Organocatalysis

Deutsche Ausgabe: DOI: 10.1002/ange.201509863
Internationale Ausgabe: DOI: 10.1002/anie.201509863

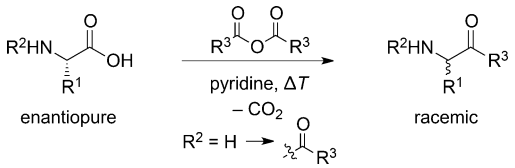
The Enantioselective Dakin–West Reaction

*Raffael C. Wende, Alexander Seitz, Dominik Niedek, Sören M. M. Schuler, Christine Hofmann, Jonathan Becker, and Peter R. Schreiner**

Dedicated to Professor Wolfgang Steglich

Abstract: *Here we report the development of the first enantioselective Dakin–West reaction, yielding α-acetamido methylketones with up to 58 % ee with good yields. Two of the obtained products were recrystallized once to achieve up to 84 % ee. The employed methylimidazole-containing oligopeptides catalyze both the acetylation of the azlactone intermediate and the terminal enantioselective decarboxylative protonation. We propose a dispersion-controlled reaction path that determines the asymmetric reprotonation of the intermediate enolate after the decarboxylation.*

Even though the Dakin–West (DW) reaction dates back to 1928,[1] it is still one of the most effective synthetic procedures to prepare α-acylamido ketones from primary α-amino acids.[2] Generally, the treatment of an amino acid with an acid anhydride and base, typically pyridine, at elevated temperature provides the desired product upon liberation of CO_2 (Scheme 1). Numerous modifications of the original reaction conditions were developed,[2] including catalytic variants,[3] broadening its scope and applicability. Unsurprisingly, the DW reaction found application in the preparation of α-acylamido ketones as valuable precursors for various biologically active compounds,[4] and even in Woodward's fundamental total synthesis of strychnine.[5] Remarkably, no asymmetric variant has been developed to date, thus restricting the use of this important reaction in modern synthetic chemistry.



Scheme 1. The Dakin–West reaction of α-amino acids.

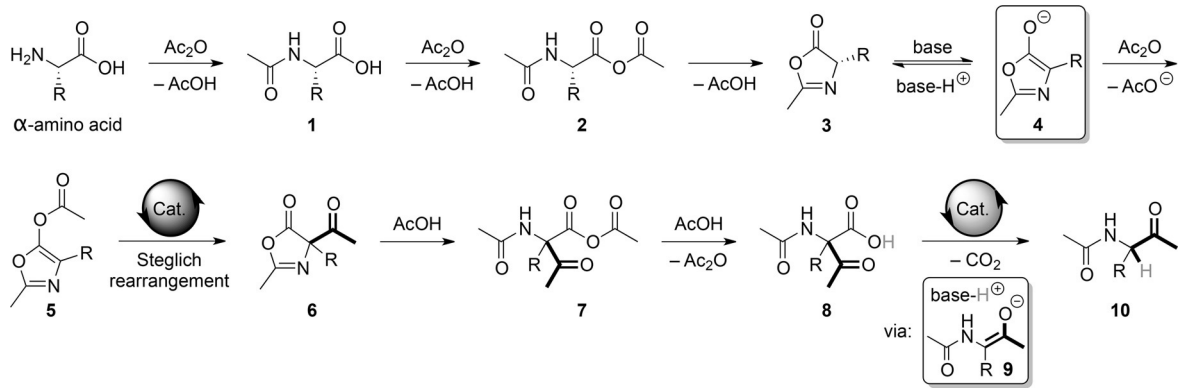
[*] M. Sc. R. C. Wende, B. Sc. A. Seitz, M. Sc. D. Niedek, Dipl.-Chem. S. M. M. Schuler, Dr. C. Hofmann, Prof. Dr. P. R. Schreiner
Institute of Organic Chemistry
Justus-Liebig University, 35392 Giessen (Germany)
E-mail: prs@uni-giessen.de
Dr. J. Becker
Institute of Inorganic and Analytical Chemistry
Justus-Liebig University, 35392 Giessen (Germany)

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/anie.201509863.

