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Diastereoselective hydrogenation of arenes and pyridines using supported ruthenium nanoparticles under mild conditions

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Florian Bourriquen,^a Julien Hervochoch,^{a,b} Ruiyang Qu,^a Stephan Bartling,^a Nils Rockstroh,^a Kathrin Junge,^{*,a} Cédric Fischmeister^b and Matthias Beller^{*,a}

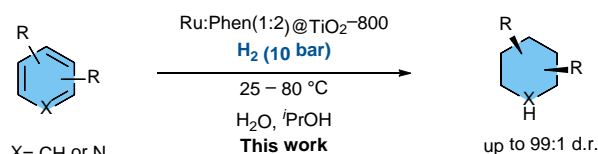
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A convenient and practical diastereoselective *cis*-hydrogenation of multi-substituted pyridines and arenes is reported. Applying a novel heterogeneous ruthenium catalyst, the corresponding piperidines and cyclohexanes are obtained in high yields (typically >80%) with a good functional group tolerance under mild conditions. The robust ruthenium supported catalyst is smoothly prepared and can be reused multiple times without activity loss.

Stereoselective catalytic hydrogenations are of fundamental importance for the generation of intermediates of pharmaceuticals, agrochemicals, and chiral building blocks.¹⁻³ In fact, these methodologies represent the industrially most applied processes in asymmetric catalysis.⁴ In addition to enantioselective hydrogenations, also diastereoselective processes continue to be important and possess significant problems in many transformations, notably the poor stereoselectivity frequently obtained. While numerous protocols for the diastereoselective hydrogenation of functional groups were established during the past decades, including ketone,⁵ imine,⁶ and alkene⁷ reductions, related reactions of substituted arenes and heteroarenes remain challenging and often several stereoisomers are obtained. On the other hand, the reduction of substituted (hetero)arenes directly yields valuable chiral cyclohexanes or six-membered (hetero)cycles, which usually require tedious multi-step syntheses involving chiral auxiliaries or the use of expensive chiral ligands utilising other metal-catalysed reactions.^{8,9}

Apart from the inherent effectiveness (one step, 100% atom efficiency), such hydrogenations are also interesting as a significantly larger pool of aromatic compounds is available from chemical suppliers compared to their aliphatic counterparts, opening access to a plethora of novel chiral

molecules. As an illustration, from the 187.000 marketed six-membered rings, 138.000 are benzene derivatives, while only 10.000 are cyclohexane-based derivatives.¹⁰ For this reason, the development of general methodologies for the stereoselective reduction of multiple substituted aromatic compounds is of paramount importance. In the past decade, notable achievements for the hydrogenation of (hetero)arenes were realised, especially in the case of nitrogen heterocycles, which have an additional defined coordination site as well as lower stabilisation energy. In this respect, the groups of Glorius,^{11,12} Du,^{13,14} Chirik,¹⁵ Stoltz¹⁶ or more recently Crudden¹⁷ developed protocols utilising either specific homogeneous catalysts, frustrated Lewis pairs or took advantage of auxiliary based approaches. An interesting system for the *cis*-hydrogenation of non-functionalised arenes was reported by Delferro and Marks, who used a supported organozirconium catalyst with remarkable selectivity.¹⁸ Likewise, a molybdenum pincer complex developed by Chirik and co-workers permits the diastereoselective hydrogenation of substituted benzene rings.¹⁹ However, both systems were inactive in the reduction of heteroarenes. Other stimulating examples for highly diastereoselective reduction of arenes and pyridines including fluorinated compounds were reported by Glorius and co-workers^{20,21} utilising rhodium-cyclic (alkyl)(amino)carbene (CAAC) complexes. Obviously, for many applications the use of a robust heterogeneous catalyst would be preferable compared to more sensitive organometallic complexes *vide supra*; however, such supported catalysts are primarily used for hydrogenation of unsubstituted (hetero)arene hydrogenation and diastereoselective examples are rare.²²⁻²⁵



Scheme 1 Diastereoselective reduction of arenes and N-containing heterocycles using supported ruthenium nanoparticles.

^a Leibniz-Institut für Katalyse e.V., Albert-Einstein-Straße 29a, 18059 Rostock (Germany).

