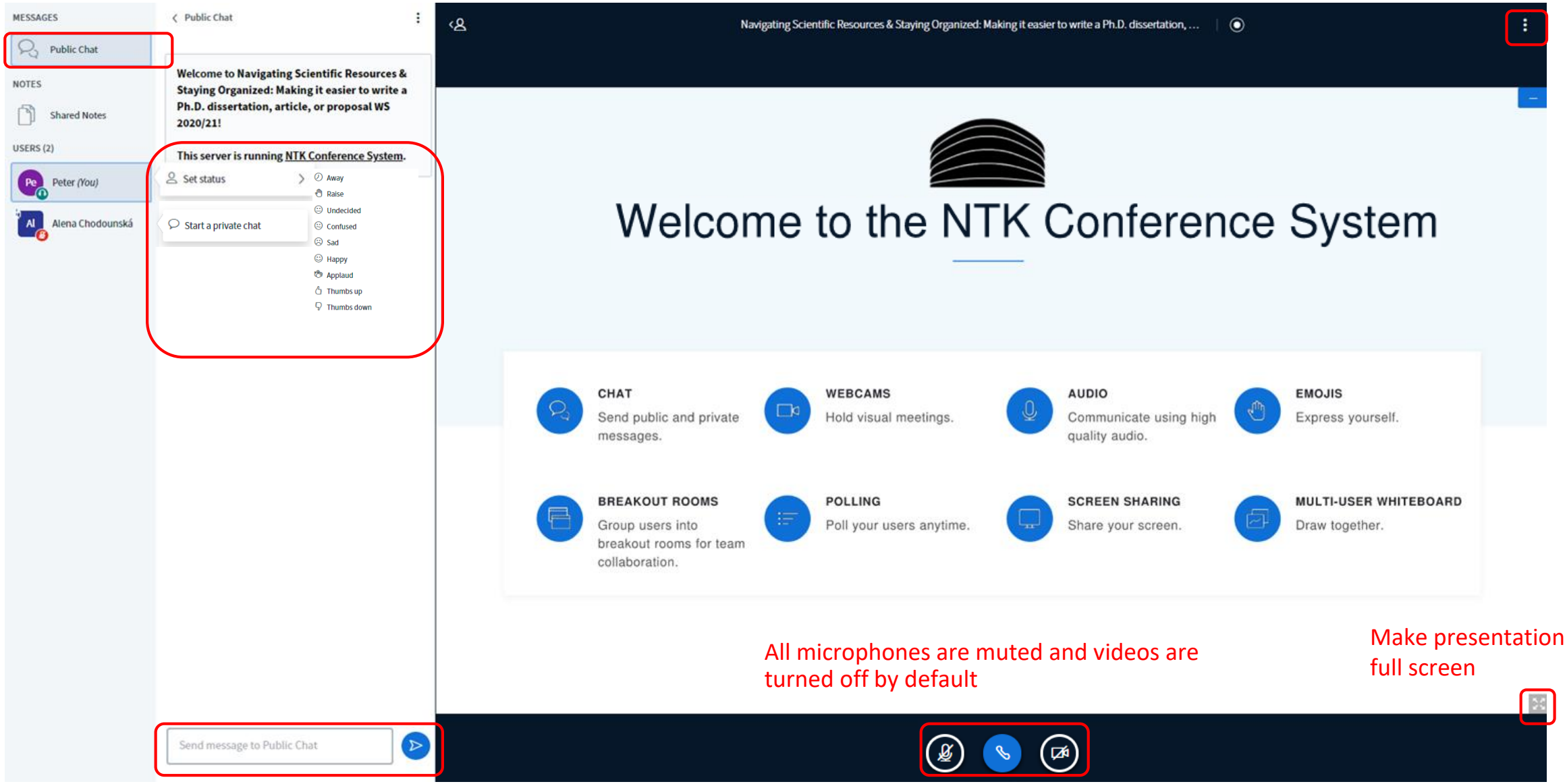
MESSAGES
Public Chat
NOTES
Shared Notes
USERS (2)
Peter (You)
Alena Chodounská
Public Chat
Welcome to Navigating Scientific Resources & Staying Organized: Making it easier to write a Ph.D. dissertation, article, or proposal WS 2020/21!
This server is running NTK Conference System.
Set status
Away
Raise
Undecided
Confused
Sad
Happy
Applaud
Thumbs up
Thumbs down
Start a private chat
Send message to Public Chat
Navigating Scientific Resources & Staying Organized: Making it easier to write a Ph.D. dissertation, ...
Welcome to the NTK Conference System
CHAT
Send public and private messages.
WEBCAMS
Hold visual meetings.
AUDIO
Communicate using high quality audio.
EMOJIS
Express yourself.
BREAKOUT ROOMS
Group users into breakout rooms for team collaboration.
POLLING
Poll your users anytime.
SCREEN SHARING
Share your screen.
MULTI-USER WHITEBOARD
Draw together.
All microphones are muted and videos are turned off by default
Make presentation full screen

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Národní technická knihovna
National Library of Technology

My first scientific article

Hands-on experiences from two PhD. candidates

Eva Karbanová and Jan Polášek

April 2022, National Library of Technology

Where do you study?

A. Czech Technical University in Prague

B. University of Chemistry and Technology Prague

C. Czech University of Life Sciences Prague

D. Charles University

E. Other

Outline

1) About scientific articles

Reasons for writing
Types of scientific articles
Characteristics of scientific articles
Stages of publication

Eva Karbanová
- Faculty of Agrobiology, Food and Natural Resources, CULS
- Doctoral studies in Applied Zoology at CULS
- NTK

2) How to write a scientific article

How to choose a journal and type of an article
Where to look for inspiration
Tips and tricks on writing

Jan Polášek (will be introduced later)

What is your main reason for writing an article?

Have you ever published a scientific article?

A. Yes, as the corresponding (lead) author

B. Yes, as a co-author

C. Not at all

Why do we write articles?

Formal goal: to fulfill requirements for a Ph.D. degree

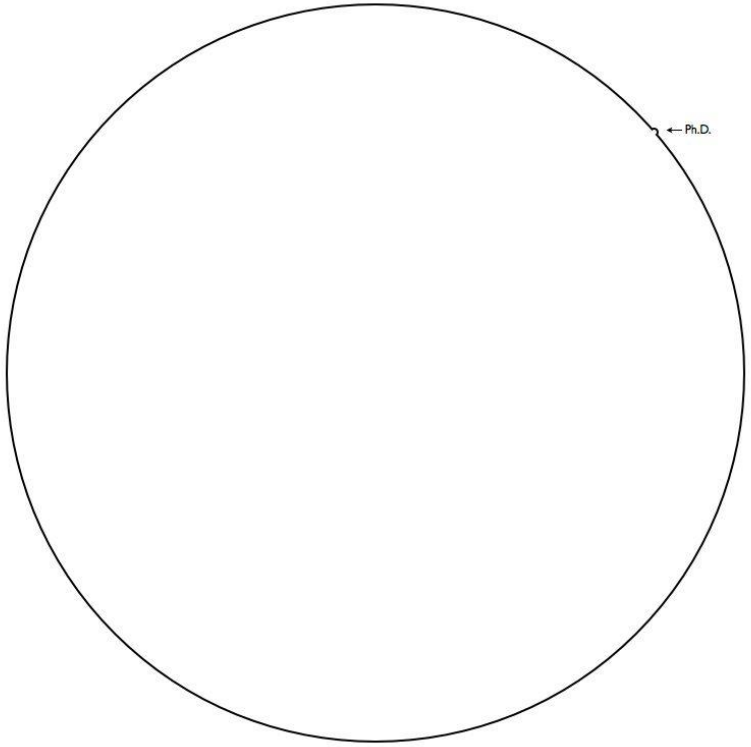
Career goal: get a job, succeed in academia
In academia, we are mainly evaluated by the quality and quantity of journal articles.

