Hydrodechlorination of Aryl Chlorides Under Biocompatible Conditions

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ABSTRACT: Developing nonenzymatic chemistry that is nontoxic to microbial organisms creates the potential to integrate synthetic chemistry with metabolism and offers new remediation strategies. Chlorinated organic compounds known to bioaccumulate and cause harmful environmental impact can be converted into less damaging derivatives through hydrodehalogenation. The hydrodechlorination of substituted aryl chlorides using Pd/C and ammonium formate in biological media under physiological conditions (neutral pH, moderate temperature, and ambient pressure) is reported. The reaction conditions were successful for a range of aryl chlorides with electron-donating and -withdrawing groups, limited by the solubility of substrates in aqueous media. Soluble substrates gave good yields (60−98%) of the reduction product within 48 h. The relative toxicities of each reaction component were tested separately and together against bacteria, and the reaction proceeded in bacterial cultures containing an aryl chloride with robust cell growth. This work offers an initial step toward the removal of aryl chlorides from waste streams that currently use bacterial degradation to remove pollutants.
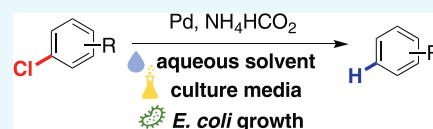
INTRODUCTION

Aryl chlorides are important synthetic intermediates,[1−3] chemical products,[4] and pharmaceutical compounds (Figure 1A).[5] Given their bioactivity and relatively unreactive bond,[6] these same compounds persist and bioaccumulate making them priority pollutants that are hazardous to environmental and human health.[7−10]

Environmentally persistent aryl chlorides are introduced by pharmaceuticals, personal care products, and agriculture (Figure 1A) and are harmful to biological systems. For instance, environmental levels of diclofenac, a nonsteroidal anti-inflammatory, have been shown to rapidly decline vulture populations in India leading to the risk of extinction.[11] A broad-spectrum antimicrobial agent, triclosan, used as a disinfectant in everything ranging from hand-soap to household items and medical devices, is known to persist in the environment and aquatic systems. Triclosan is tied to many negative health effects including carcinogenesis of the liver, endocrine disruption, and developmental disorders. In the environment, triclosan exerts selective pressure on microorganisms, altering the composition of bacterial communities.[12] Aryl chlorides are also prevalent in agrochemicals. The herbicide Agent Orange consists of the *n*-butyl esters of two chlorinated phenoxyacetic acids: 2,4-D and 2,4,5-T (shown in Figure 1) and a manufacturing byproduct, 2,3,7,8-tetrachlorodibenzodioxan (dioxin), which is associated with a large host of environmental and human health concerns due to its toxicity and persistence.[13] While the health effects of environmental levels of 2,4-D and 2,4,5-T are unknown, when these compounds are processed in wastewater treatment facilities (WWFTs), the ether bridge cleaves, leaving chlorophenols that persist in the environment and have carcinogenic properties.[14]

WWTFs rely on microbes to degrade the majority of organic pollutants to clean wastewater for reuse. Many microbes rely on P450 enzymes for the breakdown of aromatic compounds,[15] but these enzymes are ineffective on aryl chlorides and allow them to pass through WWTFs unchanged. This ability to escape degradation in WWTFs results in the release of active compounds into the environment where they cause major ecological distress. We envision a biocompatible hydrodechlorination integrating into microbial-based water treatment methods to aid in the removal of aryl chloride pollutants.

