -aminothioamides, as organocatalysts. To build up a fundament for subsequent catalytic

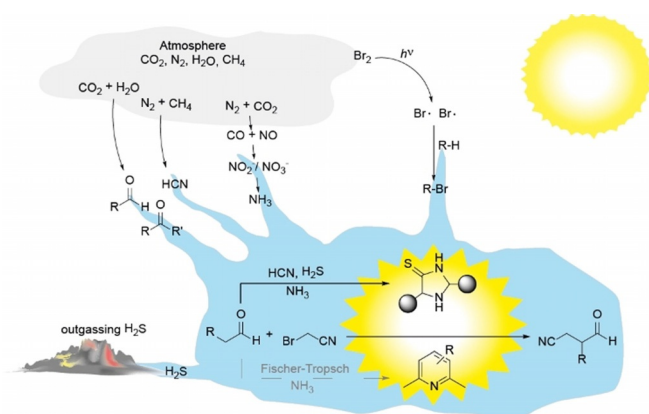
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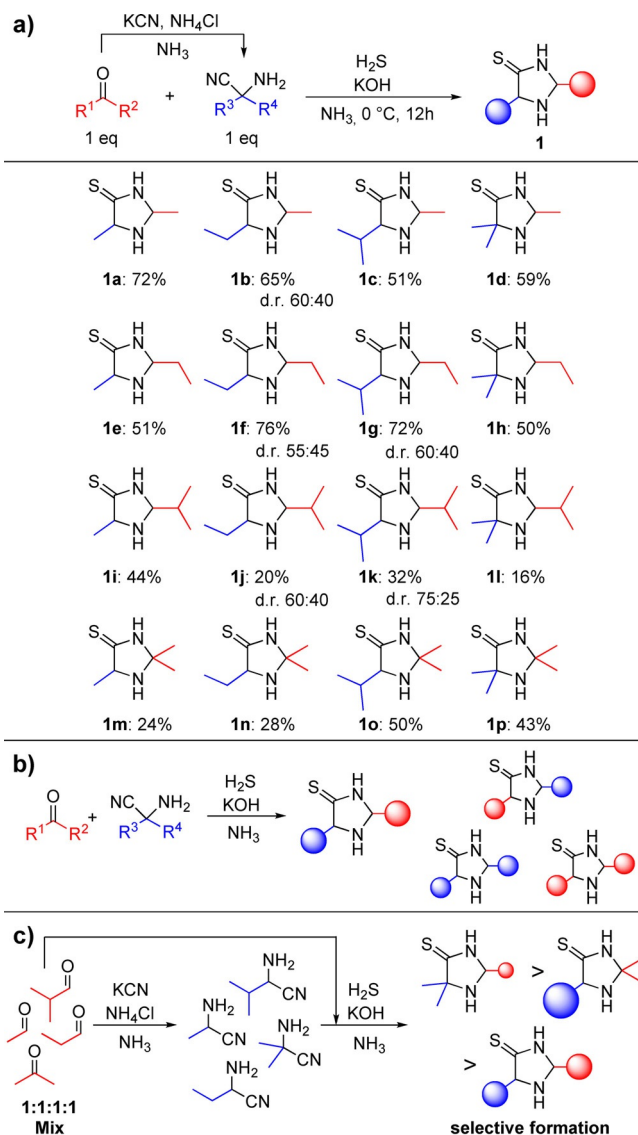


**Scheme 1.** Identified prebiotic pathway to form organocatalysts, enabling the modification of their own building blocks to increase the molecular diversity. The imidazolidine-4-thione organocatalysts are formed from carbonyl compounds in presence of ammonia, cyanide and hydrogen sulfide (upper pathway), facilitating the prebiotically plausible  $\alpha$ -alkylation of aldehydes (central pathway). 2,6-Dimethyl pyridine bases can be formed from the same prebiotic feedstock under Fischer–Tropsch catalytic conditions (lower pathway).

investigations, a library of structural variants was synthesized (Scheme 2A).

