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Leveraging an Industrial–Academic Partnership To Optimize Small Molecule Process Development within the Pharmaceutical Industry

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ABSTRACT: There is a growing trend in Ireland toward greater collaboration between academia and the pharmaceutical industry. This is an activity encouraged at a national policy level as a means of providing researchers from academic institutions the opportunity to gain important first-hand experience in a commercial research environment, while also providing industry access to expertise and resources to develop new and improved processes for timely medicines. The participating company benefits in terms of its growth, the evolution of its strategic research and development, and the creation of new knowledge that it can use to generate commercial advantage. The research institute benefits in terms of developing skill sets, intellectual property, and publications, in addition to access to identified current industry challenges. A case study is provided describing the collaborative partnership between a synthetic chemistry research team at University College Cork (UCC) and Eli Lilly and Company.

INTRODUCTION

Ireland is one of the leading locations for the pharmaceutical industry in Europe, with nine of the top ten pharmaceutical companies having manufacturing operations located in Ireland. The value of the pharmaceutical sector to the Irish economy is very significant, accounting for over 50% of all exports, and the industry currently employs over 28 000 people. The pharmaceutical sector in Ireland has traditionally focused on manufacturing, with limited research and development (R&D). However, in recent years, competition from locations such as China, India, and Singapore, which offer financially attractive locations for the manufacture of Active Pharmaceutical Ingredients (APIs), is intense. In order to secure manufacturing in Ireland, an increase in R&D activity—specifically in the area of small molecule process development—is strategically very important.[1]

To help achieve this important objective, a collaborative partnership between the pharmaceutical industry and academia is imperative to the continued success of the sector in diversifying the nature of its investment in Ireland from the original bulk active plants to higher value-added activities. Described herein are the nature and results of a collaborative multiyear partnership between a research team in the Department of Chemistry at University College Cork (UCC) with Eli Lilly and Company Small Molecule Design and Development (SMDD) and manufacturing divisions, focusing on process development and optimization for active pharmaceutical ingredients (APIs) employing novel synthetic methodologies.

Since its launch in 2009, this extremely successful collaboration has built up strong links between researchers in UCC and Lilly. The establishment of a productive collaboration is facilitated when mission and goals are shared by both the partnering institution and industrial collaborator and when needs of both parties are met. Development of the partnership between UCC and Lilly was very attractive from the university perspective as the research group gained access to information on a number of synthetic transformations which are currently challenging at an industrial level and require improvement. This allows the team to focus on important technical challenges and new product/service development, thus increasing the significance of the group's research internationally.

Recently Lilly's Irish manufacturing site (Kinsale) has, in collaboration with SMDD (Indianapolis), diversified its mission from manufacturing to be the primary center for synthetic small molecule API commercialization, concentrating on late phase product development and optimization. The key benefit to Lilly of this collaborative project was primarily through enhancement of their technical capability in process development through access to innovative novel methodologies, research facilities and expertise in the university. The enhanced profile will contribute to the long-term stability and growth of R&D within the Irish pharmaceutical sector while maintaining a world class manufacturing reputation.

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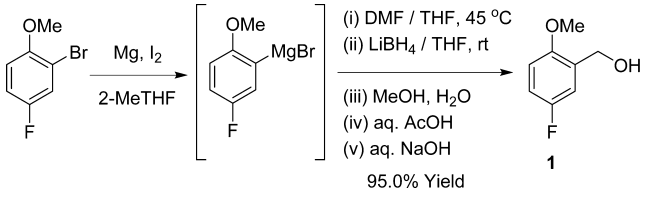
RESULTS AND DISCUSSION

In the past five years, this collaboration has successfully combined the synthetic expertise of the UCC team with the industrial muscle of Lilly which enables identification of important industrial challenges. Such domains of expertise complement one another and, when brought together in a successful working relationship, can accelerate the efficiency of drug development. For productive pharma−academia collaboration, the generation and dissemination of knowledge are imperative. It is critical that the collaboration is managed effectively and the benefit achieved maximized. In addition, the commitment and investment of time, from both the principal investigator (PI) and postdoctoral researchers in UCC and from the researchers in Lilly, is essential to the overall success of the partnership. Two postdoctoral researchers are employed full-time in UCC to work on the collaborative project, and monthly project management telecom meetings are held between UCC and Lilly (Kinsale and Indianapolis). Intermediate communication via email and telephone with exchange of ideas and expertise also occurs. To date, ten projects focusing on several targeted areas for the synthesis of bioactive compounds have been explored. This research has led to a number of publications in high impact journals and posters at international conferences, thus elevating the international visibility of Ireland as a location for process R&D. The success of this partnership between industry and academia in applying novel methodologies to particular process chemistry challenges follows.

