Synthetic Methods

DOI: 10.1002/ange.201400203

Organocatalytic Asymmetric Formation of Steroids**

*Kim Søholm Halskov, Bjarke S. Donslund, Sebastian Barfüsser, and Karl Anker Jørgensen**

Dedicated to Professor Carl Djerassi on the occasion of his 90th birthday

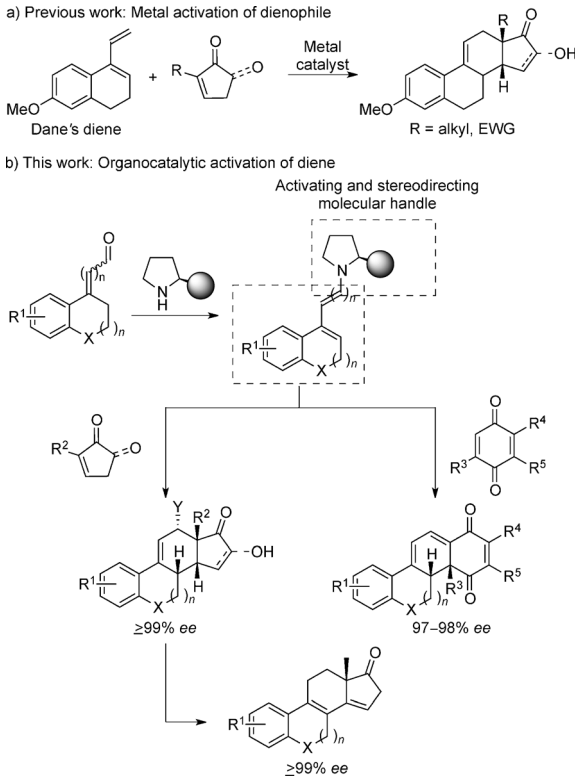
Abstract: *A novel and simple one-step approach for the construction of optically active steroids in a highly stereoselective manner by using organocatalysis is presented. The reaction of (di)enals with cyclic dienophiles in the presence of a TMS-protected prolinol catalyst leads to the construction of important 14β-steroids. This new reaction allows an easy access to optically active steroids with a variety of substituents in the A ring in high yields and up to greater than 99% ee. The reaction has been extended to include the construction of B- and D-homosteroids as well as steroids containing heteroatoms in the B ring. The angular substituent at C13 can be varied and alkyl, ester, and sulfone functionalities are introduced with excellent stereoselectivities. Simple synthetic procedures provide access to a range of naturally occurring steroids such as estrone and related analogues.*

Steroids are among the most privileged structures, and the impact of steroid-based research on modern society can hardly be overestimated. Being one of the most competitive research fields in the last century, steroids have a vital role in the development of organic synthesis, but also in medicine and biology.[1] A crucial task regarding steroids, as well as other biologically relevant compounds, is to develop reliable and general methods for their selective synthesis. This general method will allow structural diversity which is crucial for studies of biological activity.[2]

14β-Steroids are an important branch of the steroid family and possess the less common stereochemical configuration at C14. They are naturally found in the Cardenolide family, the members of which are known to possess, for example, inotropic activity and have found application in the treatment of cardiac dysfunction,[3a,b] and more recently in cancer.[3c,d] Furthermore, studies by Ehrenstein and Djerassi have demonstrated that 19-nor-14β-progesterone exhibits potent progestinal activity.[4,5] In recent years 14β-steroids have attracted renewed attention as additional pharmaceutical properties have been discovered.[6] The synthesis of the analogues used in the structure–activity reactivity studies with regard to these discoveries are mainly based on semisynthetic strategies. A purely synthetic pathway to these compounds would represent a highly interesting alternative to obtain important related structures.

One synthetic approach towards steroids relies on the formation of the core structure by a Diels–Alder reaction.[7] In the 1930s, Dane attempted this strategy, which was based on a cycloaddition between what became known as Dane's diene and a dienophile.[8] Later Quinkert et al. showed that the Diels–Alder reaction could be promoted by the application of a Lewis acid catalyst.[9] Recently, enantioselective versions of this approach, based on the activation of different dienophiles with chiral catalysts, have been reported (Scheme 1a).[10–13]

Organocatalysis has opened a new dimension in asymmetric catalysis in the last decade.[14] During the gold rush days a wide range of enamine-[15] and iminium-ion-catalyzed[16] asymmetric transformations were developed. Subsequently, emphasis on expanding organocatalysis with new



Scheme 1. Previous and current approaches towards the steroid skeleton using enantioselective Diels–Alder reactions. EWG = electron-withdrawing group.