Several methods exist for the degradation and detoxification of aryl chlorides. One method is aerobic biodegradation, though it is shown to lead to higher complexity organic chlorides that continue to persist in the environment.[16] Other methods include photochemical reactions[17] and metal-catalyzed hydroxylation that rely on the use of organic co-solvents and the latter require high pH due to hydroxide reagents.[18] Metal-catalyzed oxidation is another exciting method to degrade aryl chlorides but is not (yet) biocompatible due to strong oxidants like hydrogen peroxide.[19]
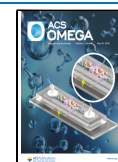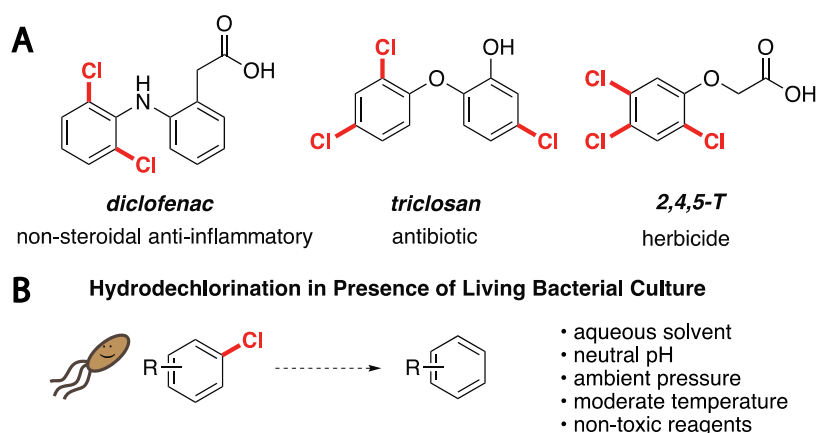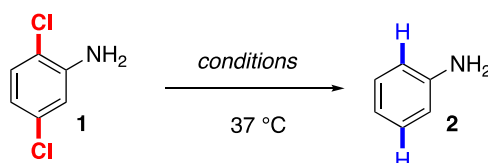
Figure 1. (A) Examples of environmentally persistent aryl chlorides found in pharmaceuticals (diclofenac), personal care products (triclosan), and agrochemicals (2,4,5-T). (B) Our work is to create a biocompatible reaction to reduce aryl Cl bonds.

Table 1. Optimization of Hydrodechlorination in Bacterial Culture Media at Ambient Temperature and Pressure, Neutral pH

entry[a]	solvent	[1] mM	catalyst	NH$_4$HCO$_2$ (equiv)	i-PrOH (equiv)	time (h)	%[b]
1	H$_2$O	200	PdCl$_2$	3	1.2	24	N.D.
2	H$_2$O	200	PdCl$_2$	9	1.2	24	76
3	9:1 H$_2$O/PEG	200	PdCl$_2$	9	1.2	24	85
4	9:1 M9MM/PEG	200	PdCl$_2$	9	1.2	24	100
5	M9MM	200	PdCl$_2$	9	1.2	48[c]	91
6	M9MM	200	Pd/C	9	1.2	24	66
7	M9MM	200	Pd/C		1.2	24	N.D.
8	M9MM	200		9		24	N.D.
9	M9MM	200	Pd/C	9		24	66
10[d]	M9MM	20	Pd/C	12		24	26
11[d]	M9MM	20	Pd/C	12		48[c]	100

[a]PEG (poly(ethylene glycol)-2000) and M9MM (M9 minimal media for bacterial growth, recipe in the Supporting Information). Catalyst loading: PdCl$_2$ is 0.5 mol %, Pd/C is 2 mg/mL unless noted. Ammonium formate 1.8 M unless noted. [b]Conversion % determined by integration of the product and the starting material on HPLC (high-performance liquid chromatography). N.D. is not detected. [c]Additional portion of the catalyst and ammonium formate spiked into reaction at 24 h. [d]Initial catalyst loading 0.2 mg/mL, ammonium formate 240 mM.

Transition-metal-mediated hydrodehalogenation[20] has been shown to occur readily in water and we were inspired by the use of mild ammonium formate as a hydrogen source; however, none of these methods has yet been shown to be compatible with microbial growth.

In recent years, there has been great interest in running transition-metal-mediated reactions in aqueous media and in the presence of whole cells.[21,22] Balskus and co-workers have developed reactions that rely on microbial metabolites as regents, therefore requiring growing cultures: Pd-catalysis to hydrogenate alkenes within hydrogen-producing bacterial culture[23] as well as Ru- and Fe-catalysis to cyclopropanate microbially produced styrene.[24] More recently, metal-catalyzed transfer reductions have been performed intracellularly utilizing both Ru- and Os-catalysis, though the goal of these studies was ultimately cell death for cancer treatment.[25,26] Biocompatible reactions have also been developed for the production of renewable feedstocks; Domaille developed a biocompatible aldol reaction to minimize metabolite toxicity and ease extraction of the product[27] and recently interfaced

this reaction with whole-cell biocatalysis.[28] Outside of transition-metal catalysis, Wang and co-workers have used Brønsted acid catalysts in conjunction with metabolite production to produce pigments.[29] Work is also being conducted to streamline the process of screening for biocompatible catalysts.[30] These works show the feasibility and application of modifying organic synthetic methods to be compatible with microbial growth.