^b Univ Rennes, CNRS, ISCR (Institut des Sciences Chimiques de Rennes) UMR 6226, F-35000 Rennes (France).

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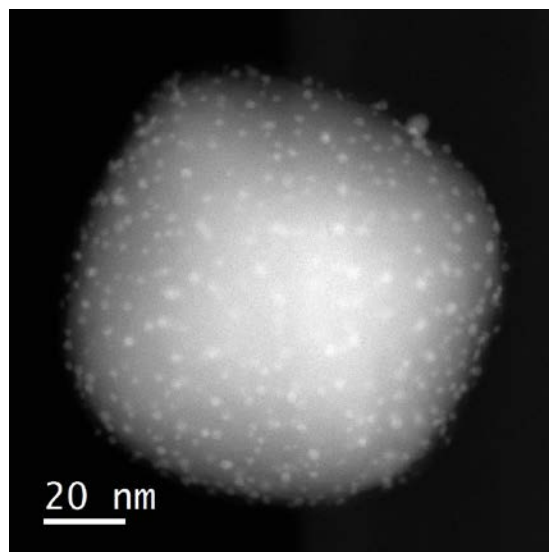
Table 1 Optimisation of reaction conditions.^a

Entry	Catalyst	Solvent	Yield of 2a [%] ^b	d.r. ^c
1	Ru@C Alfa Aesar	H ₂ O	67	95:5
2	Ru@C Sigma-Aldrich	H ₂ O	68	95:5
3	Ru@C Strem	H ₂ O	63	95:5
4	Ru@C TCI	H ₂ O	66	95:5
5	Ru:Phen(1:2)@TiO ₂ -800	H ₂ O	64	97:3
6 ^d	Ru:Phen(1:2)@TiO ₂ -800	H ₂ O	75	98:2
7 ^{d,e}	Ru:Phen(1:2)@TiO ₂ -800	H ₂ O	75	98:2
8 ^{d,e}	Ru:Phen(1:2)@TiO ₂ -800	H ₂ O: ^f PrOH (1:1)	93	97:3
9 ^{d,e}	Ru:Phen(1:2)@TiO ₂ -800	^g PrOH	<5	n/a

^aReaction conditions: 2,6-lutidine (53.6 mg, 0.5 mmol), Ru:Phen(1:2)@TiO₂-800 (0.4 mol%, 10 mg) or Ru@C (0.4 mol%, 4 mg), solvent (2 mL), H₂ (30 bar), 80 °C, 17 h. ^bDetermined by GC-FID using hexadecane as internal standard, average of two runs. ^cDiastereoisomeric ratio corresponding to the *cis* stereoisomer calculated by GC-FID, average of two runs. ^d25 °C. ^eH₂ (10 bar).

Speaking of di-substituted (hetero)arene hydrogenation in the presence of heterogeneous catalysts the *cis*-product is naturally favored,^{26, 27} but often mixtures of diastereomers are obtained.^{28, 29} A notable exception is the report of Glorius for the *trans*-hydrogenation of phenols.³⁰ Nevertheless, the development of a versatile, additive-free heterogeneous catalyst system for the hydrogenation of both arenes and heteroarenes is desirable and would constitute a valuable expansion to the current methodologies. In this respect, herein we present a general protocol for the diastereoselective preparation of substituted piperidines and cyclohexanes from the corresponding inexpensive pyridine or arene starting materials. To complement our cobalt nanoparticles,²⁷ this mild and benign methodology makes use of a reusable heterogeneous Ru catalyst in water/isopropanol as solvent and allows highly selective hydrogenations of industrially relevant substrates. In comparison to our previous work, hydrogenation is permitted at lower metal loading, temperature, and hydrogen pressure.

