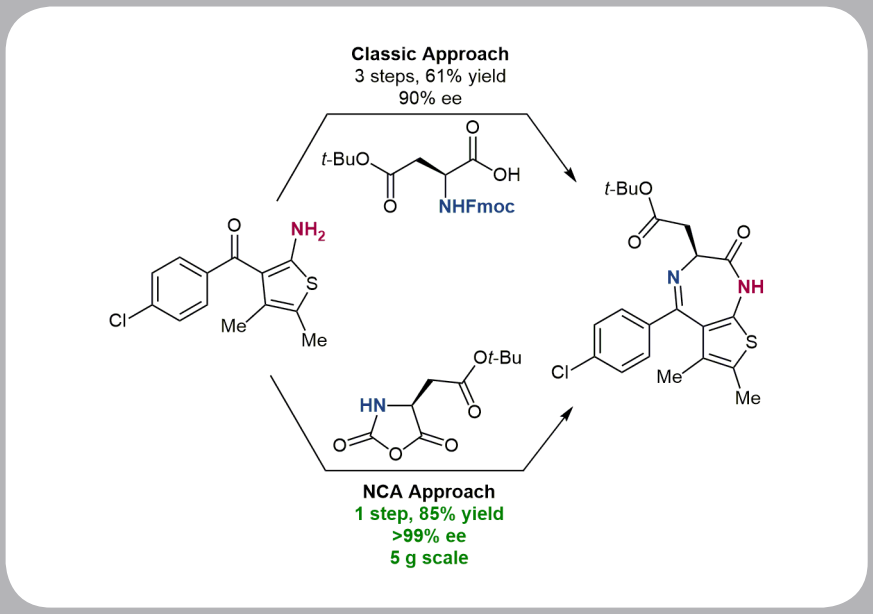
Synform

People, Trends and Views in Chemical Synthesis

2017/07

An Atom-Economical Method to Prepare Enantiopure Benzodiazepines with *N*-Carboxyanhydrides

Highlighted article by P. Fier, A. M. Whittaker



Contact
Your opinion about Synform is welcome, please correspond if you like:
marketing@thieme-chemistry.com

Thieme

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Dear Readers,

In two days the whole Thieme Chemistry Editorial Boards and Teams from all over the world will head off to the beautiful city of Porto for the 2017 meeting. There is a lot excitement for the event, which is going to be covered by a SYNFORM article that will report on what is being cooked up for the forthcoming season of Thieme Chemistry publications, including SYNFORM of course. Meanwhile, let's tuck into this new issue of SYNFORM! The opening article covers the new hypoxia-targeting anti-cancer agents discovered and developed by the group of T. Poulsen (Denmark), which is followed by the electrophilic rearrangement of aryl sulfoxides – investigated by B. Peng (P. R. of China) – leading to alkyl nitriles α-arylation. The third contribution is a Young Career Focus interview with A. L. Lawrence (UK) about his research interests and achievements so far. The closing task is assigned to Merck's P. Fier and A. Whittaker (USA) and their new strategy for preparing enantiomerically pure benzodiazepines.

Enjoy your reading!

In this issue

Literature Coverage
Synthesis of *ent*-BE-43547A$_1$ Reveals a Potent Hypoxia-Selective Anticancer Agent and Uncovers the Biosynthetic Origin of the APD-CLD Natural Products A107

Literature Coverage
Redox-Neutral α-Arylation of Alkyl Nitriles with Aryl Sulfoxides: A Rapid Electrophilic Rearrangement A112

Young Career Focus
Young Career Focus: Dr. Andrew L. Lawrence (University of Edinburgh, UK) A115

Literature Coverage
An Atom-Economical Method to Prepare Enantiopure Benzodiazepines with *N*-Carboxyanhydrides A118

Coming soon A122

Contact
If you have any questions or wish to send feedback, please write to Matteo Zanda at:
synform@outlook.com

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Synthesis of *ent*-BE-43547A$_1$ Reveals a Potent Hypoxia-Selective Anticancer Agent and Uncovers the Biosynthetic Origin of the APD-CLD Natural Products

Nat. Chem. **2017**, *9*, 264–272

Hypoxia is a state of very low oxygen levels, $p(O_2) < 5$ mmHg, encountered in some areas of solid tumors, which can lead to the development of a more malignant and resistant cellular phenotype poorly responsive to both radiotherapy and chemotherapy. Targeting hypoxic regions in tumors has been proposed as a possible novel therapeutic approach in oncology.

The first series of projects from the group of Professor Thomas Poulsen at Aarhus University (Denmark) has been focused on bioactive compounds, notably those with anticancer activities. However, the group is also interested in other types of biological activity. "All projects in our lab stem from an interest in uniting chemistry and biology with the overall aim – or perhaps vision is a better word – of contributing to an increased understanding of human disease and the development of new types of treatments," said Professor Poulsen.

The BE-43547 project sprang from studies that were initially focused on the natural depsipeptide rakicidin A (Figure 1a). Professor Poulsen explained: "This compound was previously reported to selectively kill both hypoxic cancer cells and stem-like leukaemia cells, which I found fascinating. Hypoxia designates a state of low oxygen levels in cells and it turns out that this is an important clinical parameter, as strong correlations exist between tumor hypoxia, disease progression, metastasis, and mortality (*Science* **2016**, *352*, 175)."

Rakicidin A contains a trademark chemical functionality: the 4-amido-2,4-pentadienoate group (APD group, Figure 1a blue). This structural motif is only known in three different macrocyclic depsipeptides: rakicidin, vinylamycin/microtermolide A (not shown), and BE-43547 molecules (Figure 1a). "All the APD-containing natural products also contain a lipid chain of varying length and branching," remarked Professor Poulsen. He continued: "We have therefore classified these molecules as APD-CLDs (amidopentadienoate-containing cyclolipodepsipeptides)."

"Rakicidin A was our first APD-CLD synthesis target," said Professor Poulsen, "a choice that was dictated by the fact that this compound had the most detailed bioactivity profile,

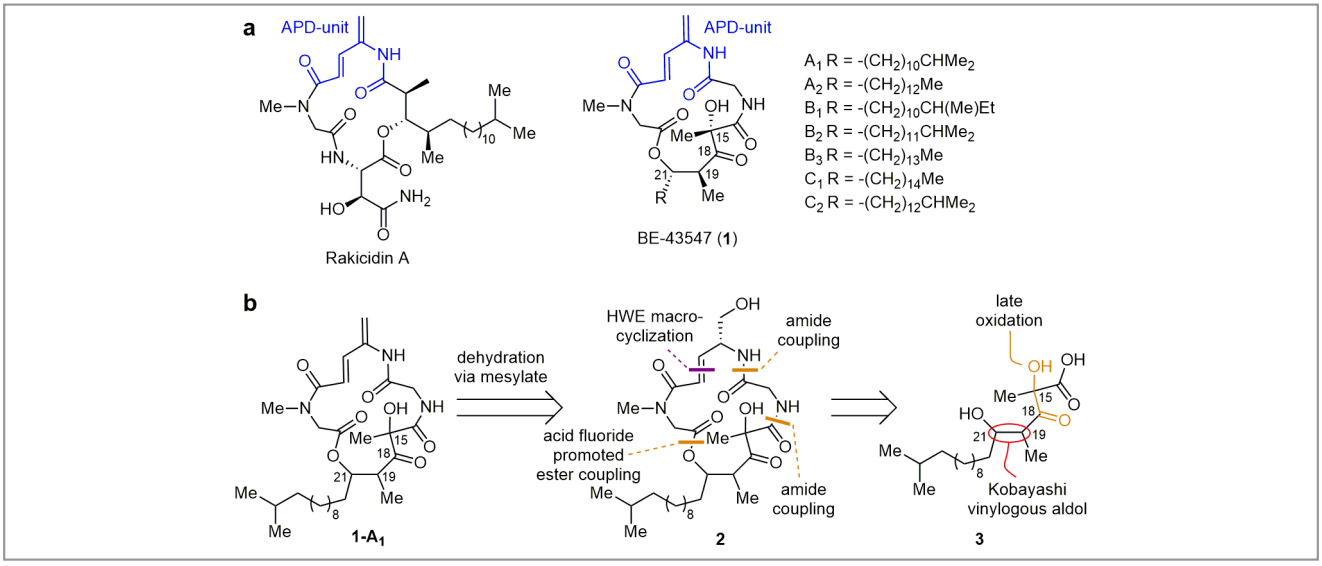


Figure 1 a) Structure of the natural products rakicidin A and BE-43547 A$_1$-C$_2$; the 4-amido-2,4-pentadienoate (APD) unit is highlighted in blue. b) Retrosynthetic analysis of BE-43547A$_1$.