We set out to create a biocompatible chemical reaction to reduce C−Cl bonds on aryl chlorides. We envisioned that such a reaction would have applications in wastewater treatment,[31] synthetic biology, semisynthesis,[32] and green chemistry methods. A biocompatible reaction is one that can be carried out in the presence of living cells.[33] To this end, we set out to optimize our reactions to run (1) in aqueous media, (2) at neutral pH, (3) at ambient pressure, (4) at moderate temperature, and then (5) test for microbial growth (Figure 1B). These constraints also pose many challenges to cleaving a C−Cl bond, as traditional methods rely on high temperatures, strong bases, and organic solvents.[20] Biocompatible chemistry

Table 2. Substrate Scope of Hydrodehalogenation in Bacterial Culture Media and Growth Conditions

	Substrate	Product	%[a]		Substrate	Product	%[a]
1			99[b]	7			21 (9)[c]
2			29	8			99[b]
3			80	9			59
4			78	10			20
5			99[b]	11			99[b]
6			62	12			53

[a]% conversion determined by integration of peaks on HPLC traces. [b]No starting material or other products were detected by HPLC or NMR data. [c]Mixture of the mono- and nonchlorinated compound, the monochlorinated compound in parentheses.

offers a cost-effective solution to the removal of aryl chlorides from waste streams that currently use bacterial degradation to remove pollutants. Herein, we give the first report on biocompatible hydrodehalogenation.

RESULTS AND DISCUSSION

The chemical literature is rich with aryl chloride reduction methods,[30,34] but none fulfilled all five of our criteria. To find and develop a biocompatible hydrodehalogenation, we began by exploring the efficiency of catalytic reductions in water as the sole solvent before moving into more complex aqueous solutions capable of supporting microbial growth (culture media). For ease of analysis, we chose 2,5-dichloroaniline (1, Table 1) to be the test substrate due to its similarity to the chlorinated aryl ring of diclofenac (Figure 1A), a nonsteroidal anti-inflammatory drug known to persist in the environment and has negative effects on wildlife populations.[35]

Inspired by Uozumi et al.'s work with palladium nanoparticles in aqueous solution at ambient temperature and pressure,[36] we began exploring ligand-free Pd-catalyzed hydrodehalogenations in water using PdCl₂ with ammonium formate and isopropanol but found no conversion (Table 1, entry 1). Tripling the equivalents of ammonium formate from those reported[36] and adding a biocompatible co-solvent, poly(ethylene glycol)-2000 (PEG), to help solubilize 1,

increased conversion to the product from 0 to 85% (entries 2−3). Increasing aqueous complexity from water to M9 minimal media, a common *Escherichia coli* growth media buffered at pH 7.1 that consists of glucose and salts (sodium and potassium phosphate, calcium and sodium chloride, magnesium sulfate, ammonium chloride), gave full conversion (entry 4). The reaction proceeds well without PEG as a co-solvent with a longer reaction time and additional catalyst (entry 5).