[*] K. S. Halskov, B. S. Donslund, Dr. S. Barfüsser, Prof. K. A. Jørgensen
Center for Catalysis, Department of Chemistry, Aarhus University
Langelandsgade 140, 8000 Aarhus C (Denmark)
E-mail: kaj@chem.au.dk

[**] This work was financially supported by Aarhus University, FNU, and the Carlsberg Foundation. Dr. Jacob Overgaard and Espen Eikeland are acknowledged for performing X-ray analysis. Mette S. Haferbier is acknowledged for assisting in starting material synthesis.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201400203.

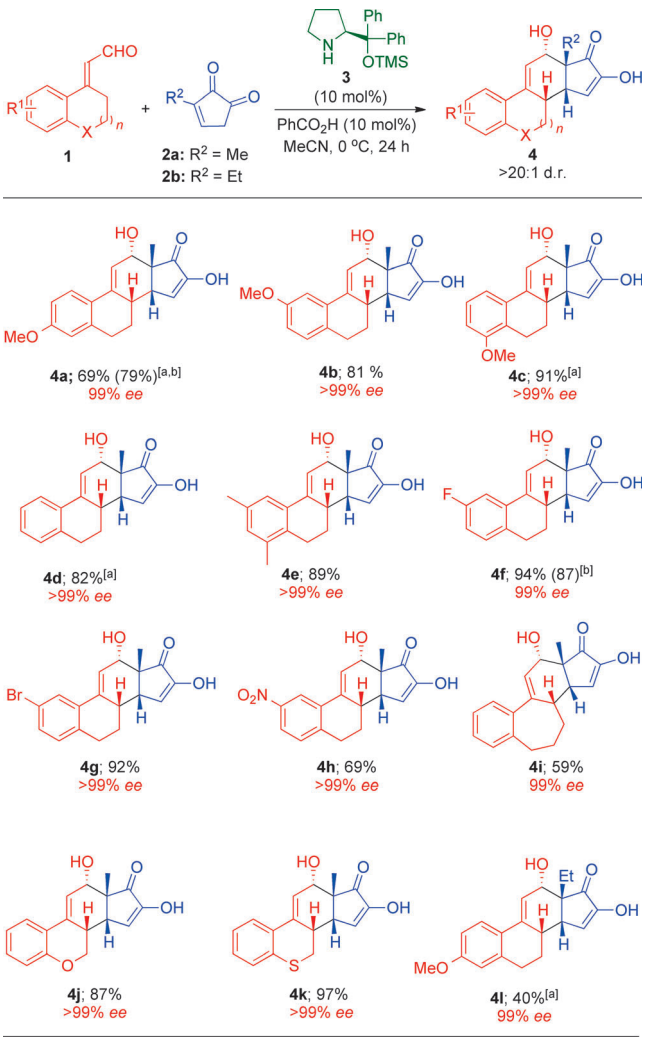
activation modes evolved and SOMO activation,[17] dienamine,[18] and trienamine[19] catalysis were introduced, as well as the concept of cascade reactions.[20] A more recent development is the application of organocatalysis in target-oriented synthesis. In this context, organocatalysis has been utilized in the formation of biologically relevant molecules[21] and in the total synthesis of complex natural products.[22]

Inspired by the application of organocatalysis for the synthesis of important molecules, we envisioned a simple and attractive approach for the formation of steroids (Scheme 1b). Previous reports, which focus on the activation of the dienophilic partner of the reaction, are all shown to react with Dane's diene, which is electron rich because of the conjugated methoxy substituent in the A ring.[8–13] Our novel approach is based on the condensation of an aminocatalyst with an enal or 2,4-dienal to form either a dienamine or trienamine, respectively, which consist of a diene moiety attached to an activating and stereoinducing molecular handle. Because of the electron donation from the catalyst the reaction can be performed with a wide range of easily available substrates.