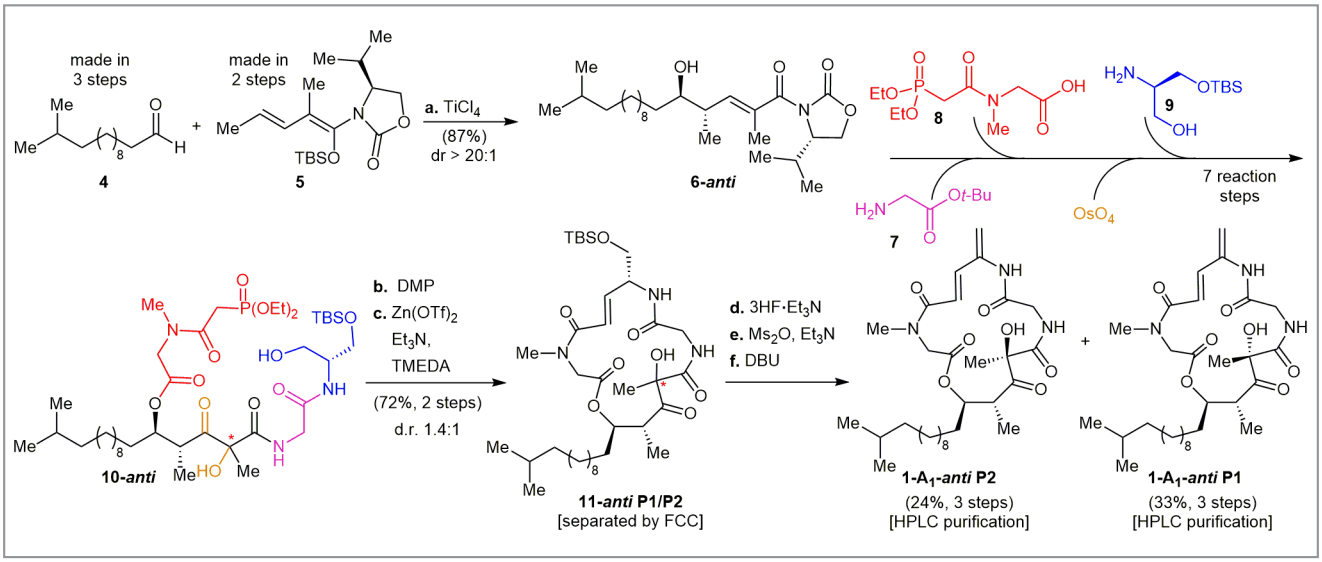
This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

although the related BE-43547 molecules were also reported to be potent cytotoxins (Japanese Patent JP10147594 A 19980602, **1998**). We synthesized rakicidin A and confirmed its biological activity (*Angew. Chem. Int. Ed.* **2016**, *55*, 1030), a challenge that the Yue Chen lab managed to overcome while we were still working on our total synthesis (*J. Am. Chem. Soc.* **2014**, *136*, 15787)." He went on, explaining: "We started our work on the BE-43547 class while we were still working on the rakicidin A synthesis and aimed our route for the A_1-congener, as this was reported to be marginally more potent than the other family members (Japanese Patent 10147594 A 19980602, **1998**), but in reality this choice was as much based on the 'A_1'-label. This rather arbitrary (and it would appear harmless) choice actually turned out to be quite troublesome, as we eventually had to re-isolate the natural product and the A_1/A_2-congeners were by far the less abundant family members."

The group designed a retrosynthetic strategy that would allow access to all possible stereoisomers (Figure 1b), since no stereochemical information was provided in the isolation patent. "Based on experience from a model system that we developed early on (*Chem. Commun.* **2011**, *47*, 12837), we predicted that the APD unit would be unstable and we therefore decided to pursue a formal dehydration of alcohol **2** to form the exocyclic double bond in the final transformation," said Professor Poulsen. He continued: "According to our plan, macrocyclization should take place at the double bond via an intramolecular Horner–Wadsworth–Emmons (HWE) olefination, and the cyclization precursor would be constructed via a series of amide and ester couplings from fragment **3** (Figure 1b)." Thus, the first main challenge for the group was to construct compound **3**, with control of all three stereogenic centers. The authors hypothesized that the two adjacent stereocenters on carbon 21 and 19 could be controlled with full flexibility using an asymmetric Kobayashi vinylogous aldol reaction (*J. Am. Chem. Soc.* **2004**, *126*, 13604; *Org. Lett.* **2012**, *14*, 5298). "This strategy was very appealing, as the precedence for obtaining stereocontrol was convincing and at the same time it would provide a double bond functionality that we could subsequently use to oxidatively install the α-ketol system. Here, we hoped that an asymmetric dihydroxylation reaction could override eventual substrate bias and achieve full control of the stereocenter at carbon 15 – an idea which ultimately stayed in the 'hope' category," said Professor Poulsen.

The forward synthesis started with a three-step synthesis of aldehyde **4** and a two-step synthesis of TBS enolate **5** (Scheme 1). The two fragments were coupled in a vinylogous aldol reaction promoted by $TiCl_4$. "As expected, the relative stereochemistry of the two new stereocenters could be controlled by the stoichiometry of $TiCl_4$," said Professor Poulsen. An excess (4 equiv) yielded the *syn*-isomer in a dr > 40:1 (not shown), while one equivalent of $TiCl_4$ yielded the *anti*-isomer (**6-*anti***) in dr > 20:1 (Scheme 1).

Professor Poulsen added: "The origin of this high diastereomeric control is not known in detail, but the usefulness is unquestionable. The aldol reaction along with the Evans auxiliary gave us complete control over the stereochemistry of carbons 21 and 19 with maximal convergence."



Scheme 1 Total synthesis of **1-A_1-*anti* P1/P2** [asterisks (red) imply a mixture of epimers at C15]

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

The aldol product **6-*anti*** was subjected to cleavage of the auxiliary, coupling with amine **7**, coupling with phosphonate **8**, dihydroxylation, alcohol-to-ketone oxidation, *tert*-butyl deprotection, and coupling with amine **9**, to yield compound **10-*anti*** (Scheme 1). The ester coupling was promoted via an in situ acid fluoride formation from the carboxylic acid **8**, a strategy that proved superior to more common esterification strategies, for example Steglich conditions.

"As already mentioned, the dihydroxylation proved to be a major challenge, and we had no success with catalytic Sharpless-type reactions along with non-asymmetric dihydroxylations using $RuCl_3$, $KMnO_4$, or OsO_4," said Professor Poulsen. "Finally, we had to resort to superstoichiometric OsO_4 in pyridine, which yielded the dihydroxylated product (dr = 1.3:1), which could be advanced to compound **10-*anti*** as the diastereomeric mixture. Working with a mixture proved a significant challenge when analyzing the products, but ultimately the low selectivity in the dihydroxylation was an advantage, since we needed to access both stereoisomers."

In the end-game sequence, alcohol **10-*anti*** was oxidized to the aldehyde and cyclized via a Horner–Wadsworth–Emmons reaction using the Helquist conditions (Scheme 1). Professor Poulsen revealed that alternatives such as using strong base or Roush–Masamune conditions (DBU, LiCl) proved unsuitable for this transformation. "After cyclization, the two diastereomers could be separated into **11-*anti* P1** and **P2**. TBS deprotection, mesylation and then elimination could yield the final products **1-A_1-*anti* P2** and **P1**. The aldol product **6-*syn*** was advanced using the same sequence of transformations to yield the two products **1-A_1-*syn* P2** and **P1**," he added.

PhD student Nikolaj Villadsen, the first author of the paper, took up the story: "I soon found that the **1-A_1** compounds demanded caution during purification. The product seemed unstable when concentrated from solution and, based on an insoluble solid we obtained in several experiments, we suspect that it can polymerize. As has been observed with other APD-CLD members, these compounds can instead be concentrated without degradation by lyophilization from a frozen mixture of DMSO or water–MeCN."

In possession of all four diastereomers of the natural product, direct comparison with the reported NMR data should now reveal which diastereomer was the natural one. The stereochemistry of carbon 15 was to be elucidated, once it was clear which compound to focus on.

Nikolaj Villadsen recalled: "To our despair, we finally concluded that none of the four synthesized compounds had a satisfying overlap with the NMR data from the patent. Only the tabulated NMR data was given, no spectra were included. We recorded NMR data in deuterated benzene, chloroform, pyridine, water, acetone, and acetonitrile to see if we could get a match, but without success. Those were not good days."

Professor Poulsen explained: "Attempted contact with any of the patent authors was unsuccessful, leaving us at what seemed to be a pretty painful dead end. We first speculated that the assigned structure was incorrect, more specifically we thought that the N-methyl group was misplaced. To advance the project, we clearly needed access to the natural product itself, but no known BE-43547 producing bacteria were available."

