Autocatalytic Double σ-bond C(sp^2)–N Transamination Metathesis Reaction

Volker Klein,[1] Florian Schuster,[1] Svetlana B. Tsogoeva[1]*

[1] Organic Chemistry Chair I and Interdisciplinary Center for Molecular Materials (ICMM), Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Nikolaus-Fiebiger-Straße 10, 91058 Erlangen, Germany

* Corresponding author. Email: svetlana.tsogoeva@fau.de

Abstract: The transamination reaction, which involves the conversion of one amine to another, traditionally relies on biological enzyme catalysts. Although chemists have recently developed few catalytic methods, mimicking these enzymes to interconvert amine groups in acyclic substrates *via* transamination metathesis of a single C(sp^2)–N bond, transamination of cyclic tertiary amines has remained a long-standing unsolved problem in synthetic chemistry.

Here, we present an unprecedented autocatalytic transamination metathesis of two C(sp^2)–N bonds in a cyclic substrate that allows for the challenging transformation to take place under exceptionally mild and environmentally friendly reaction conditions. The methodology gives rapid and atom economical access to N-substituted 1,4-dihydropyridines (1,4-DHPs), which are privileged structures in bioactive compounds, pharmaceuticals and photoelectronic functional materials.

Introduction

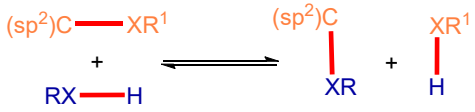
Over myriads of years of evolution, nature has developed intricate enzyme catalysts, accomplishing the transfer of amino-nitrogen from α-amino acids to α-keto-acids to produce their corresponding amino-acids. This double displacement reaction may also be called a transamination metathesis reaction, whereby two compound reactants AB and CD result in products of AC and BD. In an attempt to follow nature's efficient examples, chemists have developed few biomimetic methods for transamination metathesis of C(sp^2)–N bonds in the laboratory. The ever increasing practical importance of carbon-heteroatom bond metathesis reactions is underlined also by recent exciting examples of C(sp^2)–S and C(sp^2)–P bond metathesis processes (*1*) (Fig. 1A).

Existing rare examples of C(sp^2)–N bond metathesis include secondary amide transamidation reactions (*2, 3*) catalytic transamination of guanidines (*4*) and transamination of dimethylaminomethyleneoxindoles (*5*).

Although some rare advances have been made with regard to the transamination of N-substituted acyclic amines, which is emerging as a highly useful synthetic process, transamination of cyclic N-substituted amines has remained an unsolved problem (Fig. 1B).

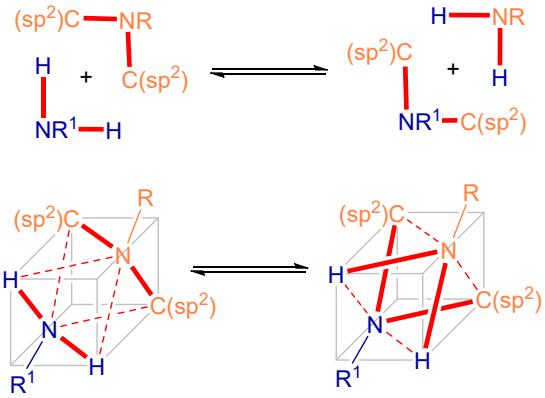
Cyclic amines are among the most valuable classes of compounds in chemistry and are ubiquitous in bioactive compounds and pharmaceuticals. In particular, compounds comprising a 1,4-dihydropyridine (1,4-DHP) scaffold play a central role in the development of blockbuster pharmaceuticals (*6-11*), model compounds of redox coenzyme nicotinamide adenine dinucleotide (NADH) (*12, 13*) and as hydride sources in synthetic chemistry (*14, 15*). Remarkably, 2,6-unsubstituted 1,4-DHPs exhibit strong blue fluorescence (*16, 17*), although 2,6-dimethyl-1,4-DHP (Hantzsch ester) is not fluorescent. These properties of 2,6-unsubstituted 1,4-DHPs open up new perspectives for their applications as photoelectronic functional materials (*18*).

