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(PSEUDO)PHASE TUNING IN THE SERVICE OF SYNTHESIS:
TECHNOLOGIES FOR SUSTAINABLE CATALYSIS

By

Justin Douglas Smith
B.S., University of Kansas, 2011
M.S., University of Louisville, 2019

A Dissertation
Submitted to the Faculty of the
College of Arts and Sciences of the University of Louisville
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in Chemistry

Department of Chemistry
University of Louisville
Louisville, Kentucky

August 2020

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A Dissertation Approved on

July 30, 2020

by the following Dissertation Committee

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Dr. Fabrice Gallou

DEDICATION

In memory of Brandon Smith

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which most prominently included the space dedicated to the memory of Dr. Gibson. Although I did not have the good fortune to know Dr. Gibson, conversation with some who did has added to the impression that Dr. Gibson was an outstanding and dedicated scientist. I did, however, have the good fortune to work in what was once Dr. Gibson's laboratory space, and even the selection and organization of glassware—which is often inscribed with “D.H.G.”—reinforces this impression.

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ABSTRACT

(PSEUDO)PHASE TUNING IN THE SERVICE OF SYNTHESIS:
TECHNOLOGIES FOR SUSTAINABLE CATALYSIS

Justin D. Smith

July 30, 2020

Strategies for manipulation of chemical phases were explored with emphasis on synthetic chemistry applications. Some strategies are fairly divergent from their origin, but all ultimately began from investigations of micellar media. Accordingly, Chapter 1 reviews the historical development of micellar catalytic processes.

Chapters 2 and 3 detail development of synthetic methods in micellar solutions of designer surfactant PS-750-M. PS-750-M was designed to create benign micellar solutions which effectively mimic toxic organic solvents; it contains a proline-based linker between its hydrophobic and hydrophilic regions which imparts increased polarity to the micellar core. Chapter 2 details an interfacial nucleophilic substitution of perfluoroarenes by sulfinate salt nucleophiles. Chapter 3 covers the development of sustainable, operationally simple conditions for palladium-catalyzed arylation of polar nitroalkanes. Both reactions were selected for the significant polarity differences between the coupling partners involved. Successful development of these methods thus helped to validate the original surfactant design strategy while also elucidating

PS-750-M's properties.

Chapter 4 extends upon the work presented in Chapter 3 but ultimately focuses on manipulation of non-micellar phases for the sequestration of halides and concomitant enhancement the nitroalkane arylation. Halides are common byproducts of coupling reactions, but they can also inhibit catalysts. Tetramethylammonium chloride and similar compounds were explored as halosequestrants. The influence of the reaction medium on sequestration was explored. In particular, tetramethylammonium chloride was found to form a beneficial supramolecular hydrate structure when used with specific relative loadings of K_3PO_4 and water. Leveraging these phase manipulations, nitroalkane arylation was made to proceed ten times faster with only one tenth the catalyst loading.

Chapter 5 explores the properties and applications of a polymeric photocatalyst. Low-molecular-weight polymer was prepared in a micellar medium. High-molecular-weight polymer remained solution-processable and could be applied as a surface coating. Irradiation of the “backside” catalyst face not in contact with the reaction mixture proved viable, thereby enabling new approaches to photocatalysis which may resolve industrial scalability issues. Benchmarking showed the polymer was superior to small-molecule organophotocatalysts. Synthesis of small-molecule models of polymer substructures revealed that the motif of dual chromophores in fixed proximity was key to the enhanced catalytic activity.

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CHAPTER 1

THE HISTORICAL DEVELOPMENT OF MICELLAR CATALYTIC PROCESSES

Micellar catalysis has been described by Romsted and coworkers as a “useful misnomer” on the basis that reaction rate enhancements observed in the presence of amphiphile aggregates might be more precisely described as acceleration and because for some reaction systems micellar media can actually have an inhibiting effect.¹ In a similar spirit, the present review draws a distinction between a “micellar catalysis process” (a process involving rate acceleration by amphiphile aggregates) and a “micellar catalytic process” (a catalytic process executed in a micellar medium). The latter is the subject of this review, and the distinction is meaningful. Although the potential of a micellar medium for sophisticated process design has been appreciated since the inception of the field,² for many years the prevailing practical interest in micellar media for organic chemistry has been the namesake rate enhancement. Today, however, rate enhancement is but one of many reliably achievable benefits with a micellar medium.³

The recycle study by Handa et al.⁴ (Figure 1.1) provides a compelling illustration: a Suzuki–Miyaura cross-coupling of heterocyclic partners **1** and **2** was performed in a 2 wt% aqueous solution of Nok designer surfactant;⁵ the sophisticated, micelle-complementary HandaPhos ligand enabled full conversion in 24 h at 25 °C with a mere 0.1 mol% palladium loading; precipitation of product **3** was induced by dilution with water; and isolation of **3** was accomplished in 90 % yield by simple filtration with aqueous surfactant and water washes. With this approach, an appropriate

Figure 1.1: Catalyst and medium recycling in a micellar catalytic process. Adapted from Handa et al.⁴

volume of the recovered reaction medium could be readjusted to the original surfactant and catalyst concentrations, and consistent results were observed in four subsequent reaction cycles. This process is noteworthy in several regards. Reaction conditions are optimally mild, and the reaction can be performed without expense of energy in temperature control, yet catalysis is still efficient. Organic solvents are completely avoided. Neither coupling partner is used in excess. Micelles are formed from β -sitosterol methoxypolyethyleneglycol succinate, an amphiphile which is “benign by design”⁶ in that it is readily obtained from economical and environmentally benign feedstocks.⁵ The rationally designed lipophilic ligand complements the medium by promoting localization of the catalyst to the nonpolar micellar core. The catalyst loading is an order of magnitude lower than comparable conventional implementations of the reaction. Both catalyst and the reaction medium are readily recovered for reuse in either the same coupling, a coupling of different reaction partners, or even a different class of coupling reaction entirely (e.g., Sonogashira cross-coupling⁷). Finally, although the efficacy of this reaction system has been demonstrated with a broad and complex scope of coupling partners,^{4,7} it should be noted that not all products will be

as amenable to precipitation and filtration, and the process illustrated in Figure 1.1 was designed with an awareness of the significance of product solubility.

Thus, the advantages of such a process over a traditional organic-solvent-based approach are independently substantial. Although rate enhancement arising from micellar catalysis phenomena are certainly welcome, there are most certainly other valuable points of interest in this process. Accordingly, this review is focused on the strategic design and manipulation of the micellar pseudophase to enable otherwise inaccessible reactivities, selectivities, and processing advantages.

In the excitement surrounding the emergence of micellar processes as a viable or even vital answer to the sunseting use of toxic workhorse organic solvents,⁸ it is easy (though certainly not intended) for one to lose sight of the older, foundational developments in related subdisciplines which set the stage for this possibility. This history is well represented in comprehensive reviews of the field’s advancement which have appeared throughout the years,^{3,9–14} but the field is at a stage where it may benefit from a narrative representation of its roots with a mind toward its future. This is partly appropriate given the current “mission-oriented” posture of the field as it seeks to provide a means through which chemistry might adapt to modern sustainability goals. Such a narrative is not a substitute for the deeper coverage of prior reviews, and it will inevitably fail to include adequate mention of many of the contributors to this broad and growing area. However, focus provided by a unifying narrative can be useful in concisely conveying the essence of the field to new audiences. To the extent justified by the practical efficacy of micellar technologies in meeting sustainability goals and the needs of other disciplines, such “evangelism” to outside audiences is defensible. Certainly such narratives exist for a similar purpose in other fields.

Furthermore, concise reconsideration of the development of the field may be of use to currently involved researchers moving into the untamed frontiers of rational

process design. Establishment of micellar reaction systems as robust, practical, general, and broadly adopted reaction systems may be viewed as the current and possibly penultimate stage of the developmental narrative. This stage was preceded by inception of the field, exploration and modeling of the underlying principles, development of practical application, and preliminary refinement toward the robustness and generality needed for wide adoption. The future of the field appears to reside in establishing and modularizing the lessons learned throughout the development of micellar reaction media and rationally using these lessons to solve specific problems and enable new possibilities. Remarkably, the essence of this destiny was present from the very beginning.

1.1 The Twitchell Process as the Origin and Archetype of Micellar Process Design

According to early reviews by Cordes and Dunlap,^{13,14} the origins of micellar catalysis date to the turn of the 20th century with the Twitchell process² (Figure 1.2). The Twitchell process is remarkable not only as the first application of micellar catalysis to an organic reaction, but also as an exemplar of process design considerations. Having ultimately been supplanted beginning in the late 1940s by the Colgate-Emery process,¹⁵ the Twitchell process is less widely known today but was revolutionary in its time and helped earn Twitchell the Perkin Medal in 1917.^{16–20} Prior to the invention of the Twitchell process, industrial hydrolysis of fats and oils was predominantly accomplished by alkaline or autoclave processes; a process with sulfuric acid was known as well, but all three approaches had significant disadvantages (Figure 1.2a,b).¹⁸

Use of a Twitchell reagent (a sulfonic acid amphiphile; Figure 1.2c) results in micellization with the polar functionalities of both the reagent and the triglycerides localized to the micelle interface, thereby promoting Brønsted catalysis. Consequently,

Figure 1.2: Overview of the Twitchell process. **a** Shortcomings of hydrolysis methods in use before the Twitchell process. **b** Illustration of the micellar nature of the Twitchell process and the resultant advantages over earlier technologies. **c** First and second generations of the Twitchell reagent. The second generation reagent is more stable and more easily prepared. **d** A picture of Ernst Twitchell at the time of receiving the Perkin Medal. Taken from Chandler.¹⁶

the process can be operated at atmospheric pressure and less than 100 °C. At the end of the reaction, the fatty acids are allowed to separate from the aqueous layer which retains the catalyst. The aqueous layer is then collected, and the catalyst is precipitated with the addition of a calcium oxide base. The resultant fatty acids were obtained in high yield and purity (suitable for use by candle and soap manufacturers without further purification), and the crude glycerine was highly attractive to refiners as it was not contaminated with salts. The process was conducted in economical wooden vats that were readily scaled to any size, and the recovered catalyst could readily be regenerated with strong acid for reuse. Accordingly, a number of parallels are evident between the advantages of the Twitchell process and recently developed processes such as the micellar coupling reaction presented in Figure 1.1, including with respect to higher yields, lower temperatures, “generational” advancement of tailored amphiphiles, enhanced recyclability, and simplified/more sustainable purification.

Academic and industrial research environments are sometimes perceived as having

complimentary differences in their balance of priorities; in this stereotypical simplification, industry is viewed as placing a higher relative priority on finding commercially valuable answers compared understanding the fundamentals of the answers; the inverse is implied for academia. Obviously “priority” is a crucial word here, since scientists simultaneously value practical significance, rigor, invention, and truth-seeking curiosity regardless of their specific station. Although an initial impulse might be to categorize Twitchell into “the industrial caste” given the great industrial significance of his work, the weakness of such a stereotype quickly becomes evident. According to Langmuir, * “Twitchell’s work has been characterized by a sound appreciation of the work of physical and organic chemists and his analytical and technical methods have been worked out, not empirically, but from theoretical premises.”¹⁸

1.2 Early Developments in Micellar Catalysis

Although the Twitchell process provided a substantial starting point for micellar catalysis and process design, the underlying chemical mechanism of the process was not yet understood, and the field remained in its infancy until the beginning of the 1960s.^{13,14} An important report during this period of infancy was Hartley’s “sign rule” analysis on the behavior of different classes of indicators at varying acidities in cationic or anionic aqueous micelles (Figure 1.3a).²³ This work provided a qualitative conceptualization of micellar localization effects and was the forerunner of future

* Arthur C. Langmuir, older brother of Irving Langmuir (the 1928 Perkin Medalist, 1932 Nobel Laureate, and namesake of the ACS interface science journal). Nine years Irving’s senior, Arthur had helped a nine-year-old Irving set up his first chemistry lab in the family cellar.²¹ While an undergraduate at Columbia’s School of Mines, Irving did not participate in university-connected extracurricular activities, opting instead to take a more independent path: Irving spent his time apart from his normal university curriculum engaged in such activities as attending evening organic chemistry classes instructed by Arthur for Pratt Institute alumni, and, according to Arthur, “On Saturdays, [Irving] worked on research toward the improvement in analytical methods at my laboratory with Ricketts and Banks and later in Brooklyn did some excellent work on the specific gravity of pure glycerol” during this time.²¹ Given the closeness between the two brothers, it is interesting to note that Arthur had given the address “The Twitchell Process and the Glycerine Trade”¹⁸ as a representative of that industry during Twitchell’s Perkin award ceremony, particularly considering Irving’s contemporary interest and work in interfacial monolayers of, e.g., fatty acids.²²

work by solution kineticists. Hartley selected ionic surfactants which were the salts of strong acids and bases and would therefore have little effect on buffer solution pH. Micellar effects were so great that apparent shifts as large as 1.5 pH units were observed. For indicator dyes studied at the transition between cationic and dicationic forms (e.g., malachite green), micellar binding was limited to the anionic sodium cetylsulfonate (SCS) micelles. The inverse was true of anionic/dianionic dyes (e.g., bromothymol blue), which could bind to cationic micelles. Dyes with a neutral (e.g., neutral red) or zwitterionic (e.g., methyl red) state at the pH examined could bind to both cationic and anionic micelles. Thus, the binding was predominantly controlled by charge rather than other structural features of the dye. The direction of apparent pH shift was less clear-cut, and other structural features of the dye appeared to have influence; nevertheless, the shift was almost exclusively alkaline for cationic micelles and was predominantly acidic for anionic micelles. Differences in the surfactant head groups may have contributed to greater variance in the direction of pH shift for the anionic surfactant. Sodium cetanesulfonic acid (SCS), the anionic surfactant, possessed a highly polar headgroup which would position its negative charge directly at the micelle–water interface. For the cationic surfactants, the methyl groups of cetyltrimethylammonium bromide (CTAI) and (to a lesser extent) the hydrocarbon arene component of cetylpyridinium bromide (CPB) resulted in hydrophobic moieties being placed at the micelle–water interface. This assumption is consistent with the lesser number of dyes with binding to CTAI compared to CPB. A subsequent report by Roe and Hartley presented an equation using ζ -potential to relate the pH in bulk solution to the pH on the surface of a colloidal particle.²⁴ Roe and Hartley further noted that the interfacial concentration of ionic species provided grounds for explaining the efficacy of the Twitchell process compared to the inefficacy of an alkaline ester hydrolysis conducted in anionic micelles. Similarly, the pH shifts of the indicator dyes was suggested to be predominantly attributable to localization of the dye to the

micelle–water interface where the pH differed from bulk solution as a consequence of the ζ -potential.

Figure 1.3: The “sign rule” proposed by Hartley rationalized the behavior of pH-sensitive dyes in micellar solutions of cationic or anionic surfactants.

Advances were also made during this period toward the synthetic application of micellar systems. One of the earliest synthetic applications of micellar catalysis was Lorand’s etherification of cellulose (Figure 1.4a).²⁵ Lorand observed that with the inclusion of the anionic surfactant sodium oleate in the aqueous etherification of cellulose with benzyl chloride, “conversion is increased to a great extent, but the effect is not proportional to the amount used.” This non-proportionality strongly indicates a micellar catalysis effect upon exceeding the critical micellar concentration (cmc). Some of the earliest instances of a catalyst being enhanced by a micellar medium occurred in the domain of enzymatic catalysis. Krebs and Hughes were among the first to report this phenomenon; they conducted studies with cetyltrimethylammonium bromide (CTAB) using bacterial glutamic decarboxylase and glutaminase initially with intact cells and then later with cell-free extracts.^{26–28} Because the enhancement occurred with both intact cells and cell extracts, it could not be explained simply in

terms of enhanced cell membrane permeability. It was postulated that the beneficial effect of CTAB arose from removal of a competitive inhibitor, which would make this process one of the first to beneficially employ micellar shielding. The excluded competitive inhibitor explanation was consistent with observed kinetics and the fact that a variety of other decarboxylase enzymes were not enhanced by the micellar conditions employed. A more extensive screening of surfactants revealed that the optimum rate consistently coincided with surfactant concentrations matching the cmc, but only with cationic surfactants; anionic and nonionic surfactants provided no benefit. Hughes discounted the possibility of the micellar system increasing the concentration of substrate in proximity to the enzyme partly on the basis that “transport of material by surface-active agents has been demonstrated only in the case of lipophilic substances” at that point in time.

In one experiment the presence of CTAB was found to accelerate the action of bacterial decarboxylase and broaden the optimum of the pH curve.(Figure 1.4b) Acceleration by CTAB was greatest at a pH of 4.1, which was incidentally the optimum pH when using intact cells without CTAB; for the cell extracts without CTAB, the optimum pH was 4.6. It is interesting to consider that (1) CTAB broadened the optimum pH peak and shifted it to a more acidic value, (2) the effect of CTAB switched from acceleration to inhibition above a pH of 4.8, and (3) added methyl orange resulted in an orange solution below the CTAB cmc and a yellow solution above the cmc (an apparent alkaline indicator shift). Given that methyl orange is somewhat surfactant-like in structure—possessing a sulfonate moiety on the opposite end of where positive charge localizes in the zwitterionic form—one possibility for the alkaline color shift other than ζ -potential alteration of surface pH (which may have decreased significance compared to other dyes given that the sulfonate will be oriented toward the micellar exterior) is that a substantial amount of methyl orange aggregates within the micelles where the acid-sensitive functionalities are shielded, resulting in an

apparent alkaline shift irrespective of the surface pH. Such an orientation would be consistent with recent molecular dynamics studies.²⁹ In a similar manner, perhaps the significance of the optimum pH range for cell extracts with CTAB relates to the middle pK_a of glutamic acid (ca. 4.3³⁰); at a pH of 4.3 the zwitterionic and monoanionic forms of glutamic acid are in roughly equal abundance, and a monoanionic species can favorably bind to the micelle followed by protonation to the zwitterionic form which is more suitable for the micellar interior. At the very least, the transition to micellar inhibition of the reaction above a pH of 4.8 coincides with departure from the buffer region surrounding the glutamic acid middle pK_a (i.e., equilibrium shifts ever more rapidly toward the monoanionic species of glutamic acid).

Earlier work in the area of micellar enzymatic catalysis, such as by Bodine and Carlson, is also noteworthy.³¹ In the wake of prior work showing that sodium oleate was a viable activator to convert protyrosinase into tyrosinase, Bodine and Carlson explored other surfactants as well. The curves presented in Figure 1.4c were supposed to exhibit a “definite critical or maximum concentration above which further addition of activator to constant enzyme concentration produces no change in reaction rate.” However, although all three anionic surfactants proved viable as activators, sodium dodecyl sulfate (SDS) in particular deviated from the expected trend. The deviation was speculated as being a consequence of “toxic effects of the reagent on the reaction,” but perhaps a micellar effect is actually involved in addition to the activation of protyrosinase.

1.3 Coalescence of the Field: Theoretical Foundation and Expansion

Duynstee and Grunwald’s report on micellar reaction kinetics using the alkaline fading of dyes³² marked the beginning of a new era.¹³ The field began to take on

Figure 1.4: Early reports suggesting the future viability of micellar catalysis in synthesis. **a** Lorand successfully applied micellar catalysis to etherification of cellulose. Adapted from Lorand.²⁵ **b** Catalytic efficiency of decarboxylase with and without micellar media as a function of pH reported by Hughes. Adapted from Hughes.²⁷ **c** Activation of protyrosinase to tyrosinase by anionic surfactants reported by Bodine and Carlson; aside from generation of tyrosinase, it appears that micellar catalysis effects may also have been operative. Adapted from Carlson.³¹

a more definite shape as researchers began to study and model systematically the underlying phenomena of micellar reaction media.³³ By the end of the 1960s the field had begun to expand dramatically,³⁴ and the vigorous interest in fundamental science and exploration of new possibilities continued apace throughout the 1970s.³⁵ Interesting developments during this period include early functional surfactants,³⁶ investigations into stereoselectivity as a consequence of micellar chirality,^{37,38} and early examples of catalyst recycling.³⁵

Supplementing the conventional “in water”³⁹ approach—which is as old as chemistry itself but requires compatible solubility of reagents—the micellar approach began to emerge as a viable platform for general aqueous synthetic organic chemistry. Other platforms include the “on water,”⁴⁰ co-solvent,⁴¹ biphasic,⁴² phase transfer,⁴³ and microemulsion⁴⁴ approaches. The seminal report in this regard for micellar catalysis was by Menger and coworkers in 1975.⁴⁵ In this report, two model reactions were explored: the oxidation of piperonal to piperonylic acid by KMnO_4 and the hydrolysis of *a-a-a*-trichlorotoluene to benzoic acid by NaOH . These reactions were conducted at gram scale with the express intention of demonstrating the viability of the micellar medium for practical synthetic organic chemistry. With the oxidation of piperonal, variation of the concentration of CTAB surfactant for an otherwise fixed protocol showed higher yields with higher surfactant loadings (ranging from none to 0.01 M). A cosolvent system consisting of 20 % dioxane performed slightly better than the aqueous system but was markedly inferior to the micellar systems. With the hydrolysis of *a-a-a*-trichlorotoluene, the on water reaction reached full conversion after 60 h, whereas the reaction with cationic CTAB micelles was finished in just 1.5 h. The hydrolysis was also found to be facilitated by micelles of the nonionic surfactant Brij 35 ($\text{C}_{12}\text{H}_{25}(\text{OCH}_2\text{CH}_2)_{23}\text{OH}$; reaction time of 11 h). Brij 35 proved more effective than the phase transfer catalyst *n*- Bu_4NBr (reaction time of 15 h), suggesting that a micellar aggregation effect was more significant than ion pairing effects.

Although organic solvent still reigned supreme, successful industrial implementation of the contemporaneously better established approaches of phase transfer catalysis⁴⁶ and water-soluble organometallic catalysts⁴⁷ began to earn a foothold for practical aqueous organic synthesis, paving the way for future work in aqueous micelles. In 1981, Whitesides and coworkers reported the first instance of micellar acceleration of a reaction involving an organometallic hydrogenation catalyst.⁴⁸ More than a decade later, Oehme and coworkers reported the first micellar enhancement of both rate

and enantioselectivity for an organometallic hydrogenation,⁴⁹ which reinvigorated interest in micellar systems.⁵⁰ Jeffery’s report of Heck reactions in water using tetra-*n*-butylammonium salt additives appeared in 1994;⁵¹ although this process may not be fully understood⁵² (see Chapter 4), its use of a solubilizing additive to permit aqueous cross-coupling chemistry is defensibly regarded as a milestone in the development of modern organometallic micellar catalysis.⁵³ The first reports by Kobayashi and coworkers on the micellar Sc(OTf)₃-catalyzed allylation of aldehydes⁵⁴ and aldol reactions of silyl enol ethers⁵⁵ appeared in 1997. In spite of the significant advancements to micellar catalysis which appeared in the 20th century, by the turn of the millennium there was in some quarters a feeling of pessimism about the state and future of the field. Rausse and coworkers asserted that micellar catalysis had failed to realize the ambitious projections made by Fendler and Fendler in 1975; specifically, an optimistic challenge to emulate enzymes in terms of efficiency and selectivity appeared to be unrealistic.⁵⁶

1.4 Establishment of Robustness and Widespread Adoption

Undaunted, in the early 2000s chemists became increasingly emboldened with respect to the bounds of aqueous chemistry. Micellar dehydration reactions were reported by Kobayashi and coworkers in 2002.⁵⁷ As a consequence of their work in click chemistry where water was often found to be the optimal medium, Sharpless and coworkers expressly asserted in 2005 that water may be mistakenly disfavored by chemists and that phase boundary phenomena of aqueous heterogeneous systems should be further investigated.⁴⁰ A bellwether moment for micellar catalysis in particular was the 2009 report by Lipshutz and coworkers on Negishi couplings in aqueous surfactant without pre-formation of the organozinc reagents.^{58,59} This surprising result in conjunction

with numerous ensuing reports on robust, general, industrially viable protocols in micellar media helped to cement aqueous surfactant as a genuinely viable alternative to organic solvent.⁶⁰ In 2014, Warner was awarded the Perkin Medal for his contributions to the field of green chemistry, nearly a century after Twitchell had received the same award;⁶¹ this outcome reflected the ever-increasing importance of sustainability in modern chemistry, a development which has reignited the pursuit and expansion of what Twitchell first put into practice over 120 years ago.⁶² In 2015 Lipshutz and coworkers reported “counter-intuitive” Kumada–Grignard-type biaryl couplings on water;⁶³ although limited in scope with many products being obtained in less than 50% yield, it was surprising that such a reaction could work at all, and in some cases isolated yields were greater than 80%. Perhaps most importantly, this reaction (internally given the codename “Green Thunder”) would seem to mark the end of undue hesitation to use of water in lieu of organic solvent. With the continued development of surfactants designed to mimic effective but problematic organic solvents,^{64,65} the adoption of micellar technology is expected to continue to increase.

1.5 Conclusions

From its very beginnings in the work of Twitchell, micellar catalysis has been sophisticated in terms of both the manipulation of chemical reactions and the operational procedures. A similar focus continues today as the field looks to achieve greater sustainability with benign micellar media which partly obviate unsustainable organic solvents, increase mildness of conditions, and facilitate more efficient recycling and purification procedures. Use of micellar catalytic processes began in narrow pockets of industry before such processes were well understood, and this work served as an inspiration and foundation for subsequent scientific inquiry even after the specific industrial implementations fell into disuse. With scientific inquiry came a much greater

understanding of the underlying principles; from this work, application to practical organic synthesis began to reemerge, and the boundaries of the practical utility of micellar media began to be explored and expanded. The increased realization of “what chemists could get away with” in water coupled with greater attention to the vital interests of sustainability and environmental health culminated in the intentional design of general and robust micellar media and methodology. Presently, micellar catalytic processes are of great interest in both academia and industry, and the expanding industrial adoption⁶⁶ suggests that, in a sense, micellar process design has come full circle and returned to its original home, “360 degrees stronger” than when it left.

CHAPTER 2

MICELLAR NUCLEOPHILIC AROMATIC SUBSTITUTION OF POLYFLUOROARENES BY SULFINATE SALTS IN AQUEOUS PS-750-M

Micellar conditions were developed for nucleophilic aromatic substitution (S_NAr) of polyfluoroarenes by weak anionic sulfinate nucleophiles, as summarized in Figure 2.1. Although this process is compelling on the basis of its sustainability features (including mild conditions, recyclable reaction medium, avoidance of toxic organic solvents, and isolation of products by filtration), the chief motivation behind developing the process was to explore micellar effects related to the surfactant PS-750-M. One of the key design objectives behind PS-750-M was to create a benign aqueous micellar system which mimicked problematic polar aprotic solvents such as DMSO, DMF, DMAc and NMP. Accordingly, S_NAr was an ideal reaction class for a model process given that the polar aprotics are the most effective solvents while water is highly unsuitable.^{67,68}

2.1 Background

As discussed in Chapter 1, micellar reaction media have reemerged in the last decade as a viable alternative to problematic organic solvents in practical synthetic chemistry.^{60,66} This reemergence has recently centered on nonionic rather than ionic micellar media, with classic anionic (e.g., SDS) and especially cationic (e.g., CTAB) receiving comparatively little attention⁶⁹ compared to prior years,³ perhaps partly due to the

Figure 2.1: Overview for S_NAr with weak ionic nucleophiles and polyfluoroarenes aqueous micelles of PS-750-M

greater generality which has increasingly been attributed to nonionic systems.⁷⁰ The practical viability of S_NAr chemistry in the presently prevailing context of nonionic micellar media has only recently been established; such work has focused almost exclusively on strong neutral nucleophiles in the presence of a base.^{66,71} In the context of older, less practically oriented physical organic investigations, micellar S_NAr processes have been predominantly studied in anionic or cationic micellar media with strong anionic nucleophiles,⁷² perhaps due to the influence of earlier reports wherein nonionic micelles were found to have little effect on reaction rate.⁷³ Consequently, the exploration of a weak anionic nucleophile such as a sulfinate salt in a modern nonionic micellar medium is of value both as an underinvestigated system and also as a potentially challenging S_NAr case suitable for assessing PS-750-M's realization of its intended design principles.

Likewise, the highly lipophilic polyfluoroarenes selected as electrophiles here might be expected to exacerbate the difficulty of the reaction in a micellar medium due to their strong affinity for the nonpolar micellar core. Meanwhile, the sulfinate salt (a conjugate base of a sulfinic acid having⁷⁴ a pK_a of ca. 2) would be expected to predominantly partition into the aqueous phase, thereby disfavoring the encounter of the two reaction partners (micellar inhibition rather than catalysis). In contrast, more hydrophilic electrophiles such as nitroarenes would be expected to be more abundant

in the outer regions of the micelle, and the orientation of the polar leaving group would also favor attack from the direction of the aqueous phase. Furthermore, protic neutral nucleophiles are far more compatible with the lipophilic micellar interior than ionic species, and the displacement can occur either directly (with the leaving group abstracting the proton) or in a base-catalyzed manner.⁷⁵

Thus, by selecting reaction partners which strongly favored opposite (pseudo)phases, it would be possible to more clearly discern the impact of medium effects. However, the improved clarity provided by this selection would be of little use if the reaction was simply too difficult in a micellar medium to proceed efficiently. One approach to developing adequately effective conditions for the study would be to screen a series of viably electron deficient arenes with decreasingly extreme lipophilicity, and then to simply acknowledge the limitations of the methodology. Although this approach might be passable for theoretical purposes, (1) the resultant methodology would lack robustness, and (2) some degree of clarity would be compromised, particularly due to the inherently discontinuous and sometimes ambiguous nature of tuning substrate properties. A second, more compelling approach seemed viable in light of a report by Lipshutz and coworkers on the beneficial effects of inorganic salt additives on Heck couplings and olefin metathesis reactions in nonionic micellar media.⁷⁶ If a benign and abundant salt additive such as NaCl could improve reactivity, then other advantages might be expected as well, including that (1) the increased salinity of the aqueous phase might promote the precipitation of the resultant products for ease of isolation and (2) unlike tuning of substrate lipophilicity, NaCl concentration would be a general and continuously variable parameter for adjustment of reaction conditions.

Based on a report by Bunton and Robinson on the influence of electrolytes on the micellar S_NAr hydroxydefluorination of 2,4-dinitrofluorobenzene,⁷³ however, it was not clear that salt additives would actually be beneficial. This report found that in the absence of electrolyte additives, the reaction was greatly accelerated by

cationic CTAB micelles, retarded by anionic SDS micelles, and almost unaffected by nonionic Igepal micelles. Presumably as a consequence of this result, inhibition of micellar catalysis by electrolyte additives was only explored with cationic micelles, wherein it was found that all screened salt additives (LiCl, NaF, NaCl, NaBr, KCl, Me₄NCl, NaNO₃, MeSO₃Na, *p*-TolSO₃Na, 1-NaphSO₃Na, and *o*-C₆H₄SO₃Na) had an inhibitory effect with *p*-TolSO₃Na being the strongest inhibitor. In the context of cationic micelles, the catalytic benefit was attributed the electrostatically favorable environment provided by the surfactant head group for nucleophile aggregation and attack, which would not be applicable with a nonionic surfactant. It was further noted that inhibition was weakest for anions of high charge density and greatest for anions attached to a large hydrophobic moiety, which would facilitate binding of the anion at the micelle–water interface thereby decreasing the effectiveness of the neighboring cationic head groups. In the context of sulfinate salt nucleophiles in a nonionic micellar medium, however, this suggested that NaCl would be among the least detrimental additive options, and that conditions might be developed to favor sulfinate salt nucleophile localization to an interfacial region between more and less polar (pseudo)phases in a manner akin to the behavior to *p*-TolSO₃Na in aqueous CTAB.

Aspects of the PS-750-M design strategy are presented in Figure 2.2. PS-750-M is a nonionic surfactant derived from proline, lauric acid, and mPEG; these feedstocks are cheap and benign. The structure of PS-750-M places a DMAc-like amidic moiety in direct proximity to the hydrocarbon chain. Within micellar aggregates, it is expected that hydrocarbon chain hydrophobicity would strongly favor the depicted amide rotamer because the other rotamer would require that the hydrocarbon chain be placed in a higher polarity region outside the inner micellar core. A similar “pulling” effect from the hydrophilic chain may also have some influence on the orientation of the ester carbonyl in micellar assemblies. More importantly, the proline ring prevents

Figure 2.2: Design significance of PS-750-M substructure. **a** PS-750-M is derived from benign materials and is designed to form micelles with elevated interior polarity arising from the proline linker region. **b** Hazardous amidic and ethereal solvents in particular are mimicked by PS-750-M; although esters are relatively green solvents, the polarity and restricted conformational freedom of the ester moiety is also significant. **c** The proline linker results in a sharp “L-shaped” bend between the lipophilic and mPEG regions, which may have an impact on micelle behavior. **d** Proximity and restricted conformational freedom of the PS-750-M carbonyl groups may promote surfactant–substrate interactions.

rotation about its C–N bond and thereby holds the two polar carbonyl groups in proximity. The proline ring geometry also results in PS-750-M having an “L-Shape.” This unconventional L-shape could conceivably have an impact on the behavior of PS-750-M micelles. In particular, this geometry may aid in providing the polar proline linker region with access to the surfactant–water interface. Given the limited conformational freedom of the carbonyl groups, PS-750-M may also benefit from surfactant–substrates such as the one proposed in Figure 2.2d.

2.2 Reaction Optimization

As a benchmark for comparison, a control experiment was conducted using traditional polar aprotic reaction media, as represented by acetone, which has the highest polarity index⁷⁷ of the polar aprotic solvents ranked as Recommended by the CHEM21 Solvent

Guide.⁷⁸ The isolated yield after 4 h for the benchmark system was 52 % (Table 2.1, entry 1). As expected, the same reaction in neat water afforded no product (entry 2). Thus, in order to maximize likelihood of a positive result, the initial screen for micellar catalysis of the reaction used a 3 wt% aqueous solution of PS-750-M with acetone as a cosolvent;⁷⁹ this approach proved successful in generating a hit, albeit with a very poor yield of 9 % (entry 3). Nevertheless, omission of PS-750-M confirmed the contribution of surfactant (entry 4). As discussed in the background section, NaCl was considered as a potential additive which might (1) disfavor solubilization of **5a** in the aqueous phase, (2) promote **5a** reactivity through a common cation effect, and (3) perhaps even favor the hypothetical surfactant–substrate binding presented in 2.2d. Accordingly, 5 equiv NaCl was added to the reaction mixture with the aim of magnifying this effect, resulting in a superior 58 % yield (entry 5). Use of 10 equiv of NaCl proved to be optimal, affording product **3** in 80 % yield (entry 6). The same amount of salt in neat water produced no product (entry 7), supporting the importance of the micellar medium.

Having achieved superior reactivity to the benchmark system, our attention returned to the acetone additive. Even when no acetone additive was used, the saline micellar medium proved superior to the benchmark reaction, providing 58 % yield (entry 8). Thus, although acetone has the expected effect of boosting the yield⁷⁹ it is not required to facilitate the reaction, and this chemistry could be employed in the complete absence of any polar aprotic solvent. With the further benefit of the acetone established, however, the additive was included in subsequent reactions in order to better demonstrate the upper limits of achievable yields. In this regard, CHEM21-ranked⁷⁸ problematic solvent additives THF and DMSO were also evaluated, but acetone proved to have both superior ranking and effect (entries 9 and 10). Yields with other sodium halides (entries 11 and 12) supported the interfacial binding hypothesis and confirmed NaCl as the best choice.

Table 2.1: Optimization of additives and reaction medium for the nucleophilic aromatic substitution of polyfluoroarenes by sulfinate salts.^a

Entry	Reaction Medium ^b	Additive	% Yield ^c
1	acetone	—	52
2	water	—	0
3	3 wt% aq. PS-750-M/acetone (4:1)	—	9
4	water/acetone (4:1)	—	5
5	3 wt% aq. PS-750-M/acetone (4:1)	NaCl ^d	58
6	3 wt% aq. PS-750-M/acetone (4:1)	NaCl	76
7	water	NaCl	0
8	3 wt% aq. PS-750-M	NaCl	57
9	3 wt% aq. PS-750-M/THF (4:1)	NaCl	57
10	3 wt% aq. PS-750-M/DMSO (4:1)	NaCl	70
11	3 wt% aq. PS-750-M/acetone (4:1)	NaF	9
12	3 wt% aq. PS-750-M/acetone (4:1)	NaBr	38
13	3 wt% aq. TPGS-750-M/acetone (4:1)	NaCl	62
14	3 wt% aq. SDS/acetone (4:1)	NaCl	1
15	3 wt% aq. Pluronic F-127/acetone (4:1)	NaCl	26
16	3 wt% aq. Tween 20/acetone (4:1)	NaCl	52

^a Conditions: polyfluoroarene **4a** (0.5 mmol, 1 equiv), sodium sulfinate salt **5a** (1.2 equiv), additive (as specified if called for, 10 equiv), and the specified reaction medium (0.5 mL) were stirred in a sealed vessel under ambient atmosphere at 25 °C according to Procedure 2.1. ^b Micellar medium:acetone ratios are expressed in terms of volume. ^c Isolated yields. ^d Used at a loading of 5 equiv.

Finally, a selection of other surfactants (Figure 2.3) was also screened. Of particular interest was the surfactant TPGS-750-M, which, as previously mentioned, has been successfully employed in large number of reactions, including S_NAr with non-ionic nucleophiles. Furthermore, the TPGS-750-M mPEG region is identical to that of PS-750-M, and the TPGS-750-M succinate linker is similar to the PS-750-M region in that succinate also possesses two carbonyls spaced two atoms apart from each other. However, the succinate carbonyls lack the restriction of rotational freedom afforded by the proline ring, leading to an increase of conformations of TPGS-750-M where

Figure 2.3: Surfactants investigated in this study.

binding to sodium cations is suboptimal. Fitting with this interpretation, TPGS-750-M proved competent in facilitating the reaction, but it was not as competent as PS-750-M (entry 13). The anionic surfactant SDS proved to be even less competent than water with the same amount of acetone additive (entries 4 and 14), which suggests that the anionic SDS–water interface shields the substrates from encounter with the nucleophiles. Pluronic F-127, a nonionic triblock copolymer surfactant with comparatively long hydrophilic PEG chains separated by a hydrophobic polypropylene glycol block, provided only 26% yield (entry 15). The surfactant Tween 20 has the same lipophilic component as PS-750-M but a shorter, branched analog to the PS-750-M mPEG region without methyl end-caps and a single-carbonyl linker region. Even with branched, uncapped hydroxyl termini and the shallower PEG-like micellar exterior, however, Tween 20 proved to be less effective than PS-750-M (entry 16).

Table 2.2: Substrate scope for micellar nucleophilic aromatic substitution of polyfluoroarenes by weak anionic sulfinate salts.^{a, b}

^a Conditions: polyfluoroarene **4** (0.25 mmol, 1 equiv), sodium sulfinate salt **5** (1 equiv), NaCl (10 equiv), acetone (0.1 mL), and 3 wt% aq. PS-750-M were stirred in a sealed vessel under ambient atmosphere at 25 °C according to Procedure 2.2.

^b Yield values are for the isolated product. ^c Reaction was conducted at 45 °C.

^d Lithium sulfinate salt was used.

2.3 Implementation

2.3.1 Exploration of Substrate Scope

The standard conditions (Procedure 2.2) were based on the optimization results with a minor variation: the polyfluoroarene and sulfinate salt were used in an equimolar rather than 1:1.2 ratio. Especially when polyfluoropyridines were used, product precipitation was visibly evident. Consequently, the products could often be isolated by simple filtration, thereby avoiding organic solvent associated with extraction and column chromatography. Once complete, reactions mixtures were admixed with 1 mL deionized water to further induce product precipitation. The vessels were then centrifuged, and supernatant liquid was removed by syringe. The solid was rinsed with water (2×0.5 mL) by admixture, centrifugation, and removal of the supernatant liquid by syringe, and then residual water was removed under reduced pressure to afford the purified product. Some reactions proceeded sluggishly and were repeated with heating at 45 °C. There was considerable overlap between products which required heating **6b,f,n,y,q,x** and products which were too soluble for efficient isolation by precipitation **6b,c,j,n,q,x**. This overlap suggests that especially high polyfluoroarene lipophilicity (as with octafluorotoluene in particular) led to (1) strong binding of the starting material to the nonpolar inner micellar core, necessitating higher reaction temperature to counteract, and (2) limited product precipitation, necessitating extraction with organic solvent for product isolation.

It is noteworthy that the high volatility of the perfluoroarene compounds may have impacted yields in some cases. Trial reactions using highly volatile substrates like pentafluoropyridine (**4b**) which were set up without use of high-density PTFE to wrap the septum resulted in lower yields, indicating permeation of the compound through the rubber closure. Although the standard method was intended to demonstrate

robustness and operational simplicity, adaptation of this method to reactions involving a precious sulfinate salt and a volatile arene electrophile could warrant use of a slight excess of electrophile. Nevertheless, even with this operationally simple protocol which typically avoided extraction with organic solvent, products could generally be obtained in good-to-excellent yields. Perhaps owing to the mildness of the conditions, both in terms of temperature and reaction medium, substitution was selective for the *para* position. Furthermore, nucleophilic substitution by chloride was not observed under any circumstances.

Sulfinate salts proved viable regardless of steric and electronic features. Electron-rich (**6a,c,d,g,h,k,q,v,x**), electron-neutral (**6b,n,p,s-u**), and electron-deficient (**6e,f,i,j,l,m,r,w**) sulfinate salts were successfully employed with the standard conditions. Sulfinate salts with steric bulk in proximity to the reactive functionality (**6d,h,x**) were also used without issue. Tolerated functionalities on the sulfinate salt were found to include methoxy (**6d**), cyano (**6e,f,m,r**), fluoro (**6i,j,w**), nitro (**6l**), trifluoromethyl (**6o**), and *N*-Boc (**6u**) groups. Both aromatic (**6c,h,o**) and aliphatic (**6s-u**) heterocycles could be readily introduced through the sulfinate salt. Given the nature of the S_NAr process,⁸⁰ the electrophiles were necessarily electron deficient. Even so, a variety of different arene functionalities were explored and found to be tolerated, including nitrile (**6a,d,p,r,s**), trifluoromethyl (**6b,c,j,q,u,x**), chloro (**6e-g,t**), acetyl (**6m,n**), ester (**6v**), and formyl (**6w**) groups. Pyridine heteroaromatics were also viable (**6e-i,k,l,t**).

2.3.2 Reaction Scalability and Medium Recyclability

2.3.2.1 Adaptation to Gram Scale and Initial Investigation of Medium Recyclability

Reaction scalability and medium recyclability were also explored. First, **4c** was reacted with **5a** at 5.5 mmol scale with 10 equiv NaCl in 10 mL 3 wt% PS-750-M/acetone (4:1) (Procedure 2.3). The reaction was monitored as complete after stirring for 2 h at 25 °C. Product **6g** precipitated throughout the course of the reaction and was poorly soluble in the reaction medium. To ensure full precipitation, the mixture was diluted with 10 mL deionized water. The product was then collected over a sintered glass frit by vacuum filtration and the collected filtrate was reserved for later use in a sealed container. After two additional water washes and drying under reduced pressure, the product was obtained in 81 % yield (1.43 g). A portion of the reserved filtrate was then combined with 5 M NaCl in 6 wt% PS-750-M and acetone in a 2:1:0.4 ratio, and the synthesis of compound **6a** was used to confirm the reproducibility of the reaction with a recycled medium.

2.3.2.2 Extended Medium Recyclability Study

An extended recycle study was conducted to demonstrate the robustness of medium recycling (Procedure 2.4). All reaction cycles were conducted at 0.25 mmol scale, and reaction times established during the exploration of substrate scope were used in lieu of monitoring. Synthesis of **6k** in the “zeroth cycle” was set up according to the standard conditions used for the substrate scope (equimolar reaction partners, 10 equiv NaCl, 0.5 mL reaction medium), except that the reaction medium partly originated from the gram-scale reaction (294 μ L filtrate from the gram-scale reaction was added to the reaction vessel followed by 147 μ L 6 wt% PS-750-M and 59 μ L acetone). (Note that as a consequence of this procedure, the NaCl loading was higher than in the

substrate scope.) Upon reaction completion, the supernatant liquid was removed from the precipitate by syringe and delivered to a vessel which had been prepared for the subsequent reaction cycle. After rinsing the precipitate with water (2×0.5 mL), which was also removed by syringe, residual liquid was driven off at 80 °C. After subjecting the vessel to high vacuum, product **6k** was confirmed by ^1H NMR to have been obtained in 92 % isolated yield.

The vessel for the first recycle contained sulfinate salt **5a** prior to the addition of the reaction medium from the first cycle. Polyfluoroarene **4b** was added immediately prior to the start of the reaction. Using the same post-reaction processing as in the zeroth cycle, the product was again obtained in 92 % isolated yield. The same procedure was used in the second and third recycles, except that the pentafluorobenzonitrile (**4a**) was used as the electrophile and the reaction was allowed to run for 8 h; product **6a** was obtained in 82 % and 84 % yield. In the fourth recycle, octafluorotoluene (**4d**) was used as the electrophile, an additional 5 equiv NaCl was included in the reaction mixture, and the reaction was conducted at 45 °C. Perhaps due to the higher NaCl loading and the slight gradual decrease in total volume of liquid throughout the study, product **6q** was obtained in 82 % yield without the need for extraction with organic solvent, and the recovered medium could presumably continue to be used in subsequent cycles. A gradual buildup of sulfinate salt **4c** in the reaction medium may also have occurred and contributed to this outcome.

Based on this study, the PS-750-M amphiphile is sufficiently stable under the reaction conditions to be viable for a minimum of five reaction cycles. Admittedly, this recycle study is quite specialized since it was cleverly designed to take advantage of the specific substrate properties (polyfluoroarene volatility and sulfinate salt susceptibility to oxidation into unviable sulfonate analogues). That being acknowledged, however, the study is an interesting illustration of a process designed to have an E Factor⁸¹ which “approaches zero” by (1) direct and complete reuse of the reaction medium

and (2) collection of the product as a solid thereby avoiding extraction with organic solvent. It must be noted, however, that although recycling of micellar reaction systems has been promoted in this fashion (i.e., not including water as waste and assuming that the reaction medium can be used indefinitely) previously in the literature,⁸¹ aqueous wastestreams are non-trivial,⁶⁶ and practical realities such as evaporation and sub-quantitative yields must also be taken into consideration.

2.3.3 Condensation Oligomerization in PS-750-M

Figure 2.4: Micellar condensation oligomerization with sulfone product **6b** in aqueous PS-750-M. Conditions: **6b** (0.28 mmol, 1 equiv), **7** (2 equiv), **8** (3 equiv), and K_2CO_3 (10 equiv) were stirred in refluxing 3 wt% aq. PS-750-M for 2 h and purified according to Procedure 2.5.

The polymeric product **9** in Figure 2.4 has been reported by Du and coworkers as a polymer of intrinsic microporosity (PIM) with potential applications in membrane gas separations.⁸² As discussed in Chapter 5, we have also discovered that such PIMs are outstanding photoredox catalysts. Although any of the sulfone products could be used to create PIMs of the same style using typical anhydrous conditions, the opportunity was taken to explore the viability of the reaction in aqueous PS-750-M. It was found that PS-750-M could readily be adapted to a base-catalyzed S_NAr reaction with neutral nucleophiles. Due to the size limitations of the micelles, only an oligomeric version of **9** could be created (see Chapter 5). This outcome is interesting, however, as a potential approach to control of oligomer size.

2.4 Micelle Characterization

The surfactant and reaction system were further investigated through cryo-TEM and DLS experiments (Figure 2.5). Both experiments were conducted for two different solution compositions: (1) aqueous PS-750-M and (2) 1 M NaCl in PS-750-M/acetone (4:1). A 3 wt% aqueous PS-750-M solution was used for cryo-TEM measurements while a 0.2 wt% solution was used for DLS. Cryo-TEM of the system without additives revealed slightly irregular spherical shapes along with a small portion of more irregular shapes which may have been closely associated, partially fused aggregates of spheres. The micelles appeared to be about equally likely to be alone or part of an aggregate. Spheres varying in diameter from ca. 40 nm to 70 nm were observed along with aggregates with effective diameters of ca. 150 nm. DLS measurements showed a size distribution with a symmetrical peakshape when plotted with logarithmically increasing diameter; the peak was centered at the average diameter of 169 nm, and the extremes of the tails were ca. 45 nm to 616 nm. The lower size limit corresponds well with the diameters observed by cryo-TEM, the average corresponds well with the aggregate observed by cryo-TEM, and the upper limit suggests that aggregation was more prevalent in the DLS experiment.

Introduction of the additives resulted in subtle but distinct changes. Cryo-TEM showed all particles were distinctly spherical in shape and aggregation was much more prevalent than in the absence of additives. Although smaller diameters were seen for spheres incorporated into aggregates, a representative non-aggregated sphere was ca. 60 nm in diameter. More typical aggregates had effective diameters of ca. 160 nm, but assemblies with effective diameters as large as ca. 300 nm were also observed. DLS measurements in the presence of additives were consistent with these changes. The plotted peakshape was similar, but it was sharper and centered at the average diameter of 219 nm with the lower and upper extremes being ca. 69 nm to 702 nm.

Figure 2.5: Characterization of micelles by cryo-TEM and DLS.

Thus, the introduction of the additives clearly increased aggregation of the micelles. This aggregation may partly explain the enhanced reactivity since exchange phenomena between micelles could increase the frequency of encounter between reaction partners. For example, exchange of a polyfluoroarene would bring it briefly into closer proximity to the surfactant–water interface. Similarly, sulfinate salts localized at the micellar exterior might be “rolled into” a greater depth of penetration as aggregated spheres shift around upon each other.

2.5 Computational Studies

Computational studies were carried out by Dr. Martin Andersson using COSMO-RS^{83,84} and are detailed in our coauthored publication.⁶⁵ The key findings are summarized here for the sake of a more complete discussion. Calculations showed that the

surfactant–water interfacial tension increased with increasing NaCl concentration and became positive above a concentration of 1 M, whereas acetone had little effect. This result was consistent with the aggregation behavior observed by cryo-TEM, which served to minimize interfacial surface area. The proline linker region of PS-750-M was found to be the most hydrophylic part of the surfactant and played a significant role in reducing interfacial tension. However, it was not possible for the surfactant–water interface to be fully occupied by the proline linker due to (1) the strong preference for the hydrocarbon chain to be in the nonpolar inner core of the micelle and (2) the size of the mPEG region. Instead, the surfactant–water interface would predominantly consist of mPEG, but with the proline contributing to the interface where possible. This may suggest an exchange process *within* the micelle consisting of an equilibrium between the majority of surfactant molecules and a subset of which escapes hydrocarbon inner core binding to bring the proline linker nearer to the surfactant–water interface.

Table 2.3: Solubility predictions for in 2.5 M NaCl and the mPEG, linker, and lipophilic regions of the surfactants TPGS-750-M and PS-750-M.^a

Region	Solubility of 4a	Solubility of 5a
2.5 M NaCl	−4.6	−0.3
TPGS-750-M mPEG region	−0.4	−1.2
TPGS-750-M linker region	−0.7	−1.3
TPGS-750-M lipophilic region	−0.9	−5.7
PS-750-M mPEG region	−0.4	−2.1
PS-750-M linker region	−0.8	−0.2
PS-750-M lipophilic region	−1.3	−7.0

^a Solubilities are presented as $\log_{10}(x)$, where x is the maximum attainable mole fraction for the phase.

COSMO-RS was also used to predict the solubilities of polyfluoroarene **4a** and sulfinate salt **5a** in 2.5 M NaCl and surfactant subdomains (Table 2.3). PS-750-M was compared against the structurally similar TPGS-750-M surfactant. The predicted solubility of **4a** was unsurprisingly very low in 2.5 M NaCl, and its predicted affinity for each surfactant region was comparable between PS-750-M and TPGS-750-M. The

influence of the polar nitrile moiety was evident with predicted **4a** solubility decreasing with increasing distance from the surfactant–water interface. The comparatively lower solubility of **4a** and especially **5a** predicted in the lipophilic region of PS-750-M compared to that of TPGS-750-M suggests that the PS-750-M micellar inner core is more strongly non-polar. It should be noted, however, that the aromatic portion and phenolic ether of TPGS-750-M is considered as part of the lipophilic region, and the TPGS-750-M aliphatic chain may be more comparable in hydrophobicity to the hydrocarbon chain of PS-750-M. Predicted solubility for **5a** was substantially higher in 2.5 M NaCl than in any region of TPGS-750-M, and solubility decreased with increasing distance from the surfactant-water interface. TPGS-750-M mPEG and succinic acid linker regions were predicted to solubilize **5a** to nearly the same extent while the predicted lipophilic region solubility was substantially lower. Remarkably, the solubility of **5a** was predicted to be *higher* in the PS-750-M proline linker region than in 2.5 M NaCl, yet the predicted solubilities in the mPEG and lipophilic regions were lower than the analogous regions of TPGS-750-M. These predictions may suggest a specific interaction with the sulfinate salt. For example, the PS-750-M carbonyl moieties have less conformational freedom than the those of TPGS-750-M, and the conformational restriction may aid in, e.g., cooperative interaction with the sulfinate counteranion. The exceptional accommodation of **5a** by the proline linker region provides support for the original design objective of mimicking polar organic solvents. Furthermore, because the solubility of **4a** in the linker and mPEG regions differs little between PS-750-M and TPGS-750-M, the ability to solubilize **5a** appears to be the deciding factor for the superiority of PS-750-M in this process.

2.6 Conclusions

The guiding design principle behind the surfactant PS-750-M was substantially validated through the development and study of a S_NAr reaction between highly lipophilic polyfluoroarenes and weak anionic sodium sulfinate salt nucleophiles. Remarkably, 5 M NaCl in 3 wt% PS-750-M outperformed neat acetone. The highest yields were obtained when acetone was used as a relatively green cosolvent, and when the more strongly polar aprotic solvent DMSO was used as cosolvent instead, reaction rate and yield actually deteriorated, suggesting that the significance of the proline linker may be greater than simply providing an analogue of polar aprotics within the micelle. PS-750-M also outperformed all other surfactants that were assessed. This process displays considerable operational simplicity; in particular, the sulfinate salts are easily handled, the products are typically sufficiently prone to precipitation that isolation by simple filtration is usually adequate, and toxic polar aprotic solvents like DMF and NMP are completely avoided. Reaction medium stability was found to be robust with recycling being viable for at least 5 reaction cycles. A wide scope of electrophiles and nucleophiles was demonstrated, the process was readily adapted to gram-scale, and the potential value of the products was demonstrated through the synthesis of a macromolecular photoredox catalyst by condensation oligomerization. Analytical and computational studies further validated the design concept and also suggested that the proline linker might be particularly crucial in enabling the reaction. In particular, calculations suggested that the saline medium may promote an intramolecular equilibrium wherein some surfactant molecules enrich the surfactant–water interface with the highly polar proline linker. This exchange process may result in a quasi-phase transfer effect, particularly given that the solubility of the sulfinate salt was predicted to actually be higher in the proline linker region than in the aqueous phase.

2.7 Supplementary Information

2.7.1 Methods

2.7.1.1 General Information

All manipulations were carried out under air unless otherwise noted. TLC plates (UV 254 indicator, aluminum backed, 175 μm to 225 μm thickness, standard grade silica gel, 230 mesh to 400 mesh) were purchased from Merck. Acetone, ethyl acetate, and hexanes were purchased from Fisher Scientific. NMR solvents were purchased from Cambridge Isotopes Laboratories. Sulfinate salts were either purchased from Sigma-Aldrich or their precursors were obtained as a gift from Novartis Pharma Basel. All compounds were purified either by simple filtration with water washing, by passing through a silica plug, or by flash chromatography using a Teledyne Isco CombiFlash Rf 150. Microwave reaction vials (10 mL volume) were purchased from Biotage. HPLC grade water was used to prepare surfactant solution. GCMS data was recorded using a Thermo Scientific Trace 1300 Gas Chromatograph coupled with a Thermo Scientific ISQ-QD Single Quadrupole Mass Spectrometer. Melting points were determined using a Thomas Hoover melting point apparatus with samples in Kimble Kimex 51 capillaries (1.5–1.8 x 90 mm). NMR spectra were recorded at 23 °C on Varian MR-400, Varian Unity INOVA 500, and Varian VNMRs 700 spectrometers (400 MHz, 500 MHz, and 700 MHz, respectively). Reported chemical shifts are referenced to residual solvent peaks. IR spectra were acquired on a FTIR Perkin Elmer Spectrum Two: UATR Two spectrometer using 1 cm^{-1} resolution. High resolution mass analyses were obtained either using a 5975C Mass Selective Detector coupled with a 7890A Gas Chromatograph (Agilent Technologies) or orbit-trap. Calibrated MALDI mass measurements were conducted on an Applied Biosystems Voyager System 6032.

DLS Particle size measurements were acquired with a Brookhaven 90 Plus Particle

Size Analyzer from Brookhaven Instrument Corporation. A 0.2 wt% aqueous solution of PS-750-M was analyzed for particle size distribution. In a separate experiment, 20 % (w/v) of acetone was dissolved in 0.2 wt% aqueous solution of PS-750-M and NaCl was admixed to obtain its 1 M concentration. After mixing for 5 min, resulting solution was immediately analyzed for particle size determination.

Cryo-TEM analysis was performed in the Facility of High Resolution Microscopy, California Nanoscience Institute, University of California, Santa Barbara. Two different samples were directly analyzed for high resolution images to determine the particle size, shape, and and morphology: (1) 3 wt% aq. PS-750-M and (2) 1 M NaCl in 4:1 3 wt% aq. PS-750-M/acetone.

2.7.1.2 Synthetic Procedures

Procedure 2.1: Optimization reactions for micellar S_NAr of polyfluoroarenes by sulfinates.

Sodium *p*-toluenesulfinate salt (**4c**, 0.6 mmol, 1.2 equiv) and additive (where indicated) were added to an oven-dried 10 mL microwave vial equipped with PTFE-coated magnetic stir bar. Subsequently, the reaction medium was added, followed by the pentafluorobenzonitrile (**4a**, 0.5 mmol, 1 equiv). The reaction vessel was fitted with a rubber septum which was then wrapped with high-density PTFE tape. The reaction mixture was allowed to stir at room temperature (25 °C). Reaction progress was monitored at 30 min by withdrawing a 20 µL aliquot, passing it through a short silica plug with ethyl acetate, and immediately subjecting the eluted solution to GCMS analysis. After 4 h had elapsed from the addition of **4a**, the septum was removed, and the reaction mixture was extracted with 1 mL portions of ethyl acetate until no product remained in the aqueous layer according to TLC (typically 3 extractions). The combined organic layers were dried over anhydrous MgSO₄, diluted with an equal volume of hexanes, and passed through a silica plug using a 1:1 mixture of hexanes and ethyl acetate as eluent. Solvent was removed by rotary evaporation and the containing vessel was placed under high vacuum for 2 h. The complete set of optimization results is provided in Table 2.4, including results from GCMS analysis 30 min after the start of the reaction.