Professor Thomas Tørring, co-senior author on the paper, added: "The only annotated biosynthetic gene cluster of an APD-CLD family member that could be found was for rakicidin D. When searching for a similar cluster we could only find a few that were clearly also encoding rakicidin-like molecules, but curiously the ones we did find had a rearrangement in one of the polyketide modules – the dehydratase and ketoreductase were swapped. This appeared to be the module responsible for constructing the APD portion of the rakicidins; therefore, we decided to use this as a BLAST query. This gave roughly twenty homologues and the corresponding biosynthetic gene clusters appeared to cover all the known APD-CLDs – and most importantly two gene clusters that looked to encode the BE-43547 molecules (Figure 2a). Interestingly, this search also revealed a series of hitherto unknown APD-containing natural products." Professor Tørring continued: "We obtained the two bacterial strains *Salinispora arenicola* CNR107 and *Micromonospora* sp. RV43, and hoped that laboratory production of the compounds was feasible. We were very encouraged when we conducted preliminary LC-MS/MS analysis of bacterial extracts and identified compounds with a fragmentation pattern that was virtually identical to the synthesized **1-A_1-*anti* P2** (Figure 2b). We now know that both rakicidin A and BE-43547 afford a fragment ion with the mass 96.045 Da, which we believe can be attributed to the APD unit and therefore is likely to be found in all APD-CLD family members."

The match in fragmentation pattern between the synthesized and natural product suggested that the assigned connectivity was correct, i.e., that the N-methyl group was correctly placed in the structure, and that the team therefore had to isolate the natural product to acquire their own NMR data. "We cultured bacteria on large scale and performed a series of extraction and purification steps to finally afford BE-43547A_1 and A_2," said Nikolaj Villadsen. He continued: "This was not a trivial procedure, but very much worth the effort when final NMR comparison between the isolated natural product and the four synthetic compounds showed **1-A_1-*anti* P2** had perfect overlap (Figure 2c). Ironically, this compound was synthesized all the way back in the spring of 2015 as the second isomer that I prepared."

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

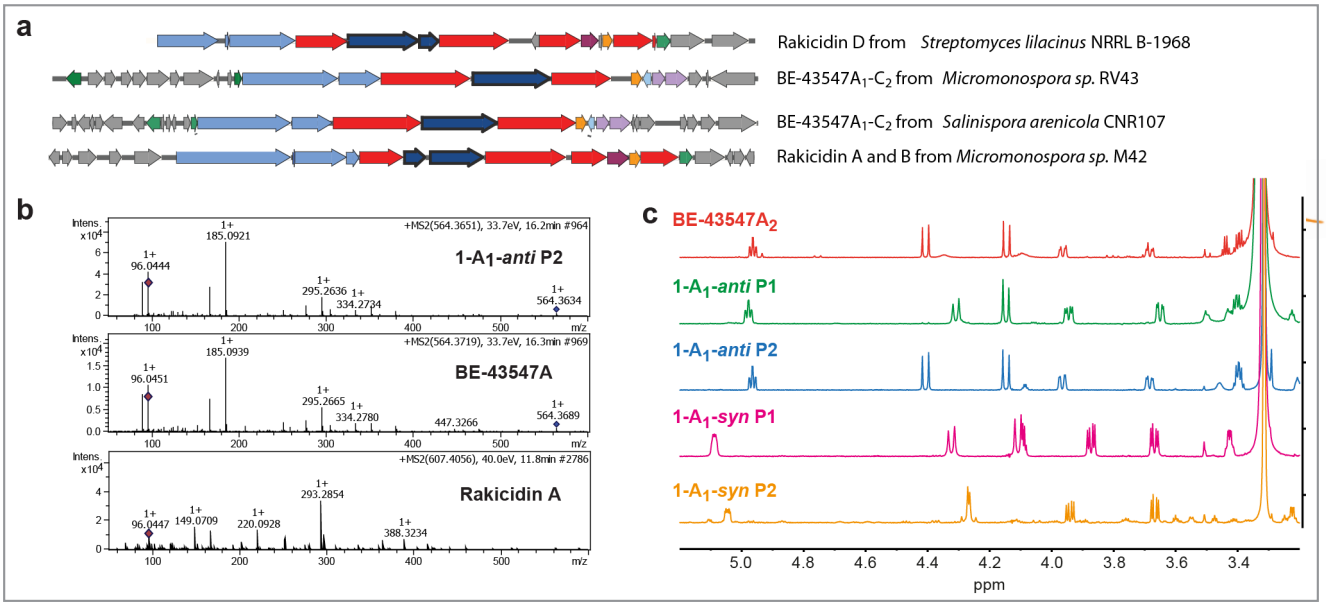


Figure 2 a) Biosynthetic gene clusters associated with APD-CLD molecules: PKS, blue (light and dark); NRPS, red; transporters, purple (light and dark); oxidases, green; thioesterases, orange. The genes encoding the PKS module with a non-canonical arrangement of the KR and DH domains are emphasized with dark blue. **b**) MS fragmentation analysis of **1-A$_1$-*anti* P2**, BE-43547A and rakicidin A. **c**) Comparison of NMR spectra of the four synthetic **1-A$_1$** diastereomers with that of isolated **1-A$_2$** shows that **1-A$_1$-*anti* P2** matches the spectral data of the natural product.

Professor Poulsen took up the story again: "CD spectroscopy showed that the synthesized compound was the enantiomer of the natural product. NOE experiments along with structure conformation optimization via DFT calculations helped us determine the stereochemistry of **1-A$_1$-*anti* P2** as (*R*,*R*,*R*)-***ent*-1-A$_1$**, and therefore the natural product has (*S*,*S*,*S*)-configuration. Evaluation of cytotoxicity under normal and low oxygen levels (normoxia and hypoxia) of the isolated and synthesized products showed that BE-43547A$_1$ possesses the same hypoxia-selective phenotype as rakicidin A and is even more selective (Figure 3). A rather curious observation that we also made was the near equipotent biological activity of the enantiomeric material."

"BE-43547A$_2$ is the most hypoxia-selective APD-CLD family member yet known, which I think is a really exciting discovery," said Professor Poulsen. "Together with clinical experts on tumor hypoxia, we are conducting preliminary investigations of their in vivo potential. However, the structure needs to be simplified – which we are working hard on realizing – while still maintaining these high levels of hypoxia selectivity in order to support a more extensive pre-clinical program. Our current biological focus on this project is to unravel the mechanism of action that underlies the potent toxicity of these compounds, studies that have so far taken us in several

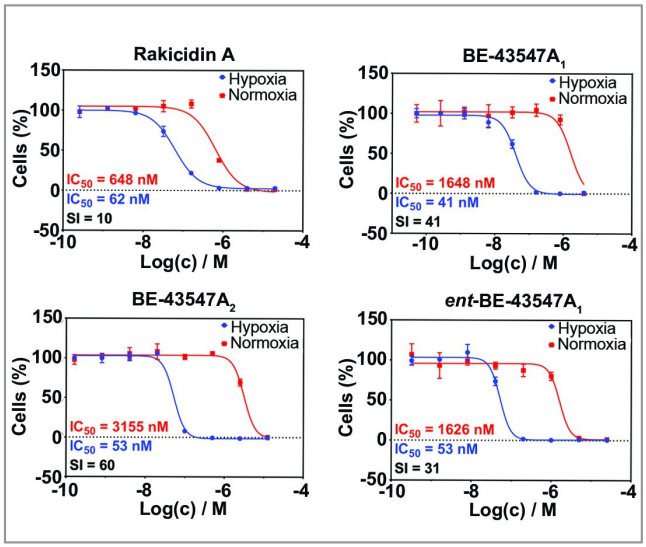


Figure 3 Viability of PANC-1 cells after treatment with rakicidin A, **1-A$_1$**, **1-A$_2$** or ***ent*-1-A$_1$** for 48 h under normoxia (21% oxygen) or hypoxia (0.1–0.5% oxygen)

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

different directions and in fact are also starting to teach us interesting things about completely different compound classes." In conclusion, Professor Poulsen said: "The high activity of the enantiomer is indicative of a mechanism that may not necessarily involve a discrete protein target which certainly does not make anything easier. This is a true detective game, which we of course hope will result in insights that one day could benefit people in need."

About the authors

Prof. T. B. Poulsen

Thomas B. Poulsen is an assistant professor at the Department of Chemistry, Aarhus University (Denmark). Thomas completed his Ph.D. with Professor Karl Anker Jørgensen in 2008 working on the development of a series of new asymmetric organocatalytic transformations. He then moved to Harvard University (USA) as a postdoctoral fellow with Professor Matthew D. Shair at the Department of Chemistry and Chemical Biology, where he worked on target-identification studies of complex anti-cancer natural products. In 2011, Thomas became an independent researcher at the Department of Chemistry, Aarhus University (Denmark), supported by an elite junior scientist program (Sapere Aude) from the Danish Research Council, and since 2012 he has been an assistant professor at the same institution. Thomas' research interests span complex molecule synthesis, chemical genetics, and cell biology.