A **Previous work:** single σ–bond C(sp^2)-X metathesis reactions

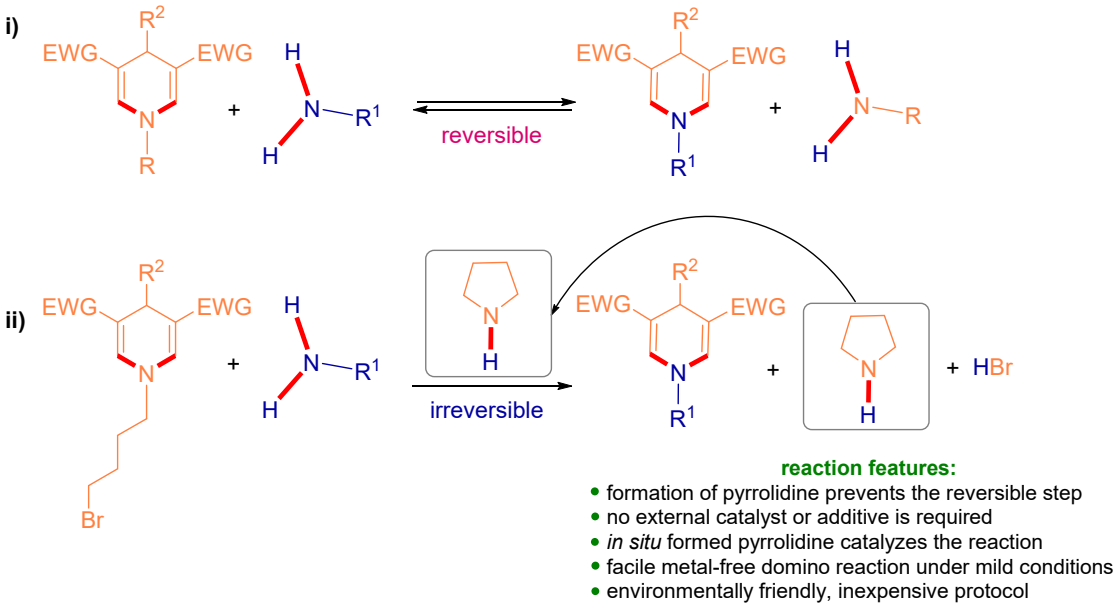


X = S, P: carbon-sulfur and carbon-phosphorus bond metathesis
X = NH, NR: transamination metathesis

B **This work:** double σ–bond C(sp^2)-N transamination metathesis reaction



C **Our Design:** Unprecedented synthesis of N-substituted 1,4-DHPs by (i) reversible or (ii) irreversible transamination



reaction features:

- formation of pyrrolidine prevents the reversible step
- no external catalyst or additive is required
- *in situ* formed pyrrolidine catalyzes the reaction
- facile metal-free domino reaction under mild conditions
- environmentally friendly, inexpensive protocol

Fig. 1. Transamination metathesis reactions. (**A**) Single σ-bond C(sp^2)-X metathesis reactions: schematic presentation of previous work (*1*). (**B**) Double σ-bond C(sp^2)-N transamination metathesis reaction (this work). (**C**) Design of autocatalytic double σ-bond C(sp^2)-N transamination reaction.

Furthermore, 4-arylated *N*-substituted 1,4-DHPs have drawn much recent attention in medicinal chemistry, finding applications as anti-asthmatic (*19*) or anti-cancer (*20*) agents and were also reported as potential remedies for overcoming drug resistance (*21*). Undoubtedly, through variation of substituents at nitrogen in 1,4-DHPs, new compounds with strikingly different and unprecedented properties can be obtained. Owing to this fact and constantly increasing applications, *N*-substituted 1,4-DHP has become a privileged scaffold for synthetic methodology development over the past few decades. Many advances have been made towards *N*-substituted 1,4-DHPs synthesis *via* modified Hantzsch reactions (*22*). However, the existing methodologies imply the synthesis of each individual *N*-substituted 1,4-DHP to obtain diverse compound libraries that are essential for structure-activity relationship (SAR) studies. Moreover, the existing methods of their synthesis suffer from significant limitations, such as long reaction time, harsh conditions and poor yields.