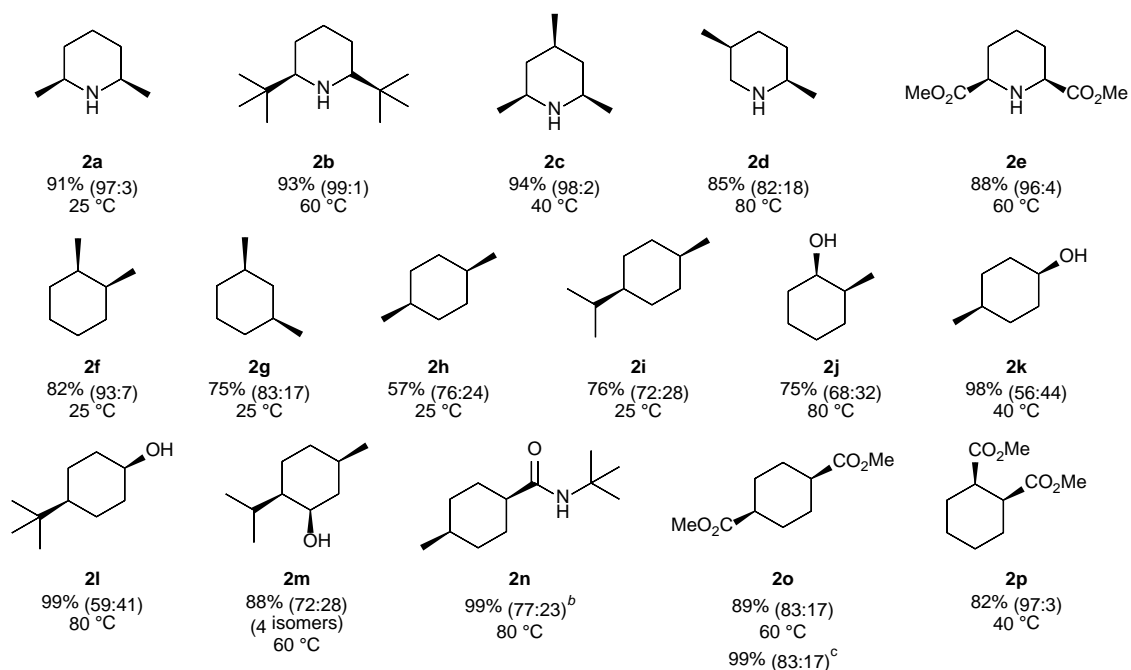
We commenced our work by testing various commercially available heterogeneous ruthenium catalysts for the diastereoselective hydrogenation of 2,6-lutidine as model substrate. Gratifyingly, moderate to good yields and very good diastereoselective ratios (d.r.) of 95:5 for the *cis*-hydrogenated product were obtained (Table 1, entries 1–4). Considering our group's previous works in the preparation and application of supported nanoparticles for various reduction reactions, we synthesised a novel Ru:Phen(1:2)@TiO₂-800³¹ material and investigated its hydrogenation performance. Applying this material, similar yields of **2a** but increased d.r. was observed. Variation of reaction conditions showed this catalyst to be active even at room temperature and 10 bar of hydrogen

**Figure 1** STEM-HAADF image of the fresh Ru@TiO₂-800 catalyst.

pressure (Table 1, entries 5–7). Using a water:isopropanol (1:1) solvent mixture drastically increased the yield to 93%. Notably, using this optimised reaction conditions, commercially available materials presented different activities (Table S4).

An advantage of heterogeneous catalysts vs. their homogeneous counterparts is the easy removal of the former from reaction mixtures by simple filtration. Moreover, catalyst recycling is in general feasible, after catalyst reactivation if required. Accordingly, we evaluated the reusability of Ru:Phen(1:2)@TiO₂-800 for the model reaction. In fact, no substantial loss of activity or selectivity was observed after four reuses of the catalyst without reactivation in between the runs (see Figure S4). This result is in accordance both with the scanning transmission electron microscopy (STEM) analyses showing no major structure change after the reaction, and the absence of Ru detected by ICP-AES in the reaction mixture after one run.