Idealistic goal: to contribute to existing knowledge in my field

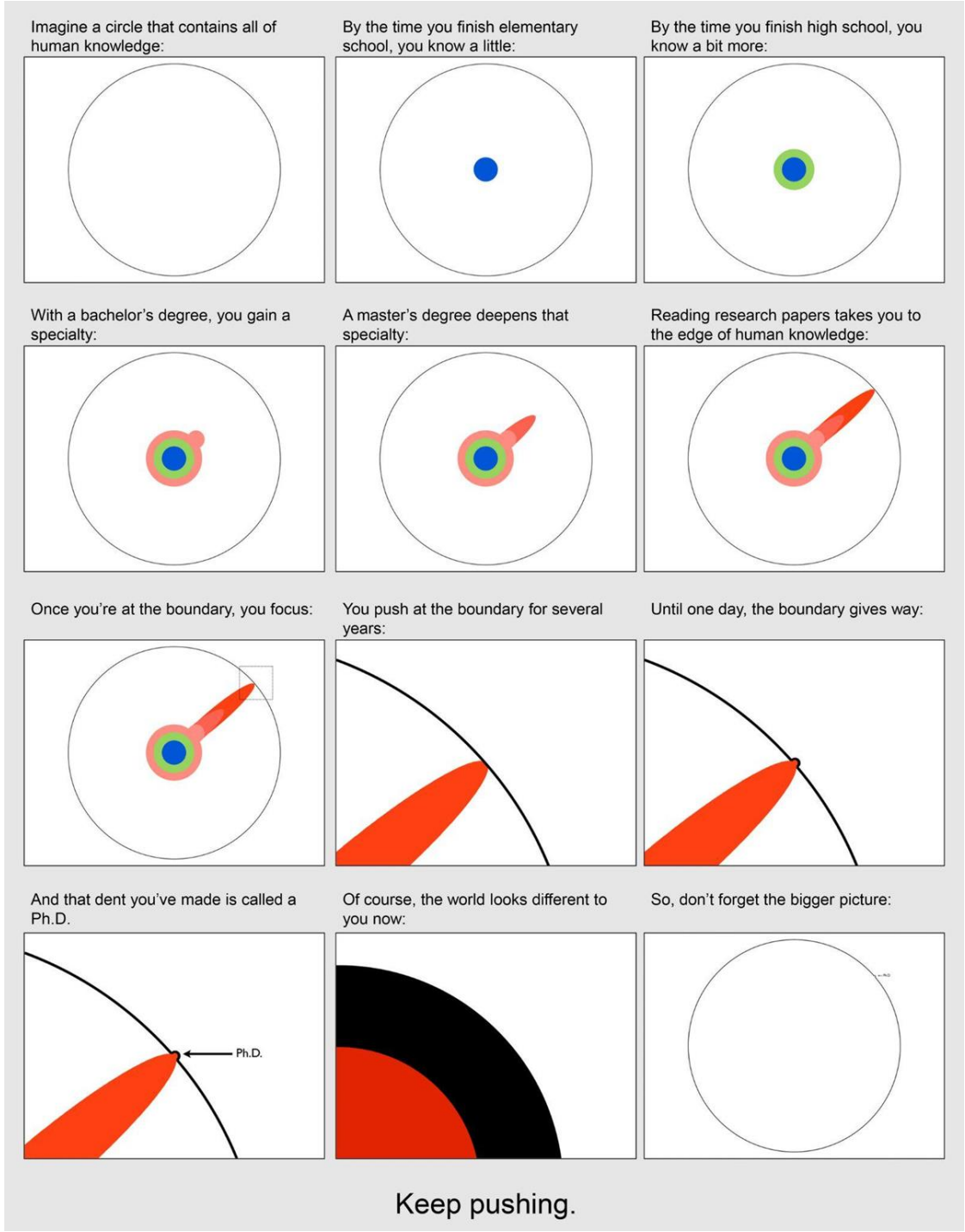
Tell your readers something useful

SOURCE: Günter Blöschl - How to write (and publish) a scientific paper in hydrology

Your goal can be to make a dent in a circle of human knowledge



SOURCE: The Illustrated Guide to the Ph.D., created by Matt Might (http://matt.might.net/articles/phd-school-in-pictures/; 2012) and shared under Creative Commons license BY-NC 2.5.



Scientific communication

- Ongoing, documented, structured dialog between scientists (across countries, times and disciplines)
- The work of one builds upon that of others ("Stand on the shoulders of giants.")
- **Peer review** – essential for quality control
- Becomes a **permanent record** of scientific progress
- Contains information obtained by **scientific methods**

Types of scientific articles

- Research article (original article)
- Methods article
- Review article
  - Literature review
  - Systematic review
  - Meta-analysis
- Short communication (letters, …)
- Discussion article (commentary, …)
- Case study (case report)

Some types of articles are more suitable to write in the early phase of a project, some in the later phase.

Each serves different objectives/aspects of scientific communication.

Good quality review articles are useful for scientific community and tend to get large numbers of citations.

Self-study tip: More information about reviews

Keep in mind while writing…

- Take away message
- Keep track of your resources
- Structure
- Language and style
  - Clear, accurate, brief
- Reproducibility
  - Reproducibility crisis

→ Citation Management Tools (webinars)

→ Search for similiar articles via Google Scholar or NTK Discovery Tool (webinars)

What is your take away message?

- The most important pieces of information you want your audience to **hear, understand and remember**, something **new**
- Try to wrap up the whole work in one sentence
- Be exact and quantitative and avoid information that is vague or relevant only to you

"The normalised jack-knife validation error is 0.15 in 37 Austrian catchments for the period 1980-2010."

"The model provided an excellent fit to the data."