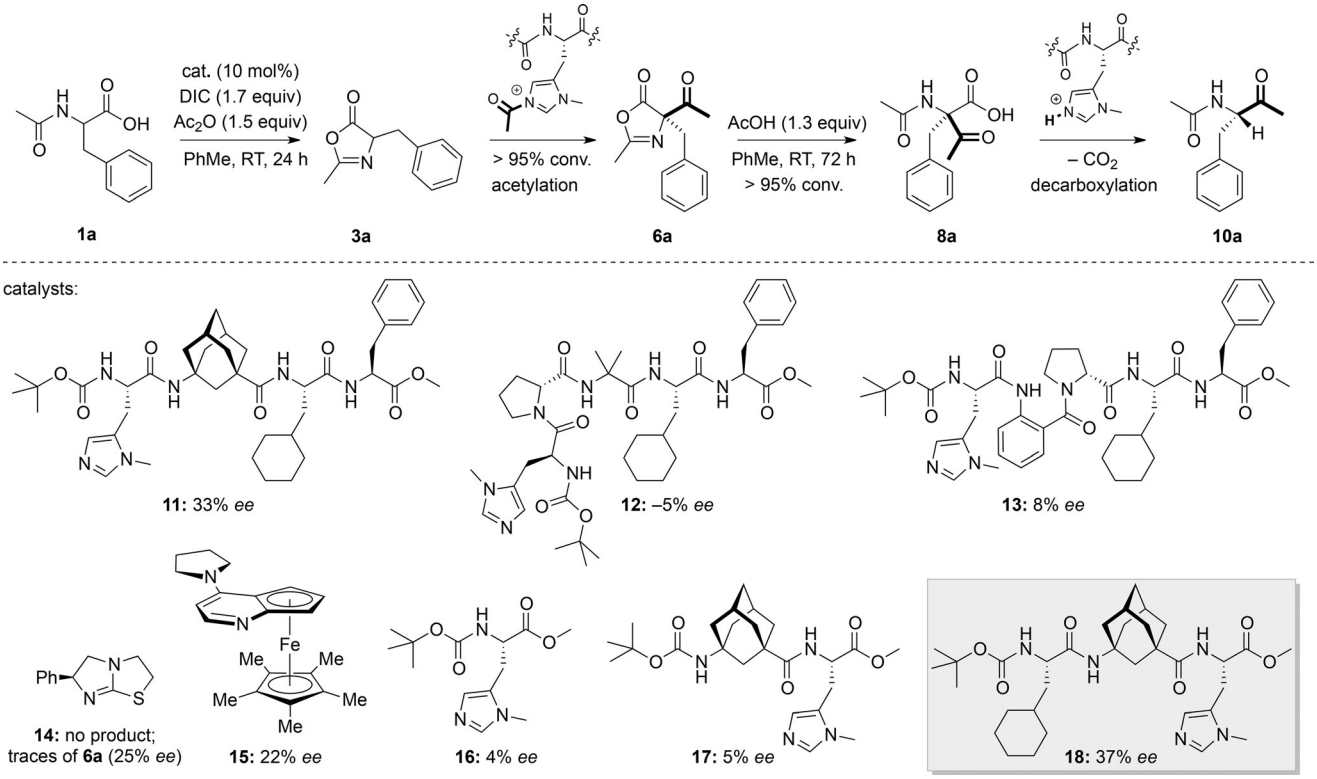
According to the currently accepted mechanism,[6] the reaction of an amino acid with the anhydride leads to the *N*-acetyl derivative **1** and subsequently to the mixed anhydride **2** (Scheme 2). Cyclization of **2** provides the oxazol-5(4*H*)-one (azlactone) **3**. Such azlactones are acidic owing to the formation of resonance stabilized enolate **4** upon deprotonation. Subsequent acetylation may occur at the enolate oxygen atom (affording **5**) or directly at the carbon atom to give **6**.[7] However, **6** is exclusively produced under the typical DW reaction conditions because of concomitant O→C acyl transfer (Steglich rearrangement).[8] Opening of **6** with acetic acid, formed in previous steps, to the mixed anhydride **7** and transacylation gives the β-keto acid **8**,[6f] which is prone to decarboxylation upon deprotonation. This final reaction step affords the desired α-acetamido methylketone **10**, likely via enolate **9**. Other pathways, for example, the acylation of **2** to directly give **7**,[9] were discussed as well but have been shown to be rather improbable. It is evident from this mechanistic picture that the intermediacy of **4** and **9** (Scheme 2) leads to the observed complete racemization, making an asymmetric reaction a difficult endeavor. We surmized, however, that an enantioselective decarboxylative protonation[10] of **8** (via **9**) would afford enantioenriched products. Herein we show that this is indeed possible with a tailor-made catalytic system.