The fresh and the recycled catalysts were investigated by STEM and energy dispersive X-ray spectroscopy (EDX). As can be seen in Figure S1, ruthenium forms groups of rather small particles between 1 and 9 nm in the as-prepared catalyst. These particles are mainly surrounded by a matrix of carbon and little nitrogen as one would expect from the synthesis procedure (Figure S2). In the case of being part of the carbon/nitrogen matrix the Ru particles appear separated from TiO₂ (Figure S1a), but also regions with closer spatial contact of Ru and TiO₂ exist (Figure 1, Figure S1b). The recovered catalyst after reaction is very similar to the fresh one (Figure S1c), which underlines the good recyclability of this material. Additionally, a few larger ruthenium particles with sizes of up to 20 nm are found (Figure S1d). The number of these larger Ru nanoparticles is however low implying a negligible influence on the catalytic performance of the material after recycling. The fresh and recycled catalyst were further characterised by X-ray photoelectron spectroscopy (XPS). At their surfaces mainly C, O, Ti, N, and Ru



Scheme 2 Substrate scope of the diastereoselective hydrogenation of pyridines and arenes. Reaction conditions: **1** (0.5 mmol), Ru:Phen(1:2)@TiO₂-800 (0.4 mol% of Ru, 10 mg), H₂O (1 mL), ⁱPrOH (1 mL), H₂ (10 bar), 17 h. ^bRu:Phen(1:2)@TiO₂-800 (0.8 mol% of Ru, 20 mg). ^c Dimethyl terephthalate (10 g), Ru:Phen(1:2)@TiO₂-800 (514 mg), H₂O (50 mL), ⁱPrOH (50 mL), H₂ (40 bar), 80 °C, 17 h.

species can be found, see quantification table for details (Table S2). The concentration of Ru at the surface of the fresh catalyst measured by XPS is about 1.7 at.% compared to 1.5 at.% for the recovered catalyst. However, Ru 3d and C 1s regions strongly overlap as can be seen in Figure S3c and S3d. Peak deconvolution leads to a binding energy of the Ru 3d_{5/2} peak of 280.3 eV for the fresh catalyst, thus suggesting Ru⁰ as the main oxidation state of ruthenium.³² For the recycled catalyst a small peak at about 281.5 eV appears, which can be attributed to a slight oxidation of the Ru to RuO₂. The Ti 2p_{3/2} peak for both samples has a binding energy of 459.0 eV which is characteristic for Ti⁴⁺. The N 1s region in Figure S3a and S3b is deconvoluted with four peaks, characteristic for pyridinic (398.5 eV), pyrrolic (399.9 eV), graphitic (401.0 eV), and oxidised pyridinic (403.0 eV) nitrogen species.^{33, 34} Whereas for the fresh catalyst mainly graphitic nitrogen can be found, pyridinic, pyrrolic, and oxidised pyridinic nitrogen peaks are stronger in the recycled catalyst, see Figure S3b.

Having a suitable catalyst material and optimised reaction conditions in hand, we evaluated the applicability of this methodology for the diastereoselective reduction of substituted pyridines and arenes (Scheme 2). Pyridines bearing both electron-donating and electron-withdrawing substituents were efficiently reduced to give preferentially the corresponding *cis*-products. Notably, a substrate featuring bulky substituents such as the ^tBu group was readily transformed into the corresponding piperidine **2b** with 93% yield and 99:1 diastereoselectivity, respectively. Furthermore, this methodology can be applied to substrates with more than two substituents, e.g. 2,4,6-trimethylpyridine (**1c**) is hydrogenated in excellent yield at 40 °C. A significant

correlation between substituents position on the pyridine ring and the ease of hydrogenation was identified. While the reduction of 2,6-dimethylpyridine (**1a**) is smoothly achieved at room temperature, a reaction temperature increase to 80 °C is necessary for the reduction of less active 2,5-dimethylpyridine (**1d**) without limiting the *cis*-selectivity. The hydrogenation of pyridines containing readily reducible groups presents a chemoselective challenge in addition to the high diastereoselective reactivity targeted with this catalyst system. Pleasingly, *cis*-dimethyl piperidine-2,6- dicarboxylate (**2e**) was successfully isolated from the corresponding pyridine in high yield and high d.r. (88% and 96:4, respectively). Interestingly, hydrogenation of quinoline provided 1,2,3,4-tetrahydroquinoline (see SI). Besides pyridines, this catalyst material can be successfully applied for the diastereoselective reduction of different substituted arenes. For example, the simplest disubstituted arenes, *ortho*, *meta*, and *para* xylenes (**2f–2h**) are efficiently hydrogenated at room temperature with a selectivity decrease from 93:7 over 83:17 to 76:24 depending on the spacing between the two substituents. Noteworthy, the temperature only has little influence on the selectivity for those compounds, as comparable diastereoselective ratios were obtained when the reaction was performed at 120 °C for one hour (see ESI). Increasing the steric bulkiness at the *para* position provided *p*-menthane **2i** in 76% yield starting from *p*-cymene. Next, the hydrogenation of phenols bearing aliphatic substituents was explored (**2j–2l**), providing the corresponding *cis*-cyclohexanols in high yields. In these cases, a lower selectivity is obtained compared to alkyl-substituted phenyl rings, which might be a result of epimerisation of the hydroxy-bearing carbon centre. Diastereoselective reduction of tri-