Reading tip: chapter Providing proper emphasis (Alley, Michael. *The Craft of Scientific Writing*. New York: Springer, 1996)

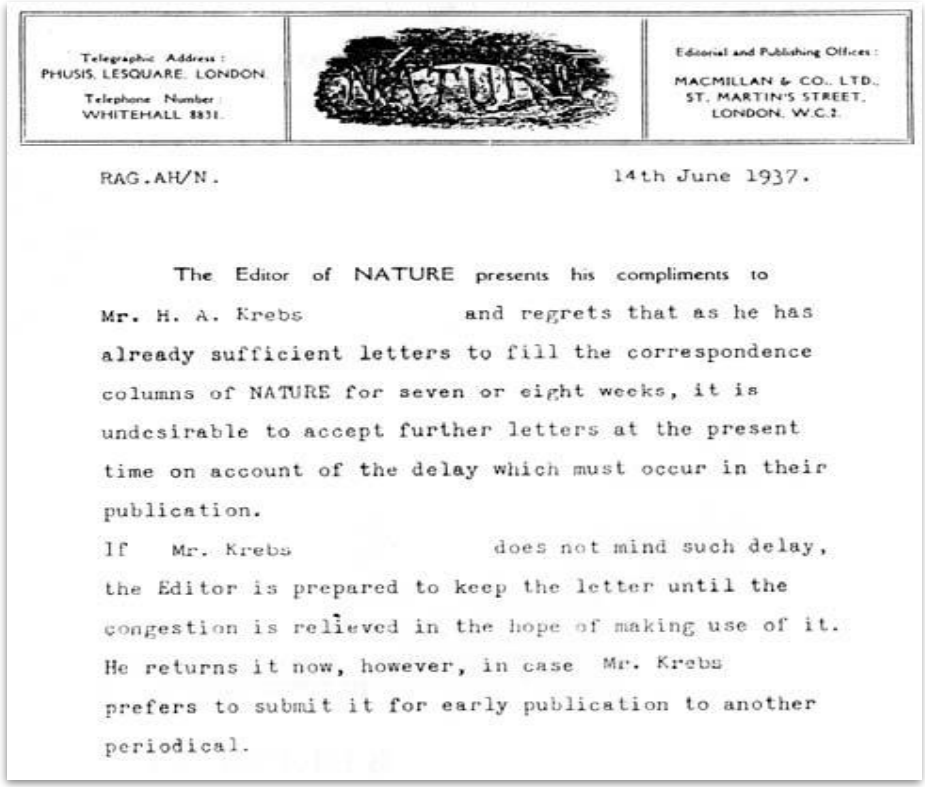
How to prepare for your first peer review

- Goal is to provide a **constructive criticism** to help authors improve their work and to assess the article's suitability for publication – Do not take it personally. Take your time to **write a proper response**
- Reviewer is usually a researcher from the same/similar field, who evaluates the **quality**, **originality**, **relevance** and **validity** of research

DOUBLE BLIND	SINGLE BLIND (CLOSED)	OPEN	PUBLIC/OPEN
Reviewer doesn't know author's identity. Author doesn't know reviewer's identity.	Reviewer knows the identity of the author. Author doesn't know the the identity of the reviewer.	Both identities are revealed to each other.	Both know each other. Reviewers are published. Readers may also comment on the article. e.g. F1000Research

Self-study link: Video about peer review.

Do not get discouraged by first failures. Even Nobel Prize winning researchers were sometimes rejected! Reasons for rejection of article can be various. But that doesn't mean you shouldn't take reviewer's notes seriously. Articles can always be improved.



Telegraphic Address: PHUSIS, LESQUARE, LONDON
Telephone Number: WHITEHALL 8831

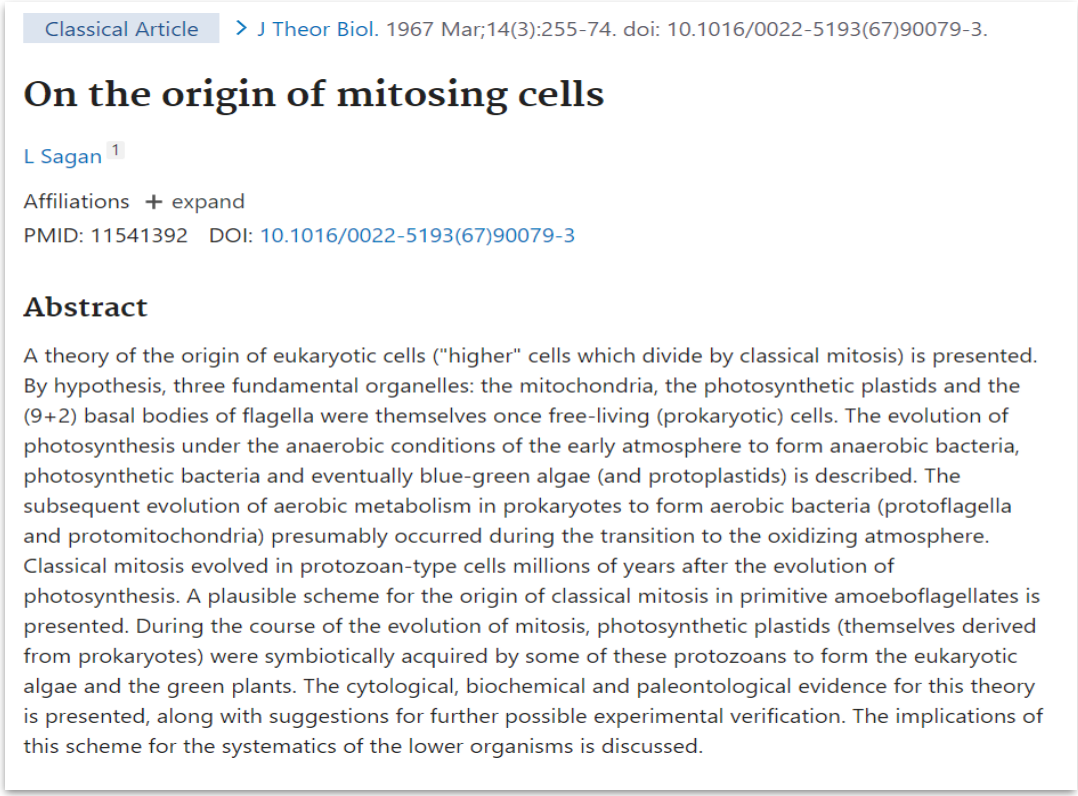
Editorial and Publishing Offices: MACMILLAN & CO., LTD., ST. MARTIN'S STREET, LONDON, W.C.2.

RAG.AH/N. 14th June 1937.

The Editor of NATURE presents his compliments to Mr. H. A. Krebs and regrets that as he has already sufficient letters to fill the correspondence columns of NATURE for seven or eight weeks, it is undesirable to accept further letters at the present time on account of the delay which must occur in their publication.

If Mr. Krebs does not mind such delay, the Editor is prepared to keep the letter until the congestion is relieved in the hope of making use of it. He returns it now, however, in case Mr. Krebs prefers to submit it for early publication to another periodical.

Rejection letter from *Nature* editor, who didn't accept letter from Sir Hans Adolf Krebs on the citrid acid cycle.
SOURCE: [Authorea.com]



Classical Article > J Theor Biol. 1967 Mar;14(3):255-74. doi: 10.1016/0022-5193(67)90079-3.