These reaction conditions were tested for toxicity to *E. coli* to ensure biocompatibility. Unfortunately, we found that PdCl₂ caused total cell death even at low concentrations. Exploring a heterogeneous catalyst seemed attractive to allow for catalyst recycling and lower cell uptake leading to less toxicity. Pd/C was screened for toxicity and found to be much less prohibitive of cell growth than PdCl₂. We optimized the hydrodehalogenation reaction in M9 minimal media using Pd/C as the catalyst (Table 1, entries 6−11). The change in the catalyst also allowed for the removal of isopropanol from the reaction,[37] while the catalyst and ammonium formate remained essential (entries 5−9). With an eye toward toxicity, we wanted to decrease the overall concentration of all components of the reaction mixture while maintaining efficacy. After a 10-fold dilution, the conversion initially dropped (entry 10); however, with an increased reaction time and a supplemental
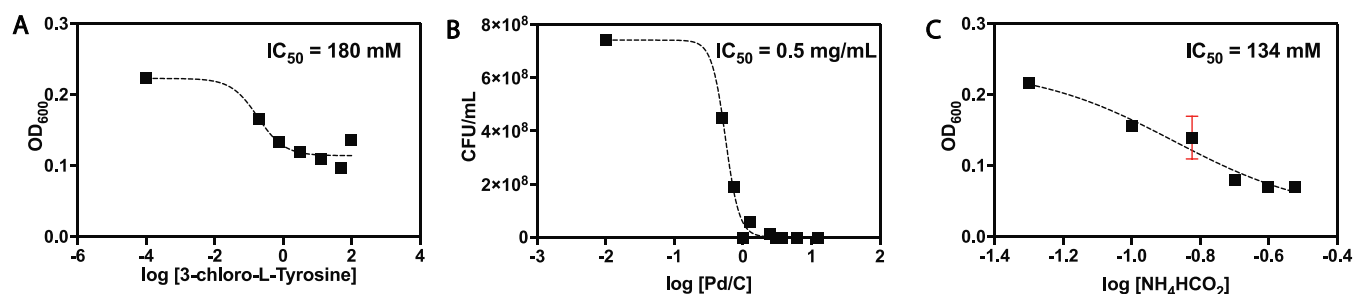
Figure 2. Representative IC_{50} plots for the reaction component needed for dehalogenation: the (A) substrate, 3-chloro-L-tyrosine (**4**), (B) catalyst, Pd/C, and (C) hydrogen source, ammonium formate.
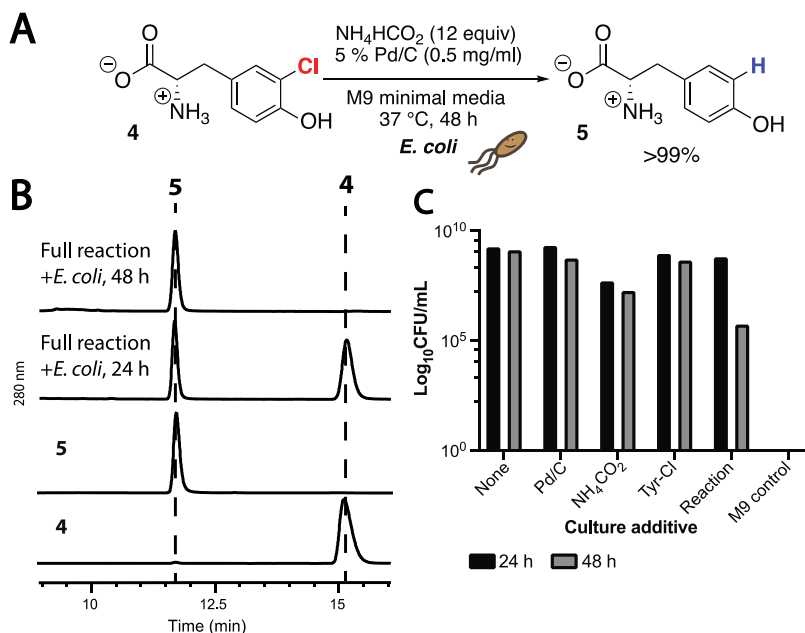
Figure 3. (A) Efficiency of hydrodehalogenation reaction in conditions compatible with bacterial growth and survival, (B) HPLC traces for monitoring reaction in the *E. coli* culture at 24 and 48 h, and (C) cell viability of the *E. coli* with each reaction component at reaction concentration (0.5 mg/mL Pd/C, 140 mM NH_4HCO_2, 11 mM **4**), the overall reaction, and M9 minimal media control.

addition of ammonium formate and catalyst, the reaction went to completion (entry 11).

With optimized reaction conditions in hand, we looked at a variety of aryl chloride substrates to better understand the reaction (Table 2). We found that more soluble compounds, anilines and phenols, gave better conversion (entries 1, 3, 4) than the less soluble *N,N*-dimethylaniline (entry 2), and the addition of PEG-2000 as a 10% co-solvent to M9 minimal media had a minimal effect on conversion, increasing conversion by 2% for *N,N*-dimethylaniline. Distal carboxylic acids gave moderate to full conversion (entries 5 and 6), whereas dichlorobenzoic acid gave a mixture of monochlorinated and fully dechlorinated products (entry 7). Screening of different carbonyl groups found that conversion tracked with the solubility of substrates with the methyl ester giving greater conversion than the aldehyde and methyl ketone analogues (entries 8−10). Of note, when entries 8−10 were run under more concentrated conditions (0.2 M substrate), the solubility trend was much starker, with 30, 15, and 0% conversion, respectively. The reaction conditions reduced nitro groups to primary amines, increasing the solubility and resulting in loss of the chloride (entries 11 and 12).

Initial attempts to move the reaction from M9 minimal media to that inoculated with *E. coli* resulted in conversion to

the product but was accompanied by total cell death, determined by the serial dilution plate assay. To gain insight into the toxicity, we calculated IC_{50} values for each reaction component and substrate in Table 2 (representative data are shown in Figure 2, comprehensive data are found in the Supporting Information). We used the IC_{50} values as a guidepost for concentrations of each reaction component to use in the *E. coli* culture. Most substrates had IC_{50} values in the low mM, potentially due to the small aryl rings passing through the cell wall and interfering with the DNA double helix.[38] 3-Chloro-L-tyrosine (**4**), however, had an IC_{50} value of 180 mM, about a 10-fold higher concentration than the optimized reaction conditions of the 20 mM substrate (Table 1). Therefore, **4** was chosen as the substrate to test the bacterial compatibility of the overall reaction.