We chose synthetic oligopeptides as catalysts[11] as these should be well-suited for binding the amino acid derived intermediates, as demonstrated for such platforms in acyl transfer reactions.[12] Incorporation of catalytically active π-methylhistidine (Pmh) in a dual role as Lewis base for the acetyl transfer (Scheme 2) and as Brønsted base in the decarboxylative protonation (Scheme 2) may allow performing the entire reaction by employing a single catalyst.

Our investigation commenced with an evaluation of appropriate reaction conditions for the proposed reaction sequence starting from DL-phenylalanine and our previously successfully employed acylation catalyst **11**[12] (Scheme 3; see the Supporting Information for details). We found that the methylimidazole moiety itself is not sufficiently basic to deprotonate the azlactone **3a** ($pK_a \approx 9$[13] vs. $pK_a = 7.3$ for protonated *N*-methylimidazole)[14] and acetic acid is continuously formed during the reaction. Addition of a base significantly increases the reaction rate but has a deleterious effect on enantioselectivity. Thus, we concluded that the mechanistic complexity of the reaction necessitates well-balanced reaction conditions to separate the acetylation of **3** and the decarboxylation. The use of a carbodiimide helps overcome these challenges: it enables fast cyclization of **1** to **3**, acts as auxiliary base in the deprotonation step, and converts



Scheme 2. Proposed mechanism for the Dakin–West reaction.



Scheme 3. Testing and optimizing reaction conditions for selected catalysts. Reactions were performed on an analytical scale (0.1 mmol). The absolute configuration of **10a** was determined to be *S* by comparison of the retention times of an authentic sample on chiral-phase HPLC. Enantiomeric excesses (a negative sign indicates the formation of the opposite enantiomer) for **6a** and **10a** were determined by chiral-phase GC. Conversion was >95% for the individual reaction steps as judged by GC-MS unless noted otherwise. For complete catalyst library see the Supporting Information.

the acetic acid produced back into the anhydride. Most importantly, the only side-product formed is the corresponding urea derivative, which cannot participate as a base in the final decarboxylation step and therefore does not erode enantioselectivity. Indeed, **3a** immediately forms when *N*,*N*′-diisopropylcarbodiimide (DIC) is used as an additive. Addition of acetic anhydride then furnishes the key intermediate **6a** with full conversion of **3a**. Further addition of acetic acid initiates the decarboxylation step, thus leading to the formation of the α-acetamido methylketone **10a** with 33% *ee*, enriched in the *S*-configured enantiomer (Scheme 3). We were able to monitor the reaction by GC-MS and observed some of the intermediates (see the Supporting Information, Figure S2).

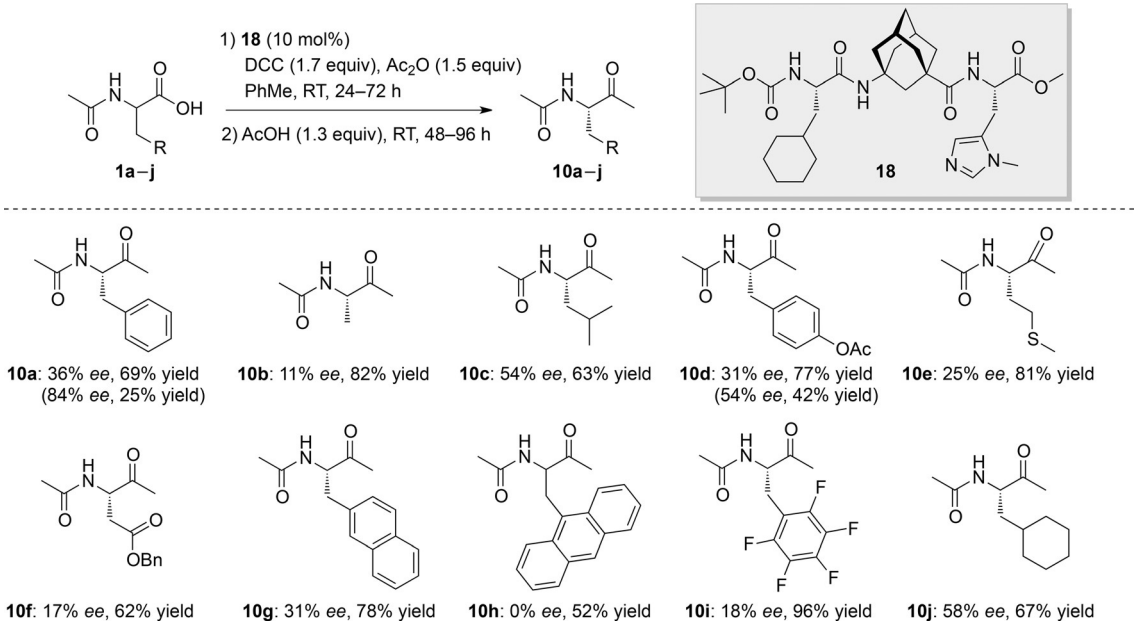
The feasibility of our catalyst design concept was next evaluated using different turns instead of the adamantane amino acid (Scheme 3).[15] Incorporation of a D-Pro-Aib-turn (**12**), frequently used by Miller et al.,[11a,16] or an 2-Abz-D-Pro pseudo-β-hairpin (**13**),[17] resulted in 5% and 8% *ee*, respectively. We also studied (*S*)-tetramisol (**14**) and the chiral (*S*)-