Prof. T. Tørring

Thomas Tørring obtained his Ph.D. working with DNA nanotechnology and protein conjugation in the laboratory of Professor Kurt V. Gothelf at Aarhus University (Denmark). He worked on genome-encoded small molecules from *V. cholerae and L. pneumophila* during a postdoctoral stay with Professor Jason Crawford at Yale University (USA). Since returning to Aarhus University as an assistant professor, his work has also expanded into more traditional NRPS and PKS derived natural products. His research interests include chemical biology, biosynthesis, and natural product chemistry.

From left: N. L. Villadsen, K. M. Jacobsen, U. B. Keiding

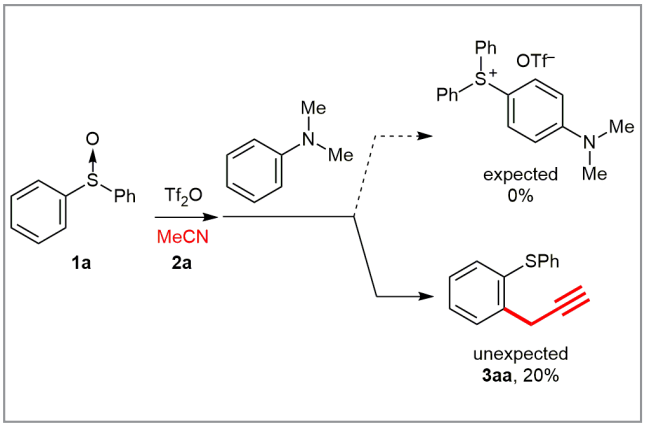
Nikolaj L. Villadsen, **Kristian M. Jacobsen**, and **Ulrik B. Keiding** all obtained their bachelor and master degrees under the supervision of assistant professor Thomas B. Poulsen at the Department of Chemistry, Aarhus University (Denmark). All three are currently Ph.D. students in the Poulsen lab.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Redox-Neutral α-Arylation of Alkyl Nitriles with Aryl Sulfoxides: A Rapid Electrophilic Rearrangement

J. Am. Chem. Soc. **2017**, *139*, 4211–4217

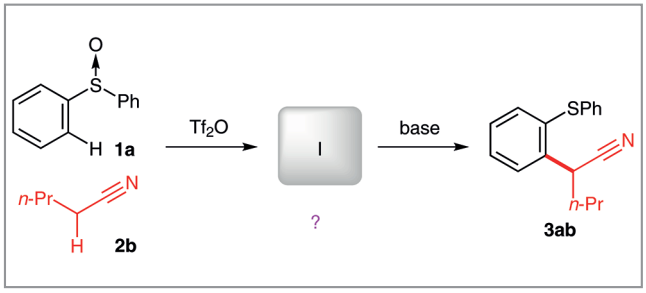
α-Aryl nitriles are structural frameworks frequently encountered in drugs and bioactive compounds. These compounds are also versatile synthetic building blocks that can be used to synthesize α-aryl amides, carboxylic acids, ketones and β-aryl amines by simple hydrolysis or reduction. Although various approaches can produce α-aryl nitriles, the use of impractical substrates, expensive and toxic transition-metal catalysts and limited functional group tolerance have been obstacles towards their synthetic applications.



Scheme 1 Serendipitous discovery of the method

Recently, Professor Bo Peng from Zhejiang Normal University (P. R. of China) disclosed a metal-free cross-coupling reaction between readily available aryl sulfoxides and alkyl nitriles, achieving an unprecedented α-arylation of nitriles. Professor Peng said: "Like other fascinating reactions found by accident, our method also came from a serendipitous discovery (Scheme 1). Initially, a Master's student – Li Shang – unexpectedly obtained *ortho*-cyanomethylated product **3aa** in his attempts to prepare a triaryl sulfonium salt. Eventually, a molecule of the solvent – acetonitrile – was unambiguously anchored on the *ortho*-position of the aryl sulfoxide." He continued: "We soon realized that this preliminary result was clearly due to a novel reaction pathway leading to α-arylation of nitriles. Therefore, we decided to study the reaction further."

Professor Peng explained: "The transformation actually consisted of two steps including the triflic anhydride (Tf_2O) treatment and subsequent base neutralization (Scheme 2). Neither step is well understood at the moment. Also, a mysterious intermediate **I**, arising as a black box, retarded optimization of the first step. However, the overall transformation could still be evaluated according to its efficiency in producing final product **3ab**. This one-pot, two-step reaction would act as a probe, eventually allowing us to identify the elusive intermediate **I**."



Scheme 2 Optimization of reaction conditions

He continued: "Although without proper understanding of the reaction, we were fortunate to get the optimum conditions that allowed us to study the reaction mechanism further. Subsequent low-temperature NMR studies not only identified the structure of the imine sulfonium **I** but also witnessed its robust formation and its extreme instability (Scheme 3). We further investigated the reaction by using DFT calculations and found that the reaction could be divided into three essential steps, including electrophilic assembling, deprotonation, and [3,3]-sigmatropic rearrangement."

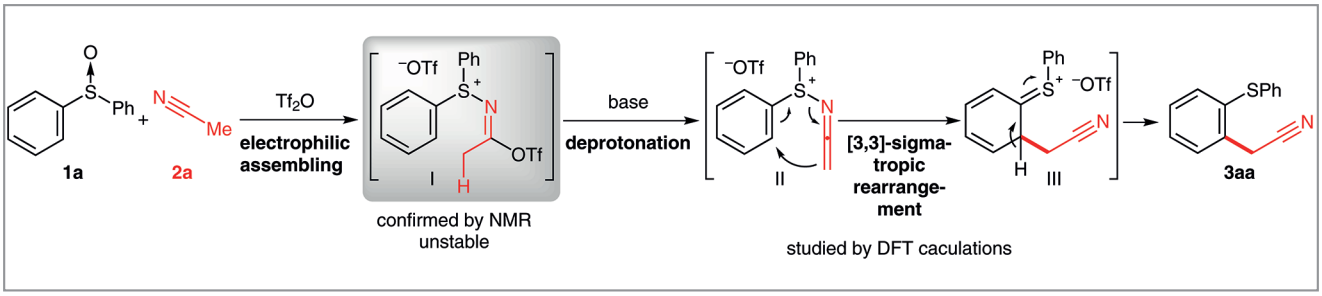
Professor Peng added: "The reaction also proved to be applicable to a wide range of aryl sulfoxides and alkyl nitriles (Scheme 4). It's remarkable that the reaction tolerated various functionalities including alkyl halide, alkynyl bromide, ether, ester, carbonate, ketone, and nitrile to produce α-aryl nitriles **3** in modest to very good yields (Scheme 4)."

Professor Peng remarked: "The transformability of products and the scalability of this reaction were demonstrated by our further efforts. But the most exciting aspect to us is the attempt to use a chiral base to induce asymmetric α-arylation of nitrile **2b** (Scheme 5). We found that the use of quinine as a chiral base indeed influenced the stereoselectivity of the