A direct and simple interconversion of functional groups at the N-atom of 1,4-DHPs, which evidently could have a broad impact on medicinal chemistry and material science, has not been reported so far. Herein, we describe development of an unprecedented transamination metathesis of two C(sp^2)–N bonds in 1,4-DHPs that allows for the challenging transformation to take place under very mild reaction conditions and involving an autocatalytic process (Fig. 1C), reducing reaction steps, effort, cost, time and waste production.

We envisioned that introduction of a suitable substituent at nitrogen, rendering the amine a good leaving group, might allow to perform the direct and irreversible transamination of N-substituted 1,4-dihydropyridines and primary amines (Fig. 1C). To validate the feasibility of the proposed double σ-bond C(sp^2)–N transamination metathesis reaction, the readily accessible N-(5-bromobutyl)-4-phenyl-3,5-dinitro-DHP **1a** was chosen as a substrate, since we expected that the released 4-bromobutan-1-amine can directly react to pyrrolidine, which is a secondary amine and cannot undergo the backward reaction to the initial DNDHP und thus makes the process effectively irreversible (Fig.-s 1C (*ii*) and 2). Remarkably, the *in situ* formed pyrrolidine side product can serve as a metal-free catalyst for the novel transamination process (Fig.-s 1C and 3C).
Notably, application of 3,5-dinitro-1,4-dihydropyridine (DNDHP), containing a pentyl group at the N-atom (instead of a bromobutyl group) resulted in a reversible transamination reaction, preventing a full conversion ((*i*), Fig. 1C). Therefore, the introduction of a bromobutyl group at N-atom of 1,4-DHP substrate is indeed highly advantageous and makes use of the instability of *in situ* formed 4-bromo-butyro-1-amine, which cyclizes to pyrrolidine (*23, 24*).

We carried out the designed reaction at room temperature in two different solvents: dichloromethane (DCM) and acetonitrile (MeCN) using different DNDHPs **1a-d** and primary amines **2a-l** (Fig. 2). All reactions were carried out for five hours. Reaction products **3a–f, 3h–l**, obtained in both solvents, were isolated in good to excellent yields (up to 95%). Only a single reaction towards **3g**, carried out for 24 h, showed merely low conversion. A possible explanation for the low yield might be the sterical hindrance exerted by the entering *tert*-butyl group. Notably, a gram scale reaction (1.25 g of **1e**) in DCM gave product **3e** in 91% yield, which is only three percent less than for the small scale experiment.