PPY* **15**,[18] reported by Fu and co-workers, as both catalysts were previously employed in an asymmetric Steglich rearrangement.[8,19] With **14** only traces of enantioenriched **6a** (25% *ee*) formed, and **10a** could not be detected. Remarkably, **15** gave 22% *ee* for the desired product and may be considered a potential catalyst for further optimization. To gain further insight into the factors determining enantioselectivity and to improve catalyst performance, we modularly built the catalyst from the C-terminal Pmh. Thus, Boc-L-Pmh-OMe (**16**) and dipeptide **17** did not provide enantioenriched product as neither catalyst is able to form a dynamic binding pocket[12] for the enolate **9a**, and they also lack the necessary hydrogen bonding contacts. However, when tripeptides were used the selectivities substantially increased (see the Supporting Information for complete catalyst library), with **18**, bearing cyclohexylalanine, being the best catalyst. The strikingly better performance of the shorter tripeptide **18** compared to that of the tetrapeptide **11** is probably a result of the C-terminal Pmh (interchange of the amide NH and C=O groups), which leads to more efficient substrate binding.

Note that most of the catalysts employed were also able to enantioselectively acetylate the azlactone intermediate. However, no correlation is apparent from the selectivity obtained for **6a** and the final product **10a**, and no amplification of stereoselectivity was observed. That is, the enantioenrichment of **10a** does not ensue from kinetic resolution of **6a**. As we anticipated by the proposed mechanism, the selectivity for **6a** is not preserved in the product and only results from the final decarboxylation and enantioselective enolate reprotonation. To further prove this observation, DMAP was used as an achiral catalyst for the in situ formation of **6a**, and **18** was only added for the decarboxylation step. However, the selectivities differed only marginally (see the Supporting Information, Table S5).

From this point on, we used **18** for substrate screening and *N*,*N*′-dicyclohexylcarbodiimide (DCC) instead of DIC because it is easier to remove the corresponding urea derivative in the purification of the final products (Scheme 4). Thus, **10a** was isolated in 69% yield with 36% *ee*. Substrates with sterically less demanding side chains, such as alanine and methionine derivatives, afforded the desired products with low selectivities but with high yields (**10b** and **10e**). The product **10c**, derived from leucine, was isolated with appreciable higher enantioselectivity (54%)and 63% yield. The tyrosine-derived **1d** gave 31% *ee* with 77% yield, whereas polar functional groups led to low selectivities (**10f**: 17%). We next employed sterically more demanding amino acids bearing aromatic side chains, namely, naphthyl- and anthranylalanine derivatives, **1g** and **1h**, respectively. Lower enantioselectivity (31% *ee*, 78% yield) resulted for **10g**, whereas **10h** was obtained in racemic form in a moderate 52% yield. Strongly electron-withdrawing side-chains, such as that in **1i**, afforded the product with excellent yield but lower selectivity (**10i**: 18% *ee*, 96% yield), and probably resulting from racemization (see the Supporting Information). To our delight, as seen for **1c**, the selectivity was further enhanced to 58% *ee* (67% yield) when the aliphatic cyclohexylalanine **1j** was used as a substrate. Importantly, **10a** and **10d** could be obtained, with up to 84% *ee* (for **10a**), after one recrystallization.