substituted arenes was eventually investigated. Here, thymol was chosen as substrate as its stereoselective hydrogenation leads to industrially important menthol isomers. Applying the Ru:Phen(1:2)@TiO₂-800 material for the reduction of thymol a mixture of menthol isomers was obtained, giving the (±)-neoisomenthol **2m** as major product (72:28 d.r.).³⁵ Benzoic acid derivatives are important intermediates for many daily life applications. In this regard, the hydrogenation of arenes possessing strong electron-withdrawing substituents is interesting. Notably, terephthalic and phthalic acid methyl esters were efficiently reduced, and no ester cleavage/hydrogenation was observed. The corresponding products **2o** and **2p** were isolated in high yields and high d.r.. Similarly, *cis*-*N*-(*tert*-butyl)-4-methyl-cyclohexane -1-carboxamide (**2n**) was isolated from the corresponding arene, highlighting the tolerance of this catalytic system for the reduction of substrates containing amide moieties. To showcase the preparative value of this methodology, a 10 gram-scale experiment was conducted with **1o**. Pleasingly, the corresponding cyclohexane derivative was isolated in quantitative yield without erosion of the selectivity using only 0.25 mol% catalyst loading. Here, for stoichiometric reasons a higher hydrogen pressure is required. Lastly, it should be noted that the here presented protocol can be used as a key step for a practical synthesis of enantiopure cyclohexanes/piperidines: according to previously reported procedures,³⁶ chiral diesters such as **2p** were selectively hydrolysed to the monoester using inexpensive pig liver esterase (PLE, EC 3.1.1.1) allowing also further functionalisation of the free carboxylic acid.