Following a modified procedure by Paventi and Edward,<sup>[18]</sup> **1 m–1 p** were formed by reacting acetone with the respective  $\alpha$ -aminonitrile—itself derived from aldehydes or ketones by Strecker type synthesis—in the presence of hydrogen sulfide. The products precipitated already during reaction after a few seconds. The reaction was performed in basic aqueous solution and thus all reaction components can be regarded as prebiotically plausible. So far, this transformation was claimed not feasible when exchanging acetone with an aldehyde. Contrary to this assumption, we were able to obtain imidazolidine-4-thiones **1 a–1 l** in yields of up to 76%, thus including aldehydes as a class of prebiotically relevant molecules.<sup>[13]</sup> In this way, a large number of derivatives could be easily accessed, and we exemplarily synthesized a total number of 16 imidazolidine-4-thiones. Since only aldehydes or ketones are needed as organic feedstock, this procedure demonstrates its potential and relevance for the emerging of the first organocatalysts on the Early Earth.

In some cases, analysis of the reaction mixture upon precipitation revealed not only the expected, but also the reversed reaction product as well as both symmetrically substituted products in different ratios (Scheme 2b). This phenomenon only occurred when the secondary aminonitrile, derived from acetone, was used, indicating a lower stability and dynamics of this aminonitrile. To further study the potential selectivity of the imidazolidine-4-thione formation and account for the parallel existence of various aldehydes on the Early Earth, we used reactant mixtures in the same procedure as described above (Scheme 2c). When only aldehydes were present, all possible products were detected with no significant preference for certain compounds. However, as soon as acetone was added, it was selectively incorporated into the imidazolidine-4-thione skeleton. Here, the product of the secondary aminonitrile,



**Scheme 2.** Overview of the synthetic approach towards the prebiotically plausible imidazolidine-4-thione organocatalysts. a) Product yields and diastereomeric ratios of the catalysts. b) Products arising from the primary reactants and from the aminonitriles and aldehydes formed due to the dynamic equilibria between them (R<sup>3</sup>, R<sup>4</sup> ≠ H). c) Selectivity in the formation of imidazolidine-4-thione organocatalysts starting from reactant libraries.

formed from acetone, with the smallest possible aldehyde is favored (Scheme 2c; Supporting Information Figure S7 and S8). As opposite building block, acetone preferentially reacted with the primary aminonitrile of the largest possible aldehyde. Also, we observed a preference in the formation of the anti-substituted diastereomers as soon as sterically more demanding aldehydes were implemented. These features are of particular interest as they underline the dynamics of these systems and the potential enrichment of single diastereomers, thus culminating in a scenario of a first evolutionary selection on a molecular level on the Early Earth.

Considering the potential of the obtained imidazolidine-4-thiones **1**, we envisioned a prebiotically plausible catalytic system for the  $\alpha$ -alkylation of small aldehydes. Due to the