The observed selectivities can effectively compete with previously reported organocatalytic enantioselective decarboxylative protonation reactions which are typically in the range of 30–60% *ee*.[10a,c,d] Organocatalytic variants that achieve higher enantioselectivities (above 70% *ee*) are rare.[20] Higher selectivities (>90% *ee*) have, so far, only been achieved either in the presence of stoichiometric amounts of base[21] or by employing transition metals, for



Scheme 4. Substrate scope and limitations. Stereochemistry for the products was assigned as *S* by analogy to **10a**. Enantiomeric excesses were determined by chiral-phase GC or HPLC. Yields refer to those of isolated products. Values within parentheses correspond to recrystallized products.

example, palladium complexes[22] or enzymes.[10a,23] Unlike the former examples, as well as decarboxylative addition reactions,[10c,d,24] the DW reaction described herein is particularly challenging as it presupposes the stereoselective transfer of the smallest electrophile, a proton, in the presence of significant amounts of acid in a complex multistep reaction (Scheme 2).

Although the exact nature of the decarboxylation step is not yet clear, the stereoinduction probably arises from the deprotonation of β-keto acid **8** (Scheme 2) by the catalyst, release of CO_2, and subsequent enantioselective reprotonation as reported for related organocatalytic decarboxylative protonation reactions.[10a,c,d,25] Thus, we computationally identified possible adducts of the protonated catalyst **18** and enolate **9j** as minima wherein the transferred proton is in close proximity to the α-carbon atom of the intermediate (1.94 Å for both structures), thus supporting our mechanistic proposal (Figure 1). These data also emphasized the importance of the amino acid at the *i*−2 position for binding. Indeed, the computed structure that would afford the observed *S* selectivity (Figure 1 A) is favored by 2.1 kcal mol^{-1} compared to the complex leading to (*R*)-**10j** (Figure 1 B). The observed selectivities mainly result from shielding of one face of the enolate by its side-chain and by the catalysts cyclohexyl residue, thus precluding unselective reprotonation, for example, by acetic acid. However, the higher selectivities observed with **1c** and **1j** are likely to originate from attractive dispersion interactions between the catalysts cyclohexyl moiety and the isopropyl and cyclohexyl residue, respectively. Whereas the competing structure does not allow efficient stacking of the cyclohexyl rings, this interaction is enhanced for the favorably bound enolate (see noncovalent interactions (NCI)[26] plot in Figure 1, C), leading to a more compact transition-state structure. Remarkably, the same effects were recently confirmed experimentally by NMR studies for the performance of **11** in enantioselective acylation reactions.[12,27] The present example provides further evidence for the importance of attractive dispersion interactions in catalysis, even in the presence of hydrogen bonds or ion pairs.[28]

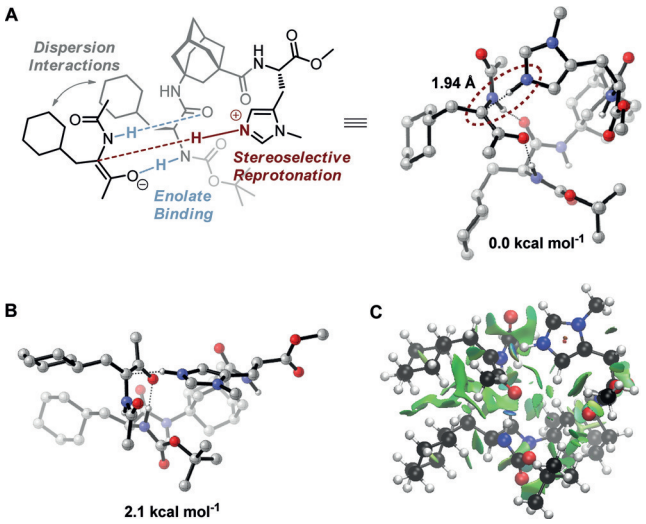


Figure 1. B3LYP-D3(BJ)/6-31+G(d,p) optimized structures representing the association of the protonated **18** with enolate **9j** and key catalyst–substrate interactions. A) Adduct leading to (*S*)-**10j**. B) Adduct leading to (*R*)-**10j**. All C–H bonds were omitted for clarity. C) NCI plot; green isosurfaces indicate attractive interactions.

