2014 ACS GCI Pharmaceutical Roundtable
Research Grant for Reduction of Amides

The ACS GCI Pharmaceutical Roundtable Medicinal Chemistry group is seeking to fund a 1 year R&D program to address the Roundtable's initiatives on the reduction of amides. Proposals should target identification and development of alternatives to the commonly employed stoichiometric hydride-based reagents or transition-metal catalyzed silane reductions, with a focus on substrates that are widely applicable to the pharmaceutical industry. Proposals are invited from public and private institutions of higher education worldwide. This collaborative project is intended for a student within the selected Principal Investigator's research group. One grant in the amount of $50,000 will be awarded to support execution of research for a period of 1 year. Deadline for receipt of proposals is **June 4th, 2014** at 5 PM EDT (GMT-4). Proposals not received by the deadline will not be considered. Submissions must be a single pdf file submitted via email to gcipr@acs.org. The Principal Investigator with the selected proposal will be notified by **August 15, 2014** of the decision**.** It is expected that research will commence in the principal investigator's lab by **Oct 1st, 2014** and last approximately 1 year.

Requirements for Submission:

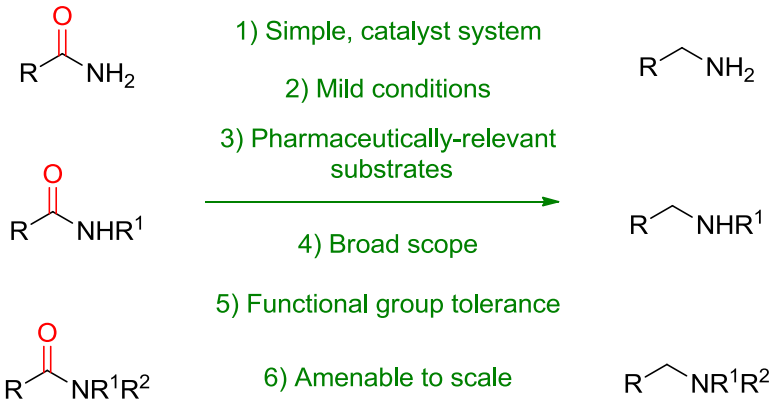
Proposals will only be accepted from public and private institutions of higher education. The grant is not limited to institutions in the United States. Proposals must be submitted by email to gcipr@acs.org through the appropriate institutional office for external funding. For international submissions with no comparable office, submit a pdf of a letter signed by an appropriate university official recognizing the terms of the grant.

Detailed Project Description:

Amines and their derivatives play a significant role in the pharmaceutical industry as pivotal intermediates and key lead compounds. Common methods to access these compounds include reductive amination of carbonyl compounds, or direct nucleophilic displacement of alkyl-halides or the analogous sulfonates. However, these methods suffer from drawbacks such as reactivity issues or problems arising from over-alkylation. An attractive alternative is the direct reduction of amides to the corresponding amines, which allows potential access to primary, secondary and tertiary amines[1]. Numerous reagents have been reported for this reduction, with the most common being hydride reagents such as lithium aluminium hydride (LAH), diborane or borane complexes. The drawbacks of these reagents are that harsh reaction conditions are often required, and as such the reactions often proceed with poor efficiency. In addition, numerous substrates such as secondary amides perform poorly in the reaction, and a number of side reactions can occur. Furthermore, the conditions are rarely applicable to molecules featuring other easily reduced functionalities. From an environmental perspective, the hydride-based stoichiometric reductions proceed to afford insoluble complexes leading to arduous work-ups, purifications, and the subsequent generation of large amounts of waste. The need for catalytic methods for amide reduction has long been recognized with the further advantage that such approaches allow a more exquisite control of selectivity through judicious modification of the catalyst metal and the surrounding ligands. Catalytic hydrosilylation has more recently emerged as a key method for the chemoselective reduction of amides but these often rely on expensive TM-catalysts such as Rh, Ru, Pt

and Ir. One promising development is the recent reporting of examples using earth abundant metals such as Zn and Fe. Bigger drawbacks of this approach currently are concerns about working with silanes, and the fact that none of the known catalytic hydrosilylation methods can directly reduce all types of amide bonds (tertiary, secondary and primary) in the presence of other easily-reduced functional groups such as nitro, ester or nitrile groups. With such widespread use in the pharmaceutical industry, development of more environmentally benign and operationally simpler alternatives for the chemoselective reduction of tertiary, secondary and primary amides under mild conditions to the corresponding amines would have a significant impact.

