Borate Esters: Simple Catalysts for the Sustainable Synthesis of Complex Amides

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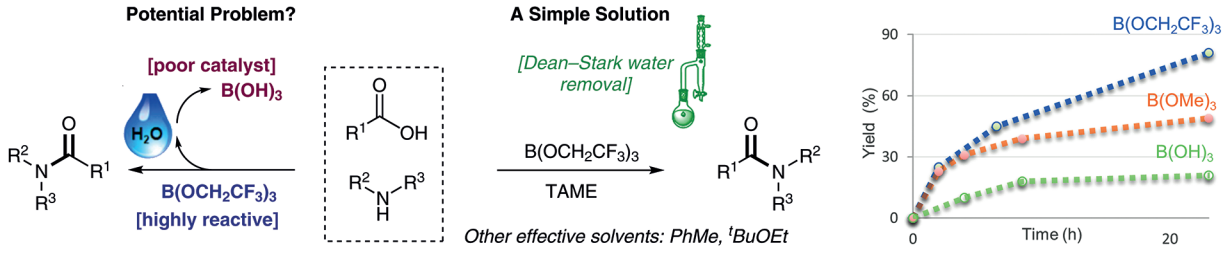
Direct amidation is an extremely important transformation in organic chemistry that is widely used by researchers throughout academia and industry, perhaps most significantly in the pharmaceutical industry. As a consequence of the inefficient stoichiometric methods that are used to achieve direct amidation reactions, there has been a renewed interest in the past 10–20 years in the development of catalysts for the reaction. In theory, an effective catalyst can enable the reaction to be achieved with only water being generated as a by-product. Catalytic approaches using boron-based systems or group IV metals have been particularly successful, but as yet these reactions suffer from significant drawbacks with high dilution conditions and large quantities of molecular sieves being required for efficient water removal. The substrate scope of these reactions is also limited with regard to the functionalised molecules required for pharmaceutical synthesis (such as functionalised polar molecules and heterocyclic compounds).

In previous work, the group of Professor Tom Sheppard at University College London (UK) developed the use of commercially available $B(OCH_2CF_3)_3$ as a stoichiometric reagent for direct amidation (*J. Org. Chem.* **2013**, *78*, 4512) and demonstrated that it is effective for amide formation with a wide range of highly functionalised amines and carboxylic acids (*Org. Biomol. Chem.* **2015**, *13*, 10888) including, remarkably, unprotected amino acids (*Chem. Commun.* **2016**, *52*, 8846). "We had hypothesised that borate esters would not be effective for use in catalytic quantities, as the water generated as the by-product of the amidation reaction should readily hydrolyse the borate ester to boric acid, an amidation catalyst with low reactivity," said Professor Sheppard. He continued: "By careful choice of reaction solvent, however, we found that efficient amidation catalysis could be achieved with a range of borate esters using a Dean–Stark water apparatus for continuous removal of water. The best solvent for the reaction was found to be tert-amyl methyl ether (TAME), which was recently identified as a greener ethereal solvent for use in process chemistry in the pharmaceutical industry (*Green Chem.* **2016**, *18*, 288). A plot of the reaction conversion against time with different catalysts clearly shows that borate esters are more effective than boric acid, and that *tris*-(2,2,2-trifluoroethyl) borate is more reactive than trimethyl borate."