It will be demonstrated that electron-donating and electron-withdrawing substituents can be present in the A ring, while the B ring can contain both oxygen and sulfur heteroatoms and can be of a different ring size. Hydroxy and alkyl substituents can be incorporated into the C ring, and furthermore, it will be shown that the size and substituents of the D ring can be varied. Finally, methyl, ethyl, ester, and sulfone functionalities are introduced as angular substituents at C13. The access to these steroids has typically relied on semisynthetic strategies, as opposed to purely synthetic strategies, because of the relative complexity of the steroid motif.[23] An important aspect of the developed reaction concept is that it provides a simple procedure to the important class of 14β-steroids. Furthermore, the approach also provides direct access to 12-hydroxy steroids. These are valuable precursors for *C*-nor-D-homosteroids[24] and play a vital role in the degradation of steroids.[25]

Preliminary experiments and optimization of the reaction conditions (see the Supporting Information) identified the diketone **2a**, which was employed in the studies by Göbel et al.,[13b] as a suitable dienophile for the reaction with an *E*/*Z* mixture of the enal **1** and the TMS-protected prolinol catalyst **3** in MeCN at 0 °C (Scheme 2).[26] With the optimal reaction conditions in hand, we went on to investigate the scope of the reaction. By the employment of the optimized reaction conditions the 14β-steroids **4** are obtained in one step in greater than 99% *ee*. Substrates with the methoxy substituent in different positions on the A ring provided their respective products in high yield and perfect stereoselectivity (**4a–c**). Steroids carrying electron-neutral (**4d**,**e**) and electron-withdrawing (**4f–h**) substituents on the aromatic moiety are also formed with the same excellent stereoselectivities. It should be noted that fluoride and bromide can be present in the A ring, the former is important from a medicinal chemistry point of view[27] and the latter useful for, for example, coupling reactions.

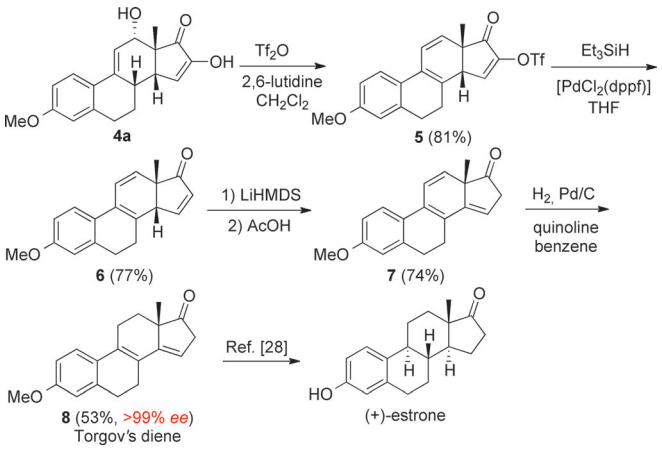
The method also allows for the formation of 14β-steroids with interesting variations on the B ring. A seven-membered ring can be incorporated (**4i**), as well as an oxygen (**4j**) or



Scheme 2. Scope of the synthesis of 14β-steroids using the organocatalytic reaction of the enals **1** with diketones **2a**,**b**. Reactions were performed on a 0.1 mmol scale with 2.0 equiv of **2**; see the Supporting Information for experimental details and assignment of absolute configuration. [a] The compounds **4a**,**c**,**d**,**l** were formed by the employment of 20 mol% of the catalyst **3** and 20 mol% of $PhCO_2H$. [b] The yield within parentheses was obtained when the reaction was performed on a 2 mmol scale. TMS = trimethylsilyl.

sulfur atom (**4k**) in the 6-position. These products were formed in excellent stereoselectivities. Finally, we investigated the possibility to vary the angular substituent in the C13 position. Since several commercially important steroid-based compounds, such as desogestrel and levonorgestrel, contain an ethyl substituent in this position, the organocatalytic reaction was attempted with the corresponding dienophile **2b**. This resulted in the formation of the product **4l** as a single stereoisomer. Furthermore, it was found that the reaction could be scaled up, thus maintaining yields and stereoselectivities (**4a**,**f**).