Procedure 2.2: Substrate scope reactions for micellar S_NAr of polyfluoroarenes by sulfinates.

Sulfinate salt **5** (0.25 mmol, 1 equiv) and sodium chloride (2.5 mmol, 10 equiv) were sequentially added to an oven-dried 10 mL microwave reaction vial equipped with a PTFE-coated magnetic stir bar. Subsequently, 3 wt% aq. PS-750-M (0.4 mL) and acetone (0.1 mL) were added, followed by addition of polyfluoroarene **4** (0.25 mmol,

1 equiv). The reaction vessel was closed with a rubber septum which was then wrapped with high-density PTFE tape. The reaction mixture was allowed to stir at room temperature 25 °C unless otherwise specified. Reaction progress was monitored by TLC (where permitted by sufficiently low volatility of **4**) and GCMS. Upon completion, the reaction mixture was admixed with 1.0 mL deionized water to further induce precipitation of the typically poorly soluble products. The vessel was centrifuged, and the supernatant liquid layer was decanted. The solid was washed with deionized water (2×0.5 mL), and residual water was removed under reduced pressure. Some products (**6b,c,j,n,q,x**) were too soluble in the diluted reaction medium for purification by precipitation; in these cases, the reaction mixture was extracted with ethyl acetate (2×0.5 mL), the contents of the combined organic layers were passed through a hexanes-wetted plug of silica gel. Volatiles were evaporated to obtain pure product as a solid. Characterization information is provided in Section 2.7.3.

Procedure 2.3: Gram-scale reactions for micellar S_NAr of polyfluoroarenes by sulfinate salts.

Sodium *p*-toluenesulfinate (**5a**, 5.5 mmol, 1 equiv) and sodium chloride (55 mmol, 10 equiv) were added to an oven-dried 25 mL round bottom flask equipped with a PTFE-coated magnetic stir bar. Subsequently, 3 wt% aq. PS-750-M (8 mL) and acetone (2 mL) were added, followed by the addition of 3-chloro-2,4,5,6-tetrafluoropyridine (**4c**, 5.5 mmol, 1 equiv). The reaction vessel was fitted with a rubber septum which was then wrapped with high-density PTFE tape, and the reaction mixture was allowed to stir at 25 °C. Reaction progress was monitored by TLC and GCMS. Upon reaction completion (after 2 h), 10 mL deionized water was admixed, and the solid material was collected over a sintered glass frit by vacuum filtration. The filtrate was placed in a sealed container for later use in recycle studies. The solid was rinsed with additional deionized (2×10 mL). Residual traces of water were removed under high vacuum and product **10a** was obtained as 1.43 g (81 %) of white flaky solid. Product purity and

identity was confirmed by ^1H NMR comparison with the fully characterized product from the substrate scope screening.

Procedure 2.4: Extended recycle study for micellar $\text{S}_{\text{N}}\text{Ar}$ of polyfluoroarenes by sulfinate salts.

Zeroth cycle. Sodium *p*-toluenesulfinate salt (**5a**, 0.25 mmol, 1 equiv) and sodium chloride (2.5 mmol, 10 equiv) were added to an oven-dried stir-bar-equipped 10 mL microwave vial. A 3 wt% ap. PS-750-M/acetone (4:1) reaction medium was established by adding 294 μL filtrate recovered from the gram-scale reaction (2.3), 147 μL 6 wt% PS-750-M, and 59 μL acetone. Pentafluoropyridine (**4b**, 0.25 mmol, 1 equiv) was added, and the vessel was sealed with a crimper and a fresh PTFE-lined septum. The reaction mixture was stirred at 25 °C for 6 h (the required reaction time established during substrate scope screening) at 25 °C. The reaction vessel was then centrifuged, and the supernatant liquid was transferred by syringe to the reaction vessel prepared for the first recycle. The pellet was rinsed with water (2 $\times$ 0.5 mL) which was removed by syringe. Residual water was removed under reduced pressure at 80 °C before placing the vessel under high vacuum. Product **6k** was obtained as a white flaky solid (71 mg, 92 %), and purity was confirmed by ^1H NMR.

First recycle. The reaction medium recovered from the zeroth cycle mixture was added to an oven-dried stir-bar-equipped 10 mL microwave vial containing **5a** (0.25 mmol, 1 equiv). Pentafluoropyridine (**4b**, 0.25 mmol, 1 equiv) was added, and the vessel was sealed with a crimper and a fresh PTFE-lined septum. The reaction mixture was stirred for 6 h at 25 °C and then processed in the same manner as described for the zeroth cycle to afford **6k** (72 mg, 92 %), and purity was confirmed by ^1H NMR.

Second recycle. The reaction medium recovered from the previous recycle mixture was added to an oven-dried stir-bar-equipped 10 mL microwave vial containing **5a** (0.25 mmol, 1 equiv). In this cycle, the polyfluoroarene was changed to pentafluorobenzonitrile (**4a**, 0.25 mmol, 1 equiv), which was added before sealing the vessel

with a crimper and a fresh PTFE-lined septum. The reaction mixture was stirred for 8 h at 25 °C and then processed in the same manner as described for the zeroth cycle to afford **6a** (67 mg, 82 %) as an off-white flaky solid, and purity was confirmed by ¹H NMR. **Third recycle.** The reaction medium recovered from the previous recycle mixture was added to an oven-dried stir-bar-equipped 10 mL microwave vial containing **5a** (0.25 mmol, 1 equiv). Pentafluorobenzonitrile (**4a**, 0.25 mmol, 1 equiv) was added, and the vessel was sealed with a crimper and a fresh PTFE-lined septum. The reaction mixture was stirred for 8 h at 25 °C and then processed in the same manner as described for the zeroth cycle to afford **6a** (69 mg, 84 %), and purity was confirmed by ¹H NMR.

Fourth recycle. In this cycle, the polyfluoroarene was changed, supplemental sodium chloride was added, and the reaction was conducted at elevated temperature. The reaction medium recovered from the previous recycle mixture was added to an oven-dried stir-bar-equipped 10 mL microwave vial containing **5a** (0.25 mmol, 1 equiv) and a supplemental portion of sodium chloride (1.25 mmol, 5 equiv). Octafluorotoluene (**4d**, 0.25 mmol, 1 equiv) was added, and the vessel was sealed with a crimper and a fresh PTFE-lined septum. The reaction mixture was stirred for 18 h at 45 °C and then processed in the same manner as described for the zeroth cycle to afford **6q** (76 mg, 82 %) as an off-white flaky solid, and purity was confirmed by ¹H NMR.

Procedure 2.5: S_NAr condensation oligomerization in PS-750-M

1,2,4,5-Tetrafluoro-3-(phenylsulfonyl)-6-(trifluoromethyl)benzene (**6b**, 0.28 mmol, 1 equiv), 2,3,5,6-tetrafluoroterephthalonitrile (**7**, 0.56 mmol, 2 equiv), 3,3,3',3'-tetramethyl-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-5,5',6,6'-tetraol (**8**, 0.84 mmol, 3 equiv), and potassium carbonate (2.8 mmol, 10 equiv) were added to an oven-dried 50 mL round bottom flask equipped with a PTFE-coated magnetic stir bar, followed by addition of 10 mL 3 wt% aq. PS-750-M. The reaction vessel was fitted with a water-jacketed reflux condenser and was magnetically stirred in an oil bath pre-heated

to 125 °C. Product formation was observed as a yellow precipitate. After 2 h, the reaction vessel was removed from heating and the solid material was collected over a sintered glass funnel by vacuum filtration with subsequent water rinses (3×10 mL). The solid material and 20 mL deionized water were added to a 50 mL round bottom flask which was then fitted with a water-jacketed reflux condenser. The suspension was then magnetically stirred in an oil bath pre-heated to 100 °C for 16 hours, at which point the vessel was allowed to cool to room temperature. The solid material was collected by vacuum filtration over a sintered glass funnel. Residual traces of water were removed under high vacuum and the product was obtained as 0.33 g (87 %) of yellow solid. Analytical data was in accordance with the literature.⁸²

2.7.2 Extended Optimization Results

Table 2.4: Complete optimization results for the nucleophilic aromatic substitution of polyfluoroarenes by sulfinate salts.^a

Entry	Reaction Medium ^b	Additive	% Conv. at 30 min ^c	% Yield at 4 h ^d
1	acetone	—	50	52
2	water	—	0	0
3	water/acetone (4:1)	—	2	5
4	3 wt% aq. PS-750-M	NaCl	19	57
5	3 wt% aq. PS-750-M/acetone (4:1)	NaCl ^d	21	58
6	3 wt% aq. PS-750-M/acetone (4:1)	—	3	9
7	3 wt% aq. PS-750-M/acetone (4:1)	NaF	2	9
8	3 wt% aq. PS-750-M/acetone (4:1)	NaCl	60	76
9	3 wt% aq. PS-750-M/acetone (4:1)	NaBr	10	38
10	3 wt% aq. TPGS-750-M/acetone (4:1)	—	3	10
11	3 wt% aq. TPGS-750-M/acetone (4:1)	NaF	6	14
12	3 wt% aq. TPGS-750-M/acetone (4:1)	NaCl	34	62
13	3 wt% aq. TPGS-750-M/acetone (4:1)	NaBr	17	43
14	3 wt% aq. SDS/acetone (4:1)	—	0	1
15	3 wt% aq. SDS/acetone (4:1)	NaF	0	1
16	3 wt% aq. SDS/acetone (4:1)	NaCl	0	1
17	3 wt% aq. SDS/acetone (4:1)	NaBr	0	2
18	3 wt% aq. Pluronic F-127/acetone (4:1)	NaCl	22	26
19	3 wt% aq. Tween 20/acetone (4:1)	NaCl	41	52
20	3 wt% aq. PS-750-M/THF (4:1)	NaCl	41	57
21	3 wt% aq. PS-750-M/DMSO (4:1)	NaCl	51	70

^a Conditions: polyfluoroarene **4a** (0.5 mmol, 1 equiv), sodium sulfinate salt **5a** (1.2 equiv), additive (as specified if called for, 10 equiv), and the specified reaction medium (0.5 mL) were stirred in a sealed vessel under ambient atmosphere at 25 °C according to Procedure 2.1.

^b Micellar medium:acetone ratios are expressed in terms of volume. ^c Determined by GCMS analysis. ^d Isolated yields. ^e Used at a loading of 5 equiv.

2.7.3 Compound Characterization

2,3,5,6-Tetrafluoro-4-tosylbenzonitrile (6a)

White solid, m.p. = 156 °C to 157 °C, 67 mg (81 %), R_f 0.38 (1:4 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 7.96 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 2.48 (s, 3H). **^{13}C NMR** (126 MHz, CDCl_3) δ (ppm) 148.7 – 148.5 (m), 146.5 – 146.4 (m), 145.1 – 145.0 (m), 143.0 – 142.8 (m), 136.9, 130.6, 128.4, 106.3, 22.0. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -128.36 – -128.95 (m, 2F), -132.79 – -133.35 (m, 2F). **IR** ν (cm^{-1}) 3098 (w), 3067 (w), 2925 (w), 2857 (w), 2248 (m), 1594 (m), 1490 (s). **HRMS** (CI) $[\text{C}_{14}\text{H}_7\text{F}_4\text{NO}_2\text{S} + \text{H}]^+$ calculated 330.0206, found (m/z) 330.0215.

1,2,4,5-Tetrafluoro-3-(phenylsulfonyl)-6-(trifluoromethyl)benzene (6b)⁸⁵

White solid, m.p. = 135 °C to 136 °C, 80 mg (89 %), R_f 0.40 (1:4 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 8.11 (d, J = 8.0 Hz, 2H), 7.75 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 8.0 Hz, 2H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 145.4 – 145.0 (m), 143.9 – 143.5 (m), 140.0, 135.5, 129.9, 128.3, 125.3 (t, $J(\text{C},\text{F})$ = 14.1 Hz), 120.2 (q, $J(\text{C},\text{F})$ = 276 Hz), 114.3 (qt, $J(\text{C},\text{F})$ = 35.6, 12.7 Hz). **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -56.87 (t, J = 21.9 Hz), -133.88 (dd, J = 20.3, 11.4 Hz), -136.52 (td, J = 22.1, 13.4 Hz). **IR** ν (cm^{-1}) 3103 (w), 3086 (w), 1650 (m), 1585 (m).

2-((2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)sulfonyl)thiophene (6c)

White solid, m.p. = 134 °C to 135 °C, 66 mg (73 %), R_f 0.23 (1:4 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 7.95 (d, J = 4.0 Hz, 1H), 7.86 (dd, J = 4.0 and 1.0 Hz, 1H), 7.22 (t, J = 4.0 Hz, 1H). **^{13}C NMR** (126 MHz, CDCl_3) δ (ppm) 145.7 (d, $J(\text{C},\text{F})$ = 16.5 Hz), 145.2 (d, $J(\text{C},\text{F})$ = 16.5 Hz), 143.4 (d, $J(\text{C},\text{F})$ = 17.1 Hz), 143.2 (d, $J(\text{C},\text{F})$ = 17.1 Hz), 140.7, 136.9, 136.2, 128.7, 125.7 (d, $J(\text{C},\text{F})$ = 13.1 Hz), 120.2 (q, $J(\text{C},\text{F})$ = 272 Hz), 114.4-114.2. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -56.9 (t, $J(\text{C},\text{F})$ = 21.1 Hz, 3F), -133.8 – -133.9 (m, 2F), -136.4 – -136.7 (m, 2F). **IR** ν (cm^{-1}) 3101 (m), 2963 (w), 2923 (m), 2858 (w). **HRMS** (CI) $[\text{C}_{11}\text{H}_3\text{F}_7\text{O}_2\text{S}_2 + \text{H}]^+$ calculated 364.9535, found (m/z) 364.9531.

4-((2,4-Dimethoxyphenyl)sulfonyl)-2,3,5,6-tetrafluorobenzonitrile (6d)

White solid, m.p. = 145 °C to 146 °C, 62 mg (66 %), R_f 0.14 (1:4 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 7.99 (d, J = 8.5 Hz, 1H), 6.63 (dd, J = 8.5 and 2.0 Hz, 1H), 6.44 (d, J = 2.0 Hz, 1H). **^{13}C NMR** (126 MHz, CDCl_3) δ (ppm) 167.2, 159.7, 148.3 (d, J = 16.0 Hz), 146.1 (d, J = 15.8 Hz), 145.7 (d, J = 12.2 Hz), 143.5 (d, J = 12.0 Hz), 132.4 (d, J = 5.5 Hz), 127.5 (t, J = 13.5 Hz), 119.9, 106.6, 105.6, 99.6 (d, J = 13.1 Hz), 98.0 (t, J = 17.2 Hz), 56.7, 55.9. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -130.0 (dt, $J(\text{C},\text{F})$ = 13.2 and 3.3 Hz, 2F), -134.0 (dt, $J(\text{C},\text{F})$ = 13.2 and 3.3 Hz, 2F). **IR** ν (cm^{-1}) 3111 (w), 3091 (w), 3025 (m), 2982 (w), 2949 (m), 2922 (m), 2869 (w), 2847 (m), 2248 (m). **HRMS** (CI) $[\text{C}_{15}\text{H}_9\text{F}_4\text{NO}_4\text{S} + \text{H}]^+$ calculated 376.0261, found (m/z) 376.0250.

4-((3-Chloro-2,5,6-trifluoropyridin-4-yl)sulfonyl)benzonitrile (6e)

White solid, m.p. = 192 °C to 193 °C, 64 mg (77%), R_f 0.51 (1:4 ethyl acetate/hexanes). **^1H NMR** (700 MHz, CDCl_3) δ (ppm) 8.22 (d, J = 8.2 Hz, 2H), 7.93 (d, J = 8.2 Hz, 2H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 152.8 – 151.3 (m), 149.3 – 147.6 (m), 142.9, 141.7 – 140 (m), 140.1 (d, $J(\text{C},\text{F})$ = 10.4 Hz), 133.5, 129.3, 119.4, 116.7, 113.1 – 112.8 (m). **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -67.78 (dd, J = 29.6 and 11.3 Hz, 1F), -82.88 (dd, J = 23.0 and 11.3 Hz, 1F), -134.59 (dd, J = 29.6 and 23.0 Hz, 1F). **IR** ν (cm^{-1}) 3098 (w), 3045 (w), 2959 (w), 2922 (m), 2852 (m), 2237 (m), 1611 (s), 1596 (s). **HRMS** (CI) $[\text{C}_{12}\text{H}_4\text{ClF}_3\text{N}_2\text{O}_2\text{S} + \text{H}]^+$ calculated 332.9707, found (m/z) 332.9714.

3-((3-Chloro-2,5,6-trifluoropyridin-4-yl)sulfonyl)benzonitrile (6f)

White solid, m.p. = 118 °C to 119 °C, 44 mg (53%), R_f 0.28 (1:4 ethyl acetate/hexanes). **^1H NMR** (700 MHz, CDCl_3) δ (ppm) 8.42 – 8.23 (m, 2H), 8.03 (d, J = 7.7 Hz, 1H), 7.81 (t, J = 7.7 Hz, 1H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 152.8 – 151.3 (m), 149.3 – 147.6 (m), 141.7 – 140.0 (m), 140.7, 140.1 – 139.9 (m), 138.5, 132.5, 132.2, 131.0, 116.5, 114.8, 113.1 – 112.8. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -67.76 (dd, J = 29.9, 11.9 Hz, 1F), -82.83 (dd, J = 23.0, 11.6 Hz, 1F), -134.63 (dd, J = 29.9, 23.0 Hz, 1F). **IR** ν (cm^{-1}) 3057 (w), 2944 (m), 2832 (m), 2238 (w), 1609 (w). **HRMS** (CI) $[\text{C}_{12}\text{H}_4\text{ClF}_3\text{N}_2\text{O}_2\text{S}]^+$ calculated 331.9629, found (m/z)

331.9629.

3-Chloro-2,5,6-trifluoro-4-tosylpyridine (6g)

White solid, m.p. = 181 °C to 182 °C, 68 mg (84 %), R_f 0.30 (3:17 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 7.98 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 2.48 (s, 3H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 152.6 – 151.2 (m), 149.1 – 147.5 (m), 147.3, 114.8 (d, $J(\text{C},\text{F})$ = 10.2 Hz), 141.6 – 139.8 (m), 136.2, 130.5, 128.7, 112.8 – 112.6 (m), 22.0. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -68.98 (dd, J = 29.6, 12.0 Hz), -84.22 (dd, J = 22.6, 12.0 Hz), -135.21 (dd, J = 29.6, 23.1 Hz). **IR** ν (cm^{-1}) 3093 (w), 3071 (w), 2961 (m), 2925 (m), 2851 (m). **HRMS** (CI) $[\text{C}_{12}\text{H}_7\text{ClF}_3\text{NO}_2\text{S} + \text{H}]^+$ calculated 321.9911, found (m/z) 321.9904.

2,3,5,6-Tetrafluoro-4-((1,2,5-trimethyl-1*H*-imidazol-4-yl)sulfonyl)pyridine (6h)

White solid, m.p. = 157 °C to 158 °C, 66 mg (82 %), R_f 0.11 (2:3 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 3.75 (s, 1H), 2.53 (s, 1H), 2.36 (s, 1H). **^{13}C NMR** (126 MHz, CDCl_3) δ (ppm) 149.5, 145.2 (d, $J(\text{C},\text{F})$ = 17.3 Hz), 145.0, 143.1 (dt, $J(\text{C},\text{F})$ = 17.3 and 7.7 Hz), 139.8 (dd, $J(\text{C},\text{F})$ = 27.8 and 7.7 Hz), 137.7 (dd, $J(\text{C},\text{F})$ = 36.5 and 7.7 Hz), 134.4 (dd, $J(\text{C},\text{F})$ = 17.3 and 7.7 Hz), 115.1, 36.7, 12.9, 10.7. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -86.4 – -86.5 (m, 2F), -138.4 – -138.6 (m, 2F). **IR** ν (cm^{-1}) 2948 (w), 1643 (m), 1526 (w). **HRMS** (CI) $[\text{C}_{11}\text{H}_9\text{F}_4\text{N}_3\text{O}_2\text{S} + \text{H}]^+$ calculated 324.0424, found (m/z) 324.0412.

2,3,5,6-Tetrafluoro-4-((4-fluorophenyl)sulfonyl)pyridine (6i)

White solid, m.p. = 171 °C to 172 °C, 69 mg (89%), R_f 0.35 (1:9 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 8.15 (dd, $J = 8.5$ and 5.5 Hz, 2H), 7.31 (dd, $J = 8.5$ and 5.5 Hz, 2H). **^{13}C NMR** (126 MHz, CDCl_3) δ (ppm) 167.2 (d, $J(\text{C},\text{F}) = 260$ Hz), 145.4 – 143.3 (m), 140.0 – 137.5 (m), 135.3, 131.1 – 131.8 (m), 131.9 (d, $J(\text{C},\text{F}) = 9.6$ Hz), 117.6 (d, $J(\text{C},\text{F}) = 22.2$ Hz). **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -85.40 – -85.56 (m, 2F), -99.00 – -99.06 (m, 1F), -137.02 – -137.19 (m, 2F). **IR** ν (cm^{-1}) 3115 (w), 1633 (w), 1590 (m). **HRMS** (CI) $[\text{C}_{11}\text{H}_4\text{F}_5\text{NO}_2\text{S} + \text{H}]^+$ calculated 309.9961, found (m/z) 309.9982.

1,2,4,5-Tetrafluoro-3-((4-fluorophenyl)sulfonyl)-6-(trifluoromethyl)benzene (6j)

White solid, m.p. = 132 °C to 133 °C, 61 mg (65%), R_f 0.56 (1:4 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 8.13 (dd, $J = 8.5$ and 5.0 Hz, 2H), 7.30 (dd, $J = 8.5$ and 0.5 Hz, 2H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 167.7, 166.2, 145.4 -14.4 (m), 136.1, 131.5 (d, $J(\text{C},\text{F}) = 9.9$ Hz), 125.2 (t, $J(\text{C},\text{F}) = 14.1$ Hz), 120.(q, $J(\text{C},\text{F}) = 275$ Hz), 117.4 (d, $J(\text{C},\text{F}) = 23$ Hz), 114.8 – 114.3 (m). **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -56.8 – -57.0 (m, 3F), -133.9 – -134.0 (m, 2F), -136.3 – -136.4 (m, 2F). **IR** ν (cm^{-1}) 3114 (w), 2958 (w), 2922 (m), 2854 (m). **HRMS** (CI) $[\text{C}_{13}\text{H}_4\text{F}_8\text{O}_2\text{S} + \text{H}]^+$ calculated 376.9883, found (m/z) 376.9877.

2,3,5,6-Tetrafluoro-4-tosylpyridine (6k)

White solid, m.p. = 183 °C to 184 °C, 70 mg (92 %), R_f 0.38 (1:9 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 7.99 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ (ppm) 147.5, 145.7 – 144.4 (m), 140.3 – 137.2 (m), 136.4, 133.6 (t, $J(\text{C},\text{F})$ = 17.4 Hz), 130.7, 128.7, 22.0. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -85.9 4– -86.03 (m, 2F), -137.10 – -137.25 (m, 2F). **HRMS** (CI) $[\text{C}_{12}\text{H}_7\text{F}_4\text{NO}_2\text{S} + \text{H}]^+$ calculated 306.0212, found (m/z) 306.0209.

2,3,5,6-Tetrafluoro-4-((3-nitrophenyl)sulfonyl)pyridine (6l)

White solid, m.p. = 127 °C to 128 °C, 48 mg (57 %), R_f 0.19 (1:4 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 8.92 (s, 1H), 8.62 (d, J = 8.2 Hz, 1H), 8.45 (d, J = 7.8 Hz, 1H), 7.91 (t, J = 8.0 Hz, 1H). **^{13}C NMR** (126 MHz, CDCl_3) δ (ppm) 148.8, 145.4 (d, $J(\text{C},\text{F})$ = 13.9 Hz), 143.4 (d, $J(\text{C},\text{F})$ = 13.9 Hz), 141.3, 139.7 (d, $J(\text{C},\text{F})$ = 36.5 Hz), 137.7 (d, $J(\text{C},\text{F})$ = 36.5 Hz), 134.1, 131.6, 130.2, 124.1. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -84.4 – -84.6 (m, 2F), -136.3 – -136.5 (m, 2F). **IR** ν (cm^{-1}) 3096 (m), 3052 (w), 2956 (w), 2926 (m), 2875 (w), 2855 (m), 1542 (s), 1352 (s). **HRMS** (CI) $[\text{C}_{11}\text{H}_4\text{F}_4\text{N}_2\text{O}_4\text{S} + \text{H}]^+$ calculated 336.9901, found (m/z) 336.9891.

4-((4-Acetyl-2,3,5,6-tetrafluorophenyl)sulfonyl)benzonitrile (6m)

White solid, m.p. = 184 °C to 185 °C, 45 mg (50 %), R_f 0.44 (1:4 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 8.21 (d, $J = 8.5$ Hz, 2H), 7.91 (d, $J = 8.5$ Hz, 2H), 2.61 (s, 3H). **^{13}C NMR** (126 MHz, CDCl_3) δ (ppm) 190.5, 145.3 (d, $J(\text{C},\text{F}) = 16.2$ Hz), 144.2, 143.2 (d, $J(\text{C},\text{F}) = 16.2$ Hz), 133.5, 129.0, 125.0, 122.1, 118.9, 116.8, 32.4. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -130.8 (d, $J(\text{C},\text{F}) = 9.4$ Hz, 2F), -134.8 (d, $J(\text{C},\text{F}) = 9.4$ Hz, 2F). **IR** ν (cm^{-1}) 3105 (m), 3048 (w), 2958 (w), 2926 (m), 2855 (w), 2236 (m), 1938 (w), 1714 (s). **HRMS** (CI) $[\text{C}_{15}\text{H}_7\text{F}_4\text{NO}_3\text{S} + \text{H}]^+$ calculated 358.0156, found (m/z) 358.0142.

1-(2,3,5,6-Tetrafluoro-4-(naphthalen-2-ylsulfonyl)phenyl)ethan-1-one (6n)

White solid, m.p. = 145 °C to 146 °C, 71 mg (74 %), R_f 0.42 (1:4 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 8.69 (s, 1H), 8.05 (d, $J = 8.5$ Hz, 1H), 8.02 – 8.00 (m, 2H), 7.94 (d, $J = 8.0$ Hz, 1H), 7.72 (dd, $J = 8.0$ and 0.5 Hz, 1H), 7.67 (dd, $J = 8.0$ and 0.5 Hz, 1H). **^{13}C NMR** (126 MHz, CDCl_3) δ (ppm) 190.8, 145.2 (d, $J(\text{C},\text{F}) = 15.4$ Hz), 144.9 (d, $J(\text{C},\text{F}) = 15.4$ Hz), 143.1 (d, $J(\text{C},\text{F}) = 18.3$ Hz), 142.8 (d, $J(\text{C},\text{F}) = 15.4$ Hz), 137.2, 136.0, 132.2, 130.5, 130.3, 130.2, 129.9, 128.8, 124.0, 123.5, 122.2, 32.3. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -134.4 – -134.6 (m, 2F), -138.8 – -138.9 (m, 2F). **IR** ν (cm^{-1}) 3077 (w), 3056 (w), 2962 (w), 2929 (m), 2851 (w), 1714 (s), 1626 (m), 1589 (m). **HRMS** (CI) $[\text{C}_{18}\text{H}_{10}\text{F}_4\text{O}_3\text{S} + \text{H}]^+$ calculated 383.0360, found (m/z) 383.0367.

2,3,5,6-Tetrafluoro-4-((6-(trifluoromethyl)pyridin-3-yl)sulfonyl)benzonitrile (6o)

White solid, m.p. = 127 °C to 128 °C, 69 mg (72 %), R_f 0.55 (1:4 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 9.37 (s, 1H), 8.58 (d, $J = 8.0$ Hz, 1H), 7.97 (d, $J = 8.0$ Hz, 1H). **^{13}C NMR** (126 MHz, CDCl_3) δ (ppm) 153.8 (q, $J(\text{C},\text{F}) = 36.3$ Hz), 149.7, 148.8 (dd, $J(\text{C},\text{F}) = 16.4$ and 6.0 Hz), 146.7 (dd, $J(\text{C},\text{F}) = 17.9$ and 4.2 Hz), 145.3 (dd, $J(\text{C},\text{F}) = 17.9$ and 4.2 Hz), 143.2 – 143.1 (m), 139.0, 138.3, 125.5 – 125.3 (m), 121.6, 121.5, 119.4, 100.2. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -68.4 (s, 3F), -127.2 – -127.3 (m, 2F), -132.4 – -132.5 (m, 2F). **IR** ν (cm^{-1}) 3104 (w), 3058 (w), 3028 (w), 2922 (m), 2844 (w), 2251 (m), 1584 (m), 1572 (m). **HRMS** (CI) $[\text{C}_{13}\text{H}_3\text{F}_7\text{N}_2\text{O}_2\text{S} + \text{H}]^+$ calculated 384.9876, found (m/z) 384.9883.

2,3,5,6-Tetrafluoro-4-(naphthalen-2-ylsulfonyl)benzonitrile (6p)

White solid, m.p. = 184 °C to 185 °C, 86 mg (94 %), R_f 0.48 (1:4 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 8.70 (s, 1H), 8.06 (d, $J = 8.0$ Hz, 1H), 8.05 (d, $J = 8.0$ Hz, 1H), 7.99 (d, $J = 8.0$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 7.76 – 7.73 (m, 1H), 7.73 – 7.69 (m, 1H). **^{13}C NMR** (126 MHz, CDCl_3) δ (ppm) 148.6 (d, $J(\text{C},\text{F}) = 16.2$ Hz), 146.5 (d, $J(\text{C},\text{F}) = 16.2$ Hz), 145.2 (d, $J(\text{C},\text{F}) = 8.9$ Hz), 143.1 (d, $J(\text{C},\text{F}) = 8.9$ Hz), 136.5, 136.2, 132.2, 131.0, 130.6, 130.5, 130.0, 128.5, 128.3, 122.1, 106.3. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -128.5 (dd, $J = 21.6$ and 13.2 Hz, 2F), -132.8 (dd, $J = 21.6$ and 13.2 Hz, 2F). **IR** ν (cm^{-1}) 3171 (w), 2924 (w), 2239 (m),

1619 (m). **HRMS** (CI) $[\text{C}_{17}\text{H}_7\text{F}_4\text{NO}_2\text{S}]^+$ calculated 366.0206, found (m/z) 366.0191.

1,2,4,5-Tetrafluoro-3-tosyl-6-(trifluoromethyl)benzene (6q)

White solid, m.p. = 159 °C to 160 °C, 76 mg (82 %), R_f 0.44 (1:4 ethyl acetate/hexanes). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 7.97 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 2.45 (s, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ (ppm) 147.0, 145.6-145.5 (m), 143.3-142.8 (m), 137.1, 130.5, 128.4, 125.7 (t, $J(\text{C},\text{F})$ = 14.3 Hz), 120.2 (q, $J(\text{C},\text{F})$ = 277 Hz), 116.0 – 113.4 (m), 21.9. **^{19}F NMR** (376 MHz, CDCl_3) δ (ppm) -56.88 (t, J = 23.3 Hz, 3F), -134.05 – -134.14 (m, 2F), -136.69 – -136.81 (m, 2F). **HRMS** (CI) $[\text{C}_{14}\text{H}_7\text{F}_7\text{O}_2\text{S}]^+$ calculated 373.0128, found (m/z) 373.0114.

4-((4-Cyanophenyl)sulfonyl)-2,3,5,6-tetrafluorobenzonitrile (6r)

Yellow solid, m.p. = 229 °C to 230 °C, 61 mg (72 %), R_f 0.47 (1:4 ethyl acetate/hexanes). **^1H NMR** (500 MHz, DMSO) δ (ppm) 8.25 (d, J = 8.6 Hz, 2H), 8.21 (d, J = 8.6 Hz, 2H). **^{13}C NMR** (126 MHz, DMSO) δ (ppm) 148.4 (d, $J(\text{C},\text{F})$ = 16.9 Hz), 146.3 (d, $J(\text{C},\text{F})$ = 20.0 Hz), 144.7 (d, $J(\text{C},\text{F})$ = 14.7 Hz), 142.8, 142.6 (d, $J(\text{C},\text{F})$ = 16.4 Hz), 134.2, 128.6, 117.9, 117.2, 107.2. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -128.65 – -129.06 (m), -133.52 (td, J = 13.8, 5.0 Hz). **IR** ν (cm^{-1}) 3098 (w), 3044 (w), 2960 (w), 2923 (m), 2853 (m), 2237 (m), 1610 (s), 1595 (s). **HRMS** (CI) $[\text{C}_{14}\text{H}_4\text{F}_4\text{N}_2\text{O}_2\text{S} + \text{H}]^+$ calculated 341.0002, found (m/z) 341.0011.

2,3,5,6-Tetrafluoro-4-((tetrahydrofuran-3-yl)sulfonyl)benzonitrile (6s)

White solid, m.p. = 133 °C to 134 °C, 60 mg (77 %), R_f 0.38 (1:4 ethyl acetate/hexanes). **^1H NMR** (700 MHz, CDCl_3) δ (ppm) 4.39 – 4.28 (m, 1H), 4.03 (ddd, J = 23.3, 13.2, 5.6 Hz, 3H), 3.85 (dd, J = 14.7, 7.5 Hz, 1H), 2.53 – 2.26 (m, 2H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 148.5 – 146.8 (m), 145.6 – 144.0 (m), 124.0 (t, $J(\text{C},\text{F})$ = 16 Hz), 106.1, 99.8 (t, $J(\text{C},\text{F})$ = 16 Hz), 68.4, 66.9, 66.2, 27.3. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -127.63 (dq, J = 12.2, 7.0 Hz, 2F), -131.93 (dq, J = 12.2, 7.0 Hz, 2F). **IR** ν (cm^{-1}) 2986 (w), 2886 (w), 2247 (w), 1468 (s). **HRMS** (CI) $[\text{C}_{11}\text{H}_7\text{F}_4\text{NO}_3\text{S} + \text{Na}]^+$ calculated 331.9975, found (m/z) 331.9974.

3-Chloro-2,5,6-trifluoro-4-((tetrahydrofuran-3-yl)sulfonyl)pyridine (6t)

Yellow solid, m.p. = 128 °C to 129 °C, 54 mg (71 %), R_f 0.14 (1:4 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 4.33 (dd, J = 10.3, 4.7 Hz, 1H), 4.24 – 4.13 (m, 1H), 4.12 – 3.97 (m, 2H), 3.89 (dd, J = 14.2, 7.7 Hz, 1H), 2.50 (dt, J = 12.8, 5.6 Hz, 1H), 2.28 (ddt, J = 13.7, 9.4, 7.0 Hz, 1H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 152.9 – 151.4 (m), 149.3 – 147.7 (m), 142.2 – 140.4 (m), 139.0 (d, $J(\text{C},\text{F})$ = 11 Hz), 113.6 – 113.3 (m), 68.4, 66.8, 64.7, 27.3. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -67.8 (dd, $J(\text{C},\text{F})$ = 29.6 and 11.7 Hz, 1F), -82.9 (dd, $J(\text{C},\text{F})$ = 23.0 and 11.7 Hz, 1F), -135.0 (dd, $J(\text{C},\text{F})$ = 30.0 and 23.0 Hz, 1F). **IR** ν (cm^{-1}) 2966 (m), 2902 (m), 2494 (w), 1715 (m), 1612 (s). **HRMS** (CI) $[\text{C}_9\text{H}_7\text{ClF}_3\text{NO}_3\text{S} + \text{H}]^+$ calculated 301.9860, found (m/z) 301.9861.

***tert*-Butyl 3-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)sulfonyl)azetidine-1-carboxylate (6u)**

White solid, m.p. = 152 °C to 153 °C, 85 mg (78 %), R_f 0.53 (2:3 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 4.40 – 4.37 (m, 2H), 4.36 – 4.31 (m, 1H), 4.30 – 4.22 (m, 2H), 1.45 (s, 9H). **^{13}C NMR** (126 MHz, CDCl_3) δ (ppm) 155.6, 145.8 (d, $J(\text{C},\text{F}) = 14.5$ Hz), 143.7 (d, $J(\text{C},\text{F}) = 15.4$ Hz), 121.8 – 121.6 (m), 120.0 (t, $J(\text{C},\text{F}) = 278$ Hz), 115.6 – 115.2 (m), 81.2, 55.4, 49.2, 28.4. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -56.87 (t, $J = 21.2$ Hz, 3F), -133.26 – -133.33 (m, 2F), -135.07 – -135.23 (m, 2F). **IR** ν (cm^{-1}) 2984 (w), 2895 (w), 1708 (m), 1606 (w). **HRMS** (CI) $[\text{C}_{15}\text{H}_{14}\text{F}_7\text{NO}_4\text{S} + \text{H} - \text{Boc}]^+$ calculated 337.0007, found (m/z) 336.9998. **MALDI-TOF** $[\text{C}_{15}\text{H}_{14}\text{F}_7\text{NO}_4\text{S} + \text{Na}]^+$ calculated 460.0429, found (m/z) 460.0459.

1-(2,3,5,6-Tetrafluoro-4-tosylphenyl)ethan-1-one (6v)

White solid, m.p. = 141 °C to 142 °C, 62 mg (69 %), R_f 0.40 (1:4 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 7.97 (d, $J = 8.0$ Hz, 2H), 7.39 (d, $J = 8.0$ Hz, 2H), 3.98 (s, 3H), 2.46 (s, 3H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 159.0, 146.7 – 145.5 (m), 137.6, 130.4 (d, $J(\text{C},\text{F}) = 40$ Hz), 128.4, 126.2, 124.2, 117.1 (t, $J(\text{C},\text{F}) = 17$ Hz), 53.9, 22.0. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -135.13 – -135.05 (m, 2F), -136.29 – -136.39 (m, 2F). **IR** ν (cm^{-1}) 3091 (w), 3070 (w), 2964 (m), 2920 (m), 2851 (m), 1741 (s), 1598 (m). **HRMS** (CI) $[\text{C}_{15}\text{H}_{10}\text{F}_4\text{O}_4\text{S} + \text{Na}]^+$ calculated 385.0134, found (m/z) 385.0141.

2,3,5,6-Tetrafluoro-4-((4-fluorophenyl)sulfonyl)benzaldehyde (6w)

Cream white solid, m.p. = 111 °C to 112 °C, 59 mg (70 %), R_f 0.28 (3:7 ethyl acetate/hexanes). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 10.28 (s, 1H), 8.13 (dd, J = 7.6 and 5.6 Hz, 2H), 7.30 (t, J = 8.8 Hz). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 181.4, 167.6, 166.1, 147.6-143.3 (m), 136.1 (d, $J(\text{C},\text{F})$ = 4.0 Hz), 131.5 (d, $J(\text{C},\text{F})$ = 10.2 Hz), 126.0 (dd, $J(\text{C},\text{F})$ = 15.0, 4.0 Hz), 118.4 (dd, $J(\text{C},\text{F})$ = 1.7, 1.1 Hz), 117.4 (dd, $J(\text{C},\text{F})$ = 23.2, 1.1 Hz). **^{19}F NMR** (376 MHz, CDCl_3) δ (ppm) -99.83 (d, J = 5.6 Hz, 1F), -134.98 (m, -134.94 – -135.02, 2F), -141.71 (m, -141.66 – -141.75, 2 F). **IR** ν (cm^{-1}) 3114 (w), 2957 (w), 2924 (m), 2892 (w), 2875 (w), 2854 (w), 2770 (w), 1910 (w), 1717 (s), 1641 (w), 1589 (s). **MALDI-TOF** $[\text{C}_{13}\text{H}_5\text{F}_5\text{O}_3\text{S}]^+$ calculated 335.983, found (m/z) 335.973.

1,2,4,5-Tetrafluoro-3-(trifluoromethyl)-6-((2,4,6-triisopropylphenyl)sulfonyl)benzene (6x)

White solid, 87 mg (72 %), R_f 0.32 (3:17 ethyl acetate/hexanes). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 6.91 (s, 2H), 3.56 – 3.51 (m, 2H), 2.95 – 2.79 (m, 1H), 1.20-1.19 (m, 6H), 1.11 – 0.99 (m, 12H). **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -56.03 (dd, J = 21.6 and 6.6 Hz, 3F), -136.32 (d, J = 9.8 Hz, 2F), - 141.08 (d, J = 9.8 Hz, 2F). **MALDI-TOF** $[\text{C}_{22}\text{H}_{23}\text{F}_7\text{O}_2\text{S}]^+$ calculated 484.130, found (m/z) 484.133.

2.7.4 NMR Spectra

2,3,5,6-Tetrafluoro-4-tosylbenzonitrile (6a) ^1H NMR

2,3,5,6-Tetrafluoro-4-tosylbenzonitrile (6a) ^{13}C NMR

2,3,5,6-Tetrafluoro-4-tosylbenzonitrile (6a) ^{19}F NMR

1,2,4,5-Tetrafluoro-3-(phenylsulfonyl)-6-(trifluoromethyl)benzene (6b)
¹H NMR

1,2,4,5-Tetrafluoro-3-(phenylsulfonyl)-6-(trifluoromethyl)benzene (6b)
¹³C NMR

1,2,4,5-Tetrafluoro-3-(phenylsulfonyl)-6-(trifluoromethyl)benzene (6b)
¹⁹F NMR

2-((2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)sulfonyl)thiophene (6c)
¹H NMR

2-((2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)sulfonyl)thiophene (6c)
¹³C NMR

2-((2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)sulfonyl)thiophene (6c)
¹⁹F NMR

4-((2,4-Dimethoxyphenyl)sulfonyl)-2,3,5,6-tetrafluorobenzonitrile (6d)
¹H NMR

4-((2,4-Dimethoxyphenyl)sulfonyl)-2,3,5,6-tetrafluorobenzonitrile (6d)
¹³C NMR

4-((2,4-Dimethoxyphenyl)sulfonyl)-2,3,5,6-tetrafluorobenzonitrile (6d)
¹⁹F NMR

4-((3-Chloro-2,5,6-trifluoropyridin-4-yl)sulfonyl)benzonitrile (6e)
¹H NMR

4-((3-Chloro-2,5,6-trifluoropyridin-4-yl)sulfonyl)benzonitrile (6e)

^{13}C NMR

4-((3-Chloro-2,5,6-trifluoropyridin-4-yl)sulfonyl)benzonitrile (6e)

^{19}F NMR

3-((3-Chloro-2,5,6-trifluoropyridin-4-yl)sulfonyl)benzonitrile (6f) ¹H NMR

3-((3-Chloro-2,5,6-trifluoropyridin-4-yl)sulfonyl)benzonitrile (6f)
¹³C NMR

3-((3-Chloro-2,5,6-trifluoropyridin-4-yl)sulfonyl)benzonitrile (6f)
¹⁹F NMR

3-Chloro-2,5,6-trifluoro-4-tosylpyridine (6g) ^1H NMR

3-Chloro-2,5,6-trifluoro-4-tosylpyridine (6g) ^{13}C NMR

3-Chloro-2,5,6-trifluoro-4-tosylpyridine (6g) ^{19}F NMR

2,3,5,6-Tetrafluoro-4-((1,2,5-trimethyl-1*H*-imidazol-4-yl)sulfonyl)pyridine
(6h) ¹H NMR

2,3,5,6-Tetrafluoro-4-((1,2,5-trimethyl-1*H*-imidazol-4-yl)sulfonyl)pyridine
(6h) ^{13}C NMR

2,3,5,6-Tetrafluoro-4-((1,2,5-trimethyl-1*H*-imidazol-4-yl)sulfonyl)pyridine
(6h) ^{19}F NMR

2,3,5,6-Tetrafluoro-4-((4-fluorophenyl)sulfonyl)pyridine (6i) ^1H NMR

2,3,5,6-Tetrafluoro-4-((4-fluorophenyl)sulfonyl)pyridine (6i) ^{13}C NMR

2,3,5,6-Tetrafluoro-4-((4-fluorophenyl)sulfonyl)pyridine (6i) ^{19}F NMR

1,2,4,5-Tetrafluoro-3-((4-fluorophenyl)sulfonyl)-6-(trifluoromethyl)benzene (6j) ^1H NMR

Chemical structure: FC(F)(F)S(=O)(=O)c1cc(F)c(F)c(F)c1

¹³C NMR spectrum (CDCl₃) showing peaks at the following chemical shifts (ppm): 144.9285, 144.9280, 143.930, 143.854, 143.523, 143.436, 136.067, 131.554, 131.538, 125.281, 125.201, 125.122, 122.475, 120.901, 119.338, 117.770, 117.486, 117.395, 114.775, 114.645, 114.573, 114.500, 114.444, 114.373, 114.306, 114.320, 114.342, 76.579.

Chemical structure: 1-(4-fluorophenyl)-2,3,4,5-tetrafluorobenzene-1-sulfonate

¹³C NMR spectrum (ppm):

- 56.824
- 56.870
- 56.894
- 56.919
- 56.926
- 56.944
- 56.965
- 56.972
- 99.825
- 133.972
- 133.990
- 134.056
- 134.074
- 136.320
- 136.348
- 136.365

Integration values: 3.00, 1.00, 1.97, 1.56

2,3,5,6-Tetrafluoro-4-tosylpyridine (6k) ^1H NMR

2,3,5,6-Tetrafluoro-4-tosylpyridine (6k) ^{13}C NMR

2,3,5,6-Tetrafluoro-4-tosylpyridine (6k) ¹⁹F NMR

2,3,5,6-Tetrafluoro-4-((3-nitrophenyl)sulfonyl)pyridine (6l) ^1H NMR

2,3,5,6-Tetrafluoro-4-((3-nitrophenyl)sulfonyl)pyridine (6l) ^{13}C NMR

2,3,5,6-Tetrafluoro-4-((3-nitrophenyl)sulfonyl)pyridine (6l) ^{19}F NMR

4-((4-Acetyl-2,3,5,6-tetrafluorophenyl)sulfonyl)benzonitrile (6m) ^1H NMR

4-((4-Acetyl-2,3,5,6-tetrafluorophenyl)sulfonyl)benzonitrile (6m)
 ^{13}C NMR

4-((4-Acetyl-2,3,5,6-tetrafluorophenyl)sulfonyl)benzonitrile (6m)
¹⁹F NMR

1-(2,3,5,6-Tetrafluoro-4-(naphthalen-2-ylsulfonyl)phenyl)ethan-1-one (6n)
¹H NMR

1-(2,3,5,6-Tetrafluoro-4-(naphthalen-2-ylsulfonyl)phenyl)ethan-1-one (6n)
¹³C NMR

1-(2,3,5,6-Tetrafluoro-4-(naphthalen-2-ylsulfonyl)phenyl)ethan-1-one (6n)
¹⁹F NMR

2,3,5,6-Tetrafluoro-4-((6-(trifluoromethyl)pyridin-3-yl)sulfonyl)benzonitrile (6o) ^1H NMR

2,3,5,6-Tetrafluoro-4-((6-(trifluoromethyl)pyridin-3-yl)sulfonyl)benzonitrile (6o) ^{13}C NMR

2,3,5,6-Tetrafluoro-4-((6-(trifluoromethyl)pyridin-3-yl)sulfonyl)benzonitrile (6o) ^{19}F NMR

2,3,5,6-Tetrafluoro-4-(naphthalen-2-ylsulfonyl)benzonitrile (6p) ^1H NMR

2,3,5,6-Tetrafluoro-4-(naphthalen-2-ylsulfonyl)benzonitrile (6p) ^{13}C NMR

2,3,5,6-Tetrafluoro-4-(naphthalen-2-ylsulfonyl)benzonitrile (6p) ^{19}F NMR

1,2,4,5-Tetrafluoro-3-tosyl-6-(trifluoromethyl)benzene (6q) ^1H NMR

1,2,4,5-Tetrafluoro-3-tosyl-6-(trifluoromethyl)benzene (6q) ^{13}C NMR

1,2,4,5-Tetrafluoro-3-tosyl-6-(trifluoromethyl)benzene (6q) ^{19}F NMR

4-((4-Cyanophenyl)sulfonyl)-2,3,5,6-tetrafluorobenzonitrile (6r) ^1H NMR

4-((4-Cyanophenyl)sulfonyl)-2,3,5,6-tetrafluorobenzonitrile (6r) ^{13}C NMR

4-((4-Cyanophenyl)sulfonyl)-2,3,5,6-tetrafluorobenzonitrile (6r) ^{19}F NMR

2,3,5,6-Tetrafluoro-4-((tetrahydrofuran-3-yl)sulfonyl)benzonitrile (6s)
¹H NMR

2,3,5,6-Tetrafluoro-4-((tetrahydrofuran-3-yl)sulfonyl)benzonitrile (6s)
¹³C NMR

2,3,5,6-Tetrafluoro-4-((tetrahydrofuran-3-yl)sulfonyl)benzonitrile (6s)
¹⁹F NMR

3-Chloro-2,5,6-trifluoro-4-((tetrahydrofuran-3-yl)sulfonyl)pyridine (6t)
¹H NMR

3-Chloro-2,5,6-trifluoro-4-((tetrahydrofuran-3-yl)sulfonyl)pyridine (6t)
¹³C NMR

3-Chloro-2,5,6-trifluoro-4-((tetrahydrofuran-3-yl)sulfonyl)pyridine (6t)
¹⁹F NMR

tert-Butyl 3-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)sulfonyl)azetidine-1-carboxylate (6u) ^1H NMR

tert-Butyl 3-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)sulfonyl)azetidine-1-carboxylate (6u) ^{13}C NMR

tert-Butyl 3-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)sulfonyl)azetidine-1-carboxylate (6u) ^{19}F NMR

1-(2,3,5,6-Tetrafluoro-4-tosylphenyl)ethan-1-one (6v) ^1H NMR

1-(2,3,5,6-Tetrafluoro-4-tosylphenyl)ethan-1-one (6v) ^{13}C NMR

1-(2,3,5,6-Tetrafluoro-4-tosylphenyl)ethan-1-one (6v) ^{19}F NMR

2,3,5,6-Tetrafluoro-4-((4-fluorophenyl)sulfonyl)benzaldehyde (6w)
 ^1H NMR

2,3,5,6-Tetrafluoro-4-((4-fluorophenyl)sulfonyl)benzaldehyde (6w)
¹³C NMR

2,3,5,6-Tetrafluoro-4-((4-fluorophenyl)sulfonyl)benzaldehyde (6w)
¹⁹F NMR

1,2,4,5-Tetrafluoro-3-(trifluoromethyl)-6-((2,4,6-triisopropylphenyl)sulfonyl)benzene (6x) ^1H NMR

1,2,4,5-Tetrafluoro-3-(trifluoromethyl)-6-((2,4,6-triisopropylphenyl)sulfonyl)benzene (6x) ^{19}F NMR

CHAPTER 3

PALLADIUM CROSS-COUPPLING OF ARYL BROMIDES WITH POLAR NITROALKANE COUPLING PARTNERS IN AQUEOUS PS-750-M

The arylation of short-chain nitroalkanes was used as a model reaction to test the efficacy of the surfactant PS-750-M in facilitating micellar reactions with polar substrates, as illustrated in 3.1. As discussed in Chapter 2, PS-750-M was designed to mimic problematic polar aprotic solvents, and it was anticipated that the polarity of the PS-750-M micellar core would better accommodate the polar nitroalkane coupling partners. This expectation was supported by the marked superiority of PS-750-M for this transformation over the analogous surfactants TPGS-750-M and PTS. Furthermore, the micellar reaction medium (1) was suitable for couplings with a wide variety of (hetero)aryl halide substrates, and (2) could be recycled with partial recovery of the catalyst.

3.1 Background

In 1997, Palucki and Buchwald reported a direct α -arylation of ketones (pK_a ca. 26 in DMSO) using aryl bromides and catalyzed by Tol-BINAP and BINAP palladium complexes (Figure 3.2a).⁸⁶ This reaction was discovered by the authors while exploring cyclohexanol as a coupling partner for a Buchwald–Hartwig reaction with an aryl halide; the alcohol was oxidized in situ and subsequently α -arylated to afford the

Figure 3.1: Overview of palladium-catalyzed nitroalkane arylation in aqueous PS-750-M.

unexpected side product in 2% yield. The authors proposed that following oxidative addition of the aryl halide, the bromide ligand is displaced by the enolate with the resultant intermediate being in equilibrium between the two points of enolate ligation; subsequent reductive elimination then affords the desired product and the Pd(0) form of the catalyst. The high selectivity observed for one hydrogen-bearing α -carbon over another noted as supporting evidence for the deprotonation taking place prior to coordination with the complex. Similar reactions involving resonance-stabilized carbon have since been reported by a variety of authors (Figure 3.2b), including esters⁸⁷ (pK_a ca. 30 in DMSO), nitroalkanes⁸⁸ (pK_a ca. 17 in DMSO), sulfones⁸⁹ (pK_a ca. 29 in DMSO), diaryl methanes⁹⁰ (pK_a ca. 32 in DMSO), and even *p*-nitrotoluene⁹¹ (pK_a ca. 20 in DMSO). The polarity of nitroethane and the suspected anionic nature of the coupling partner at the time of catalyst binding in this reaction system stood out as particularly attractive for our intended purpose. Namely, we wished to study the extent to which micelles of PS-750-M accommodate polar reaction partners in transition-metal-catalyzed processes. Much of the discussion along these lines from Chapter 2 applies here as well.

Figure 3.2: Palladium-catalyzed direct arylation of carbon acids using aryl halides. **a** α -Arylation of ketones reported by Palucki and Buchwald along with their originally hypothesized mechanism. **b** Example arylation of selected other carbon acids; the nitroalkane arylation reaction discussed in this chapter is highlighted. All schemes are adapted from the listed references.

3.2 Reaction Optimization

4-Bromotoluene (**11a**) was selected as the aryl bromide for the optimization reaction on the basis of its simplicity and lipophilicity, expecting that it would strongly favor localization into the micellar core. Nitroethane (EtNO_2) was selected for the coupling partner as the highest polarity (and therefore most challenging) primary nitroalkane for a micellar system (nitromethane was not used due to its reported propensity for side reactions⁸⁸). The first parameter to be optimized with the catalyst (Table 3.1). Initial conditions were adapted from a prior report⁹² of the reaction conducted in organic solvent: aryl bromide **11a** (0.25 mmol, 1 equiv), EtNO_2 (10 equiv), K_3PO_4 (1.2 equiv), Pd catalyst **13** (5 mol%), and 0.5 mL 3 wt% aqueous PS-750-M under argon atmosphere at 45 °C. In the absence of catalyst, there was no reaction. A series of π -allyl/crotyl Pd precatalysts were screened in hopes of finding an initial hit. Catalyst

13a showed no conversion, but the *t*-butyl analogue **13b** provided 8 % conversion within the timeframe of the experiment. Replacement of one of the *t*-butyl groups with an electron-rich monoaryl (**13c**) resulted in a complete loss of reactivity, suggesting that phosphine steric bulk was particularly important. Indeed, with a bulky ferrocene QPhos ligand **13d**, 4 % conversion was observed. SPhos provided comparable results despite its less bulky cyclohexyl groups (pre-catalyst **13e**), suggesting that the biaryl moiety may be particularly effective. The slightly greater steric bulk of XPhos in **13f** may have contributed to its performance being comparable to that of **13b**. The remaining π -allyl pre-catalysts contained allyl rather than crotyl ligands and triflate rather than chloride counterions. (The chloride analogues of these catalysts were reportedly not stable, so they were converted to the triflates by salt metathesis with AgOTf.⁹³) These catalysts showed substantial improvement in reaction conversion, and it was not immediately evident to what degree the improvement arose from difference in biaryl phosphine, π -allyl ligand, and counterion. As had been seen with earlier pre-catalysts, the pre-catalyst with the less bulky BrettPhos ligand (**13g**, 18 %) was outperformed by the one with *t*-BuBrettPhos (**13h**, 74 %). However, the best results were obtained with **13i**, which achieved full conversion in less than the timeframe of the experiment. The *t*-BuXPhos ligand of **13i** thus appeared to be the key to optimal activity. Aside from steric bulk it also seemed plausible that the most effective phosphines might also benefit from lipophilicity. This possibility would be consistent with *t*-BuBrettPhos (more polar) being less effective than *t*-BuXPhos (less polar) despite having a sterically similar environment.

To gain further insight into the contributing factors to catalyst efficacy, and also to potentially find a simpler, cheaper alternative catalyst system if possible, several non- π -allyl catalyst possibilities were also explored. In the absence of a phosphine ligand, Pd provided no catalysis (Table 3.1, entries 11 and 13). The sophisticated HandaPhos ligand (**14a**) is highly effective for Suzuki-Miyaura and Sonogashira couplings, but its

Table 3.1: Initial catalyst screening in the optimization of micellar Pd-catalyzed coupling of aryl bromides and nitroalkanes.^a

Entry	Catalyst	% conv. ^b
1	—	0
2	13a	0
3	13b	8
4	13c	0
5	13d	4
6	13e	3
7	13f	8
8	13g	18
9	13h	74
10	13i	100
11	Pd(OAc) ₂	0
12	Pd(OAc) ₂ / 14a	5 ^{c,d,e,f}
13	Pd ₂ dba ₃	0 ^{c,g}
14	Pd ₂ dba ₃ / 14b	44 ^{c,d,g}
15	Pd ₂ dba ₃ / 14c	60 ^{c,d,g}
16	Fe NPs ^h	0 ^{c,e}

π-Allyl pre-catalysts

13a

13b

13c

13d

13e

13f

13g

13h

13i

Ligands

14a

14b (R = Cy)

14c (R = t-Bu)

^a Conditions: aryl bromide **11a** (0.25 mmol, 1 equiv), EtNO₂ (10 equiv), K₃PO₄ (1.2 equiv), Pd catalyst **13** (5 mol%), and 0.5 mL 3 wt% aqueous PS-750-M under argon atmosphere at 45 °C.

^b Percent conversion of **11a** to **12a** was determined by GCMS analysis.

^c Reaction was conducted for 24 h. ^d The specified ligand and Pd source were pre-complexed in dry toluene at 45 °C for 30 min with the solvent being removed and the other reaction components being added under argon atmosphere prior to the start of the reaction. ^e Reaction was conducted with only 5 equiv EtNO₂. ^f Pd(OAc)₂ and HandaPhos were used at 1.5 mol% loadings.

^g Pd₂dba₃ was used at a loading of 2.5 mol% in order to match the Pd loading of the other entries.