On the origin of mitosing cells

L Sagan [1]

Affiliations + expand

PMID: 11541392 DOI: 10.1016/0022-5193(67)90079-3

Abstract

A theory of the origin of eukaryotic cells ("higher" cells which divide by classical mitosis) is presented. By hypothesis, three fundamental organelles: the mitochondria, the photosynthetic plastids and the (9+2) basal bodies of flagella were themselves once free-living (prokaryotic) cells. The evolution of photosynthesis under the anaerobic conditions of the early atmosphere to form anaerobic bacteria, photosynthetic bacteria and eventually blue-green algae (and protoplastids) is described. The subsequent evolution of aerobic metabolism in prokaryotes to form aerobic bacteria (protoflagella and protomitochondria) presumably occurred during the transition to the oxidizing atmosphere. Classical mitosis evolved in protozoan-type cells millions of years after the evolution of photosynthesis. A plausible scheme for the origin of classical mitosis in primitive amoeboflagellates is presented. During the course of the evolution of mitosis, photosynthetic plastids (themselves derived from prokaryotes) were symbiotically acquired by some of these protozoans to form the eukaryotic algae and the green plants. The cytological, biochemical and paleontological evidence for this theory is presented, along with suggestions for further possible experimental verification. The implications of this scheme for the systematics of the lower organisms is discussed.

Groundbreaking article of Lynn Margulis on evolution by endosymbiosis was rejected by 15 journals before finally published, because the topic was too new and nobody could evaluate.
Sagan L. On the origin of mitosing cells. J Theor Biol. 1967 Mar;14(3):255-74. doi: 10.1016/0022-5193(67)90079-3. PMID: 11541392.

Typical structure of a scientific article
(I.M.R.A.D. structure)

I	**Title**	What is it about?
	Abstract	What was done in a nutshell?
	Introduction	Why did you do it?
M	**Methods / Theory**	How did you do it?
R, A	**Results, Analysis**	What did you find?
D	**Discussion**	What does it mean?
	Summary and conclusions	What have you learned, what are the major findings?
	Acknowledgements	Who helped you?
	References	Upon whose work did you build yours?
	Appendices	Additional information

SOURCE: ethz.ch and Improving the writing of research papers: IMRAD and beyond

Language and style tips

- Keep it simple and clear
- Avoid redundancy and duplicities
- Everything should be clear/defined
- Accurate description of an experiment allows its reproduciblity
- Choose the right tense
  - When reporting what has been done, use past tense
  - Present tense – general truths
  - Future tense – perspectives
- **Rewriting is a necessary part of the process**

Reduce wordiness:

small ~~in size~~
~~true~~ facts
adequate ~~enough~~
aggregate ~~together~~
near ~~to~~

In the future, corresponding regions of the fear circuit observed in this study could serve as a basis for further study.

x

Corresponding regions of the fear circuit observed in this study could serve as a basis for further study.

Tissue examination was done by light microscopy.

x

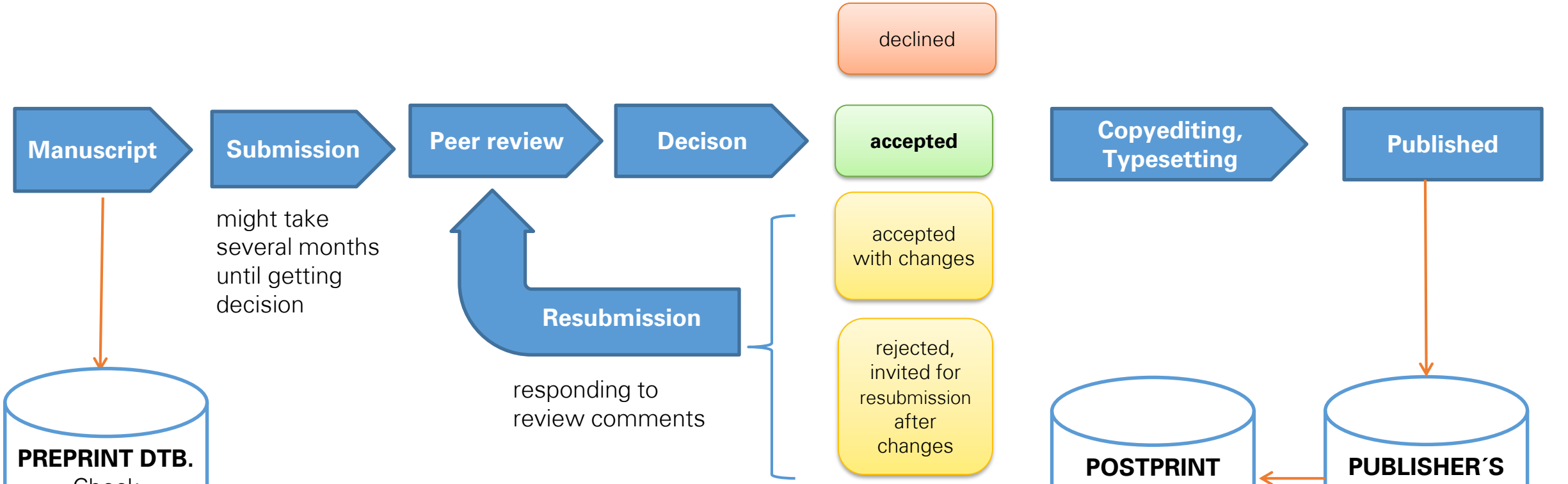
Tissues were examined by light microscopy.

Who is your audience?

Before writing, **consider**:

- What is the **target group** (readers) of the chosen journal?
- What is the **scope of the journal?** Is it general or very specific? Does it fit my topic?
- Is the purpose of the journal to inform about new methods, cases etc. rather than about findings?
- How knowledgable are readers in my field? (multidisciplinary audience)