The development of the first enantioselective Dakin–West reaction opens a new avenue to further develop related reactions. We now focus on the detailed investigation and elucidation of the decarboxylation step with the goal to rationally design novel and highly selective catalysts. Moreover, we will investigate the applicability of functionalized anhydrides, for example, towards the synthesis of enantiomerically enriched halo- and acyloxymethyl ketones that are frequently found chemical warheads in serine, cysteine, and threonine protease inhibitors.[29]

Acknowledgments

We gratefully acknowledge financial support by the Deutsche Forschungsgemeinschaft (SPP1807 Dispersion, Schr 597/27-1).

Keywords: amino acids · noncovalent interactions · organocatalysis · peptides · protonation

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 2719–2723
Angew. Chem. **2016**, *128*, 2769–2773

[1] a) H. D. Dakin, R. West, *J. Biol. Chem.* **1928**, *78*, 91–104; b) H. D. Dakin, R. West, *J. Biol. Chem.* **1928**, *78*, 745–756.
[2] a) G. L. Buchanan, *Chem. Soc. Rev.* **1988**, *17*, 91–109; b) F. K. Behbahani, T. S. Daloee, *Monatsh. Chem.* **2014**, *145*, 683–709.
[3] a) W. Steglich, G. Höfle, *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 981; *Angew. Chem.* **1969**, *81*, 1001; b) G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569–583; *Angew. Chem.* **1978**, *90*, 602–615.
[4] a) T. T. Curran, *J. Fluorine Chem.* **1995**, *74*, 107–112; b) A. G. Godfrey, D. A. Brooks, L. A. Hay, M. Peters, J. R. McCarthy, D. Mitchell, *J. Org. Chem.* **2003**, *68*, 2623–2632; c) C.-M. Kam, M. G. Götz, G. Koot, M. McGuire, D. Thiele, D. Hudig, J. C. Powers, *Arch. Biochem. Biophys.* **2004**, *427*, 123–134; d) J. Yu, L. Tang, Y. Yang, R. Ji, *Eur. J. Med. Chem.* **2008**, *43*, 2428–2435; e) K. Otake, S. Azukizawa, M. Fukui, K. Kunishiro, H. Kamemoto, M. Kanda, T. Miike, M. Kasai, H. Shirahase, *Bioorg. Med. Chem.* **2012**, *20*, 1060–1075; f) B. Dulla, K. T. Kirla, V. Rathore, G. S. Deora, S. Kavela, S. Maddika, K. Chatti, O. Reiser, J. Iqbal, M. Pal, *Org. Biomol. Chem.* **2013**, *11*, 3103–3107.
[5] R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, K. Schenker, *Tetrahedron* **1963**, *19*, 247–288.
[6] a) G. H. Cleland, C. Niemann, *J. Am. Chem. Soc.* **1949**, *71*, 841–843; b) J. W. Cornforth, D. F. Elliott, *Science* **1950**, *112*, 534–535; c) C. S. Rondestvedt, B. Manning, S. Tabibian, *J. Am. Chem. Soc.* **1950**, *72*, 3183–3184; d) W. Steglich, G. Höfle, *Tetrahedron Lett.* **1968**, *9*, 1619–1624; e) W. Steglich, G. Höfle, *Chem. Ber.* **1971**, *104*, 3644–3652; f) G. Höfle, A. Prox, W. Steglich, *Chem. Ber.* **1972**, *105*, 1718–1725; g) N. L. Allinger, G. L. Wang, B. B. Dewhurst, *J. Org. Chem.* **1974**, *39*, 1730–1735; h) L. Dalla-Vechia, V. G. Santos, M. N. Godoi, D. Cantillo, C. O. Kappe, M. N. Eberlin, R. O. M. A. de Souza, L. S. M. Miranda, *Org. Biomol. Chem.* **2012**, *10*, 9013–9020.
[7] T. H. Black, *Org. Prep. Proced.* **1989**, *21*, 179–217.