^h Fe-ppm Pd nanoparticles were prepared by sequentially adding anhydrous FeCl₃ (5 mol%), **14b** (5 mol%), and Pd(OAc)₂ (0.5 mol%) under argon atmosphere, followed by admixing of 1 mL dry THF for 15 min; a ca. 50 μL volume of a 0.2 M solution of MeMgBr in THF was admixed for 5 min before quenching with a 1 mL volume of 3 wt% aq. PS-750-M, thereby affording active nanoparticles; aryl bromide (0.5 mmol, 1 equiv), EtNO₂ (5 equiv), and K₃PO₄ (1.2 equiv) were sequentially added under argon atmosphere followed by an additional 1 mL of surfactant solution; reaction was allowed to stir at 45 °C.

synthesis is difficult and resource-intensive,^{4,7} so in order for its use to be warranted, it would need to provide comparable performance in the present reaction. Consequently it was screened with Pd and ligand loadings of 1.5 mol%. However, only 5 % conversion was observed within the timeframe of the experiment. Although this performance is superior to that of most of the other catalyst systems screened, it is still inferior compared to **13i** for this particular reaction (for more readily comparable results with **13i** at lower catalyst and nitroalkane loadings, see Table 3.2, entry 13). When XPhos and *t*-BuXPhos were pre-complexed with Pd₂dba₃ immediately prior to the reaction, quite good conversion rates were obtained (entries 14 and 15, 44 % and 60 %) were obtained. Nevertheless, **13i** remained clearly superior, suggesting that the π -allyl ligand was especially important. The possibility of catalysis with Pd-doped Fe nanoparticles⁹⁴ was also checked, but no reactivity was observed, suggesting that the role of molecular catalyst in this reaction might be important and not easily duplicated by a nanomaterial.

Thus, **13i** was selected for use in the remainder of the study. Further optimization (Table 3.2) confirmed that K₃PO₄ was an appropriate base for the micellar system, and that a 1.2equiv base loading was adequate. The reaction did not proceed at all without a base (entry 8), suggesting the importance of the anionic form of EtNO₂ in the reaction. Given the strict requirement for a base, the 1.2equiv loading was deemed particularly appropriate given the operationally simple ambient atmosphere handling of (hygroscopic) K₃PO₄ aliquots used throughout most of this study. The extra 0.2equiv provided margin for error in this regard. Interestingly, organic bases gave roughly comparable results (entries 1 and 2), but inorganic bases appeared to increase in strength with increasing polyionicity. Discernibly lower reaction conversions were first observed when moving from a catalyst loading of 2.5equiv to a loading of 2equiv, so the former loading was selected as optimal. Essentially no reactivity was observed when conducting the reaction at room temperature (Table 3.2, entry 11), so

Table 3.2: Optimization of base, base loading, catalyst loading, temperature, and nitroalkane loading for the micellar Pd-catalyzed coupling of aryl bromides and nitroalkanes.^a

Entry	Base	equiv base	mol% 13i	°C	equiv EtNO ₂	% conv. ^b
1	<i>i</i> -Pr ₂ NEt	2	5	45	10	68
2	NEt ₃	2	5	45	10	60
3	K ₂ CO ₃	2	5	45	10	81
4	KOH	2	5	45	10	51
5	K ₃ PO ₄	2	5	45	10	100
6	K ₃ PO ₄	1.2	5	45	10	100
7	K ₃ PO ₄	1	5	45	10	92
8	K ₃ PO ₄	0	5	45	10	0
9	K ₃ PO ₄	1.2	2.5	45	10	100
10	K ₃ PO ₄	1.2	2	45	10	95
11	K ₃ PO ₄	1.2	2.5	25	10	traces
12	K ₃ PO ₄	1.2	2.5	45	5	100
13	K ₃ PO ₄	1.2	2.5	45	2	85

^a Conditions: aryl bromide **11a** (0.25 mmol, 1 equiv), EtNO₂ (as indicated), base (as indicated), catalyst **13i** (as indicated), and 0.5 mL 3 wt% aqueous PS-750-M under argon atmosphere at 45 °C (unless stated otherwise). ^b Percentage conversion of **11a** to **12a** was determined by GCMS analysis.

45 °C was chosen as the standard reaction temperature. Finally, conversion was first observed to become discernably lower when moving from a nitroalkane loading from 5 equiv to 2 equiv, so 5 equiv was adopted for the standard conditions, although lower loadings would probably be viable if given reaction enough time.

Table 3.3: Effects of additives on the catalyst.^a

Entry	Pd source	Additive	% Yield ^b
1	3 mol% Pd(OAc) ₂	—	45
2	1.5 mol% Pd ₂ dba ₃	—	31
3	3 mol% Pd(OAc) ₂	3 mol% AgOTf	42
4	3 mol% Pd(OAc) ₂	0.01 mol% AgOTf	42
5	1.5 mol% Pd ₂ dba ₃	3 mol% AgOTf	28
6	3 mol% Pd(OAc) ₂	4 mol% propylene ^c	90
7	3 mol% Pd(OAc) ₂	3 mol% allyl bromide	89

^a Conditions: a stir-bar-equipped, oven-dried 10 mL microwave vial was charged with palladium (as indicated), **14c** (3 mol%), and additive (as indicated), and 1 mL dry toluene; the vessel was sealed and pre-complexation was conducted at 50 °C for 15 min; toluene was removed under reduced pressure; under positive pressure of argon, the vessel was then charged with aryl bromide (0.5 mmol, 1 equiv), K₃PO₄ (1.2 equiv), EtNO₂ (5 equiv), and 0.5 mL 3 wt% aqueous PS-750-M; the reaction mixture was stirred under argon atmosphere at 45 °C

^b Percent conversion of **11a** to **12a** was determined by GCMS analysis.

^c Propylene was used as a 0.1 M solution in hexanes.

3.2.1 Mechanistic Insights

During the course of this investigation, additional experiments were conducted to gain better insight into the reaction mechanism. As shown in Table 3.3, the influence of different additives on the reaction was examined using Pd(OAc)₂ or Pd₂dba₃ and **14c** for the catalyst (note that these reactions were conducted at a 3 mol% loading for both ligand and palladium). Because AgOTf was used in the synthesis of **13i**, it was used as an additive in Table 3.3 to assess the presence of any synergistic

catalytic effects arising from residual silver; the additive had essentially no effect. The π -allyl component of **13i** is generally understood to serve as part of a precatalyst complex which is air- and moisture-stable yet easily activated under mild reaction conditions to release the Pd(0) form of the actual catalyst.⁹³ To initially assess the significance of the π -allyl component under our reaction conditions, Pd(OAc)₂ and **14c** were precomplexed in the presence of propylene and allyl bromide. Remarkably, the presence of allyl species in the precomplexation resulted in a dramatic increase in reactivity. It was thus postulated that in our micellar medium the π -allyl component of **13i** may contribute to the catalytic activity by tuning the catalyst’s electronic properties as a π -acid ligand. If true, this would require that **13i** function as a monodentate ligand without non-classical metal–arene ligation.⁹⁵ Further work is necessary to explore this hypothesis.

3.3 Implementation

3.3.1 Exploration of Substrate Scope

Having established presumptive standard conditions for the coupling reaction in micellar media, it was necessary to assess generality and robustness of the process with a substrate scope screening. Typical parameters (e.g., substrate electronics, sterics, and functionality) as well as parameters more specific to micellar media (e.g., substrate lipophilicity, presumed favored micellar/interfacial orientation, and potential for micellar shielding of vulnerable functionalities) were taken into consideration. Bromoarenes electronics were broadly tolerated, and successful couplings were observed for electron-rich (**12a,f,n-q,t,v,ab,ac**), electron-neutral (**12h,j**), and electron-deficient (**12b-e,g,i,k-m,r,s,u,w-aa**) substrates. At the standard reaction temperature of 45 °C, substituents *ortho* to the bromo group were not well tolerated. Only **12h** was obtained in spite of *ortho* steric bulk, and the reaction using *n*-PrNO₂ instead was

Table 3.4: Substrate scope for micellar Pd-catalyzed cross-coupling of aryl bromides and polar nitroalkanes.^{a, b}

^a Conditions: bromoarene **11** (0.5 mmol, 1 equiv), EtNO₂ or *n*-PrNO₂ (5 equiv), K₃PO₄ (1.2 equiv), **13** (2.5 mol%) and 3 wt% aq. PS-750-M were sequentially added to a stir-bar-equipped 10 mL microwave vial by adding solid components under ambient atmosphere, closing the vial with a rubber septum, thrice evacuating/argon-backfilling, and then adding liquid reagents by syringe; septum punctures were covered with electrical tape, the septum was wrapped with high-density PTFE tape, and then reaction mixture was magnetically stirred at 45 °C in a thermostated oil bath. ^b Yield values are for the isolated product. ^c Reaction was conducted at 0.25 mmol scale. ^d Reaction was conducted at 60 °C.

not viable.

Esters (**12b,g,r,z**) were well-tolerated and hydrolysis was not an issue. Nitriles were relatively well-tolerated in some cases (**12c,aa**), but less so in others (**12ad**). A repeated reaction in an attempt to obtain **12aa** in higher yield was unsuccessful due to the reaction stalling at a lower conversions; this result may suggest that degradation of the nitroalkane over time between reaction attempts could play a role in lowering the efficacy of the reaction with certain substrates (see Chapter 4). Fluoro groups (**12d,l,p,w,x,z,aa,ac**) were well tolerated in alkyl and aryl environments. The lower reaction temperature may have assisted in avoiding S_NAr displacement of fluoride from moderately electron-deficient arenes (**12l,w,z,aa**), but most remarkably even the highly vulnerable perfluorobenzamido group of **12ac** remained unaffected, suggesting that a micellar shielding effect may have been responsible. The reaction was found to be selective for bromo groups when comparable chloro groups were present (**12e,s**). As was originally reported by Vogl and Buchwald,⁸⁸ the reaction can take place at the site an aryl chloride. However, a direct comparison showed that while 4-bromotoluene (**11a**) achieved full conversion with EtNO₂ in 24 h at 45 °C under the standard conditions, only 50 % conversion was observed with 4-chlorotoluene at 65 °C and otherwise identical conditions. Thus, the focus of this investigation remained on aryl bromides (see Chapter 4 for a deeper investigation into the differences between chloro, bromo, and iodo group reaction sites). Alkyl aryl ethers (**12f,g,t**) presented no problems; alkyl benzyl and cyclic alkyl ethers were also tolerated (**12ab**). Ketone substrates (**12m,u**) worked well and Aldol side products were not observed. Although the amide of **12ac** was tolerated, this viability may be related to its electron-deficiency or the steric bulk in both positions *ortho* to the anilinic nitrogen; other amides were problematic. Trifluoromethyl groups (**12x**) and a 1,3-benzodioxole derivative were also tolerated (**12ae**).

A variety of heterocyclic systems were also tolerated, including those based on pyri-

dine (**12i**, although heating at 60 °C was required), quinoline (**12k**), benzo[*b*]thiophene (**12n,v**), and furan (**12o**). In the case of **12o**, the reaction was efficient, but volatility of **12o** led to significant product loss during purification; departure from the standard purification protocol used in this study (e.g., distillation instead of column chromatography) would likely improve the isolated yield. Some heteroaromatic systems were not tolerated, however. No reaction was observed with 2-bromobenzo[*d*]thiazole. Similarly, reactions with 2-bromothiophene failed to achieve more than 10 % conversion. Given the successful preparation of **12n,o,v**, it may be that the position of the bromo group is particularly important, and bromides installed on carbons next to heteroatoms may poison the catalyst. Alternately, the lone pair of some heteroaromatics may strongly ligate to the catalyst, requiring higher temperature to permit efficient deligation. The necessity of higher heating for the synthesis of **12i** (where bromo is *ortho* to the nitrogen and the other *ortho* position is unsubstituted) but not for **12k** (where bromo is *meta* to the nitrogen and the second ring provides steric bulk and some degree of fixed 1,3-allylic strain) could be consistent with either hypothesis.

With respect to nitroalkane coupling partner, *n*-PrNO₂ was also examined. Further extension of the alkyl chain length should be viable based on the results by Vogl and Buchwald in the original disclosure of the reaction,⁸⁸ but these substrates were outside the purview of this investigation due to their lower polarity. As is suggested by the exclusive formation of monoarylation products, the nitroalkane scope is likely limited by steric encumbrance.

3.3.2 Reaction Scalability

Reaction scalability was first verified with **11a** and EtNO₂ by adapting the standard conditions from 0.5 mmol scale to 5.85 mmol scale (1.00 g of **11a**). The catalyst loading was also decreased from 2.5 mol% to 1.0 mol%, yet the reaction was monitored as complete after only 14 h, and the product was obtained in 90 % isolated yield. Notably,

this outcome was better than what would be anticipated from the optimization results, and while it may be possible that the larger scale is somehow directly beneficial to this micellar process, slight differences in setup are most likely responsible. In particular, this project had aimed to show that the operational simplicity of, e.g., handling reagents under ambient atmosphere rather than in a glovebox, could still lead to high, reproducible yields.* Although this objective was accomplished as evinced by the substrate scope, catalyst loading, and reaction temperature of the optimized conditions, it may be that sensitivity of the process to light and trace oxygen could be responsible for the difference in outcome observed at large scale. Due to the amount of catalyst being expended in the gram-scale reaction, an abundance of caution was exercised to ensure success; for instance: (1) the air-free reservoir of surfactant solution was freshly sparged with argon immediately before use; (2) a fresh septum was used to close the vessel; (3) after wrapping the septum with PTFE tape, it was also wrapped with a layer of electrical tape; and (4) the reaction vessel was wrapped with aluminum foil to exclude light. Furthermore, the ratio of headspace volume to reaction mixture volume was approximately 2:1 in the gram-scale setup and approximately 19:1 during optimization. The influence of such differences is further explored in Chapter 4.

*This aim was intended to emphasize some of the advantages of a micellar medium. For example, “exclusion” of water is accomplished by the hydrophobicity and shielding of the micellar cores, and the bulk medium is already water, so trace differences in water are negligible. In contrast, water is excluded from organic solvents by drying and handling materials with anhydrous technique, and trace water can have more substantial effects (i.e., the addition of 0.1 wt% water to 3 wt% aqueous PS-750-M increases water content negligibly, but the addition of 0.1 wt% water to THF which had been dried 72 h over 3 Å molecular sieves⁹⁶ would increase the molar water content 800 fold); such changes can affect mesoscale solvent structuring and solute vulnerability.

3.4 Investigation of the Micellar medium

3.4.1 Recycle Study

The recyclability of the reaction medium was also explored as a demonstration of surfactant stability and process robustness. In lieu of periodic monitoring, a fixed reaction time of 24 h determined previously was used for each entry in the recycle study, and GCMS monitoring was only performed shortly prior to the end of this time period to confirm reaction completion. For the “zeroth cycle,” **12a** was prepared at 0.5 mmol scale according to the standard conditions. Once the reaction was confirmed complete at the end of the 24 h reaction period, a 0.3 mL volume of MTBE was added to the reaction mixture and stirred for 2 min. After settling, the organic layer was collected by syringe, and then a subsequent extraction with 0.2 mL MTBE was likewise performed. The combined organic layers were dried over anhydrous Na₂SO₄, volatiles were removed under reduced pressure, and the crude material was purified by column chromatography to afford **12a** in 92 % yield, as confirmed by ¹H NMR.

The aqueous system remaining in the reaction vessel was kept under argon atmosphere throughout the extraction process. For each recycle reaction, a half-portion of **13i** (1.25 mol%) was added to the reaction vessel under argon atmosphere, and the solution was allowed to stir for 5 min. Subsequently, full portions of EtNO₂, K₃PO₄, and **11a** were sequentially added under argon atmosphere. After fully resealing the vessel, the reaction was allowed to run for 24 h before being extracted as described for the zeroth cycle. Isolated yields for the first through fourth recycles were 92 %, 91 %, 90 %, and 92 %. The lack of deterioration in yield throughout these five reaction cycles indicates that (1) the stability of PS-750-M is competent for reproducible implementation of this process, and (2) PS-750-M is well-retained in the aqueous phase during extraction, making it suitable for this style of recycling. The recycle

study also illustrated the suitability of the medium for the “medium recycle strategy” for lowering E Factor. It is noteworthy that half-portions of **13i** were adequate for sustained reactivity throughout recycles; this suggests that partial catalyst retention in the aqueous phase occurred causing some of the catalyst to be recycled along with the medium. This promising indication of catalyst recycling could be systematically investigated with a dedicated study assessing changes in reaction rate between cycles.

3.4.2 Screening of Similar Surfactants

In order to better assess whether the success of PS-750-M in facilitating the arylation of short, polar nitroalkanes was actually attributable to its underlying design principles, similar reaction media were explored with 3,5-bis(trifluoromethyl)bromobenzene (**11b**). The high lipophilicity of **11b** was expected to make it a particularly challenging substrate for micellar implementations of this reaction. As shown in Table 3.5, surfactants TPGS-750-M and PTS were roughly twice as effective as neat water, indicating that micellar catalysis is indeed beneficial. PTS was somewhat less effective than TPGS-750-M. Because the racemic vitamin E hydrophobic region is shared between these surfactants, this difference must be attributable to either the linker or hydrophilic regions. The sebacic acid linker of PTS has a much longer hydrocarbon component than that of the succinic acid linker in TPGS-750-M; this corresponds to a larger nonpolar micellar core region in PTS, which may decrease the accessibility of **11b** for the catalyst. The hydrophilic ethylene oxide chain of PTS is not end-capped with a methyl group and is also shorter than that of TPGS-750-M; these differences might be expected to result in a shorter polarity gradient for PTS micelles. These differences suggest that PTS is less suitable for accommodating *n*-PrNO₂ in its micelles.

PS-750-M was substantially better than either PTS or TPGS-750-M. TPGS-750-M and PS-750-M contain the same mPEG hydrophilic region, so the difference in efficacy must be attributable to the linker or lipophilic regions. The increased polarity of

Table 3.5: Comparison of micellar media for the Pd-catalyzed coupling of 3,5-bis(trifluoromethyl)bromobenzene and *n*-PrNO₂.^a

Entry	Reaction medium	% conv. ^b
1	water	13
2	3 wt% PS-750-M	84 ^c
3	3 wt% TPGS-750-M	28
4	3 wt% PTS	22

PS-750-M

TPGS-750-M

PTS

^a Conditions: as described for the substrate scope, except with the indicated variation in reaction medium. ^b Percentage conversion of **11b** to **12x** was determined by GCMS analysis. ^c Isolated yield from substrate scope results.

the proline linker might be expected to better accommodate *n*-PrNO₂. The “L-shaped” geometry caused by the proline linker may also play a role, potentially affecting movement of surfactant molecules within the micelle. Although the design strategy for PS-750-M was mainly focused on the proline linker polarity, it may also be the case that the shorter hydrophobic region is also beneficial for permitting such intramicellar movement of surfactant molecules. Furthermore, the proximal carbonyl moieties with limited conformational variability might facilitate transport of carbanions in a manner similar to what was suggested in Chapter 2 for sulfonates (see Figure 2.2d). As suggested in the comparison of PTS and TPGS-750-M, the larger hydrophobic component of TPGS-750-M (compared to PS-750-M) may decrease the rate of encounter between **11b** and the catalyst.

3.5 Conclusions

The palladium-catalyzed arylation of EtNO₂ was successfully adapted to micellar solutions of PS-750-M, which appeared to better accommodate the higher polarity of this coupling partner. The π -allyl catalyst **13i** was found to be optimal for the trans-

formation, and control experiments indicated that the π -allyl ligand was especially important for high catalytic activity; one possible explanation which may warrant further investigation is that micellar medium caused the catalyst to behave differently (e.g., by retaining the π -ally component as a π -acid ligand). Following optimization, the conditions were successfully applied to a wide scope of aryl bromides with most good to excellent yields being obtained. Similar results were obtained when using *n*-PrNO₂, and the reaction was readily adapted to gram scale as well. In addition to facilitating the transformation at low temperatures in a sustainable reaction medium (especially as compared to the originally reported solvent, 1,2-dimethoxyethane) with an operationally simple methodology, micellar process manipulation was also considered. In particular, product **12ac** was successfully prepared without the occurrence of S_NAr alkylation of its sensitive pentafluorophenyl moiety, indicating that a micellar shielding effect was in play. The micellar system was also amenable to recycling across multiple reactions. PS-750-M was also compared against structurally similar surfactants using a particularly lipophilic aryl halide; the substantial superiority of PS-750-M in this experiment was very much consistent with the original surfactant design objective of obviating toxic polar organic solvents.

3.6 Supplementary Information

3.6.1 Compound Characterization

1-Methyl-4-(1-nitroethyl)benzene (12a)⁹⁷

The reaction mixture was heated at 45 celsius for 24 hour. Pale colorless oil, 76 mg (92 %), R_f 0.45 (9:1 hexanes/ethyl acetate). **¹H NMR** (400 MHz, CDCl₃) δ (ppm) 7.36 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 5.59 (q, J = 6.9 Hz, 1H), 2.37 (s, 3H), 1.88 (d, J = 7.2 Hz, 3H). **IR** ν (cm⁻¹) 2991 (w), 1613 (w), 1546 (s).

Dimethyl 5-(1-nitroethyl)isophthalate (12b)

White solid, m.p. = 115 °C to 118 °C, 110 mg (82 %), R_f 0.41 (7:3, hexanes/ethyl acetate). **¹H NMR** (400 MHz, CDCl₃) δ (ppm) 8.70 (s, 1H), 8.31 (s, 2H), 5.708 (q, J = 7.2 Hz, 1H), 3.95 (s, 6H), 1.95 (d, J = 7.2 Hz, 3H). **¹³C NMR** (176 MHz, CDCl₃) δ (ppm) 165.5, 136.4, 132.9, 132.8, 132.0, 131.9, 131.7, 85.3 (d, J = 5.45 Hz), 52.8, 52.7, 19.4 (d, J = 10.2 Hz). **IR** ν (cm⁻¹) 3006 (w), 2958 (w), 1720 (s), 1554 (s). **HRMS** (CI) [C₁₂H₁₃NO₆ + H]⁺ calculated 268.0816, found (m/z) 268.0811.

4-(1-Nitroethyl)benzonitrile (12c)⁹⁸

Pale oil, 69 mg (78 %), R_f 0.40 (4:1, hexanes/ethyl acetate). **¹H NMR** (400 MHz,

CDCl_3) δ (ppm) 7.71 (d, $J = 8.4$ Hz, 2H), 7.58 (d, $J = 8.0$ Hz, 2H), 5.65 (q, $J = 7.2$ Hz, 1H), 1.90 (d, $J = 6.8$ Hz, 3H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 140.1, 132.9, 128.4, 118.0, 113.9, 85.4, 19.4. **IR** ν (cm^{-1}) 2993 (w), 2232 (m), 1733 (m), 1549 (s).

1-Fluoro-3-(1-nitroethyl)benzene CAS number 29865-67-6 (12d)

Yellow oil, 64 mg (75 %), R_f 0.49 (4:1, hexanes/ethyl acetate). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 7.38 (dd, $J = 8$ Hz and $J = 6.0$ Hz, 1H), 7.23 (d, $J = 4$ Hz, 1H), 7.19 (d, $J = 9.2$ Hz, 1H), 7.11 (td, $J = 8.4$ Hz and 2 Hz, 1H), 5.60 (q, $J = 7.2$ Hz, 1H), 1.88 (d, $J = 7.2$ Hz, 3H). **IR** ν (cm^{-1}) 2995 (w), 1595 (m), 1548 (s).

1-Chloro-4-(1-nitroethyl)benzene (12e)⁹⁷

Pale oil, 61 mg (66 %), R_f 0.49 (4:1, hexanes/ethyl acetate). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 7.42 – 7.38 (m, 4H), 5.59 (q, $J = 7$ Hz, 1H), 1.88 (d, $J = 6.8$ Hz, 3H). **IR** ν (cm^{-1}) 2991 (w), 1808 (w), 1547 (s).

1-Methoxy-4-(1-nitroethyl)benzene (12f)⁹⁷

Pale oil, 77 mg (83 %), R_f 0.60 (4:1, hexanes/ethyl acetate). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 7.40 (d, $J = 8.4$ Hz, 2H), 6.91 (d, $J = 8.8$ Hz, 2H), 5.57 (q, $J = 7$ Hz, 1H), 3.18 (s, 3H), 1.87 (d, $J = 6.8$ Hz, 3H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm)

160.7, 128.9, 127.7, 114.3, 85.8, 55.4, 19.4. **IR** ν (cm⁻¹) 2939 (w), 2840 (m), 1611 (m), 1546 (s), 1514 (s), 1457 (m).

4-Methoxybenzyl 4-(1-nitroethyl)benzoate (12g)

Pale solid, m.p. = 40 °C to 41 °C, 68 mg (80 %), R_f 0.33 (4:1, hexanes/ethyl acetate). **¹H NMR** (700 MHz, CDCl₃) δ (ppm) 8.09 (d, J = 7.7 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 5.65 (q, J = 7.0 Hz, 1H), 5.30 (s, 2H), 3.81 (s, 3H), 1.91 (d, J = 7.0 Hz, 3H). **¹³C NMR** (176 MHz, CDCl₃) δ (ppm) 165.8, 159.8, 140.1, 131.7, 130.5, 130.3, 127.9, 127.5, 114.1, 85.7, 67.0, 55.43, 19.6. **IR** ν (cm⁻¹) 2959 (w), 2838 (w), 1716 (s), 1612 (m), 1550 (s), 1514 (s). **HRMS** (ESI) [C₁₇H₁₇NO₅ + Na]⁺ calculated 338.1004, found (m/z) 338.0998.

1-(1-Nitroethyl)naphthalene (12h)

Pale yellow oil, 88 mg (88 %), R_f 0.39 (9:1, hexanes/ethyl acetate). **¹H NMR** (700 MHz, CDCl₃) δ (ppm) 8.10 (d, J = 8.4 Hz, 1H), 7.92 (t, J = 6.3 Hz, 2H), 7.69 (d, J = 7 Hz, 1H), 7.61 (t, J = 7.3 Hz, 1H), 7.56 – 7.52 (m, 2H), 6.48 (q, J = 7 Hz, 1H), 2.09 (d, J = 7 Hz, 3H). **¹³C NMR** (176 MHz, CDCl₃) δ (ppm) 133.9, 131.3, 130.5, 129.3, 127.5, 126.3, 125.4, 125.1, 122.2, 82.0, 19.5. **IR** ν (cm⁻¹) 3054 (w), 2995 (w), 1599 (w), 1545 (s), 1512 (m), 1449 (m). **HRMS** (CI) [C₁₂H₁₁NO₂]⁺ calculated 201.0790, found (m/z) 201.0780.

5-Methyl-2-(1-nitroethyl)pyridine (12i)

Yellow oil, 54 mg (65 %), R_f 0.52 (7:3, hexanes/ethyl acetate). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 8.44 (s, 1H), 7.56 (d, $J = 8$ Hz, 1H), 7.33 (d, $J = 8$ Hz, 1H), 5.72 (q, $J = 6.8$ Hz, 1H), 2.35 (s, 3H), 1.92 (d, $J = 6.8$ Hz, 3H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 151.7, 150.31, 137.9, 134.3, 121.9, 86.8, 18.4. **IR** ν (cm^{-1}) 2926 (w), 1693 (m), 1632 (w), 1568 (s), 1510 (m), 1479 (m). **HRMS** (CI) $[\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2 - \text{H}]^+$ calculated 165.0659, found (m/z) 165.0652.

(1-Nitroethyl)benzene (12j)⁹⁷

White pale oil, 69 mg (91 %), R_f 0.41 (9:1, hexanes/ethyl acetate). **^1H NMR** (700 MHz, CDCl_3) δ (ppm) 7.47 – 7.41 (m, 5H), 5.62 (q, $J = 7$ Hz, 1H), 1.90 (d, $J = 7$ Hz, 3H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 135.6, 129.8, 129.1, 127.5, 86.2, 19.5. **IR** ν (cm^{-1}) 2992 (w), 1735 (m), 1546 (s), 1498 (m), 1455 (m).

3-(1-Nitroethyl)quinoline (12k)

Orange solid, m.p. = 62 /celsius to 94 /celsius, 66 mg (65 %), R_f 0.33 (1:1, hexanes/ethyl acetate). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 8.98 (d, $J = 1.2$ Hz, 1H), 8.25 (s, 1H), 8.12 (d, $J = 8.8$ Hz, 1H), 7.84 (d, $J = 8$ Hz, 1H), 7.765 (t, $J = 7.6$ Hz, 1H), 7.59 (t, $J = 7.6$ Hz, 1H), 5.82 (q, $J = 6.8$ Hz, 1H), 2.03 (d, $J = 6.8$ Hz, 3H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 149.3, 148.6, 135.2, 130.8, 129.4, 128.2, 127.6, 127.4, 84.0, 19.5. **IR** ν (cm^{-1}) 3143 (w), 3063 (w), 2773 (w), 1682 (m), 1619 (w), 1569 (m),

1495 (m). **HRMS** (CI) $[\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_2 + \text{H}]^+$ calculated 203.0815, found (m/z) 203.0814.

1,3-Difluoro-5-(1-nitropropyl)benzene (12l)

Yellow oil, 66 mg (70 %), R_f 0.33 (9:1, hexanes/ethyl acetate). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 7.00 (d, $J = 5.6$ Hz, 2H), 6.87 (t, $J = 8.8$ Hz, 1H), 5.56 (q, $J = 6.8$ Hz, 1H), 1.87 (d, $J = 6.8$ Hz, 3H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 163.9 (d, $J = 12.3$ Hz), 162.5 (d, $J = 12.1$ Hz), 138.7, 110.9 (q, $J = 16.4$ Hz and 4.7 Hz), 105.7 (t, $J = 25.2$ Hz), 85.1, 19.4. **^{19}F NMR** (376 MHz, CDCl_3) δ (ppm) -107.75 (t, $J = 5$ Hz). **IR** ν (cm^{-1}) 3094 (w), 2941 (w), 1732 (m), 1624 (m), 1599 (s), 1552 (s), 1448 (m). **HRMS** (CI) $[\text{C}_8\text{H}_7\text{F}_2\text{NO}_2 + \text{H}]^+$ calculated 188.0518, found (m/z) 188.0520.

1-(4-(1-Nitroethyl)phenyl)ethan-1-one (12m)

Yellow oil, 65 mg (67 %), R_f 0.36 (7:3, hexanes/ethyl acetate). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 7.98 (d, $J = 8$ Hz, 2H), 7.55 (d, $J = 7.6$ Hz, 2H), 5.66 (q, $J = 7$ Hz, 1H), 2.60 (s, 3H), 1.91 (d, $J = 6.8$ Hz, 3H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 197.4, 140.1, 138.2, 129.1, 127.8, 85.7, 26.1, 19.5. **IR** ν (cm^{-1}) 2994 (w), 1682 (s), 1609 (m), 1542 (s), 1550 (s), 1417 (m). **HRMS** (CI) $[\text{C}_{10}\text{H}_{11}\text{NO}_3 + \text{H}]^+$ calculated 194.0812, found (m/z) 194.0809.

6-(1-Nitroethyl)benzo[d]thiophene (12n)

Pale orange solid, m.p. = 42 °C to 45 °C, 80 mg (77%), R_f 0.35 (9:1, hexanes/ethyl acetate). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 8.00 (s, 1H), 7.84 (d, J = 8 Hz, 1H), 7.53 (d, J = 5.6 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 5.2 Hz, 1H), 5.74 (q, J = 6.8 Hz, 1H), 1.97 (d, J = 7.2 Hz, 3H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 140.6, 140.1, 131.6, 128.5, 124.2, 123.7, 123.5, 121.8, 86.4, 19.7. **IR** ν (cm^{-1}) 3104 (w), 2934 (w), 1733 (w), 1599 (w), 1535 (s), 1463 (m). **HRMS** (CI) $[\text{C}_{10}\text{H}_9\text{NO}_2\text{S} + \text{H}]^+$ calculated 208.0427, found (m/z) 208.0423.

3-(1-Nitroethyl)furan (12o)

Orange oil, 23 mg (32%), R_f 0.42 (9:1, hexanes/ethyl acetate). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 7.56 (s, 1H), 7.43 (s, 1H), 6.53 (s, 1H), 5.56 (q, J = 6.8 Hz, 1H), 1.84 (d, J = 6.8 Hz, 3H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 144.1, 141.4, 121.5, 109.1, 78.4, 19.2. **IR** ν (cm^{-1}) 3139 (w), 2963 (w), 1549 (s), 1506 (m), 1454 (w). **HRMS** (CI) $[\text{C}_6\text{H}_7\text{NO}_3 + \text{H}]^+$ calculated 142.0499, found (m/z) 142.0503.

2,2-Difluoro-5-(1-nitropropyl)benzo[d][1,3]dioxole (12p)

Yellow oil, 113 mg (92%), R_f 0.17 (9:1, hexanes/dichloromethane). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 7.26 (s, 1H), 7.19 (d, 1H, J = 8.8 Hz), 7.08 (d, 1H, J = 8.4 Hz), 5.34 (t, 1H, J = 7.2 Hz), 2.56–2.41 (m, 1H), 2.16–2.02 (m, 1H), 0.99 (t, 3H, J = 7.2 Hz). **^{13}C NMR** (100 MHz, CDCl_3) δ (ppm) 144.6 (d, J = 51.6 Hz),

131.8 (t, $J = 255.2$ Hz), 130.5, 124.2. **^{19}F NMR** (376 MHz, CDCl_3) δ (ppm) -49.8. **IR** ν (cm^{-1}) 3133 (w), 3093 (w), 3062 (w), 2980 (m), 2942 (m), 2885 (m), 1551 (s). **HRMS** (CI) $[\text{C}_{10}\text{H}_9\text{F}_2\text{NO}_4 + \text{H}]^+$ calculated 246.0572, found (m/z) 246.0576.

1-Methyl-4-(1-nitropropyl)benzene (12q)⁹⁹

Pale oil, 58 mg (65 %), R_f 0.47 (9:1, hexanes/ethyl acetate). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 7.35 (d, $J = 8$ Hz, 2H), 7.20 (d, $J = 8$ Hz, 2H), 5.34 (dd, $J = 6.5$ Hz and 2.5 Hz, 1H), 2.54 – 2.45 (m, 1H), 2.36 (s, 3H), 2.14 – 2.05 (m, 1H), 0.98 (t, $J = 6.5$ Hz, 3H). **IR** ν (cm^{-1}) 2977 (w), 2938 (w), 2882 (w), 1614 (w), 1546 (s), 1515 (m), 1458 (m).

Dimethyl 5-(1-nitropropyl)isophthalate (12r)

White solid, m.p. = 70 °C to 71 °C, 108 mg (77 %), R_f 0.43 (7:3, hexanes/ethyl acetate). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 8.70 (t, $J = 1.5$ Hz, 1H), 8.32 (d, $J = 1.5$ Hz, 2H), 5.47 (dd, $J = 6.5$ Hz, and 2.0 Hz, 1H), 3.96 (s, 6H), 2.62 – 2.53 (m, 1H), 2.20 – 2.12 (m, 1H), 1.0 (t, $J = 7.2$ Hz, 3H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 165.5, 135.4, 133.2, 132.0, 131.6, 92.0, 52.8, 27.4, 10.7. **IR** ν (cm^{-1}) 2953 (w), 1718 (s), 1606 (w), 1547 (s), 1436 (m). **HRMS** (ESI) $[\text{C}_{13}\text{H}_{15}\text{NO}_6 + \text{Na}]^+$ calculated 304.0797, found (m/z) 304.0792.

1-Chloro-4-(1-nitropropyl)benzene (12s)⁹⁹

Yellow oil, 42 mg (83 %), R_f 0.44 (4:1, hexanes/ethyl acetate). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 7.42 – 7.37 (m, 4H), 5.34 (t, $J = 7.5$ Hz, 1H), 2.55 – 2.43 (m, 1H), 2.14 – 2.03 (m, 1H), 0.98 (t, $J = 7.6$ Hz, 3H). **IR** ν (cm^{-1}) 2977 (w), 2939 (w), 2882 (w), 1547 (s), 1493 (m).

1-Methoxy-4-(1-nitropropyl)benzene (12t)

Yellow oil, 64 mg (65 %), R_f 0.32 (9:1, hexanes/ethyl acetate). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 7.40 – 7.38 (m, 2H), 9.92 – 6.89 (m, 2H), 5.32 (dd, $J = 7$ Hz and 2.0 Hz, 1H), 3.81 (s, 3H), 2.53 – 2.44 (m, 1H), 2.13 – 2.04 (m, 1H), 0.97 (t, $J = 7.5$ Hz, 3H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 160.7, 129.3, 126.7, 114.3, 92.7, 55.4, 27.3, 10.8. **IR** ν (cm^{-1}) 2975 (w), 2939 (w), 1840 (w), 1611 (m), 1545 (s), 1514 (s), 1460 (m).

1-(4-(1-Nitropropyl)phenyl)ethan-1-one (12u)⁸⁸

Yellow semisolid, 78 mg (75 %), R_f 0.24 (4:1, hexanes/ethyl acetate). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 7.98 (d, 2H, $J = 8.5$ Hz), 7.56 (d, 2H, $J = 8.0$ Hz), 5.42 (dd, 1H, $J = 8.5$ Hz and 6.5 Hz), 2.60 (s, 3H), 2.57–2.46 (m, 1H), 2.19–2.07 (m, 1H), 0.99 (t, 3H, $J = 7.5$ Hz).

6-(1-Nitropropyl)benzo[d]thiophene (12v)

Pale yellow oil, 89 mg (80 %), R_f 0.45 (9:1, hexanes/ethyl acetate). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 8.00(s, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.52 (d, $J = 5.6$ Hz, 1H), 7.47(d, $J = 8.4$ /hertz, 1H), 7.35 (d, $J = 5.6$ Hz, 1H), 5.49 (t, $J = 7.6$ Hz, 1H), 2.64 – 2.53 (m, 1H), 2.25 – 2.14 (m, 1H), 1.01 (t, $J = 7.2$ Hz, 3H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 140.7, 140.1, 130.6, 128.4, 124.2, 123.8, 123.7, 122.3, 93.2, 27.6, 10.8. **IR** ν (cm^{-1}) 3105 (w), 2975 (w), 2937 (w), 2880 (w), 1734 (w), 1544 (s), 1462 (m). **HRMS** (CI) $[\text{C}_{11}\text{H}_{11}\text{NO}_2\text{S} + \text{H}]^+$ calculated 222.0583, found (m/z) 222.0584.

1,3-Difluoro-5-(1-nitropropyl)benzene (12w)

Pale yellow oil, 42 mg (42 %), R_f 0.44 (9:1, hexanes/ethyl acetate). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 7.01 (d, $J = 6.0$ Hz, 2H), 6.87 (t, $J = 8.8$ /hertz, 1H), 5.31 (t, $J = 7.8$ Hz, 1H), 2.52 – 2.41 (m, 1H), 2.14 – 2.03 (m, 1H), 1.00 (t, $J = 7.2$ Hz, 3H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 163.9 (d, $J = 12.8$ Hz), 162.5 (d, $J = 3$ Hz), 137.7, 111.2 (q, $J = 16.4$ Hz and 4.75 Hz), 105.5 (d, $J = 25$ Hz), 91.9, 27.5, 10.6. **^{19}F NMR** (376 MHz, CDCl_3) δ (ppm) - 107.83 (t, $J = 7.2$ Hz). **IR** ν (cm^{-1}) 3096 (w), 2979 (w), 1623 (m), 1598 (s), 1552 (s), 1464 (m). **HRMS** (CI) $[\text{C}_9\text{H}_9\text{F}_2\text{NO}_2 + \text{H}]^+$ calculated 202.0674, found (m/z) 202.0667.

1-(1-Nitropropyl)-3,5-bis(trifluoromethyl)benzene (12x)

Pale yellow oil, 63 mg (84 %), R_f 0.30 (9:1, hexanes/ethyl acetate). **^1H**

NMR (500 MHz, CDCl₃) δ (ppm) 7.94 (s, 3H), 5.49 (dd, 1H, J = 9.0 Hz and 6.5 Hz), 2.64–2.52 (m, 1H), 2.20–2.10 (m, 1H), 1.04 (t, 3H, J = 7.5 Hz). **¹³C NMR** (126 MHz, CDCl₃) δ (ppm) 136.7, 132.8 (q, J = 33.6 Hz), 128.3, 124.1, 123.0 (q, J = 273.0 Hz), 91.8, 27.8, 10.7. **¹⁹F NMR** (470 MHz, CDCl₃) δ (ppm) –63.0. **IR** ν (cm^{–1}) 3101 (w), 3072 (w), 2983 (m), 2945 (m), 2888 (m), 1557 (s). **HRMS** (CI) [C₁₁H₉F₆NO₂ – F]⁺ calculated 282.0548, found (m/z) 282.0541.

4-(1-Nitropropyl)benzonitrile (12y)

Pale yellow oil, 31 mg (33 %), R_f 0.32 (4:1, hexanes/ethyl acetate). **¹H NMR** (500 MHz, CDCl₃) δ (ppm) 7.71 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 5.40 (q, J = 6.5 Hz and 2.5 Hz, 1H), 2.55 – 2.49 (m, 1H), 2.14 – 2.07 (m, 1H), 1.00 (t, J = 7.2 Hz, 3H). **¹³C NMR** (176 MHz, CDCl₃) δ (ppm) 139.1, 132.9, 128.7, 118.1, 114.0, 92.3, 27.6, 10.7. **IR** ν (cm^{–1}) 2979 (w), 2940 (w), 2232 (m), 1734(m), 1549 (s), 1506 (m), 1460 (w). **HRMS** (CI) [C₁₀H₁₀N₂O₂ + H]⁺ calculated 191.0815, found (m/z) 191.0807.

Methyl 2-fluoro-4-(1-nitropropyl)benzoate (12z)

Yellow semisolid, 41 mg (68 %), R_f 0.13 (9:1, hexanes/ethyl acetate). **¹H NMR** (400 MHz, CDCl₃) δ (ppm) 7.98 (t, 1H, J = 7.6 Hz), 7.34–7.24 (m, 2H), 5.39 (t, 1H, J = 7.6 Hz), 3.94 (s, 3H), 2.56– 2.42 (m, 1H), 2.18–2.04 (m, 1H), 1.00 (s, 3H, J = 6.8 Hz). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm) 164.3, 161.9 (d, J = 260.5 Hz), 140.9 (d, J = 8.4 Hz), 123.5 (d, J = 3.1 Hz), 120.0 (d, J = 10.6 Hz), 116.5 (d, J = 23.5 Hz), 91.9, 52.7, 27.6, 10.6. **¹⁹F NMR** (376 MHz, CDCl₃) δ (ppm)

–107.6 (dd, $J = 10.9$ Hz and 7.9 Hz). **IR** ν (cm^{-1}) 3096 (w), 3073 (w), 3054 (w), 2977 (m), 2957 (m), 2941 (w), 2921 (m), 2885 (m), 2850 (m), 1723 (s), 1624 (m), 1551 (s). **HRMS** (CI) $[\text{C}_{11}\text{H}_{12}\text{FNO}_4 + \text{H}]^+$ calculated 242.0823, found (m/z) 242.0814.

2-Fluoro-5-(1-nitropropyl)benzonitrile (12aa)

Yellow oil, 27 mg (52%), R_f 0.12 (4:5, hexanes/ethyl acetate). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 7.79–7.68 (m, 2H), 7.29 (t, 1H, $J = 8.5$ Hz), 5.37 (dd, 1H, $J = 8.0$ Hz and 7.0 Hz), 2.56–2.42 (m, 1H), 2.14–2.00 (m, 1H), 1.00 (t, 3H, $J = 7.5$ Hz). **^{13}C NMR** (126 MHz, CDCl_3) δ (ppm) 163.8 (d, $J = 264.3$ Hz), 134.8 (d, $J = 8.6$ Hz), 133.4, 131.6, 117.5 (d, $J = 20.2$ Hz), 113.1, 102.7, 91.2, 27.6, 10.6. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) –104.0– –104.2 (m, 1F). **IR** ν (cm^{-1}) 3128 (w), 3074 (w), 3056 (w), 2978 (m), 2923 (m), 2884 (w), 2852 (m), 2238 (m), 1551 (s). **HRMS** (CI) $[\text{C}_{10}\text{H}_9\text{FN}_2\text{O}_2 + \text{H}]^+$ calculated 209.0721, found (m/z) 209.0725.

3-((4-(1-Nitropropyl)benzyl)oxy)tetrahydrofuran (12ab)

Yellow oil, 54 mg (82%), R_f 0.14 (4:1, hexanes/ethyl acetate). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 7.44 (d, 2H, $J = 8.0$ Hz), 7.37 (d, 2H, $J = 8.0$ Hz), 5.36 (t, 1H, $J = 8.4$ Hz), 4.55–4.46 (m, 2H), 4.21 (s, 1H), 3.91 (q, 1H, $J = 7.6$ Hz), 3.89–3.77 (m, 3H), 2.56–2.43 (m, 1H), 2.16–1.95 (m, 3H), 0.97 (t, 3H, $J = 7.6$ Hz). **^{13}C NMR** (100 MHz, CDCl_3) δ (ppm) 140.2, 133.9, 128.1, 128.0, 92.9, 79.4, 72.9, 70.5, 67.2, 32.7, 27.4, 10.7. **IR** ν (cm^{-1}) 3060 (w), 3034 (w), 2975 (m), 2940 (m), 2868 (m), 1547 (s). **HRMS** (CI) $[\text{C}_{14}\text{H}_{19}\text{NO}_4 - \text{H}]^+$ calculated 264.1230, found (m/z) 264.1224.

***N*-(2,6-Dimethyl-4-(1-nitropropyl)phenyl)-2,3,4,5,6-pentafluorobenzamide (12ac)**

White powder, m.p. = 158 °C to 160 °C, 43 mg (59 %), R_f 0.23 (4:1, hexanes/ethyl acetate). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 7.53 (s, 1H), 7.18 (s, 2H), 5.31 (t, J = 6.8 Hz, 1H), 2.56–2.44 (m, 1H), 2.23 (s, 6 H), 2.107–2.00 (m, 1H), 1.00 (t, J = 6.8 Hz, 1H). **^{13}C NMR** (100 MHz, CDCl_3) δ (ppm) 156.1, 144.7 (d, J = 161.7 Hz), 142.1 (d, J = 167.8 Hz), 139.1, 136.6, 134.4, 133.8, 127.8, 111.5 (t, J = 19.7 Hz), 92.8, 27.4, 18.5, 10.8. **^{19}F NMR** (376 MHz, CDCl_3) δ (ppm) –140.2 – –140.5 (m, 2F), –150.2 (t, J = 20.7 Hz, 1F), –159.5 – –157.8 (m, 1F). **IR** ν (cm^{-1}) 3228 (m), 3196 (s), 3138 (s), 3041 (m), 1918 (s) 2850 (s), 1662 (s). **HRMS** (ESI) $[\text{C}_{18}\text{H}_{15}\text{F}_5\text{N}_2\text{O}_3 + \text{H}]^+$ calculated 403.1081, found (m/z) 403.1077.

3.6.2 NMR Spectra

1-Methyl-4-(1-nitroethyl)benzene (12a) ^1H NMR

Dimethyl 5-(1-nitroethyl)isophthalate (12b) ^1H NMR

Dimethyl 5-(1-nitroethyl)isophthalate (12b) ^{13}C NMR

4-(1-Nitroethyl)benzonitrile (12c) ^1H NMR

4-(1-Nitroethyl)benzonitrile (12c) ^{13}C NMR

1-Fluoro-3-(1-nitroethyl)benzene CAS number 29865-67-6 (12d) ^1H NMR

1-Chloro-4-(1-nitroethyl)benzene (12e) ^1H NMR

1-Methoxy-4-(1-nitroethyl)benzene (12f) ^1H NMR

1-Methoxy-4-(1-nitroethyl)benzene (12f) ^{13}C NMR

4-Methoxybenzyl 4-(1-nitroethyl)benzoate (12g) ^1H NMR

4-Methoxybenzyl 4-(1-nitroethyl)benzoate (12g) ^{13}C NMR

1-(1-Nitroethyl)naphthalene (12h) ^1H NMR

1-(1-Nitroethyl)naphthalene (12h) ^{13}C NMR

5-Methyl-2-(1-nitroethyl)pyridine (12i) ^1H NMR

5-Methyl-2-(1-nitroethyl)pyridine (12i) ^{13}C NMR

(1-Nitroethyl)benzene (12j) ^1H NMR

(1-Nitroethyl)benzene (12j) ^{13}C NMR

3-(1-Nitroethyl)quinoline (12k) ^1H NMR

3-(1-Nitroethyl)quinoline (12k) ^{13}C NMR

1,3-Difluoro-5-(1-nitropropyl)benzene (12l) ^1H NMR

1,3-Difluoro-5-(1-nitropropyl)benzene (12l) ^{13}C NMR

1,3-Difluoro-5-(1-nitropropyl)benzene (12l) ^{19}F NMR

1-(4-(1-Nitroethyl)phenyl)ethan-1-one (12m) ^1H NMR

1-(4-(1-Nitroethyl)phenyl)ethan-1-one (12m) ^{13}C NMR

6-(1-Nitroethyl)benzo[d]thiophene (12n) ¹H NMR

6-(1-Nitroethyl)benzo[d]thiophene (12n) ¹³C NMR

3-(1-Nitroethyl)furan (12o) ^1H NMR

3-(1-Nitroethyl)furan (12o) ^{13}C NMR

2,2-Difluoro-5-(1-nitropropyl)benzo[d][1,3]dioxole (12p) ^1H NMR

2,2-Difluoro-5-(1-nitropropyl)benzo[d][1,3]dioxole (12p) ^{13}C NMR

2,2-Difluoro-5-(1-nitropropyl)benzo[d][1,3]dioxole (12p) ^{19}F NMR

1-Methyl-4-(1-nitropropyl)benzene (12q) ^1H NMR

Dimethyl 5-(1-nitropropyl)isophthalate (12r) ^1H NMR

Dimethyl 5-(1-nitropropyl)isophthalate (12r) ^{13}C NMR

1-Chloro-4-(1-nitropropyl)benzene (12s) ^1H NMR

1-Methoxy-4-(1-nitropropyl)benzene (12t) ^1H NMR

1-Methoxy-4-(1-nitropropyl)benzene (12t) ^{13}C NMR

1-(4-(1-Nitropropyl)phenyl)ethan-1-one (12u) ^1H NMR

6-(1-Nitropropyl)benzo[d]thiophene (12v) ^1H NMR

6-(1-Nitropropyl)benzo[d]thiophene (12v) ¹³C NMR

1,3-Difluoro-5-(1-nitropropyl)benzene (12w) ^1H NMR

1,3-Difluoro-5-(1-nitropropyl)benzene (12w) ^{13}C NMR

1,3-Difluoro-5-(1-nitropropyl)benzene (12w) ^{19}F NMR

CC(C)(F)C1=CC=C(C(F)(F)F)C(F)(F)F1 CC(C)(F)C1=CC=C(C(F)(F)F)C(F)(F)F1

1-(1-Nitropropyl)-3,5-bis(trifluoromethyl)benzene (12x) ^{19}F NMR

4-(1-Nitropropyl)benzonitrile (12y) ^1H NMR

4-(1-Nitropropyl)benzonitrile (12y) ^{13}C NMR

Methyl 2-fluoro-4-(1-nitropropyl)benzoate (12z) ^1H NMR

Methyl 2-fluoro-4-(1-nitropropyl)benzoate (12z) ^{13}C NMR

Methyl 2-fluoro-4-(1-nitropropyl)benzoate (12z) ^{19}F NMR

2-Fluoro-5-(1-nitropropyl)benzonitrile (12aa) ^1H NMR

2-Fluoro-5-(1-nitropropyl)benzonitrile (12aa) ^{13}C NMR

2-Fluoro-5-(1-nitropropyl)benzonitrile (12aa) ^{19}F NMR

3-((4-(1-Nitropropyl)benzyl)oxy)tetrahydrofuran (12ab) ^1H NMR

3-((4-(1-Nitropropyl)benzyl)oxy)tetrahydrofuran (12ab) ^{13}C NMR

N-(2,6-Dimethyl-4-(1-nitropropyl)phenyl)-2,3,4,5,6-pentafluorobenzamide (12ac) ^1H NMR

N-(2,6-Dimethyl-4-(1-nitropropyl)phenyl)-2,3,4,5,6-pentafluorobenzamide (12ac) ^{13}C NMR

N-(2,6-Dimethyl-4-(1-nitropropyl)phenyl)-2,3,4,5,6-pentafluorobenzamide (12ac) ^{19}F NMR

CHAPTER 4

SYNERGISTIC HALOSEQUESTRATION IN
PALLADIUM-CATALYZED NITROALKANE ARYLATION:
INSIGHT INTO THE INFLUENCE OF
TETRAALKYLAMMONIUM SALTS, HALIDE
SOLVATION, AND SUPRAMOLECULAR HYDRATES

New, sustainable variations on the classic technique of halosequestration were developed and explored in order to make the nitroalkane arylation reaction discussed in Chapter 3 more industrially viable. As shown in Figure 4.1, the micellar conditions originally developed for this reaction suffered three primary drawbacks: (1) aryl iodides were not viable substrates; (2) the reaction time was too long; and (3) the loading of the somewhat expensive catalyst was too high. Through use of halosequestrative conditions, aryl iodides became viable, and reactions with aryl bromides could be conducted in one tenth the time with one tenth the catalyst—effectively a hundred-fold increase in reactivity.

4.1 Background

Pseudophase manipulation in the service of synthetic chemistry is well-precedented^{11,32,56,100} and has recently grown substantially in prominence due to rising concerns about the waste and hazards associated with traditional organic

Figure 4.1: Overview of halosequestrative improvements to the Pd-catalyzed arylation of nitroalkanes.

solvents.^{81,101,102} In particular, designer surfactants have been developed with the aim of establishing and optimizing micellar conditions for broad classes of transformations.^{5,64,103,104} In addition to replacing organic solvent with water as the bulk reaction medium, micellar catalysis can also lower temperatures and reaction times by, e.g., localizing the reactants in high concentration within the micelles.⁹ Directed enhancements to this particular type of pseudophase manipulation by targeted adjustment of surfactant design has been used to broaden the range of reactions for which this methodology is viable; for example, the surfactant PS-750-M was designed with the intention of introducing higher polarity to the non-polar micellar interior, thereby better mimicking polar aprotic solvents.^{64,65} Other research focuses on the practical realization of new or underdeveloped implementations of pseudophase manipulation; for example, application of the micellar shielding effect¹⁰⁵ has enabled the monofluorination of indoles (selectively over difluorination or oxidation) by partitioning the substrate and especially the fluorinated product into the less-polar inner core of aqueous PS-750-M micelles, which exhibit low oxygen solubility and limit micellar penetration of the fluorinating agent to the outer-core–inner-core interface.¹⁰⁶ A particularly underdeveloped use of pseudophase manipulation is halosequestration, which—in the context of green chemistry¹⁰⁷—is itself an underdeveloped process. For example, transition-metal-mediated coupling reactions frequently produce halide salt byproducts which can deleteriously impact

the reaction (e.g., by blocking catalyst ligation sites); a pseudophase system which promotes separation of halides and halide-sensitive reaction components should ameliorate such issues.

Although halosequestration in certain synthetic applications is well known, its use is generally restricted to situations of absolute necessity due to significant drawbacks associated with conventional halosequestrants (salts of Ag, Pb, or Tl), such as their cost, scarcity, toxicity, or potential reactivity. In order to unlock the full potential of this process, it is essential that greener halosequestrative techniques be developed. In 2014 Larrosa and coworkers identified Me_4NCl as a viable silver replacement in the arylation of sp^2 and sp^3 C–H bonds.¹⁰⁸ The importance of this realization has yet to be fully appreciated, however, because it has thus far been framed in the context of *avoiding Ag usage* rather than in the context of *sustainably enhancing reactivity*. The former framing absolutely represents a laudable accomplishment in its own right, particularly as part of a larger research enterprise wherein the same group has developed Ag-free alternatives to the Hunsdieker reaction.^{109,110} Nevertheless, the latter framing is important. Because Ag can play a variety of different roles in C–H activation processes such as that of a terminal oxidant or a transition state participant,^{111,112} Me_4NCl cannot replace Ag in many cases;¹¹³ consequently, attention to this innovation has been limited largely to the C–H activation community where it may be regarded merely as an occasionally viable sustainability enhancement when halide abstraction is needed to regenerate the active catalyst.¹¹⁴ When considered alongside the precedent of other reactions which are accelerated by inclusion of tetralkylammonium salts, however, a bigger picture emerges pointing to the general value and significance of halosequestration.

Particularly relevant in this regard are the Jeffery conditions for the Mizoroki–Heck reaction, which cause substantial improvements in yield, selectivity, and reaction temperature through inclusion of $n\text{-Bu}_4\text{NCl}$ and use of an inorganic base.^{52,115} Jeffery

Figure 4.2: Broad classification of halosequestration and their relevance to the conditions developed for the improved Pd-catalyzed arylation of nitroalkanes. **a** Explanations and examples of primary, secondary, and tertiary halosequestration. **b** Influence of halides on selected reaction pathways in the proposed mechanism for Pd-catalyzed nitroalkane arylation. Equilibria potentially benefiting from halosequestration are highlighted. **c** Halosequestrative effects attributed to the three halosequestrative additives explored in this study; color coding corresponds to the Venn diagram.

originally hypothesized in 1984 that solid–liquid phase transfer catalysis (PTC)¹¹⁶ of the base was responsible for the observed enhancements.¹¹⁵ The following year, however, Hallberg and coworkers disclosed that similar enhancements could be achieved through inclusion of AgNO₃ as an additive.^{117,118} Despite being aware (and in fact a contributor^{119–123}) of such reports on the enhancement of the Mizoroki–Heck reaction by salts of the halophilic metals Ag and Tl, Jeffery appears to have tacitly maintained the PTC hypothesis for tetralkylammonium salt additives (or at least a related hypothesis that the identity of the tetralkylammonium salt anion is inconsequential^{51,124}) in subsequent published work.^{125–128} Regardless of whether the significance of the halophilic nature of the tetralkylammonium cations was ultimately recognized, these earlier hypotheses continue to be echoed in the present,¹²⁹ even though Jeffery’s later publications laid

the groundwork for new understanding.^{52,125–127} Since then, Jeffery-like conditions incorporating a peralkylammonium cation have been developed for a number of other reactions, including the Suzuki,¹³⁰ Sonogashira,¹³¹ Stille,¹³² and Ullmann¹³³ couplings, yet halosequestration has not been identified as a contributing factor. Assuming that the halosequestrative action of an affordable tetralkylammonium salt is responsible for the enhancement of these reactions, a modified sustainability analysis becomes defensible. If the inclusion of such additives, which contain no endangered elements,¹³⁴ allows for at least comparable results with a substantially lower catalyst loading, then the value of the catalyst saved must be compared against the value of the additive expended. Depending on the preciousness of the catalyst in question, the use of such additives might rightly be characterized as more sustainable, despite the higher local process mass intensity (PMI).¹³⁵

Furthermore, other types of halosequestration might be beneficially employed. We propose three different categories of halosequestration (Figure 4.2a): (1) primary halosequestration, wherein the halide is converted to a less reactive species, such as AgX in the Kornblum oxidation;¹³⁶ (2) secondary halosequestration, wherein halide activity is attenuated by local interactions in the reaction mixture, as is seen in solvent effects on halide equilibria;¹³⁷ and (3) tertiary halosequestration, wherein the halide is confined to a separate environment, such as molecular sieves in the Fuchikami base-free carbonylation.¹³⁸ As shown in Figure 4.2b, there are multiple equilibria in the nitroalkane arylation reaction which might benefit from halosequestration. Our efforts to improve this reaction (Figure 4.1) ultimately led to methodology which synergistically leveraged all three halosequestration types (the halosequestrative function of each reaction modification is presented in Figure 4.2c). The limitations of our preliminary conditions⁶⁴ contrasted against the triply halosequestrative conditions shows the significance of the halosequestrative approach; namely, comparable or better results can be obtained in one tenth of the time with one tenth of the catalyst through

halosequestration, and the practical scope is expanded to include aryl iodides, which have also proven problematic in related reactions^{92,139} (Figure 4.1). The imaginary scales in Figure 4.1 illustrates how halosequestrative conditions can be more sustainable despite having a superficially higher PMI. Ideally, a metric like PMI should account for the intrinsic mass intensity associated with the preparation of input materials¹⁴⁰ (e.g., cumulative PMI, cPMI), in which case the sustainability of halosequestrative additives becomes apparent. For the sake of simplicity in this illustration, input material costs are assumed to adequately correlate with, and serve as a proxy for, cPMI.¹⁴¹ Accordingly, the imaginary scales compare the monetary value on either side rather than the mass. In this case, the cost of Pd catalyst **16** (\$584,180/mol) is so much greater than that of the additive (\$20/mol) that trading 29,000 mol of Me₄NCl for 1 mol of **16** would still be cost beneficial, assuming the reaction outcome remained unchanged. On a per-reaction basis for the actual conditions employed, halosequestration results in a nearly 90 % reduction in cost (see Section ??) without even accounting for the ca. 10-fold improvement in rate.