From the IC_{50} determinations, we discovered that ammonium formate was the culprit causing cell death in our optimized conditions (134 mM vs 480 mM). We adjusted the amount of ammonium formate to 140 mM and scaled the amount of the substrate so the ratio between ammonium formate and the substrate remained consistent. A similar adjustment to the amount of Pd/C from 0.2 to 0.07 mg/mL unfortunately led to a decrease in conversion to **5**, from >99% to 25% over 48 h. Upon increasing the amount of Pd/C to the

IC$_{50}$ value (0.5 mg/mL), full conversion to dechlorinated product **5** (Figure 3A,B) was restored.

Cell viability and health assays showed growth in the overall reaction as well as in each control culture of the individual reaction component. No cell growth was observed in the M9 minimal media control without addition of *E. coli* starter culture (Figure 3C). To our knowledge, this is the first biocompatible hydrodechlorination reaction reported.

The relatively low toxicity of solid-supported catalyst Pd/C over homogeneous PdCl$_2$ allows for additional catalyst loading to maintain efficiency at low substrate levels; this is important as chlorinated pollutants, like those shown in Figure 1A, exist in low concentrations in both wastewater influent and our water supply (ranging up to 6 μg/L).[39] Initial experiments decreasing substrate concentration have been successful and have only been restricted by the lower detection limits of our current instrumentation. Compared to **4**, 2,6-dichlorophenol is more toxic with an IC$_{50}$ value of 1.2 mM (194 mg/L). When 2,6-dichlorophenol was subjected to the optimized biocompatible reaction conditions (Figure 3) but at 1.2 mM of the substrate, 10-fold less than the concentration of **4**, conversion to the dechlorinated product was maintained.

In some WWTFs, aryl chlorides are removed by absorption onto activated carbon and/or degradation through ozonolysis.[40] However, the energy requirements for these processes, in addition to operating costs and facilities, are prohibitive for communities with fewer resources.[41] Many WWTFs rely solely on microbial degradation to remove small-molecule pollutants. Aerobic microbial degradation takes place over an optimal timespan of 18 h, though can range from 6 to 24 h,[42] with a reaction time of 48 h; we are near a time range for these reactions to be utilized in these systems. By developing a biocompatible hydrodehalogenation reaction, we are one step closer to increasing the degradation efficiency of aryl chlorides by integrating the reaction into facilities that rely on microbial degradation.

CONCLUSIONS

We have reported the first known biocompatible hydrodechlorination reaction that gives complete conversion of chlorinated aryl compound, 3-chloro-L-tyrosine **4** to the dechlorinated derivative, L-tyrosine **5**, with conditions that allow for bacterial growth and survival. This reaction was optimized by determining the toxicity of each reaction component to *E. coli* and scaling the reaction near or under the IC$_{50}$ value of each. By designing the reaction to be compatible with bacterial growth and survival, we designed a reaction with an aqueous solvent, at ambient pressure, moderate temperature, neutral pH, and without toxic by-products.

Future studies include recycling the catalyst, using earth-abundant metal catalysts in place of palladium, and working with a more complex microbial community to track the decomposition of environmentally persistent aryl halides after the hydrohalogenation reaction.

EXPERIMENTAL SECTION

General Procedure for Hydrodehalogenation in Aqueous Media. Under a sterile field, a 10 mL culture tube was charged with M9 minimal media (5 mL), substrate (0.10 mmol, 1.0 equiv), ammonium formate (63 mg, 1.2 mmol, 12 equiv), and 5 wt % Pd/C (1 mg, 0.2 mg/mL). After

addition, the culture tube was capped and the mixture was shaken at a 60° angle in an aerated incubator at 37 °C and 210 rpm. After 24 h, an additional aliquot of Pd/C (1 mg, 0.2 mg/mL) and ammonium formate (63 mg, 1.2 mmol) was added to the reaction mixture under a sterile field. The reaction tube was placed back in the incubator to shake for additional 24 h. At various timepoints, an aliquot (100 μL) of the resulting mixture was added to an Eppendorf tube, with a 1:1 mixture of acetonitrile and water (900 μL), vortexed, and filtered (0.2 μm) into a vial for HPLC analysis to determine percent conversion.