Upon evaluation of the scope of the reaction, we decided to pursue the application of the developed strategy beyond the 14β-steroid structure to access a wider range of known steroids and novel steroid analogues. To achieve this, a synthetic procedure, inspired by the previous work of Göbel

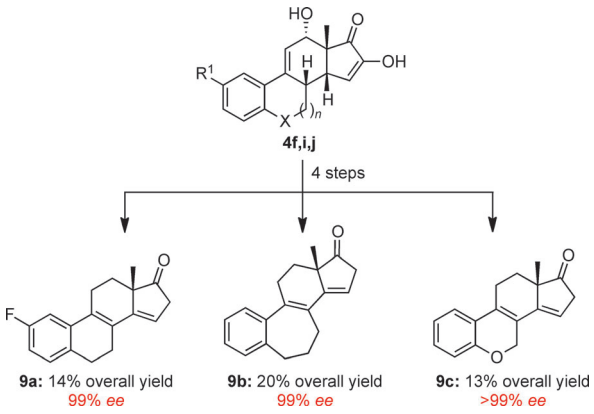


Scheme 3. Synthesis of Torgov's diene (**8**), thus leading to a formal synthesis of (+)-estrone from **4a**. See the Supporting Information for details. dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, HMDS = hexamethyldisilazide, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

et al.,[13b] was developed to convert the product **4a** into Torgov's diene **8**, which is a key intermediate in the synthesis of naturally occurring steroids such as (+)-estrone. This synthetic procedure is outlined in Scheme 3. First the enol in **4a** is protected with simultaneous elimination of the hydroxy substituent of the C ring and subsequent reduction to **6**. This sequence is followed by a double-bond transposition to form **7**, which is reduced to **8** (Torgov's diene), from which (+)-estrone can be made.[10,13b,28] The formation of **8** proceeds without deterioration of the enantiomeric excess.

With a reliable route to **8** in hand, we pursued the synthesis of analogues of this class of steroids. Following the same synthetic steps as presented in Scheme 3, compounds **4f,i,j** were converted into their respective Torgov's diene analogues **9a–c** (Scheme 4). Each compound could be synthesized in four steps in decent overall yields under non-optimized reaction conditions and without deterioration of the established enantiomeric excess.

Having demonstrated the synthetic utility of the reaction, we decided to pursue further variations of the formed steroid products presented in Scheme 2 by expanding the scope to use



Scheme 4. Synthesis of Torgov's diene analogues **9a–c** under non-optimized reaction conditions. See the Supporting Information for details.

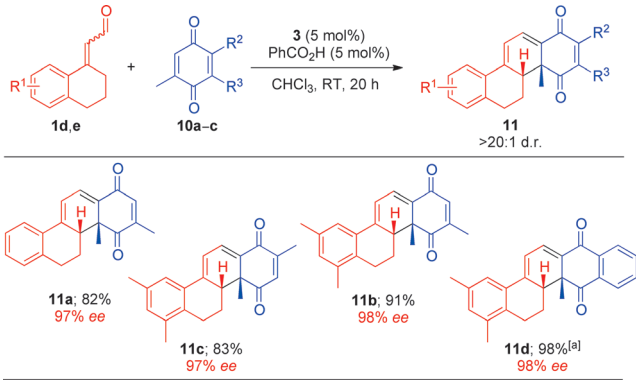
dienophiles other than the diketones **2a,b**. Based on the optimization process (see Table 1 in the Supporting Information), we hypothesized that the observed low diastereoselectivity in the reaction with the β-ketoester **2c** (Scheme 5), as opposed to the high diastereoselectivity observed with **2a**,

Scheme 5. Organocatalyzed asymmetric Diels–Alder reaction between the enal **1d** and the sulfone dienophile **2d** to form **4n**. Reaction performed on a 0.1 mmol scale using 1.2 equiv of **2**. See the Supporting Information for details.