4.2 Development of Halosequestrative Conditions

4.2.1 Enabling Use of Aryl Iodides Through Primary Halosequestration

The initial stages of this study began with an investigation into the atypical unsuitability of aryl iodides with our preliminary conditions. In the absence of additives, the model reaction conditions for the coupling of 4-iodoanisole (**15a**) with 1-nitropropane (*n*-PrNO₂) resulted in only 23 % conversion after 14 hour, and subsequent monitoring showed no further aryl halide consumption (Table 4.1, entry 1). In contrast, the typically more difficult bromide analog 4-bromoanisole (**15b**) provided 68 % conversion

under nearly comparable conditions (see Supplementary Information Section 4.6, Table 4.9). Given that the only apparent difference between these systems was the identity of the halide, it was suspected that catalyst inhibition by iodide anions (e.g., through increasing equilibration to an off-cycle PdI_2 species) might be responsible.

Initially, a selection of additives known to reverse catalyst inactivation under similar circumstances¹⁴² was screened. Inclusion of *i*-PrOH, which has been reported to protect against catalyst inactivation from oxygen exposure in the Pd-catalyzed cyanation of iodoarenes,¹⁴³ was moderately beneficial (Table 4.1, entry 2; 30 %), yet the reaction still stalled out well before achieving full conversion, suggesting *i*-PrOH was not functioning as a reductant. Likewise, reducing additives polymethylhydrosiloxane (PMHS) and Zn dust, which have been reported to regenerate the active species in the Pd-catalyzed aromatic azidocarbonylation of iodoarenes,¹⁴⁴ were detrimental even at low loadings (entries 3 and 4; 15 % and 18 %, respectively); this outcome is consistent with the deleterious reduction of the allyl ligand of **16**, which is hypothesized to function as a π -acid ligand that is crucial to high catalytic activity in this reaction⁶⁴ (see Chapter 3). The nucleophilic amine base 1,4-diazabicyclo[2.2.2]octane (DABCO) has been reported to function exceptionally well as a ligand for Suzuki–Miyaura cross-couplings with very low catalyst loadings,¹⁴⁵ and some authors have suggested that such conditions are effectively ligandless, with the “homeopathic” catalyst loading being converted to DABCO-stabilized Pd clusters *in situ*.^{142,146} When used as an additive in the present study, DABCO was beneficial (entry 5; 33 %), but the reaction still shut down well before reaching full conversion. Given the importance of the phosphine ligand in enabling the arylation of nitroalkanes⁸⁸ and the limited benefit afforded by DABCO additive, it seems unlikely that the reaction is facilitated by stabilized Pd nanoparticles. Instead, DABCO might function as a non-detrimental ligand which competes with iodide for catalyst ligation; this scenario would be consistent with Jeffery’s penultimate report on modified conditions for the Mizoroki–Heck

reaction, wherein an excess of DABCO as the base suppressed alkene isomerization and desilylation in arylation products of allyltrimethylsilanes, in spite of the inclusion of stoichiometric *n*-Bu₄NBr.¹²⁷ Such isomerization and desilylation has been shown to be halide-promoted by Hallberg and coworkers.^{118,147,148} Isomerization via a hydridopalladium halide species is likewise avoided or promoted in another Jeffery report by using *n*-Bu₄NOAc or *n*-Bu₄NCl, respectively.¹²⁵

Table 4.1: Selective additive screening results for the enhancement of aryl iodide reactivity in the Pd-catalyzed arylation of nitroalkanes.^{a, b}

Entry	Additive	% Conv. ^c	Entry	Additive	% Conv. ^c
1	—	23	16	Et ₄ NOTs	34
2	<i>i</i> -PrOH	30	17	Et ₄ NOAc	8
3	PMHS ^d	15	18	Me ₄ NCl	54
4	Zn dust ^e	18	19	Me ₄ NBr	28
5	DABCO	33	20	Me ₃ NCH ₂ CO ₂	32
6	<i>i</i> -Pr ₂ NEt ^f	20	21	Ca(OH) ₂ ^e	24
7	DBU	13	22	CsCl	26
8	AgNO ₃ ^g	35	23	NaCl ^h	5
9	I ₂ ^d	0	24	Na ₂ SO ₄	24
10	<i>n</i> -Bu ₄ NCl	48	25	KO ₂ CCF ₃	23
11	<i>n</i> -Bu ₄ NI	3	26	KOTf	19
12	<i>n</i> -Bu ₄ NPF ₆	23	27	Me ₄ NCl, KCl	52
13	Et ₄ NCl	25	28	CF ₃ CH ₂ OH	32
14	Et ₄ HSO ₄	26	29	Me ₄ NCl, EtOH	55
15	Et ₄ NOTf	30	30	Me ₄ NCl, <i>i</i> -PrOH	71

^a Conditions: **15a** (1 equiv, 0.25 mmol), *n*-PrNO₂ (5 equiv), additive (2 equiv), K₃PO₄ (3 equiv), **16** (2.5 mol%), 3 wt% aq. PS-750-M (0.5 M with respect to **15a**, argon-sparged), argon atmosphere, 45 °C, 14 h, according to Procedure 4.1. ^b See Supplementary Information Section 4.6, Table 4.8 for detailed additive screening results. ^c Determined by GCMS. ^d Used 0.25 equiv additive. ^e Used 0.5 equiv additive. ^f Substantial homocoupling side product formation (26 %) also observed. ^g Used 1 equiv additive and monitored at 17 h; 35 % is the sum of the desired product (25 %) and its ketone derivative (10 %); at 30 min, 13 % conversion exclusively to the desired product was observed. ^h Used 10 equiv additive.

Use of *i*-Pr₂NEt as a sterically hindered amine additive (entry 6; 20 %) resulted in slightly less desired product than the control reaction (entry 1; 23 %) yet also caused

substantial homocoupling (26 % of the starting material converted to the biaryl). Thus, although *i*-Pr₂NEt was detrimental, a higher degree of total conversion was achieved, further suggesting that the presence of a species able to compete with halides for catalyst ligation may decrease catalyst inactivation. With the non-nucleophilic amidine base 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) as the additive, only 13 % conversion was observed (entry 7), indicating that the benefits associated with DABCO and *i*-Pr₂NEt are not derived from an increase in base loading. Furthermore, when DABCO or DBU were used as bases in place of K₃PO₄, rather than as additives, 5 % and 24 % conversion, respectively, was observed (see Supplementary Information Section 4.6, Table 4.10).

By using of 1 equiv of the quintessential primary halosequestant AgNO₃, a 35 % conversion to product was observed (entry 8). Unfortunately, AgNO₃ also appeared to promote oxidation of the desired product into its ketone derivative. Subsequent monitoring showed no further conversion of starting material, but the extent of improvement strongly suggested that halosequestration might be a viable strategy. This notion was further evinced by the use of 0.25 equiv I₂ as the additive, which completely shut down the reaction (entry 9; 0 %). In this case, inactivation by oxidative addition of molecular iodine may have occurred during reaction setup before the addition of nitroalkane. Adopting Jeffery-like conditions with *n*-Bu₄NCl as the additive resulted in a maximum of 48 % conversion (entry 10). When *n*-Bu₄NI was used as the additive, a meagre 3 % conversion was observed (entry 11), indicating that the mere presence of the quaternary ammonium cation is not enough to prevent inactivation. Furthermore, in contrast to the result with I₂, a degree of conversion approximately corresponding to a single catalyst turnover was observed with *n*-Bu₄N₄I, suggesting that oxidative addition to form a Pd^{II} species is a prerequisite to catalyst inactivation. In light of these results, we began to investigate various peralkylammonium salts. With the non-coordinating anion of *n*-Bu₄NPF₆, (entry 12; 23 %) there was almost no difference from the control

reaction, but this outcome may be a result of strong ion pairing in this specific salt. Tetraethyl- and tetramethylammonium salts were also investigated (entries 13–20). Me₄NCl provided the best result with 54 % conversion after 14 hour (entry 18). The inferiority of Et₄NCl (entry 13; 25 %) to both *n*-Bu₄NCl and Me₄NCl is consistent with trends in both the distance between ions in the pairs,¹⁴⁹ susceptibility of the cation to Hofmann elimination,¹⁵⁰ and solubility relative to analogous iodides.¹⁵¹ Three other counteranions were identified as being comparable or superior in efficacy to chloride (entry 13; 25 %): hydrogen sulfate, triflate, and tosylate (entries 14–16; 26 %, 30 %, and 34 %, respectively). Owing to cost, commercial availability, and atom economy, chloride salts were used in subsequent investigations. Nevertheless, The efficacy of these counteranions is noteworthy in that (1) if stabilization of the Pd complex by chloride^{152–154} is significant, such stabilization is at least not the only important factor in play, and (2) the greater efficacy afforded by, e.g., a peralkylammonium tosylate may be necessary in more demanding implementations of this technology. The acetate counteranion was actually detrimental (entry 17; 8 %) and likely inhibits the catalyst in this reaction. The bromide counteranion was modestly beneficial (entry 19; 28 %) but far less efficacious than chloride (entry 18; 54 %), which is consistent with (1) the viability of aryl bromides in the absence of halosequestant and (2) the accelerating effect of Me₄NCl with aryl bromides. Although less substantial than the result obtained with Me₄NCl, the zwitterionic biomolecule glycine betaine led to an appreciable improvement (entry 20, 32 %), suggesting that an even more environmentally benign halosequestration system might be developed at the cost of some degree of efficacy.

Alkali and alkaline earth metal salts were also examined (entries 21–26). Calcium oxide has been fruitfully employed by Alcántara and co-workers for the halosequestrative effect of Ca in a modified Arndt–Eistert synthesis of α -diazoketones, wherein only 1 equiv diazomethane is required and both ketene and haloketone formation are

suppressed.¹⁵⁵ When $\text{Ca}(\text{OH})_2$ was used as the base in the present study only 6 % conversion to product was observed (see Supplementary Information Section 4.6, Table 4.10), but when used as an additive it was perhaps slightly beneficial (entry 21; 24 %). Kozlowski and co-workers reported that in the related arylation of nitroacetates (which likewise worked well for aryl bromides but was unsuitable for aryl iodides) bases with Li, Na, and K cations were ineffective, yet analogous bases with Cs and Rb cations were effective.¹³⁹ The trends in base effectiveness were plausibly rationalized as arising from differences in solubility or impedance of ligand exchange based on propensity to bond with nitronate anions. Aryl iodides unsuitability was hypothesized to arise from the influence of the halide on transmetallation. When screening the alkali carbonate series as the base in the absence of an additive in the present study, we observed increasing efficacy moving down the periodic table (4 %, 13 %, 15 %, and 16 % for Li_2CO_3 , Na_2CO_3 , K_2CO_3 , and Cs_2CO_3 , respectively; see Supplementary Information Section 4.6, Table 4.10). This trend seems attributable to differences in solubility rather than a propensity of the cation to pair with iodide since the reactions did not go to completion and K_2CO_3 was nearly as effective as Cs_2CO_3 . When using CsCl as an additive, however, a modest improvement to 27 % conversion was observed (entry 22) despite the concomitant introduction of chloride anions. Chloride anions were confirmed to be detrimental when present in sufficient abundance; use of 10 equiv NaCl as the additive resulted in only 5 % conversion (entry 23), while 2 equiv of Na_2SO_4 was perhaps slightly beneficial (entry 24; 24 %), suggesting Na^+ and SO_4^{2-} ions are benign to the reaction. Inclusion of potassium trifluoroacetate likewise had no effect (entry 25; 23 %), as would be expected from a non-nucleophilic anion which is readily displaced from Pd by halides.¹⁵⁶ Potassium triflate was surprisingly somewhat detrimental (entry 26; 19 %) despite triflate being the counteranion of **16**; it may be that the abundance of triflate in this case actually does lead to a decrease in halide ligation to Pd but consequently results in unstable triflate complexes which subsequently decompose.¹⁵⁷

Having surveyed a broad variety of additives and identified Me₄NCl as the optimal primary halosequesterant, we briefly explored inclusion of a second additive. Inclusion of KCl as the second additive led to a slight decrease in yield (entry 27; 52 %) compared to using only Me₄NCl (entry 18; 54 %), further supporting that chloride anions in sufficient abundance are detrimental. Seeking a more sustainable alternative to 2,2,2-trifluoroethanol, which had proven efficacious in single additive studies (entry 28; 32 %), we tried combining Me₄NCl with ethanol, but only a slight improvement in conversion was observed (entry 29; 55 %). With the inclusion of *i*-PrOH instead, however, a substantial improvement to 71 % conversion was observed (entry 30). An additional double additive screening with a lower base loading of 2 equiv provided further insight into the function of the additives (see Supplementary Information Section 4.6, Table 4.11). In particular, inclusion of *i*-PrOH as a second additive was slightly detrimental (20 %) compared to Me₄NCl alone (24 %) at this base loading while CF₃CH₂OH was beneficial (32 %) to roughly the same degree that it had been in the single additive study. These results suggest that CF₃CH₂OH and *i*-PrOH assist the reaction in different ways. CF₃CH₂OH may benefit the reaction by providing catalyst stabilization, which is not related to base loading, whereas the efficacy of *i*-PrOH may arise partly from, e.g., promotion of potassium iodide formation.

4.2.2 Sub-mol% Catalyst Loadings with Secondary Halosequestration

The results of the double additive screening prompted a re-optimization of reaction medium. In the presence of Me₄NCl, PS-750-M was no longer needed and was actually modestly detrimental (Table 4.2, entries 1 and 2; 54 % and 72 %, respectively). It has been speculated that aqueous tetraalkylammonium halides might operate in a similar capacity to surfactants in facilitating transition-metal-mediated chemistry.¹⁵⁸ However, aqueous 3 wt% cetrimonium chloride (CTAC; entry 3; 43 %) was inferior to

both aqueous PS-750-M and neat water in the presence of the Me₄NCl additive.

Table 4.2: Selective additive screening results for the enhancement of aryl iodide reactivity in the Pd-catalyzed arylation of nitroalkanes.^a

Reaction scheme: 1-iodo-4-methoxybenzene (**15a**) reacts with *n*-PrNO₂ (5 equiv), Me₄NCl (2 equiv), and K₃PO₄ (3 equiv) in a reaction medium (0.5 M, Ar-sparged) at 45 °C under atmospheric pressure to yield 1-(4-methoxyphenyl)-2-nitropropane (**10b**).

Entry	Reaction Medium	mol% 16	Time in h	% Conv. ^b
1	3 wt% aq. PS-750-M	2.5	14	54
2	water	2.5	14	72
3	3 wt% aq. CTAC	2.5	14	43
4	water	2.5	4	33
5	1:1 <i>i</i> -PrOH/water	2.5	4	96
6	<i>i</i> -PrOH	2.5	4	100
7	<i>i</i> -PrOH	0.2	1	21
8	tetrahydrofuran	0.2	1	15
9	1,2-dimethoxyethane	0.2	1	18
10	water	0.2	1	7
11	dimethyl sulfoxide	0.2	1	1
12	toluene	0.2	1	6
13	hexanes	0.2	1	7
14	methyl tert-butyl ether	0.2	1	7
15	MeOH	0.2	1	7
16	EtOH	0.2	1	15
17	ethylene glycol	0.2	1	11
18	<i>n</i> -PrOH	0.2	1	78
19	<i>t</i> -BuOH	0.2	1	88

^a Conditions: **15a** (1 equiv, 0.25 mmol), *n*-PrNO₂ (5 equiv), Me₄NCl (2 equiv), K₃PO₄ (3 equiv), **16**, reaction medium (0.5 M with respect to **15a**, argon-sparged), argon atmosphere, 45 °C, 14 h, according to Procedure 4.2.

^b Determined by GCMS.

In light of the previously obtained results with *i*-PrOH, we next sought to explore *i*-PrOH/water mixtures and found that pure *i*-PrOH provided the best results, achieving full conversion in less than 4 hour (entries 4–6). The greatly accelerated rate in *i*-PrOH necessitated lowering both the catalyst loading and the reaction time, and subsequent studies were conducted at less than one tenth of the original catalyst loading and less than one tenth of the original reaction time. The result with *i*-PrOH under these conditions (entry 7; 21 %) proved superior to the results with two solvents which

have previously been identified as optimal in non-halosequestrative implementations of this reaction, tetrahydrofuran⁹² (THF; entry 8; 15 %) and 1,2-dimethoxyethane⁸⁸ (DME; entry 9; 18 %); these three solvents were in turn superior to neat water (entry 10; 7 %), indicating that (1) the basis for the superiority of THF and DME under non-halosequestrative conditions may be preserved in halosequestrative conditions and (2) these two solvents may also be well suited for supporting the halosequestrative process, albeit to a lesser extent than *i*-PrOH. A selection of other non-protic solvents was also explored. Dipolar aprotic solvent dimethyl sulfoxide resulted in only 1 % conversion (entry 11), which was worse than any other solvent system that was screened. Although not conclusive, this result suggests that the solvent influence on the nucleophilicity of the halide ions may be significant; it is known that the nucleophilicity order of halides reverses and nucleophilicity greatly increases upon switching from polar protic to polar aprotic reaction media.¹³⁷ If such an influence is indeed in play, it would suggest that solvents might be selected for complementarity with the aryl halide and halosequestant. Low polarity hydrocarbon solvents toluene (entry 12; 6 %) and hexanes (entry 13; 7 %) performed roughly as well as neat water, as did the sterically hindered ether methyl tert-butyl ether (MTBE; entry 14; 7 %). The lower yield with MTBE compared to THF and DME points to the importance of the steric inaccessibility of the oxygen lone pairs. Finally, a variety of other alcohol solvents was examined (entries 15–19). MeOH did not exhibit enhanced conversion and provided the same result as neat water (entry 15; 7 %), but EtOH proved to be twice as effective, providing 15 % conversion (entry 16). Despite possessing the same hydroxyl group to carbon ratio as MeOH, ethylene glycol was more effective (entry 17; 11 %) yet inferior to its dimethyl ether analogue (entry 9; 18 %). Further elongation of the alcohol alkyl chain appeared to be highly beneficial, as *n*-PrOH afforded 78 % conversion (entry 18). Chain elongation was not the sole determinant of alcohol efficacy, however, as *t*-BuOH was found to be the optimal solvent, providing

88 % conversion after 1 hour at a 0.2 mol% catalyst loading. Although other higher alcohols were also found to be efficacious, *t*-BuOH was selected due to (1) its status as a green solvent,⁷⁸ (2) the superior processability afforded by its low melting point relative to other higher alcohols, and (3) its literature precedent in solvent structuring studies (*vide infra*).

4.2.3 Exploratory Substrate Scope with Benchtop Preparation

We next sought to assess the generality of the remarkably enhanced reactivity afforded by the new reaction conditions. Additional control studies optimization of the nitroalkane, K₃PO₄, and Me₄NCl loadings (see Supplementary Information Section 4.6, Tables 4.12 and 4.13) led to the development of the standard reaction conditions for substrate scope: 1 equiv aryl halide, 5 equiv nitroalkane, 1.5 equiv Me₄NCl, 3 equiv K₃PO₄, 1 M global concentration in *t*-BuOH with respect to aryl halide, argon atmosphere, and 45 °C. The catalyst loading for entries in the exploratory substrate scope (Table 4.3) was selected based on a prescreening process such that full conversion would be achieved in ca. 3 h to 4 h (Table 4.4). The exploratory scope and prescreening results were obtained using operationally simple benchtop handling of reagents. Remarkably, in addition to enabling the coupling with aryl iodides, the halosequestrative conditions also greatly enhanced the reactivity of aryl bromides relative to our preliminary conditions. Using halosequestrative conditions, *o*-arylated *n*-PrNO₂ product **10b** was obtained in 87 % isolated yield from electron rich aryl bromide **15b** after 3 hour with a 0.3 mol% loading of catalyst **16**; under non-halosequestrative conditions, only 65 % isolated yield was obtained after 22 hour with a 2.5 mol% catalyst loading. Products were likewise efficiently obtained under halosequestrative conditions from electron deficient (**10c**, 82 %, 4 hour, 0.5 mol% **16**) and electron neutral (**10d**, 88 %, 0.7 mol% **16**) aryl bromides compared to non-halosequestrative conditions (**10c**, 84 %, 0.7 mol% **16**).

35 hour, 2.5 mol% **16**; **10d**, 82 %, 15 hour, 2.5 mol% **16**). Reaction scalability was not an issue, and **10b** and **10c** were successfully adapted to gram scale. For highly active substrates like **15f**, even lower catalyst loadings were possible, and the resultant heteroarylated EtNO₂ product **10e** was obtained in 90 % isolated yield after 3 hour with a catalyst loading of only 0.02 mol%. Aryl iodides were completely tolerated, and **10f** was obtained from **15g** in 92 % isolated yield after 3 hour with a catalyst loading of only 0.1 mol%. Products **10g** and **10a** were also efficiently obtained with halosequestrative conditions. It appeared that the halosequestrative conditions were compatible with a similar breadth of substrates as our previously reported conditions⁶⁴ (see Chapter 3), with ketone (**10f**), alkene (**10i**), trifluoromethyl (**10c**), various ether (**10b,d–f,a,j**), tertiary amine (**10j**), benzylic (**10d,f,g**), and pyridyl (**10e**) moieties being tolerated.

Table 4.3: Exploratory substrate scope with benchtop preparation.^{a,b}

^a Yields are for the isolated product. ^b Except as otherwise noted, halosequestrative conditions were used: aryl halide **15** (1 equiv, 0.5 mmol), EtNO₂ or *n*-PrNO₂ (5 equiv), Me₄NCl (1.5 equiv), K₃PO₄ (3 equiv), **16**, *t*-BuOH (1 M with respect to aryl halide, argon-sparged), argon atmosphere, 45 °C, according to Procedure 4.6. ^c Non-halosequestrative results were previously reported⁶⁴ (see Chapter 3) with the following conditions: aryl bromide **15** (1 equiv, 0.50 mmol or 0.25 mmol), EtNO₂ or *n*-PrNO₂ (5 equiv), K₃PO₄ (1.2 equiv), **16** (2.5 mol%), 3 wt% aq. PS-750-M (0.50 M with respect to aryl bromide, argon-sparged), argon atmosphere, 45 °C, according to Procedure ??.

^d Performed at 6 mmol scale according to Procedure 4.7.

The exploratory substrate scope served to confirm that (1) the methodology

was practically viable and (2) prescreening predictions were reliable. Thus, a more expansive examination of the scope was undertaken in the form of prescreening reactions. Although the ultimate confirmation of the *viability of a substrate with a particular protocol* is indeed isolated product yield, there are circumstances in which isolated yields can be misleading. In particular, for isolated yields to be used to compare the *suitability of substrates for particular reaction conditions*, several assumptions are necessarily made, including:

1. The reaction was closely monitored to ensure that the reaction time corresponds to the underlying reaction rate.
2. The method of reaction monitoring did not variably influence the isolated yield for different substrates.
 - A slower substrate might be expected to have been monitored more times, which could be significant depending on the monitoring technique and factors such as the relative size of reaction medium and aliquot volumes.
 - In addition to differences in the number of times monitoring perturbations were introduced, some substrates might be more vulnerable to perturbations than others (e.g., differing rates of product decomposition arising from the introduction of trace oxygen during monitoring).
3. Product purification negligibly or consistently impacted the isolated yield.
 - Product properties such as stability, solubility, and volatility could have an impact if not properly accounted for.
4. Setup, monitoring, and isolation were performed in a consistent manner between substrates (e.g., isolated yields were obtained by a single person or by multiple people with negligible differences in technique).

Several aspects of the halosequestrative version of the reaction warranted the focus on prescreening results in the interest of better controlled experimentation.

First, a major point of interest with these conditions was their ability to enable lower catalyst loadings, and the prescreening method provided an efficient way to assess the required catalyst loading for a particular substrate. The reaction also turned out to be particularly oxygen sensitive at sub-mol% catalyst loadings (vide infra), and it was found that reactions monitored at 1 h and again at 3 h would often show substantially lower conversions compared to otherwise identical reactions monitored only at 3 h. Product susceptibility to decomposition (nitro to ketone via the Nef reaction) appeared to be variable (e.g., with arene electron deficiency). Prescreening results showed that decomposition was not a significant issue during the course of the reaction, and isolation of electron-deficient **10c** in 82 % yield showed that decomposition could be minimized with efficiently executed purification technique. However, even isolated product was observed to gradually decompose with air exposure, so decomposition was regarded as a point of potential inconsistency. Furthermore, since this reaction had already been thoroughly explored under non-halosequestrative conditions^{64,88,92} (see Chapter 3), this investigation was more heavily focused on halosequestration as a technique rather than the specific model transformation used in exploring the technique.

Based on both the isolated scope and pre-screening results, halosequestration appeared to restore the normal order of aryl halide reactivity (I > Br > Cl) typically expected for Pd-catalyzed coupling reactions (Table 4.4, **15a–c** and **15r–t**). An interesting exception, however, was **15o** vs. **15p**, which might be attributable to sterics during oxidative addition on account of the larger size of the iodo group in conjunction with 1,3-allylic crowding. As had been previously reported,⁸⁸ aryl halides with neighboring steric bulk from ortho-substituents were typically more difficult than less hindered analogs and were generally more viable for arylation with EtNO₂ than with *n*-PrNO₂ (**15m–q**). It was generally the case that EtNO₂ was more reactive than *n*-PrNO₂ (**15b,n,p,s,v,y,ak**), presumably predominantly on the basis of sterics.

Table 4.4: Prescreening results for the halosequestrative Pd-catalyzed coupling of aryl halides and primary nitroalkanes.^{a, b}

		Conversion ranges		
		≥ 95%	≥ 60%, < 95%	≥ 30%, < 60%
		< 10%	< 30%	< 10%
		no reaction		
		15a	15b	15c
		<i>n</i> -PrNO ₂ , 99%	EtNO ₂ , 97% <i>n</i> -PrNO ₂ , 28%	EtNO ₂ , 1% <i>n</i> -PrNO ₂ , 2%
		15d	15e	15f
		<i>n</i> -PrNO ₂ , 16%	<i>n</i> -PrNO ₂ , 11%	EtNO ₂ , 99%
		15g	15h	15i
		<i>n</i> -PrNO ₂ , 64%	<i>n</i> -PrNO ₂ , 25%	<i>n</i> -PrNO ₂ , 63%
		15j	15k	15l
		<i>n</i> -PrNO ₂ , 15%	EtNO ₂ , 68%	<i>n</i> -PrNO ₂ , 10%
		15m	15n	15o
		EtNO ₂ , 100%	EtNO ₂ , 4% <i>n</i> -PrNO ₂ , 0%	EtNO ₂ , 2%
		15p	15q	15r
		EtNO ₂ , 5% <i>n</i> -PrNO ₂ , 1%	EtNO ₂ , 0%	EtNO ₂ , 95%
		15s	15t	15u
		EtNO ₂ , 40% <i>n</i> -PrNO ₂ , 10%	EtNO ₂ , 7%	EtNO ₂ , 67%
		15v	15w	15x
		EtNO ₂ , 100% <i>n</i> -PrNO ₂ , 72%	<i>n</i> -PrNO ₂ , 5%	EtNO ₂ , 13%
		15y	15z	15aa
		EtNO ₂ , 51% <i>n</i> -PrNO ₂ , 5%	EtNO ₂ , 25% ^d	EtNO ₂ , 3%
		15ab	15ac	15ad
		EtNO ₂ , 1%	EtNO ₂ , 3%	<i>n</i> -PrNO ₂ , 0%
		15ae	15af	15ag
		EtNO ₂ , 0%	EtNO ₂ , 0%	EtNO ₂ , 2% ^d
		15ah	15ai	15aj
		EtNO ₂ , 1% ^d	EtNO ₂ , 18% ^d	EtNO ₂ , 1% ^d
		15ak	15al	
		EtNO ₂ , 99% <i>n</i> -PrNO ₂ , 2%	EtNO ₂ , 1%	

^a Listed percentages are for conversion to product after 1 h as determined by GCMS analysis.

^b Conditions: aryl halide **15** (1 equiv, 0.5 mmol), EtNO₂ or *n*-PrNO₂ (5 equiv), Me₄NCl (1.5 equiv), K₃PO₄ (3 equiv), **16** (0.1 mol%), *t*-BuOH (1.0 M with respect to aryl halide, argon-sparged), argon atmosphere, 45 °C, according to Procedure 4.5.

^c Prescreening was used to predict the loading of **16** needed for full conversion in 3 h for isolated substrate scope reactions. It was generally found that prescreening conversion (*y*%) was between 10 % and 95 %, then a catalyst loading of $\frac{7}{y}$ mol% would be appropriate. If *y* was greater than 95 or less than 10, then rescreening at a lower or higher catalyst loading, respectively, was necessary.

^d Substantial (>10 %) non-ketone side product formation was detected.

In addition to the functional group tolerance associated with **15a–l** which was established in the exploratory substrate scope, the prescreening suggested that alkyne (**15u**), methyl ketone (**15v**), ester (**15w**, moderately S_NAr-vulnerable fluoro (**15y**), and cyano (**15ak**) were also most likely tolerated since side products were not detected by GCMS. Although a reasonable amount of conversion to the desired product for **15z** reacted with EtNO₂ was observed, side products arising from S_NAr attack by deprotonated nitroalkane to displace the aryl nitro group were detected in appreciable quantities. When attempting to run this reaction for 3 h with a 3 mol% catalyst loading, more than half of the conversion was associated with S_NAr side products. Although modifications to the procedure (such as sequence order of nitroalkane addition, selection of a less nucleophilic nitroalkane, use of a lower reaction temperature, etc.) might make **15x** more viable, our previous micellar approach may be preferable if a micellar shielding effect can be harnessed to prevent S_NAr. Benzo[*d*][1,3]dioxole **15x** appeared difficult but viable, affording 13 % conversion within the timeframe of the experiment with the more reactive EtNO₂. Heteroaromatics **15aa–ac** showed some conversion, suggesting that they may be viable, especially at an elevated temperature. Not even trace product was detected for five-membered heteroaromatics with more than one heteroatom, regardless of whether the halide was attached to the five-membered ring (**15ad–af**), which could be consistent with such moieties poisoning the catalyst.

When an aryl bromide or iodide substrate also contained an aryl chloride, the reaction selectively took place at the site of the heavier halide (**15r,s**). Chloro groups were reactive, however (**15c,j,t**). In the simple case of phenyl chloride (**15j**), the reaction readily proceeded, and a 66 % isolated yield was obtained, but other aryl chlorides were less active. For example, only 1 % conversion was observed in the prescreening reaction with 4-chloroanisole (**15c**) and EtNO₂, whereas full conversion was observed for the iodo and bromo analogues (**15a,b**). To further explore aryl chloride reactivity in halosequestrative conditions, three variations of the prescreening

reaction were conducted for the arylation of *n*-PrNO₂ with **15c**: one reaction with Me₄NCl as the additive, one with Me₄NBr as the additive, and one with no additive. All three variations resulted in only 2 % conversion to **10b** within the timeframe of the experiment, suggesting that the primary halosequesterant had no effect with this substrate.

Incompatible substrates were particularly of interest. Unsurprisingly, an aldehyde substrate and a chalcone substrate were not tolerated, with side products via Henry reaction or 1,4-addition, respectively, being detected instead of the desired products. Similarly, prescreening indicated that 4-bromophenol (**15ag**), 4-bromoaniline (**15ah**), and 4-bromo-*N,N*-dimethylaniline (**15ai**) were not suitable substrates. In each case, although appreciable consumption of starting material was observed, side products were detected in much greater abundance than the desired product. The mass spectra of the side products indicated that they arose from alkylation of the α -carbon of the desired products by a further equivalent of nitroalkane. This outcome may be consistent with Vogl and Buchwald's seemingly judicious selection of 3-bromo-*N,N*-dimethylaniline as a substrate in their original report,⁸⁸ where the *meta* substitution pattern does not permit extension of resonance stabilization into the substituent during an attack by a carbanion of a second equivalent of nitroalkane. In the case of substrate **15l**, however, it was possible to obtain desired product **10j** in 41 % isolated yield, despite the presence of the *para*-morpholino group, which likewise made **10j** susceptible to reaction with a second nitroalkane equivalent. Arylation of EtNO₂ with **15k** was also modestly successful, with **10i** being obtained in 48 % isolated yield; atypical insoluble material observed during workup suggested that desired product formation was competing against polymerization. Although modest, the success achieved with **10i** and **10j** without deviating from the standard conditions highlights an important utility of halosequestrative enhancement: minimization of product exposure to reaction conditions. The lowered catalyst loading requirements for

achieving full conversion likewise provide margin to overload the catalyst in the interest of further minimizing reaction time when needed. It is likely that other modifications to the standard conditions could also assist with accommodating substrates similar to **15l**, such as lowering the nitroalkane loading, but we defer such refinements to later, more specialized investigations of this reaction system.

Table 4.5: Investigation of isoxazole formation.^a

Entry	Variation	mol% 17 ^b
1	As written	0.015
2	Omitting Me ₄ NCl	0.0014
3	Air atmosphere, omitting Me ₄ NCl	0.043

^a Conditions: EtNO₂ (5 equiv, 2.5 mmol), Me₄NCl (2 equiv, if specified), K₃PO₄ (3 equiv), *t*-BuOH (0.5 mL, 0.5 M with respect to omitted **15a**, argon-sparged), argon atmosphere (if specified), 45 °C, 3 h, according to Procedure 4.6 except that aryl halide and catalyst were omitted; note that equiv and mol% values are expressed relative to the omitted aryl halide to simplify comparison of **17** abundance with typical catalyst loadings.

^b Determined by GCMS with a 5 µL decane internal standard admixed immediately prior to analysis at 3 h.

Aside from preventing degradation of desired products, the short reaction times enabled by halosequestrative conditions have the potential to minimize problems associated with catalyst inactivation—an issue that becomes increasingly important with decreasing catalyst loading. This possibility is particularly noteworthy in light of another observation made during our investigations: reaction shutdown often correlated with the appearance of a trialkylisoxazole-like product in GCMS results. The mass spectrum was consistent with either trimethylisoxazole (**17**) or triethylisoxazole depending on whether EtNO₂ or *n*-PrNO₂ was used, and a reexamination of GCMS data obtained in our earlier work⁶⁴ (see Chapter 3) confirmed that the formation of these species concomitant with reaction shutdown was not specific to halosequestrative con-

ditions. Indeed, the mechanism and intermediates of trialkylisoxazole formation from primary nitroalkanes under similar conditions have previously been investigated.¹⁵⁹ It is noteworthy that isoxazoles are 5-membered heterocycles with two heteroatoms, just like the three totally unreactive heteroaromatic substrates (**15d–f**). Inclusion of a compound bearing a 3,5-dimethylisoxazolyl moiety at a 2 mol% loading was found to retard the arylation of **15a** by a factor of 0.7 (see Supplementary Information Section 4.6, Table 4.14). This result suggests that although trialkylisoxazoles likely contribute to catalyst inhibition, byproducts or intermediates from their formation, such as 1,3-dioximes intermediates, may play a greater role. We probed the extent of trimethylisoxazole-like product formation in three reactions omitting **15** and **16** (Table 4.5): (1) with Me₄NCl; (2) without Me₄NCl; and (3) without Me₄NCl and with air as the reaction headspace. The increase in **17** caused by the presence of Me₄NCl highlights the concern that tetraalkylammonium enhancement of nucleophilicity¹⁶⁰ could prove problematic in some circumstances. However, although the presence of Me₄NCl increased the rate at which **17** formed by a factor of ca. 10, Me₄NCl was previously observed to increase the rate of conversion of **15a** to **10b** by a factor of ca. 20, so Me₄NCl actually appears to decrease the extent of isoxazole-like product formation relative to desired product formation. The use of air instead of argon for the headspace of the reaction vessel increased the formation of **16** by an even greater degree (a factor of ca. 30), suggesting that the deleterious effect of oxygen on the reaction may be indirect through the promotion of this undesired side reaction; this scenario is consistent with the non-linear increase in retardation of the desired reaction over time observed when using air as the headspace (see Supplementary Information Section 4.6, Table ??). For traces of oxygen (rather than 21 vol% of a headspace volume ca. 3 times greater than that of the reaction mixture), the increase in trimethylisoxazole-related product formation should be outpaced by the increase in desired product formation afforded by Me₄NCl. Given that the difficulty of excluding

trace oxygen tends to increase with reaction scale, halosequestrative acceleration may also be viewed as a tool to assist with scale-up.

Retention of catalyst activity was anticipated to be particularly important for toleration of aryl nitriles. In our earlier work⁶⁴ (see Chapter 3), coupling of 4-bromobenzonitrile (**15ak**) with EtNO₂ was accomplished in 78 % isolated yield in 22 hour, but with *n*-PrNO₂ only 33 % isolated yield could be obtained; likewise, the arylation of *n*-PrNO₂ with 5-bromo-2-fluorobenzonitrile (**15al**) was only accomplished in 52 % isolated yield. One possible explanation appears to be that the generally slower reactivity with *n*-PrNO₂ provided sufficient time for catalyst inactivation, thereby preventing full conversion of starting material. Remarkably, during the prescreening for EtNO₂ arylation with **15ak** in the present investigation, the reaction mixture *solidified* within 5 minute. The stir bar was promptly freed through manual application of a strong external magnet, but the mixture remained a very thick paste. After the 1 hour reaction time of the prescreening procedure, 99 % conversion was observed, necessitating an additional prescreen at a lower catalyst loading. The catalyst loading was only slightly decreased (from 0.1 mol% to 0.08 mol%) because the global concentration was also decreased (from 1 M to 0.625 M) so as to avoid issues with stirring. The mixture stirred without issue, but even after 3 hour, less than 0.1 % conversion was detected; this result was not expected, considering that the optimization studies had been successfully conducted at a 0.5 M global concentration. Repeating the prescreening of **15ak** with 0.1 mol% catalyst and 1 Molar global concentration once again led to substantial thickening of the reaction mixture and full conversion within 1 hour. When prescreening **15ak** with *n*-PrNO₂ instead of EtNO₂, thickening of the reaction mixture was not an issue, and 2 % conversion was observed (a 2 % conversion prescreening result suggests that a relatively high 3.5 mol% catalyst loading is needed for full conversion in ca. 3 hour). This level of conversion indicated that the reaction was proceeding, albeit slowly. A similar solidification of the reaction medium with full

conversion during prescreening with EtNO₂ was also observed for two other substrates: **15f** and **15v**. With **15f**, the thickening of the reaction mixture was less severe, so dilution was not attempted when repeating the prescreening with a 0.01 mol% catalyst loading, and 51 % conversion was observed at 1 hour, indicating that there was no issue. With **15v**, however, the thickening was substantial, and the repeat prescreening was attempted with a 0.05 mol% catalyst loading and a 0.5 Molar global concentration, but less than 1 % conversion was observed at 1 hour. We noticed that compared to substrates where solidification of the reaction mixture was not observed, the nitronate products of these three substrates have strong resonance stabilization. In the case of nitronates derived from the arylation products of EtNO₂, all points of free rotation (not including methyl rotation) would be limited by conjugation, except for the methoxy group of **10e**, which incidentally was less associated with solidification than the other two products. In light of these observations, we began to suspect that the solidification of the reaction mixture might arise from an extended supramolecular structure incorporating the nitronate salts of these products. Unexpectedly, this suspicion soon proved to be indirectly helpful during our reassessment of the influence of water.

4.2.4 Identification and Optimization of Water, K₃PO₄, and Me₄NCl Interdependence

The standard reaction conditions were initially developed by quickly handling reagents under ambient atmosphere and then establishing an inert atmosphere by evacuation/argon-backfilling just prior to the addition of liquid reaction components (“benchtop preparation”). This approach was based on the assumption that the impact of adsorbed atmospheric water was negligible, which is consistent with the original report by Vogl and Buchwald⁸⁸ and the fact that our preliminary conditions used aqueous surfactant. As demonstrated in our exploratory survey of substrate

scope, this operational simplicity did not come at the cost of reproducibility, and substrate prescreening results were reliably used to set the catalyst loadings such that full conversion was achieved in 3 h to 4 h. Because both K_3PO_4 and Me_4NCl are hygroscopic, aliquots of these reagents will gradually build up ambient moisture with benchtop handling. Unaccounted-for mass contribution from adsorbed water would lead to an underloading of these reagents, which in turn might be expected to decrease conversion rates; introduction of the adsorbed water into the reaction mixture might likewise be expected to decrease conversion rates (Table 4.2). However, when repeating experiments with older aliquots, slight *increases* in conversion were consistently observed, which necessitated further investigation (Figure 4.3).

Figure 4.3: Identification and optimization of interdependent K_3PO_4 , Me_4NCl , and water loadings. **a** Default reaction conditions which are varied in subsequent panels. **b** Effect of increased $\text{K}_3\text{PO}_4/\text{Me}_4\text{NCl}$ air exposure from reagent aliquot age/usage on base loading results with benchtop reagent handling (Procedure 4.3, reaction monitoring at 1 h). **c** Effect of increased $\text{K}_3\text{PO}_4/\text{Me}_4\text{NCl}$ air exposure from reagent aliquot age/usage and on halosequestrant loading results using 2 equiv, 3 equiv, or 4 equiv K_3PO_4 with benchtop reagent handling (Procedure 4.3, reaction monitoring at 1 h). **d** Effect of water loading as a fraction of a mixed $\text{H}_2\text{O}/t\text{-BuOH}$ solvent system with glovebox reagent handling (Procedure 4.8, reaction monitoring at 2 h).

The optimization reaction (Figure 4.3a) was revisited using older aliquots of K_3PO_4 and Me_4NCl (4.3). As shown in Figure 4.3b, the newer reagent aliquots showed a clear optimum base loading at 3 equiv K_3PO_4 , with linear decreases on either side of the

maximum. With the older aliquots, linear trends with approximately the same slopes were observed, but the yield was increased at all points, and although the maximum extent of conversion was observed for 4 equiv K_3PO_4 , it appeared that the true optimum was somewhere between 3 equiv and 4 equiv. The difference between results with older and newer aliquots at 1 equiv to 3 equiv (ca. 3 % conversion) vs. 4 equiv to 5 equiv (ca. 11 %) showed that the general increase in conversion was not attributable to, e.g., a misloading of the catalyst in one of the screenings. Instead, unaccounted-for mass from adsorbed water led to an underloading of K_3PO_4 for the screening with the older aliquots, causing the uncorrected graph to appear shifted toward higher loadings. In light of the maximum observed value at 4 equiv K_3PO_4 with the older aliquots, a screening of Me_4NCl loading with 4 equiv K_3PO_4 was conducted. Remarkably, comparison against the Me_4NCl loading screen with 3 equiv K_3PO_4 and an additional screen with 2 equiv K_3PO_4 (Figure 4.3c) revealed that the optimal Me_4NCl loading was dependent upon the base loading, and the optimum was consistently observed at a roughly 2:1 base:sequestrant ratio. The full screening of Me_4NCl loading with 3 equiv K_3PO_4 showed a roughly linear rise in extent of conversion with Me_4NCl loading up to the 1.5 equiv optimum; all higher loadings resulted in roughly half the extent of conversion observed at the optimum (a similar trend was also observed in *i*-PrOH; see Supplementary Information Section 4.6, Table 4.12). The sharp decrease in conversion upon exceeding the optimum Me_4NCl loading was less severe when using older reagent aliquots at 2 equiv or 4 equiv K_3PO_4 loading, and interpolation between these two datasets suggested that the older aliquots would have resulted in higher conversions for the Me_4NCl loading screening with 3 equiv K_3PO_4 .

To elucidate the differences in these trends with older reagent aliquots and the apparent benefit of trace water, a screening of $\text{H}_2\text{O}/t\text{-BuOH}$ solvent compositions was conducted with glovebox handling of K_3PO_4 and Me_4NCl to strictly control water content (Figure 4.3d). The resultant graph showed a remarkable, non-monotonic

Table 4.6: Effect of water, K₃PO₄, and Me₄NCl relative ratios on reaction rate with glovebox reagent handling.^a

Entry	equiv Water	equiv K ₃ PO ₄	equiv Me ₄ NCl	% Conv. ^b
1	2	2	1	40
2	2	2	1.5	32
3	3	2	1	26
4	3	2	1.5	28
5	3	3	1	39
6	3	3	1.5	46
7	3	4	1.5	41

^a Conditions: **15a** (1 equiv, 0.5 mmol), *n*-PrNO₂ (5 equiv), Me₄NCl (2 equiv, handled in glovebox), K₃PO₄ (3 equiv, handled in glovebox), **16**, reaction medium (0.5 M with respect to **15a**, argon-sparged), argon atmosphere, 45 °C, 2 h, according to Procedure 4.8. ^b Determined by GCMS.

dependence on water loading, with the most prominent feature being a roughly symmetric spike in efficacy centered at a loading of 2 equiv H₂O. Reexamination of the base loading results in Figure 4.3b in light of this peak supported that the general increase in conversion with the older reagent aliquots arose due to a more optimal water loading. Glovebox-based optimization was further used to explore the relationship between water, base, and halosequestant. When using the optimal water:base:sequestant ratio of 2:2:1 at a water loading of 2 equiv, a conversion of 40 % within the timeframe of the experiment was observed (Table 4.6, entry 1). Upon increasing the sequestant loading to 1.5 equiv, a substantial decrease in conversion was observed (entry 2); this response to this deviation from the optimal water:base:sequestant ratio was consistent with the abrupt drop in conversion at Me₄NCl loadings above the optimum seen in the benchtop screening of Me₄NCl loading. Increasing the water loading of the conditions in entry 1 led to an even more substantial decrease in conversion (entry 3), further supporting the importance of maintaining the optimal ratio. Likewise, when both water and sequestant loadings were increased but kept at the same 2:1 relative ratio

while maintaining the base loading from entry 1, a substantial decrease in conversion was also observed (entry 4), indicating that all three components are interrelated. The conversion observed using a 3:3:1 ratio (39 %, entry 5) was inferior to the optimal 2:2:1 ratio at the 3 equiv water loading (46 %, entry 6) and even the 2 equiv water loading despite the lower base loading (entry 1). Finally, deviating from the ideal conditions in entry 6 by increasing the base loading to 4 equiv resulted in a deterioration in yield (41 %, entry 7), confirming that the optimal conditions had been found.

It is noteworthy that the rate of the glovebox-based screening method was roughly half that of the benchtop-based method. Although these methods differed in ostensibly minor ways (such as reaction scale, reaction vessel, and mode of catalyst delivery), the main difference appeared to be the manner in which water was introduced (adsorption onto reagents vs. addition by microliter syringe). To probe this possibility, the glovebox-based method was modified to use $\text{K}_3\text{PO}_4 \cdot \text{H}_2\text{O}$ as the base. Despite having the optimum water loading, this reaction produced only 6 % conversion within the timeframe of the experiment. Although reaction mixtures for both K_3PO_4 and $\text{K}_3\text{PO}_4 \cdot \text{H}_2\text{O}$ appeared the same at the end of the experiment, distinct morphological differences between the two systems were evident during reaction setup and the early stages of heating; in particular, the suspension with K_3PO_4 contained a relatively consistent and fine particulate matter whereas with $\text{K}_3\text{PO}_4 \cdot \text{H}_2\text{O}$ some larger solid chunks were present and the opacity of the stirred suspension was lower. These observations suggested that pre-structuring of reaction components has a significant influence on reactivity. It may be that the adsorption of atmospheric water provides superior pre-structuring.

4.3 Investigation of Mesoscale Structure by Conductometric Titration.

Two types of conductometric titrations were used to correlate mesoscale structuring of the reaction medium to reactivity and macroscopic morphology (Figure 4.4). The selection of *t*-BuOH as the solvent conveniently aligned with the precedent established by Kunz and coworkers for the conductometric investigation of mesoscale structuring effects of water/*t*-BuOH mixtures on the photocatalytic oxidation of benzyl alcohol;^{161,162} the conductometric titration of water/*t*-BuOH mixtures at 25 °C from these reports is presented in Figure 4.4a alongside a repetition of the experiment at our reaction temperature of 45 °C (hereafter referred to as the “conventional titration”). Regions of linearity in the conductivity curves are highlighted according to the corresponding solvent structuring domain. Approximate points of divergence from linearity are indicated as thick vertical dashed gray lines labeled **a1–a5** which extend into the graphs in Figure 4.4b,c for ease of comparison. The emergence of inverse structuring (water-in-oil emulsions or reverse micelles) begins at **a1**, and full linearity for this structuring domain is achieved by **a2**. At **a3** there is an abrupt transition from inverse structuring to bicontinuous structuring (sponge-like interpenetrating networks of oil and water). Divergence from linearity for the bicontinuous structuring domain begins at **a4**, and linearity begins for the direct structuring domain (oil-in-water emulsions or regular micelles) at **a5**¹⁶³ (see Supplementary Information Section 4.6, Figure 4.7). Naturally, the conductivities were higher at 45 °C, but the conductivity curves were otherwise similar. Figure 4.4b presents the results of a second conductometric titration (hereafter referred to as the “hydrate titration”), in which Me₄NCl and K₃PO₄ were included and maintained at constant concentrations mirroring the reaction conditions used in the water loading study (0.75 M and 1.5 M, respectively). Regions of interest are labelled **i–xvi**, and locations of representative qualitative observations

are indicated with dotted gray vertical lines labeled **b1–b28**, which extend into the graph in Figure 4.4c for ease of comparison and correspond to photos of the titration vessel in Figure 4.4d. At every titration point, conductivity measurements were taken while the system was under vigorous agitation by an overhead stirrer. For titration points prior to the formation of three transparent liquid phases (**b27**), conductivity measurements were also taken after the system was allowed to fully settle following agitation. Although analysis of trends in the graph is predominantly based on the stirred values, the relative differences observed for the settled values provide additional information. Finally, Figure 4.4c contains the water loading study results from Figure 4.3d overlaid with the vertical lines from Figure 4.4a,b; locations of representative qualitative observations are indicated with dashed gray vertical lines labeled **c1–c12**, which correspond to photos of reaction vessels immediately prior to placement in the 45 °C oil bath (Figure 4.4e).

With the introduction of water, the volume occupied by the solid material in the hydrate titration mixture greatly increased (**b1** vs. **b2**), and the conductivity curve sharply rose and then settled into a steadily increasing trend (region **i**). In region **ii**, a comparably sharp rise in conductivity settled into a steadily increasing trend with roughly the same slope as in region **i**. At the start of start of region **iii** there was an abrupt, slight drop in conductivity, after which the conductivity returned to its same rate of increase. The abrupt changes in conductivity in regions **i–iii** consistently occurred immediately above Me_4NCl hydration numbers ($\frac{n_{\text{H}_2\text{O}}}{n_{\text{Me}_4\text{NCl}}}$; see Figure 4.5a) divisible by 0.5 (hydration numbers of 0, 0.5, and 3 at the start of each region, respectively). Very slight changes to the linear stirred and/or settled conductivity trends in region **ii** were also discernible immediately above hydration numbers of 1, 1.5, and 2. This correlation with hydration number suggested that the changes in mixture structuring arose from an interaction predominantly between water and Me_4NCl rather than water and K_3PO_4 . The point of maximal reaction conversion

Figure 4.4 (previous page): Correlation of conventional and hydrate conductometric titration results with the influence of water loading on the halosequestrative Pd-catalyzed coupling of aryl halides and primary nitroalkanes. Conductometric titration entailed water dilution of *t*-BuOH with either an initial loading of 0.1 wt% NaBr (conventional titration) or a maintained concentration of 1.5 M K₃PO₄ and 0.75 M Me₄NCl (hydrate titration). **a** Conventional titration results at 45 °C plotted alongside literature values at 25 celsius;¹⁶¹ linear regions of the curves associated with various solvent structuring types are highlighted and fitted with trendlines; points of transition between regions of the 45 °C curve are labelled **a1–a5** and marked with thick vertical dashed gray lines which extend into the two lower graphs. **b** Conductivity measurements from the hydrate titration at 45 °C in actively stirred and settled states; locations of representative photos from the titration are labelled **b1–b28** and marked with vertical dotted gray lines which extend into the lower graph; regions of interest are labelled **i–xiv**. **c** Reaction conversion results at different water/*t*-BuOH solvent compositions (nitroalkane arylation with 0.5 mmol 4-iodoanisole, 5 equiv *n*-PrNO₂, 0.1 mol% catalyst **16**, 3 equiv K₃PO₄, 1.5 equiv Me₄NCl, and 1 mL water/*t*-BuOH mixture after 2 h at 45 °C under argon atmosphere and using glovebox handling of reagents); locations of representative photos from the setup of these reactions just prior to placement in the heating bath are labelled **c1–c12** and marked with vertical dashed gray lines. **d** Representative photos from different points in the hydrate titration. **e** Representative photos for the setup of reactions at different solvent compositions.

aligned with the center of a combination of region **ii** and **iii** at a hydration number of 2, and the beginning and end of this conversion peak coincided with the beginning of region **ii** and the end of region **iii**, suggesting that this structuring domain was responsible for the enhancement in reactivity. Most remarkably, the settled solid of the titration mixture at the reaction conversion optimum (**b7**) uniquely exhibited a morphology indicative of an extended network, with perpendicular, persistent fissures developing and a greater amount of unlevelled solid persisting by the stirrer shaft than at any other point in the titration. Taken together, these observations strongly implied that formation of a Me₄NCl dihydrate structure was responsible for the tripling of yield at $x_{\text{H}_2\text{O}} = 0.127$ vs. $x_{\text{H}_2\text{O}} = 0$.

The difference in conductivity between the stirred and standing states of the hydrate titration remained roughly constant until region **iv**, at which point the difference initially broadened to a local maximum and then narrowed to a minimum. The roughly constant difference throughout regions **i–iii** implied that the behavior of the charge carriers was the same in this domain as it had been in the absence of water. The

minimum difference at the end of region iv coincided with a hydration number of 4. Throughout regions **v–vii**, the conductivity remained roughly constant, despite the increasing abundance of water. Regions **v–vii** also coincided with the peak in reaction conversion centered at b13 and c4, suggesting that a Me_4NCl pentahydrate structure might be responsible for the spike in reaction conversion. The morphology of the solid in the titration mixture at **b13** also implied extended structuring; it exhibited well-formed unleveled solid with right angles reminiscent of an underlying cubic architecture. Within region vii, however, the conductivity began to rise again slightly; once possible explanation here appeared to be that the initial onset of inverse structuring anticipated from the conventional titration (**a1**) might be involved. Throughout region **viii**, there was a strong linear increase in conductivity, and upon transitioning into region ix there was an abrupt and dramatic increase in conductivity which coincided with distinct morphological changes. At **b16** the solid in the titration mixture appeared to partially melt with stirring, such that roughly half the volume of solid from **b15** remained. On moving to **b17**, the volume of solid initially decreased further with stirring (**b17-1**), but with continued stirring it once again increased (**b17-2**). By the end of region **ix**, the volume of solid once again substantially decreased (**b18**). With the abrupt jump in conductivity to the new domain of linearity in region **x** there also appeared a global maximum for the difference between the settled and stirred conductivity measurements. This difference quickly narrowed by the end of region **x** along with a further decrease in volume of solid in the titration mixture.

At **b19**, the liquid had developed a haze and a loose suspension of solid sat atop a durable layer of solid which was not broken up by vigorous agitation from the stirrer. This haze was incident with the anticipated onset of fully inverse solvent structuring (**a2**). In region **xi** the conductivity decreased at a constant rate. Meanwhile, the loose suspension disappeared, leaving an increasingly hazy liquid with a highly durable cake of solid at the bottom. Upon entering into region **xii**, the settled conductivity

measurement was less than that of the stirred state for the first time; this change coincided with the morphological change that the durable solid cake became slightly more diffuse in appearance at its edges and could be somewhat remolded by application of the stirrer (**b21**). As the cake continued to loosen with increasing titration (**b22**), the conductivity rose. In region **xiii**, the stirred conductivity moved into a new domain of linearity while the difference between stirred and settled conductivity greatly increased; this increase coincided with the appearance of water droplets on the sides of the vessel upon settling (**b23**). The cake was also increasingly loosened up, and the solid which remained stuck to the walls of the vessel developed a liquid corona upon settling; by the end of the region, almost all such solid was released from the walls into a loose opaque layer with a clear liquid phase gradually appearing above it upon standing (**b24**). The difference between stirred and settled conductivity contracted to almost zero at **b25**, which coincided with the removal of the last portion of solid which adhered to the wall of the vessel. Beyond this point, the stirred conductivity actually continued along the same linear trend from region **xiii**, but upon crossing the anticipated onset of bicontinuous structuring (**a3**) a sharp drop in conductivity was observed coincident with the appearance of a new phase (**b26**). The new phase developed beneath the opaque, formerly bottom layer, and by **b27** the opacity of this newly middle layer changed to translucence (**b27-1**), which became transparent upon extended standing (**b27-1**). Stirring to uniform composition (**b28**) became increasingly difficult in the bicontinuous domain, but implementation of a modified agitation method (see 4.12 for details) allowed collection of further datapoints which showed an ostensibly exponential increase in conductivity (region **xv**). Presumably due to being too large of a volume for the capabilities of our experimental setup, we were unable to stir the titration mixture to uniform composition at $x_{\text{H}_2\text{O}} > 0.777$ (region **xvi**).