In conclusion, this work presents Ru:Phen(1:2)@TiO₂-800 as a novel supported catalyst system, which allows for the stereoselective hydrogenation of di- and tri-substituted arenes and pyridines. Hydrogenation is achieved in an aqueous medium under comparably mild conditions with a good to high diastereoselectivity towards the *cis*-products. The synthetic applicability of this methodology is highlighted with the multi-gram scale synthesis of dimethyl *cis*-1,4-cyclohexanedicarboxylate. It should be noted that the here presented approach allows for a straightforward and atom-efficient synthesis of substituted cyclohexanes and piperidines. For many such products this transformation will be advantageous compared to traditional stereoselective synthesis.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- N. B. Johnson, I. C. Lennon, P. H. Moran and J. A. Ramsden, *Acc. Chem. Res.*, 2007, **40**, 1291.
- V. Andrushko and N. Andrushko, in *Stereoselective Synthesis of Drugs and Natural Products*, eds. V. Andrushko and N. Andrushko, John Wiley & Sons, Inc., Hoboken, NJ, USA, 2013, DOI: 10.1002/9781118596784.ssd001, pp. 1.
- C. S. G. Seo and R. H. Morris, *Organometallics*, 2019, **38**, 47.
- H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner and M. Studer, *Adv. Synth. Catal.*, 2003, **345**, 103.
- R. Noyori and T. Ohkuma, *Angew. Chem., Int. Ed.*, 2001, **40**, 40.
- J.-H. Xie, S.-F. Zhu and Q.-L. Zhou, *Chem. Rev.*, 2011, **111**, 1713.
- S. Kraft, K. Ryan and R. B. Kargbo, *J. Am. Chem. Soc.*, 2017, **139**, 11630.
- D.-S. Wang, Q.-A. Chen, S.-M. Lu and Y.-G. Zhou, *Chem. Rev.*, 2012, **112**, 2557.
- M. P. Wiesenfeldt, Z. Nairoukh, T. Dalton and F. Glorius, *Angew. Chem., Int. Ed.*, 2019, **58**, 10460.
- See Electronic Supplementary Information for details.
- F. Glorius, N. Spielkamp, S. Holle, R. Goddard and C. W. Lehmann, *Angew. Chem., Int. Ed.*, 2004, **43**, 2850.
- M. Heitbaum, R. Fröhlich and F. Glorius, *Adv. Synth. Catal.*, 2010, **352**, 357.
- Y. Liu and H. Du, *J. Am. Chem. Soc.*, 2013, **135**, 12968.
- Q. Zhou, L. Zhang, W. Meng, X. Feng, J. Yang and H. Du, *Org. Lett.*, 2016, **18**, 5189.
- S. Kim, F. Loose, M. J. Bezdek, X. Wang and P. J. Chirik, *J. Am. Chem. Soc.*, 2019, **141**, 17900.
- A. N. Kim, A. Ngamthiporn, E. R. Welin, M. T. Daiger, C. U. Grünanger, M. D. Bartberger, S. C. Virgil and B. M. Stoltz, *ACS Catal.*, 2020, **10**, 3241.
- J. J. Clarke, Y. Maekawa, M. Nambo and C. M. Crudden, *Org. Lett.*, 2021, **23**, 6617.
- M. M. Stalzer, C. P. Nicholas, A. Bhattacharyya, A. Motta, M. Delferro and T. J. Marks, *Angew. Chem., Int. Ed.*, 2016, **55**, 5263.
- M. V. Joannou, M. J. Bezdek and P. J. Chirik, *ACS Catal.*, 2018, **8**, 5276.
- M. P. Wiesenfeldt, Z. Nairoukh, W. Li and F. Glorius, *Science*, 2017, **357**, 908.
- Z. Nairoukh, M. Wollenburg, C. Schleppehorst, K. Bergander and F. Glorius, *Nat. Chem.*, 2019, **11**, 264.
- W. Ipatiew, *Berichte der deutschen chemischen Gesellschaft*, 1908, **41**, 991.
- M. Freifelder and G. R. Stone, *The Journal of Organic Chemistry*, 1961, **26**, 3805.
- M. Fang, N. Machalaba and R. A. Sánchez-Delgado, *Dalton Transactions*, 2011, **40**, 10621.
- A. D. Dwivedi, R. K. Rai, K. Gupta and S. K. Singh, *ChemCatChem*, 2017, **9**, 1930.
- F. Martínez-Espinar, P. Blondeau, P. Nolis, B. Chaudret, C. Claver, S. Castellón and C. Godard, *J. Catal.*, 2017, **354**, 113.
- K. Murugesan, T. Senthamarai, A. S. Alshammari, R. M. Altamimi, C. Kreyenschulte, M.-M. Pohl, H. Lund, R. V. Jagadeesh and M. Beller, *ACS Catal.*, 2019, **9**, 8581.
- N. Douja, R. Malacea, M. Banciu, M. Besson and C. Pinel, *Tetrahedron Lett.*, 2003, **44**, 6991.
- T. Maegawa, A. Akashi, K. Yaguchi, Y. Iwasaki, M. Shigetsura, Y. Monguchi and H. Sajiki, *Chem. Eur. J.*, 2009, **15**, 6953.
- M. Wollenburg, A. Heusler, K. Bergander and F. Glorius, *ACS Catal.*, 2020, **10**, 11365.
- This abbreviation denotes Metal:Ligand(ratio)@Support-Pyrolysis temperature.
- D. J. Morgan, *Surf. Interface Anal.*, 2015, **47**, 1072.
- F. Jaouen, J. Herranz, M. Lefevre, J.-P. Dodelet, U. I. Kramm, I. Herrmann, P. Bogdanoff, J. Maruyama, T. Nagaoka and A. Garsuch, *ACS Appl. Mater. Interfaces*, 2009, **1**, 1623.
- B. J. Matsoso, K. Ranganathan, B. K. Mutuma, T. Leretholi, G. Jones and N. J. Coville, *RSC Adv.*, 2016, **6**, 106914.
- This isomer was identified by comparison of GC retention times of known menthol isomers.

Journal Name

36 G. Sabbioni and J. B. Jones, *J. Org. Chem.*, 1987, **52**, 4565.