Dehalogenation Procedure in the Presence of *E. coli*. Into a sterile 10 mL polystyrene culture tube were added M9 minimal media (2.5 mL) and starter culture of *E. coli* (2.5 mL, OD 1.0). To the resulting culture, were added 5 wt % Pd/C (1.75 mg, 2.5 mg/mL), ammonium formate (56.5 mg, 0.90 mmol, 6 equiv), and 3-chloro-L-tyrosine (**4**, 32 mg, 0.15 mmol, 1.0 equiv). The culture tube was capped to allow oxygen exchange for aerobic growth of *E. coli* and placed into an orbital shaker incubator at 37 °C, shaking at 210 rpm. After 24 h, an additional aliquot of Pd/C (1.75 mg, 2.5 mg/mL) and ammonium formate (56.5 mg, 0.9 mmol) was added to the reaction mixture under sterile field. The reaction tube was placed back in the incubator to shake for an additional 24 h. HPLC timepoints were made at 24, 26, and 48 h to determine percent conversions. Cell plate assays were done at 24 and 48 h to determine toxicity. After a total reaction time of 48 h, the culture was cooled to room temperature and 6 M NaOH was added until pH >10. The solution was then filtered through a 0.2 μm filter. The filtrate was stirred and 6 M HCl was added dropwise until pH <4. The acidified solution was concentrated *in vacuo*. The resulting residue contained products and M9 salts. To the resulting residue was added 20% NaOD in D$_2$O. The solution was transferred to a conical tube, centrifuged at 13.4 rpm for 10 min, and the supernatant was transferred to the NMR tube for analysis. Both ^{1}H NMR and HPLC analyses showed complete conversion to L-tyrosine (**5**) at 48 h.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c01204.

> Detailed procedures and methods for media preparation, substrate screen, IC$_{50}$ measurements, procedure with *E. coli*, biocompatibility measurements, IC$_{50}$ data, and conversion data for all substrates with HPLC chromatographs and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) Bellina, F.; Rossi, R. Transition Metal-Catalyzed Direct Arylation of Substrates with Activated sp3-Hybridized C−H Bonds and Some of Their Synthetic Equivalents with Aryl Halides and Pseudohalides. *Chem. Rev.* **2010**, *110*, 1082−1146.

(2) Buchwald, S.; Mauger, C.; Mignani, G.; Scholz, U. Industrial-Scale Palladium-Catalyzed Coupling of Aryl Halides and Amines −A Personal Account. *Adv. Synth. Catal.* **2006**, *348*, 23−39.

(3) Brennführer, A.; Neumann, H.; Beller, M. Palladium-Catalyzed Carbonylation Reactions of Aryl Halides and Related Compounds. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114−4133.

(4) Juhler, R. K.; Sorensen, S. R.; Larsen, L. Analysing transformation products of herbicide residues in environmental samples. *Water Res.* **2001**, *35*, 1371−1378.

(5) Fang, W.-Y.; Ravindar, L.; Rakesh, K. P.; Manukumar, H. M.; Shantharam, C. S.; Alharbi, N. S.; Qin, H.-L. Synthetic approaches and pharmaceutical applications of chloro-containing molecules for drug discovery: A critical review. *Eur. J. Med. Chem.* **2019**, *173*, 117−153.

(6) Grushin, V. V.; Alper, H. Transformations of Chloroarenes, Catalyzed by Transition-Metal Complexes. *Chem. Rev.* **1994**, *94*, 1047−1062.

(7) Boyd, E. M.; Killham, K.; Wright, J.; Rumford, S.; Hetheridge, M.; Cumming, R.; Meharg, A. A. Toxicity Assessment of Xenobiotic Contaminated Groundwater Using Lux Modified Pseudomonas Fluorescens. *Chemosphere* **1997**, *35*, 1967−1985.

(8) Meharg, A. A.; Wright, J.; Osborn, D. Chlorobenzenes in Rivers Draining Industrial Catchments. *Sci. Total Environ.* **2000**, *251−252*, 243−253.

(9) Oliver, B. G.; Nicol, K. D. Chlorinated Contaminants in The Niagara River. *Sci. Total Environ.* **1984**, *39*, 57−70.

(10) Oliver, B. G.; Nicole, K. D. Chlorobenzenes in Sediments, Water, and Selected Fish from Lakes Superior, Huron, Erie, and Ontario. *Environ. Sci. Technol.* **1982**, *16*, 532−536.