The steady decrease in reaction conversion from **c6** to **c7** appeared as though it

may have arisen from the full onset of inverse structuring at **a3**, and the abrupt jump in conversion followed again by a steady decline from **c8** to just before **c11** similarly appeared to be related to the bicontinuous structuring domain. Likewise, the drop in reaction conversion at **c11** followed by a steady decline through **c12** coincided well with the anticipated onset of direct structuring at **a5**, and the drop from **c12** to the pure water system is consistent with the onset of direct structuring ($x_{\text{H}_2\text{O}} > 0.994$).¹⁶⁴ The onsets of these solvent structuring domains anticipated from the conventional titration did not align perfectly with the onsets of the corresponding trends in reaction conversion, but some degree of deviation is expected given the presence of other components in the reaction mixture, such as *n*-PrNO₂. The similar rate of decrease in reaction conversion for the fully inverse, bicontinuous, and direct structuring domains suggests that beyond **a2**, increasing water loading affects the reaction in a consistent manner, regardless of the solvent structuring domain. This behavior is in stark contrast to water loadings prior to **a2**, where trends in reaction conversion are either flat plateaus or nearly symmetric peaks.

The pre-**a2** reaction conversion and reaction mixture morphology strongly suggested the involvement of clathrate-like hydrate structures, but more conclusive identification and characterization of this structure is complicated by its in situ generation in the presence of multiple species that may or may not contribute yet also perform another function in the reaction. Tetraalkylammonium clathrate-like hydrates are known for hydroxide, halides, and phosphates,¹⁶⁵ and a precedent exists for substantial stabilization of such structures by enclosure of alkali metal cations into hydrate polyhedra.¹⁶⁶ Low melting di- and heptahydrates of *t*-BuOH (0.7°C and −8.2°C, respectively) have also been confirmed.¹⁶⁷ Despite the low melting points, these hydrates incorporate the alcohol hydroxyl group into their clathrate lattices, indicating that they may likewise be involved in mixed hydrate structures. The crystal structure of tetra-*n*-butylammonium 2-nitropropan-2-ide contains nitronate dimers which receive

hydrogen bonds to their oxygen atoms from the α -methylene hydrogens of four cations, resulting in an infinite three-dimensional structure, and cryoscopic studies in benzene found persistence of the dimers in solution, indicating some form of supramolecular ion pairing.¹⁶⁸ Similarly, α -nitrobenzyl lithium crystallizes with ethanol into a hydrogen-bonded supramolecular structure.¹⁶⁹ However, our recognition of the interrelationship of K_3PO_4 , water, and Me_4NCl (Table 4.6) led us to design the hydrate titration experiment to omit nitroalkane (as well as catalyst and aryl halide), and agreement of the hydrate titration conductivity curve with reactivity trends (Figure 4.4b,c) suggests that the nitroalkane is not involved in the beneficial superstructure. Initial attempts to obtain a crystal suitable for X-ray diffraction from water, K_3PO_4 , and Me_4NCl were unsuccessful, both by direct combination in a 5:2:1 ratio and by water evaporation from a solution. In the former case, the mixture could not be induced to melt. In the latter case, extensive heating at 80 °C under high vacuum could not drive the system below a hydration number of 7.5 (as determined by weight). Furthermore, the 7.5-hydrate could not be induced to melt, and given the ternary nature of the system, melting is essential to ensure adequate mixing of components, especially for lower hydrates. The presence of K_3PO_4 is particularly problematic in this regard, as it almost certainly contributes to a high melting point and simultaneously facilitates tetramethylammonium decomposition at high temperatures.¹⁷⁰

The foregoing considerations limit the extent to which comparison can be made to related systems known in the literature. The hydration number of saturated aqueous Me_4NCl at 25 °C is 2.68, and although low-melting clathrates are believed to exist,^{171–173} their exact structures have not been established. Tetramethylammonium fluoride has been thoroughly investigated and is known to form 1-, 2.33-, 4-, and 5-hydrates, but its hydrate melting diagram does not align with our results,^{174,175} and fluoride might be expected to behave quite differently given its kosmotropic nature.¹⁷⁶ Interestingly, the hydrates of tetramethylammonium hydroxide (Me_4NOH), which

have been thoroughly investigated by Mootz and co-workers,^{170,177} exhibit striking parallels with our conductivity and reaction conversion data. Me_4NOH forms 2-, 4-, 4.6-, 5-, 6.67-, 7.5-, 8.75-, and 10-hydrate structures, half of which are stable at room temperature. The first characterization of Me_4NOH actually used material prepared by ion exchange of KOH and Me_4NCl in methanol,¹⁷⁸ but although this somewhat mirrors our conditions, the in situ generation of Me_4NOH alone would not be consistent with our results: (1) added water has no impact on reaction conversion until a Me_4NCl :water ratio of 1:1; and (2) deviation from the optimum 2:2:1 water: K_3PO_4 : Me_4NCl ratio toward higher base loading is detrimental (Table 4.6, entries 6 and 7). Accordingly, since the nature of our in situ system must differ, comparison to trends in $\text{Me}_4\text{NOH} \cdot x\text{H}_2\text{O}$ melting point is currently only justifiable as a proxy for the relative stability of a variety of hydrate structures compatible with tetramethylammonium. Figure 4.5 compares conductivity and reaction conversion results from the present investigation against $\text{Me}_4\text{NOH} \cdot x\text{H}_2\text{O}$ phase transition data.¹⁷⁷ The positions of the known Me_4NOH hydrates are labeled with vertical dashed yellow lines. The melting points of these specific hydrates are marked with light blue diamonds; solid–solid phase transitions identified by Mootz and Stäben are represented as horizontal light blue lines; incongruent melting occurs above these lines such that the structure associated with the higher-melting phase (which has a different hydration number) appears alongside liquid with the hydration number of the lower-melting phase.¹⁷⁷ The vertical regions of alternating shades of gray labeled **I–IX** delineate $\text{Me}_4\text{NOH} \cdot x\text{H}_2\text{O}$ incongruent melting domains. Points where the melting curve passes our reaction temperature or the temperature of reaction setup (ca. 25 °C) are labelled with vertical dashed green lines **m1–m4**. Thick gray vertical dashed gray lines for positions **a1–a3** from Figure 4.4a are also provided.

Mootz and Seidel reported that Me_4NOH samples with hydration numbers less than 2 decomposed before melting. Reactions set up with corresponding hydration numbers (region **I**) were loose suspensions; as $x_{\text{H}_2\text{O}}$ increased, so did the aggregation of the solid in small clusters (photo **c1** vs. **c2**). Region **II** ranges from the lowest reported water loading for $\text{Me}_4\text{NOH} \cdot x\text{H}_2\text{O}$ to exhibit a solid phase transition at 35°C to the lowest loading for a solid phase transition at 42°C . The reaction conversion in region **II** decreased in a linear fashion, including the reaction with the water loading for which the $\text{Me}_4\text{NOH} \cdot x\text{H}_2\text{O}$ melting point was below the reaction temperature.

aligns perfectly with region **iii** in the conductometric titration during which there was a noticeable decrease in the volume of solid in the titration mixture (**b9** vs. **b10**). If the solid in the reaction vessel is likewise disposed toward a greater degree transition to liquid phase here, such changes do not appear to impact reactivity, but the amount of solid remaining in our in situ system suggests that the

Figure 4.5: Comparison with Me_4NOH hydrate structures with conductometric titration results and water loading reactivity screening results. **(a)** Phase transitions for $\text{Me}_4\text{NOH} \cdot x\text{H}_2\text{O}$ reported by Mootz and Stäben91 with incongruent melting domains labeled I-IX. The top panel shows the melting point curve (blue line with diamonds) and specific hydrate phase transition (yellow diamonds) against the molar ratio $n_{\text{H}_2\text{O}} / n_{\text{Me}_4\text{N}^+}$. The middle panel shows settled and stirred conductivity (red and purple lines) against the molar ratio. The bottom panel shows reaction conversion (%) against the molar ratio. **(b)** Illustration of interconversion between two hypothetical hydrate structures analogous to $\text{Me}_4\text{NOH} \cdot x\text{H}_2\text{O}$.

overall melting point was not exceeded. However, a distinct morphological change in the reaction mixture solid was observed beginning in region **II**: the brief stirring of reaction mixtures prior to placement in the 45 °C oil bath resulted in an abrupt formation of a rigid extended structure throughout the solution which was gradually broken up with further stirring. This effect became more pronounced with increasing water loading; it was not observed at the lowest water loading reaction in region **II** and was most severe for **c3** at the beginning of region **III** (photo **c3** shows this extended structuring prior to further stirring). At the slightly higher water loading corresponding to the tetrahydrate, however, the extended structuring throughout the solution was not observed. Accordingly, this phenomenon appears to be a macroscopic indicator of an increasing abundance of incongruent melting related to the phase transition line intersecting the local minimum of the melting curve, which may be lower in our system. The improvement to optimal reactivity at **c2** appears to be directly related to the concentration of the dihydrate structure: (1) the symmetry of the conversion peak at **c2** suggests that the immediately pre- and post-dihydrate structures have comparable or negligible impact, as does the constant extent of conversion observed prior to the onset of the peak; (2) the peak is centered exactly at a hydration number of 2, and the peak begins immediately above a hydration number of 1 and returns to the same degree of conversion immediately above a hydration number of 3. $\text{Me}_4\text{NOH} \cdot 2 \text{H}_2\text{O}$ has the lowest density of the Me_4NOH hydrate series, and its crystal structure consists of sheets of ${}_{\infty}[\text{HO}^-(\text{HOH})_{4/2}]$ *spiro* chains wherein hydroxide anions receive but do not donate hydrogen bonds.¹⁷⁰ The lack of hydrogen bond donation from hydroxide makes the existence of, e.g., a chloride analog conceivable. If such a structure is formed in situ, it may promote iodosequestration by intercalation and/or facilitation of anion exchange.

The reaction conducted at the water loading between **m1** and **m2** and immediately after the local minimum of the melting point curve resulted in roughly the same degree

of conversion as the two reactions prior to the onset of the dihydrate peak. This similarity may suggest that water loadings in the region between the melting point curve local minimum and the beginning of region **III** have no impact on conversion due to the absence of both dihydrate structures and region **III** structures. Region **III** begins at the lowest water loading associated with a Me_4NOH tetrahydrate phase transition. The sharp drop in reaction conversion at **c3** suggests that the appearance tetrahydrate structuring is detrimental relative to anhydrous conditions. This drop also coincides with the onset of constant stirred conductivity in the hydrate titration (region **iv**), and the difference between stirred and settled conductivity also became roughly constant at the exact water loading for tetrahydrate formation. These conductivity values remained constant throughout the majority of region **III**, implying a consistent system structuring. Reaction conversion increased moving from **c3** to the local maximum at **c4**; concurrently, the solid aggregates became increasingly crystalline in appearance. At **c5**, reaction conversion decreased, and during setup much of the solid material coalesced into a singular mass which stuck to the walls of the reaction vessel, but some of the solid continued to exhibit the appearance of crystallinity. These observations align with the structural similarity of the 4-, 4.6-, and 5-hydrate Me_4NOH structures, which facilitates interconversion with the addition or removal of water.^{170,177} The interconversion of analogous hypothetical 4- and 4.6-hydrate structures is depicted in Figure 4.5b. The sodalite-like structure of the 4.6-hydrate is particularly interesting given the precedent for sodalite sequestration of iodide¹⁷⁹ and the prevalence of the structural motif in zeolites.¹⁸⁰

Above **a1**, the possibility exists for water to contribute to either the hydrate formation or inverse structuring of the solvent. However, the 6.67-, 7.5-, 8.75-, and 10-hydrates all appear at points of transition in the hydrate titration conductivity curve. The transition at the position of the 7.5-hydrate is particularly noteworthy given that: (1) the solid in the hydrate titration vessel appeared to partially melt upon

crossing this threshold; and (2) the lowest hydration number that could be obtained from evacuation of an aqueous 2:1 solution of K_3PO_4 and Me_4NCl was also 7.5, which coincided with the disappearance of the liquid which was coexistent with the solid at room temperature. Thus, the melting point of the 7.5-hydrate for our system is $> 80^\circ\text{C}$ and the melting point of the presumed 8.75-hydrate of our system is below 25°C . Accordingly, the melting diagram of our system is distinct, so **m3** and **m4** are not important for our system. Between the positions of the 7.5- and 10-hydrates, the reaction conversion is nearly constant and roughly equal to the value at **c3**. It is plausible that molten hydrate structures exhibit a comparable effect on reactivity. If true, this would strongly support that the benefit of the hydrate structure is based on tertiary halosequestration. The position of the decahydrate nearly coincides with **a2** and the end of region **V**. The disappearance of loose solid from the titration vessel in **b19** is consistent with the disappearance of high-melting 7.5-hydrate at the end of region **V**. The development of solution haziness and the stiff solid cake at **b19** could also suggest that water transferred from the hydrate to the solution to enable inverse structuring, leaving the poorly hydrated solid as a cake. The stability of the cake may be attributable to the presence of molten 8.75-hydrate given that region **VI** begins with the appearance of the cake (**b19**) and ends just as the cake begins to soften (**b21**). However, due to the onset of inverse structuring and the presence of a solid which could not be agitated effectively, the hydration number associated with the solid may be substantially lower, and incongruent melting domains **VI–VIII** may not correlate to our system. Nevertheless, the beginning of **VIII** coincides with a distinct narrowing of the difference between stirred and settled conductivity. Conductivity actually declines after **a3** until the beginning of region **IX**, which corresponds to the end of hydrate structuring.

4.4 Preliminary Exploration of More Sustainable Halosequestration

4.4.1 Choline Chloride as a Benign Halosequesterant

Me_4NCl represents a substantial sustainability improvement over silver salts, but Me_4NCl is not completely benign. In particular, it is toxic to aquatic life. Previous investigation of tetraalkylammonium salts has presumed a preeminent role of phase transfer catalysis. Perhaps as a consequence, choline salts have seemingly been overlooked. Preliminary investigation of other additives in *t*-BuOH (Table 4.14) found that choline chloride resulted a 6-fold improvement in conversion compared to the absence of an additive; under the conditions employed, choline chloride was superior to *n*-Bu₄NCl, but not as effective as Me_4NCl . However, since choline chloride is an essential nutrient, its greenness may warrant use over Me_4NCl , especially if further optimization improves the relative efficacy of choline chloride. A preliminary assessment of the influence of water loading on choline chloride efficacy showed a nonmonotonic relationship with reaction conversion, and the morphology observed during reaction setup likewise suggests that a tertiary halosequestration hydrate effect may be involved (Figure 4.6).

4.4.2 Amberlite[®] as a Tertiary Halosequesterant Synergistically Enhanced by Anion Shuttling

Molecular sieves and Amberlite[®] (IRA-400 chloride form) were also explored as tertiary halosequesterants (see Supplementary Information Section 4.6, Table 4.15). For this reaction, molecular sieves (3 Å, 4 Å, 5 Å, and 13X) were not beneficial; it may be that molecular sieve halosequestration is not suitable for basic conditions.

Figure 4.6: Results with choline chloride **a** Reaction conversion as a non-monotonic function of water loading with choline chloride as the primary halosequesterant. Conditions: **15a** (1 equiv, 0.5 mmol), $n\text{-PrNO}_2$ (5 equiv), choline chloride (1.5 equiv, handled in glovebox), K_3PO_4 (3 equiv, handled in glovebox), **16**, reaction medium (0.5 M with respect to **15a**, argon-sparged), argon atmosphere, 45 °C, 4 h, according to Procedure 4.9. **b** Reaction system morphology with choline chloride for different water loadings immediately prior to reaction start, 1 h after removal from heating, and 12 h after removal from heating.

Amberlite[®], however, was beneficial and provided additional evidence for tertiary halosequestration. Three different preparations of Amberlite[®] were explored: wet (used as received, 41 wt% water), dry (dried under high vacuum), and pulverized (vacuum-dried and then ground to a fine powder by mortar and pestle). Wet and pulverized preparations were beneficial, while the dry preparation showed at best only a slight improvement regardless of loading. These results suggest that accessibility of the tetraalkylammonium site is important for additive efficacy. An additional experiment was conducted using 0.5 equiv Me_4NCl in tandem with dry and pulverized Amberlite[®] preparations (Table 4.7). Although unpulverized Amberlite[®] was only barely beneficial on its own, inclusion of 0.5 equiv Me_4NCl resulted in a substantial improvement to conversion that could not be attributed to Me_4NCl alone. Accordingly, it appears that when Me_4NCl is present, it also serves as an anion shuttle which deposits abstracted iodide in the dry Amberlite[®] spheres. This synergistic benefit strongly points to the involvement of tertiary halosequestration. If indeed so, this tandem additive

Table 4.7: Synergistic effect of Amberlite® IRA-400-Cl as a tertiary halosequesterant and Me₄NCl as an anion shuttle.^a

Entry	Amberlite® State	equiv Me ₄ NCl	% Conv. ^b
1	omitted	0	2
2	dry ^d	0	3
3	dry powder ^e	0	15
4	omitted	0.5	24
5	dry ^d	0.5	43
6	dry powder ^e	0.5	46

^a Conditions: **15a** (1 equiv, 0.25 mmol), *n*-PrNO₂ (5 equiv), Me₄NCl, Amberlite® IRA-400-Cl (1.5 equiv), K₃PO₄ (3 equiv), **16**, *t*-BuOH (0.5 M with respect to **15a**, argon-sparged), argon atmosphere, 45 °C, 3 h, according to Procedure 4.10.

^b Determined by GCMS. ^c A molecular weight of 243.1 g mol⁻¹ was used for the ideal constitutional unit of dry Amberlite® IRA-400-Cl (see Procedure 4.10 for details).

^d Dry Amberlite® was obtained by subjecting the material to high vacuum until a constant mass was observed; this process resulted in a 41 % decrease in mass. ^e The powdered form of Amberlite® was obtained by pulverizing vacuum-dried material with a mortar and pestle.

experiment may prove useful in assessing whether halosequestration is beneficial in other reaction systems. Furthermore, the tandem system provides the opportunity to recover sequesterant and decrease the loading of Me₄NCl.

4.5 Conclusions

The Pd-catalyzed arylation of nitroalkanes has been used as a model reaction to explore sustainable halosequestration strategies. Simultaneous implementation of primary, secondary, and tertiary halosequestration strategies resulted in a dramatic improvement to catalyst efficiency: nitroalkane couplings with aryl bromides were readily accomplished ten times faster with one tenth the catalyst loading. Additive screening identified Me₄NCl as an optimally effective metal-free primary haloseques-

trant, and its use expanded the aryl halide scope to include aryl iodides. Reevaluation of the reaction medium led to the selection of *t*-BuOH as a solvent suitable for secondary halosequestration. Small amounts of moisture were found to benefit the reaction, and an ideal 2:2:1 ratio of water:K₃PO₄:Me₄NCl was identified. Assessment of system mesostructure through conductometric titration suggested the formation of a supramolecular hydrate structure. The water loading corresponding to a dihydrate was found to be three times as effective as anhydrous conditions. Preliminary investigations into analogous systems with choline chloride and Amberlite® (1) suggest that this benefit may arise through tertiary halosequestration and (2) illustrate the potential for even greener halosequestrative conditions to be developed in the future. Trends in reaction conversion with Me₄NCl for $x_{\text{H}_2\text{O}} > 0.448$ closely coincided with known inverse, direct, and bicontinuous water/*t*-BuOH structuring domains; these three domains exhibit a similar gradual decrease in conversion with increasing water loading. If the bicontinuous structuring region of the conversion graph is removed, the end of the inverse region and beginning of the direct structuring regions align well, which may suggest a similarity in influence between water-in-oil and oil-in-water microemulsions; the enhancement to conversion in the bicontinuous domain may be indicative of improved halide transfer between oil and water regions compared to microemulsion systems. This work thus also raises the possibility that poly- and pseudophase suitability for halosequestration may be an important consideration in the development of designer surfactants and related systems. Along these lines, further exploration of the possibility of beneficial supramolecular hydrate structures is particularly warranted.

4.6 Supplementary Information

4.6.1 Methods

4.6.1.1 General Information

All manipulations were carried out under air unless otherwise noted. Reaction molarity listed in reaction schemes is relative to the limiting reagent. All flash chromatography was conducted using a Teledyne Isco CombiFlash Rf 150. NMR spectra were recorded at 23 °C using Varian MR-400, Varian Unity INOVA 500, and Varian VNMRs 700 spectrometers (400 MHz, 500 MHz, and 700 MHz, respectively). Reported chemical shifts are referenced to residual solvent peaks. GCMS data was obtained using a Thermo Scientific Trace 1300 Gas Chromatograph coupled with a Thermo Scientific ISQ-QD Single Quadrupole Mass Spectrometer. High-resolution mass analyses were obtained either using a 5975C Mass Selective Detector coupled with a 7890A Gas Chromatograph (Agilent Technologies) or orbit-trap.

TLC plates (UV 254 indicator, aluminum backed, 175 μm to 225 μm thickness, standard grade silica gel, 230 mesh to 400 mesh) were purchased from Merck. Silica gel (60 Å pore size, 230 mesh to 400 mesh) was purchased from Silicycle. Anhydrous *t*-BuOH was supplied by EMD Millipore and was stored over activated 3 Å molecular sieves in an air free flask under argon atmosphere for 24 h prior to use; a heating mantle was used to maintain a temperature just above the melting point. Surfactant solutions were prepared in HPLC-grade water. PS-750-M (also known as FI-750-M) was prepared as previously reported;⁶⁴ CTAC was supplied by Chem-Impex. Other solvents were obtained from commercial suppliers and dried using standard protocols. 4-Iodoanisole (**15a**) was supplied by Sigma-Aldrich and used as received. Catalyst **16** was received as a gift from Johnson Matthey. Anhydrous K_3PO_4 and Me_4NCl were supplied by Acros Organics and were stored in a glovebox; ca. 15 g aliquots were

taken out and stored in a vacuum desiccator over anhydrous sodium sulfate when not in use. Nitroalkanes EtNO₂ and *n*-PrNO₂ were supplied by TCI America and Sigma-Aldrich, respectively; they were distilled from calcium hydride onto activated 3 Å molecular sieves in air-free flasks and stored under argon atmosphere. Amberlite® IRA-400 chloride form was supplied by Sigma-Aldrich. Other substrates and reagents were obtained from commercial suppliers and used as received.

4.6.1.2 Synthetic Procedures

Nitroalkane arylation reactions were prepared either with operationally simple benchtop handling of reagents (General Procedure 4A) or under strictly anhydrous conditions in a glovebox (General Procedure 4B). Specific nitroalkane arylation experiments (Procedures 4.1–4.10) used slight deviations from the general procedures.

General Procedure 4A: Reaction setup with benchtop handling of reagents.

Reactions were conducted in 4 mL glass screw-top vials equipped with a PTFE-coated stir bar. Addition of catalyst **16** was dependent on catalyst loading. For catalyst loadings of 2.5 mol%, **16** was added directly to the reaction vessel. For lower loadings, a fresh stock solution of **16** in methylene chloride was prepared, and an appropriate volume of stock solution was delivered to the reaction vessel by microliter syringe; the reaction vessel was then stirred at 45 °C for 10 minute to remove the solvent. Aryl halide (1 equiv) and additive(s) (at specified loadings) were added according to their phase at room temperature. Additive(s) (if solid), aryl halide (if solid), and K₃PO₄ (3 equiv) were measured out on weigh paper and sequentially added to the reaction vessel (except for hygroscopic additives, which were added directly to the reaction vessel so as to minimize air exposure). The vial was closed by inserting the screw-top into the narrow end of a 14/20 rubber septum such that the top of the glass was seated against the flat part of the septum. The septum flap was folded down, and the reaction vessel was thrice evacuated/argon-backfilled. While still connected to the argon line, the reaction vessel was sequentially charged with aryl halide (if liquid), additive(s) (if liquid), and nitroalkane (5 equiv, argon-sparged for 15 minute prior to use) by syringe, and then the reaction mixture was stirred for 10 second. The reaction medium (at the specified volume, argon-sparged for 15 minute prior to use) was then added by syringe, and the reaction mixture was stirred for an additional 10 second. Any solid on the vessel walls above the reaction mixture was scraped down with the

stir bar by application of a strong external magnet. The reaction vessel was removed from the argon line and septum punctures were immediately covered with a piece of electrical tape. The entire septum was then wrapped with high-density PTFE tape, and the reaction vessel was placed to stir in an aluminum reactor block pre-heated to 45 °C.

General Procedure 4B: Reaction setup with glovebox handling of reagents.

Reactions were conducted in oven-dried 10 mL glass microwave vials equipped with a PTFE-coated stir bar. A fresh 5 μ M stock solution of catalyst **16** in methylene chloride was prepared, and the stock solution was delivered to the reaction vessel by microliter syringe (200 μ L, 0.1 mol% **16**). The microwave vial was fitted with a rubber septum, and then a vent needle and a needle connected to the argon line were inserted into the septum. The reaction vessel was placed to stir in an oil bath pre-heated to 45 °C for 15 minute. The vent needle was then removed, high vacuum was applied for 1 minute, and the vessel was backfilled with argon. The septum was briefly removed for the addition of aryl halide **15a** (1 equiv, 0.5 mmol). The septum was returned to the vessel, which was thrice evacuated/argon-backfilled and then sent into the glovebox where anhydrous Me₄NCl (at the specified loading) and K₃PO₄ (at the specified loading) were added. The vessel was removed from the glovebox and returned to the argon line, anhydrous *n*-PrNO₂ (5 equiv, argon-sparged for 15 minute prior to use) was added by syringe and the vessel contents were stirred for 10 second. A 1 mL volume of the specified water/*t*-BuOH solvent composition was established in the vessel by sequential microliter syringe addition of appropriate volumes of anhydrous *t*-BuOH (argon-sparged for 15 minute prior to use) and deionized water (argon-sparged for 15 minute prior to use). The reaction mixture was stirred for an additional 10 second. Any solid on the vessel walls above the reaction mixture was scraped down with the stir bar by application of a strong external magnet. The reaction vessel was then removed from the argon line and septum punctures were immediately covered with a

piece of electrical tape. The entire septum was then wrapped with high-density PTFE tape, and the reaction vessel was placed to stir in an oil bath pre-heated to 45 °C.

Procedure 4.1: Additive screening in aqueous PS-750-M.

Reactions were prepared according to General Procedure 4A using **15a** as the aryl halide (0.25 mmol), *n*-PrNO₂ as the nitroalkane, 2.5 mol% **16**, the specified additive(s) at the specified loading(s), and 3 wt% aq. PS-750-M as the reaction medium (0.5 mL). A 20 µL aliquot was taken after 14 hour for GCMS analysis.

Procedure 4.2: Solvent screening.

Reactions were prepared according to General Procedure 4A using **15a** as the aryl halide (0.25 mmol), *n*-PrNO₂ as the nitroalkane, the specified loading of **16**, Me₄NCl as the additive (2 equiv), and the specified reaction medium (0.5 mL). A 20 µL aliquot was taken at the specified reaction time for GCMS analysis.

Procedure 4.3: Benchtop screening of *n*-PrNO₂, K₃PO₄, and Me₄NCl loadings.

Reactions were prepared according to General Procedure 4A using **15a** as the aryl halide (0.25 mmol), *n*-PrNO₂ as the nitroalkane, the specified loading of **16**, Me₄NCl as the additive (at the specified loading), and the specified reaction medium (0.5 mL); K₃PO₄ and *n*-PrNO₂ were used at the specified loadings rather than at the default loadings stated in General Procedure 4A. A 20 µL aliquot was taken at the specified reaction time for GCMS analysis. The same aliquots of K₃PO₄ and Me₄NCl were used for the newer and older aliquot experiments in Figure 4.3a,b, but they were used at different points in time. Specifically, ca. 15 g each of K₃PO₄ and Me₄NCl were removed from the glovebox in 20 mL vials. Within 4 days of removal from the glovebox, 5.25 g K₃PO₄ was used in the course of setting up 16 reactions. The “newer aliquot” reactions were conducted 5 days after removal of the aliquots from the glovebox and consumed 2.95 g K₃PO₄ for 18 reactions (in addition the screenings of K₃PO₄

and Me₄NCl, the *n*-PrNO₂ loading was also screened). The Me₄NCl loading screens with either 2 equiv or 4 equiv K₃PO₄ were started 24 hour later (“older aliquot”) and consumed an additional 1.31 g K₃PO₄. The “older aliquot” screening of base loading occurred 7 days after removal of the aliquots from the glovebox.

Procedure 4.4: Global concentration screening.

Reactions were prepared according General Procedure 4A using **15a** as the aryl halide (0.5 mmol), *n*-PrNO₂ as the nitroalkane, the specified loading of **16**, Me₄NCl as the additive (1.5 equiv), and *t*-BuOH as the reaction medium. As opposed to what is stated in General Procedure 4A, the catalyst was delivered by adding an appropriate volume of a 5 μ M stock solution of **16** in dry, argon-sparged *t*-BuOH with a microliter syringe immediately prior to the addition of *n*-PrNO₂. The volume of additional *t*-BuOH needed for the specified global concentrations took into account the volume already contributed by the stock solution. A 20 μ L aliquot was taken after 1 hour for GCMS analysis.

Procedure 4.5: Substrate prescreening to determine catalyst loading.

Reactions were prepared according to General Procedure 4A using the specified aryl halide (0.5 mmol), the specified nitroalkane, 0.1 mol% **16**, Me₄NCl as the additive (1.5 equiv), and *t*-BuOH as the reaction medium (0.5 mL). A 20 μ L aliquot was taken after 1 hour for GCMS analysis. Some substrate prescreening reactions were also monitored after 3 hour, and full conversion was consistently observed after 3 hour for substrates that exhibited ca. 65 % conversion or greater after 1 hour. Accordingly, the extent of conversion to product after 1 hour was used to select the catalyst loading for the exploratory substrate scope. Specifically, for substrates showing between 10 % and 95 % conversion after 1 hour, the catalyst loading was scaled so as to expect ca. 70 % conversion in 1 hour assuming a first-order contribution of the catalyst to the rate. Substrates showing greater than 95 % conversion in 1 hour were re-subjected to

prescreening using a lower catalyst loading.

Procedure 4.6: Exploratory substrate scope.

Reactions were prepared according to General Procedure 4A using the specified aryl halide (0.5 mmol), the specified nitroalkane, the catalyst **16** loading determined from prescreening results, Me₄NCl as the additive (1.5 equiv), and *t*-BuOH as the reaction medium (0.5 mL). A 20 μ L aliquot was taken for GCMS after ca. 230 minute, and substrates showing less than full conversion were allowed to react for an additional hour. Accordingly, after either 3 h or 4 hour, the reaction vessel was allowed to cool and then admixed with 0.5 mL saturated aq. ammonium chloride. The organic layer was collected and combined with subsequent extractions of the aqueous layer (3 $\times$ 0.5 mL ethyl acetate or *t*-BuOH). Combined organic layers were washed with brine (1 $\times$ 0.5 mL) and dried over anhydrous MgSO₄. Solvent was removed under reduced pressure, and crude material was purified by flash chromatography on silica gel (hexanes, hexanes/diethyl ether, or hexanes/ethyl acetate). Following removal of solvent under reduced pressure, the purified product was confirmed by ¹H NMR. Characterization details are presented in Section 4.6.4.

Procedure 4.7: Gram-scale reactions.

Reactions were prepared according to General Procedure 4A using the specified aryl halide (6 mmol), the specified nitroalkane, the catalyst loading determined from prescreening results, Me₄NCl as the additive (1.5 equiv), and *t*-BuOH as the reaction medium (6 mL). As opposed to what is stated in General Procedure 4A, the reaction was conducted in a 20 μ L Schlenk tube, and the catalyst was added directly to the reaction vessel without use of a stock solution. Product isolation was analogous to that of the reactions conducted at 0.5 mmol scale.

Procedure 4.8: Glovebox screening of water, K₃PO₄ and Me₄NCl loadings.

Reactions were prepared according to General Procedure 4B. A 40 μ L aliquot

was taken after 2 hour for GCMS analysis. The volumes of *t*-BuOH and water were selected so as to result in a 1.00 mL total volume at 25 °C according to interpolation of known water/*t*-BuOH mixture densities.¹⁸¹

Procedure 4.9: Choline chloride experiments.

Reactions were prepared according to General Procedure 4B, except that choline chloride (1.5 equiv) was used instead of Me₄NCl. A 40 µL aliquot was taken after 4 hour for GCMS analysis. The volumes of *t*-BuOH and water were selected so as to result in a 1.00 mL total volume at 25 °C according to interpolation of known water/*t*-BuOH mixture densities.¹⁸¹

Procedure 4.10: Amberlite® IRA-400-Cl additive experiments.

Reactions were prepared according to General Procedure 4A using **15a** as the aryl halide (0.25 mmol), *n*-PrNO₂ as the nitroalkane, 0.1 mol% **16**, Amberlite® IRA-400-Cl as an additive (1.5 equiv or omitted as specified, in the specified powdered or unpowdered form), Me₄NCl as a second additive (0.5 equiv or omitted as specified), and dry *t*-BuOH as the reaction medium (0.5 mL). The K₃PO₄ used was freshly removed from the glovebox immediately prior to reaction setup. A 40 µL aliquot was taken after 3 hour for GCMS analysis. The stated Amberlite® IRA-400-Cl equiv values correspond to the trimethylalkylammonium moiety; the molecular weight for the ideal constitutional unit was calculated from the product specification to be 349.8 g mol⁻¹ for the wet form (assuming 41 wt% water content) and 243.1 g mol⁻¹ for the dry form.*

*The product specification lists the exchange capacity as 3.8 meq g⁻¹, which corresponds to (0.0038 mol g⁻¹)⁻¹ = 263.16 g mol⁻¹; assuming 41 wt% water content, this corresponds to 155.9 g mol⁻¹ for the dry form; however, these values are in terms of chloride content. The product specification lists the percentage cross-linking as 8 %, which corresponds to 223.1 g mol⁻¹ for an ideal polymerization if the trimethylalkylammonium:chloride ratio is 1:1; given that this value is larger than the dry value calculated on the basis of the listed exchange capacity (155.9 g mol⁻¹), there is more chloride than trimethylalkylammonium. A ratio of 23:36 reconciles the polymer composition and the exchange capacity, and the 349.8 g mol⁻¹ and 243.1 g mol⁻¹ values were calculated on this basis.

4.6.1.3 Conductometric Titration Procedures

Conductivity measurements were obtained with an Oakton CON 510 conductivity meter equipped with an ECCONSEN91W electrode. The temperature of the measurement cell was maintained at 45.0 ± 0.2 °C according to the built-in temperature sensor of the electrode using an external water jacket connected to a thermostated circulator bath. Commercial anhydrous *t*-BuOH was stored over activated 4 Å molecular sieves for at least 24 h prior to use and measured by mass.

Procedure 4.11: Conventional conductometric titration.

The conventional titration was performed as previously described.^{161–163} The oven-dried measurement cell was charged with sodium bromide (12.3 mg, vacuum-oven-dried), closed with a rubber septum, and then evacuated/argon-backfilled. An argon balloon needle was allowed to deflate and was inserted into the septum as soon as deflation was complete. The measurement cell was tared, and then *t*-BuOH was added by syringe until the desired mass was found to have been delivered by weight (12.30 g). Under a cone of argon, the rubber septum was exchanged with one that had been bored and snugly fit around the end of the conductivity probe. The new septum was likewise fitted with a deflated argon balloon needle. The measurement cell was inserted into the external water jacket, the electrode was lowered to an appropriate depth, and circulation was initiated. An initial 650 µL volume of deionized water was then added by syringe, and the temperature was allowed to stabilize. The mixture was subjected to continuous magnetic stirring throughout the course of the titration. Further deionized water was added by syringe, and conductivity readings were allowed to stabilize after each addition. The position of marker **a5** in Figure 4.4 was determined as shown in Figure 4.7.

Figure 4.7: Determination of the phase boundary location between bicontinuous and direct structuring domains for the conventional conductometric titration. The boundary is labeled as **a5** in Figure 4.4a and was determined following the method of Clause and coworkers.¹⁶³

Procedure 4.12: Hydrate conductometric titration.

A 50 mL volumetric flask with a known mass was charged with anhydrous K_3PO_4 (16.981 g) and Me_4NCl (4.388 g) in a glovebox. The flask was removed from the glovebox, placed in an ice bath, and charged with ca. 25 mL deionized water. The flask was stoppered and mixed by swirling until most of the solid had dissolved. The solution was diluted with additional deionized water until the liquid level was slightly below the calibration mark of the flask. The flask was then closed with a ground glass stopper of known mass, thoroughly mixed by inversion, and then left to stand overnight. Additional water was added to bring the total volume to 50.0 mL and the flask was again mixed by inversion. The water content was determined by weight to be 42.335 g. The known composition of this stock solution was then used to calculate the volumes of stock solution and deionized water needed to maintain the salt concentrations in the measurement cell for each step of the titration. Inside a glovebox, the oven-dried measurement cell was charged with the initial loadings of anhydrous K_3PO_4 (4.488 g) and Me_4NCl (1.160 g) needed for the desired concentrations in the initial system in the measurement cell (1.5 M and 0.75 M, respectively). The measurement cell was then closed with a rubber septum and removed from the glovebox.

An argon balloon needle was allowed to deflate and was inserted into the septum as soon as deflation was complete. The measurement cell was tared, and then *t*-BuOH was added by syringe until the desired mass was found to have been delivered by weight (11.00 g). Under a cone of argon, the rubber septum was exchanged with one that had been bored and snugly fit around (1) the end of the conductivity probe and (2) a short length of PTFE tubing through which was threaded the flexible shaft of an overhead stirrer. The new septum was likewise fitted with a deflated argon balloon needle. The measurement cell was inserted into the external water jacket, the electrode was lowered to an appropriate depth, circulation was initiated, and the temperature was allowed to stabilize. For the anhydrous system and after each

addition of stock solution and deionized water, the mixture was agitated with overhead stirring for ca. 30 s and then allowed to settle for about 1 min. The overhead stirrer would then be ramped up to max speed, and the stirred conductivity measurement was taken once the reading stabilized. Stirring was then stopped and the mixture was allowed to stand until the conductivity reading stabilized, at which point the settled conductivity value was recorded. The measurement process was repeated to confirm reproducibility. In instances where values were not immediately reproduced, the measurement process was repeated until reproducibility was observed, and the final values were used. Each addition of stock solution or deionized water was performed by lowering the syringe needle to just above the liquid level in the measurement cell, delivering the appropriate volume, and then lifting the needle tip back up so as not to be at risk of collision with the stir shaft.

The stir shaft was kept at a sufficient depth to make contact with the bottom of the measurement cell and to bow somewhat; this bowing resulted in a wiping motion by the shaft when stirring which helped to keep solid from accumulating on the walls above the liquid level. After acquiring the readings for $x_{\text{H}_2\text{O}} = 0.550$, the top of the stir shaft was detached from the stirrer, and the shaft was used to scrape all remaining solid above the liquid level down into the mixture without opening the measurement cell. At water loadings of $x_{\text{H}_2\text{O}} = 0.655$ and higher, the mixture separated into three distinct phases, and the action of the overhead stirrer alone was not enough to evenly mix all layers. After initial attempts at adequate stirring for $x_{\text{H}_2\text{O}} = 0.655$, the last settled conductivity reading was taken and then the electrode height was adjusted in order to better facilitate stirring. The extra agitation afforded by allowing an object to collide with the stir shaft above the measurement cell enabled adequate mixing up to a water loading as high as $x_{\text{H}_2\text{O}} = 0.777$. Without this augmented agitation, the bottommost phase visibly failed to be fully incorporated. The lowest stable conductivity reading attainable with augmented agitation was used.

Attempts to perform the hydrate titration using continuous magnetic stirring were unsuccessful. The stir bar frequently became stuck. Stir rates that were sufficiently slow to maintain stirring were too slow to evenly distribute solid material in the measurement cell. Implementation of overhead stirring required a flexible stirrer shaft due to the space limitations of the measurement cell. A custom stirrer shaft was prepared from chemically inert FEP tubing as follows. Two perpendicular diameter-length cuts were made on the end of a ca. 40 cm length of FEP tubing (1.6 mm i.d.) to a depth of ca. 1 cm. The resultant strips were folded out to form makeshift propeller blades. A short truncated cone of glass with a base diameter slightly larger than 1.6 mm was then inserted narrow-end-first into the cut end of the FEP tubing. The glass was forced into the tube to a depth where its wide end was past the ends of the cuts, thereby sealing off the inside of the tube. A piece of durable metal cable (e.g., bicycle brake cable) used to fill the remainder of the tubing, thereby ensuring the structural integrity of the stir shaft. This shaft was then threaded through a ca. 3 cm length of PTFE tubing with an i.d. equal to the o.d. of the FEP tubing. The PTFE tubing was then inserted into a hole bored into the rubber septum used to seal the measurement cell. When the measurement cell was fully assembled, the stirrer shaft was attached to a Fisher Scientific overhead stirrer (model 5VB-C, style 1-15-80).

4.6.2 Supplementary Optimization Results

Table 4.8: Detailed additive screening results.^a

Entry	Additive (equiv)	% conv. 10b + 18^b	% conv. 18^b	% conv. 19^b
1	Me ₄ NCl (2), <i>i</i> -PrOH (2)	71	1	3
2	Me ₄ NCl (2), EtOH (2)	55	2	5
3	Me ₄ NCl (2)	54	0	5
4	Me ₄ NCl (2), KCl (2)	52	3	7
5	<i>n</i> -Bu ₄ NCl (2)	48	0	12
6	Et ₄ NOTf (4)	36	3	5
7	AgNO ₃ (1) ^c	35	10	1
8	Et ₄ NOTs (2)	34	0	6
9	DABCO (2)	33	0	4
10	CF ₃ CH ₂ OH (2)	32	0	1
11	glycine betaine (2)	32	0	7
12	<i>i</i> -PrOH (2)	30	1	4
13	Et ₄ NOTf (2)	30	1	4
14	Et ₄ NOTf (0.5)	28	0	6
15	Me ₄ NBr (2)	28	0	6
16	FeSO ₄ · 7 H ₂ O (0.25)	27	0	18
17	CsCl (2)	26	1	9
18	PhSO ₂ Na (2)	26	0	2
19	Et ₄ NHSO ₄ (2)	26	1	22
20	acetophenone (2)	25	1	9
21	Et ₄ NCl (2)	25	0	8
22	Mg(OH) ₂ (2)	24	0	7
23	SDS (0.006)	24	0	8
24	Ca(OH) ₂ (0.5)	24	0	4
25	Na ₂ SO ₄ (2)	24	0	10
26	<i>n</i> -Bu ₄ NPF ₆ (2)	23	4	7
27	KO ₂ CCF ₃ (2)	23	0	8
28	—	23	0	9
29	MgSiO ₃ (2)	23	0	6
30	<i>i</i> -Pr ₂ NEt (2)	20	0	25
31	KOTf (2)	19	0	0
32	<i>n</i> -HexBr (5), CuI (0.1)	19	0	3
33	Zn dust (0.5)	18	0	5
34	CaCl ₂ · 2 H ₂ O (0.5)	17	1	5
35	SDS (0.05)	17	0	2

Continued on next page...

Table 4.8 – *Continued from previous page.*

Entry	Additive (equiv)	% Conv. 10b + 18 ^b	% Conv. 18 ^b	% Conv. 19 ^b
36	CaCl ₂ (0.5)	17	1	7
37	PhNO ₂ (2)	16	0	6
38	ascorbic acid (1)	16	0	10
39	1-naphthyl-SO ₃ Na (2)	15	0	7
40	PMHS (0.25)	15	0	3
41	Bi ₂ O ₃ (2)	14	0	4
42	DBU (2)	13	1	0
43	MgCl ₂ (2)	11	0	11
44	HNBu ₃ BPH ₄ (2)	9	0	0
45	Et ₄ NOAc (2)	8	0	9
46	MgSO ₄ (2)	8	0	8
47	NaBPh ₄ (2)	6	0	0
48	PMHS (2)	5	0	1
49	Zn dust (2)	5	0	8
50	NaCl (10)	5	0	0
51	neutral Al ₂ O ₃ (2)	4	0	0
52	HMDS (2)	4	0	0
53	H ₄ NBF ₄ (2)	4	0	1
54	Cu(BF ₄) ₂ (2)	4	0	4
55	allyl bromide (2)	4	0	0
56	<i>n</i> -Bu ₄ NI (2)	3	0	5
57	FeSO ₄ · 7 H ₂ O (2)	3	0	14
58	Tf ₂ O (1)	2	0	0
59	H ₄ NCl (2)	2	0	0
60	Bi(NO ₃) ₃ (2)	1	0	1
61	I ₂ (0.25)	0	0	1
62	BiCl ₃ (2)	0	0	1
63	AlCl ₃ (2)	0	0	0
64	succinic anhydride (1)	0	0	0

a Reactions were prepared according to Procedure 4.1 using **15a** (0.25 mmol), *n*-PrNO₂, 2.5 mol% **16**, the specified additive(s) at the specified loading(s), and 3 wt% aq. PS-750-M as the reaction medium; an aliquot for GCMS monitoring was taken at 14 h.

b Results are given as the percentage of **15a** converted into the indicated products based on GCMS peak areas corresponding to **15a**, **10b**, **18**, and **19**.

c Monitored at 17 h; at 30 min, 13 % conversion exclusively to **10b** was observed.

Table 4.9: Representative screening results in non-*t*-BuOH solvent systems.^a

Entry	Aryl halide	Reaction medium	equiv K ₃ PO ₄	Additive	°C	Time (h)	% conv. ^b
1	4-iodoanisole	water	3	Me ₄ NCl	45	4	33
2	4-iodoanisole	1:3 <i>i</i> -PrOH/water	3	Me ₄ NCl	45	4	70
3	4-iodoanisole	1:1 <i>i</i> -PrOH/water	3	Me ₄ NCl	45	4	96
4	4-iodoanisole	dry THF	3	–	70	24	6
5	4-iodoanisole	dry THF	3	Me ₄ NCl	70	24	96
6	4-bromoanisole	3 wt% PS-750-M	1.2	–	45	16	70
7	4-bromoacetophenone	3 wt% PS-750-M	1.2	–	45	16	69
8	4-bromoacetophenone	3 wt% PS-750-M	1.2	KBr	45	16	47
9	4-bromoacetophenone	3 wt% PS-750-M	1.2	Me ₄ NCl	45	16	80

^a Reactions were prepared according to Procedure 4.2 (except as specified otherwise) using the specified aryl halide (0.25 mmol, 1 equiv), *n*-PrNO₂ (5 equiv), 2.5 mol% **16**, the specified additive (2 equiv), and the specified reaction medium; an aliquot for GCMS monitoring was taken at the specified time; K₃PO₄ and Me₄NCl were handled in a glovebox for entries 4 and 5. ^b Results are given as the percentage of **15** converted into either **10** or its ketone derivative based on GCMS peak areas corresponding to **15**, **10**, and the ketone derivative.

Table 4.10: Base screening in aqueous surfactant without halosequestrative additives.^a

Entry	Base	% conv. 10b and 18 ^b	% conv. 18 ^b	% conv. 19 ^b
1	K ₃ PO ₄	23	0	10
2	K ₃ PO ₄ · H ₂ O	22	1	8
3	Li ₂ CO ₃	4	0	0
4	Na ₂ CO ₃	13	0	1
5	K ₂ CO ₃	15	0	11
6	Cs ₂ CO ₃	16	0	8
7	DABCO	5	0	5
8	DBU	24	3	3
9	Ca(OH) ₂	6	0	0
10	Mg(OH) ₂	2	0	1

^a Reactions were prepared according to Procedure 4.1 (except that the indicated base was used instead of K₃PO₄) using **15a** (0.25 mmol), *n*-PrNO₂, 2.5 mol% **16**, no additive, and 3 wt% aq. PS-750-M as the reaction medium; an aliquot for GCMS monitoring was taken at 14 h. ^b Results are given as the percentage of **15a** converted into the indicated products based on GCMS peak areas corresponding to **15a**, **10b**, **18**, and **19**.

Table 4.11: Double additive screening with only 2 equiv K₃PO₄.^a

Entry	Second additive	% conv. 10b and 18 ^b	% conv. 18 ^b	% conv. 19 ^b
1	—	24	0	11
2	glycine betaine	25	0	10
3	CsCl	24	0	10
4	DABCO	20	0	2
5	<i>i</i> -PrOH	20	0	9
6	CF ₃ CH ₂ OH	32	0	1

^a Reactions were prepared according to Procedure 4.1 (except that K₃PO₄ loading was 2 equiv) using **15a** (0.25 mmol), *n*-PrNO₂, 2.5 mol% **16**, Me₄NCl (2 equiv) as the first additive, the specified second additive (2 equiv), and 3 wt% aq. PS-750-M as the reaction medium; an aliquot for GCMS monitoring was taken at 14 h. ^b Results are given as the percentage of **15a** converted into the indicated products based on GCMS peak areas corresponding to **15a**, **10b**, **18**, and **19**.

Table 4.12: Control studies in *i*-PrOH.^a

Entry	Variation	Time (h)	% conv. ^b
1	none	1	100
2	air atmosphere	2	74
3	air atmosphere	4	82
4	no Me ₄ NCl	1	5
5	no Me ₄ NCl	2	19
6	no Me ₄ NCl	4	22
7	no Me ₄ NCl	24	41
8	no Me ₄ NCl	72	45

^a Reactions were prepared according to Procedure 4.2 using **15a** (0.25 mmol), *n*-PrNO₂, 2.5 mol% **16**, Me₄NCl (2 equiv), and *i*-PrOH as the reaction medium; aliquots for GCMS monitoring was taken at the specified times; results for entries 1 and 2 were obtained from the same reaction; results for entries 4–8 were obtained from the same reaction. ^b Results are given as the percentage of **15a** converted into either **10b** or **18** based on GCMS peak areas corresponding to **15a**, **10b**, and **18**.

Table 4.13: Initial benchtop optimization results.^a

Entry	Reaction medium	equiv $n\text{-PrNO}_2$	equiv K_3PO_4	equiv Me_4NCl	mol% 16	M of 15a	°C	Time in h	% conv. ^b
1	3 wt% PS-750-M	5	3	0	2.5	0.5	45	14	23
2	3 wt% PS-750-M	5	5	0	2.5	0.5	45	14	31
3	3 wt% PS-750-M	5	2	2	2.5	0.5	45	14	24
4	3 wt% PS-750-M	5	3	2	2.5	0.5	45	14	53
5	3 wt% PS-750-M	5	4	2	2.5	0.5	45	14	87
6	3 wt% PS-750-M	5	5	2	2.5	0.5	45	14	98
7	3 wt% PS-750-M	5	5	0	2.5	0.5	45	14	31
8	3 wt% PS-750-M	5	5	0.5	2.5	0.5	45	14	50
9	3 wt% PS-750-M	5	5	1	2.5	0.5	45	14	75
10	3 wt% PS-750-M	5	5	2	2.5	0.5	45	14	100
11	3 wt% PS-750-M	1	5	2	2.5	0.5	45	14	20
12	3 wt% PS-750-M	2.5	5	2	2.5	0.5	45	14	84
13	3 wt% PS-750-M	5	5	2	2.5	0.5	45	14	98
14	<i>i</i> -PrOH	5	1	2	2.5	0.5	25	2	31
15	<i>i</i> -PrOH	5	1.5	2	2.5	0.5	25	2	38
16	<i>i</i> -PrOH	5	2	2	2.5	0.5	25	2	56
17	<i>i</i> -PrOH	5	3	2	2.5	0.5	25	2	88
18	<i>i</i> -PrOH	5	4	2	2.5	0.5	25	2	100
19	<i>i</i> -PrOH	5	3	0	0.3	0.5	45	1	5
20	<i>i</i> -PrOH	5	3	1	0.3	0.5	45	1	28

Continued on next page...

Table 4.13 – Continued from previous page.

Entry	Reaction medium	equiv <i>n</i> -PrNO ₂	equiv K ₃ PO ₄	equiv Me ₄ NCl	mol% 16	M of 15a	°C	Time in h	% conv. ^{<i>b</i>}
21	<i>i</i> -PrOH	5	3	1.5	0.3	0.5	45	1	39
22	<i>i</i> -PrOH	5	3	2	0.3	0.5	45	1	41
23	<i>i</i> -PrOH	5	3	2.5	0.3	0.5	45	1	17
24	<i>i</i> -PrOH	5	3	3	0.3	0.5	45	1	14
25	<i>i</i> -PrOH	5	3	4	0.3	0.5	45	1	13
26	<i>i</i> -PrOH	5	3	6	0.3	0.5	45	1	9
27	<i>i</i> -PrOH	5	3	8	0.3	0.5	45	1	8
28	<i>t</i> -BuOH	5	3	1.5	0.3	0.25	45	1	66 ^{<i>d</i>}
29	<i>t</i> -BuOH	5	3	1.5	0.3	0.5	45	1	79 ^{<i>d</i>}
30	<i>t</i> -BuOH	5	3	1.5	0.3	1	45	1	99 ^{<i>d</i>}
31	<i>t</i> -BuOH	5	3	1.5	0.1	1	45	1	32 ^{<i>d</i>}
32	<i>t</i> -BuOH	5	3	1.5	0.1	1.5	45	1	15 ^{<i>d</i>}
33	<i>t</i> -BuOH	5	3	1.5	0.1	5	45	1	34 ^{<i>d,e</i>}

^{*a*} Reactions were prepared according to Procedure 4.3 (expect as specified otherwise) using **15a** (0.25 mmol) and *n*-PrNO₂; an aliquot for GCMS monitoring was taken at the specified time.

^{*b*} Results are given as the percentage of **15a** converted into either **10b** or **18** based on GCMS peak areas corresponding to **15a**, **10b**, and **18**.

^{*c*} Defined as mol aryl halide per L reaction medium.

^{*d*} Catalyst was delivered to the reaction vessel as a 5 μM stock solution in argon-sparged *t*-BuOH prior to the addition of *n*-PrNO₂, as described in Procedure 4.4.

^{*e*} Stirring was poor; the reaction mixture was a thick paste.

Table 4.14: Double additive studies in *t*-BuOH.^a

Entry	equiv Me ₄ NCl	Second additive (loading)	% conv. 10b + 18 ^b	% conv. 18 ^b	% conv. 19 ^b
1	0	–	2	0	0
2	1.5	–	40	0	0
3	1.5	DABCO (20 mol%)	8	0	0
4	1.5	isoxazole 20 (2 mol%)	27	0	0
5	0	<i>n</i> -Bu ₄ NCl (1.5 equiv)	8	0	0
6	0	<i>n</i> -Bu ₄ PCl (1.5 equiv)	1	0	0
7	0	PNPCl (1.5 equiv)	0	0	0
8	0	choline chloride (1.5 equiv)	13	0	0
9	0	3 Å molecular sieves (12.5 mg; activated powder ^c)	2	0	0
10	0	4 Å molecular sieves (12.5 mg; activated powder ^c)	1	0	0
11	0	5 Å molecular sieves (12.5 mg; activated powder ^c)	1	0	0
12	0	13X molecular sieves (12.5 mg; activated powder ^c)	1	0	0

^a Reactions were prepared according to Procedure XXXX using **15a** (0.25 mmol), *n*-PrNO₂, 0.1 mol% **16**, Me₄NCl (at the specified loading) as the first additive, the specified second additive at the specified loading, and *t*-BuOH as the reaction medium; an aliquot for GCMS monitoring was taken at 1 h. ^b Results are given as the percentage of **15a** converted into the indicated products based on GCMS peak areas corresponding to **15a**, **10b**, **18**, and **19**.

^c Molecular sieves were activated in a vacuum oven at > 200 °C for 16 h prior to use.

Table 4.15: Additional Amberlite® IRA-400-Cl double additive studies in *t*-BuOH.^a

Entry	equiv Me ₄ NCl	Second additive (loading)	% conv. 10b + 18 ^b	% conv. 18 ^b	% conv. 19 ^b
1	0	—	2	0	0
2	1.5	—	40	0	0
3	0	Amberlite® IRA-400-Cl (0.375 equiv ^c ; wet ^d)	2	0	0
4	0	Amberlite® IRA-400-Cl (0.75 equiv ^c ; wet ^d)	3	0	0
5	0	Amberlite® IRA-400-Cl (1.5 equiv ^c ; wet ^d)	5	0	0
6	0	Amberlite® IRA-400-Cl (3 equiv ^c ; wet ^d)	12	0	0
7	0	Amberlite® IRA-400-Cl (0.5 equiv ^c ; dry ^e)	3	0	0
8	0	Amberlite® IRA-400-Cl (1 equiv ^c ; dry ^e)	3	0	0
9	0	Amberlite® IRA-400-Cl (1.5 equiv ^c ; dry ^e)	3	0	0
10	0	Amberlite® IRA-400-Cl (3 equiv ^c ; dry ^e)	3	0	0
11	0	Amberlite® IRA-400-Cl (3 equiv ^c ; dry ^e powder ^f)	10	0	0
12	0.5	—	18	0	0
13	0.5	Amberlite® IRA-400-Cl (1.5 equiv ^c ; wet ^d)	7	0	0
14	0.5	Amberlite® IRA-400-Cl (1.5 equiv ^c ; dry ^e)	23	0	0

^a Reactions were prepared according to Procedure XXXX using **15a** (0.25 mmol), *n*-PrNO₂, 0.1 mol% **16**, Me₄NCl (at the specified loading) as the first additive, the specified second additive at the specified loading, and *t*-BuOH as the reaction medium; an aliquot for GCMS monitoring was taken at 1 h. ^b Results are given as the percentage of **15a** converted into the indicated products based on GCMS peak areas corresponding to **15a**, **10b**, **18**, and **19**. ^c Molecular weights of 349.8 g mol⁻¹ (for the wet form) and 243.1 g mol⁻¹ (for the dry form) were used for the ideal constitutional unit of Amberlite® IRA-400-Cl based on calculations described on page XXXXX. ^d “Wet” Amberlite® IRA-400-Cl was used as received and contained 40 wt% to 47 wt% water according to the product specification. ^e “Dry” Amberlite® IRA-400-Cl was obtained by subjecting the material to high vacuum until a constant mass was observed; this process resulted in a 41 % decrease in mass. ^f The powder was obtained by grinding dry Amberlite® IRA-400-Cl with a mortar and pestle.