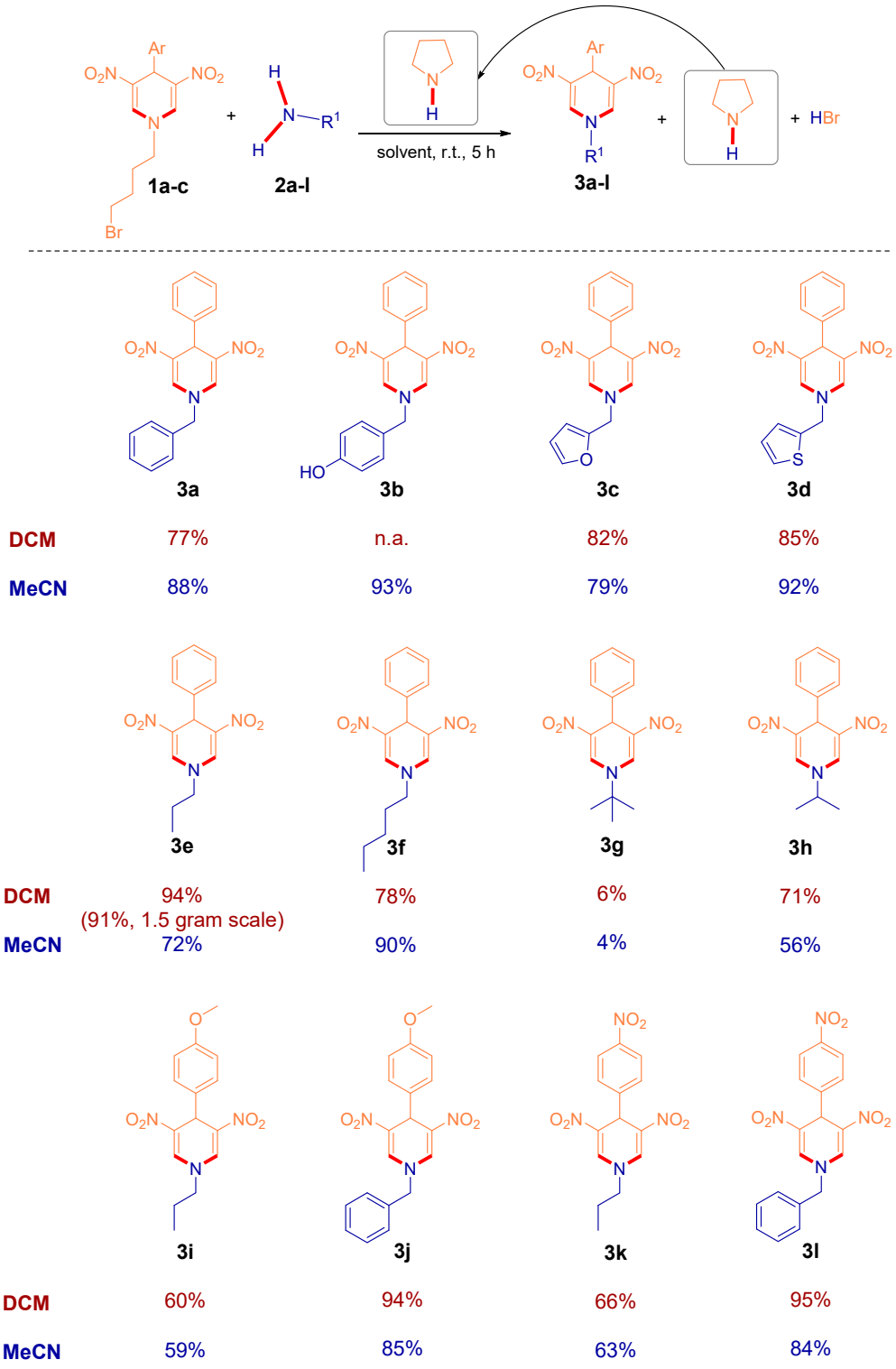
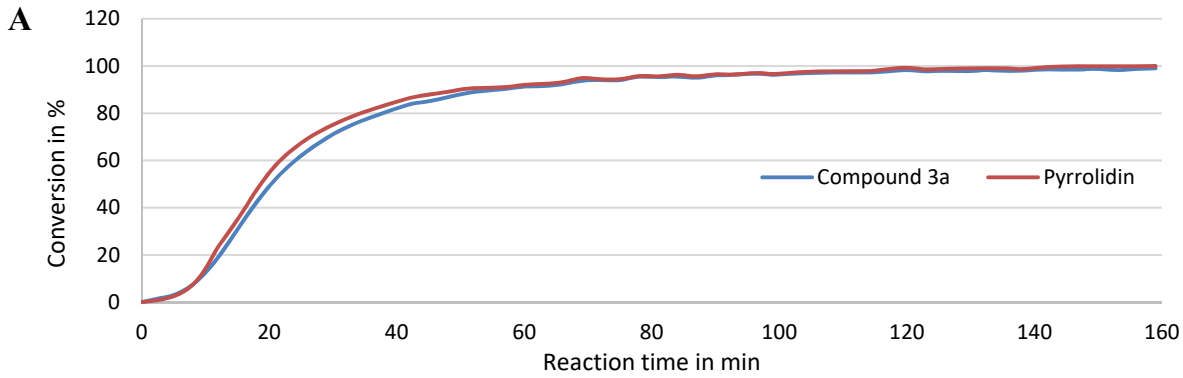
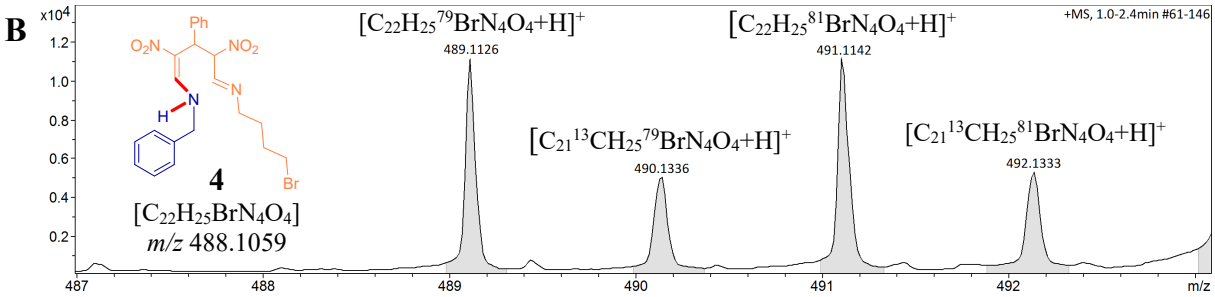