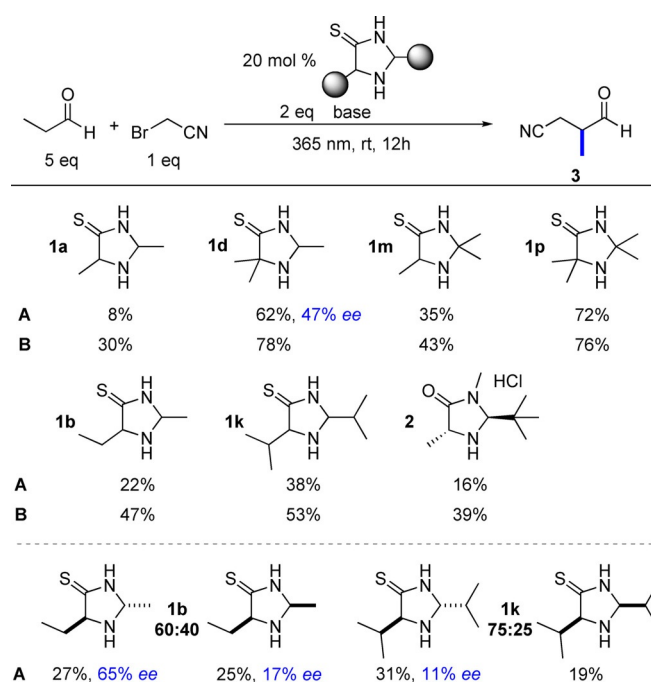
structural similarities of the synthesized imidazolidine-4-thiones to the MacMillan catalysts, we started to investigate their catalytic activity in an established  $\alpha$ -alkylation procedure of the latter. In these systems, larger aldehydes are treated with alkyl halides possessing an electron-withdrawing group in the presence of a MacMillan catalyst **2**, Ru(bpy)<sub>3</sub>Cl<sub>2</sub> as photosensitizer and 2,6-lutidine. Here, we focused on the  $\alpha$ -cyanomethylation,<sup>[15b]</sup> as the products would give access to prebiotically relevant, more complex molecules by hydrolysis of the nitrile group and further transformation of the aldehyde functionality. The existence of 2-bromoacetonitrile is plausible under the conditions on the Early Earth, formed in a photoinduced radical recombination of interstellar abundant bromine<sup>[19]</sup> and CH<sub>3</sub>CN.<sup>[20]</sup> In addition, the sun is considered as an important energy supplier in the resource-poor environment at that time, whereby photoreactions have been highly probable. In our photocatalytic setup, the 365 nm LED lamp accounts for the high content of UV-A radiation (320–400 nm), while diminishing the photodegradation of substrates. We also tested the outer limits of UV-A radiation (340 and 405 nm), observing higher yields at higher wavelengths (Supporting Information Figure S4, Table S6). For the following system optimization, we chose 365 nm to represent the center of the wavelength range.

Indeed, initial screening of imidazolidine-4-thione **1p** in the  $\alpha$ -alkylation reaction gave the  $\alpha$ -cyanomethylated *n*-octanal in 81% yield, proving itself as potential prebiotic organocatalyst. In the next steps we investigated these organocatalysts under realistic reaction conditions on the Early Earth. Going from *n*-octanal to the smaller, prebiotically plausible propanal<sup>[13,21]</sup> still gave the desired product in 72% yield. Furthermore, the existence of Ru(bpy)<sub>3</sub>Cl<sub>2</sub> as photosensitizer can be excluded. Surprisingly, when this reaction was performed without any photosensitizer, we obtained the  $\alpha$ -cyanomethylated propanal with no effect on the reaction yields (Supporting Information Table S1), thus overcoming the need for an additional reagent as well as the limits of metal complexes. The  $\alpha$ -cyanomethylation of propanal can further be performed in acetonitrile or even in an excess of propanal without any additional solvent (Supporting Information Table S2). Exchanging 2,6-lutidine for other basic molecules turned out to be more challenging (Supporting Information Table S3). Since different common bases were tested without any success in acetonitrile or DMSO, our focus shifted towards bases structurally related to 2,6-lutidine. 2,4,6-Trimethylpyridine (collidine) and quinolines, such as quinoline, isoquinoline and 2-methylquinoline, were detected in the Murchison meteorite, and are suggested to be formed by Fischer–Tropsch type catalysis of aldehydes and ammonia or photochemically from benzene and naphthalene derivatives in H<sub>2</sub>O/NH<sub>3</sub> ices, respectively.<sup>[22]</sup> All these pathways are compatible with the here presented synthesis of the imidazolidine-4-thiones **1**. Indeed, collidine and 2-methylquinoline were suitable prebiotic substitutes for 2,6-lutidine (Supporting Information Table S3). Here, the steric hindrance in close proximity to the aromatic nitrogen atom seems to be decisive for product formation. For pyridine, 3,5-lutidine, quinoline and isoquinoline only a mixture of various side products under consumption of

the aldehyde was obtained. Thereby, we can show that the  $\alpha$ -alkylation of aldehydes is feasible under prebiotic conditions using solar radiation as primary energy source (Scheme 3).