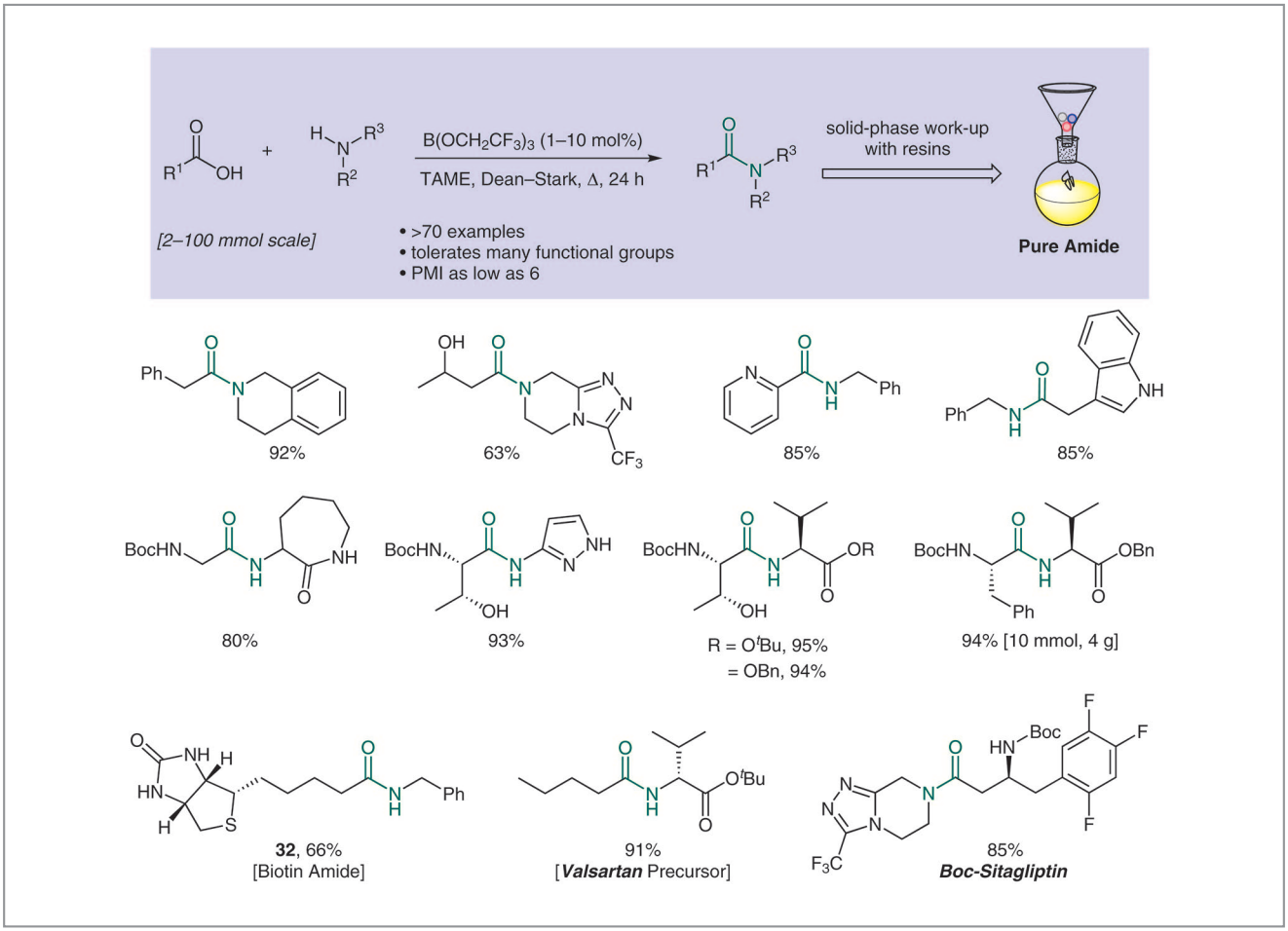
Remarkably, this catalytic amidation system proved to be more reactive than the group's previous stoichiometric amidation method, with an unprecedented substrate scope. "Amides could be prepared from numerous primary/secondary amines, including poorly nucleophilic examples such as acyclic secondary amines, hindered anilines and a sulfonamide," explained Marco Sabatini, the graduate student who developed the chemistry. He remarked: "In terms of the carboxylic acid component, amides derived from natural products and amino acids (both with/without protecting groups on the nitrogen!) were obtained in good to excellent yields." The high reactivity of amino acid derivatives enabled a selection of dipeptides to be prepared and the development of a one-pot direct amidation/condensation of unprotected amino acids to give imidazolidinones. This latter method enabled the