Case Study 1. Telescoped Approach to Aryl Hydroxymethylation in the Synthesis of a Key Pharmaceutical Intermediate.[2] The synthetic route to produce benzyl alcohol **1**, an important pharmaceutical intermediate for production of edivoxetine hydrochloride has been developed by UCC using a rational, mechanistic-based approach (Scheme 1). This approach

Scheme 1. Tandem Bouveault formylation/hydride addition to produce an edivoxetine·HCl intermediate

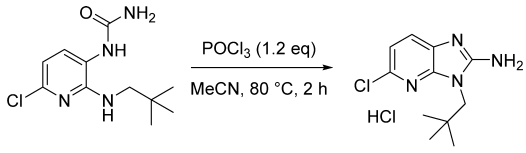


enabled telescoping of two synthetic steps, a Bouveault formylation and hydride reduction, into a single efficient process which is readily amenable to large scale manufacture. This novel approach replaces highly hazardous chloromethylation chemistry that produces bischloromethyl ether as a byproduct, which is dangerous on all scales of operation.

This optimized procedure has been implemented by Lilly to produce in excess of 300 kg of compound **1** for commercial validation of edivoxetine·HCl. Telescoping of synthetic steps is particularly attractive to the pharmaceutical industry as this approach affords significant process safety advantages and reduces the overall process mass intensity. It is anticipated that this methodology, developed at UCC, could be readily extended for the synthesis of other useful pharmaceutical, fine chemical, and agricultural product intermediates where other hydroxymethylation processes are currently in operation. In addition, the Bouveault formylation/hydride addition strategy should be readily amenable to continuous manufacturing where metric ton quantities of intermediate **1** are required in the future.[3]

Case Study 2. Preparation of 2-Aminopyridoimidazoles and 2-Aminobenzimidazoles via Phosphorus Oxychloride-Mediated Cyclization of Aminoureas.[4] As part of Lilly's studies towards the treatment of human malignancies, they wished to access the 2-aminoimidazole **2**. A novel preparation of this desired intermediate **2** via the cyclization of (2-aminopyridin-3-yl)urea in the presence of phosphorus oxychloride was developed by Lilly (Scheme 2). Significantly this route obviates

Scheme 2. Phosphorus oxychloride mediated cylization of aminoureas

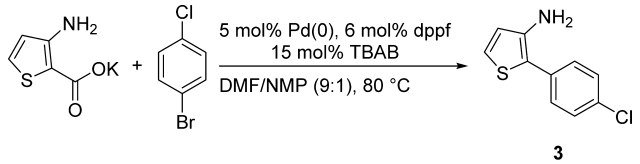


the use of hazardous reagents such as cyanogen bromide and thus is of great significance with regard to process safety. In addition, an important emerging area in the pharmaceutical industry is green solvent selection. Recently there has been a strong movement in the EU to eliminate the use of traditional polar aprotic solvents such as DMF, NMP, and DMAc due to reproductive toxicity issues.[5] It is noteworthy for this system that the optimum solvent is acetonitrile, which promotes a productive cyclization and avoids these hazardous solvents.

This methodology was demonstrated by UCC for a range of urea substrates featuring modification of the amine substituent, the electronic properties of the pyridine ring, and the nature of the aromatic structure. The phosphorus oxychloride-mediated cyclisation of aminoureas provides an effective route to a range of 2-aminopyridoimidazole and 2-aminobenzimidazole products obtained in good yields (up to 79%) and with excellent levels of purity (up to 99.9%).