Despite the demonstrated utility of palladium and related transition metals for catalytic hydrosilylation (for note on hydrogenation, see reference 2), the drivers for replacement of precious metals (such as Pd, Rh, Ir, etc.) with Cu, Ni, Fe or Co alternatives are numerous. High cost, fluctuating global supply, human toxicity, and limited natural abundance are just a few of the drawbacks associated with precious metals. In response, we wish to address this within the RFP by looking at either alternative catalyst systems based on earth abundant metals, or with metal-free approaches to amide reduction. In addition, approaches involving *in situ* based amide activation to facilitate reduction are also considered to be within the scope of the RFP. Several approaches that demonstrate this "metal-free" approach have recently been reported, and provide a promising alternative direction.



In sharp contrast to the typical protocols currently being utilized within medicinal chemistry in the pharmaceutical industry, a more desirable future state involves:

- A 'one-pot' reaction utilizing a catalytic reagent for the reliable reduction of amides with an inexpensive, non-toxic and safe reducing agent;
- Proceed to completion without exotherm concerns;
- Demonstrated to be effective for the reduction of tertiary, secondary and primary amides;
- Simplified work-up for high yield of desired amine products with minimal waste generation;
- Functional group tolerance for groups such as nitro, nitrile and ester;
- Expanded substrate compatibility to include heterocyclic motifs commonly found in drug substances;
- A non-toxic air and moisture stable, readily available catalyst;
- Low catalyst loadings, and possible potential to recycle;
- Simple and inexpensive nitrogen and/or oxygen based ligands if applicable;
- Lower oxygen sensitivity;

- Near ambient temperature reactions;
- Environmentally responsible solvent systems.

The direct reduction of amides under mild conditions addresses numerous green chemistry principles. The avoidance of difficult separations saves large volumes of solvent, lowers waste substantially, and new approaches should remove hazardous, toxic substances from the process. In addition, energy savings will be recognized by carrying the reactions under less harsh conditions. The replacement of a TM in a catalytic hydrolsilylation process translates to less cost, lower concern for human toxicity in drug substances, and a dramatic decrease in the environmental impact associated with isolating and refining the metal.

The overarching theme of this proposal is to support the development of new methodology for the reduction of amides, which can be easily exploited within medicinal chemistry laboratories, but also easily translated into a development setting due to the ease and simplicity of the new methods. Additional favorable criteria are outlined below:

- Widespread utility/ease of access/operational simplicity: Ligands, catalysts and metal sources should be readily available from commercial sources or prepared with a minimal number of steps from inexpensive starting materials;
- Substrate scope: The scope should be significantly diverse to accommodate a wide range of functional groups and heterocycles with a preference for pharmaceutically relevant scaffolds;
- The proposed methods/innovations should employ greener solvents to the extent possible. For further solvent guidance, refer to the ACS GCI Pharmaceutical Roundtable Solvent Selection Guide.
- Simplification of work-up/purification methods.

Reactions of Interest Include:

- Reduction of tertiary, secondary and primary amides : *Demonstrating scope with a diverse set of substrates to demonstrate scope in terms of sterics and electronics as well as functional group tolerance*
- Potential Substrates : *Alkyl amides, aryl amides and heterocyclic amides (pyridines, pyrimidines, imidazoles, pyrazoles, benzimidazoles, triazoles, etc.);*

References

1) *Green Chemistry*, **2007**, *9*, 411. Amide reduction is also a featured section in the Green Chemistry Articles of Interest published twice a year in OPRD. See for example, *Org. Proc. Res. Dev.*, **2013**, *17*, 1394.
2) Although within scope, it should be noted that the ACS GCIPR has previously funded a proposal on the hydrogenation of amides to amines (2010) under Ru-mediated catalysis. Proposals evaluating alternative and more sustainable hydrogenation catalyst systems are considered within scope of the current RFP. Details on the previous grant can be found at https://gcipharmaroundtable.groupsite.com/file_cabinet/227817 .

Project Goal:
Provide alternative methodology for the simple reduction of all types of amides. The solutions should be applicable to a wide variety of substrates and ideally, should employ readily-available and environmentally benign reagents and catalysts.

Project Timeline:
It is expected that 1 year of research support will be sufficient to provide progress toward intended goals.

Proposal Format:
A maximum of 6 pages, as described below, plus CVs is requested. All of the information below must be submitted as a single PDF file. All components described in sections A, B, and C must be included in the same PDF file to assure the proposal is reviewed in its entirety.