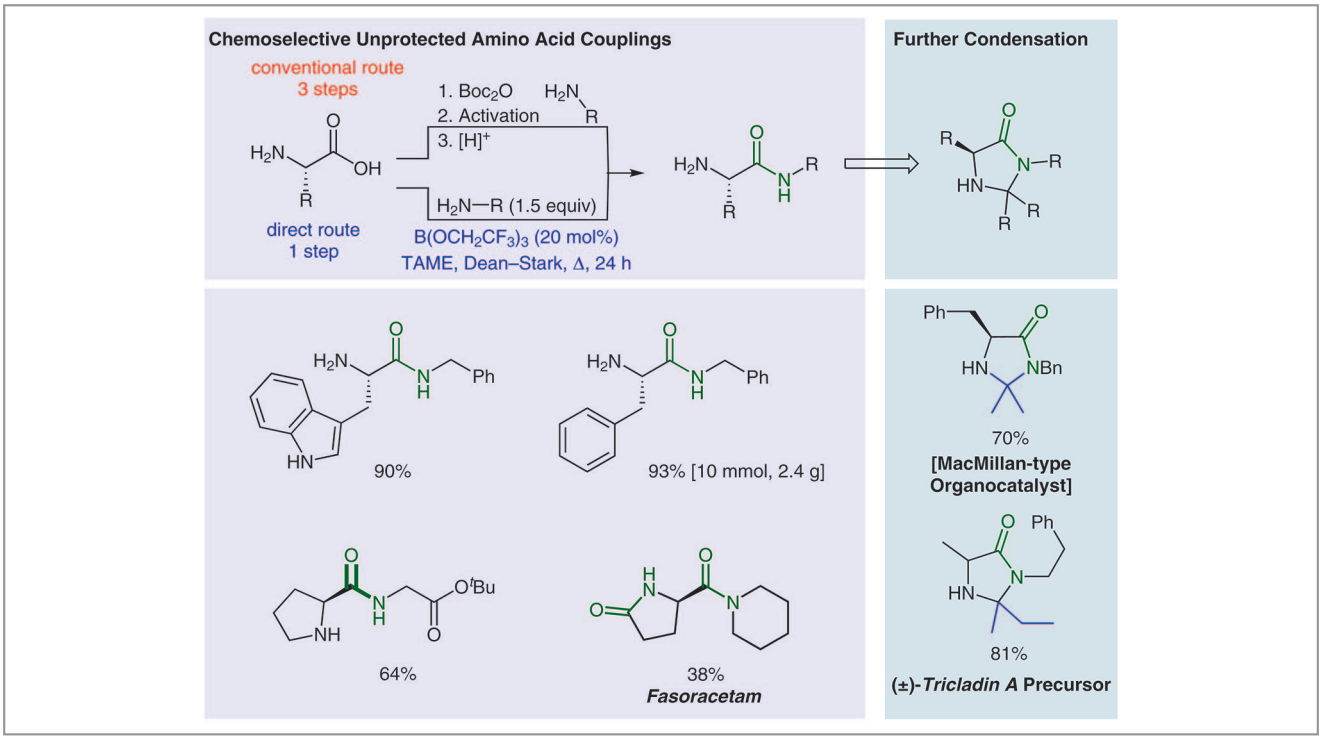
Scheme 1

group to synthesise an organocatalyst, a chiral auxiliary and a natural product. Mr. Sabatini said: "Due to the importance of direct amidation in the pharmaceutical industry, we also demonstrated that the key amidation steps used in the synthesis of several APIs could be achieved efficiently using our catalytic method. Many of the amides were synthesised on multigram scale, and the majority of these amidation products could be purified using a simple solid-phase workup method which significantly reduces the solvent requirements of the process."

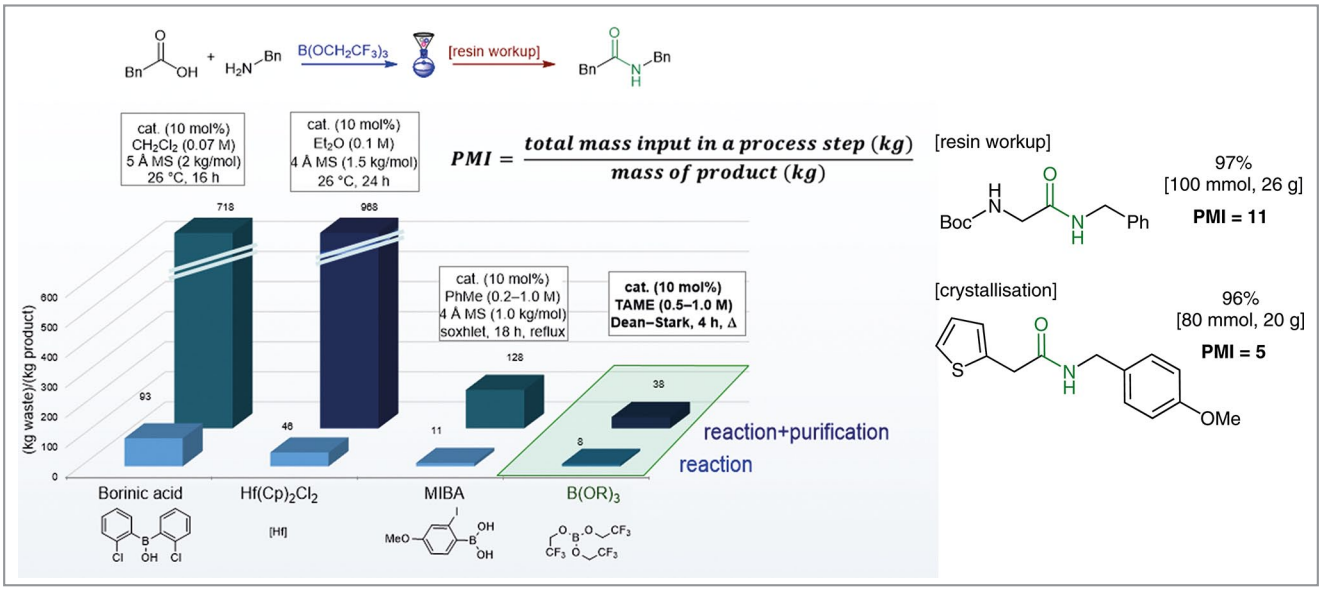
Dr. Lee Boulton, an industrial collaborator on the project at GSK, explained that the concepts of green chemistry and sustainability have been the focus of the pharmaceutical industry for some time. "As a result, significant effort has been invested around improvements in efficiency and waste reduction in both research and development and full-scale manufacturing," he added. "There are a number of measures to capture the overall sustainability of a process, but the challenge is to identify key metrics that drive behaviours in greener, safer, innovative and more sustainable processes. The pharmaceutical industry, through the ACS Green Chemistry Round Table, has selected Process Mass Intensity (PMI) as a key benchmark when comparing such processes (*Org. Process Res. Dev.* **2011**, *15*, 912)." The PMI of a process is defined as the total mass of materials used to produce a specified mass of product. "In the ideal world this would approach unity. The use of PMI to compare our borate-catalysed system against current methods provides an excellent way to exemplify its green credentials," remarked Professor Sheppard. He continued: "Our approach compares favourably to other recently reported catalytic amidation methods, as a consequence of both the reaction setup (higher concentration, no molecular sieves) and the efficient workup method (no aqueous workup needed)." He concluded: "Upon scaling the reaction up to 80–100 mmol (20–26 g of amide) further improvements to the efficiency could be