(11) Oaks, J. L.; Gilbert, M.; Virani, M. Z.; Watson, R. T.; Meteyer, C. U.; Rideout, B. A.; Shivaprasad, H. L.; Ahmed, S.; Iqbal Chaudhry, M. J.; Arshad, M.; Mahmood, S.; Ali, A.; Ahmed Khan, A. Diclofenac residues as the cause of vulture population decline in Pakistan. *Nature* **2004**, *427*, 630−633.

(12) Yueh, M.-F.; Tukey, R. H. Triclosan: A Widespread Environmental Toxicant with Many Biological Effects. *Annu. Rev. Pharmacol. Toxicol.* **2016**, *56*, 251−272.

(13) Hites, R. A. Dioxins: An Overview and History. *Environ. Sci. Technol.* **2011**, *45*, 16−20.

(14) Garba, Z. N.; Zhou, W.; Lawan, I.; Xiao, W.; Zhang, M.; Wang, L.; Chen, L.; Yuan, Z. An overview of chlorophenols as contaminants and their removal from wastewater by adsorption: A review. *J. Environ. Manage.* **2019**, *241*, 59−75.

(15) Jandhyala, S. M.; Talukdar, R.; Subramanyam, C.; Vuyyuru, H.; Sasikala, M.; Reddy, D. N. Role of the normal gut microbiota. *World J. Gastroenterol.* **2015**, *21*, No. 8787.

(16) Beil, S.; Happe, B.; Timmis, K. N.; Pieper, D. H. Genetic and biochemical characterization of the broad spectrum chlorobenzene dioxygenase from Burkholderia sp. strain PS12 - Dechlorination of 1,2,4,5-tetrachlorobenzene. *Eur. J. Biochem.* **1997**, *247*, 190−199.

(17) Tanaka, A.; Fuku, K.; Nishi, T.; Hashimoto, K.; Kominami, H. Functionalization of Au/TiO$_2$ Plasmonic Photocatalysts with Pd by Formation of A Core−Shell Structure for Effective Dechlorination of Chlorobenzene under Irradiation of Visible Light. *J. Phys. Chem. C* **2013**, *117*, 16983−16989.

(18) Enthaler, S.; Company, A. Palladium-catalysed hydroxylation and alkoxylation. *Chem. Soc. Rev.* **2011**, *40*, 4912−4924.

(19) Sorokin, A.; De Suzzoni-Dezard, S.; Poullain, D.; Noel, J.-P.; Meunier, B. CO$_2$ as the Ultimate Degradation Product in the H$_2$O$_2$ Oxidation of 2,4,6-Trichlorophenol Catalyzed by Iron Tetrasulfophthalocyanine. *J. Am. Chem. Soc.* **1996**, *118*, 7410.

(20) Alonso, F.; Beletskaya, I. P.; Yus, M. Metal-Mediated Reductive Hydrodehalogenation of Organic Halides. *Chem. Rev.* **2002**, *102*, 4009.

(21) Nguyen, D. P.; Nguyen, H. T. H.; Do, L. H. Tools and methods for investigating synthetic metal-catalyzed reactions in living cells. *ACS Catal.* **2021**, *11*, 5148−5165.

(22) Destito, P.; Vidal, C.; López, F.; Mascareñas, J. L. Transition Metal-Promoted Reactions in Aqueous Media and Biological Settings. *Chem. − Eur. J.* **2021**, *27*, 4789−4816.

(23) Sirasani, G.; Tong, L.; Balskus, E. P. A Biocompatible Alkene Hydrogenation Merges Organic Synthesis with Microbial Metabolism. *Angew. Chem., Int. Ed.* **2014**, *53*, 7785−7788.

(24) Wallace, S.; Balskus, E. P. Interfacing Microbial Styrene Production with a Biocompatible Cyclopropanation Reaction. *Angew. Chem., Int. Ed.* **2015**, *54*, 7106−7109.

(25) Bose, S.; Ngo, A. H.; Do, L. H. Intracellular Transfer Hydrogenation Mediated by Unprotected Organoiridium Catalysts. *J. Am. Chem. Soc.* **2017**, *139*, 8792−8795.

(26) Coverdale, J. P. C.; Romero-Canelón, I.; Sanchez-Cano, C.; Clarkson, G. J.; Habtemariam, A.; Wills, M.; Sadler, P. J. Asymmetric Transfer Hydrogenation by Synthetic Catalysts in Cancer Cells. *Nat. Chem.* **2018**, *10*, 347−354.