A) Title Page (1 page, 12 pt font, 1-inch margins)
1. Project Title:
2. Principal Investigator
3. Title / Position(s)
4. Telephone Number(s)
5. Fax Number(s)
6. Postal Mailing Address
7. E-Mail Address
8. Research Group website

B) Proposed Plan of Work *(5 pages, 12 pt font, 1-inch margins)*
1. Abstract: Summary statement of how the proposed work meets the overall criteria of identification and development of alternatives for the reduction of tertiary, secondary and primary amides. (500 words or less)
2. Background: Provide a brief assessment of the proposed project in the context of the current state of knowledge, demonstrating awareness of green chemistry improvements over current technology. (limit to 1 page or less)
3. Objectives: Briefly state the project objectives.
4. Project Approach: Include specific aims, investigations planned, and preliminary results.
5. References
6. Project Timeline
7. Estimated Budget: The total amount requested would include all direct and indirect costs, including fringe benefits, student assistantships, etc. The total award is limited to $50,000 for a grant period of 12 months.
    a. Institutional overhead costs (indirect costs) are limited to 10% of the grant amount.
    b. Funding would start in October 2014, or later as agreed between the Principal Investigator and the Roundtable.
    c. Post-doctoral associate salary and benefits are supported.
    d. Graduate student stipend and benefits are supported. Proposals for support of advanced graduate students are highly favored.
    e. PI salary supplements will not be supported.
    f. Laboratory supplies and instrument use charges are supported.
    g. No funds may be allocated for travel, equipment purchase or repair, or administrative support.

8. Current funding list for the PI including title of grant award, agency, award amount and duration – limit to 1 page or less
9. Brief facilities description for the PI – limit to one page or less
10. Listing of any existing background intellectual property and/or collaborations that might limit the freedom to operate any of the results arising from any research funded by ACS GCI.

C) Curriculum Vitae of Project Team Members: Please submit a two page curriculum vitae of all project team members. (Does not count toward your page limit.)

Report Requirements:

- As a collaborative research project, the Roundtable will work closely with the principal investigator and student(s) to provide industrial direction, when appropriate, in a manner that respects the independence of the researcher/student.
    - Teleconferences with Roundtable members will be held monthly to discuss project status, provide suggestions and feedback pertaining to reaction conditions/optimization, solvent selection and pharmaceutically relevant substrates.
    - Written progress updates are due monthly from initiation of research for discussion during teleconferences.
    - Updates are to include research milestones/significant outcomes, summary of progress to date noting any deviations from the proposal, and research plans for upcoming months.
- A final comprehensive report including research outcomes and final budget is due one month after the end of the grant period.
    - The report must be submitted as an Adobe PDF document electronically to gcipr@acs.org. The report will be shared with the member companies of the Roundtable.
    - The content of the report will be targeted for publication in a peer review technical journal within six months of the conclusion of the research. As a collaborative research project, the paper will be written by the principal investigator and student(s) performing the work, with the Roundtable as co-authors.

Intellectual Property, Publication Acknowledgement, and Terms of the Grant:

- The primary purpose of this grant is to publish research to make information publicly available.
- Every patent, United States or foreign, that results from research funded (in part or in its entirety) by the ACS Green Chemistry Institute Pharmaceutical Roundtable Research Grant shall be immediately dedicated to the public, royalty free.
- Each publication prepared in connection with the ACS GCI Pharmaceutical Roundtable Research Grant shall make acknowledgement to the ACS GCI Pharmaceutical Roundtable Research Grant, in the following manner. "Acknowledgement is made to the ACS GCI Pharmaceutical Roundtable Research Grant for support (or partial support) of this research."
- Acceptance of a Roundtable Research Grant will be conditioned upon agreement by the grantee institution that in the event the principal investigator is unable for any reason to conduct the research proposed, the funds, if previously paid by the Roundtable, shall, upon demand, be returned in full to the Roundtable, and further, that in the event the PI is unable for any reason to continue with the

research after it has commenced, this grant shall be terminated forthwith and the unexpended and unencumbered balance of any funds theretofore advanced shall be returned to the Roundtable.

- The grantee institution, by acceptance of this grant, provides assurance that support normally provided by the institution for research of the faculty member will not be diminished.
- Applicants may have only one research grant with the ACS GCI Pharmaceutical Roundtable at a time. Current research grant holders may apply for a new grant provided the current grant will be closed by September 1st, 2014. In order to close a grant, the required reports must be received and approved by the ACS GCI Pharmaceutical Roundtable.

For additional information:

Website: www.acs.org/gcipharmaroundtable
Email: gcipr@acs.org