Scheme 2



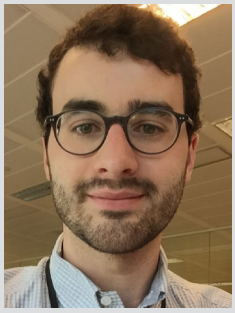
Scheme 3



Scheme 4

made (PMI of 11 using solid-phase workup; PMI of 5 when the amide could be purified by direct crystallisation from the reaction mixture)." Dr. Boulton added: "This represents a highly efficient chemical process, especially for an amidation reaction, and as a result GSK expect to add this method to their favoured reagent list for amide formation reactions."

About the authors



M. T. Sabatini

Marco Sabatini was born and raised in Garches (France). He received his MChem from the University of Bath (UK) in 2014, carrying out his research project under the supervision of Dr. Simon Lewis. He then joined Tom Sheppard's research group at University College London (UK) in 2014 as a graduate student, where he has been working on the development of novel catalytic methods for amide bond formation in collaboration with Lee Boulton at GlaxoSmithKline.

Dr. L. T. Boulton

Lee Boulton graduated from The University of Reading (UK) in 1992 and then went on to complete a PhD under the guidance of Dr. David Hodgson investigating the preparation of alkenylstannanes for use in cross-couplings. After postdoctoral studies at Scripps (USA) with Professor K. C. Nicolaou, looking at the preparation of the core structure of the Phomoidride series of compounds, he moved back to the UK and to Parke-Davis in Cambridge. From Parke-Davis, Lee then moved to ChiroTech Technology and then onto GlaxoSmithKline in Stevenage (UK). Within the API Chemistry department at GSK, Lee has worked on a range of assets and is now focussing on embedding chemical technologies into development and manufacturing routes.

Prof. T. D. Sheppard

Tom Sheppard grew up in a small village in Lancashire (UK). He obtained his BA and MSci degrees from the University of Cambridge (UK) in 1999, carrying out a research project with Professor Ian Fleming. After working in the pharmaceutical industry at Glaxo-Wellcome for a year, he returned to the University of Cambridge for a PhD (2004) with Professor Steven Ley on the development of butane-2,3-diacetal desymmetrised glycolic acid. He then moved to University College London (UK) to carry out postdoctoral research with Professor William Motherwell, working on novel zinc-mediated cyclopropanation reactions. In 2007, he was awarded an EPSRC Advanced Research Fellowship and appointed to a lectureship at University College London, and in 2013 he was promoted to Reader (Associate Professor) in Organic Chemistry. His research is focused on novel synthetic organic methodology, including organoboron chemistry, transition-metal catalysis and biocatalysis, with a growing emphasis on sustainable chemical processes.

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