Stages of publication

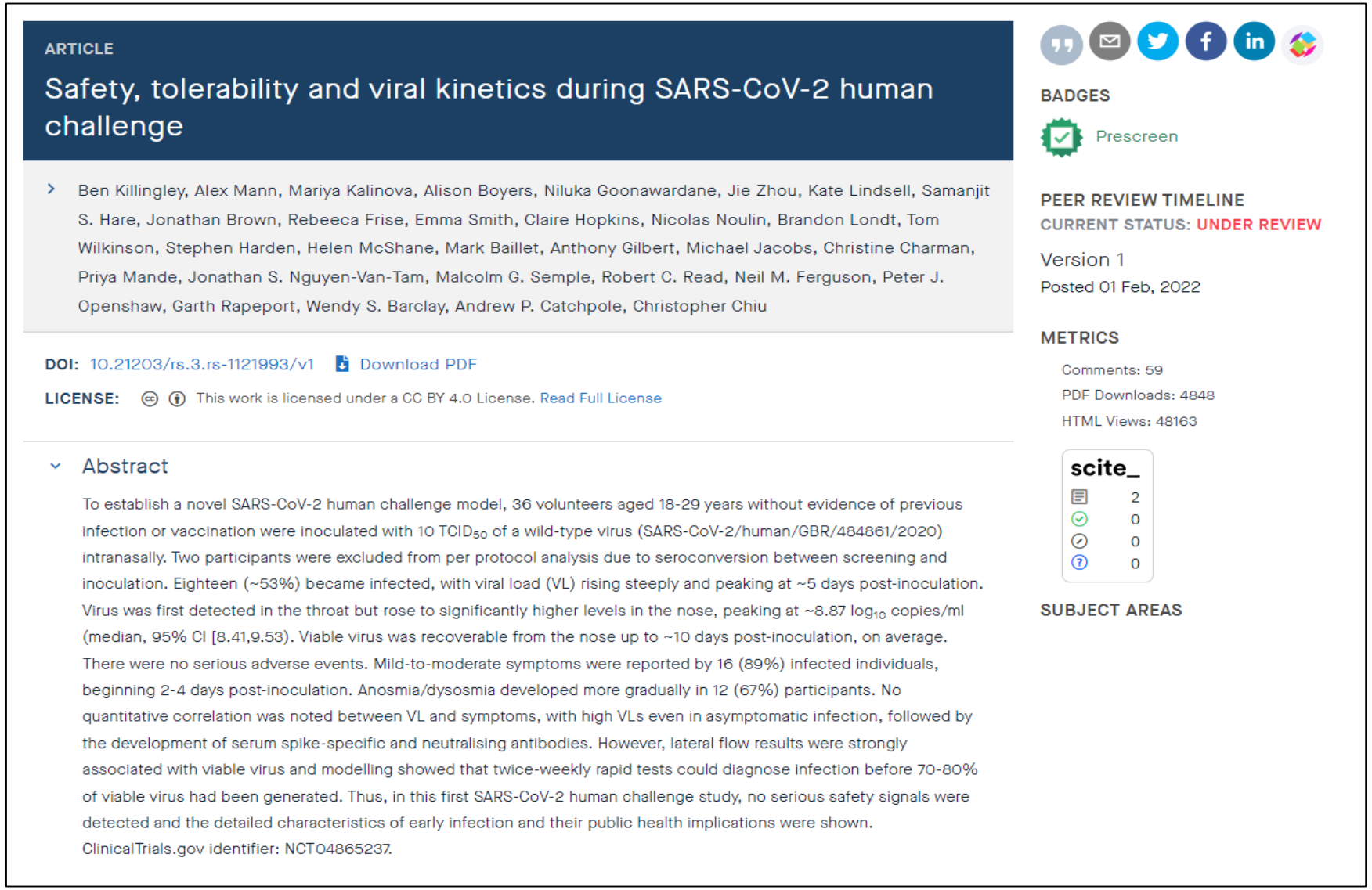


Examples:
- arXiv
- BioRXiv
- MedRXiv

Examples
- CTU repository
- ETH repository
- ResearchGate

Examples
- DOAJ
- IEEE
- ScienceDirect

Example of preprints use – when you need to present your results quickly.
Coronavirus infection on human volunteers to understand the nature of the illness.



ARTICLE

Safety, tolerability and viral kinetics during SARS-CoV-2 human challenge

Ben Killingley, Alex Mann, Mariya Kalinova, Alison Boyers, Niluka Goonawardane, Jie Zhou, Kate Lindsell, Samanjit S. Hare, Jonathan Brown, Rebeeca Frise, Emma Smith, Claire Hopkins, Nicolas Noulin, Brandon Londt, Tom Wilkinson, Stephen Harden, Helen McShane, Mark Baillet, Anthony Gilbert, Michael Jacobs, Christine Charman, Priya Mande, Jonathan S. Nguyen-Van-Tam, Malcolm G. Semple, Robert C. Read, Neil M. Ferguson, Peter J. Openshaw, Garth Rapeport, Wendy S. Barclay, Andrew P. Catchpole, Christopher Chiu

DOI: 10.21203/rs.3.rs-1121993/v1 Download PDF

Abstract

To establish a novel SARS-CoV-2 human challenge model, 36 volunteers aged 18-29 years without evidence of previous infection or vaccination were inoculated with 10 $TCID_{50}$ of a wild-type virus (SARS-CoV-2/human/GBR/484861/2020) intranasally. Two participants were excluded from per protocol analysis due to seroconversion between screening and inoculation. Eighteen (~53%) became infected, with viral load (VL) rising steeply and peaking at ~5 days post-inoculation. Virus was first detected in the throat but rose to significantly higher levels in the nose, peaking at ~8.87 log_{10} copies/ml (median, 95% CI [8.41,9.53). Viable virus was recoverable from the nose up to ~10 days post-inoculation, on average. There were no serious adverse events. Mild-to-moderate symptoms were reported by 16 (89%) infected individuals, beginning 2-4 days post-inoculation. Anosmia/dysosmia developed more gradually in 12 (67%) participants. No quantitative correlation was noted between VL and symptoms, with high VLs even in asymptomatic infection, followed by the development of serum spike-specific and neutralising antibodies. However, lateral flow results were strongly associated with viable virus and modelling showed that twice-weekly rapid tests could diagnose infection before 70-80% of viable virus had been generated. Thus, in this first SARS-CoV-2 human challenge study, no serious safety signals were detected and the detailed characteristics of early infection and their public health implications were shown. ClinicalTrials.gov identifier: NCT04865237.

BADGES

Prescreen

PEER REVIEW TIMELINE

CURRENT STATUS: UNDER REVIEW

Version 1

Posted 01 Feb, 2022

METRICS

Comments: 59

PDF Downloads: 4848

HTML Views: 48163

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SUBJECT AREAS

Ben Killingley, Alex Mann, Mariya Kalinova et al. Safety, tolerability and viral kinetics during SARS-CoV-2 human challenge, 01 February 2022, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-1121993/v1]

A scientific article is not a thesis

	BACHELOR OR MASTER THESIS	RESEARCH ARTICLE
AUTHOR		
REVIEWER		
READER		
CONTENT		

A scientific article is not a thesis

	BACHELOR OR MASTER THESIS	RESEARCH ARTICLE
AUTHOR	Student	Researcher (might be a student)
REVIEWER		
READER		
CONTENT		

A scientific article is not a thesis

	BACHELOR OR MASTER THESIS	RESEARCH ARTICLE
AUTHOR	Student	Researcher (might be a student)
REVIEWER	Supervisor, consultant, opponent	Reviewers, journal editor
READER		
CONTENT		

A scientific article is not a thesis

	BACHELOR OR MASTER THESIS	RESEARCH ARTICLE
AUTHOR	Student	Researcher (might be a student)
REVIEWER	Supervisor, consultant, opponent	Reviewers, journal editor
READER	Supervisor, opponent, colleagues, other students, sometimes restricted acces …	Journal readers, researchers, educators, journalists, decision makers and general public.
CONTENT		

A scientific article is not a thesis

	BACHELOR OR MASTER THESIS	RESEARCH ARTICLE
AUTHOR	Student	Researcher (might be a student)
REVIEWER	Supervisor, consultant, opponent	Reviewers, journal editor
READER	Supervisor, opponent, colleagues, other students, sometimes restricted acces …	Journal readers, researchers, educators, journalists, decision makers and general public.
CONTENT	Longer in general, usually broader theoretical part, does not necessarily include an experiment (depending on the field etc.)	Less theory, bringing new insights/knowledge (depending on the field etc.).

How to write a scientific article (?)