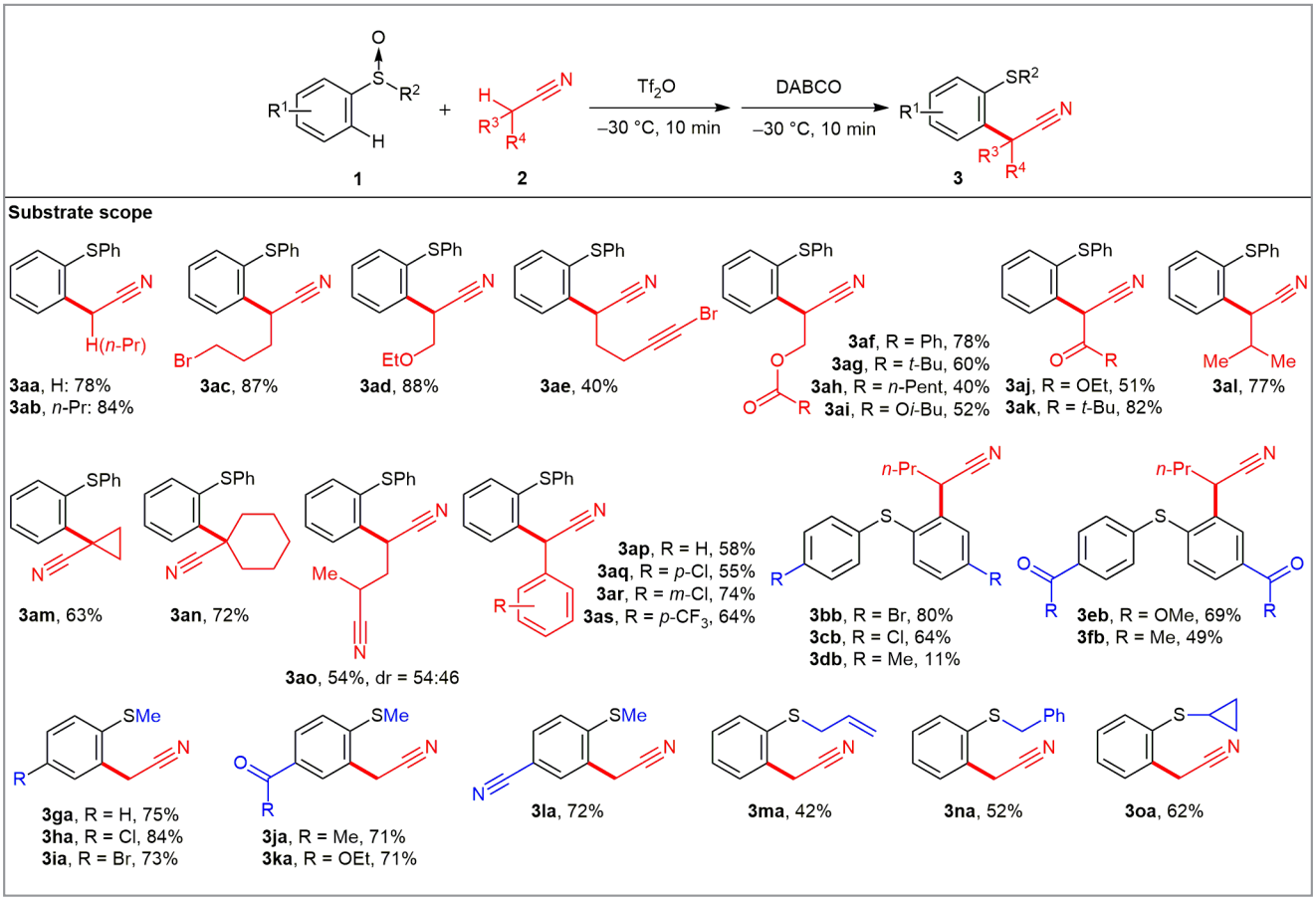
This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

reaction. Although a low enantiomeric ratio (er = 57:43) was observed, this preliminary result still confirmed the feasibility of developing T_2O/chiral-base-mediated asymmetric α-arylation of alkyl nitriles."

Professor Peng concluded: "We were very lucky. An accidental discovery led us to a robust arylation transformation (Scheme 1). The advent of the reaction not only provides a new method to access α-aryl nitriles but also promotes the development of other 'S–N' bond breaking induced [3,3]-sigmatropic rearrangements. We envision that the electrophilic rearrangement protocol would become a unique type of Claisen rearrangement in the future."

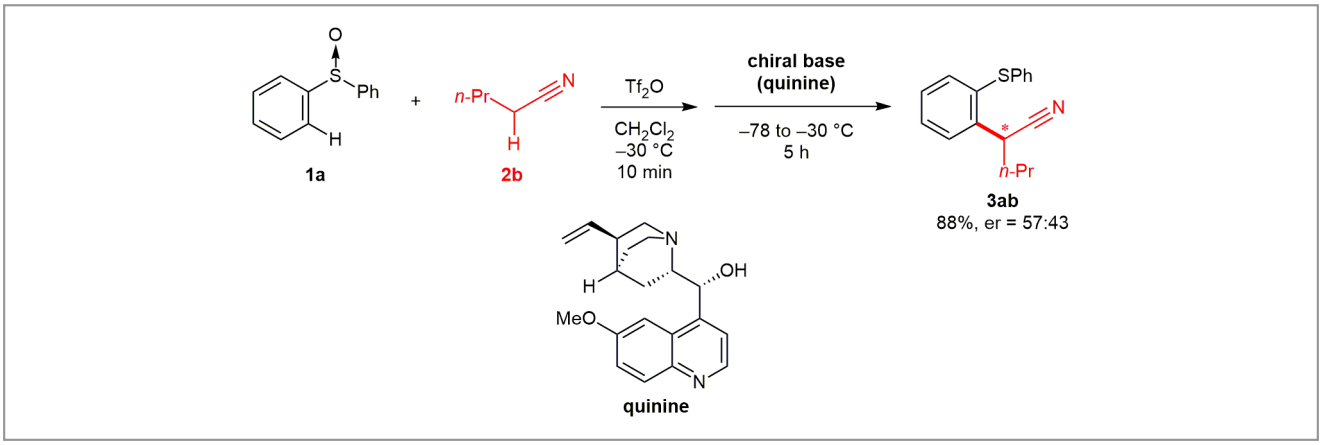


Scheme 3 Proposed mechanism supported by NMR studies and DFT calculations



Scheme 4 Substrate scope (new bonds highlighted in red bold)

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.



Scheme 5 Attempts of chiral-base-induced asymmetric α-arylation of nitriles

About the authors

L. Shang

Li Shang obtained his B.Sc. degree from Anyang Normal University (P. R. of China) in 2014. He then studied as a Master's student at Zhejiang Normal University (P. R. of China). In 2015, he joined the research group of Professor Bo Peng. His research focuses on the study of unprecedented sulfur(IV) species.

Prof. Y. Chang

Yonghui Chang was born in Henan province (P. R. of China) in 1975. He studied chemical engineering technology at Hunan University (P. R. of China), receiving his B.E. in 1998 and his Ph.D. in biochemistry technology under the guidance of Professor Hanjie Ying at Nanjing Technology University (P. R. of China) in 2009. After working as a lecturer at Hainan Normal University (P. R. of China) for two years, he became an Associate Professor in 2011. He has broad research interests, covering density functional theory (DFT) based mechanistic studies, ionic liquids and molecular recognition.

Prof. B. Peng

Bo Peng graduated from Nanjing University of Science and Technology (P. R. of China) with his B.Sc. degree, and then obtained his Ph.D. from Dalian University of Technology (P. R. of China) in 2010. After postdoctoral research at the Max-Planck-Institut für Kohlenforschung (Germany) and the University of Illinois at Urbana-Champaign (USA), he started his independent career as a principle investigator at Zhejiang Normal University (P. R. of China) in 2015. In the same year, he was named as a Qianjiang Scholar. His current interests focus on the formation and transformation of highly reactive but unstable organic species.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Young Career Focus: Dr. Andrew L. Lawrence (University of Edinburgh, UK)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Dr. Andrew L. Lawrence (University of Edinburgh, UK).

Biographical Sketch

Dr. A. L. Lawrence

Andy Lawrence completed his undergraduate studies at the University of Oxford (UK) in 2006 and subsequently obtained a DPhil in 2010 under the supervision of Professor Sir Jack Baldwin and Dr. Rob Adlington. Andy then moved to Australia to spend two years as a postdoctoral researcher with Professor Mick Sherburn at the Australian National University (ANU) in Canberra. In 2012, Andy secured an Australian Research Council Fellowship, which allowed him to begin his independent academic career at the ANU. In 2013, he moved back to the UK for a Lectureship at the University of Edinburgh, where he is now Senior Lecturer. Andy has been awarded a 2016 Thieme Chemistry Journals Award and the 2017 RSC Hickinbottom Award.

INTERVIEW

SYNFORM *What is the focus of your current research?*

Dr. A. L. Lawrence We are interested in developing and improving the science and art of organic synthesis. Our research effort is primarily focused on the total synthesis of natural products, developing new synthetic methodology, and exploring new strategies and concepts in chemical synthesis.

SYNFORM *When did you get interested in synthesis?*

Dr. A. L. Lawrence My earliest interest in synthesis goes all the way back to my first year of undergraduate studies at St. John's College, Oxford (UK). I was very fortunate to be tutored by Professor George Fleet, a masterful teacher of organic chemistry. During this early exposure to classic organic chemistry (aldol chemistry, Grignard reagents, electrophilic additions to alkenes, etc.) it became apparent to me that the opportunities for creativity and discovery, even when one knows just a limited number of reactions, are limitless.

SYNFORM *What do you think about the modern role and prospects of organic synthesis?*

Dr. A. L. Lawrence In my opinion, organic synthesis is as important now as it has ever been. The field is continually evolving and it is hard to predict how it will look in the future, but the synthesis of organic compounds will always be important. I feel strongly, however, that the synthesis community must resist the urge to justify our existence solely through the applications of the molecules we make (medicines, functional materials, etc.). That is not to say we should not embrace applied synthesis and cross-disciplinary research, we absolutely should! But we should ensure that the importance of organic synthesis as a science in its own right, worthy of study for the pursuit of new knowledge and understanding, is broadly com-

© Georg Thieme Verlag Stuttgart • New York – Synform **2017/07**, A115–A117 • Published online: June 19, 2017 • DOI: 10.1055/s-0036-1590293

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

municated to the wider scientific community. Otherwise, the belief that organic synthesis is a 'solved problem' will erroneously grow within the scientific community. In terms of the future of organic synthesis, areas that I think are particularly exciting all revolve around the concept of generating and harnessing complexity, both on the single molecule level and in systems.