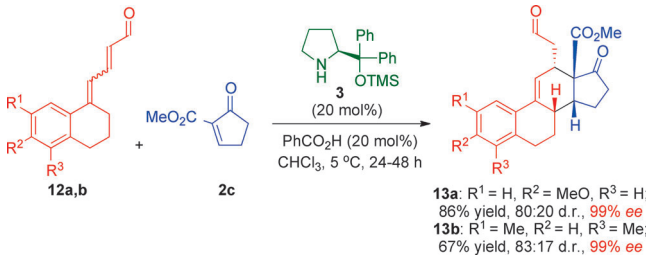
might be explained by the ability of both the ester and ketone carbonyl functionalities of **2c** to separately participate in interactions with the dienamine, thus promoting both an *endo* and *exo* approach of the dienophile to the dienamine. As a consequence, a similar substrate to **2c**, one carrying a noncarbonyl electron-withdrawing substituent, which we expect to interact in the same manner as **2a,b**, might be able to participate in the reaction and form the steroid product with high diastereoselectivity. The introduction of a sulfone functionality in the dienophile (**2d**) provided the intended product **4n** as a single diastereoisomer in 61% yield and 96% *ee* (Scheme 5). This reaction shows that heteroatom functionality, in form of a sulfone substituent, can be introduced in the angular position at C13 of the steroid skeleton.

We envisioned that the organocatalytic approach to the stereoselective formation of steroids could be utilized with alternative dienophiles to achieve further variations of the D ring. In this regard, quinone-based dienophiles were identified as suitable reaction partners leading to D-homosteroids (Scheme 6). This core structure is found in compounds of the Withanolide family such as Salpichrolides and Nicandrenon.[29] 2,6-Dimethylbenzoquinone (**10a**) was found to react with the enals **1d,e** to form their respective products **11a,b** in high yields and excellent stereoselectivities in the presence of 5 mol% of the catalyst **3**.[18e,30] By the employment of 2,5-dimethylbenzoquinone (**10b**) and menadione (**10c**) excellent results were also achieved (**11c,d**). However, slightly higher catalyst and acid loadings were necessary for the latter. The relative stereochemistry was assigned from an X-ray structure of **11a** (see the Supporting Information).

After the development of reliable methods which enable variations of the A, B, and D rings of the steroid core, we focused on the possibility to achieve variations on the C ring. In this regard we envisioned that changing from a dienamine catalysis strategy to the recently described trienamine catalysis strategy[19] would facilitate the stereoselective incorporation of an alkyl substituent at the 12-position. The results of these efforts are presented in Scheme 7. It was found that the



Scheme 6. Organocatalyzed asymmetric synthesis of the *D*-homosteroid products **11** by reaction between enals **1d,e** and the quinone-based dienophiles **10**. Reaction performed on a 0.1 mmol scale. See the Supporting Information for details. [a] The compound **11d** was formed by the employment of 10 mol% of **3**, 10 mol% of $PhCO_2H$, and a reaction time of 48 h.



Scheme 7. Trienamine-catalyzed asymmetric Diels–Alder reaction between the dienals **12a,b** and dienophile **2c** to form **13**. Reactions performed on a 0.1 mmol scale. See the Supporting Information for details.

dienals **12a,b** reacted with the dienophile **2c**, thus affording the products **13a,b** in good to excellent yields, good diastereoselectivities, and excellent enantioselectivities.

In conclusion, a simple and highly stereoselective organocatalytic approach to 14β-steroids has been presented. The methodology displays a broad generality, which allows the introduction of a wide range of variations in the formed products. These include various substituents on different positions on the A ring, the incorporation of heteroatoms in the B ring, modification of the B ring to a seven-membered ring, hydroxy- or alkyl substituents at the 12-position of the C ring, and the introduction of various substituents in the angular position at C13. Furthermore, the developed reaction concept has been extended to include reactions with quinones and proceed to form D-homosteroids in excellent yields and stereoselectivities. In addition, a procedure has been developed which allows rapid transformation of the formed products into analogues of Torgov's diene. From these compounds 14α-steroids such as (+)-estrone and related steroids with variations of the A and B rings are accessible.