4.6.3 Sustainability Analysis for Halosequestrative Conditions

Input material prices are listed in Table 4.16. It should be noted that PS-750-M only recently became commercially available, and packages sizes commensurate with the scaling of the other input materials were not listed; consequently, its cost is overrepresented.

The calculated values in Table 4.17 are based on a hypothetical reaction conducted at a 1 mol scale with a global concentration of 0.5 M (relative to the aryl halide). The catalyst loading is based on results obtained at 0.5 mmol and 6 mmol scales. PS-750-M is used as a 3 wt% aqueous solution. The optimal halosequestrative conditions actually use a 1 M global concentration, so the values below represent a conservative estimate of the relative value of the halosequestrative conditions. The estimate is also conservative insofar as the value of the decreased reaction time is not accounted for. With these assumptions, halosequestrative conditions represent an 88 % reduction of input material cost and a 3.7 % increase in input material mass.

Calculations made using various other assumptions are provided in Table 4.18. Neglecting the price of water results in virtually no change from the above values. Note that micellar conditions can also be used with Me_4NCl (Tables 4.1 and 4.2), and aqueous surfactant may provide benefits not reflected in the input material price (such as enabling direct reuse of the medium for a multi-step synthetic sequence). Indeed, when neglecting the price and mass contributions of reaction medium (i.e., assuming perfect recovery), the percent increase in mass for switching to the halosequestrative conditions is 65 %. Conversely, the scenario which most strongly favors halosequestrative conditions (1 M aryl halide concentration, 2 equiv K_3PO_4 , 1 equiv Me_4NCl , 2 equiv water; efficacy assumed based on Table 4.6 entries 1 and 6) corresponds to an 88 % reduction in cost and a 32 % reduction in mass of the input materials.

Table 4.16: Input material costs for halosequestrative and non-halosequestrative conditions.^a

Input material	CAS number	Supplier	Product code	Item size	Price in USD
4-bromoanisole	104-92-7	MilliporeSigma	B56501-500G	500 g	150.00
<i>n</i> -PrNO ₂	108-03-2	MilliporeSigma	N22851-500ML	500 mL	66.80
K ₃ PO ₄ , anhydrous	7778-53-2	MilliporeSigma	RDD019-2.5KG	2.5 kg	158.00
catalyst 16	1798782-25-8	King Scientific ^b	KS-0000O4GB	1 g	810.00
Me ₄ NCI	75-57-0	MilliporeSigma	8221565000	5 kg	282.00
<i>t</i> -BuOH	75-65-0	MilliporeSigma	B85927-20L	20 L	620.00
PS-750-M	2135447-74-2	MilliporeSigma	911151-25G	25 g	755.00
water (reaction medium)	7732-18-5	MilliporeSigma	38796-1L	1 L	25.50

^a Prices are for the largest listed package size as of January 23, 2020. ^b Not available from MilliporeSigma.

Table 4.17: Comparison of halosequestrative and non-halosequestrative process mass intensity and material cost.

Non-halosequestrative Conditions				Halosequestrative Conditions			
Input Material	equiv Loading	Price in USD	kg Mass	Input Material	equiv Loading	Price in USD	kg Mass
4-bromoanisole	1	56.11	0.187	4-bromoanisole	1	56.11	0.187
1-nitropropane	5	59.63	0.445	1-nitropropane	5	59.63	0.445
K ₃ PO ₄ , anhydrous	1.2	16.10	0.255	K ₃ PO ₄ , anhydrous	3	40.24	0.637
catalyst 16	0.025	14,604.50	0.018	catalyst 16	0.003	1,752.54	0.002
PS-750-M	0.05653	1,812.00	0.060	Me ₄ NCI	1.5	9.27	0.164
water	107.7	49.47	1.940	<i>t</i> -BuOH	20.53	60.49	1.522
–	–	–	–	water	3	1.38	0.054
		16,597.81	2.905			1,979.66	3.011

Table 4.18: Comparison of process mass intensity and price between halosequestrative and non-halosequestrative conditions under various circumstances.

Variation in Calculation	Non-haloseq.		Haloseq.		% change	
	Price in USD	kg Mass	Price in USD	kg Mass	Price	Mass
Assuming 0.5 M global concentration for both haloseq. and non-haloseq. conditions (default assumptions).	16,598	2.905	1,980	3.012	-88	3.7
Neglecting price of water.	16,548	2.905	1,978	3.012	-88	3.7
Neglecting contributions of reaction medium (e.g., assuming full recovery of reaction medium).	14,736	0.905	1,919	1.490	-87	65
Using a lower base/sequestrant/water loading for haloseq. conditions of 2 equiv, 1 equiv, and 2 equiv, respectively.	16,598	2.905	1,963	2.739	-88	-5.7
Using a 1 M global concentration for haloseq. conditions.	16,598	2.905	1,949	2.232	-88	-23
Using a 1 M global concentration for haloseq. conditions; using a lower base/sequestrant/water loading for haloseq. conditions of 2 equiv, 1 equiv, and 2 equiv, respectively.	16,598	2.905	1,932	1.959	-88	-32
Neglecting contributions of catalyst.	1,993	2.887	227	3.010	-89	4.2
Neglecting contributions of catalyst; neglecting price of water.	1,944	2.887	226	3.010	-88	4.2
Neglecting contributions of catalyst; neglecting contributions of reaction medium (e.g., assuming full recovery of reaction medium).	132	0.887	167	1.488	26	68
Neglecting contributions of catalyst; using a lower base/sequestrant/water loading for haloseq. conditions of 2 equiv, 1 equiv, and 2 equiv, respectively.	1,993	2.887	211	2.737	-89	-5.2
Neglecting contributions of catalyst; using a 1 M global concentration for haloseq. conditions.	1,993	2.887	196	2.230	-90	-23

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Table 4.18 – *Continued from previous page.*

Variation in Calculation	Non-haloseq.		Haloseq.		% Change	
	Price in USD	kg Mass	Price in USD	kg Mass	Price	Mass
Neglecting contributions of catalyst; using a 1 M global concentration for haloseq. conditions; using a lower base/sequestrant/water loading for haloseq. conditions of 2 equiv, 1 equiv, and 2 equiv, respectively.	1,993	2.887	180	1.957	-91	-32
Only contributions from catalyst.	14,605	0.018	1,753	0.002	-88	-88
Only contributions from coupling partners	116	0.632	116	0.632	0	0
Only contributions from base, sequestrant, and water of hydration.	16	0.255	51	0.855	216	236
Only contributions from base, sequestrant, and water of hydration; using a lower base/sequestrant/water loading for haloseq. conditions of 2 equiv, 1 equiv, and 2 equiv, respectively.	16	0.255	34	0.570	111	124

4.6.4 Compound Characterization

1-Methoxy-4-(1-nitropropyl)benzene (10b)⁶⁴

Colorless oil, 85 mg (87 %), R_f 0.38 (4:1, hexanes/diethyl ether). ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.40 (d, 2H, $J = 9.0$ Hz), 6.91 (d, 2H, $J = 9.0$ Hz), 5.32 (dd, 1H, $J = 8.6$ Hz, 6.6 Hz), 3.81 (s, 3 H), 2.48 (doublet of sextets, 1H, $J = 8.5$ Hz, 7.4 Hz), 2.09 (septet, 1H, $J = 7.4$ Hz), 0.97 (t, 3H, $J = 7.4$ Hz).

1-(1-Nitropropyl)-3,5-bis(trifluoromethyl)benzene (10c)⁶⁴

Pale yellow oil, 1480 mg (82 %), R_f 0.13 (hexanes). ^1H NMR (500 MHz, CDCl_3) δ (ppm) 7.94 (m, 3H), 5.49 (dd, 1H, $J = 9.2$ Hz, 6.6 Hz), 2.59 (doublet of sextets, 1H, $J = 8.8$ Hz, 7.3 Hz), 2.15 (septet, 1H, $J = 7.1$ Hz), 1.05 (t, 3 H, $J = 7.3$ Hz).

3-((4-(1-Nitropropyl)benzyl)oxy)tetrahydrofuran (10d)⁶⁴

Pale yellow oil, 115 mg (88 %), R_f 0.14 (3:2, hexanes/diethyl ether). ^1H NMR (500 MHz, CDCl_3) δ (ppm) 7.44 (d, 2H, $J = 7.7$ Hz), 7.37 (d, 2H, $J = 8.1$ Hz), 5.36 (dd, 1H, $J = 8.5$ Hz, 6.7 Hz), 4.55–4.46 (m, 2H), 4.21 (s, 1H), 3.93 (q, 1H, $J = 8.1$ Hz), 3.90–3.76 (m, 3H), 2.50 (septet, 1H, $J = 7.3$ Hz), 2.10 (septet, 1H, $J = 7.3$ Hz), 2.08–1.96 (m, 2H), 0.98 (t, 3H, $J = 7.3$ Hz).

2-Methoxy-6-(1-nitroethyl)pyridine (10e)

Pale yellow oil, 81 mg (89 %), R_f 0.36 (4:1, hexanes/diethyl ether). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 7.60 (t, 1H, $J = 7.7$ Hz), 6.97 (d, 1H, $J = 7.3$ Hz), 6.74 (d, 1H, $J = 8.4$ Hz), 5.63 (q, 1H, $J = 7.0$ Hz), 3.91 (s, 3H), 1.91 (d, 3H, $J = 7.0$ Hz). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 164.0, 151.8, 139.5, 115.0, 111.9, 86.7, 53.6, 18.1. **HRMS** (APCI) $[\text{C}_8\text{H}_{10}\text{N}_2\text{O}_3 + \text{H}]^+$ calculated 183.0764, found (m/z) 183.0763.

6-Methoxy-5-(1-nitropropyl)-2,3-dihydro-1H-inden-1-one (10f)

Pale yellow oil, m.p. = 88 °C to 90 °C, 115 mg (92 %), R_f 0.26 (3:2, hexanes/diethyl ether). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 7.50 (s, 2H), 7.18 (s, 2H), 5.87 (dd, 1H, $J = 8.6$ Hz, 6.6 Hz), 3.85 (s, 3H), 3.06 (t, 2H, $J = 5.6$ Hz), 2.67 (t, 2H, $J = 5.7$ Hz), 2.43 (septet, 1H, $J = 7.5$ Hz), 2.08 (septet, 1H, $J = 7.1$ Hz), 0.98 (t, 3H, $J = 7.4$ Hz). **^{13}C NMR** (100 MHz, CDCl_3) δ (ppm) 206.5, 156.7, 147.5, 138.7, 130.5, 125.6, 104.3, 85.8, 56.1, 36.8, 26.8, 25.2, 10.8. **HRMS** (ESI) $[\text{C}_{13}\text{H}_{15}\text{NO}_4 + \text{H}]^+$ calculated 250.1074, found (m/z) 250.1072.

1-Butyl-4-(1-nitropropyl)benzene (10g)

Pale beige oil, 102 mg (92 %), R_f 0.27 (39:1, hexanes/diethyl ether). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 7.37 (d, 2H, $J = 8.2$ Hz), 7.20 (d, 2H, $J = 8.2$ Hz), 5.34

(dd, 1H, $J = 8.6$ Hz, 6.2 Hz), 2.61 (t, 2H, $J = 7.8$ Hz), 2.50 (doublet of sextets, 1H, $J = 9.0$ Hz, 7.4 Hz), 2.10 (septet, 1H, $J = 7.0$ Hz), 1.59 (dddd, 2H, $J = 6.1$ Hz, 7.5 Hz, 8.2 Hz, 8.9 Hz), 1.35 (sextet, 2H, $J = 7.4$ Hz), 0.98 (t, 3H, $J = 7.4$ Hz), 0.92 (t, 3H, $J = 7.4$ Hz). **^{13}C NMR** (100 MHz, CDCl_3) δ (ppm) 145.0 , 131.9 , 129.1 , 127.8 , 93.1 , 35.5 , 33.6 , 27.4 , 22.5 , 14.1 , 10.8 . **HRMS** (ESI) $[\text{C}_{13}\text{H}_{19}\text{NO}_2 + \text{Na}]^+$ calculated 244.1308 , found (m/z) 244.1308 .

1-Methoxy-3-(1-nitropropyl)benzene (10a)⁸⁸

Colorless oil, 88 mg (90 %), R_f 0.35 (9:1, hexanes/diethyl ether). **^1H NMR** (700 MHz, CDCl_3) δ (ppm) 7.31 (t, 1H, $J = 8.0$ Hz), 7.04 (d, 1H, $J = 7.8$ Hz), 7.00 (t, 1H, $J = 2.0$ Hz), 6.93 (ddd, 1H, $J = 8.2$ Hz, 2.4 Hz, 0.7 Hz), 5.33 (dd, 1H, $J = 8.9$ Hz, 6.5 Hz), 3.82 (s, 3H), 2.49 (doublet of sextets, 1H, $J = 8.9$ Hz, 7.2 Hz), 2.11 (septet, 1H, $J = 7.2$ Hz), 0.98 (t, 3H, $J = 7.3$ Hz).

(1-Nitropropyl)benzene (10h)¹⁸²

Colorless oil, 54 mg (66 %), R_f 0.23 (39:1, hexanes/diethyl ether). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 7.50 – 7.36 (m, 5H), 5.37 (dd, 1H, $J = 9.0$ Hz, 6.6 Hz), 2.52 (doublet of sextets, 1H, $J = 8.6$ Hz, 7.0 Hz), 2.12 (septet, 1H, $J = 7.1$ Hz), 0.99 (t, 3H, $J = 7.4$ Hz).

4-(4-(1-Nitropropyl)phenyl)morpholine (10i)

Yellow solid, m.p. = 91 °C to 92 °C, 51 mg (41 %), R_f 0.22 (3:2, hexanes/diethyl ether). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 7.36 (d, 2H, $J = 8.6$ Hz), 6.89 (d, 2H, $J = 8.6$ Hz), 5.30 (dd, 1H, $J = 8.6$ Hz, 6.9 Hz), 3.84 (t, 4H, $J = 4.9$ Hz), 3.18 (t, 4H, $J = 4.7$ Hz), 2.47 (septet, 1H, $J = 7.4$ Hz), 2.08 (septet, 1H, $J = 7.0$ Hz), 0.96 (t, 3H, $J = 7.2$ Hz). **^{13}C NMR** (100 MHz, CDCl_3) δ (ppm) 152.2, 128.9, 125.3, 115.3, 92.8, 66.8, 48.6, 27.1, 10.8. **HRMS** (ESI) $[\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_3 + \text{H}]^+$ calculated 251.1389, found (m/z) 251.1389.

1-(1-Nitroethyl)-4-vinylbenzene (10j)

Light brown oil, 43 mg (48 %), R_f 0.32 (9:1, hexanes/ethyl acetate). **^1H NMR** (700 MHz, CDCl_3) δ (ppm) 7.45–7.41 (m, 4H), 6.71 (dd, 1H, $J = 17.7$ Hz, 10.9 Hz), 5.79 (dd, 1H, $J = 17.4$ Hz, 0.7 Hz), 5.60 (q, 1H, $J = 7.2$ Hz), 5.31 (d, 1H, $J = 10.9$ Hz), 1.90 (d, 3H, $J = 7.2$ Hz). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 139.2, 136.0, 134.9, 127.8, 126.9, 115.5, 86.0, 19.5. **HRMS** (EI) $[\text{C}_{10}\text{H}_{11}\text{NO}_2]^+$ calculated 177.0785, found (m/z) 177.0784.

4.6.5 NMR Spectra

1-Methoxy-4-(1-nitropropyl)benzene (10b) ^1H NMR

1-(1-Nitropropyl)-3,5-bis(trifluoromethyl)benzene (10c) ^1H NMR

3-((4-(1-Nitropropyl)benzyl)oxy)tetrahydrofuran (10d) ^1H NMR

2-Methoxy-6-(1-nitroethyl)pyridine (10e) ^1H NMR

2-Methoxy-6-(1-nitroethyl)pyridine (10e) ^{13}C NMR

6-Methoxy-5-(1-nitropropyl)-2,3-dihydro-1H-inden-1-one (10f) ^1H NMR

6-Methoxy-5-(1-nitropropyl)-2,3-dihydro-1H-inden-1-one (10f) ^{13}C NMR

1-Butyl-4-(1-nitropropyl)benzene (10g) ^1H NMR

1-Butyl-4-(1-nitropropyl)benzene (10g) ^{13}C NMR

1-Methoxy-3-(1-nitropropyl)benzene (10a) ^1H NMR

(1-Nitropropyl)benzene (10h) ^1H NMR

4-(4-(1-Nitropropyl)phenyl)morpholine (10i) ^1H NMR

4-(4-(1-Nitropropyl)phenyl)morpholine (10i) ^{13}C NMR

1-(1-Nitroethyl)-4-vinylbenzene (10j) ^1H NMR

1-(1-Nitroethyl)-4-vinylbenzene (10j) ^{13}C NMR

CHAPTER 5

ORGANOPOLYMER WITH DUAL CHROMOPHORES AND FAST CHARGE-TRANSFER PROPERTIES FOR SUSTAINABLE PHOTOCATALYSIS

Photocatalytic polymers offer an alternative to prevailing organometallics and nanomaterials, and they may benefit from polymer-mediated catalytic and material enhancements. A double-strand polymer photoredox catalyst designated as **MPC-1** was developed and was found to be more than five times as effective in a benchmarking reaction than the next best organophotoredox catalyst screened. The outstanding efficacy of the catalyst was attributed to the fixed proximity of two different chromophores in the polymer chain, and this conclusion was supported by the synthesis and evaluation of molecules which modeled **MPC-1** substructures. Oligomeric and polymeric **MPC-1** preparations both promoted efficient hydrodehalogenation of α -halocarbonyl compounds while exhibiting different solubility properties. The polymer was readily recovered by filtration, and **MPC-1**-coated vessels were found to enable batch and flow photocatalysis, even with opaque reaction mixtures, via “backside irradiation.”

5.1 Background

In spite of their comparative unsustainability, heterogeneous photocatalysts containing transition metal-based organometallic complexes and nanomaterials are well-

Figure 5.1: Overview of macromolecular photocatalyst **MPC-1** application to α -halocarbonyl compound hydrodehalogenation as model reaction used to demonstrate the efficacy and advantages of the catalyst.

precedented,¹⁸³ yet reports on heterogeneous organophotocatalysts are comparatively sparse.¹⁸⁴ Recently documented implementations include immobilization of dyes on various resins, silica, and polymer supports,^{185–189} dye entrapment in polyethylene pellets,¹⁸⁵ soft gel dye entrapment,¹⁹⁰ immobilization of dyes onto metal-oxide films,¹⁹¹ and incorporation into polymers as unconjugated pendant groups.¹⁹² Although π -conjugated polymers are well-recognized with the 2000 Nobel Prize in Chemistry,¹⁹³ their direct application as macromolecular photocatalysts (MPCs) for organic synthesis is still nascent (Figure 5.2).^{194–196} Carbon nitride systems have received substantial attention as inherently photocatalytic organopolymers, but their two-dimensional networks suffer from a lack of solution processability.¹⁹⁷

The archetypal polymer of intrinsic microporosity, **PIM-1**, was first reported in 2004 by Budd and coworkers as a fluorescent yellow double-strand polymer prepared from a reaction of tetrafluoroterephthalonitrile (**24**) and a tetrahydroxyspirobiindane (**25**) (Figure 5.3),¹⁹⁸ yet to the best of our knowledge, its photoredox catalytic properties had not previously been reported. The precedent for the terephthalonitrile

Figure 5.2: Structures of prior-precedent polymeric photoredox catalysts. These catalysts are notably not solution processable.

motif of **PIM-1** in organophotoredox catalysis^{184,199,200} suggests that **PIM-1** and its analogues could be competent MPCs. Beyond the typical advantages of heterogenization (i.e., improved catalyst recyclability and product purity), organopolymer MPCs offer the possibility of leveraging a tunable macromolecular structure to enhance catalytic properties. A variety of reports have appeared documenting the modular tunability of **PIM-1** properties through nitrile derivatization or co-incorporation of different monomers, especially for the purpose of changing the gas permeability of the resultant analogue.^{201,202} **MPC-1**, the **PIM-1** analogue developed for this study, proximally incorporates two distinct chromophores which are separated by a flexible, conjugation-breaking spirocyclic comonomer (Figure 5.3). This structural arrangement of chromophores might be expected to provide catalytic enhancements in a manner analogous to organometallic systems (i.e., long-lived charge transfer could exist between two proximal polymer chromophores akin to triplet metal-to-ligand charge transfer states in molecular organometallic photoredox catalysts).²⁰³

Aside from potential enhancement of excited state lifetime and catalyst–substrate redox processes, material properties arising from the macromolecular structure provide additional means by which to adjust the overall catalytic process. In particular, catalyst solubility is tunable by monomer choice, feed ratio, and extent of polymerization.

Figure 5.3: Structure of macromolecular photoredox catalyst **MPC-1**. **a** Constituent monomers and representative structure of **MPC-1**. The polymer is prepared by nucleophilic aromatic substitution, and chromophore subunits are randomly distributed. **MPC-1** is an analogue of **PIM-1**, which lacks sulfone monomer **26**. **b** Poly(*p*-phenylene) (**PPP**) as an example of conventional conjugated organopolymer MPCs. **c** The spirocyclic moiety arising from **25** results in isolated but proximal chromophore systems which are not conjugatively linked.

With appropriate solubility properties, organopolymer MPCs have the potential to be readily solution-processed into macroscopic structures such as thin-films, and it may be possible for the charge transfer process to enable photoactivation when irradiating the film on the face not in contact with the reaction mixture (i.e., the face in contact with the wall of the vessel) (Figure 5.4). Such a “backside irradiation” process could enable efficient photoactivation of systems suffering from poor light transmittance such as large-scale batch reactions and opaque reaction mixtures.

Hydrodehalogenation is a mechanistically straightforward model reaction suitable for demonstration of photoredox catalyst efficacy and is also of general interest to the chemistry community. Thousands of halogenated natural products have been discovered in organisms ranging from bacteria to humans,²⁰⁴ including chloramphenicol, one of the first three broad-spectrum antibiotics.^{205,206} Conversely, halogens also feature

Figure 5.4: Processability of **MPC-1** and its application to backside irradiation. **(a)** Preparations of **MPC-1** have been cast into thin-film thimbles and applied as a coating to flow cells and batch reaction vessels. **(b)** Comparison of conventional frontside irradiation and the backside irradiation approach enabled by **MPC-1**.

in many persistent organic contaminants which are not readily degraded by microbial systems.²⁰⁷ Control of halogenation allows for modulation of the biological activity of chemical scaffolds, whether drug compounds or environmental contaminants,^{208–210} and appreciation of the role of halogen binding in drug-target binding affinity increasingly influences drug discovery, development, and lead optimization.^{211–214} Hydrodehalogenations have also long been utilized in synthetic strategy to remove halides that have served their purpose, e.g., for alkene protection,²¹⁵ iodocyclization,²¹⁶ or as a blocking group,²¹⁷ and similar opportunities for the beneficial application of this approach continue to appear. Traditional hydrodehalogenation methods, however, suffer from a number of problems with respect to toxicity, selectivity, recyclability, functional group tolerance, product purification, and operational simplicity. However, with recent advances in the scope of the three prevailing alternatives—ground-state organometallic catalysis,²¹⁸ metallophotoredox catalysis,²¹⁹ and organophotoredox catalysis²²⁰—the older methods should now be deprecated. Of these modern approaches, organophotoredox catalysis exhibits the best sustainability profile and is therefore an appropriate

basis for a sustainability-oriented MPC system.

5.2 Development of MPC-1-catalyzed Dehalogenation of α -Halocarbonyl Compounds

5.2.1 Preliminary Investigation and Optimization of Conditions

The methodology developed in our earlier report on the synthesis of polyfluoro(hetero)aryl sulfones via micellar catalysis (see Chapter 2) provided access to a wide variety of possible monomers for inclusion with **24** and **25** in the preparation of a **PIM-1** analogue.⁶⁵ Sulfone **26** was selected with the intention of imbuing the resultant MPC system (designated as **MPC-1**) with suitable photophysical and solubility properties. In particular, we suspected that incorporation of **24** as a second chromophore subunit in the polymer would support the formation of long-lived charge transfer states during photoexcitation (ultrafast spectroscopic and computational studies investigating this hypothesis were undertaken by our physical chemistry collaborators Dr. Jinjun Liu, Abed Jamhawi, and Anam C. Paul and our detailed in our coauthored publication²²¹). An initial preparation of the **MPC-1** system (designated as **MPC-1-0**) was expeditiously synthesized in a one-pot adaptation of a previously reported polymerization procedure⁸² starting from the precursors of **26**; the targeted ratio of monomeric units of **24**, **25**, and **26** was 2:3:1. **MPC-1-0** was encouragingly obtained as a bright yellow solid with a strong absorbance near 435 nm, suggesting the possibility of visible-light catalysis with blue LED irradiation (see Supplementary Information Section 5.7, Figure 5.21). Although adequate for preliminary investigation, this preparation exhibited incomplete solubility in chloroform and under-incorporation of the sulfone monomeric

unit; these deficiencies were attributed to incomplete sulfonylation and concomitant branching/cross-linking defects (see Section 5.7.2 for details). For initial reactivity screening, *N*-methyl-2-pyrrolidone (NMP) was selected as the reaction solvent given its aptitude for solubilization of structurally similar polymers.²²² NMP fully dissolved the polymer, and α -keto bromide **22a** underwent hydrodehalogenation in the presence of *i*-Pr₂NEt sacrificial reductant, 1 mol% **MPC-1-0** (based on the molecular weight of the constitutional unit of an ideal regular polymer), and blue LED irradiation (Table 5.1, entry 1). Control experiments confirmed that the **MPC-1** system catalyzed the transformation and that sacrificial reductant, blue LED irradiation, and oxygen-free atmosphere are all essential to catalysis (see Supplementary Information Section 5.7, Table 5.8). Screening catalyst loading confirmed that 1 mol% **MPC-1-0** was suitable for preliminary optimization (see Supplementary Information Section 5.7, Table 5.9). Solvent screening revealed a clear correlation between reaction efficiency and solvent polarity index.²²³ (Table 5.1, entries 1–6), suggesting the reaction pathway involves excited state charge separation, which is more effectively stabilized by more polar solvents.²²⁴ NMP was the only solvent capable of fully dissolving the polymer, but the ability of the solvent to dissolve **MPC-1-0** (which was used as a finely ground powder) was of limited importance, indicating that the catalyst worked well in both homogenous and heterogeneous states. Indeed, although NMP was the most effective solvent, dimethyl sulfoxide (DMSO) was nearly as competent and is a far greener choice.⁷⁸ Water is arguably the greenest solvent, has the highest polarity index, and appeared competent with 41 % conversion after 1 h, but the poor solubility of **22a** in water led to clumping of the substrate into a solid mass on the spin vane, preventing the reaction from going to completion. An aqueous solution of anionic surfactant sodium dodecyl sulfate (SDS, entry 8) likewise permitted partial reaction progress, but the reaction mixture eventually developed clumping and opacity that prevented reaction completion. Isolated yields of reactions run with *i*-Pr₂NEt were consistently

poor (ca. 40 %) due to side reactions, but switching the reductant to Hantzsch ester (**HE**) dramatically increased reaction rate and yield (entry 9). Following optimization of **HE** loading, acetone was deemed sufficiently competent and was selected as a green and easily distillable reaction medium.⁷⁸ With the final optimized conditions, dehalogenated product **23a** was successfully obtained in 92 % isolated yield after 3 h in acetone with 1.5 equiv **HE** and 1 mol% **MPC-1-0** (entry 10). Full optimization results are provided in Supplementary Information Section 5.7 Tables 5.9–5.16.

Table 5.1: Selected optimization of **MPC-1**-catalyzed hydrodehalogenation reaction conditions.^a

Entry	Reductant	Solvent	% Yield. ^b
1	<i>i</i> -Pr ₂ NEt	NMP	47 ^c
2	<i>i</i> -Pr ₂ NEt	2-MeTHF	5
3	<i>i</i> -Pr ₂ NEt	chloroform	14
4	<i>i</i> -Pr ₂ NEt	acetone	15
5	<i>i</i> -Pr ₂ NEt	acetonitrile	23
6	<i>i</i> -Pr ₂ NEt	DMSO	45
7	<i>i</i> -Pr ₂ NEt	water	41 ^d
8	<i>i</i> -Pr ₂ NEt	3 wt% aq. SDS	32 ^d
9	HE	NMP	100 ^e
10	1.5 equiv HE	acetone	92 ^f

^a Conditions: **22a** (0.25 mmol, 1 equiv), **MPC-1-0** (1 mol% approximating the molecular weight as 1529 g mol⁻¹ for the ideal constitutional unit), reductant (1 equiv), solvent (0.5 mL, argon-sparged), argon atmosphere, 10x75 mm borosilicate test tube (spin-vane-equipped, septum/PTFE-tape-sealed), blue LED irradiation, 37 °C, 1 h, according to General Procedure 5A, unless otherwise noted. ^b Determined by ¹H NMR. ^c Average of two runs (44 % and 49 %). ^d Purely aqueous and surfactant-based reaction media suffered from solution turbidity and/or clumping of solids which prevented reactions from going to completion and led to aliquots being unrepresentative of progress in the overall mixture. ^e 81 % at 5 min. ^f Isolated yield after 3 h.

5.2.2 Reaction Scope and Scalability with Oligomeric MPC-1-1

A new procedure was developed to produce oligomeric **MPC-1**, designated as **MPC-1-1**, while avoiding the defects associated with the one-pot procedure used for **MPC-1-0**. Polymerization was conducted in 3 wt% aqueous PS-750-M surfactant using separately synthesized sulfone **26**; the feed ratio of monomers **24**, **25**, and **26** was 2:3:1. PS-750-M was designed to mimic toxic polar aprotic solvents such as DMF (see Chapter 2),⁶⁴ which had been employed in the synthesis of **MPC-1-0**. Typically, **PIM-1** analogues are synthesized under anhydrous conditions.⁸² By intentionally using an aqueous system, it was possible to severely restrict polymer chain length through the facile termination of chain growth by hydroxide replacement of fluorine; the micelles assisted in protecting the aromatic fluorides until polymer size was sufficiently large to precipitate out of the solution. **MPC-1-1** successfully obtained as an opaque yellow solid that was readily soluble in acetone. NMR and gel permeation chromatography (GPC) measurements suggested that the average chain length of **MPC-1-1** was sufficiently long to incorporate 4–7 chromophore subunits (i.e., monomer units of **24** or **26**); although successful in producing oligomeric chains, this method was still susceptible to branching defects and appeared to under-incorporate the terephthalonitrile monomeric unit (see Section 5.7.2). Using **MPC-1-1** under the optimized reaction conditions afforded **23a** in 86 % isolated yield after 3 h, indicating that activity of the oligomeric preparation was slightly inferior to **MPC-1-0**.

It was initially suspected that the catalytic activity of **MPC-1** preparations would improve with higher degrees of polymerization; because **MPC-1-1** represents a non-arbitrary lower limit in this regard, it was used to establish well-defined baseline substrate scope results. A wide-range of α -halocarbonyl compounds were amenable to hydrodehalogenation under the established conditions. As suggested by the chemos-

Table 5.2: α -Halocarbonyl compound hydrodehalogenation scope with **MPC-1-1**^{a,b}

^a Conditions (unless otherwise noted): halide **22** (0.25 mmol, 1 equiv), **MPC-1-1** (1 mol%, approximated as 1529 g mol⁻¹), **HE** (1.5 equiv), acetone (0.5 mL, argon-sparged), argon atmosphere, 10x75-mm borosilicate test tube (spin-vane-equipped, septum/PTFE-tape-sealed), blue LED irradiation, 37 °C, according to General Procedure 5B. ^b Reported yields are isolated. ^c Substrate failed to approach full conversion after 96 h with General Procedure 5B; result was obtained with General Procedure 5C, which used 1.0 mL acetone, 2 mol% **MPC-1-1** and supplemental addition of 1 equiv **HE** at 72 h. ^d **MPC-1-0** was used as the catalyst. ^e 3.0 equiv of **HE** was used, and both bromides were reduced.

electivity in the reaction used for optimization, aryl halides (which exhibit a larger reduction potential) were unaffected by the reaction conditions (Table 5.2, **22a–h**). Aside from ketones (**22a–n**), alkyl aryl ethers (**22e**), aryl nitro groups (**22l**), amides (**22o**), and esters (**22p**) were also well tolerated. α -Keto chlorides, bromides, and iodides were reduced with rates that increased with decreasing magnitude of substrate reduction potential (**22b–d**). With a sufficient quantity of reductant, geminal bromides were both reduced (**22m**); when only 1 equiv reductant was used, a roughly equal mixture of acetophenone and 2-bromoacetophenone products was observed. Greater steric bulk around the halide did not prevent reduction, but rate was affected in accordance with the effect of the geminal alkyl substituents on the stabilization of a radical intermediate (**22h–j**). In addition to α -aryl keto carbonyl systems (**22a–m**), reduction was successful with strained aliphatic (**22n**) and heteroaromatic (**22q**) ketones, as well as for α -amide (**22o**) and α -ester (**22p**) systems. The reactions were generally clean, affording only oxidized **HE** and the desired product.

Figure 5.5: Hydrodehalogenation with **MPC-1-1** at gram scale. Conditions: **22b** (5.0 mmol), **MPC-1-1** (0.2 mol%), **HE** (10.0 mmol), acetone (10.0 mL, argon-sparged), argon atmosphere, 25 mL round-bottom flask (stir-bar-equipped, septum/PTFE-tape-sealed), blue LED irradiation, 37 °C, 24 h.

Scalability and catalyst recovery were demonstrated with the gram-scale hydrodehalogenation of **22b** (Figure 5.5). With a lowered catalyst loading, i.e., 0.2 mol%, product **23b** was afforded in 99 % isolated yield after 24 h. In addition to the lower catalyst loading, the longer reaction time is partly attributable to the change in reaction vessel and the resultant decrease in flux of irradiation. The reaction was

worked up by removing acetone under reduced pressure and extracting the product with 1:14 ethyl acetate/hexanes, a solvent system in which **MPC-1-1** was insoluble. To liberate product entrapped in the polymeric phase, ethyl acetate was admixed first before precipitating the polymer back out with the addition of hexanes. A preliminary recycle study using this extraction technique confirmed that the catalyst remained active in subsequent cycles, but buildup of residual Hantzsch pyridine caused the reaction rate to decrease (see Section 5.7.1.5). This limitation to recyclability was overcome with the development of a longer-chain **MPC-1** preparation, **MPC-1-2**, which was fully recyclable and retained its catalytic efficiency over multiple recycles (vide infra).

5.3 Synthesis and Evaluation of Polymeric MPC-1-2

Rigorous polymerization conditions were devised to yield long chains with limited cross-linking defects. Monomer **24** was purified by sublimation, monomer **25** was recrystallized from methanol/water, monomer **26** was purified by column chromatography, and potassium carbonate was dried in a vacuum oven at 200 °C overnight prior to use. The polymerization was conducted in a thick-walled Schlenk tube under argon atmosphere at 90 °C in dry *N,N*-dimethylacetamide (DMAc). Activated 3 Å molecular sieves were included in the reaction mixture to scavenge moisture. Upon reaction completion, the reaction mixture was extracted with chloroform and the product was precipitated out with the addition of methanol. Resultant polymer preparation **MPC-1-2** was thus obtained as a translucent yellow solid. To assess the significance of different polymer chain lengths within **MPC-1-2**, which had a moderate polydispersity index, a portion of the material was further processed by thrice reprecipitating from chloroform with methanol such that the polymer mass

in the precipitate was approximately equal to the polymer mass in the combined supernatant layers; the higher molecular weight fractionation from the precipitate is designated as **MPC-1-2_{HMW}**, and the lower molecular weight fractionation from the supernatant layers is designated as **MPC-1-2_{LMW}**.

Figure 5.6: ^1H NMR peak assignments for **MPC-1-2**. Integrations are in strong agreement with monomer feed ratio.

MPC-1-2 ^1H NMR integrations were in good agreement with the 2:3:1 feed ratio of **24**, **25**, and **26** (Figure 5.6): the alkyl methyl signals from **25** (labeled as **i**) integrated to 36; the methylene signals of **25** (**ii**) and the overlapping aryl methyl signals of **26** (**iii** and **iv**) integrated to 18; the *N*-methyl signals of **26** (**v**) integrated to 3; and the aromatic signals of **25** (labeled as **vi** and **vii**) integrated to 12. Sulfone **26** was moderately over-incorporated in fractionation **MPC-1-2_{LMW}** (3:1.14 ratio of **25** and **26**) and under-incorporated in **MPC-1-2_{HMW}** (3:0.88 ratio of **25** and **26**). This variation for the fractionations suggests that either (1) the fractionation method is partly affected by the solubility of randomly incorporated constituent monomers or (2) shorter chains tend to incorporate greater amounts of **26** (see Section 5.7.2). Acetone admixed with **MPC-1-2_{LMW}** developed coloration but did not completely dissolve the solid, whereas acetone admixed with **MPC-1-2_{HMW}** remained colorless, suggesting that an acetone-soluble component in **MPC-1-2** had been at least mostly

confined to the **MPC-1-2_{LMW}** fractionation.

GPC results were obtained using an Omnisec GPC from Malvern, which was equipped with four on-line detectors: a dual-angle light scattering detector, a UV detector, an RI detector, and a viscosity detector (Table 5.3). In the chromatogram (Figure 5.7), the refractive index peak of **MPC-1-2** is situated between **MPC-1-2_{LMW}** and **MPC-1-2_{HMW}** while its distribution covered the range of both components, which was consistent with the tabulated results. Minor peaks indicating the existence of oligomers were observed at retention volume > 19 mL for **MPC-1-2** and its fractionations. All four samples were fully soluble in the tetrahydrofuran eluent, and Mark–Houwink plots were also constructed to assess their structures (Figure 5.8). The curves of **MPC-1-2** and its fractionations overlapped with each other at a wide range, which implied a similar Mark–Houwink exponent (M–H a) and the same branching degree with the different polymer compositions.

FTIR measurements showed that all monomers were incorporated into the derivative polymers, and **MPC-1-2** lacked the hydroxyl stretches present in **MPC-1-1** (see Supplementary Information Section 5.7, Figure 5.22). Both **MPC-1-1** and **MPC-1-2** exhibited high thermal stability when subjected to thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC), which showed very little change up to 200 °C, followed by a gradual loss of mass until 450 °C (see Supplementary Information Section 5.7, Figure 5.23). A sheet of **MPC-1-2** was subjected to scanning electron microscopy (SEM); the sheet was observed to be regular and smooth (Figure 5.9). High-resolution transmission electron microscopy (HRTEM) imaging of **MPC-1-1** and **MPC-1-2** showed that **MPC-1-2** had a more regular macrostructure consisting of large layers of stacked sheets while **MPC-1-1** had smaller planes of sheets with smaller and rounder edges (Figure 5.10). At high magnification, both samples were seen to exhibit a similar porous structure.

Table 5.3: GPC results for various MPC-1 preparations.^a

Polymer	mL RV ^d	with PS Standard ^b				with PMMA Standard ^c							
		M _n	M _w	M _z	Đ ^e	M-H	α ^f	M _n	M _w	M _z	Đ ^e	M-H	α ^f
MPC-1-1	18.95	4,047	4,777	5,896	1.18	0.892		2,540	2,925	3,471	1.15	0.837	
MPC-1-2 _{LMW}	16.10	37,790	63,360	102,300	1.68	0.528		24,450	38,870	58,450	1.59	0.534	
MPC-1-2	15.48	52,990	91,030	156,300	1.72	0.575		34,150	55,870	88,930	1.64	0.572	
MPC-1-2 _{HMW}	14.84	119,600	157,400	220,300	1.32	0.530		77,860	96,610	124,900	1.24	0.510	

^a MPC-1 samples were dissolved in the tetrahydrofuran eluent and analyzed with a Malvern Omnisec GPC instrument. MPC-1-0 was not completely soluble in the eluent and was thus not analyzed. Molecular weight values are provided in Da. ^b PS: Polystyrene. ^c PMMA: Poly(methyl methacrylate). ^d RV: Retention volume. ^e Đ: Polymer dispersity. ^f M-H α : Mark-Houwink α parameter.

Figure 5.7: GPC normalized UV chromatograms.

Figure 5.8: Mark-Houwink α plots of MPC-1 preparations.

Figure 5.9: Scanning electron microscopy image of a sheet of MPC-1-2.

Figure 5.10: High-resolution transmission electron microscopy images of MPC-1-1 and MPC-1-2.

Having made and characterized a variety of **MPC-1** preparations, we sought to assess their catalytic activities and generalize the results by benchmarking against well-known organophotoredox catalysts. Higher isolated yields for hydrodehalogenation of bromide **22a** and chloride **22b** were obtained in less time with **MPC-1-2** compared to **MPC-1-1** (Table 5.4). Unsurprisingly, **MPC-1-2** exhibited improved catalytic activity in acetone when used as a fine powder instead of larger pieces, which would be expected to remain undissolved and thereby exclude interior active units from participating in catalysis. Accordingly, to better exclude influence of active unit entrapment in the interior of undissolved solid, the catalytic activities of **MPC-1-2** and its fractionations were compared with the hydrodehalogenation of **22b** in chloroform, a reaction medium in which all were fully soluble; observed activities were nearly the same (Table 5.5). **MPC-1-2** was benchmarked against six common organophotoredox catalysts¹⁸⁴ using the same model reaction in acetone (Table 5.6). **MPC-1-2** proved to be the best by far, catalyzing more than five times as much product formation as its nearest competitor in the timeframe of the experiment. Leveraging the improved catalytic activity of **MPC-1-2**, difficult substrate **22o** was hydrodehalogenated with significant improvements to reaction rate and yield, and a vicinal dibromide was efficiently converted into the corresponding alkene (Figure 5.11).

Table 5.4: Head-to-head comparison of **MPC-1-1** and **MPC-1-2** efficacy.^a

	Catalyst	Substrate	Time in h	% Yield ^b
	MPC-1-1	22a	3	86
	MPC-1-2	22a	1	94
	MPC-1-1	22b	6	96
	MPC-1-2	22b	3	99

^a Conditions: **22** (0.25 mmol, 1 equiv), **MPC-1** (1 mol% approximating the molecular weight as 1529 g mol⁻¹ for the ideal constitutional unit), **HE** (1.5 equiv), acetone (0.5 mL, argon-sparged), argon atmosphere, 10x75 mm borosilicate test tube (spin-vane-equipped, septum/PTFE-tape-sealed), blue LED irradiation, 37 °C, according to General Procedure ?? except that **MPC-1-2** was used where indicated. ^b Isolated yields.

Table 5.5: Comparison **MPC-1-2** fractionations in chloroform.^a

	Catalyst	% Yield
	MPC-1-2_{LMW}	71
	MPC-1-2	70
	MPC-1-2_{LMW}	67

^a Conditions: **22b** (0.25 mmol, 1 equiv), **MPC-1** (1 mol% approximating the molecular weight as 1529 g mol⁻¹ for the ideal constitutional unit), **HE** (1.5 equiv), chloroform (0.5 mL, argon-sparged), argon atmosphere, 10x75 mm borosilicate test tube (spin-vane-equipped, septum/PTFE-tape-sealed), blue LED irradiation, 37 °C, 2 h, according to 5.15 except that chloroform was used as the solvent. ^b Determined by ¹H NMR.

Table 5.6: Benchmarking **MPC-1-2** against small-molecule organophotoredox catalysts.^a

Catalyst ^b	% Yield ^c
MPC-1-2	70
PTH ^d	13
PDI ^e	9
Rhodamine B	8
Fluorescein	6
Eosin Y, 2 Na ⁺	5
Fluorenone	1

fluorescein

rhodamine B

eosin Y, 2Na⁺

PDI

fluorenone

PTH

Small-molecule organophotoredox catalysts

^a Conditions: **22b** (0.25 mmol, 1 equiv), catalyst (1 mol% for **MPC-1-2** or 3 mol% for small-molecule catalysts), **HE** (1.5 equiv), acetone (0.5 mL, argon-sparged), argon atmosphere, 10x75 mm borosilicate test tube (spin-vane-equipped, septum/PTFE-tape-sealed), blue LED irradiation, 37 °C, 2 h, according to 5.15. ^b Because the ideal constitutional unit of **MPC-1** used in the calculation of mol% polymer catalyst loading contains three chromophores, **MPC-1-2** was used at a catalyst loading of 1 mol% while the small-molecule catalysts were used at a loading of 3 mol%. ^c Determined by ¹H NMR. ^d PTH: 10-phenylphenothiazine. ^e PDI: *N,N*-bis(2,6-diisopropylphenyl)perylene-3,4,9,10-bis(dicarboximide).

Figure 5.11: Enhanced conditions **MPC-1-2** for efficient hydrodehalogenation of a less reactive substrate and deprotection of a brominated ene-aldehyde. Conditions: **22** (0.25 mmol, 1 equiv), **MPC-1-2_{LMW}** (1 mol% approximating the molecular weight as 1529 g mol⁻¹ for the ideal constitutional unit), **HE** (3 equiv), DMSO (1 mL, argon-sparged), argon atmosphere, 10x75 mm borosilicate test tube (spin-vane-equipped, septum/PTFE-tape-sealed), blue LED irradiation, 37 °C, 2 h, according to 5D.

5.4 Recyclability of MPC-1-2

The altered solubility properties of **MPC-1-2** appeared promising for improved recycling techniques. A batch reaction recycle study was conducted using **MPC-1-2_{LMW}** for the hydrodehalogenation of **22b** under standard conditions (Figure 5.12). The partial solubility of **MPC-1-2_{LMW}** in the reaction medium was readily overcome upon reaction completion with the addition of methanol, whereupon the suspension was passed through a fritted glass funnel to separate the catalyst from the rest of the reaction mixture. The catalyst could then be returned to the reaction vessel as a solid or through solution processing to pass it through the frit; these two approaches worked equally well. Six reaction cycles were conducted in this manner without appreciable decrease in catalyst activity. The complete acetone solubility and limited methanol solubility of **MPC-1-1** made this approach infeasible for the oligomeric system.

To further demonstrate the unique possibilities afforded by an innately photocatalytic solution-processable polymer, a new approach to catalyst recycling under flow conditions was envisioned wherein the photocatalytic polymer would be coated on the walls of a flow cell. The reaction solvent would be selected so as not to dissolve the coating. Following a post-reaction rinse, the flow cell could then be reused in subsequent reactions. Although a precedent exists for flow cells containing heterogenized photoredox catalyst immobilized by polymer support or sol-gel techniques,²²⁵ to the best of our knowledge the wall-coating of a transparent and inherently photocatalytic polymer on the walls of a flow cell had not yet been reported. We fashioned a prototype large-volume flow cell to accommodate the poorly soluble reductant and coated its walls by dissolving **MPC-1-2_{HMW}** in dichloromethane, which was allowed to evaporate as the cell was rotated. The flow cell was loaded with **HE** and an acetonitrile solution of **22b** was peristaltically circulated from a reservoir through the cell, which was subjected to blue LED irradiation (Figure 5.13). The polymer

coating was retained on the walls of the flow cell throughout the course of the reaction, and after 26 h the reactor loop was drained into the reservoir and the product was isolated in 83 % yield, confirming the viability of the concept. It is noteworthy that **MPC-1-2_{HMW}** was required for retention of the coating; unfractionated **MPC-1-2** was gradually stripped from the walls under reaction conditions.

Figure 5.13: Flow chemistry with **MPC-1-2_{HMW}** as a thin-film coating. Conditions: **22b** (0.7 mmol, 1 equiv, placed in the reservoir), **HE** (1.5 equiv, placed in the reactor cell), acetonitrile (3.5 mL, argon-sparged), argon atmosphere, peristaltic circulation through an **MPC-1-2_{HMW}**-coated (2.5 mol%) reactor cell under blue LED irradiation, 37 °C, 26 h, according to Procedure 5.18.

5.5 Mechanistic Studies and Assessment of Back-side Irradiation

A series of control studies were conducted with halide **22b** which confirmed that hydrodehalogenation product **23b** only formed in the simultaneous presence of **MPC-1**, **HE**, and blue LED irradiation; no conversion was observed when one of these components was omitted (see Supplementary Information Section 5.7, Table 5.8). Subsequently, the ground-state redox potentials of the control reaction components were determined experimentally by cyclic voltammetry, and the excited-state redox potentials of the catalyst were estimated using the polymer emission wavelength. On the basis of this information, a plausible mechanism is proposed (Figure 5.14). The need for the sacrificial reductant indicates that, as is often the case with the monomeric analog *p*-dicyanobenzene, **MPC-1** is operating as an excited-state oxidant,¹⁸⁴ and the reactivity-determining potential is that of the reduced form, **MPC-1**^{•−} ($E_{ox} = -1.42$ V vs. SCE). Thus, following photoexcitation, **MPC-1**^{*} ($E_{red} = 1.01$ V vs. SCE) is reductively quenched through single electron transfer (SET) from reductant **HE** ($E_{ox} = 0.89$ V vs. SCE). Subsequently, SET from **MPC-1**^{•−} to halide **22b** ($E_{red} = -1.24$ V vs. SCE) leads to homolytic cleavage of the carbon–halogen bond. The resultant alkyl radical is then converted to the product by forming a bond with a methylene hydrogen from **HE**^{•+} as it establishes aromaticity to form Hantzsch pyridine.

Well-defined models of **MPC-1** substructures **28a–e** were synthesized to better elucidate the effects of chain formation and dual chromophores (see Section 5.7.1.3). The activity of the models was assessed with the same reaction conditions used for the benchmarking studies (Table 5.7); the catalyst loading was adjusted to maintain a constant amount of active chromophore units across experiments. Catalyst model **28a**, which contained one sulfone chromophore, was inferior to all other models with only 27 % yield after 2 h. The other single chromophore model, **28b**, which contained

Figure 5.14: Proposed mechanism for MPC-1-catalyzed hydrodehalogenation.

the terephthalonitrile motif, was highly active, providing 99 % product in the same timeframe. As the chain length was increased with models **28c** and **28d**, the yield decreased (97 % and 84 %, respectively); this observation was in agreement with the expectation that yield would decrease with decreasing molecular concentration of catalyst even though active unit loading was held constant. However, when using catalyst model **28e**, which replaced the middle terephthalonitrile unit in **10** with the less active sulfone chromophore, the activity was superior to even single terephthalonitrile model **28b**; this improved activity in spite of lower molecular catalyst concentration and partial use of the less effective sulfone chromophore is in agreement with the charge transfer state hypothesis. An additional experiment using a 1:2 ratio of models **28a** and **28b** afforded only 93 % yield, indicating that the dual-chromophore activity enhancements are only present when the two chromophore types are incorporated into the same molecule.

To further demonstrate the impact of this catalyst, backside irradiation technology was explored as a proof-of-concept. This technology could prove useful for reaction mixtures with low light transmittance. Four reactions were set up in parallel; two

Table 5.7: MPC-1 subunit model study.^a

Catalyst ^b	mol% ^c	% Yield ^d
28a	3	27
28b	3	99
28c	1.5	97
28d	1	84
28e	1	100
28a, 28b	1, 2	93

^a Conditions: **22b** (0.25 mmol, 1 equiv), catalyst, **HE** (1.5 equiv), acetone (0.5 mL, argon-sparged), argon atmosphere, 10x75 mm borosilicate test tube (spin-vane-equipped, septum/PTFE-tape-sealed), blue LED irradiation, 37 °C, 2 h, according to Procedure 5.15.

^b Subunit model catalysts were used as mixtures of isomers; a single isomer is depicted for simplicity. ^c The catalyst loading was scaled such that the number of chromophore units (defined as the constituent monomer units arising from **24** and **26**) in the reaction mixture remained constant between runs.

^d Determined by ¹H NMR.

vessels contained a wall coating of **MPC-1-2_{HMW}**, and two contained the catalyst as a suspension; in one of each of the vessel sets, the reaction mixture was made opaque with the inclusion of charcoal (Figure 5.15). The hydrodehalogenation of **22b** was more efficient with a wall coating than with a suspension, even with the inclusion of charcoal, supporting that the backside irradiation process played a role. Likewise, coated vessels are not affected by the occlusion of light caused by undissolved **HE**: the trend in conversion over time for coated reaction vessels lacks the inflection point observed for vessels with catalyst suspension; this inflection point is attributable to opaque, poorly soluble **HE** being sufficiently converted to Hantzsch pyridine to allow for improved light transmittance.

Figure 5.15: Charcoal occlusion study. **a** Yield as a function of time for the model reaction with catalyst employed as a coating or a suspension in the presence and absence of charcoal as an opaque additive. Conditions: **22b** (0.2 mmol, 1 equiv), **MPC-1-2_{HMW}** (1 mol%, as a suspension or applied to the walls of the vessel as a coating), **HE** (1.5 equiv), charcoal (4 mg, if called for), acetonitrile (1.0 mL, argon-sparged), argon atmosphere, 10x75 mm borosilicate test tube (partially etched glass, spin-vane-equipped, septum/PTFE-tape-sealed), blue LED irradiation, according to Procedure 5.19. **b** Appearance of the reaction vessels in the photoreactor.

5.6 Conclusions

A photocatalytically active double-strand polymer system, **MPC-1**, was developed and successfully employed in the hydrodehalogenation of α -halocarbonyl compounds in mostly excellent yields. Variation of the polymerization technique demonstrated the robustness of the substituent chromophores and led to the development of **MPC-1-2**, an optimal preparation with improved catalytic activity and solubility properties. The recyclability of the photocatalyst was demonstrated in batch reactions, and a proof-of-concept flow cell reactor demonstrated the efficacy of the polymer when used as a transparent wall coating. The backside irradiation approach employed in the flow reaction was found to be superior to use of the catalyst as a suspension and was effective even when the reaction mixture was made opaque with the addition of charcoal. Well-defined compounds were synthesized to clearly model the polymer substructure, and their catalytic activities supported that dual chromophores in fixed proximity was essential to the elevated activity of the polymer.

5.7 Supplementary Information

5.7.1 Methods

5.7.1.1 General Information

All manipulations were carried out under air unless otherwise noted. Solvent molarity listed in reaction schemes is relative to the limiting reagent. The molecular weight for all **MPC-1** preparations (**MPC-1-0**, **MPC-1-1**, **MPC-1-2**, **MPC-1-2_{LMW}**, and **MPC-1-2_{HMW}**) was approximated as 1529 g mol^{-1} , which corresponds to the constitutional unit of an ideal regular polymerization at the monomer ratio used in all preparations; the optimal polymer preparation, **MPC-1-2**, was in very close

agreement with this approximation based on NMR and GPC measurements. An analysis of the divergence of other preparations from this approximation is provided in Section 5.7.2. All flash chromatography was conducted using a Teledyne Isco CombiFlash Rf 150. NMR spectra were recorded at 23 °C on Varian MR-400, Varian Unity INOVA 500, and Varian VNMRs 700 spectrometers (400, 500 and 700 MHz, respectively). Reported chemical shifts are referenced to residual solvent peaks. GCMS data was obtained using a Thermo Scientific Trace 1300 Gas Chromatograph coupled with a Thermo Scientific ISQ-QD Single Quadrupole Mass Spectrometer. Infrared absorbance spectra were acquired on a PerkinElmer Spectrum Two spectrometer using 1 cm^{-1} . High-resolution mass analyses were obtained either using a 5975C Mass Selective Detector coupled with a 7890A Gas Chromatograph (Agilent Technologies) or orbit-trap. MALDI-TOF analyses were obtained using a Bruker Autoflex III. SEM was conducted with a TESCAN Vega3 SEM. HRTEM was conducted with a 200-kV FEI Tecnai F20 FEG-TEM/STEM. GPC was conducted on an Omnisec GPC from Malvern equipped with four on-line detectors: a dual-angle light scattering detector, a refractive index detector, a UV detector, and a viscosity detector. Samples were fully dissolved in THF and eluted through two columns (Viscotek, LT5000L and LT 3000L) at a rate of 1 mL min^{-1} . **MPC-1-0** was not fully soluble in THF and was not analyzed.

TLC plates (UV 254 indicator, aluminum backed, $175\text{ }\mu\text{m}$ to $225\text{ }\mu\text{m}$ thickness, standard grade silica gel, 230 mesh to 400 mesh) were purchased from Merck. Silica gel ($60\text{ }\text{\AA}$ pore size, 230 mesh to 400 mesh) was purchased from Silicycle. Sand was purchased from Fisher Chemical. Celite 545 was purchased from Acros Organics. Acetone, ethyl acetate, hexanes, methanol, ethanol, *N,N*-dimethylformamide, dimethyl sulfoxide, dichloromethane, tetrahydrofuran, and HPLC-grade water were purchased from Fisher Chemical. Pentane, chloroform and 2-methyltetrahydrofuran were purchased from Sigma-Aldrich. *N,N*-Dimethylacetamide was purchased from

Acros Organics. *N*-Methyl-2-pyrrolidone was purchased from Antec Inc. Acetonitrile was purchased from Pharmco Products Inc. 1,4-Dioxane was purchased from EMD Chemicals. NMR solvents were purchased from Cambridge Isotope Laboratories. Dry solvents were prepared using standard procedures.²²⁶ Surfactant solutions were prepared in HPLC-grade water. PS-750-M was prepared as previously reported.⁶⁴ TPGS-750-M and sodium dodecyl sulfate were supplied by Sigma-Aldrich.

1,3,5-Trimethyl-1*H*-pyrazole-4-sulfonyl chloride supplied by Maybridge was received as a gift from Novartis Pharmaceuticals. *N,N*-Diisopropylethylamine, sodium bicarbonate, and anhydrous potassium carbonate were purchased from Fisher Chemical. Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Hantzsch ester) was purchased from Combi-Blocks Inc. and Oakwood Chemicals, and both sources were confirmed to work equally well when adjusting loading based on NMR purity. 2,3,5,6-Tetrafluoroterephthalonitrile, 3,3,3',3'-Tetramethyl-1,1'-spirobiindane-5,5',6,6'-tetraol, 2-bromo-1-(4-bromophenyl)ethan-1-one, 1-([1,1'-biphenyl]-4-yl)-2-bromoethan-1-one, 2-bromo-1-(2-fluoro-5-methoxyphenyl)ethan-1-one, 1-(benzofuran-2-yl)-2-bromoethan-1-one, and 2-bromo-1-(3-bromo-4-fluorophenyl)ethan-1-one were purchased from Sigma-Aldrich. 2-Chloro-1-(2,4-dichlorophenyl)ethan-1-one and 2-bromo-1-(4-nitrophenyl)ethan-1-one were purchased from Oxchem Corporation and Oakwood Chemicals, and both sources were confirmed to work equally well. 2-Bromo-1,3-diphenylpropane-1,3-dione was purchased from Chem-Impex. (1*R*,3*S*,4*S*)-3-Bromo-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one was purchased from TCI. Sodium sulfinate, 2-bromo-1-(4-bromophenyl)propan-1-one, benzyl 2-bromoacetate and 1,2-dibromoethane were purchased from Acros Organics. 2-Chloro-1-(4-fluorophenyl)ethan-1-one, 2-bromo-2-methyl-1-phenylpropan-1-one, and tetrabutylammonium hexafluorophosphate were purchased from Oakwood Chemicals. 2,3,4,5,6-Pentafluorobenzonitrile was purchased from Matrix Scientific. 3-Bromo-1,3,4,5-tetrahydro-2*H*-benzo[*b*]azepin-2-one was purchased from Ark Pharm. 2-Bromo-1-(2,4-dichlorophenyl)ethan-1-one and 1-(2,4-

dichlorophenyl)-2-iodoethan-1-one were prepared by heating a 0.2 M dry acetone solution of 2-chloro-1-(2,4-dichlorophenyl)ethan-1-one at 70 °C in a thick-walled sealed reaction vessel with 1.5 equiv of sodium bromide and sodium iodide, respectively, and spectral data was in agreement with the literature.^{227,228} 2,2-Dibromo-1-phenylethan-1-one was prepared as previously reported.²²⁹ 2,3-Dibromo-2-methyl-3-phenylpropanal was prepared from 2,3-dibromo-2-methyl-3-phenylpropanal through the dropwise addition of 2 M bromine in DCM to a 0.2 M DCM solution of substrate at 0 °C followed by room temperature stirring and quenching with aqueous sodium sulfite, and spectral data was in agreement with the literature.²³⁰

5.7.1.2 Preparation of polymer photocatalysts

Polymer syntheses were partly adapted from published procedures.^{65,82,198}

Procedure 5.1: Preparation of sodium 1,3,5-trimethyl-1*H*-pyrazole-4-sulfinate.