Product formation was observed for all imidazolidine-4-thione catalysts **1**. Remarkably, the yields increased when performing the reaction under our developed prebiotic conditions in acetonitrile with collidine (**B**) compared to the established procedure in DMSO with 2,6-lutidine (**A**). The chiral catalysts **1a**, **1m**, **1b**, **1k** gave moderate to good yields, whereas **1d** as well as the achiral catalyst **1p** revealed outstanding performance. Using **1p**, the catalytic setup was further applied to *n*-butanal, *n*-pentanal and *n*-hexanal, all detected in carbonaceous chondrites,<sup>[13]</sup> providing the respective  $\alpha$ -cyanomethylated aldehydes in yields between 71–82% (Supporting Information Table S4). Moreover, when comparing the different diastereomers of **1b** and **1k**, it turned out that the preferentially formed anti-substituted isomer also shows higher catalytic activity, an effect that increases with steric hindrance. When using imidazolidine-4-thiones **1** instead of the MacMillan catalyst **2**, our setup is further able to tolerate oxygen, even with a remarkable increase in reaction yields (Supporting Information Table S5). This shows the robustness of the catalytic system and further highlights its potential role on the Early Earth.

To gain a deeper insight into the different catalyst activities, we compared the relative reaction rates of the respective catalysis by reaction progress analysis using in situ <sup>1</sup>H NMR kinetic measurements (Figure 1; Supporting Information Figure S1, S5



**Scheme 3.** Product yields and enantioselectivities of the  $\alpha$ -cyanomethylation of *n*-propanal for selected catalysts. **A:** Reaction performed in DMSO with 2,6-lutidine under aerobic conditions. **B:** Reaction performed in acetonitrile with collidine under aerobic conditions. The enantiomeric excess (ee) was determined by enantioselective GC measurements (heptakis(2,3-di-O-methyl-6-O-TBDMS)- $\beta$ -cyclodextrin in PS 086 column, 7 m x 0.25 mm I.D.; film thickness 0.25  $\mu$ m) of the corresponding alcohol. The yield was determined from the crude mixture by <sup>1</sup>H NMR analysis.

and **5b**, Table S7 and S8). The results show that the achiral catalyst **1p** not only affords the highest yield but also performs with an enhanced reaction rate. Further, a correlation was observed between the formation ratio and the activity of the studied imidazolidone-4-thiones. Catalysts with dimethyl residues were not only preferably formed but also show higher reaction rates, which promotes product enrichment and underpins the importance of organocatalysts in product replication.

Further, we crystallized several imidazolidine-4-thiones (**1b**, **1h**, **1m**, **1p**) out of their racemic solution and were pleased to observe an enantiomerically pure crystal for **1b** ((2*R*,5*S*)-5-ethyl-2-methylimidazolidine-4-thione) (Supporting Information Figure S13, Table S9). In contrast to the formation of a racemic compound, this conglomerate can lead to spontaneous resolution, a phenomenon which is comprehensively proposed as a plausible hypothesis for the origin of molecular chirality.<sup>[23]</sup> This feature is rather rare as most of the organocatalysts studied so far, including nearly all of the proteinogenic amino acids, crystallize as racemic compounds.<sup>[24]</sup>

Giving a possible first hint for the enrichment of single enantiomers on the Early Earth, we studied the enantioselectivity of our organocatalytic  $\alpha$ -alkylation. We separated the isomers of the most active chiral catalyst **1d**, the conglomerate **1b** and the sterically most demanding imidazolidine-4-thione **1k** by preparative chiral HPLC and compared their enantioselectivities (Scheme 3; Supporting Information Figure S9, S10, S11 and S12). Small substituents as in **1d** and **1b** led to enantiomeric excesses (*ee*) of up to 65%. Introduction of bulky isopropyl residues, however, drastically reduced the *ee*. Thereby, the catalysts showing the best selectivity are formed from the prebiotically more abundant smaller aldehydes and ketones.<sup>[13]</sup> Moreover, the already observed superiority of the preferentially formed diastereomer (anti-substituted) in terms of catalytic activity is perceived even more strongly regarding its enantioselectivity. Using the anti-substituted imidazolidine-4-thione **1b**, which represents the diastereomer crystallizing as conglomerate,

gave **3** with 65% *ee* compared to 17% *ee* in case of the *syn*-substituted isomer.