Received: January 8, 2014
Published online: February 19, 2014

Keywords: asymmetric synthesis · cycloaddition · organocatalysis · steroids · synthesis design

[1] a) C. Djerassi in *Steroids Made it Possible (Profiles, Pathways and Dreams)* (Ed: J. I. Seeman), ACS, Washington, DC, **1990**; b) K. C. Nicolaou, T. Montagnon, *Molecules that Changed the World*, Wiley-VCH, Weinheim, **2008**, p. 79; c) J.-F. Biellmann, *Chem. Rev.* **2003**, *103*, 2019.
[2] See: a) S. L. Schreiber, *Science* **2000**, *287*, 1964; b) M. D. Burke, S. L. Schreiber, *Angew. Chem.* **2004**, *116*, 48; *Angew. Chem. Int. Ed.* **2004**, *43*, 46; c) J. Verma, V. M. Khedkar, E. C. Coutinho, *Curr. Top. Med. Chem.* **2010**, *10*, 95.
[3] For reviews, see: a) S. H. Rahimtoola, T. Tak, *Curr. Probl. Cardiol.* **1996**, *21*, 781; b) P. J. Hauptmann, R. A. Kelly, *Circulation* **1999**, *99*, 1265; c) T. Mijatovic, E. van Quaguebeke, B. Delest, O. Debeir, F. Darro, R. Kiss, *Biochim. Biophys. Acta Rev. Cancer* **2007**, *1776*, 32; d) I. Prassas, E. P. Diamandis, *Nat. Rev. Drug Discovery* **2008**, *7*, 926.
[4] a) W. M. Allen, M. Ehrenstein, *Science* **1944**, *100*, 251; b) M. Ehrenstein, *J. Org. Chem.* **1944**, *9*, 435.
[5] a) C. Djerassi, M. Ehrenstein, G. W. Barber, *Ann. Chem.* **1958**, *612*, 93; b) C. Djerassi, *Steroids* **1992**, *57*, 631.
[6] See: a) WO2000053619A1; b) US6949531; c) US7169769.
[7] For a recent review, see: M. Ibrahim-Ouali, *Steroids* **2009**, *74*, 133.
[8] a) E. Dane, *Angew. Chem.* **1939**, *52*, 655; b) E. Dane, J. Schmitt, *Liebigs Ann. Chem.* **1938**, 536.
[9] a) G. Quinkert, M. del Grosso, A. Bucher, J. W. Bats, G. Dürner, *Tetrahedron Lett.* **1991**, *32*, 3357; b) G. Quinkert, M. del Grosso, A. Bucher, M. Bauch, W. Döring, J. W. Bats, G. Dürner, *Tetrahedron Lett.* **1992**, *33*, 3617; c) G. Quinkert, M. del Grosso, A. Döring, W. Döring, R. I. Schenkel, M. Bauch, G. T. Dambacher, J. W. Bats, G. Zimmermann, G. Dürner, *Helv. Chim. Acta* **1995**, *78*, 1345.
[10] a) Q.-Y. Hu, P. D. Rege, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 5984; b) E. Canales, E. J. Corey, *Org. Lett.* **2008**, *10*, 3271.
[11] K. Shibatomi, K. Futatsugi, F. Kobayashi, S. Iwasa, H. Yamamoto, *J. Am. Chem. Soc.* **2010**, *132*, 5625.
[12] C. Schotes, A. Mezzetti, *J. Am. Chem. Soc.* **2010**, *132*, 3652.
[13] a) T. Schuster, M. Bauch, G. Dürner, M. W. Göbel, *Org. Lett.* **2000**, *2*, 179; b) M. Weimar, G. Dürner, J. W. Bats, M. W. Göbel, *J. Org. Chem.* **2010**, *75*, 2718.
[14] See: a) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2013**; b) D. W. C. MacMillan, *Nature* **2008**, *455*, 304; c) A. Moyano, R. Rios, *Chem. Rev.* **2011**, *111*, 4703; d) P. Melchiorre, *Angew. Chem.* **2012**, *124*, 9886; *Angew. Chem. Int. Ed.* **2012**, *51*, 9748; e) J.-L. Li, T.-Y. Liu, Y.-C. Chen, *Acc. Chem. Res.* **2012**, *45*, 1491; f) R. C. Wende, P. R. Schreiner, *Green Chem.* **2012**, *14*, 1821; g) U. Scheffler, R. Mahrwald, *Chem. Eur. J.* **2013**, *19*, 14346; h) H. Jiang, Ł. Albrecht, K. A. Jørgensen, *Chem. Sci.* **2013**, *4*, 2287; i) I. D. Jurberg, I. Chatterjee, R. Tannert, P. Melchiorre, *Chem. Commun.* **2013**, *49*, 4869.
[15] For reviews on enamine catalysis, see: a) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471; b) P. M. Pihko, I. Majander, A. Erkkilä, *Top. Curr. Chem.* **2009**, *291*, 145.
[16] For reviews on iminium ion catalysis, see: a) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416; b) S. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; c) J. B. Brazier, N. C. Tomkinson, *Top. Curr. Chem.* **2009**, *291*, 281.
[17] See: a) T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582; b) H.-Y. Jang, J.-B. Hong, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, *129*, 7004; c) K. C. Nicolaou, R. Reingruber, D. Sarlah, S. Bräse, *J. Am. Chem. Soc.* **2009**, *131*, 2086.