Fig. 2. Scope of transamination metathesis reactions towards DNDHPs. Reaction conditions for DNDHPs **3a-f, 3h-l**: primary amine (1.2 equiv), solvent, rt, 5 h; DNDHP **3g**: reaction time: 24 h.





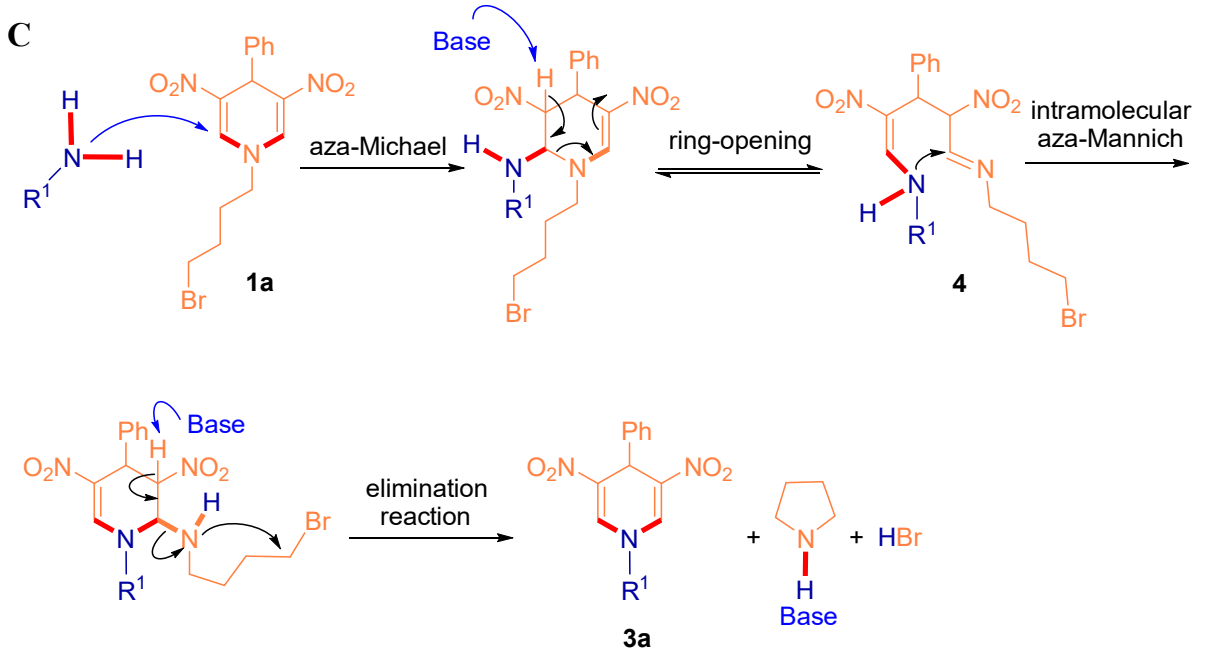


Fig. 3. Mechanistic studies. (**A**) Conversion of **1a** to **3a** and formation of pyrrolidine in CD_2Cl_2. (**B**) ESI TOF HRMS measurement showing typical isotope pattern $[M+H]^+$ for product intermediate **4**. (**C**) Proposed reaction mechanism for transamination metathesis reaction.