In summary, we identified a class of prebiotic organocatalysts and demonstrated their possible importance for the emergence of life by enabling the selective  $\alpha$ -alkylation of aldehydes under prebiotic conditions. These imidazolidine-4-thiones form readily out of an abundant prebiotic feedstock with diastereomeric enrichments. The preferentially formed isomers show superior catalytic performance with regard to activity and enantioselectivity, implicating the possible occurrence of an early form of selection on the primitive Earth. We also observed the enantiomerically pure crystallization of single enantiomers, thereby opening a plausible pathway for the origin of symmetry breaking, leading to homochirality. In addition to the access to substituted aldehydes shown in this work, which seems necessary for compartmentalization to form cellular structures, also the formation of the canonical amino acids is plausible. Due to the similarity to established organocatalysts, many prebiotic functionalizations through organocatalysis are conceivable, making these catalysts promising candidates for the ongoing endeavors to elucidate the origin of life.

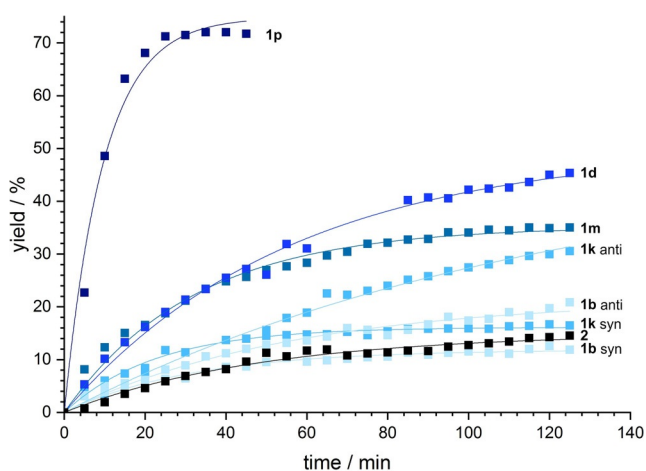
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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** aldehydes · alkylation · organocatalysis · origin of life · photocatalysis



**Figure 1.** Reaction monitoring of the  $\alpha$ -cyanomethylation of *n*-propanal with in situ  $^1\text{H}$  NMR kinetic measurements. The reaction was performed in DMSO with 2,6-lutidine under aerobic conditions.

- [1] A. Butlerow, *Liebigs Ann. Chem.* **1861**, *120*, 295–298.
- [2] a) S. L. Miller, *Science* **1953**, *117*, 528–529; b) S. L. Miller, *J. Am. Chem. Soc.* **1955**, *77*, 2351–2361.
- [3] a) S. Becker, I. Thoma, A. Deutsch, T. Gehrke, P. Mayer, H. Zipse, T. Carell, *Science* **2016**, *352*, 833–836; b) J. Oró, *Nature* **1961**, *191*, 1193–1194; c) M. W. Powner, B. Gerland, J. D. Sutherland, *Nature* **2009**, *459*, 239.
- [4] J. S. Teichert, F. M. Kruse, O. Trapp, *Angew. Chem. Int. Ed.* **2019**, *58*, 9944–9947; *Angew. Chem.* **2019**, *131*, 10049–10052.
- [5] a) C. Meinert, S. V. Hoffmann, P. Cassam-Chenaï, A. C. Evans, C. Giri, L. Nahon, U. J. Meierhenrich, *Angew. Chem. Int. Ed.* **2014**, *53*, 210–214; *Angew. Chem.* **2014**, *126*, 214–218; b) G. Balavoine, A. Moradpour, H. B. Kagan, *J. Am. Chem. Soc.* **1974**, *96*, 5152–5158.
- [6] a) G. E. Tranter, *Nature* **1985**, *318*, 172–173; b) M. Quack, *Angew. Chem. Int. Ed.* **2002**, *41*, 4618–4630; *Angew. Chem.* **2002**, *114*, 4812–4825.
- [7] a) A. Córdova, W. Zou, I. Ibrahim, E. Reyes, M. Engqvist, W.-W. Liao, *Chem. Commun.* **2005**, 3586–3588; b) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496–497; *Angew. Chem.* **1971**, *83*, 492–493; c) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621; d) M. Klussmann, H. Iwamura, S. P. Mathew, D. H. Wells, U. Pandya,