Personal experience and opinion

Jan Polášek

- Organic chemistry at MUNI Brno
- 4 years at Synthon s.r.o. (Pharmaceutical industry)
- Doctoral studies at CUNI/IOCB Prague
- NTK

Let us tackle the challenge!

1. How to choose a journal?
2. Learn about the chosen journal
3. Choose your form
4. Learn from others
5. Read the guidelines!
6. Writing is creative work
7. Final tips and tricks

"Ever tried. Ever failed. No matter. Try again. Fail again. Fail better.“ Samuel Beckett

How do I choose a journal?

- Where do you usually find relevant research?
- Scope of the journal
- Citation metrics eg. Impact factor / Cite Score of the journal (exercise)
  - Journal Citation Reports / Scopus Index Journal
- NTK: Webinar Introduction to Web of Science & Scopus; Bibliometric services, CitDat2
- Open access and publication costs
- Future at stake – Predatory journals
- NTK: Webinar academic Integrity, April 19

Learning about chosen journal

- What do the most cited articles in last 5 years in the journal have in common?
- Does it “really” suit my findings?
- How does the peer review process look like?

Get in shape! (Choose your form)

- Start: Compilation of literature – Review
- During research: Unexpected finding – Short communication – Letter
- Rounded research: Wider exploration of a field – Research article
- Side quest: Report of improvements in a procedure – Methods paper

Learn from others

- Read articles of the chosen journal
  - The most cited ones in the journal in last 5 years (or less in some fields)
  - Read critically (STEMskiller)
- Look also at the published work of your peers
  - Senior authors are sometimes “allowed” to bend the rules
- Understand the structure of the articles

Read the guidelines!

- Journals usually have guidelines for authors
- Read the guidelines (e.g. JACS)
  - Can be quite extensive
  - Fast formats can be available
  - Format of citations, graphs and figures
  - Authorship and data management instruction (repositories)
  - Frustrating to be turned away for formal reasons

ORGANIC CHEMISTRY

Scalable Birch reduction with lithium and ethylenediamine in tetrahydrofuran

James Burrows, Shogo Kamo, Kazunori Koide*

The Birch reduction dearomatizes arenes into 1,4-cyclohexadienes. Despite substantial efforts devoted to avoiding ammonia and cryogenic conditions, the traditional, cumbersome, and dangerous procedure remains the standard. The Benkeser reduction with lithium in ethylenediamine converts arenes to a mixture of cyclohexenes and cyclohexanes; this is operationally easier than the Birch reduction but does not afford 1,4-cyclohexadienes. Here, we report a Birch reduction promoted by lithium and ethylenediamine (or analogs) in tetrahydrofuran at ambient temperature. Our method is easy to set up, inexpensive, scalable, rapid, accessible to any chemical laboratory, and capable of reducing both electron-rich and electron-deficient substrates. Our protocol is also compatible with organocuprate chemistry for further functionalization.

Dearomatization is widely used in chemical synthesis (*1*). The Birch reduction dearomatizes arenes into 1,4-cyclohexadienes with lithium, sodium, or potassium in liquid ammonia at ≤−33°C (Fig. 1A) (*2*, *3*) and has been employed throughout the pharmaceutical industry (*4*, *5*), perfumery industry (*6*, *7*), and academia (*8*–*11*).

Liquid ammonia must be prepared with specialized equipment and carefully dissipated after the reaction is complete. Both steps are time consuming; for example, removal of 1 L of liquid ammonia (850 L as gas) can take up to 12 hours (*12*), and as much as 7.5 L of liquid ammonia per mole of substrate may be needed (*5*, *13*). Even on a 3.5-mmol scale, the Birch process requires 7 hours from setting up equipment to the completion of biphasic extraction (*14*). These logistical challenges make it difficult to perform multiple Birch reductions in parallel. Also, the liquid ammonia solvent has long been deemed necessary to solubilize alkali metals to form the solvated electron.

To overcome these challenges, researchers have developed ammonia-free conditions. For example, the Benkeser group used lithium and neat ethylamine, ethylenediamine, or a mixture of primary and secondary amines, providing a mixture of over-reduced products, and did not use any other solvents (Fig. 1B) (*15*–*17*). Arenes could be reduced to the Birch-type products with lithium in a mixture of methylamine and isopropanol, but overreduction appeared inevitable (*18*). Benzoic acid was reduced to benzaldehyde in 25% yield in the presence of lithium, methylamine, and ammonium nitrate (*19*). The benefit of ethylenediamine as a solvent for dissolving metal reductions was also demonstrated by others (*20*). The Dolby group reduced three substates to the corresponding Birch-type products in 45% to quantitative yield using lithium, ethylenediamine, *n*-propylamine, and *t*-butanol (*4*). This method was moderately successful in one instance (*21*) and was not effective in the *N*-detosylation of a challenging substrate (*22*). Donohoe and House reported the reduction of electron-deficient arenes and heterocycles using di-*tert*-butylbiphenyl ($1000/mol; Sigma-Aldrich) and lithium at −78°C (Fig. 1C) (*23*). Their method was highly oxygen sensitive and as lengthy as the standard Birch procedure (*14*). An's method (Fig. 1D) requires sodium and 3 to 9 equivalents of 15-crown-5 ($1579/mol; Sigma-Aldrich) and is limited to electron-rich or neutral substrates (*24*). The Baran group described an electrochemical reduction of electron-rich arenes (Fig. 1E) with 3.5 to 10 equivalents of tri(pyrrolidin-1-yl)phosphine oxide ($5040/mol; Sigma-Aldrich) and 3 equivalents of 1,3-dimethylurea ($5/mol; Sigma-Aldrich), both of which must be removed from the product by column chromatography (*13*). Their 0.45-mol scale reaction took 3 days in a flow reactor without tri(pyrrolidin-1-yl)phosphine oxide (*13*). The Sugai group treated arenes with lithium and ethylenediamine in tetrahydrofuran (THF) or Et_2O but did not isolate 1,4-cyclohexadiene products (*25*, *26*) and indicated that THF might be a ligand for a lithium ion (*25*).

Despite these efforts, the original, cumbersome, and dangerous Birch protocol remains the current standard (*14*, *27*). Because of the

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA.
*Corresponding author. Email: koide@pitt.edu

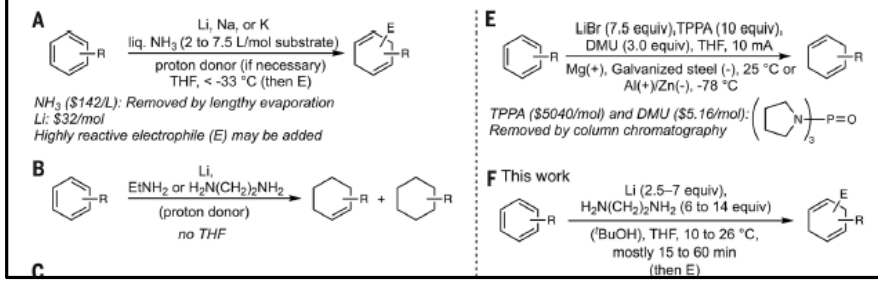

Fig. 1. Previous Birch reductions and this work. (**A**) General Birch reduction. (**B**) Benkeser's ammonia-free reduction. (**C**) Donohoe's ammonia-free Birch reduction. (**D**) An's ammonia-free Birch reduction. (**E**) Baran's electrochemical reduction. (**F**) This work. liq., liquid; EWG, electron-withdrawing group; DBB, 4,4′-di-*tert*-butylbiphenyl; TPPA, tri(pyrrolidin-1-yl)phosphine oxide; DMU, 1,3-dimethylurea.