[8] a) W. Steglich, G. Höfle, *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 61; *Angew. Chem.* **1968**, *80*, 44; b) W. Steglich, G. Höfle, *Chem. Ber.* **1969**, *102*, 883 – 898; c) W. Steglich, G. Höfle, *Tetrahedron Lett.* **1970**, *11*, 4727 – 4730.
[9] P. A. Levene, R. E. Steiger, *J. Biol. Chem.* **1928**, *79*, 95 – 103.
[10] a) J. Blanchet, J. Baudoux, M. Amere, M.-C. Lasne, J. Rouden, *Eur. J. Org. Chem.* **2008**, 5493 – 5506; b) J. T. Mohr, A. Y. Hong, B. M. Stoltz, *Nat. Chem.* **2009**, *1*, 359 – 369; c) Y. Pan, C.-H. Tan, *Synthesis* **2011**, 2044 – 2053; d) S. Nakamura, *Org. Biomol. Chem.* **2014**, *12*, 394 – 405.
[11] 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; c) B. Lewandowski, H. Wennemers, *Curr. Opin. Chem. Biol.* **2014**, *22*, 40 – 46.
[12] C. E. Müller, D. Zell, R. Hrdina, R. C. Wende, L. Wanka, S. M. M. Schuler, P. R. Schreiner, *J. Org. Chem.* **2013**, *78*, 8465 – 8484.
[13] J. De Jersey, B. Zerner, *Biochemistry* **1969**, *8*, 1967 – 1974.
[14] J. J. Klicić, R. A. Friesner, S.-Y. Liu, W. C. Guida, *J. Phys. Chem. A* **2002**, *106*, 1327 – 1335.
[15] L. Wanka, C. Cabrele, M. Vanejews, P. R. Schreiner, *Eur. J. Org. Chem.* **2007**, 1474 – 1490.
[16] a) E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481 – 2495; b) J. T. Blank, S. J. Miller, *Biopolymers* **2006**, *84*, 38 – 47.
[17] R. V. Nair, A. S. Kotmale, S. A. Dhokale, R. L. Gawade, V. G. Puranik, P. R. Rajamohanan, G. J. Sanjayan, *Org. Biomol. Chem.* **2014**, *12*, 774 – 782.
[18] J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 11532 – 11533.
[19] F. R. Dietz, H. Gröger, *Synthesis* **2009**, 4208 – 4218.
[20] a) H. Brunner, P. Schmidt, *Eur. J. Org. Chem.* **2000**, 2119 – 2133; b) H. Brunner, M. A. Baur, *Eur. J. Org. Chem.* **2003**, 2854 – 2862; c) T. Seitz, J. Baudoux, H. Bekolo, D. Cahard, J.-C. Plaquevent, M.-C. Lasne, J. Rouden, *Tetrahedron* **2006**, *62*, 6155 – 6165; d) T. Tite, M. Sabbah, V. Levacher, J.-F. Briere, *Chem. Commun.* **2013**, *49*, 11569 – 11571.
[21] M. Amere, M.-C. Lasne, J. Rouden, *Org. Lett.* **2007**, *9*, 2621 – 2624.
[22] a) J. T. Mohr, T. Nishimata, D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2006**, *128*, 11348 – 11349; b) S. C. Marinescu, T. Nishimata, J. T. Mohr, B. M. Stoltz, *Org. Lett.* **2008**, *10*, 1039 – 1042; c) R. Doran, P. J. Guiry, *J. Org. Chem.* **2014**, *79*, 9112 – 9124; d) R. Zhao, Z. Sun, M. Mo, F. Peng, Z. Shao, *Org. Lett.* **2014**, *16*, 4178 – 4181.
[23] a) K. Okrasa, C. Levy, M. Wilding, M. Goodall, N. Baudendistel, B. Hauer, D. Leys, J. Micklefield, *Angew. Chem. Int. Ed.* **2009**, *48*, 7691 – 7694; *Angew. Chem.* **2009**, *121*, 7827 – 7830; b) R. Lewin, M. Goodall, M. L. Thompson, J. Leigh, M. Breuer, K. Baldenius, J. Micklefield, *Chem. Eur. J.* **2015**, *21*, 6557 – 6563.
[24] Z.-L. Wang, *Adv. Synth. Catal.* **2013**, *355*, 2745 – 2755.
[25] A. Sengupta, R. B. Sunoj, *J. Org. Chem.* **2012**, *77*, 10525 – 10536.
[26] E. R. Johnson, S. Keinan, P. Mori-Sánchez, J. Contreras-García, A. J. Cohen, W. Yang, *J. Am. Chem. Soc.* **2010**, *132*, 6498 – 6506.
[27] A. Kolmer, PhD thesis, Technical University Darmstadt, **2015**.
[28] J. P. Wagner, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2015**, *54*, 12274 – 12296; *Angew. Chem.* **2015**, *127*, 12446 – 12471.
[29] J. C. Powers, J. L. Asgian, Ö. D. Ekici, K. E. James, *Chem. Rev.* **2002**, *102*, 4639 – 4750.

Received: October 21, 2015
Revised: December 6, 2015
Published online: January 25, 2016