1,3,5-Trimethyl-1*H*-pyrazole-4-sulfonyl chloride* (1 equiv, 5 mmol) was added to a stirred solution of sodium bicarbonate (2 equiv, 10 mmol) and sodium sulfite (2 equiv, 10 mmol) in 20 mL HPLC-grade water in a 100 mL teardrop-shaped evaporating flask that had been heated at 80 °C for 10 min. The vessel was fitted with a rubber septum that was further secured with steel wire. The reaction was monitored as complete after 1 h by TLC. Water was removed by rotary evaporation under reduced pressure. The resultant white solid was partly purified with five cycles of dissolution/suspension in

*Note regarding starting material purity: 1,3,5-Trimethyl-1*H*-pyrazole-4-sulfonyl chloride should be slightly bluish in appearance; multiple suppliers provided a yellowish compound that turned out to be almost entirely 1,3,5-trimethyl-1*H*-pyrazole-4-sulfonic acid. Compound purchased from Maybridge was satisfactory. The sulfonyl chloride could be obtained from the sulfonic acid by reacting with 3 equiv oxalyl chloride and 20 mol% dry DMF in dry DCM.

approximately 20 mL hot ethanol and collection over a fritted glass funnel by vacuum filtration. The filtrate ethanol was removed by rotary evaporation under reduced pressure and the resultant white solid was placed under high vacuum for 30 min. The crude product consisted of a mixture of sulfinic and sulfonic salts and was used in the subsequent reaction without further purification; yield of the desired product was estimated to be 38 % by ^1H NMR.

Procedure 5.2: Preparation of MPC-1-0.

To an oven-dried, thick-walled air-free flask containing a PTFE-coated magnetic stir bar, sodium 1,3,5-trimethyl-1*H*-pyrazole-4-sulfinate (approximately 1 equiv, 0.4 mmol), potassium carbonate (1 equiv, 0.4 mmol), and 3,4,7,8-tetramethyl-1,10-phenanthroline[†] (1 mol%, 0.004 mmol) were added. The vessel was thrice evacuated/argon backfilled and 2,3,4,5,6-pentafluorobenzonitrile (1 equiv, 0.4 mmol) and dry DMF (0.8 mL) were added by syringe. The vessel was sealed and allowed to stir in an oil bath pre-heated to 100 °C until TLC monitoring indicated that all 2,3,4,5,6-pentafluorobenzonitrile had been consumed (2 h). The reaction mixture was allowed to cool to room temperature and then 2,3,5,6-tetrafluoroterephthalonitrile (2 equiv, 0.8 mmol), 3,3,3',3'-tetramethyl-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-5,5',6,6'-tetraol (3 equiv, 1.2 mmol), and additional potassium carbonate (9 equiv, 3.6 mmol) were added through a weigh-paper funnel followed by the addition of dry toluene (3.2 mL). The vessel was re-sealed and lowered into an oil bath pre-heated to 160 °C to stir for 70 min. Subsequently, the reaction mixture was allowed to cool to room temperature, and the contents were

[†]Phenanthroline was not necessary for the reaction and had been included as part of a separate investigation.

poured into 40 mL methanol. Volatiles were removed under reduced pressure to obtain the crude product as a yellowish semi-solid. The crude material was dissolved in 30 mL chloroform and the polymer was reprecipitated with the slow addition of methanol (ca. 40 mL). The vivid yellow precipitate was collected on a fritted glass funnel, and the solid was then suspended in 50 mL deionized water. The aqueous suspension was refluxed for 12 h, allowed to cool to room temperature, and then filtered with a fritted glass funnel. The bright yellow solid was then dried under reduced pressure for 12 h at 100 °C. Note that ^1H NMR signal integrations are scaled according to a 15:1 ratio of incorporated **24** and **26**. The limited solubility of the material precluded GPC analysis in THF and suggested the presence of crosslinks and chain branching defects arising from the para substitution of pentafluorobenzonitrile not being accomplished separately, potentially leaving the para position open to substitution by the tetraol. Yellow solid, 549 mg. ^1H NMR (500 MHz, CDCl_3) δ (ppm) 7.10–5.92 (m, 48H), 3.99–3.40 (m, 3H), 3.25–2.79 (m, 5H), 2.79–1.85 (m, 57H), 1.85–0.97 (m, 144H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm) 149.9, 147.1, 139.4, 112.5, 110.7, 109.5, 94.3, 59.0, 57.3, 43.8, 31.5, 30.1.

Procedure 5.3: Preparation of 2,3,5,6-tetrafluoro-4-((1,3,5-trimethyl-1*H*-pyrazol-4-yl)sulfonyl)benzonitrile (26**).**

2,3,4,5,6-Pentafluorobenzonitrile (1 equiv, 2 mmol, 255 μL) was combined with crude sodium 1,3,5-trimethyl-1*H*-pyrazole-4-sulfinate (approximately 1 equiv, 2 mmol) and 4 mL DMSO in a round-bottom flask. The vessel was capped with a yellow plastic cap and allowed to stir at room temperature for 12 h.[‡] The reaction mixture was

[‡]An alternative synthetic procedure using environmentally benign aqueous PS-750-M surfactant

diluted with 8 mL ice-cold deionized water and extracted with ethyl acetate (3×12 mL). The organic layer was dried over anhydrous magnesium sulfate and subjected to rotary evaporation under reduced pressure. The crude light brown oil was purified by flash chromatography (hexanes/ethyl acetate). Eluent was removed by rotary evaporation and the white powdery solid was thrice triturated in pentane and re-subjected to rotary evaporation. Product was not subjected to high vacuum for concern of losing the product through sublimation. White powder, m.p. = 138 °C to 141 °C, 434 mg (62 %), R_f 0.29 (1:1, hexanes/ethyl acetate). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 3.77 (s, 3H), 2.54 (s, 3H), 2.38 (s, 3H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 149.4, 147.5 (dddd; JCF = 266.5, 17.6, 5.1, and 2.3 Hz), 144.8, 144.1 (dddd; JCF = 261.7, 13.2, 4.9, and 2.9 Hz), 128.4 (t, JCF = 14.3 Hz), 115.7, 106.4 (t, JCF = 3.4 Hz), 98.1 (t, JCF = 17.1 Hz), 36.6, 13.0, and 10.6 ppm. **^{19}F NMR** (470 MHz, CDCl_3) δ (ppm) -128.86 – -128.93 (m, 2F), -134.36 – -134.43 (m, 2F). **HRMS** (CI) $[\text{C}_{13}\text{H}_9\text{F}_4\text{N}_3\text{O}_2\text{S} + \text{Na}]^+$ calculated 370.0249, found (m/z) 370.0256.

Procedure 5.4: Preparation of MPC-1-1.

2,3,5,6-Tetrafluoroterephthalonitrile (monomer **24**, 99 %, Sigma-Aldrich) and 3,3,3',3'-tetramethyl-1,1'-spirobiindane-5,5',6,6'-tetraol (monomer **25**, 96 %, Sigma-Aldrich) were used as received. 2,3,5,6-Tetrafluoro-4-((1,3,5-trimethyl-1H-pyrazol-4-yl)sulfonyl)benzonitrile (monomer **26**, 1 equiv, 0.115 mmol, 39.9 mg), **24** (2 equiv, 0.230 mmol, 46.5 mg), **25** (3 equiv, 0.345 mmol, 122 mg), and potassium was also employed⁶⁵ (see Chapter 2).

carbonate (10 equiv, 1.15 mmol, 159 mg) were added to a stir-bar-equipped round-bottom flask which was then fitted with a water-jacketed reflux condenser. A 4.6 mL volume of 3 wt% aqueous PS-750-M surfactant was added by syringe through the condenser and the reaction apparatus was lowered into an oil bath pre-heated to 125 °C where the mixture was allowed to stir. After 30 min, the bath temperature was lowered to 100 °C for the remaining 1.5 h. The vivid yellow solid was collected over a fritted glass funnel with vacuum filtration, rinsing the flask and the filter cake with deionized water to remove the surfactant. The solid was then collected back into the round-bottom flask, combined with 15 mL deionized water, and refluxed for 9 h using an oil bath pre-heated to 125 °C. The solid was once again collected by vacuum filtration onto a fritted glass funnel and washed with deionized water. The solid was then collected in a glass vessel and subjected to high vacuum for 2 h. The solid was then dissolved in DCM and passed through a Celite plug. The solvent was removed by rotary evaporation and the residue was triturated in pentane, which was also removed by rotary evaporation. The solid was placed on high vacuum for 24 h. Note that ¹H NMR signal integrations are scaled according to a 19:13 ratio of incorporated **24** and **26**. Yellow solid, 215 mg. **¹H NMR** (400 MHz, CDCl₃) δ (ppm) 6.81–5.98 (m, 128H), 5.98–5.00 (m, 26H), 3.78–3.07 (m, 57H), 2.60–1.66 (m, 242H), 1.29–0.98 (m, 384H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm) 149.5, 149.0, 146.8, 141.4, 140.0, 139.5, 136.4, 112.2, 110.3, 109.8, 108.4, 94.0, 59.0, 57.3, 43.7, 43.5, 36.5, 31.8, 31.5, 30.5, 30.1, 13.3, 11.0.

Procedure 5.5: Preparation of MPC-1-2.

Prior to use, 2,3,5,6-tetrafluoroterephthalonitrile (monomer **24**, 99 %, Sigma-Aldrich) was sublimed at 155 °C with an established (but not active) vacuum, and 3,3,3',3'-tetramethyl-1,1'-spirobiindane-5,5',6,6'-tetraol (monomer **25**, 96 %, Sigma-Aldrich) was recrystallized from methanol/water. Unactivated 3 Å molecular sieves (8 mesh to 12 mesh; 400 mg) and oven-dried potassium carbonate (9 equiv, 2.7 mmol, 373 mg) were added to a thick-walled air-free flask with a PTFE-coated stir bar and subjected to a vacuum oven at 28 in Hg and greater than 200 °C for 14 h. 2,3,5,6-Tetrafluoro-4-((1,3,5-trimethyl-1H-pyrazol-4-yl)sulfonyl)benzonitrile (1 equiv, 0.3 mmol, 104 mg), 2,3,5,6-tetrafluoroterephthalonitrile (2 equiv, 0.6 mmol, 120 mg), and 3,3,3',3'-tetramethyl-1,1'-spirobiindane-5,5',6,6'-tetraol (3 equiv, 0.9 mmol, 373 mg) were added to the vessel through a weigh paper funnel and the vessel was briefly evacuated once by high vacuum and backfilled with argon. Dry DMAc was added with positive argon pressure and then the vessel was sealed. The vessel was shaken briefly to more evenly incorporate material on the walls of the vessel, and then the vessel was placed in a sand bath heated to 90 °C to stir at 800 rpm. The mixture was monitored every 5 min by briefly removing the vessel and shaking so as to evenly incorporate material on the walls of the vessel; changes in the coating left on the vessel walls and the solution appearance and viscosity were observed over time. At 50 min the liquid had become too viscous to effectively coat the vessel walls when shaking. At 60 min the stir bar was observed to intermittently slow, struggling against the increased viscosity. At 70 min the viscosity had become sufficiently high that the stir bar was whipping tiny bubbles into the reaction mixture, and at this point the vessel

was removed from heating and allowed to cool to room temperature. After cooling, the vessel contents solidified. The vessel was then unsealed and 4 mL deionized water was added, which caused the solidified polymer to break from coating the walls. The vessel was resealed and the contents were subjected to stirring at 1700 rpm while heating at 110 °C in a sand bath for 10 min, with the stirring being intermittently turned on and off to help break the stir bar free from the polymer. The suspension was then stirred vigorously at room temperature for 5 min. The supernatant liquid and some of the suspension was removed by syringe and transferred to a test tube. The reaction vessel was then thrice rinsed by stirring with 2 mL portions of deionized water which were also transferred into the test tube. The test tube was centrifuged, and its supernatant liquid was removed. The test tube contents were then twice admixed with 2 mL deionized water, centrifuged, and likewise separated from the supernatant liquid. The test tube contents were dissolved in chloroform and transferred back into the reaction vessel. Additional chloroform was added to bring the total volume added to 10 mL, and then 10 mL deionized water was also added. The mixture was stirred, allowed to settle, and the chloroform layer was syringe-transferred to a test tube. The aqueous layer was then extracted with 2×1 mL chloroform to complete the transfer. The combined chloroform layers were then mixed with 1 mL deionized water, and the aqueous layer was transferred to the reaction vessel. Subsequently, the combined chloroform layers were combined with 10 mL methanol, which caused the majority of the polymer to precipitate. The test tube was subjected to centrifugation and the supernatant liquid was decanted away. The centrifuge pellet was dissolved in chloroform, transferred to a glass storage vial, subjected to rotary evaporation under reduced pressure to remove the chloroform, and then placed in a vacuum oven. The oven was evacuated to 710 mmHg and then heated to 130 °C and allowed to sit for 14 h. The vacuum was then re-established to 710 mmHg and allowed to sit for 2 h, at which point the vacuum was briefly re-established, and then the oven was vented,

and the material was allowed to cool. Translucent yellow solid, 369 mg. ^1H NMR (400 MHz, CDCl_3) δ (ppm) 6.99–6.23 (m, 12H), 4.04–3.40 (m, 3H), 2.80–1.92 (m, 18H), 1.49–1.27 (m, 36H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 149.8, 147.1, 139.9, 139.6, 139.3, 112.5, 110.7, 109.6, 94.3, 59.0, 57.3, 43.7, 36.4, 31.5, 30.1, 29.5, 13.4, 11.0.

Procedure 5.6: Fractionation of MPC-1-2.

A 28 mg portion of **MPC-1-2** was dissolved in 1 mL chloroform and reprecipitated with 30 drops of methanol. The supernatant liquid was decanted. Precipitated solid was twice more reprecipitated from chloroform with methanol in the same manner. The solid thus obtained was designated as **MPC-1-2_{HMW}**. Solvent was removed from the combined supernatant layers under reduced pressure to give the fractionation designated as **MPC-1-2_{LMW}**. After the fractionations were subjected to high vacuum, they were obtained with approximately equal masses (14 mg).

5.7.1.3 Synthesis of MPC-1 Subunit Models

All polymer subunit models were prepared as mixtures of isomers; for simplicity, only one product structure is depicted and named in each case.

Procedure 5.7: Preparation of end-capped spirobiindane monomer (29a).

IUPAC name: 3,3,8',8'-tetramethyl-2,2',3,3',7',8'-hexahydrospiro[indene-1,6'-indeno[5,6-b][1,4]dioxine]-5,6-diol

A stir-bar-equipped 20 mL vial was charged with 3,3,3',3'-tetramethyl-1,1'-spirobiindane-5,5',6,6'-tetraol (monomer **25**, 2 equiv, 12.0 mmol) and potassium carbonate (4 equiv, 24.0 mmol). The vessel was fitted with a rubber septum and thrice evacuated/argon-backfilled before adding 18 mL dry DMF by syringe. 1,2-Dibromoethane (1 equiv, 6.0 mmol) was added by syringe and then the septum punctures were covered with electrical tape and the septum was wrapped with PTFE tape. The mixture was allowed to stir at room temperature for 5 min before it was placed to stir in a sand bath pre-heated to 100 °C. After 12 h, the vessel was allowed to cool to room temperature. The reaction mixture was combined with 20 mL ice-cold deionized water and extracted with ethyl acetate (3x25 mL). The combined organic layers were dried over sodium sulfate and subjected to rotary evaporation under reduced pressure. The crude dark brown oil was purified by flash chromatography (hexanes/ethyl acetate). Off-white solid, 528 mg (24 %), R_f 0.22 (7:3, hexanes/ethyl acetate). **¹H NMR** (700 MHz, DMSO) δ (ppm) 8.57 (s, 1H), 8.55 (s, 1H), 6.66 (s, 1H), 6.51 (s, 1H), 6.10 (s, 1H), 6.07 (s, 1H), 4.20–4.14 (m, 4 H), 2.19 (dd, 2H, J = 12.6 Hz and 4.2 Hz), 2.03 (d, 2H, J = 12.6 Hz), 1.29 (s, 3H), 1.26 (s, 3H), 1.23 (s, 3H), 1.21 (s, 3H). **¹³C NMR** (176 MHz, DMSO) δ (ppm) (144.7, 144.7, 144.5, 143.3, 142.7, 142.7, 142.2, 140.3, 111.6, 110.0, 109.9, 108.4, 63.9, 63.9, 59.5, 59.3, 56.4, 42.5, 42.5, 31.5, 31.4, 30.5, 30.3). **HRMS** (ESI) $[C_{23}H_{26}O_4 + Na]^+$ calculated 755.3554, found (m/z) 755.3553.

Procedure 5.8: Preparation of single sulfone subunit model (28a).

IUPAC name for depicted isomer: 8,8,8'',8'',10',10',24',24'-octamethyl-16'-[(1,3,5-trimethyl-1H-pyrazol-4-yl)sulfonyl]-2,2'',3,3'',7,7'',8,8''-octahydrodispiro[indeno[5,6-b][1,4]dioxine-6,8'-[4,14,18,28]tetraoxaheptacyclo[15.11.0.03,15.05,13.07,11.019,27.021,25]octacosane-22',6''-indeno[5,6-b][1,4]dioxine]-1',3'(15'),5'(13'),6',11',16',19'(27'),20',25'-nonaene-2'-carbonitrile

A stir-bar-equipped 4 mL vial was charged with 2,3,5,6-tetrafluoro-4-((1,3,5-trimethyl-1H-pyrazol-4-yl)sulfonyl)benzonitrile (monomer **26**, 1 equiv, 0.040 mmol), intermediate **29a** (2.1 equiv, 0.084 mmol), and potassium carbonate (4.5 equiv, 0.180 mmol). The vessel was fitted with a rubber septum and thrice evacuated/argon-backfilled before adding 400 μ L dry THF by syringe. The septum puncture was sealed with electrical tape and the septum was wrapped with PTFE tape. The vessel was placed to stir on a reaction block pre-heated to 65 °C. After 10 h, the solvent was removed under reduced pressure, the stir bar was removed, and the remaining crude material was dissolved in DCM. Silica was admixed into the vessel and then DCM was removed under reduced pressure. The resultant solid was dry-loaded onto the top of a hexanes-wetted column and subjected to flash chromatography (hexanes/ethyl acetate). Yellow solid, 31 mg (91 %), R_f 0.21, 0.24, and 0.35 (1:1, hexanes/ethyl acetate). **¹H NMR** (700 MHz, CDCl₃) δ (ppm) 6.94–6.03 (m, 8H), 4.39–4.03 (m, 8H), 3.80–3.43 (m, 3H), 2.61–2.32 (m, 6H), 2.32–2.25 (m, 4H), 2.23–2.04 (m, 4H), 1.46–1.26 (m, 24H). **¹³C NMR** (176 MHz, CDCl₃) δ (ppm) 149.4, 149.3, 149.0, 148.8, 148.8, 148.7, 148.0, 148.0, 145.5, 145.5, 144.0, 143.4, 143.4, 143.2, 143.2, 143.2, 142.6,

142.6, 142.3, 139.9, 139.9, 139.9, 139.8, 139.6, 139.6, 139.6, 139.1, 139.1, 139.1, 139.0, 136.4, 136.3, 123.3, 118.2, 112.3, 112.2, 110.4, 110.3, 110.3, 110.1, 110.0, 93.8, 64.5, 64.4, 59.7, 59.6, 59.3, 59.2, 57.2, 57.2, 57.1, 43.5, 43.5, 43.5, 43.5, 43.4, 43.3, 31.8, 31.8, 31.5, 31.4, 30.6, 30.5, 30.4, 30.2, 29.8. **HRMS** (ESI) $[\text{C}_{59}\text{H}_{57}\text{N}_3\text{O}_{10}\text{S} + \text{H}]^+$ calculated 1000.3837, found (m/z) 1000.3838; $[\text{C}_{59}\text{H}_{57}\text{N}_3\text{O}_{10}\text{S} + \text{Na}]^+$ calculated 1022.3657, found (m/z) 1022.3654.

Procedure 5.9: Preparation of single terephthalonitrile subunit model (28b).

IUPAC name for depicted isomer: 8,8,8'',8'',10',10',24',24'-octamethyl-2,2'',3,3'',7,7'', 8,8''-octahydrodispiro[indeno[5,6-b][1,4]dioxine-6,8'-[4,14,18,28]tetraoxaheptacyclo[15.11.0.03,15.05,13.07,11.019,27.021,25]octacosane-22',6''-indeno[5,6-b][1,4]dioxine]-1', 3'(15'),5'(13'),6',11',16',19'(27'),20',25'-nonaene-2',16'-dicarbonitrile

A stir-bar-equipped 4 mL vial was charged with 2,3,5,6-tetrafluoroterephthalonitrile (monomer **24**, 1 equiv, 0.050 mmol), intermediate **29a** (2.1 equiv, 0.105 mmol), and potassium carbonate (4.5 equiv, 0.225 mmol). The vessel was fitted with a rubber septum and thrice evacuated/argon-backfilled before adding 400 μL dry DMF by syringe. The septum puncture was sealed with electrical tape and the septum was wrapped with PTFE tape. The vessel was placed to stir on a reaction block pre-heated to 65 °C. After 2 h, the vessel was allowed to cool to room temperature. The reaction mixture was diluted with 400 μL ice-cold water, extracted (3 $\times$ 800 μL DCM), and dried

over anhydrous magnesium sulfate. Solvent was removed under reduced pressure and the crude material was purified by column chromatography (hexanes/ethyl acetate). Yellow solid, 33 mg (77 %), R_f 0.25, 0.30, and 0.38 (4:1, hexanes/ethyl acetate). **^1H NMR** (700 MHz, CDCl_3) δ (ppm) 6.82–6.74 (m, 2H), 6.67–6.62 (m, 2H), 6.49–6.43 (m, 2H), 6.28–6.21 (m, 2H), 4.32–4.13 (m, 8H), 2.35–2.26 (m, 4H), 2.22–2.16 (m, 2H), 2.16–2.10 (m, 2H), 1.37–1.27 (m, 24H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 149.7, 148.4, 145.5, 143.4, 143.2, 142.6, 139.3, 139.3, 139.2, 112.7, 112.6, 112.3, 112.2, 110.4, 110.4, 110.3, 109.7, 109.7, 109.6, 94.1, 94.1, 94.1, 77.3, 77.2, 77.0, 64.5, 64.4, 59.7, 59.6, 59.3, 59.2, 57.2, 43.5, 43.4, 31.8, 31.8, 31.5, 31.5, 30.5, 30.4, 30.2, 30.1. **HRMS** (ESI) $[\text{C}_{54}\text{H}_{48}\text{N}_2\text{O}_8 + \text{Na}]^+$ calculated 875.3303, found (m/z) 875.3301.

Procedure 5.10: Preparation of end-capped spirobiindane–terephthalonitrile dimer (29b).

IUPAC name: 7,8-difluoro-3,3,8',8'-tetramethyl-2,2',3,3',7',8'-hexahydrospiro[benzo[b]indeno[5,6-e][1,4]dioxine-1,6'-indeno[5,6-b][1,4]dioxine]-6,9-dicarbonitrile

A stir-bar-equipped 4 mL vial was charged with intermediate **29a** (1 equiv, 0.8 mmol), 2,3,5,6-tetrafluoroterephthalonitrile (monomer **24**, 1 equiv, 0.050 mmol), and potassium carbonate (4.5 equiv, 0.225 mmol). The vessel was fitted with a rubber septum and thrice evacuated/argon-backfilled before adding 3.2 mL dry DMF by syringe. The septum puncture was sealed with electrical tape and the septum was wrapped with PTFE tape. The vessel was allowed to stir at room temperature for 3 h. The reaction mixture was diluted with 3.2 mL ice-cold water and extracted (4×4 mL ethyl acetate). Combined organic layers were dried over sodium sulfate. Solvent was removed under reduced pressure and the crude material was purified by column

chromatography (hexanes/ethyl acetate).

Procedure 5.11: (Preparation of end-capped spirobiindane–terephthalonitrile–spirobiindane trimer (29c) and double terephthalonitrile subunit model 28c).

IUPAC name of depicted **29c** isomer: 5,6-dihydroxy-3,3,8'',8'',10',10',24',24'-octamethyl-2,2'',3,3'',7'',8''-hexahydrodispiro[indene-1,8'-[4,14,18,28]tetraoxaheptacyclo[15.11.0.03,15.05,13.07,11.019,27.021,25]octacosane-22',6''-indeno[5,6-b][1,4]dioxine]-1'(17'),2',5'(13'),6',11',15',19'(27'),20',25'-nonaene-2',16'-dicarbonitrile

IUPAC name of depicted **28c** isomer: 8,8,8''',8''',10',10',10'',10'',24',24',24'',24''-dodecamethyl-2,2''',3,3''',7,7''',8,8'''-octahydrotrispiro[indeno[5,6-b][1,4]dioxine-6,8':22',8''-bis([4,14,18,28]tetraoxaheptacyclo[15.11.0.03,15.05,13.07,11.019,27.021,25]octacosane)-22'',6''''-indeno[5,6-[0]b][1,4]dioxin]-1',1''(17''),2'',3'(15'),5'(13'),5''(13''),6',6'',11',11'',15'',16',19'(27'),19''(27''),20',20'',25',25''-octadecaene-2',2'',16',16''-tetracarbonitrile

A stir-bar-equipped 4 mL vial was charged with intermediate **29b** (1 equiv, 0.135 mmol), 3,3,3',3'-tetramethyl-1,1'-spirobiindane-5,5',6,6'-tetraol (monomer **25**, 3 equiv, 0.405 mmol), and potassium carbonate (2.5 equiv, 0.338 mmol). The vessel was fitted with a rubber septum and thrice evacuated/argon-backfilled before adding 1.35 mL dry THF by syringe. The septum puncture was sealed with electrical tape and the septum was wrapped with PTFE tape. The vessel was placed to stir in a

reaction block pre-heated to 65 °C for 14 h. The solvent was removed under reduced pressure, the stir bar was removed, and the remaining crude material was dissolved in DCM. Silica was admixed into the vessel and then DCM was removed under reduced pressure. The resultant solid was dry-loaded onto the top of a DCM-wetted column and subjected to flash chromatography (DCM/ethyl acetate).

Results for intermediate **29c**: Yellow solid, 69 mg (62 %), R_f 0.23 and 0.17 (7:3, hexanes/ethyl acetate). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 6.86–6.73 (m, 2H), 6.73–6.61 (m, 2H), 6.51–6.41 (m, 2H), 6.33–6.20 (m, 2H), 5.14 (s, 1H), 4.98 (s, 1H), 4.31–4.16 (m, 4H), 2.43–2.25 (m, 4H), 2.25–2.07 (m, 4H), 1.40–1.28 (m, 24H). **^{13}C NMR** (100 MHz, CDCl_3) δ (ppm) 149.7, 148.4, 145.5, 145.2, 143.5, 143.4, 143.2, 142.6, 141.9, 139.4, 139.3, 112.7, 112.2, 110.6, 110.4, 108.8, 94.2, 64.4, 59.6, 59.2, 57.3, 57.2, 43.5, 43.4, 42.8, 31.8, 31.5, 30.5, 30.2, 29.9. **HRMS** (ESI) $[\text{C}_{52}\text{H}_{46}\text{N}_2\text{O}_8 + \text{Na}]^+$ calculated 849.3146, found (m/z) 849.3145.

Results for **28c**: Yellow solid, 17 mg (19 %), R_f 0.55 and 0.49 (7:3, hexanes/ethyl acetate). **^1H NMR** (700 MHz, CDCl_3) δ (ppm) 6.89–6.71 (m, 4H), 6.71–6.56 (m, 2H), 6.56–6.34 (m, 4H), 6.34–6.13 (m, 2H), 4.39–3.99 (m, 8H), 2.43–2.24 (m, 6H), 2.24–2.08 (m, 6H), 1.41–1.28 (m, 36H). **^{13}C NMR** (176 MHz, CDCl_3) δ (ppm) 149.8, 149.7, 148.4, 147.1, 145.5, 145.5, 143.4, 143.2, 142.6, 139.7, 139.5, 139.5, 139.2, 112.7, 112.6, 112.5, 112.4, 112.3, 112.2, 110.7, 110.4, 109.6, 94.2, 64.5, 59.6, 59.3, 59.2, 59.0, 57.3, 57.2, 43.8, 43.5, 43.4, 31.8, 31.8, 31.5, 30.5, 30.4, 30.2, 30.1, 30.1, 30.0, 29.8. **HRMS** (ESI) $[\text{C}_{83}\text{H}_{68}\text{N}_4\text{O}_{12} + \text{H}]^+$ calculated 1313.4907, found (m/z) 1313.4916; $[\text{C}_{83}\text{H}_{68}\text{N}_4\text{O}_{12} + \text{Na}]^+$ calculated 1335.4726, found (m/z) 1335.4736.

Procedure 5.12: Preparation of triple terephthalonitrile subunit model (28d).

IUPAC name for depicted isomer: 8,8,8''',8''',10',10',10'',10'',10''',10''',24',24',24'',24',24'',24'''-hexadecamethyl-2,2''',3,3''',7,7''',8,8'''-octahydrotetrspirop[indeno[5,6-b][1,4]dioxine-6,8':22',8'':22'',8'''-tris([4,14,18,28]tetraoxaheptacyclo[15.11.0.03,15.05,13.07,11.019,27.021,25]octacosane)-22''',6''''-indeno[5,6-b][1,4]dioxine]-1',1'',1'''(17'''),2''',3'(15'),3''(15''),5'(13'),5''(13''),5'''(13'''),6',6'',6''',11',11'',11''',15'',16',16'',19'(27'),19''(27''),19'''(27'''),20',20'',20''',25',25'',25'''-heptacosane-2',2'',2''',16',16'',16'''-hexacarbonitrile

A stir-bar-equipped 4 mL vial was charged with 2,3,5,6-tetrafluoroterephthalonitrile (monomer **24**, 1 equiv, 0.019 mmol), intermediate **29c** (2.2 equiv, 0.042 mmol), and flame-dried potassium carbonate (4.5 equiv, 0.086 mmol). The vessel was fitted with a rubber septum and thrice evacuated/argon-backfilled before adding 200 µL dry DMF by syringe. The septum puncture was sealed with electrical tape and the septum was wrapped with PTFE tape. The vessel was placed to stir in a reaction block pre-heated to 90 °C for 2.5 h. The vessel was allowed to cool to room temperature. The reaction mixture was diluted with 0.5 mL ice-cold water and extracted (3x0.5 mL ethyl acetate). Combined organic layers were dried over sodium sulfate. Solvent was removed under reduced pressure. Crude material was purified by flash chromatography (hexanes/ethyl acetate). Yellow solid, 33 mg (98 %), R_f 0.55 to 0.36 (7:3, hexanes/ethyl acetate). **¹H NMR** (400 MHz, CDCl₃) δ (ppm) 6.88–6.71 (m, 6H), 6.71–6.56 (m, 2H), 6.55–6.35 (m, 6H), 6.34–6.15 (m, 2H), 4.36–4.05 (m, 8H), 2.44–2.24 (m, 8H), 2.24–2.05 (m, 8H),

1.39–1.29 (m, 48H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm) 149.8, 148.4, 147.1, 145.5, 143.4, 143.2, 142.6, 139.7, 139.5, 139.4, 139.2, 112.7, 112.5, 112.2, 110.7, 110.4, 109.6, 94.2, 64.4, 59.6, 59.2, 59.0, 57.3, 57.2, 43.8, 43.5, 43.4, 32.1, 31.8, 30.4, 30.2, 30.1, 29.8, 29.5. **MALDI-TOF** [C₁₁₂H₈₈N₆O₁₆ + Na]⁺ calculated 1795.61, found (*m/z*) 1795.94.

Procedure 5.13: Preparation of terephthalonitrile–sulfone–terephthalonitrile subunit model (28e).

IUPAC name for depicted isomer: 8,8,8''',8''',10',10',10'',10'',10''',10''',24',24',24'',24''',24''',24'''-hexadecamethyl-16''-[(1,3,5-trimethyl-1H-pyrazol-4-yl)sulfonyl]-2,2''',3,3''',7,7''',8,8'''-octahydrotetraspiro[indeno[5,6-b][1,4]dioxine-6,8':22',8'':22'',8'''-tris([4,14,18,28]tetraoxaheptacyclo[15.11.0.03,15.05,13.07,11.019,27.021,25]octacosane)-22''',6''''-indeno[5,6-b][1,4]dioxine]-1',1'',1'''(17'''),2''',3'(15'),3''(15''),5'(13'),5''(13''),5'''(13'''),6',6'',6''',11',11'',11''',15''',16',16'',19'(27'),19''(27''),19'''(27'''),20',20'',20''',25',25'',25'''-heptacosane-2',2'',2''',16',16'''-pentacarbonitrile

A spin-vane-equipped 3 mL test tube was charged with 2,3,5,6-tetrafluoro-4-((1,3,5-trimethyl-1*H*-pyrazol-4-yl)sulfonyl)benzonitrile (monomer **26**, 1 equiv, 0.030 mmol), intermediate **29c** (2.2 equiv, 0.066 mmol), and potassium carbonate (4.5 equiv, 0.135 mmol). The vessel was fitted with a rubber septum and thrice evacuated/argon-backfilled before adding 300 μ L dry THF by syringe. The septum puncture was sealed with electrical tape and the septum was wrapped with PTFE

tape. The vessel was placed to stir in a sand bath pre-heated to 65 °C for 10 h. After TLC indicated that the reaction was still not complete, the solvent was removed under reduced pressure, the vessel was thrice evacuated/argon-backfilled, and 300 μ L dry DMF was added by syringe. The vessel was placed to stir in a sand bath pre-heated to 90 °C for 2 h. The vessel was allowed to cool to room temperature. The reaction mixture was diluted with 300 μ L chloroform and admixed with ca. 0.5 g mol⁻¹ crushed ice. The organic layer was set aside and the aqueous layer extracted (3 $\times$ 300 μ L chloroform). Combined organic layers were washed (1 $\times$ 1 mL ice-cold water, 1 $\times$ 1 mL brine) and the dried over sodium sulfate. Solvent was removed under reduced pressure. Crude material was purified by flash chromatography (hexanes/DCM). Yellow solid, 30 mg (52%), R_f 0.21 to 0.03 (7:3, hexanes/ethyl acetate). **¹H NMR** (400 MHz, CDCl₃) δ (ppm) 6.98–6.53 (m, 8H), 6.53–6.13 (m, 8H), 4.38–4.05 (m, 8H), 3.88–3.47 (m, 3H), 2.71–2.36 (m, 6H), 2.36–2.26 (m, 8H), 2.24–2.07 (m, 8H), 1.39–1.27 (m, 48H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm) 149.7, 149.5, 148.4, 147.1, 146.7, 145.5, 143.4, 143.2, 142.6, 139.8, 139.6, 139.5, 139.2, 132.2, 129.0, 121.8, 112.7, 112.2, 110.6, 110.4, 109.6, 94.2, 64.4, 59.6, 59.2, 59.0, 57.2, 43.7, 43.5, 43.4, 36.4, 32.1, 31.8, 31.5, 30.4, 30.1, 29.8, 29.5, 22.8, 14.3, 13.4, 11.0. **MALDI-TOF** [C₁₁₇H₉₇N₇O₁₈S + Na]⁺ calculated 1942.65, found (m/z) 1942.63.

5.7.1.4 Hydrodehalogenation Procedures

Solvents were used as received and not dried prior to use.

General Procedure 5A: Optimization of hydrodehalogenation.

Except where otherwise noted, optimization reactions were conducted as follows. Solid reaction components were added to a spin-vane-equipped 10x75-mm borosilicate test tube that was then fitted with a 14/20 rubber septum. The septum was wrapped with PTFE tape, and the vessel was thrice evacuated and argon backfilled. Liquid reaction components (including 1 equiv DMSO internal standard[§]) were then added by syringe; the solvent (which had been sparged with argon for at least 10 min) was added last. The septum punctures were covered with electrical tape and the reaction vessel was placed in the photoreactor to stir under blue LED irradiation at 37 °C. Samples for ¹H NMR monitoring of reaction progress were prepared by transferring a 20 µL reaction mixture aliquot into an empty NMR tube, quickly followed by the addition of 400 µL deuterated chloroform and capping of the tube.

General Procedure 5B: Hydrodehalogenation with MPC-1-1.

The halide (1 equiv, 0.25 mmol) was added according to its phase at room temperature. Solid reaction components—**MPC-1-1** (1 mol%), **HE** (1.5 equiv, 0.375 mmol), and halide (if solid)—were added to a spin-vane-equipped 10x75-mm borosilicate test tube that was then inserted into the narrow opening of a 14/20 rubber septum. The septum was wrapped with PTFE-tape, and the vessel was thrice evacuated/argon-backfilled. Halide (if liquid) and then 0.5 mL acetone (which had been sparged with argon for at least 10 min) were added by syringe. The septum punctures were covered with electrical tape, and the reaction vessel was placed in the photoreactor to stir under blue LED irradiation at 37 °C. Following reaction completion (as monitored by

[§]When DMSO was used as the solvent, acetonitrile was used as the internal standard.

TLC or GCMS), the solvent was removed under reduced pressure, 0.5 mL deionized water was added, and the mixture was extracted with ethyl acetate (3×0.5 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resultant crude residue was purified by flash chromatography.

General Procedure 5C: Extended hydrodehalogenation with MPC-1-1 for difficult substrates with higher dilution and portionwise addition of reductant.

This method was employed for substrates that did not approach full conversion after 96 h with General Procedure 5B. The halide (1 equiv, 0.25 mmol) was added according to its phase at room temperature. Solid reaction components—**MPC-1-1** (2 mol%), the first portion of **HE** (1.5 equiv, 0.375 mmol), and halide (if solid)—were added to a spin-vane-equipped 10x75-mm borosilicate test tube that was then inserted into the narrow opening of a 14/20 rubber septum. The septum was wrapped with PTFE tape, and the vessel was thrice evacuated/argon-backfilled. Halide (if liquid) and then 1 mL acetone (which had been sparged with argon for at least 10 min) were added by syringe. The septum punctures were covered with electrical tape, the solvent level was marked on the outside of the vessel, and the vessel was placed in the photoreactor to stir under blue LED irradiation at 37 °C. Every 24 h, the reaction was monitored by TLC and GCMS, the solvent was replenished with sparged acetone to a slightly greater level than that of the initial volume, and the reaction mixture was directly sparged for several minutes. Following GCMS analysis at 72 h and prior to replenishing the solvent level, an additional 1 equiv **HE** was added under an argon cone, and the vessel was resealed and returned to the photoreactor. Workup and isolation were conducted as presented in General Procedure 5B.

General Procedure 5D: Enhanced dehalogenation with MPC-1-2, higher

dilution, and DMSO.

The halide (1 equiv, 0.25 mmol), **MPC-1-2_{LMW}** (1 mol%), and **HE** (3 equiv, 0.75 mmol) were added to a spin-vane-equipped 10x75-mm borosilicate test tube that was then inserted into the narrow opening of a 14/20 rubber septum. The septum was wrapped with PTFE tape, and the vessel was thrice evacuated/argon-backfilled. A 1 mL volume of DMSO (which had been sparged with argon for at least 10 min) was added by syringe. The septum punctures were covered with electrical tape, and the reaction vessel was placed in the photoreactor to stir under blue LED irradiation at 37 °C. The reaction was monitored for completion by TLC. Following reaction completion, the reaction mixture was transferred to a 16x100-mm test tube, 1 mL ice-cold deionized water was added, and the mixture was extracted with ethyl acetate (3x1 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resultant crude residue was purified by flash chromatography.

Procedure 5.14: Gram-scale hydrodehalogenation.

Halide **22b** (1 equiv, 5.0 mmol, 1176 mg), **MPC-1-1** (0.2 mol%, 15 mg), and the first portion of **HE** (1.1 equiv, 5.5 mmol, 1436 mg), were added to a stir-bar-equipped 25 mL round-bottom flask which was then fitted with a rubber septum. The septum was wrapped with PTFE tape, and the vessel was thrice evacuated/argon-backfilled. A 10 mL volume of acetone (which had been sparged with argon for 10 min) was added by syringe. The septum punctures were covered with electrical tape, and the reaction vessel was placed in the photoreactor to stir under blue LED irradiation at 37 °C. Reaction monitoring at 15 h by ¹H NMR showed ca. 60 % conversion to product **23b** and also indicated that the first **HE** portion had been exhausted. At 16 h, the second portion of **HE** (0.9 equiv, 4.5 mmol, 1175 mg) was added while briefly opening the vessel under an argon cone. At 24 h, the vessel was removed from the photoreactor and acetone was removed under reduced pressure. Extractions were conducted by admixing

ethyl acetate to solubilize the polymeric residue and then admixing a 9–14 times larger volume of hexanes to reform the polymeric phase. Supernatant organic layers were combined, solvent was removed under reduced pressure, and the crude reaction mixture was purified by flash chromatography (ethyl acetate/hexanes), affording product **23b** in 99 % isolated yield (936 mg clear faintly yellow oil), as confirmed by ^1H NMR.

Procedure 5.15: Benchmarking studies.

Reaction vessels were prepared using halide **22b** according to Procedure 5B (except with different catalysts) unless otherwise noted. The molecular weight for **MPC-1** preparations was approximated as 1529 g mol^{-1} , based on the constitutional unit of an ideal regular polymerization; this constitutional unit contained three chromophores (two terephthalonitrile units and one sulfone unit). The loading for other catalysts was adjusted so as to keep the number of active units constant. Accordingly, the catalyst loading was 3 mol% with respect to active catalytic units. After stirring for 2 h under blue LED irradiation, mesitylene was added by microsyringe, and the reaction mixture was agitated to uniformly incorporate the internal standard. A 20 μL aliquot was then withdrawn by syringe and transferred to an empty NMR tube, quickly followed by the addition of 400 μL deuterated chloroform and capping of the tube. A combined set of benchmarking results is presented in Table 5.17.

5.7.1.5 Recycle and Backside Irradiation Study Procedures

Procedure 5.16: Batch recycle study with MPC-1-1.

A recycle study with oligomeric **MPC-1-1** was conducted using halide **22b** and Procedure 5B for the zeroth cycle. Each recycle, additional halide **22b** (59 mg, 0.25 mmol) and reductant **HE** (98 mg, 0.38 mmol, 1.5 equiv) were added to the recovered **MPC-1-1** catalyst (3.8 mg, 1 mol%, approximated as 1529 g mol^{-1}) originating from the zeroth cycle; the reaction vessel was sealed, thrice evacuated/argon-backfilled,

and then filled with 0.5 mL argon-sparged acetone before being subjected to 6 h of irradiation by blue LEDs. Use of acetone and **HE** sacrificial reductant resulted in an initially turbid reaction mixture, which became clear as the reaction neared completion. The catalyst was recovered for reuse by precipitation during workup. The workup process involved: (a) removal of acetone under reduced pressure; (b) addition of 0.2 mL ethyl acetate; (c) redissolution of the crude mixture under stirring; (d) addition of 2.8 mL hexanes; (e) precipitation of the polymer under stirring; (f) consolidation of the polymer by centrifugation; and (g) collection of the supernatant extract. Three extractions were conducted per workup. Following workup, the combined organic layers for a particular run had the solvent removed under reduced pressure and the crude residue was purified by flash chromatography. The solubility properties of **MPC-1-1** precluded its recovery using the technique employed for **MPC-1-2_{LMW}**.

Procedure 5.17: Batch recycle study with MPC-1-2.

The recycle study with polymeric **MPC-1-2_{LMW}** was conducted using halide **22b** and Procedure 5B (except that the catalyst and workup were changed) for the zeroth cycle. Each recycle: additional halide **22b** (1 equiv, 0.25 mmol) and **HE** (1.5 equiv, 0.375 mmol) were added to the recovered **MPC-1-2_{LMW}** catalyst (1 mol%, 3.8 mg) originating from the zeroth cycle; the reaction vessel was septum/PTFE-tape-sealed, thrice evacuated/argon-backfilled, and then filled with 0.5 mL argon-sparged acetone; the punctures were sealed with electrical tape, and the reaction vessel was placed in the photoreactor to stir under blue LED irradiation at 37 °C. For each cycle: after 3 h in the photoreactor, the vessel was removed from irradiation and its contents were diluted with 0.5 mL methanol; the resultant suspension was then passed through a fritted glass funnel, rinsing with additional methanol; the recovered solid catalyst was returned to the reaction vessel; the filtrate solvent was removed under reduced pressure, and the resultant crude residue was purified by flash chromatography (ethyl acetate/hexanes) to provide product **23b** as a clear slightly yellow oil. Product purity

was confirmed by ^1H NMR. The catalyst was typically returned to the reaction vessel by passing it through the frit with DCM which was subsequently removed under reduced pressure, but after the third recycle the catalyst was returned to the reaction vessel as a solid using a spatula, and no deterioration in activity was observed.

Procedure 5.18: Flow reactor study.

The setup for the flow reactor is pictured in Figures 5.13 and 5.16. **MPC-1-2_{HMW}** (2.5 mol%, 26.5 mg) was dissolved in a minimal volume of DCM and transferred into a glass flow cell. Keeping the path through the cell parallel to the ground, the cell was rotated so as to coat the walls as the DCM evaporated. Small portions of DCM were added to the cell to reapply any portions of the film which formed without adhering to the glass. Once the catalyst was evenly coated on the flow cell walls, the vessel was subjected to rotary evaporation and then high vacuum for 2 h. Halide **22b** (1 equiv, 0.700 mmol) was placed in a conical microwave vial, and **HE** (1.5 equiv, 1.05 mmol) was added to the **MPC-1-2_{HMW}**-coated flow cell. The microwave vial was fitted with a septum that had been punctured to allow two pieces of PTFE tubing to be threaded into the vessel. The other two ends of PTFE tubing pieces were connected to the flow cell, and the entire apparatus was thrice evacuated/argon-backfilled before adding 3.5 mL of argon-sparged acetonitrile to the microwave vial reservoir and placing an argon balloon needle into its septum. The reservoir was swirled until the halide completely dissolved, and then one of the pieces of PTFE tubing was attached to a peristaltic pump near the photoreactor. The reactor cell was suspended in the photoreactor horizontally so as to allow the bed of **HE** to sit evenly across the bottom of the flow cell. Within the microwave vial, one piece of PTFE tubing was inserted all the way to the bottom of the solution while the other was kept close to the top of the vessel. The microwave vial was covered with aluminum foil to exclude the possibility of irradiation of the reservoir having any impact on the reaction. Peristaltic pumping was initiated, and the reaction was monitored by GCMS. After 26 h, the reaction

was stopped, and the flow loop was drained by lifting the PTFE tubing above the reservoir liquid level. The flow loop was subsequently rinsed with 2.0 mL acetonitrile. The solvent in the reservoir was removed under reduced pressure and the product was isolated by flash chromatography in 83 % yield, as confirmed by NMR.

Figure 5.16: Experimental setup for flow reaction. **(a)** Top view of flow cell in under irradiation attached to the reservoir by PTFE tubing. Tubing at the top of the picture goes to the peristaltic pump. An argon balloon needle is attached to the reservoir. **(b)** Side view of the reservoir with the protective foil covering removed.

Procedure 5.19: Charcoal occlusion study.

Four 10x75-mm borosilicate test tubes were etched with a diamond Dremel bit so that etches were not more than ca. 1 mm apart and covered at least the bottom 25 mm of the tubes. Catalyst was delivered to all tubes as equal volumes of DCM-dissolved **MPC-1-2_{HMW}**. Two of the vessels were designated to use the catalyst as a coating, and for these vessels the DCM was removed by evaporation, then a minimal amount of

DCM was added to spin coat the catalyst such that it covered the bottom 25 mm of the tubes; after spin coating, these vessels were subjected to rotary evaporation and high vacuum, and then two 0.5 mL hexanes rinses were added and removed under reduced pressure. The other two vessels were designated to use the catalyst as a suspension, and for these vessels 0.5 mL hexanes was added to the DCM to precipitate the polymer, and then the solvent was removed by rotary evaporation; an additional 0.5 mL hexanes was added and the polymer precipitate was triturated before removing the hexanes by rotary evaporation. All four vessels were then subjected to high vacuum for 2 h. To each vessel was added a spin vane (pointed end up), halide **22b** (1 equiv, 0.2 mmol), and Hantzsch ester (1.5 equiv, 0.3 mmol). For one vessel using the catalyst as a coating and one vessel using the catalyst as a suspension, 4 mg activated charcoal was added. Vessels were then septum-sealed, thrice evacuated/argon-backfilled, and then filled with 1 mL acetonitrile (which had been sparged with argon for 1 h). Punctures were covered with electrical tape and septa were wrapped with PTFE tape before placing the vessels in the photoreactor, and the stir plate was adjusted to stir just fast enough for the charcoal to be evenly dispersed throughout the reaction vessels. Reactions were periodically monitored by NMR analysis of 20 μ L aliquots. Immediately prior to the first monitoring, mesitylene internal standard was admixed. Tabulated results are provided in Table 5.18.

5.7.2 Ideality of MPC-1 Preparations

The ideality of the different **MPC-1** preparations was first assessed using NMR and GPC. A comparison of ^1H NMR data is provided in Figure 5.17 and analysis of the **MPC-1-2** spectrum is presented in Figure 5.6. GPC results are summarized in Table 5.3. **MPC-1-0** was not fully soluble in chloroform, so its NMR spectra may not be representative of the entire sample, and it was not fully soluble in tetrahydrofuran, so

it was not subjected to GPC analysis. These properties most likely arose from cross-linking that was only possible with the method used for **MPC-1-0**, wherein monomer **26** was formed in the same pot as the subsequent polymerization (examples of possible impurities and defects are presented in Figure 5.18). The ^1H NMR was similar to that of the more ideal **MPC-1-2**, but monomer **26** was significantly under-incorporated in **MPC-1-0** on the basis of the *N*-methyl peak integration (ratio for monomer units **25** and **26** is 3:0.18 on this basis, as compared to an ideal ratio of 3:1), and small peaks were uniquely observed near 3.00 ppm. The low incorporation of **26** suggests incomplete sulfonylation of pentafluorobenzonitrile. The unique peaks are potentially attributable to the formation of structural irregularities (although the sharper peaks in this area are likely from trace solvent impurities). Accordingly, **MPC-1-0** was only used during the most preliminary proof-of-concept stage of the project and was quickly superseded with the other **MPC-1** preparations that were more amenable to characterization.

Based on ^1H NMR, **MPC-1-1** appeared to over-incorporate **26**. The ratio of **25:26** is 3:1.78 on the basis of the aryl protons of incorporated **25** versus the aryl methyl protons of incorporated **26** (the *N*-methyl peak region likely overestimates the abundance of the sulfone due to residual traces of surfactant). A rough end-group analysis using the phenolic peak area between 5.00 and 6.15 ppm is possible, but it must be noted that any branching defects arising from hydroxide substitution of **24** or **26** would lead to overestimation of the end-group abundance while chain cyclization could lead to underestimation of end-group abundance. Based on the integration, the ratio of **25** to complete sets of four terminal hydroxyl groups is 1:0.83. Thus, a full set of four terminal hydroxyl groups are present for every 4.82 monomer units of **25**. Rounding to the nearest whole number gives 5 monomer units of **25** in the typical chain, which accommodates 4–7 units of either **24** or **26**. This estimate is consistent with the estimates derived from GPC. The ^1H NMR integrations for **MPC-1-2** were

nearly ideal, and peak locations were consistent with the spectrum for polymer subunit model **28e**. Multiple signals for the methyl peaks of the pyrazole moiety presumably arise from isomeric environments (see Figure 5.19). As noted in the main text, **26** was over-incorporated in **MPC-1-2_{LMW}** and under-incorporated in **MPC-1-2_{HMW}**. GPC results suggest that **MPC-1-2** and its fractionations predominantly consisted of long chains but also contained a small oligomeric component.

Figure 5.17: ^1H NMR comparison of all **MPC-1** preparations and model ideal constitutional unit **28e**.

5.7.3 Supplementary Polymer Characterization Data

5.7.3.1 Cyclic voltammetry

Cyclic voltammetry measurements were conducted with a Gamry Interface 1000 potentiostat using a glassy carbon working electrode (0.071 cm^2 surface area), a platinum wire counter electrode, and a silver wire pseudo-reference electrode. Prior

Figure 5.18: Example hypothetical impurities and defects uniquely arising in **MPC-1-0**

Figure 5.19: Example possible isomers of single sulfone subunit model **28a**

to use, the working electrode was polished with aqueous alumina slurry, and both the working and counter electrodes were cleaned by washing sequentially with water, ethanol, acetone, and dichloromethane and then sonicating in dichloromethane for 15 min. A three-neck electrochemical cell was washed and oven-dried prior to use. Measurements were taken at a scan rate of 200 mV s^{-1} under a nitrogen atmosphere using a 25 mL volume of 0.1 M *n*-Bu₄NPF₆ in dichloromethane. Potentials were referenced to ferrocene and adjusted to be presented relative to SCE by adding 0.380 V. In the presence of the supporting electrolyte, **MPC-1-2** exhibited limited solubility. Voltammograms were obtained for the solvent blank, and after each sequential addition of **MPC-1-2**, ferrocene, halide **22b**, and Hantzsch ester to the electrochemical cell (Figure 5.20).

Figure 5.20: Voltammograms of MPC-1-2 referenced to ferrocene and with additives. **a** Referenced to ferrocene. **b** With the addition of halide **22b**. **c** With the addition of **HE**.

5.7.3.2 Supplemental Spectroscopy

Figure 5.21: Overlapping **MPC-1-0** absorption and blue LED emission spectra indicating the suitability of the selected irradiation source. Steady-state absorption was measured on a Cary Bio 50 UV-Vis spectrometer (Agilent Technologies) with a quartz cuvette in chloroform using the chloroform-soluble component of **MPC-1-0** which passed through a cotton plug. Blue LED emission was measured by routing the LED light into an LS 55 fluorescence spectrometer (PerkinElmer).

Figure 5.22: FTIR of polymer preparations and constituent monomers.

5.7.3.3 Gravimetric Analysis

Figure 5.23: TGA and DSC for MPC-1-1 and MPC-1-2.

5.7.4 Supplementary Hydrodehalogenation Optimization and Results

Figure 5.24: Photoreactor setup for parallel batch reactions. Reaction vessels were suspended above the stir plates by an elastic cord. The reactor was equipped with a thermometer which confirmed that the temperature with the heat from the lights and stir plates was consistently 37 °C.

5.7.4.1 Hydrodehalogenation Control Reactions

Table 5.8: Hydrodehalogenation control experiments.^a

Entry	Variation	% Yield ^b
	1	no catalyst	0
	2	no reductant	0
	3	no light ^c	0
	4	no catalyst, no light ^c	0
	5	no catalyst, no reductant	0

^a Reaction vessels were prepared according to General Procedure 5B, except with the indicated omissions. After stirring for 2 h under blue LED irradiation, mesitylene (0.25 equiv, 0.125 mmol, 17.5 μ L) was added by microsyringe and the reaction mixture was agitated to uniformly incorporate the internal standard. A 20 μ L aliquot was then withdrawn by syringe and transferred to an empty NMR tube, quickly followed by the addition of 400 μ L deuterated chloroform and capping of the tube. ^b Determined by ¹H NMR. ^c For the omission of light, the vessel was wrapped with aluminum foil, and the NMR tube was also covered with foil until just before adding to the instrument to minimize the influence of ambient light.

5.7.4.2 Extended Hydrodehalogenation Optimization

Table 5.9: Optimization of catalyst loading.^a

Entry	mol% MPC-1-0	¹ H NMR % Yield ^b at				
		1 h	2 h	3 h	4 h	5 h
1	0.1	39	46	66	81	89
2	1	47	71	92	98	100
3	2	59	91	100	100	100
4	4	62	91	97	100	100

^a Conducted according to General Procedure 5A except as otherwise noted. Screening of catalyst loading was performed with a different photoreactor setup than the subsequent optimizations; the employed setup provided a lower temperature and less irradiation. Optimization of catalyst loading revealed that the best conversion was obtained with 2 mol% **MPC-1-0**. A 4 mol% loading showed no improvement and was actually slightly less effective. Because a 1 mol% loading was nearly as competent while also being twice as economical, this loading was used in subsequent optimization. ^b Determined by ¹H NMR.

Table 5.10: Optimization of *i*-Pr₂NEt loading.^a

Entry	equiv <i>i</i> -Pr ₂ NEt	% Yield ^b
1	0.0	0
2	0.5	27
3	1.0	44
4	2.0	55
5	4.0	44

^a Conducted according to General Procedure 5A except as otherwise noted. A 2 equiv loading of reductant was observed to be optimal, but 1 equiv was competent for the purposes of screening and was used in subsequent optimizations. Part of the reasoning behind this decision is that preliminary isolated yields and GCMS data suggested that using *i*-Pr₂NEt as reductant led to side product formation. The decrease in efficacy at 4 equiv was perhaps attributable to a change in polymer solubility, dilution, or increased side product formation. The control case wherein no reductant was used confirmed that it was required. ^b Determined by ¹H NMR.

Table 5.11: Optimization of light source.^a

Entry	Light Source	% Yield ^b
	1	dark ^{c,d}	20
	2	9 W CFL ^e	22
	3	38 W white LED ^e	29
	4	48 W blue LED	44

^a Conducted according to General Procedure 5A except as otherwise noted.