SYNFORM *Your research group is active in the area of total synthesis of complex natural molecules. Could you tell us more about your research and its aims?*

Dr. A. L. Lawrence I am interested in the total synthesis of natural products for many reasons, ranging from the potential applications of the target molecules to the esoteric challenge posed by their complex architectures. However, I feel justifications along these lines really don't do justice to how important natural products are. I think Prelog said it best when he stated *"Natural products are the result of three billion years of development of the living world, and they have survived the natural selection process over a long period of evolution. I am convinced they always carry a message, which it is our job to decipher".*[1] This is how I think about our total synthesis research, we are trying to decipher the hidden messages encoded within the structures of these products of evolution. For example, we are currently interested in how and why symmetry is broken in the biosynthesis of various natural products. By investigating and mimicking these natural processes in vitro we hope to make important discoveries concerning how the breaking of symmetry can be better exploited in synthesis.

SYNFORM *What is your most important scientific achievement to date and why?*

Dr. A. L. Lawrence My view on what our most important contribution is changes all the time; when I talk to one of my co-workers, their passion and enthusiasm convinces me that their most recent work is the most important…until of course I talk to the next co-worker. But in terms of our published work, I think we have made some important contributions in the areas of cycloaddition chemistry (Figure 1a),[2,3] redox catalysis (Figure 1b),[4,5] and domino reaction sequences (Figure 1c).[5–9]

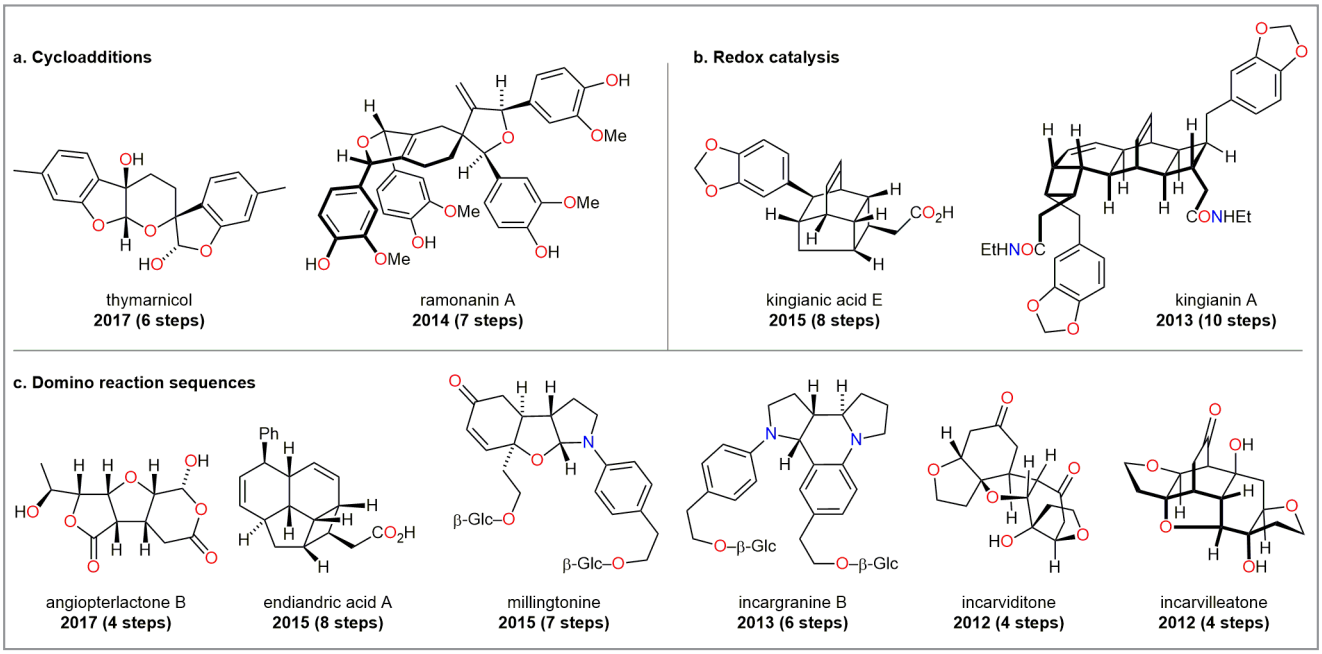


Figure 1 Natural product targets synthesized by the Lawrence group

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

REFERENCES

(1) (a) V. Prelog *Naturwiss. Rundsch.* **1985**, *38*, 259;
(b) A. Eschenmoser *Angew. Chem. Int. Ed.* **2011**, *50*, 12412.
(2) I. De Silvestro, S. L. Drew, G. S. Nichol, F. Duarte, A. L. Lawrence *Angew. Chem. Int. Ed.* **2017**, DOI: 10.1002/anie.201701481R1.
(3) R. S. Harvey, E. G. Mackay, L. Roger, M. N. Paddon-Row, M. S. Sherburn, A. L. Lawrence *Angew. Chem. Int. Ed.* **2015**, *54*, 1795.
(4) S. L. Drew, A. L. Lawrence, M. S. Sherburn *Angew. Chem. Int. Ed.* **2013**, *52*, 4221.
(5) S. L. Drew, A. L. Lawrence, M. S. Sherburn *Chem. Sci.* **2015**, *6*, 3886.
(6) P. D. Brown, A. C. Willis, M. S. Sherburn, A. L. Lawrence *Org. Lett.* **2012**, *14*, 4537.
(7) P. D. Brown, A. C. Willis, M. S. Sherburn, A. L. Lawrence *Angew. Chem. Int. Ed.* **2013**, *52*, 13273.
(8) P. D. Brown, A. L. Lawrence *Angew. Chem. Int. Ed.* **2016**, *55*, 8421.
(9) M. I. Thomson, G. S. Nichol, A. L. Lawrence, *Org. Lett.* **2017**, DOI: 10.1021/acs.orglett.7b00929.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

An Atom-Economical Method to Prepare Enantiopure Benzodiazepines with *N*-Carboxyanhydrides

Org. Lett. **2017**, *19*, 1454–1457

The benzodiazepine scaffold can be found in many marketed drugs, such as Valium and Klonopin (Figure 1). Importantly, benzodiazepines are finding resurgence in medicinal chemistry with new indications such as anticancer therapeutics. As part of a Merck drug development program, Dr. Patrick Fier and Dr. Aaron Whittaker from Merck & Co. (Rahway, USA) were tasked with developing an efficient synthesis of a benzodiazepine-based molecule.

However, known approaches involve multistep sequences and lead to racemization of the stereocenter at the alpha position. Dr. Fier said: "We considered that a more direct method to access benzodiazepines could be realized by employing *N*-carboxyanhydrides (NCAs) as the amino acid coupling partner. It was proposed that *o*-ketoanilines could react with an NCA first as a nucleophile and then, upon loss of carbon dioxide, a β-amino amide intermediate would be generated which would then be suited to condense with the carbonyl group (Scheme 1). This proposed reaction sequence was appealing since it would generate water and CO_2 as the only stoichiometric byproducts."

Dr. Fier continued: "We were pleased to find that the *N*-carboxyanhydrides used for this study were readily prepared as crystalline compounds in a single step from unprotected amino acids and COX_2 reagents, such as triphosgene. None of the NCAs used in this study required purification, as the pure compounds precipitated from solution during their preparation."

The authors investigated the reactivity between 2-aminobenzophenone and an NCA derived from phenylalanine. However, it was quickly realized that simply heating an equimolar amount of the two reagents led to oligomerization of the NCA. "This side reaction was not surprising since (i) the electrophilicity of the ketone is lower than that of the anhydride carbonyl of the NCA, (ii) the nucleophilicity of the primary amine generated upon NCA opening is greater than that of the aniline, and (iii) the formation of seven-membered rings is slow," explained Dr. Fier. He continued: "To suppress this oligomerization pathway we decided to perform the reaction in two stages under different pH regimes. The N-acylation step would proceed under acidic conditions such that the liberated primary amino group would exist as the ammonium salt, suppressing further reactions with the NCA, while the less basic aniline would exist largely as the free base and be suitably reactive toward the NCA. After complete consumption of the NCA, the intramolecular condensation step would occur by buffering the reaction medium to permit the primary amino group to react with the carbonyl group."