To investigate the mechanism of this transamination process, the reactions of **1a** and benzylamine was monitored *via* ^{1}H-NMR. One equivalent of **1a** was mixed with 1 equiv. of benzylamine in deuterated dichloromethane (used also as internal standard) and a ^{1}H-NMR spectrum was recorded every three minutes over 159 minutes (see SI). The conversion rate was determined by comparing the integral heights of the starting material and the products. After plotting the conversion of the starting material and of the formation of pyrrolidine and of **3a** against the reaction time, sigmoidal curves are obtained, which are characteristic for autocatalytic processes (Fig. 3A). From this, it can be deduced, that formation of pyrrolidine promotes as an autocatalyst the formation of further product **3a**.
To gain deeper insight into the reaction mechanism, ESI-TOF HRMS of the reaction mixture was also performed (Fig. 3B). ^{1}H-NMR spectroscopy indicated absence of an intermediate species after 90 minutes, so HRMS reaction monitoring was stopped after 90 minutes. Besides the peaks for the starting materials and the product, another isotope pattern of bromide and carbon was visible in the mass spectrum and the structure of the intermediate could be assigned to intermediate **4**. Notably, also ^{1}H-NMR studies indicated the formation of this species (see SI).
With all these data in hand, a possible reaction mechanism is proposed (Fig. 3C). In the first step of this four-step domino process, primary amine attacks DNDHP (**1a**) at C-2 *via* an aza-Michael type reaction. Subsequent deprotonation of the product intermediate by *in situ* formed pyrrolidine promotes ring opening towards intermediate **4**. Next, a ring closure occurs *via* an intramolecular aza-Mannich reaction followed by elimination under formation of new DNDHP and pyrrolidine.

In conclusion, we present a double transamination metathesis reaction that allows for the elusive overall transformation to take place under extremely mild metal-free conditions. The metathesis of two C(sp^2)–N bonds proceeds at room temperature within only 5 hours and without use of any external catalyst or additives. Instead, *in situ* formed pyrrolidine acts as an autocatalyst in this four-step domino process (aza-Michael / ring-opening / intramolecular aza-Mannich / elimination reaction) resulting in novel DNDHPs in mostly very good to excellent yields (up to 95%). The methodology allows the rapid structural diversification of 1,4-DHPs, with a good functional group tolerance. We anticipate that the autocatalytic transamination metathesis reaction, introduced here, will create new attractive opportunities in synthesis of new 1,4-DHPs of interest for life and material sciences.

1. Z. Lian, B. N. Bhawal, P. Yu, B. Morandi, Palladium-catalyzed carbon-sulfur or carbon-phosphorus bond metathesis by reversible arylation. *Science* **356**, 1059-1063 (2017).
2. C. M. Bell, D. A. Kissounko, S. H. Gellman, S. S. Stahl, Catalytic Metathesis of Simple Secondary Amides. *Angew. Chem.* **119**, 775-777 (2007).
3. E. L. Baker, M. M. Yamano, Y. Zhou, S. M. Anthony, N. K. Garg, A two-step approach to achieve secondary amide transamidation enabled by nickel catalysis. *Nat. Commun.* **7**, 11554 (2016).
4. H. Shen, Z. Xie, Titanacarborane Amide Catalyzed Transamination of Guanidines. *Organometallics* **27**, 2685-2687 (2008).
5. S. J. Park, C. G. Cho, K. I. Lee, Transamination of dimethylaminomethyleneoxindole. *Bull. Korean Chem. Soc.* **25**, 349-350 (2004).
6. J. A. Birrell, J. Hirst, Investigation of NADH Binding, Hydride Transfer, and NAD+ Dissociation during NADH Oxidation by Mitochondrial Complex I Using Modified Nicotinamide Nucleotides. *Biochemistry* **52**, 4048-4055 (2013).