Case Study 3. A Practical Synthesis of Biaryls via a Thermal Decarboxylative Pd-Catalyzed Cross-Coupling Reaction Operating at Moderate Temperature.[6,7] Reported applications of the palladium-catalyzed decarboxylative cross-coupling reaction for biaryl formation involve copper as a cocatalyst or require microwave technology, and generally temperatures of 130−170 °C are necessary to promote the reaction. For Lilly's development needs, multigram quantities of 3-amino-2-(4-chlorophenyl)thiophene (**3**) were required. A one-step approach towards the synthesis of **3**, involving decarboxylative cross-coupling of aminothiophene carboxylate and 1-bromo-4-chlorobenzene was considered (Scheme 3).

Scheme 3. Thermal decarboylative Pd-catalyzed cross coupling reactions



Optimization of the reaction in UCC led to the development of a mild, robust decarboxylative cross-coupling using catalytic Pd(0) and TBAB at a relatively low temperature of 80 °C, in a mixed-solvent system of DMF and NMP.[5] This route advantageously avoids the use of a metal cocatalyst and microwave irradiation.

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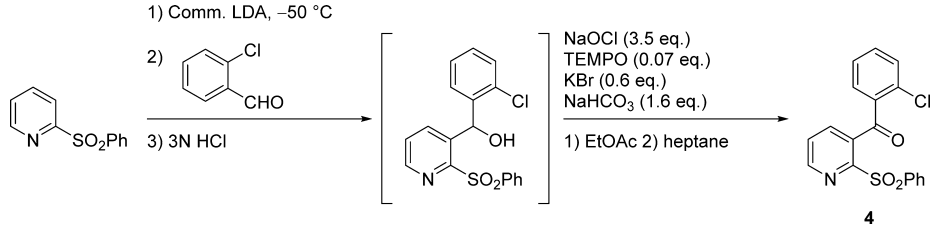
Scheme 4. Telescoped synthesis to produce ketone 4



Having established the optimum conditions, the scope and generality of the reaction was also explored by UCC. A palladium catalyzed decarboxylative cross-coupling has been demonstrated on a variety of heterocyclic acids and aryl halides in modest yields.[6]

Case Study 4. Process Development and Pilot-Plant Synthesis of (2-Chlorophenyl)[2-(phenylsulfonyl)pyridin-3-yl]methanone (4).[8] The synthetic route for the preparation of **4**, an important intermediate in the synthesis of a potent NK1-II inhibitor which has been studied clinically for the treatment of depression at Lilly, has been optimized at UCC. A highly selective telescoped ortho lithiation/condensation/oxidation process was developed and successfully scaled to clinical pilot plant (Scheme 4). The lithiation step was developed to operate at −50 °C using commercial lithium diisopropylamide (LDA). The efficient Anelli−Montanari oxidation using catalytic TEMPO (7 mol %) was used to oxidize the intermediate alcohol to produce 25 kg of **4**. This was the initial project which kicked off the Lilly−UCC collaboration.

After completion of the pilot-plant campaign, second-generation approaches to **4** were developed to improve process greenness where the lithiation step was operated at −10 °C, the highly efficient AZADO catalyst was used at a 1 mol % loading as a substitute for TEMPO in the Anelli−Montanari oxidation, and the process-mass intensity (PMI) was reduced by 25%. This is one of the first reports describing the synthetic utility of the now commercially available AZADO catalyst, which has since been utilized by both academic and industrial groups.[9]

CONCLUSIONS

Both Eli Lilly and UCC recognize the strategic benefit of this partnership which serves as a model for collaboration. This pharma−academia collaboration provides Lilly with the means by which to advance technologically, at lower cost than using company resources, and with less inherent risk. It also provides industry access to a greater breadth and depth of knowledge and technologies than would normally be possible through their own internal research engine. For UCC the benefits include increased visibility in cutting edge research in process pharmaceutical synthesis, including collaborative publications, and access to real identified industry challenges. In addition, the postdoctoral researchers involved in the collaboration, and indeed the broader research team gained very valuable experience in working at the academic−industry interface which provides an excellent foundation for future careers in the pharma industry.

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Notes

The authors declare no competing financial interest.

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