The authors of this study knew that high conversion of the NCA in the N-acylation stage would be required prior to buffering the solution for the condensation stage. With these considerations in mind, a survey of different acids, stoichiometry, solvents, concentrations, and bases was conducted. The most general and mild conditions were identified as 1.0 equivalent of *o*-ketoaniline, 1.2 equivalents of NCA, 2.0 equivalents of CF_3CO_2H, in toluene (0.2 M), at 60 °C for 30 minutes. "With high conversion of the NCA, the cyclization step seemed inevitable, but the identity and the stoichiometry of the base were critical," said Dr. Fier. "Because of the low rate of forma-

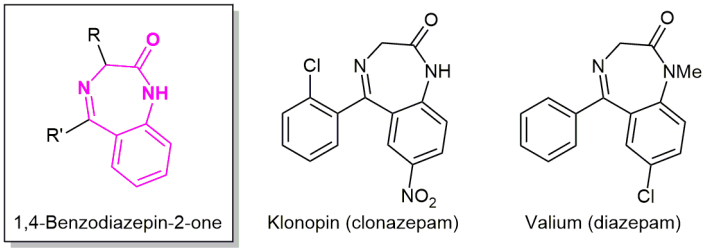
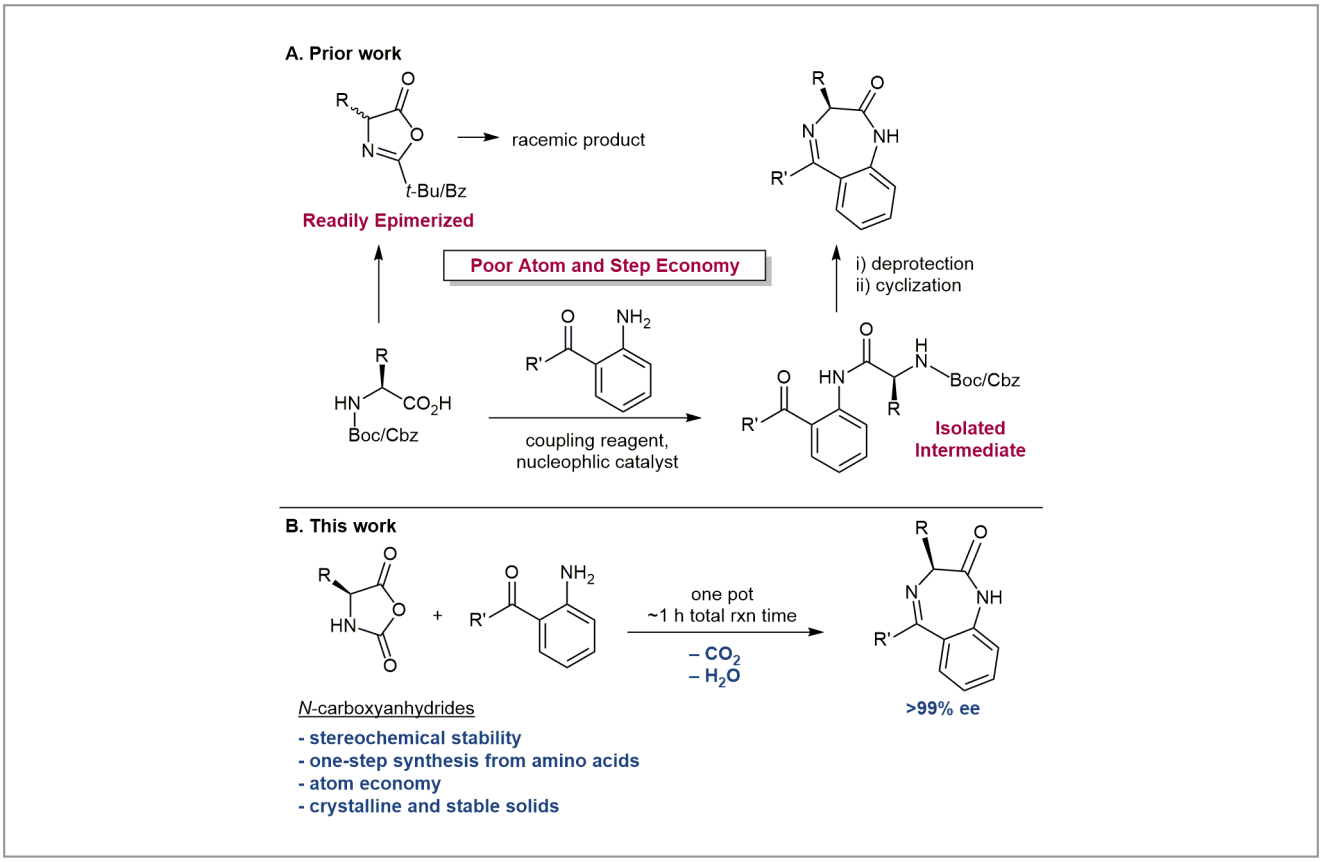


Figure 1

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.



Scheme 1

tion of seven-membered rings, we had to identify conditions that did not lead to racemization of the stereocenter of the β-amino amide intermediates. We eventually settled on 2.0 equivalents of Et_3N followed by heating to 80 °C for 30 minutes."

"We were pleased with the scope of this new reaction sequence," remarked Dr. Whittaker. "Acetophenone- and benzophenone-derived substrates worked equally well, and the conditions were tolerant of aryl halides, nitriles, esters, *ortho*-substituents, and various heterocycles. Substrates with electron-donating or -withdrawing groups reacted in good yields, and *N*-carboxyanhydrides derived from glycine, benzyl aspartic acid, *O*-methyl serine, valine and *tert*-leucine, reacted in good yields."

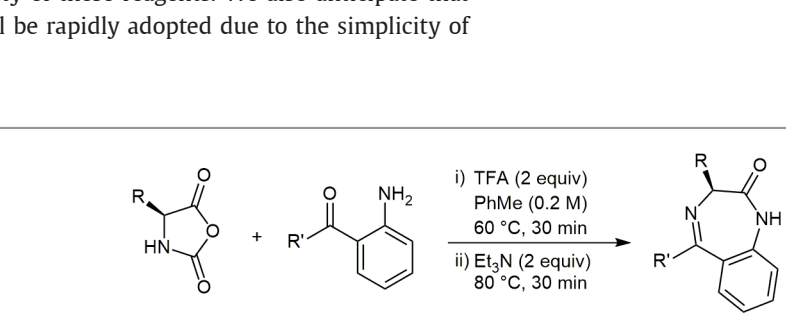
To explore the robustness of their method towards generating highly enantioenriched benzodiazepines, the Merck pair selected a few substrates deemed most likely to racemize under standard coupling conditions. Every substrate tested gave excellent stereo-retention (≥99%) including compounds containing a strongly electron-withdrawing *para*-CN, -benzyl, -methoxymethyl, -indolyl, or -carboxyl groups (Scheme 2). Even a phenylglycine-derived NCA, which is highly susceptible to racemization, gave 99% ee. The phenylglycine substrate was found to slowly racemize (94% ee after 2 h at 80 °C) upon standing in a solution buffered by Et_3N; therefore, the more hindered base DIPEA was selected.

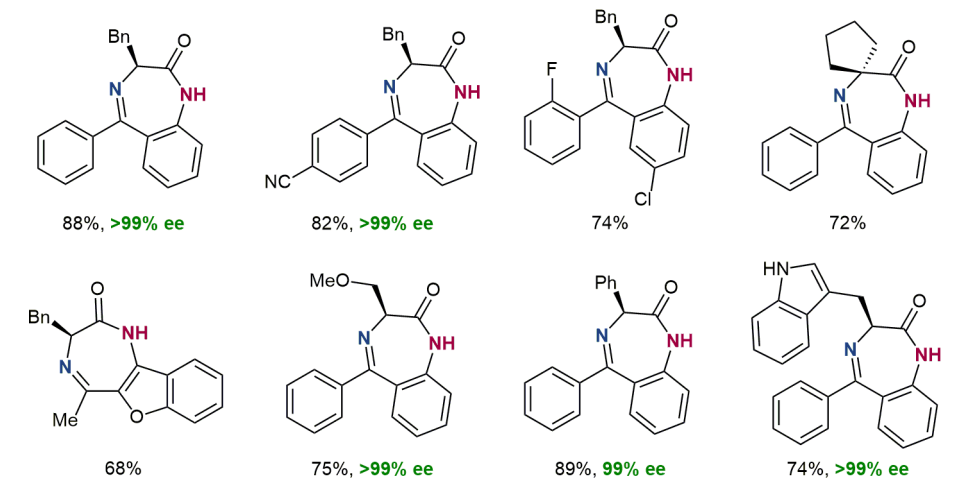
"Our newly developed method was used to target a common intermediate en route to a bromodomain and extra-terminal (BET) bromodomain inhibitor under development for anticancer applications," explained Dr. Whittaker, adding: "The reported routes to this compound rely on a three-step sequence from N-protected aspartic acid derivatives. The highest yielding route reported occurs in only 61% yield over three steps and provides the product in 90% ee from an enantiopure aspartic acid building block (Scheme 3)."

"By employing the method we developed with an aspartic acid derived NCA, the targeted molecule was formed in just one hour in 85% yield and >99% ee on a 5 g scale, and was isolated without chromatography," said Dr. Fier.