7. P. Skae, R. J. Parry, Determination of the Stereochemistry of Hydride Transfer from NADPH to FAD Catalyzed by VlmR, a Flavin Reductase from the Valanimycin Biosynthetic Pathway. *Org. Lett.* **3**, 1117-1119 (2001).
8. I. Sabakhi *et al.*, Design, Synthesis and Biological Evaluation of New 1, 4-Dihydropyridine (DHP) Derivatives as Selective Cyclooxygenase-2 Inhibitors. *Iran. J. Pharm. Res.* **14**, 1087-1093 (2015).
9. Y. He *et al.*, Synthesis, insecticidal, and antibacterial activities of novel neonicotinoid analogs with dihydropyridine. *Chem. Cent. J.* **7**, 76-76 (2013).
10. V. K. Sharma, S. K. Singh, Synthesis, utility and medicinal importance of 1,2- & 1,4-dihydropyridines. *RSC Adv.* **7**, 2682-2732 (2017).
11. E. Carosati *et al.*, 1,4-Dihydropyridine Scaffold in Medicinal Chemistry, The Story So Far And Perspectives (Part 2): Action in Other Targets and Antitargets. *Curr. Med. Chem.* **19**, 4306-4323 (2012).
12. T. Marcelli, P. Hammar, F. Himo, Phosphoric acid catalyzed enantioselective transfer hydrogenation of imines: a density functional theory study of reaction mechanism and the origins of enantioselectivity. *Chemistry (Easton)* **14**, 8562-8571 (2008).
13. S. J. Connon, Asymmetric organocatalytic reductions mediated by dihydropyridines. *Org. Biomol. Chem.* **5**, 3407-3417 (2007).
14. X.-Q. Zhu, H.-Y. Wang, J.-S. Wang, Y.-C. Liu, Application of NAD(P)H Model Hantzsch 1,4-Dihydropyridine as a Mild Reducing Agent in Preparation of Cyclo Compounds. *J. Org. Chem.* **66**, 344-347 (2001).
15. S. G. Ouellet, A. M. Walji, D. W. MacMillan, Enantioselective organocatalytic transfer hydrogenation reactions using Hantzsch esters. *Acc. Chem. Res.* **40**, 1327-1339 (2007).
16. V. Nair, R. J. Offerman, G. A. Turner, Novel fluorescent 1,4-dihydropyridines. *J. Am. Chem. Soc.* **108**, 8283-8285 (2002).
17. S. Sueki *et al.*, Synthesis of 1,4-Dihydropyridines and Their Fluorescence Properties. *Eur. J. Org. Chem.* **2014**, 5281-5301 (2014).
18. Z. Guo, A. Shao, W.-H. Zhu, Long wavelength AIEgen of quinoline-malononitrile. *J. Mater. Chem. C.* **4**, 2640-2646 (2016).
19. T. R. Reddy *et al.*, Montmorillonite K-10 catalyzed green synthesis of 2,6-unsubstituted dihydropyridines as potential inhibitors of PDE4. *Eur. J. Med. Chem.* **62**, 395-404 (2013).
20. S. Valente *et al.*, 1,4-Dihydropyridines Active on the SIRT1/AMPK Pathway Ameliorate Skin Repair and Mitochondrial Function and Exhibit Inhibition of Proliferation in Cancer Cells. *J. Med. Chem.* **59**, 1471-1491 (2016).
21. K. Ohsumi *et al.*, N-Alkylated 1,4-Dihydropyridines: New Agents to Overcome Multidrug Resistance. *Chem. Pharm. Bull. (Tokyo)* **43**, 818-828 (1995).
22. S. L. Cui, J. Wang, X. F. Lin, Y. G. Wang, Domino reaction of 3-(2-formylphenoxy)propenoates and amines: a novel synthesis of 1,4-dihydropyridines from salicaldehydes, ethyl propiolate, and amines. *J. Org. Chem.* **72**, 7779-7782 (2007).
23. R. F. Brown, N. M. Van Gulick, Notes - The Geminal Alkyl Effect on the Rates of Ring Closure of Bromobutylamines. *J. Org. Chem.* **21**, 1046–1049 (1956).
24. J. v. Braun, E. Beschke, Die Aufspaltung des Pyrrolidins nach der Halogenphosphormethode. *Chem. Ber.* **39**, 4119–4125 (1906).

Acknowledgments
S.B.T. thanks Deutsche Forschungsgemeinschaft (DFG) for funding by grants TS87/17-1; TS87/23-1, and the Solar Technologies go Hybrid (Research Network SolTech) initiative of the Bavarian State Ministry for Science, Research and Art for research funding.

Competing interests
The authors declare no competing interests.