(27) Domaille, D. W.; Hafenstine, G. R.; Greer, M. A.; Goodwin, A. P.; Cha, J. N. Catalytic upgrading in bacteria-compatible conditions via a biocompatible aldol condensation. *ACS Sustainable Chem. Eng.* **2016**, *4*, 671−675.

(28) Stewart, K. N.; Hicks, E. G.; Domaille, D. W. Merger of Whole Cell Biocatalysis with Organocatalysis Upgrades Alcohol Feedstocks in a Mild, Aqueous, One-Pot Process. *ACS Sustainable Chem. Eng.* **2020**, *8*, 4114−4119.

(29) Liu, L.; Zhang, X.; Wang, Z. Highly Efficient Production of Tailored *Monascus* Pigments by Using a Biocompatible Chemical Reaction Interfacing with Microbial Metabolism. *ACS Sustainable Chem. Eng.* **2021**, *9*, 3347−3356.

(30) Rubini, R.; Ivanov, I.; Mayer, C. A Screening Platform to Identify and Tailor Biocompatible Small-Molecule Catalysts. *Chem. − Eur. J.* **2019**, *25*, 16017−16021.

(31) Xia, C.; Liu, Y.; Zhou, S.; Yang, C.; Liu, S.; Xu, J.; Yu, J.; Chen, J.; Liang, X. The Pd-catalyzed hydrodechlorination of chlorophenols in aqueous solutions under mild conditions: A promising approach to practical use in wastewater. *J. Hazard. Mater.* **2009**, *169*, 1029−1033.

(32) Sadler, J. C.; Dennis, J. A.; Johnson, N. W.; Wallace, S. Interfacing non-enzymatic catalysis with living microorganisms. *RSC Chem. Biol.* **2021**, *2*, 1073−1083.

(33) Wallace, S.; Schultz, E. E.; Balskus, E. P. Using non-enzymatic chemistry to influence microbial metabolism. *Curr. Opin. Chem. Biol.* **2015**, *25*, 71−79.

(34) Keane, M. A. Supported Transition Metal Catalysts for Hydrodechlorination Reactions. *ChemCatChem* **2011**, *3*, 800−821.

(35) Mehinto, A. C.; Hill, E. M.; Tyler, C. R. Uptake and biological effects of environmentally relevant concentrations of the nonsteroidal anti-inflammatory pharmaceutical diclofenac in rainbow trout (*Oncorhynchus mykiss*). *Environ. Sci. Technol.* **2010**, *44*, 2176−2182.

(36) Nakao, R.; Rhee, H.; Uozumi, Y. Hydrogenation and Dehalogenation under Aqueous Conditions with an Amphiphilic-Polymer-Supported Nanopalladium Catalyst. *Org. Lett.* **2005**, *7*, 163−165.

(37) Anwer, M. K.; Sherman, D. B.; Roney, J. G.; Spatola, A. F. Applications of Ammonium Formate Catalytic Transfer Hydrogenation. 6. Analysis of Catalyst, Donor Quantity, and Solvent Effects upon the Efficacy of Dechlorination. *J. Org. Chem.* **1989**, *54*, 1284−1289.

(38) Prakash, A. S.; Denny, W. A.; Gourdie, T. A.; Valu, K. K.; Woodgate, P. D.; Wakelin, L. P. DNA-directed alkylating ligands as potential antitumor agents: sequence specificity of alkylation by intercalating aniline mustards. *Biochemistry* **1990**, *29*, 9799−9807.

(39) Krzmarzick, M. J.; Novak, P. J. Removal of chlorinated organic compounds during wastewater treatment: achievements and limits. *Appl. Microbiol. Biotechnol.* **2014**, *98*, 6233−6242.

(40) Eggen, R. I. L.; Hollender, J.; Joss, A.; Schaerer, M.; Stamm, C. Reducing the Discharge of Micropollutants in the Aquatic Environment: The Benefits of Upgrading Wastewater Treatment Plants. *Environ. Sci. Technol.* **2014**, *48*, 7683−7689.

(41) Owen, R.; Jobling, S. Environmental science: The hidden costs of flexible fertility. *Nature* **2012**, *485*, 441.

(42) Boonnorat, J.; Kanyatrakul, A.; Prakhongsak, A.; Honda, R.; Panichnumsin, R.; Boonapatcharoen, N. Effect of hydraulic retention time on micropollutant biodegradation in activated sludge system augmented with acclimatized sludge treating low-micropollutants wastewater. *Chemosphere* **2019**, *230*, 606−615.