BURROWS, James, Shogo KAMO a Kazunori KOIDE. Scalable Birch reduction with lithium and ethylenediamine in tetrahydrofuran. *Science*. 2021, 374(6568), 741-746. ISSN 0036-8075.
Dostupné z: doi:10.1126/science.abk3099

Scalable Preparation of Methylated Ando-Type Horner–Wadsworth–Emmons Reagent

Robert K. Bressin, Julia L. Driscoll, Yanping Wang, and Kazunori Koide*

Department of Chemistry, University of Pittsburgh, 219 Parkman Avenue, Pittsburgh, Pennsylvania 15260, United States

Supporting Information

ABSTRACT: The Horner–Wadsworth–Emmons (HWE) reactions are vital to the chemical synthesis of complex molecules, forging a carbon–carbon double bond in the generation of α,β-unsaturated enoates from aldehydes or ketones. Despite their frequent use, the *Z*-stereoselective formation of α,β-unsaturated esters from aldehydes have been mostly limited to the use of the commercially available Still–Gennari reagent. Ando developed an alternative reagent to achieve the same formation with less expensive reagents. However, an α-methylated Ando-HWE reagent has remained difficult to prepare, hindering a reliable route to α,β-disubstituted *Z*-enoates. Here, we report the development of a preparative synthesis of a methylated Ando-HWE reagent for the highly *Z*-selective HWE reaction. Costing $0.49/mmol, this synthesis is significantly cheaper than the currently available Still–Gennari reagent ($11/mmol, Millipore Sigma 2018). The purification procedure does not require chromatography, with recrystallization as the only purification method, making it highly amenable to large-scale production.

KEYWORDS: *olefination, Wittig reactions, synthetic methods, alkylation, Horner–Wadsworth–Emmons reaction*

INTRODUCTION

Methods for generating new carbon–carbon bonds are powerful reactions that are widely used in the synthesis of complex molecules. The Horner–Wadsworth–Emmons (HWE) olefination has found widespread use in generating predominantly *E*-α,β-unsaturated esters from aldehydes. The generation of a *Z*-enoate has been more difficult, but two types of reagents have been developed to obtain this selectivity: the Still–Gennari reagent, (2,2,2-trifluoroethyl)phosphonoester **1a**[1] and Ando-type reagents, bis(*O*-aryl)phosphonates **1b**.[2] As shown in Scheme 1, α-alkylation of these types of reagents (step 1) followed by an HWE reaction (step 2) will generate this reagent costs $1.00/mmol, even without including the cost of purification. Alternatively, the Ando group developed reagent **1b** using electron-withdrawing aryloxy groups on the phosphorus atom, which presumably accelerate the formation of a *cis* oxaphosphetane, leading to formation of the *Z*-olefin with high stereoselectivities.[2] These bis(*O*-aryl)phosphonates and their associated reagents cost less to prepare, and the preparation is scalable. Touchard exploited the wide availability of phenols to develop phosphonate **1c**, which could be isolated in a pure form as a solid.[25,26] α-Alkylation of these reagents has been demonstrated with several examples in DMSO using NaH and haloalkanes; however, these reactions typically proceed with modest yields (~65%) and require column chromatography.[27,28] Despite poor synthetic accessibility, these α-alkylated reagents demonstrated similar *Z*-selectivity as the unsubstituted bis(*O*-aryl)phosphonates in the HWE reaction.

To harness the HWE reaction as a reliable route to trisubstituted *Z*-α,β-unsaturated enoates, it is necessary to develop a method to selectively monoalkylate phosphonates such as **1c**. In this manuscript, we report a scalable and inexpensive method for the preparation of the α-substituted phosphonate **2c** for *Z*-selective olefination reactions.

RESULTS AND DISCUSSION

To develop the required monoalkylation method, phosphonate **1c** was prepared according to the literature.[25] The two unsolved problems were the chemoselectivity for the formation of compounds **2c** and **4** and the overall yield of the reaction. A series of bases, solvents, and additives were screened to determine the optimal conditions to maximize formation of **2c**. Treatment of **1c** with MeI and NaH in DMF led to a mixture of the starting material, the desired monomethylated product **2c**, and the undesired dimethylated product **4** as previously noted by Ando (run 1, Table 1).[27] The use of DBU gave a better chemoselectivity between **2c** and **4**, but only with 67% conversion (run 2). To activate MeI, we tested $AgNO_3$ (run 3) and Ag_2O (run 4) and found that the latter was more efficient, providing a mixture of **2c** and **4** in 92% conversion with a ratio of 93:7.

BRESSIN, Robert K., Julia L. DRISCOLL, Yanping WANG a Kazunori KOIDE. Scalable Preparation of Methylated Ando-Type Horner–Wadsworth–Emmons Reagent. *Organic Process Research & Development.* 2019, 23(2), 274-277. ISSN 1083-6160. Dostupné z: doi:10.1021/acs.oprd.8b00423

the rate should be linearly proportional to the alcohol concentration. Instead, we observed a bell-shaped trend (fig. S4B), which indicates that protonation may occur intramolecularly through LiN-6. The slight preference between related substrates with different steric environments (Fig. 4D) bodes well with this hypothesis. Notably, the reaction mixture containing ^{n}BuOPh turned light blue with 8 equivalents of *t*-butanol, although the desired reduction did not occur. This suggests that excess alcohol may outcompete amino groups on the lithium at an earlier stage of the reaction, forming less-reductive solvated electrons, similar to work with SmI_2 (*51*). A mass effect may have obscured the additional role of *t*-butanol in the past; traditionally, the amine has been used in greater excess than the alcohol, outcompeting the alcohol for coordination to the lithium.

When <1 equivalents of *t*-butanol were present in the reduction of ^{n}BuOPh, the monoolefin was formed in ~20% yield. This is similar to the Benkeser reduction without alcohol (Fig. 1B) (*15*–*17*, *52*–*54*). Although the addition of an alcohol under the Benkeser-type conditions gave Birch-type products (*4*, *18*, *55*), these findings have not garnered widespread use. The alcohol is necessary to synthesize Birch products by protonating both the organolithiated species (LiN-5 or LiN-6) and the lithium amide in the reaction mixture (*18*). The protonation of the lithium amide then hinders the isomerization of the 1,4-diene to the 1,3-diene, which slows the formation of the monoolefin. Potential effects of *t*-butoxide would warrant further investigation.