[18] For a review on dienamine catalysis, see: a) D. B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem.* **2012**, 865; for selected examples, see: b) S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973; c) R. M. de Figueiredo, R. Fröhlich, M. Christmann, *Angew. Chem.* **2008**, *120*, 1472; *Angew. Chem. Int. Ed.* **2008**, *47*, 1450; d) G. Bencivenni, P. Galzerano, A. Mazzanti, G. Bartoli, P. Melchiorre, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20642; e) T. K. Johansen, C. V. Gómez, J. R. Bak, R. L. Davis, K. A. Jørgensen, *Chem. Eur. J.* **2013**, *19*, 16518.

[19] For a review on trienamine catalysis, see: a) I. Kumar, P. Ramaraju, N. A. Mir, *Org. Biomol. Chem.* **2013**, *11*, 709; for seminal work, see: b) Z.-J. Jia, H. Jiang, J.-L. Li, B. Gschwend, Q.-Z. Li, X. Yin, J. Grouleff, Y.-C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053.

[20] See: a) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167; b) Ł. Albrecht, H. Jiang, K. A. Jørgensen, *Angew. Chem.* **2011**, *123*, 8642; *Angew. Chem. Int. Ed.* **2011**, *50*, 8492; c) H. Pellissier, *Adv. Synth. Catal.* **2012**, *354*, 237.

[21] See: a) M. Waser in *Asymmetric Organocatalysis in Natural Product Syntheses*, Springer, Vienna, **2012**; b) R. M. de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575; c) J. Alemán, S. Cabrera, *Chem. Soc. Rev.* **2013**, *42*, 774.

[22] See: a) E. Marqués-López, R. P. Herrera, *Comprehensive Enantioselective Organocatalysis*: *Catalysts*, *Reactions*, *and Applications* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2013**, p. 1359; b) E. Marqués-López, R. P. Herrera, M. Christmann, *Nat. Prod. Rep.* **2010**, *27*, 1138.

[23] For a recent review, see: R. Singh, G. Panda, *Tetrahedron* **2013**, *69*, 2853.

[24] P. Heretsch, S. Rabe, A. Giannis, *J. Am. Chem. Soc.* **2010**, *132*, 9968.

[25] S. Qu, E. P. Kolodziej, S. A. Long, J. B. Gloer, E. V. Patterson, J. Baltrusaitis, G. D. Jones, P. V. Benchetler, E. A. Cole, K. C. Kimbrough, M. D. Tarnoff, D. M. Cwiertny, *Science* **2013**, *342*, 347.

[26] a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem. Int. Ed.* **2005**, *44*, 794; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; c) K. L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248.

[27] a) K. Müller, C. Fach, F. Diederich, *Science* **2007**, *317*, 1881; b) K. L. Kirk, *Org. Process Res. Dev.* **2008**, *12*, 305.

[28] a) S. N. Ananchenko, I. V. Torgov, *Tetrahedron Lett.* **1963**, *4*, 1553; b) Y.-Y. Yeung, R.-J. Chein, E. J. Corey, *J. Am. Chem. Soc.* **2007**, *129*, 10346.

[29] L.-X. Chen, H. He, F. Qiu, *Nat. Prod. Rep.* **2011**, *28*, 705.

[30] a) J. E. Cole, W. S. Johnson, P. A. Robins, J. Walker, *J. Chem. Soc.* **1962**, 244; b) J. Das, R. Kubela, G. A. MacAlpine, Z. Stojanac, Z. Valenta, *Can. J. Chem.* **1979**, *57*, 3308.