- A. Armstrong, D. G. Blackmond, *Nature* **2006**, *441*, 621–623; e) L.-W. Xu, Y. Lu, *Org. Biomol. Chem.* **2008**, *6*, 2047–2053.
- [8] a) E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759–5812; b) H. Wennemers, *Chem. Commun.* **2011**, *47*, 12036–12041.
- [9] a) A. Córdova, W. Notz, C. F. Barbas III, *Chem. Commun.* **2002**, 3024–3025; b) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799.
- [10] a) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337; b) A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas, *J. Am. Chem. Soc.* **2002**, *124*, 1842–1843.
- [11] a) B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423–2425; b) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; *Angew. Chem.* **2004**, *116*, 5248–5286.
- [12] E. L. Shock, M. D. Schulte, *Geochim. Cosmochim. Acta* **1990**, *54*, 3159–3173.
- [13] J. C. Aponte, D. Whitaker, M. W. Powner, J. E. Elsilá, J. P. Dworkin, *ACS Earth Space Chem.* **2019**, *3*, 463–472.
- [14] A.-N. Alba, M. Viciano, R. Rios, *ChemCatChem* **2009**, *1*, 437–439.
- [15] Ru-based: a) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77–80; b) E. R. Welin, A. A. Warkentin, J. C. Conrad, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2015**, *54*, 9668–9672; *Angew. Chem.* **2015**, *127*, 9804–9808; c) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875–10877; Fe-based: d) A. Gualandi, M. Marchini, L. Mengozzi, M. Natali, M. Lucarini, P. Ceroni, P. G. Cozzi, *ACS Catal.* **2015**, *5*, 5927–5931; Ir-based: e) H.-W. Shih, M. N. Vander Wal, R. L. Grange, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 13600–13603.
- [16] M. Neumann, S. Földner, B. König, K. Zeitler, *Angew. Chem. Int. Ed.* **2011**, *50*, 951–954; *Angew. Chem.* **2011**, *123*, 981–985; D. Ravelli, M. Fagnoni, A. Albin, *Chem. Soc. Rev.* **2013**, *42*, 97–113.
- [17] a) M. Silvi, E. Arceo, I. D. Jurberg, C. Cassani, P. Melchiorre, *J. Am. Chem. Soc.* **2015**, *137*, 6120–6123; b) E. Arceo, I. D. Jurberg, A. Álvarez-Fernández, P. Melchiorre, *Nat. Chem.* **2013**, *5*, 750–756; c) A. Bahamonde, P. Melchiorre, *J. Am. Chem. Soc.* **2016**, *138*, 8019–8030.
- [18] M. Paventi, J. T. Edward, *Can. J. Chem.* **1987**, *65*, 282–289.
- [19] N. F. W. Ligterink, M. Kama, *Astron. Astrophys.* **2018**, *614*, A112.
- [20] A. P. C. Mann, D. A. Williams, *Nature* **1980**, *283*, 721–725.
- [21] F. Goesmann, H. Rosenbauer, J. H. Bredehöft, M. Cabane, P. Ehrenfreund, T. Gautier, C. Giri, H. Krüger, L. Le Roy, A. J. MacDermott, S. McKenna-Lawlor, U. J. Meierhenrich, G. M. Muñoz Caro, F. Raulin, R. Roll, A. Steele, H. Steining, R. Sternberg, C. Szopa, W. Thiemann, S. Ulamec, *Science* **2015**, *349*, aab0689.
- [22] a) Z. Martins, *Life* **2018**, *8*, 28; b) P. G. Stoks, A. W. Schwartz, *Geochim. Cosmochim. Acta* **1982**, *46*, 309–315.
- [23] W. A. Bonner, *Orig. Life Evol. Biosph.* **1991**, *21*, 59–111.
- [24] a) C. Viedma, *Orig. Life Evol. Biosph.* **2001**, *31*, 501–509; b) A. Collet, M. J. Brienne, J. Jacques, *Chem. Rev.* **1980**, *80*, 215–230.

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