Literature has shown that more acidic alcohols (e.g., methanol and ethanol) give faster reductions but lower yields than bulkier alcohols (e.g., isopropanol and *t*-butanol) because of an off-reaction with lithium to create H_2 (*45*, *50*). Although our data mostly support such a notion, we wish to consider other factors based on the data with trifluoroethanol (52%), methanol (33%), and ethanol (58%) (table S2) combined with the structural requirements of the amine (Fig. 2A), including optimal bite angle (*56*) (ethylenediamine versus 1,2-diamino-2-methypropane). For example, fig. S5 describes how the equilibrium between a monomer and higher-order aggregates of various ligated lithium intermediates can be affected by the amine ligand among other factors.

The switch of the solvent from an amine to an ethereal solvent (THF) was essential for this work. Altundas's conditions (ammonia gas in a balloon, lithium, and THF) (*30*) suggested that the amine might not be needed as a solvent. 1,2-Dimethoxyethane was ineffective as the solvent, which indicates that only one molecule of THF binds to a lithium ion to form reactive species. The role of THF as a ligand for the alkali metal ion most likely had not been considered before because the ethereal solvent was previously used in smaller amounts than the amine solvent.

The method discussed in this paper could reverse the chemoselectivity for the reduction of $PhCO_2H$ and ^{n}BuOPh by two orders of magnitude with triethylenetetramine (61-fold difference under the standard Birch reduction conditions in favor of $PhCO_2H$ and twofold difference under our conditions in favor of ^{n}BuOPh). More broadly, the structure-reactivity relationship indicates the potential for (reverse) chemoselective reduction in synthesis. To control the selectivity, inner- and outer-sphere electron transfer processes may be considered (*22*, *24*). Our work also suggests a broader role for the alcohol than previously considered, including the product selectivity with naphthalene and indole systems. Also, this study gives a platform to investigate solvated electrons at room temperature.

In addition to the theoretical advancements, the practicality of the technology should render the lithium-mediated reduction and deprotection more accessible to a broader scientific community and more amenable to the time-economic synthesis of complex molecules (*57*). Finally, the scope of the Birch reduction may be expanded by combining the chemistry of organolithium with other organometallic chemistry.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S6
Tables S1 and S2
NMR Spectra
References (*68*–*77*)

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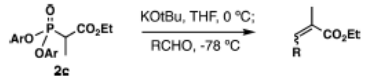
phosphonate **2c** with various aldehydes commonly used to test similar olefination reagents. These results are summarized in Table 3. Compound **2c** shows comparable *Z*-selectivity to the nonalkylated **1c**[25] and related alkylated reagents[27] with near-perfect selectivity with aromatic (Table 3, run 1) and branched (runs 2 and 3) aldehydes and lower selectivity with conjugated and linear substrates (runs 4 and 5). The yields for the more challenging substrates were lower than those from the literature[25,27] due to the shorter times.

Table 3. HWE Reactions of 2c with Aromatic/Aliphatic Aldehydes in THF



2c

run	RCHO	time (h)	yield (%)[a]	ratio (*Z*/*E*)[a]
1	PhCHO	3	94	97:3
2	$^{c}C_6H_{11}CHO$	3	36	94:6
3	^{n}BuCH(Et)CHO	3	60(brsm)	100:0
4	$^{n}C_7H_{15}CHO$	3	84	86:14
5	^{i}PrCH=CHCHO	3	69	70:30

[a]Determined by the ^{1}H NMR analyses of the crude mixtures.

In conclusion, we have developed a method to prepare phosphonate **2c** in high yield and chemoselectivity. The procedure is devoid of column chromatography and does not require expensive reagents. The preparation of phosphonate **2c** from PCl_3 costs $0.49/mmol including all reagents and solvents. The use of commercial THF without distillation further simplifies the procedure. This reagent demonstrated high *Z*-selectivity in the HWE reaction with several aldehydes.

EXPERIMENTAL SECTION

Nondistilled THF (250 mL; water <0.008%) was added to a 1-L round-bottom flask under a nitrogen atmosphere. Phosphonate **1c** (105.42 g, 243.76 mmol) was added to the flask, and the resulting reaction mixture was cooled to 0 °C on ice. The mixture was then treated with MeI (15.10 mL, 243.75 mmol) in one portion at 0 °C. The reaction mixture was kept at 0 °C while KO^{t}Bu (27.35 g, 243.75 mmol) was added slowly to the flask in small portions (**Caution: exothermic**). The resulting mixture was allowed to stir for 1 h at 23 °C. The reaction was cooled to 0 °C, and DBU (72.50 mL, 487.50 mmol) was added slowly, followed by MeI (15.10 mL, 243.75 mmol). The resulting slurry was allowed to stir for 1 h at 23 °C. The reaction was cooled to 0 °C and quenched using saturated aqueous NH_4Cl (200 mL), THF was removed under reduced pressure, and the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (1 × 200 mL) and dried over Na_2SO_4. The organic layers were then filtered through a cotton plug, and the organic solvents were evaporated under reduce pressure to yield a pale-yellow oil (108.45 g, quantitative yield, 78% purity by ^{1}H NMR analysis). The material was recrystallized from hot hexanes to yield white crystals (72.7 g; 87% purity by ^{1}H NMR).

R_f = 0.34 (20% EtOAc in hexanes); mp = 70–72 °C; IR (film): ν_{max} = 3460, 3083, 2960, 2872, 1741 (C=O), 1488, 1442, 1300 (P=O), 1257, 1182, 1087, 1055, 945, 757 cm^{-1}; ^{1}H NMR (300 MHz, 293 K, $CDCl_3$): δ 7.73 (app d, J = 8.1 Hz, 1H; *Ar*), 7.64 (app d, J = 8.1 Hz, 1H; *Ar*), 7.34–7.31 (app m, 2H; *Ar*), 7.14–7.02 (m, 4H; *Ar*), 4.14 (dq, J = 10.7, 6.9 Hz, 1H; CH_2CH_3), 4.00 (dq, J = 10.7, 6.9 Hz, 1H; CH_2CH_3), 3.47 (dq, J = 24.0, 7.2 Hz, 1H; P(O)CHCH$_3$), 1.68 (dd, J = 19.5, 7.2 Hz, 3H; P(O)CHCH_3), 1.35 (s, 9H; ^{t}*Bu*), 1.31 (s, 9H; ^{t}*Bu*), 1.08 (t, J = 6.9 Hz, 3H; CH_2CH_3); ^{13}C NMR (100 MHz, 293 K, $CDCl_3$): 168.4 (d, J = 4 Hz), 151.0 (d, J = 10 Hz), 150.6 (d, J = 9 Hz), 138.9 (d, J = 4 Hz), 138.8 (d, J = 4 Hz), 127.5, 127.5, 127.3, 127.3, 124.4, 124.3, 119.8 (d, J = 3 Hz), 119.6 (d, J = 3 Hz), 61.9, 41.7 (d, J = 138 Hz), 34.7, 30.2, 30.09, 13.8, 12.0 (d, J = 6 Hz) ppm; HRMS (ES+) calcd for $C_{25}H_{35}O_3P$ [M + H]$^{+}$ 447.22949, found 447.23151.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.8b00423.

^{1}H and ^{13}C NMR spectra for compound **2c** (PDF)

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Notes

The authors declare no competing financial interest.

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Thank you for your attention!