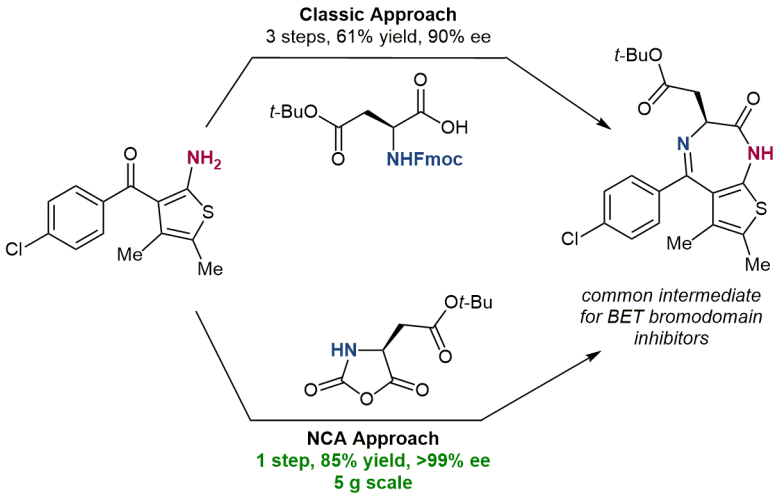
This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Dr. Fier concluded: "We believe that NCA reagents are under-utilized in synthesis, and our future work will further explore the utility of these reagents. We also anticipate that this method will be rapidly adopted due to the simplicity of the procedure, wide availability of the reagents, and the value of the products in drug discovery and development."





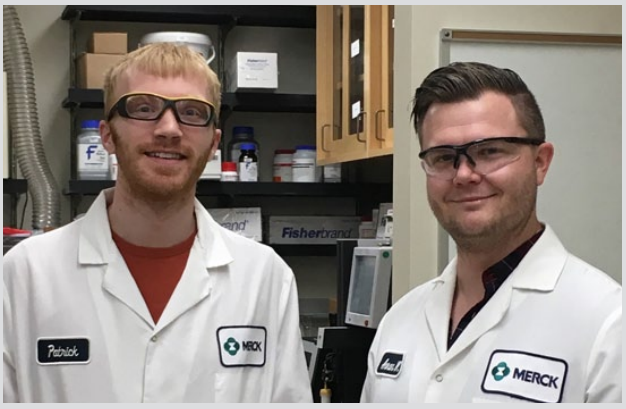
Scheme 2



Scheme 3

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

About the authors



Dr. P. S. Fier (left), Dr. A. M. Whittaker (right)

Patrick Fier received his Ph.D. at the University of California, Berkeley (USA) from Professor John Hartwig's group. As a graduate student, he developed several methods to incorporate fluorine and fluoroalkyl groups into organic molecules. Since 2015, he has been a process chemist at Merck where he works on the development of scalable, and robust synthetic routes to complex drug molecules.

Aaron Whittaker received his Ph.D. in 2013 at the University of Washington (USA) under the supervision of Professor Gojko Lalic. At the UW, Aaron developed new copper-catalyzed methods for hydroamination, aryl amination, allylic substitution, semi-reduction, and hydrodefluorination. Upon receiving his Ph.D, Aaron moved to the University of California, Irvine (USA) to do postdoctoral research with Professor Vy Dong. At UCI, Aaron developed nickel-catalyzed transfer hydrogenations that enabled the oxidative coupling of alcohols and amines with aldehydes to generate esters and amides. Since 2015, Aaron has been a process chemist at Merck & Co., Inc. where he focuses on developing new methods to enable large-scale synthesis of medicinally relevant molecules.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

© Georg Thieme Verlag Stuttgart • New York – Synform **2017/07**, A118–A121 • Published online: June 19, 2017 • DOI: 10.1055/s-0036-1590294

Coming soon

SYNLETT Highlight

Synthesis of the Main Red Wine Anthocyanin Metabolite: Malvidin-3-*O*-β-Glucuronide

Literature Coverage

Arylation of Hydrocarbons Enabled by Organosilicon Reagents and Weakly Coordinating Anions

Literature Coverage

Divergent Prebiotic Synthesis of Pyrimidine and 8-Oxo-purine Ribonucleotides

Further highlights

Synthesis **Review: Construction of Boron-Containing Aromatic Heterocycles**
(by B. Su, R. Kinjo)

Synlett **Account: Syntheses of Diverse Natural Products via Dual-Mode Lewis Acid Induced Cascade Cyclization Reactions**
(by C.-S. Lee and co-workers)

Synfacts **Synfact of the Month in category "Organo- and Biocatalysis": Acyloin Rearrangement of α-Hydroxy Acetals to α-Alkoxy Ketones**

For current SYNFORM articles, please visit www.thieme-chemistry.com
SYNFORM issue 2017/08 is available from July 18, 2017
at www.thieme-connect.com/ejournals

Impressum

Editor
Matteo Zanda, NRP Chair in Medical Technologies, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK
and
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare
Via Mancinelli, 7, 20131 Milano, Italy
Editorial Assistant: Alison M. Sage
synform@outlook.com; fax: +39 02 23993080

Editorial Office
- Managing Editor: Susanne Haak, susanne.haak@thieme.de, phone: +49 711 8931 786
- Scientific Editor: Michael Binanzer, michael.binanzer@thieme.de, phone: +49 711 8931 768
- Scientific Editor: Stefanie Baumann, stefanie.baumann@thieme.de, phone: +49 711 8931 776
- Scientific Editor: Selena Boothroyd, selena.boothroyd@thieme.de
- Assistant Scientific Editor: Kathrin Ulbrich, kathrin.ulbrich@thieme.de, phone: +49 711 8931 785
- Senior Production Editor: Thomas Loop, thomas.loop@thieme.de, phone: +49 711 8931 778
- Production Editor: Thorsten Schön, thorsten.schoen@thieme.de, phone: +49 711 8931 781
- Editorial Assistant: Sabine Heller, sabine.heller@thieme.de, phone: +49 711 8931 744
- Senior Marketing Manager: Julia Stötzner, julia.stoetzner@thieme.de, phone: +49 711 8931 771
- Postal Address: Chemistry Journals, Editorial Office, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany,
- Homepage: www.thieme-chemistry.com

Publication Information
Synform will be published 12 times in 2017 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for Synthesis, Synlett and Synfacts.

Publication Policy
Product names which are in fact registered trademarks may not have been specifically designated as such in every case. Thus, in those cases where a product has been referred to by its registered trademark it cannot be concluded that the name used is public domain. The same applies as regards patents or registered designs.

Ordering Information for Print Subscriptions to Synthesis, Synlett and Synfacts
The Americas: Thieme Publishers New York, Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
Via e-mail: customerservice@thieme.com
Via website: www.thieme-chemistry.com
Phone: +1 212 760 0888; Fax: +1 212 947 1112
Order toll-free within the USA: +1 800 782 3488

Europe, Africa, Asia, and Australia: Thieme Publishers Stuttgart, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany.
Via e-mail: customerservice@thieme.de
Via website: www.thieme-chemistry.com
Phone: +49 711 8931 421; Fax: +49 711 8931 410

Current list prices are available through www.thieme-chemistry.com.

Online Access
The online versions of Synform as well Synthesis, Synlett, Synfacts and SynOpen are available through www.thiemeconnect.com/products/ejournals/journals) where it is also possible to register for a free trial account. For information on multi-site licenses and pricing for corporate customers as well as backfiles, please contact our regional offices:

The Americas: esales@thieme.com, phone: +1 212 584 4695
Europe, Africa, Asia, and Australia: eproducts@thieme.de, phone: +49 711 8931 407
India: eproducts@thieme.in, phone +91 120 45 56 600
Japan: brhosoya@poplar.ocn.ne.jp, phone +81 3 3358 0692

Manuscript Submission to Synthesis, Synlett, and SynOpen
Manuscript submissions will be processed exclusively online via http://mc.manuscriptcentral.com/synthesis, http://mc.manuscriptcentral.com/synlett and http://mc.manuscriptcentral.com/synopen, respectively. Please consult the Instructions for Authors before compiling a new manuscript. The current version and the Word template for manuscript preparation are available for download at www.thieme-chemistry.com.

Copyright
This publication, including all individual contributions and illustrations published therein, is legally protected by copyright for the duration of the copyright period. Any use, exploitation or commercialization outside the narrow limits set by copyright legislation, without the publisher's consent, is illegal and liable to criminal prosecution. This applies to translating, copying and reproduction in printed or electronic media forms (databases, online network systems, Internet, broadcasting, telecasting, CD-ROM, hard disk storage, microcopy edition, photomechanical and other reproduction methods) as well as making the material accessible to users of such media (e.g., as online or offline backfiles).

Copyright Permission for Users in the USA
Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Georg Thieme Verlag KG Stuttgart · New York for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of US$ 25.00 per copy of each article is paid directly to CCC, 22 Rosewood Drive, Danvers, MA 01923, USA, 0341-0501/02.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.