^b Determined by ¹H NMR. ^c The reaction vessel was protected from light by an aluminum foil covering and allowed to sit in the photoreactor next to the other reactions. ^d A second aliquot taken at 7 h showed 24% conversion. ^e Reaction temperature was maintained with an oil bath.

Table 5.12: Optimization of atmosphere.^a

Entry	Atmosphere	% Yield ^b
	1	oxygen	22
	2	air	23
	3	argon	44

^a Conducted according to General Procedure 5A except as otherwise noted.

^b Determined by ¹H NMR.

Table 5.13: Optimization of reaction medium.^a

Entry	Solvent	% Yield ^b
	1	2-methyltetrahydrofuran	5
	2	1,4-dioxane	14
	3	acetone	15
	4	dimethyl sulfoxide	45
	5	<i>N,N</i> -dimethylformamide	23
	6	<i>N,N</i> -dimethylacetamide	33
	7	chloroform	14
	8	acetonitrile	23
	9	3 wt% aq. PS-750-M	57 ^c
	10	3 wt% aq. TPGS-750-M	82 ^c
	11	3 wt% aq. SDS	32 ^c
	12	water	41 ^c
	13	NMP	44

^a Conducted according to General Procedure 5A except as otherwise noted. ^b Determined by ¹H NMR. ^c Reaction suffered from clumping of reactants and/or solution turbidity; aliquots were consequently not representative of the total reaction mixture; extraction and analysis of the representative entry 10 reaction at 15 h confirmed that turbidity and clumping prevented the reaction from going to completion.

Table 5.14: Optimization of conditions with Hantzsch ester.^a

Entry	equiv HE	% Yield ^b
	1	0.5	38
	2	1.0	78
	3	2.0	72

^a Conducted according to General Procedure 5A except as otherwise noted. Reactions were conducted in acetonitrile, a less toxic solvent that allowed enough time for reproducible comparison of conversions. The reaction was fastest with 1 equiv reductant (probably due to excess turbidity from undissolved **HE** blocking transmittance). When only 0.5 equiv **HE** was used, all reductant was observed to have been exhausted with only achieving 38 % conversion. A loading of 1.5 equiv instead of 2.0 equiv was selected for further study as a compromise between reaction rate and sufficient stoichiometric excess to ensure reactions went to completion. ^b Determined by ¹H NMR.

Table 5.15: Comparison of different polymer preparations with bromide substrate **22a**.^a

Entry	Catalyst	Time in h	% Yield ^b
	1	MPC-1-0	3	92
	2	MPC-1-1	3	86
	3	MPC-1-2_{LMW} ^c	1	94

^a Conducted according to General Procedure 5B except as otherwise noted. ^b Isolated yield.

^c The polymer used in this reaction had been recovered after six reaction cycles in the recycle study.

Table 5.16: Assessment of optimization with chloride substrate **22b**.^a

Entry	Catalyst	mol% Catalyst	M 22b Concentration	Atmosphere	% Yield ^b
1	MPC-1-1	0.1	0.50	argon	2
2	MPC-1-1	1.0	0.50	argon	9
3	MPC-1-1	2.0	0.50	argon	12
4	MPC-1-1	4.0	0.50	argon	6
5	MPC-1-1	1.0	0.25	argon	19
6	MPC-1-1	1.0	0.50	air	0
7	MPC-1-2	1.0	0.50	argon	69

^a Conducted according to Procedure 5.15 except as otherwise noted. ^b Determined by ¹H NMR.

5.7.4.3 Extended benchmarking results

Table 5.17: Benchmarking of catalytic activity.^a

Entry	Catalyst	mol% Catalyst	Solvent	% Yield ^b
1	MPC-1-1	1	acetone	9
2	MPC-1-2^c	1	acetone	44
3	MPC-1-2	1	acetone	69
4	MPC-1-2_{LMW}	1	chloroform	71
5	MPC-1-2	1	chloroform	70
6	MPC-1-2_{HMW}	1	chloroform	67
7	PTH	3	acetone	13
8	PDI	3	acetone	9
9	rhodamine B	3	acetone	8
10	fluorescein	3	acetone	6
11	eosin Y, 2 Na ⁺	3	acetone	5
12	fluorenone	3	acetone	1
13	28a	3	acetone	27
14	28b	3	acetone	99
15	28c	1.5	acetone	97
16	28d	1	acetone	84
17	28e	1	acetone	100
18	28a, 28b	1, 2	acetone	93

^a Conducted according to Procedure 5.15 except as otherwise noted.

^b Determined by ¹H NMR. ^c **MPC-1-2** was used as moderately large pieces rather than as a fine powder.

5.7.4.4 Tabulated charcoal occlusion results

Table 5.18: Tabulated charcoal occlusion results.^a

Reaction scheme showing the conversion of 2,4-dichlorobenzaldehyde (22b) to 2,4-dichlorobenzaldehyde (23b) under the following conditions: $h\nu$ (blue LED), MPC-1-2_{HMW} (1 mol%), HE (1.5 equiv), additive (4 mg), acetonitrile (0.2 M, Ar-sparged), etched 3 mL test tube, Ar atm, 37 °C.

Entry	Time in h	Catalyst Form	Additive	30a Area ^b	23b Area ^b	% Yield vs. 22b	% Yield vs. MesH
1	2	coating	—	0.389	0.606	60.9	60.6
2	2	suspension	—	0.692	0.258	27.2	25.8
3	2	coating	charcoal	0.653	0.325	33.2	32.5
4	2	suspension	charcoal	0.786	0.162	17.1	16.2
5	4	coating	—	0.063	0.960	93.8	96.0
6	4	suspension	—	0.635	0.373	37.0	37.3
7	4	coating	charcoal	0.356	0.650	64.6	65.0
8	4	suspension	charcoal	0.719	0.258	26.4	25.8
9	6	coating	—	0.039	0.909	95.9	90.9
10	6	suspension	—	0.500	0.474	48.7	47.4
11	6	coating	charcoal	0.190	0.809	81.0	80.9
12	6	suspension	charcoal	0.690	0.300	30.3	30.0
13	8	coating	—	0.049	0.953	95.1	95.3
14	8	suspension	—	0.247	0.734	74.8	73.4
15	8	coating	charcoal	0.155	0.869	84.9	86.9
16	8	suspension	charcoal	0.565	0.389	40.8	38.9

^a Conducted according to Procedure 5.19.

^b Values are scaled such that the mesitylene peak to 6.79 ppm integrates to 1.

5.7.5 Estimation of the Number of Chromophore Units in Chains of Various MPC-1 Preparations

A simplistic estimation of the number of chromophore units in typical chains of various **MPC-1** preparations was made by tabulating the molecular weights for polymer chains of various lengths and compositions and comparing them with the molecular weights obtained by GPC. For each GPC molecular weight, the nearest lesser and greater molecular weight values of particular chain compositions are provided along with the corresponding number of chromophores (monomeric units of **24** and **26** are considered to be chromophores). The compositions involve different ratios of the different fragments, **m1**, **m2**, and **m3** (originating from monomers **24**, **25**, and **26**, respectively) (Figure 5.25. The ratio of (**m1**+**m3**):**m2** is 1:1 when the number of monomer units is even; in this case the chain terminates on one end with a chromophore and on the other end with an **m2** fragment. When the number of monomer units is odd, it is possible for the chain to terminate with either two chromophores or two **m2** fragments. Compositions with chains ending in two chromophores are described here as “disfavoring **m2**,” and compositions with chains ending in two **m2** fragments are described as “favoring **m2**.” Calculated molecular weight values and chromophore counts for various compositions are provided in Tables 5.19–5.29).

Figure 5.25: Fragments of MPC-1 used in estimating chain length.

Using this approach for **MPC-1-1**, the number of chromophore units for a typical chain is assumed to be between 4 and 9 on the basis of the GPC M_n values estimated by

the polystyrene (PS) and poly(methyl methacrylate) (PMMA) calibration standards (Tables 5.19–5.21). If it is assumed that the monomeric composition matched the feed ratio (**m1:m3** of 2:1), the typical number of chromophores is estimated to be 7–8 (PS standard) or 4–5 (PMMA standard) (Table 5.19). For **MPC-1-1**, the same ranges are obtained when using the ratio estimated by ^1H NMR integrations (**m1:m3** of 13:19, see Section 5.7.2) (5.21). Based on the ratios estimated by ^1H NMR (see Section 5.7.2), the typical chromophore counts for **MPC-1-2_{LMW}**, **MPC-1-2**, and **MPC-1-2_{HMW}** are estimated to be 73–74, 103–104, and 237–238, respectively (PS standard), or 47–48, 67–68, and 154–155, respectively (PMMA standard).

Table 5.19: Chromophore count estimation for **MPC-1-1** GPC values assuming ideal 2:1 **m1:m3** ratio.

		m1:m3 = 2:1, Favor m2				m1:m3 = 1:2, Disfavor m2			
GPC Values		Nearest Lesser Mass		Nearest Greater Mass		Nearest Lesser Mass		Nearest Greater Mass	
M_x	Standard	Da	Count	Da	Count	Da	Count	Da	Count
M_n	PS	4,047	7	4,157	8	3,853	8	4,157	8
	PMMA	2,540	4	2,629	5	2,324	5	2,629	5
M_w	PS	4,777	9	4,922	9	4,774	10	5,078	10
	PMMA	2,925	5	2,933	5	2,785	6	3,089	6
M_z	PS	5,896	11	5,991	11	5,842	12	6,147	12
	PMMA	3,471	6	3,550	7	3,245	7	3,550	7

Table 5.20: Chromophore count estimation for **MPC-1-1** GPC values assuming incorporation of only one monomer.

		m1:m3 = 0:1, Favor m2				m1:m3 = 1:0, Disfavor m2			
GPC Values		Nearest Lesser Mass		Nearest Greater Mass		Nearest Lesser Mass		Nearest Greater Mass	
M_x	Standard	Da	Count	Da	Count	Da	Count	Da	Count
M_n	PS	4,047	6	4,286	7	3,872	9	4,176	9
	PMMA	2,540	4	2,767	4	2,491	6	2,795	6
M_w	PS	4,777	7	4,893	8	4,637	10	4,793	11
	PMMA	2,925	4	3,070	5	2,795	6	2,951	7
M_z	PS	5,896	9	6,109	10	5,714	13	6,018	13
	PMMA	3,471	5	3,678	6	3,412	8	3,716	8

Table 5.21: Chromophore count estimation for **MPC-1-1** GPC values assuming **m1:m3** ratio based on ^1H NMR.

		m1:m3 = 13:19, Favor m2				m1:m3 = 19:13, Disfavor m2			
GPC Values		Nearest Lesser Mass		Nearest Greater Mass		Nearest Lesser Mass		Nearest Greater Mass	
M_x	Standard	Da	Count	Da	Count	Da	Count	Da	Count
M_n	PS	4,047	7	4,149	7	3,844	7	4,147	8
	PMMA	2,540	4	2,776	5	2,472	5	2,776	5
M_w	PS	4,777	8	4,912	9	4,608	9	4,912	9
	PMMA	2,925	5	3,080	5	2,776	5	3,079	6
M_z	PS	5,896	10	6,128	11	5,823	11	6,128	11
	PMMA	3,471	6	3,688	6	3,384	6	3,540	7

Table 5.22: Chromophore count estimation for **MPC-1-2_{LMW}** GPC values assuming ideal 2:1 **m1:m3** ratio.

		m1:m3 = 2:1, Favor m2				m1:m3 = 1:2, Disfavor m2			
GPC Values		Nearest Lesser Mass		Nearest Greater Mass		Nearest Lesser Mass		Nearest Greater Mass	
M_x	Standard	Da	Count	Da	Count	Da	Count	Da	Count
M_n	PS	37,790	74	38,092	74	37,788	74	37,944	75
	PMMA	24,450	47	24,491	48	24,334	48	24,491	48
M_w	PS	63,360	124	63,472	124	63,168	124	63,471	125
	PMMA	38,870	76	39,013	76	38,709	76	39,012	77
M_z	PS	102,300	200	102,296	201	102,296	201	102,452	201
	PMMA	58,450	114	58,425	115	58,425	115	58,582	115

Table 5.23: Chromophore count estimation for **MPC-1-2_{LMW}** GPC values assuming incorporation of only one monomer.

		m1:m3 = 0:1, Favor m2				m1:m3 = 1:0, Disfavor m2			
GPC Values		Nearest Lesser Mass		Nearest Greater Mass		Nearest Lesser Mass		Nearest Greater Mass	
M _x	Standard	Da	Count	Da	Count	Da	Count	Da	Count
M _n	PS	37,790	62	37,708	62	37,488	82	37,792	82
	PMMA	24,450	40	24,339	40	24,438	53	24,594	54
M _w	PS	63,360	104	63,231	104	63,275	138	63,580	138
	PMMA	38,870	63	38,620	64	38,869	85	39,174	85
M _z	PS	102,300	168	102,122	168	102,261	222	102,417	223
	PMMA	58,450	96	58,369	96	58,210	127	58,514	127

Table 5.24: Chromophore count estimation for **MPC-1-2_{LMW}** GPC values assuming **m1:m3** ratio based on ¹H NMR.

		m1:m3 = 13:8, Favor m2				m1:m3 = 8:13, Disfavor m2			
GPC Values		Nearest Lesser Mass		Nearest Greater Mass		Nearest Lesser Mass		Nearest Greater Mass	
M _x	Standard	Da	Count	Da	Count	Da	Count	Da	Count
M _n	PS	37,790	73	37,769	73	37,769	73	37,925	74
	PMMA	24,450	47	24,324	47	24,324	47	24,481	48
M _w	PS	63,360	122	63,287	123	63,286	123	63,590	123
	PMMA	38,870	75	38,837	75	38,837	75	38,993	76
M _z	PS	102,300	198	102,248	198	102,248	198	102,552	199
	PMMA	58,450	113	58,397	113	58,397	113	58,553	114

Table 5.25: Chromophore count estimation for **MPC-1-2** GPC values assuming ideal 2:1 **m1:m3** ratio.

		m1:m3 = 2:1, Favor m2				m1:m3 = 1:2, Disfavor m2			
GPC Values		Nearest Lesser Mass		Nearest Greater Mass		Nearest Lesser Mass		Nearest Greater Mass	
M_x	Standard	Da	Count	Da	Count	Da	Count	Da	Count
M_n	PS	52,990	103	52,771	104	52,770	104	53,075	104
	PMMA	34,150	67	34,123	67	34,123	67	34,426	68
M_w	PS	91,030	178	90,988	179	90,987	179	91,291	179
	PMMA	55,870	109	55,829	110	55,828	110	56,132	110
M_z	PS	156,300	306	156,260	307	156,111	307	156,416	307
	PMMA	88,930	174	88,694	174	88,850	175	89,155	175

Table 5.26: Chromophore count estimation for **MPC-1-2** GPC values assuming incorporation of only one monomer.

		m1:m3 = 0:1, Favor m2				m1:m3 = 1:0, Disfavor m2			
GPC Values		Nearest Lesser Mass		Nearest Greater Mass		Nearest Lesser Mass		Nearest Greater Mass	
M_x	Standard	Da	Count	Da	Count	Da	Count	Da	Count
M_n	PS	52,990	87	52,900	87	52,988	115	53,144	116
	PMMA	34,150	56	34,062	56	34,108	74	34,264	75
M_w	PS	91,030	149	90,881	150	90,905	198	91,209	198
	PMMA	55,870	91	55,635	92	55,751	121	55,907	122
M_z	PS	156,300	257	156,206	257	156,294	340	156,599	340
	PMMA	88,930	146	88,753	146	88,907	193	89,063	194

Table 5.27: Chromophore count estimation for **MPC-1-2_{HMW}** GPC values assuming ideal 2:1 **m1:m3** ratio.

			m1:m3 = 2:1, Favor m2				m1:m3 = 1:2, Disfavor m2			
GPC Values			Nearest Lesser Mass		Nearest Greater Mass		Nearest Lesser Mass		Nearest Greater Mass	
M _x	Standard	Da	Da	Count	Da	Count	Da	Count	Da	Count
M _n	PS	119,600	119,572	234	119,728	235	119,424	235	119,728	235
	PMMA	77,860	77,838	152	77,994	153	77,689	153	77,994	153
M _w	PS	157,400	157,328	308	157,484	309	157,180	309	157,484	309
	PMMA	96,610	96,338	189	96,642	189	96,494	190	96,798	190
M _z	PS	220,300	220,159	432	220,463	432	220,159	432	220,315	433
	PMMA	124,900	124,618	244	124,922	245	124,617	245	124,922	245

Table 5.28: Chromophore count estimation for **MPC-1-2_{HMW}** GPC values assuming incorporation of only one monomer.

			m1:m3 = 0:1, Favor m2				m1:m3 = 1:0, Disfavor m2			
GPC Values			Nearest Lesser Mass		Nearest Greater Mass		Nearest Lesser Mass		Nearest Greater Mass	
M _x	Standard	Da	Da	Count	Da	Count	Da	Count	Da	Count
M _n	PS	119,600	119,442	196	119,745	197	119,455	260	119,759	260
	PMMA	77,860	77,815	128	78,119	128	77,855	169	78,011	170
M _w	PS	157,400	157,118	258	157,421	259	157,215	342	157,520	342
	PMMA	96,610	96,350	158	96,653	159	96,431	210	96,735	210
M _z	PS	220,300	220,012	362	220,317	362	220,146	478	220,302	479
	PMMA	124,900	124,606	205	124,911	205	124,825	271	124,981	272

Table 5.29: Chromophore count estimation for **MPC-1-2_{HMW}** GPC values assuming **m1:m3** ratio based on ¹H NMR.

		m1:m3 = 12:5, Favor m2				m1:m3 = 5:12, Disfavor m2			
GPC Values		Nearest Lesser Mass		Nearest Greater Mass		Nearest Lesser Mass		Nearest Greater Mass	
M _x	Standard	Da	Da	Count	Da	Da	Count	Da	Count
M _n	PS	119,600	119,471	237	119,776	119,471	237	119,628	238
	PMMA	77,860	77,571	154	77,875	77,571	154	77,874	155
M _w	PS	157,400	157,246	312	157,551	157,246	312	157,402	313
	PMMA	96,610	96,533	191	96,689	96,384	192	96,689	192
M _z	PS	220,300	220,254	437	220,558	220,254	437	220,410	438
	PMMA	124,900	124,822	247	124,978	124,674	248	124,978	248

5.7.6 Characterization of Substrate Scope Compounds

1-(4-Bromophenyl)ethan-1-one (23a)¹²

From 2-bromo-1-(4-bromophenyl)ethan-1-one with Procedure A in 3 h: 43 mg (86 %). From 2-bromo-1-(4-bromophenyl)ethan-1-one with Procedure A (except that **MPC-1-0** was used instead of **MPC-1-1**) in 3 h: 46 mg (92 %). From 2-bromo-1-(4-bromophenyl)ethan-1-one with Procedure A (except that **MPC-1-2_{LMW}** which had already been recycled five times was used instead of **MPC-1-1**) in 1 h: 47 mg (94 %). White solid, R_f 0.27 (9:1, hexanes/ethyl acetate). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ (ppm) 7.82 (d, 2H, $J = 8.5$ Hz), 7.61 (d, 2H, $J = 9.0$ Hz), 2.59 (s, 3H).

1-(2,4-Dichlorophenyl)ethan-1-one (23b)¹³

From 2-chloro-1-(2,4-dichlorophenyl)ethan-1-one with Procedure A in 6 h: 45 mg (96 %). From 2-chloro-1-(2,4-dichlorophenyl)ethan-1-one with Procedure A (except that **MPC-1-2_{LMW}** which had been recycled twice, as a representative example, was used) in 3 h: 47 mg (99 %). From 2-bromo-1-(2,4-dichlorophenyl)ethan-1-one with Procedure A in 3 h: 39 mg (83 %). From 1-(2,4-dichlorophenyl)-2-iodoethan-1-one with Procedure A in 1 h: 38 mg (81 %). Clear light greenish yellow oil, R_f 0.24 (9:1, hexanes/ethyl acetate). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ (ppm) 7.54 (d, 1H, $J = 8.5$ Hz), 7.45 (s, 1H), 7.31 (d, 1H, $J = 8.0$ Hz), 2.64 (s, 3H).

1-(2-Fluoro-5-methoxyphenyl)ethan-1-one (23d)¹⁴

From 2-bromo-1-(2-fluoro-5-methoxyphenyl)ethan-1-one with Procedure A in 3 h: 39 mg (93 %). Clear faintly yellow oil, R_f 0.18 (9:1, hexanes/ethyl acetate). **¹H NMR** (400 MHz, CDCl₃) δ (ppm) 7.45 (dd, 1H, J = 9.2 Hz and 2.8 Hz), 7.16 (td, 1H, J = 8.0 Hz and 2.8 Hz), 6.92 (dd, 1H, J = 9.2 Hz and 2.8 Hz), 3.90 (s, 3H), 2.61 (s, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ (ppm) 198.5, 157.8, 155.6 (d, J = 73.1 Hz), 129.1 (d, J = 6.2 Hz), 120.1 (d, J = 23.1 Hz), 116.7 (d, J = 24.1 Hz), 113.1 (d, J = 7.7 Hz), 56.2, 31.9. **¹⁹F NMR** (376 MHz, CDCl₃) δ (ppm) -123.51 (td, 1F, J = 8.1 Hz and 4.1 Hz).

1-(4-Fluorophenyl)ethan-1-one (23e)¹⁵

From 2-chloro-1-(4-fluorophenyl)ethan-1-one with Procedure B in 96 h: 26 mg (75 %). Clear yellow oil, R_f 0.28 (9:1, hexanes/ethyl acetate). **¹H NMR** (500 MHz, CDCl₃) δ (ppm) 7.98 (dd, 2H, J = 8.5 Hz and 6.0 Hz), 7.13 (t, 2H, J = 8.5 Hz), 2.59 (s, 3H).

1-(3-Bromo-4-fluorophenyl)ethan-1-one (23f)¹⁶

From 2-bromo-1-(3-bromo-4-fluorophenyl)ethan-1-one with Procedure A in 3 h:

45 mg (83 %). White solid, R_f 0.20 (9:1, hexanes/ethyl acetate). **^1H NMR** (400 MHz, CDCl_3) δ (ppm) 8.18 (d, 1H, $J = 6.4$ Hz), 7.90 (td, 1H, $J = 6.4$ Hz and 2.4 Hz), 7.20 (t, 1H, $J = 8.0$ Hz). **^{13}C NMR** (126 MHz, CDCl_3) δ (ppm) 195.4, 163.2, 134.8, 134.4, 129.6 (d, $J = 8.7$ Hz), 116.8 (d, $J = 23.1$ Hz), 109.9 (d, 21.2 Hz), 26.6. **^{19}F NMR** (376 MHz, CDCl_3) δ (ppm) -99.63 (m, 1F).

1-(4-Bromophenyl)propan-1-one (23g)¹²

From 2-bromo-1-(4-bromophenyl)propan-1-one with Procedure A in 3 h: 50 mg (87 %). White solid, R_f 0.34 (9:1, hexanes/ethyl acetate). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 7.83 (d, 2H, $J = 8.0$ Hz), 7.60 (d, 2H, $J = 9.0$ Hz), 2.97 (q, 2H, $J = 7.0$ Hz), 1.22 (t, 3H, 7.0 Hz).

1,3-Diphenylpropane-1,3-dione (23h)¹⁷

From 2-bromo-1,3-diphenylpropane-1,3-dione with Procedure A in 5 h: 49 mg (94 %). White solid, R_f 0.41 (9:1, hexanes/ethyl acetate). **^1H NMR** (500 MHz, CDCl_3) δ (ppm) 16.88 (s, 1H), 8.00 (d, 4H, $J = 7.5$ Hz), 7.56 (t, 2H, 7.0 Hz), 7.50 (t, 4H, 8.0 Hz), 6.87 (s, 1H).

2-Methyl-1-phenylpropan-1-one (23i)¹⁸

From 2-bromo-2-methyl-1-phenylpropan-1-one with Procedure B in 96 h: 34 mg (92 %). Clear yellow oil. **¹H NMR** (500 MHz, CDCl₃) δ (ppm) 7.96 (d, 2H, J = 7.5 Hz), 7.55 (t, 1H, J = 7.0 Hz), 7.46 (t, 2H, J = 8.0 Hz), 3.56 (septet, 1H, J = 7.0 Hz), 1.22 (d, 6H, J = 65).

1-([1,1'-Biphenyl]-4-yl)ethan-1-one (23j)¹⁹

From 1-([1,1'-biphenyl]-4-yl)-2-bromoethan-1-one with Procedure A (except that **MPC-1-0** was used instead of **MPC-1-1**) in 3 h: 45 mg (92 %). White flaky solid, R_f 0.24 (9:1, hexanes/ethyl acetate). **¹H NMR** (400 MHz, CDCl₃) δ (ppm) 8.04 (d, 2H, J = 7.6 Hz), 7.69 (d, 2H, J = 8.0 Hz), 7.63 (d, 2H, J = 8.0 Hz), 7.48 (t, 2H, J = 7.6 Hz), 7.41 (t, 1H, J = 7.6 Hz), 2.64.

1-(4-Nitrophenyl)ethan-1-one (23k)²⁰

From 2-bromo-1-(4-nitrophenyl)ethan-1-one with Procedure A in 35 h: 29 mg (70 %). Pale yellow solid, R_f 0.33 (3:2, dichloromethane/hexanes). **¹H NMR** (500 MHz, CDCl₃) δ (ppm) 8.33 (d, 2H, J = 8.5 Hz), 8.12 (d, 2H, J = 8.5 Hz), 2.69 (s, 3H).

Acetophenone (23l)²¹

From 2,2-dibromo-1-phenylethan-1-one with Procedure A (modified to use 3 equiv Hantzsch ester) in 3 h: 30 mg (85 %). Light yellow oil, R_f 0.27 (9:1, hexanes/ethyl acetate). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.96 (d, 2H, $J = 7.2$ Hz), 7.56 (d, 2H, $J = 7.2$ Hz), 7.47 (t, 2H, $J = 7.2$ Hz), 2.62 (s, 3H).

(1*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one (23m)²²

From (1*R*,3*S*,4*S*)-3-bromo-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one with Procedure B in 96 h: 30 mg (79 %). Off-white solid, R_f 0.42 (9:1, hexanes/ethyl acetate). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ (ppm) 2.34 (dt, 1H, $J = 18.5$ Hz and 3.5 Hz), 2.07 (t, 1H, $J = 4.5$ Hz), 1.98 to 1.91 (m, 1H), 1.83 (d, 1H, $J = 18.0$ Hz), 1.42 to 1.30 (m, 2H), 0.95 (s, 3H), 0.90 (s, 3H), 0.82 (s, 3H).

1,3,4,5-Tetrahydro-2*H*-benzo[*b*]azepin-2-one (23c)²³

From 3-bromo-1,3,4,5-tetrahydro-2*H*-benzo[*b*]azepin-2-one with Procedure A in 70 h: 20 mg (50 %). From 3-bromo-1,3,4,5-tetrahydro-2*H*-benzo[*b*]azepin-2-one with Procedure C in 4 h: 40 mg (100 %). Yellow solid, R_f 0.23 (1:1, hexanes/ethyl acetate). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ (ppm) 7.83 (s, 1H), 7.25 to 7.22 (m, 2H), 7.13 (t, 1H, $J = 7.0$ Hz), 6.98 (d, 1H, $J = 7.5$ Hz), 2.81 (t, 2H, $J = 7.0$ Hz), 2.36 (t, 2H, $J = 7.5$ Hz), 2.24 (m, 2H).

Benzyl acetate (23n)²⁴

From benzyl 2-bromoacetate with Procedure A in 4 h: 33 mg (89 %). Faintly yellow oil, R_f 0.22 (9:1, hexanes/ethyl acetate). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.42 to 7.29 (m, 5H), 5.11 (s, 2H), 2.11 (s, 3H).

1-(Benzofuran-2-yl)ethan-1-one (23o)²⁵

From 1-(benzofuran-2-yl)-2-bromoethan-1-one with Procedure A in 4 h: 40 mg (100 %). Light yellow solid, R_f 0.32 (4:1, hexanes/ethyl acetate). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.71 (d, 1H, $J = 8.0$ Hz), 7.58 (d, 1H, $J = 8.0$ Hz), 7.50 (s, 1H), 7.48 (t, 1H, 7.6 Hz), 7.32 (t, 1H, $J = 6.8$ Hz).

(*E*)-2-Methyl-3-phenylacrylaldehyde (27)²⁶

From 2,3-dibromo-2-methyl-3-phenylpropanal with Procedure C in 3 h: 32 mg (88 %). Clear brown oil, R_f 0.24 (19:1, hexanes/ethyl acetate). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ (ppm) 9.60 (s, 1H), 7.53 (d, 2H, $J = 7.5$ Hz), 7.45 (t, 2H, $J = 7.5$ Hz), 7.40 (t, 1H, $J = 7.5$ Hz), 7.27 (s, 1H), 2.09 (s, 3H).

5.7.7 NMR Spectra

1-(4-Bromophenyl)ethan-1-one (23a) ^1H NMR

1-(2,4-Dichlorophenyl)ethan-1-one (23b) ^1H NMR

1-(2-Fluoro-5-methoxyphenyl)ethan-1-one (23d) ^1H NMR

1-(2-Fluoro-5-methoxyphenyl)ethan-1-one (23d) ^{13}C NMR

1-(2-Fluoro-5-methoxyphenyl)ethan-1-one (23d) ^{19}F NMR

1-(4-Fluorophenyl)ethan-1-one (23e) ^1H NMR

1-(3-Bromo-4-fluorophenyl)ethan-1-one (23f) ^1H NMR

1-(3-Bromo-4-fluorophenyl)ethan-1-one (23f) ^{13}C NMR

1-(3-Bromo-4-fluorophenyl)ethan-1-one (23f) ^{19}F NMR

1-(4-Bromophenyl)propan-1-one (23g) ^1H NMR

1,3-Diphenylpropane-1,3-dione (23h) ^1H NMR

2-Methyl-1-phenylpropan-1-one (23i) ^1H NMR

1-([1,1'-Biphenyl]-4-yl)ethan-1-one (23j) ^1H NMR

1-(4-Nitrophenyl)ethan-1-one (23k) ^1H NMR

Acetophenone (23l) ^1H NMR

Product exposure to vacuum minimized to prevent loss; yield adjusted to account for solvent impurities remaining in NMR.

(1*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one (23m) ^1H NMR

1,3,4,5-Tetrahydro-2*H*-benzo[*b*]azepin-2-one (23c) ¹H NMR

Benzyl acetate (23n) ¹H NMR

1-(Benzofuran-2-yl)ethan-1-one (23o) ^1H NMR

(*E*)-2-Methyl-3-phenylacrylaldehyde (27) ^1H NMR

REFERENCES

- (1) Romsted, L. S.; Bunton, C. A.; Yao, J. *Curr. Opin. Colloid Interface Sci.* **1997**, *2*, 622–628.
- (2) Twitchell, E. Process of Decomposing Fats or Oils into Fatty Acids and Glycerin US Patent, 601603A, 1898.
- (3) Sorella, G. L.; Strukul, G.; Scarso, A. *Green Chem.* **2015**, *17*, 644–683.
- (4) Handa, S.; Andersson, M. P.; Gallou, F.; Reilly, J.; Lipshutz, B. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 4914–4918.
- (5) Klumphu, P.; Lipshutz, B. H. *J. Org. Chem.* **2014**, *79*, 888–900.
- (6) Anastas, P. T. In *Benign by Design*, Anastas, P. T., Farris, C. A., Eds.; ACS Symposium Series, Vol. 577; American Chemical Society: Washington, DC, 1994, pp 2–22.
- (7) Handa, S.; Smith, J. D.; Zhang, Y.; Takale, B. S.; Gallou, F.; Lipshutz, B. H. *Org. Lett.* **2018**, *20*, 542–545.
- (8) Lipshutz, B. H. *J. Org. Chem.* **2017**, *82*, 2806–2816.
- (9) Dwars, T.; Paetzold, E.; Oehme, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 7174–7199.
- (10) Taşcioğlu, S. *Tetrahedron* **1996**, *52*, 11113–11152.
- (11) Bunton, C. A.; Savelli, G. In *Advances in Physical Organic Chemistry*, Gold, V., Bethell, D., Eds.; Academic Press: 1986; Vol. 22, pp 213–309.
- (12) Fendler, J.; Fendler, E. J., *Catalysis in Micellar and Macromolecular Systems*; Academic Press: 1975; 545 pp.
- (13) Cordes, E. H.; Dunlap, R. B. *Acc. Chem. Res.* **1969**, *2*, 329–337.
- (14) DUNLAP, R. B. Studies on Reaction Kinetics in Micellar Systems, Ph.D. United States – Indiana: Indiana University, 1968, 217 pp.
- (15) Barnebey, H. L.; Brown, A. C. *J Am Oil Chem Soc* **1948**, *25*, 95–99.
- (16) Chandler, C. F. *J. Ind. Eng. Chem.* **1917**, *9*, 193–194.
- (17) Twitchell, E. *J. Ind. Eng. Chem.* **1917**, *9*, 194–195.
- (18) Langmuir, A. C. *J. Ind. Eng. Chem.* **1917**, *9*, 195–196.
- (19) Ittner, M. H. *J. Ind. Eng. Chem.* **1917**, *9*, 196–197.

- (20) Schmidt, H. B. *J. Ind. Eng. Chem.* **1917**, *9*, 197–198.
- (21) Rosenfeld, A. In *The Collected Works of Irving Langmuir: With Contributions in Memoriam Including a Complete Bibliography of His Works*, Suits, C. G., Way, H. E., Eds.; Elsevier: 1962, pp 5–232.
- (22) Langmuir, I. *PNAS* **1917**, *3*, 251–257.
- (23) Hartley, G. S. *Trans. Faraday Soc.* **1934**, *30*, 444–450.
- (24) Hartley, G. S.; Roe, J. W. *Trans. Faraday Soc.* **1940**, *35*, 101–109.
- (25) Lorand, E. J. *Ind. Eng. Chem.* **1939**, *31*, 891–897.
- (26) Krebs, H. A. *Biochem. J.* **1948**, *43*, 51–57.
- (27) Hughes, D. E. *Biochem. J.* **1949**, *45*, 325–331.
- (28) Hughes, D. E. *Biochem. J.* **1950**, *46*, 231–236.
- (29) Mchedlov-Petrosyan, N. O.; Farafonov, V. S.; Lebed, A. V. *Journal of Molecular Liquids* **2018**, *264*, 683–690.
- (30) Neuberger, A. *Biochem J* **1936**, *30*, 2085–2094.
- (31) Bodine, J. H.; Carlson, L. D. *J. Cell. Comp. Physiol.* **1940**, *16*, 71–83.
- (32) Duynstee, E. F. J.; Grunwald, E. *J. Am. Chem. Soc.* **1959**, *81*, 4540–4542.
- (33) Bunton, C. A.; Romsted, L. S.; Savelli, G. *J. Am. Chem. Soc.* **1979**, *101*, 1253–1259.
- (34) Fendler, E. J.; Fendler, J. H. In *Advances in Physical Organic Chemistry*, Gold, V., Ed.; Academic Press: 1970; Vol. 8, pp 271–406.
- (35) Bunton, C. A. *Pure Appl. Chem.* **1977**, *49*, 969–979.
- (36) Brown, J. M.; Bunton, C. A. *J. Chem. Soc. Chem. Commun.* **1974**, 969–971.
- (37) Bunton, C. A.; Robinson, L.; Stam, M. F. *Tetrahedron Lett.* **1971**, *12*, 121–124.
- (38) Moss, R. A.; Sunshine, W. L. *J. Org. Chem.* **1974**, *39*, 1083–1089.
- (39) Breslow, R. In *Organic Reactions in Water*; John Wiley & Sons, Ltd: 2007, pp 1–28.
- (40) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2005**, *44*, 3275–3279.
- (41) Yalkowsky, S. H., *Solubility and Solubilization in Aqueous Media*, 1 edition; American Chemical Society: Washington, D.C. : New York, 1999; 480 pp.
- (42) Joo, F.; Papp, E.; Katho, A. *Top. Catal.* **1998**, *5*, 113–124.
- (43) Liotta, C., *Phase Transfer Catalysis: Principles and Techniques*; Elsevier: 2012; 379 pp.
- (44) Holmberg, K. *Eur. J. Org. Chem.* **2007**, 731–742.
- (45) Menger, F. M.; Rhee, J. U.; Rhee, H. K. *J. Org. Chem.* **1975**, *40*, 3803–3805.
- (46) Cassar, L. *Ann. N. Y. Acad. Sci.* **1980**, *333*, 208–224.

- (47) Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1524–1544.
- (48) Nuzzo, R. G.; Haynie, S. L.; Wilson, M. E.; Whitesides, G. M. *J. Org. Chem.* **1981**, *46*, 2861–2867.
- (49) Oehme, G.; Paetzold, E.; Selke, R. *J. Mol. Catal.* **1992**, *71*, L1–L5.
- (50) Lindstroem, U. M. *Chem. Rev.* **2002**, *102*, 2751–2771.
- (51) Jeffery, T. *Tetrahedron Lett.* **1994**, *35*, 3051–3054.
- (52) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130.
- (53) Lipshutz, B. H.; Ghorai, S. *Aldrichimica Acta* **2012**, *45*, 3–16.
- (54) Kobayashi, S.; Wakabayashi, T.; Oyamada, H. *Chem. Lett.* **1997**, *26*, 831–832.
- (55) Kobayashi, S.; Wakabayashi, T.; Nagayama, S.; Oyamada, H. *Tetrahedron Lett.* **1997**, *38*, 4559–4562.
- (56) Ruasse, M.-F.; Blagoeva, I. B.; Ciri, R.; García-Río, L.; Leis, J. R.; Marques, A.; Mejuto, J.; Monnier, E. *Pure Appl. Chem.* **1997**, *69*, 1923–1932.
- (57) Manabe, K.; Iimura, S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971–11978.
- (58) Krasovskiy, A.; Duplais, C.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2009**, *131*, 15592–15593.
- (59) Bhonde, V. R.; O'Neill, B. T.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 1849–1853.
- (60) Gallou, F.; Isley, N. A.; Ganic, A.; Onken, U.; Parmentier, M. *Green Chem.* **2016**, *18*, 14–19.
- (61) Perkin Medal Awarded for the First Time for Green Chemistry <https://www.warnerbabcock.com/perkin-medal-awarded-for-the-first-time-for-green-chemistry/> (accessed 04/23/2020).
- (62) Romney, D. K.; Arnold, F. H.; Lipshutz, B. H.; Li, C.-J. *J. Org. Chem.* **2018**, *83*, 7319–7322.
- (63) Bhattacharjya, A.; Klumphu, P.; Lipshutz, B. H. *Nat. Commun.* **2015**, *6*, 1–6.
- (64) Brals, J.; Smith, J. D.; Ibrahim, F.; Gallou, F.; Handa, S. *ACS Catal.* **2017**, *7*, 7245–7250.
- (65) Smith, J. D.; Ansari, T. N.; Andersson, M. P.; Yadagiri, D.; Ibrahim, F.; Liang, S.; Hammond, G. B.; Gallou, F.; Handa, S. *Green Chem.* **2018**, *20*, 1784–1790.
- (66) Steven, A. *Synthesis* **2019**, *51*, 2632–2647.
- (67) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1–32.
- (68) Acevedo, O.; Jorgensen, W. L. *Org. Lett.* **2004**, *6*, 2881–2884.
- (69) Lipshutz, B. H.; Ghorai, S.; Cortes-Clerget, M. *Chem. - Eur. J.* **2018**, *24*, 6672–6695.

- (70) Lipshutz, B. H. *Curr. Opin. Green Sustain. Chem.* **2018**, *11*, 1–8.
- (71) Isley, N. A.; Linstadt, R. T. H.; Kelly, S. M.; Gallou, F.; Lipshutz, B. H. *Org. Lett.* **2015**, *17*, 4734–4737.
- (72) Bunton, C. A. *Adv. Colloid Interface Sci.* **2006**, *123-126*, 333–343.
- (73) Bunton, C. A.; Robinson, L. B. *J. Org. Chem.* **1969**, *34*, 780–785.
- (74) Burkhard, R. K.; Sellers, D. E.; DeCou, F.; Lambert, J. L. *J. Org. Chem.* **1959**, *24*, 767–769.
- (75) Terrier, F. In *Modern Nucleophilic Aromatic Substitution*; John Wiley & Sons, Ltd: 2013, pp 1–94.
- (76) Lipshutz, B. H.; Ghorai, S.; Leong, W. W. Y.; Taft, B. R.; Krogstad, D. V. *J. Org. Chem.* **2011**, *76*, 5061–5073.
- (77) Snyder, L. R. *J. Chromatogr. A* **1974**, *92*, 223–230.
- (78) Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehada, S.; Dunn, P. J. *Green Chem.* **2016**, *18*, 288–296.
- (79) Gabriel, C. M.; Lee, N. R.; Bigorne, F.; Klumphu, P.; Parmentier, M.; Gallou, F.; Lipshutz, B. H. *Org. Lett.* **2017**, *19*, 194–197.
- (80) In Terrier, F. *Modern Nucleophilic Aromatic Substitution*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2013, pp 205–278.
- (81) Lipshutz, B. H.; Isley, N. A.; Fennewald, J. C.; Slack, E. D. *Angew. Chem. Int. Ed.* **2013**, *52*, 10952–10958.
- (82) Du, N.; Robertson, G. P.; Song, J.; Pinnau, I.; Thomas, S.; Guiver, M. D. *Macromolecules* **2008**, *41*, 9656–9662.
- (83) Klamt, A.; Eckert, F.; Arlt, W. *Annu. Rev. Chem. Biomol. Eng.* **2010**, *1*, 101–122.
- (84) Andersson, M. P.; Bennetzen, M. V.; Klamt, A.; Stipp, S. L. S. *J. Chem. Theory Comput.* **2014**, *10*, 3401–3408.
- (85) Alsop, D. J.; Burdon, J.; Tatlow, J. C. *J. Chem. Soc.* **1962**, 1801–1805.
- (86) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109.
- (87) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996–8002.
- (88) Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 106–111.
- (89) Zheng, B.; Jia, T.; Walsh, P. J. *Org. Lett.* **2013**, *15*, 1690–1693.
- (90) Zhang, J.; Bellomo, A.; Creamer, A. D.; Dreher, S. D.; Walsh, P. J. *J. Am. Chem. Soc.* **2012**, *134*, 13765–13772.
- (91) Inoh, J.-I.; Satoh, T.; Pivsa-Art, S.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 4673–4676.
- (92) Walvoord, R. R.; Kozlowski, M. C. *J. Org. Chem.* **2013**, *78*, 8859–8864.

- (93) DeAngelis, A. J.; Gildner, P. G.; Chow, R.; Colacot, T. J. *J. Org. Chem.* **2015**, *80*, 6794–6813.
- (94) Handa, S.; Wang, Y.; Gallou, F.; Lipshutz, B. H. *Science* **2015**, *349*, 1087–1091.
- (95) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473.
- (96) Williams, D. B. G.; Lawton, M. *J. Org. Chem.* **2010**, *75*, 8351–8354.
- (97) Baruah, A.; Kalita, B.; Barua, N. C. *Synlett* **2000**, *2000*, 1064–1066.
- (98) Kamimura, A.; Ono, N. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3629–3635.
- (99) Xu, J.; Li, X.; Wu, J.; Dai, W.-M. *Tetrahedron* **2014**, *70*, 6384–6391.
- (100) Schwuger, M.-J.; Stickdorn, K.; Schomaecker, R. *Chem. Rev.* **1995**, *95*, 849–864.
- (101) Parmentier, M.; Gabriel, C. M.; Guo, P.; Isley, N. A.; Zhou, J.; Gallou, F. *Curr. Opin. Green Sustain. Chem.* **2017**, *7*, 13–17.
- (102) Kitanosono, T.; Masuda, K.; Xu, P.; Kobayashi, S. *Chem. Rev.* **2018**, *118*, 679–746.
- (103) Krause, N. *Curr. Opin. Green Sustain. Chem.* **2017**, *7*, 18–22.
- (104) Lipshutz, B. H.; Ghorai, S.; Abela, A. R.; Moser, R.; Nishikata, T.; Duplais, C.; Krasovskiy, A.; Gaston, R. D.; Gadwood, R. C. *J. Org. Chem.* **2011**, *76*, 4379–4391.
- (105) Herries, D. G.; Bishop, W.; Richards, F. M. *J. Phys. Chem.* **1964**, *68*, 1842–1852.
- (106) Bora, P. P.; Bihani, M.; Plummer, S.; Gallou, F.; Handa, S. *ChemSusChem* **2019**, *12*, 3037–3042.
- (107) Anastas, P. T.; Warner, J. C., *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, New York, 2000; 152 pp.
- (108) Arroniz, C.; Denis, J. G.; Ironmonger, A.; Rassias, G.; Larrosa, I. *Chem. Sci.* **2014**, *5*, 3509–3514.
- (109) Perry, G. J. P.; Quibell, J. M.; Panigrahi, A.; Larrosa, I. *J. Am. Chem. Soc.* **2017**, *139*, 11527–11536.
- (110) Quibell, J. M.; Perry, G. J. P.; Cannas, D. M.; Larrosa, I. *Chem. Sci.* **2018**, *9*, 3860–3865.
- (111) Bay, K. L.; Yang, Y.-F.; Houk, K. N. *J. Organomet. Chem.* **2018**, *864*, 19–25.
- (112) Whitaker, D.; Burés, J.; Larrosa, I. *J. Am. Chem. Soc.* **2016**, *138*, 8384–8387.
- (113) Colletto, C.; Islam, S.; Juliá-Hernández, F.; Larrosa, I. *J. Am. Chem. Soc.* **2016**, *138*, 1677–1683.
- (114) Pichette Drapeau, M.; Gooßen, L. J. *Chem. - Eur. J.* **2016**, *22*, 18654–18677.
- (115) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287–1289.
- (116) Vander Zwan, M. C.; Hartner, F. W. *J. Org. Chem.* **1978**, *43*, 2655–2657.

- (117) Karabelas, K.; Hallberg, A. *Tetrahedron Lett.* **1985**, *26*, 3131–3132.
- (118) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896–3900.
- (119) Jeffery, T. *Tetrahedron Lett.* **1990**, *31*, 6641–6644.
- (120) Jeffery, T. *J. Chem. Soc. Chem. Commun.* **1991**, 324.
- (121) Jeffery, T. *Tetrahedron Lett.* **1991**, *32*, 2121–2124.
- (122) Jeffery, T. *Tetrahedron Lett.* **1992**, *33*, 1989–1992.
- (123) Jeffery, T. *Tetrahedron Lett.* **1993**, *34*, 1133–1136.
- (124) Jeffery, T.; Galland, J.-C. *Tetrahedron Lett.* **1994**, *35*, 4103–4106.
- (125) Jeffery, T.; David, M. *Tetrahedron Lett.* **1998**, *39*, 5751–5754.
- (126) Jeffery, T. *Tetrahedron Lett.* **1999**, *40*, 1673–1676.
- (127) Jeffery, T. *Tetrahedron Lett.* **2000**, *41*, 8445–8449.
- (128) Jeffery, T.; Ferber, B. *Tetrahedron Lett.* **2003**, *44*, 193–197.
- (129) Jagtap, S. *Catalysts* **2017**, *7*, 267.
- (130) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170–7173.
- (131) Urgaonkar, S.; Verkade, J. G. *J. Org. Chem.* **2004**, *69*, 5752–5755.
- (132) Ley, S. V.; Ramarao, C.; Gordon, R. S.; Holmes, A. B.; Morrison, A. J.; McConvey, I. F.; Shirley, I. M.; Smith, S. C.; Smith, M. D. *Chem. Commun.* **2002**, 1134–1135.
- (133) Yang, C.-T.; Fu, Y.; Huang, Y.-B.; Yi, J.; Guo, Q.-X.; Liu, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 7398–7401.
- (134) Chattopadhyay, D. *Resonance* **2017**, *22*, 79–87.
- (135) Jimenez-Gonzalez, C.; Ponder, C. S.; Broxterman, Q. B.; Manley, J. B. *Org. Process Res. Dev.* **2011**, *15*, 912–917.
- (136) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113–4114.
- (137) Glugla, P. G.; Byon, J. H.; Eckert, C. A. *Ind. Eng. Chem. Fund.* **1985**, *24*, 379–385.
- (138) Urata, H.; Hu, N.-X.; Maekawa, H.; Fuchikami, T. *Tetrahedron Lett.* **1991**, *32*, 4733–4736.
- (139) Metz, A. E.; Berritt, S.; Dreher, S. D.; Kozlowski, M. C. *Org. Lett.* **2012**, *14*, 760–763.
- (140) Roschangar, F.; Sheldon, R. A.; Senanayake, C. H. *Green Chem.* **2015**, *17*, 752–768.
- (141) Li, J.; Eastgate, M. D. *React. Chem. Eng.* **2019**, *4*, 1595–1607.

- (142) Crabtree, R. H. *Chem. Rev.* **2015**, *115*, 127–150.
- (143) Ren, Y.; Liu, Z.; He, S.; Zhao, S.; Wang, J.; Niu, R.; Yin, W. *Org. Process Res. Dev.* **2009**, *13*, 764–768.
- (144) Miloserdov, F. M.; McMullin, C. L.; Belmonte, M. M.; Benet-Buchholz, J.; Bakmutov, V. I.; Macgregor, S. A.; Grushin, V. V. *Organometallics* **2014**, *33*, 736–752.
- (145) Li, J.-H.; Liu, W.-J. *Org. Lett.* **2004**, *6*, 2809–2811.
- (146) Slaght, V. F.; de Vries, A. H. M.; de Vries, J. G.; Kellogg, R. M. *Org. Process Res. Dev.* **2010**, *14*, 30–47.
- (147) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1986**, *51*, 5286–5290.
- (148) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 4909–4914.
- (149) Kuba, A.; Hawlicka, E. *Phys. Chem. Chem. Phys.* **2003**, *5*, 4858–4863.
- (150) Edson, J. B.; Macomber, C. S.; Pivovar, B. S.; Boncella, J. M. *J. Membr. Sci.* **2012**, *399–400*, 49–59.
- (151) Nakayama, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3717–3722.
- (152) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033–3040.
- (153) Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375–8384.
- (154) Schroeter, F.; Strassner, T. *Inorg. Chem.* **2018**, *57*, 5159–5173.
- (155) Pace, V.; Verniest, G.; Sinisterra, J.-V.; Alcántara, A. R.; De Kimpe, N. *J. Org. Chem.* **2010**, *75*, 5760–5763.
- (156) Ohff, M.; Ohff, A.; van der Boom, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687–11688.
- (157) Amatore, C.; Carre, E.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818–1826.
- (158) Lipshutz, B. H.; Ghorai, S. *Aldrichimica Acta* **2008**, *41*, 59–72.
- (159) Lockhart, R. W.; Ng, K. W.; Nott, P. E.; Unrau, A. M. *Can. J. Chem.* **1969**, *47*, 3107–3112.
- (160) Veenstra, G. E.; Zwanenburg, B. *Synthesis* **1975**, *1975*, 519–520.
- (161) Krickl, S.; Buchecker, T.; Meyer, A. U.; Grillo, I.; Touraud, D.; Bauduin, P.; König, B.; Pfitzner, A.; Kunz, W. *Phys. Chem. Chem. Phys.* **2017**, *19*, 23773–23780.
- (162) Buchecker, T.; Krickl, S.; Winkler, R.; Grillo, I.; Bauduin, P.; Touraud, D.; Pfitzner, A.; Kunz, W. *Phys. Chem. Chem. Phys.* **2017**, *19*, 1806–1816.
- (163) Clausse, M.; Zradba, A.; Nicolas-Morgantini, L. In *Microemulsion Systems*, 1st ed.; Surfactant Science Series 24; Marcel Dekker, Inc.: New York, 1987, pp 387–425.
- (164) Finney, J. L.; Bowron, D. T.; Soper, A. K. *J. Phys.: Condens. Matter* **2000**, *12*, A123–A128.

- (165) Nakayama, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 877–880.
- (166) Mootz, D.; Stäben, D. *J. Am. Chem. Soc.* **1994**, *116*, 4141–4142.
- (167) Mootz, D.; Stäben, D. *Z. Für Naturforschung B* **1993**, *48*, 1325–1330.
- (168) Reetz, M. T.; Hütte, S.; Goddard, R. *Z. Für Naturforschung B* **1994**, *50*, 415–422.
- (169) Klebe, G.; Böhn, K. H.; Marsch, M.; Boche, G. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 78–79.
- (170) Mootz, D.; Seidel, R. *J Incl Phenom Macrocycl Chem* **1990**, *8*, 139–157.
- (171) Harmon, K. M.; Budrys, N. M. *J. Mol. Struct.* **1991**, *249*, 149–159.
- (172) Kanno, H.; Shimada, K.; Katoh, T. *J. Phys. Chem.* **1989**, *93*, 4981–4985.
- (173) Kanno, H.; Ohnishi, A.; Tomikawa, K.; Yoshimura, Y. *J. Raman Spectrosc.* **1999**, *30*, 705–713.
- (174) Stäben, D.; Mootz, D. *Z. Für Naturforschung B* **1993**, *48*, 1057–1064.
- (175) McLean, W. J.; Jeffrey, G. A. *J. Chem. Phys.* **1967**, *47*, 414–417.
- (176) Collins, K. D.; Neilson, G. W.; Enderby, J. E. *Biophysical Chemistry* **2007**, *128*, 95–104.
- (177) Mootz, D.; Stäben, D. *Z. Für Naturforschung B* **1992**, *47*, 263–274.
- (178) Walker, J.; Johnston, J. *J. Chem. Soc., Trans.* **1905**, *87*, 955–961.
- (179) Brenchley, M. E.; Weller, M. T. *Zeolites* **1994**, *14*, 682–686.
- (180) Nakazawa, T.; Kato, H.; Takase, T.; Ueta, S. *Genshiryoku Bakkuendo Kenkyu* **1999**, *6*, 71–73.
- (181) Kipkemboi, P. K.; Eastal, A. J. *Can. J. Chem.* **1994**, *72*, 1937–1945.
- (182) Seebach, D.; Lehr, F. *Helv. Chim. Acta* **1979**, *62*, 2239–2257.
- (183) Kisch, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 812–847.
- (184) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075–10166.
- (185) Schmaderer, H.; Hilgers, P.; Lechner, R.; König, B. *Adv. Synth. Catal.* **2009**, *351*, 163–174.
- (186) Ribeiro, S. M.; Serra, A. C.; Rocha Gonsalves, A. *J. Mol. Catal. Chem.* **2010**, *326*, 121–127.
- (187) Gazi, S.; Ananthakrishnan, R. *Appl. Catal. B Environ.* **2011**, *105*, 317–325.
- (188) Kurfirť, M.; Špačková, J.; Svobodová, E.; Cibulka, R. *Monatshefte Für Chem. - Chem. Mon.* **2018**, *149*, 863–869.
- (189) Zhang, T.; Liang, W.; Huang, Y.; Li, X.; Liu, Y.; Yang, B.; He, C.; Zhou, X.; Zhang, J. *Chem. Commun.* **2017**, *53*, 12536–12539.
- (190) Bachl, J.; Hohenleutner, A.; Dhar, B. B.; Cativiela, C.; Maitra, U.; König, B.; Díaz, D. D. *J. Mater. Chem. A* **2013**, *1*, 4577.

- (191) Dongare, P.; MacKenzie, I.; Wang, D.; Nicewicz, D. A.; Meyer, T. J. *Proc. Natl. Acad. Sci.* **2017**, *114*, 9279–9283.
- (192) Iida, H.; Mizoguchi, T.; Oh, S.-D.; Yashima, E. *Polym. Chem.* **2010**, *1*, 841.
- (193) Heeger, A. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 2591–2611.
- (194) Zhang, M.; Rouch, W. D.; McCulla, R. D. *Eur. J. Org. Chem.* **2012**, *2012*, 6187–6196.
- (195) Wang, X.; Maeda, K.; Thomas, A.; Takanabe, K.; Xin, G.; Carlsson, J. M.; Domen, K.; Antonietti, M. *Nat. Mater.* **2009**, *8*, 76–80.
- (196) Ghasimi, S.; Bretschneider, S. A.; Huang, W.; Landfester, K.; Zhang, K. A. I. *Adv. Sci.* **2017**, *4*, 1700101.
- (197) Zhao, Z.; Sun, Y.; Dong, F. *Nanoscale* **2015**, *7*, 15–37.
- (198) Budd, P. M.; Elabas, E. S.; Ghanem, B. S.; Makhseed, S.; McKeown, N. B.; Msayib, K. J.; Tattershall, C. E.; Wang, D. *Adv. Mater.* **2004**, *16*, 456–459.
- (199) Pandey, G.; Hajra, S.; Ghorai, M. K.; Kumar, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 8777–8787.
- (200) Ohkubo, K.; Suga, K.; Morikawa, K.; Fukuzumi, S. *J. Am. Chem. Soc.* **2003**, *125*, 12850–12859.
- (201) Totten, L. A.; Roberts, A. L. *Crit. Rev. Environ. Sci. Technol.* **2001**, *31*, 175–221.
- (202) Bezzu, C. G.; Carta, M.; Tonkins, A.; Jansen, J. C.; Bernardo, P.; Bazzarelli, F.; McKeown, N. B. *Adv. Mater.* **2012**, *24*, 5930–5933.
- (203) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617–1622.
- (204) Gribble, G. W. *Chemosphere* **2003**, *52*, 289–297.
- (205) Ehrlich, J.; Bartz, Q. R.; Smith, R. M.; Joslyn, D. A.; Burkholder, P. R. *Science* **1947**, *106*, 417–417.
- (206) Wright, P. M.; Seiple, I. B.; Myers, A. G. *Angew. Chem. Int. Ed.* **2014**, *53*, 8840–8869.
- (207) Hardman, D. J. *Crit. Rev. Biotechnol.* **1991**, *11*, 1–40.
- (208) Pathak, T. P.; Miller, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 6120–6123.
- (209) Renner, M. K.; Jensen, P. R.; Fenical, W. *J. Org. Chem.* **1998**, *63*, 8346–8354.
- (210) Sturini, M.; Speltini, A.; Maraschi, F.; Pretali, L.; Profumo, A.; Fasani, E.; Albini, A.; Migliavacca, R.; Nucleo, E. *Water Res.* **2012**, *46*, 5575–5582.
- (211) Xu, Z.; Yang, Z.; Liu, Y.; Lu, Y.; Chen, K.; Zhu, W. *J. Chem. Inf. Model.* **2014**, *54*, 69–78.
- (212) Xu, Z. et al. *J. Med. Chem.* **2011**, *54*, 5607–5611.

- (213) Hardegger, L. A.; Kuhn, B.; Spinnler, B.; Anselm, L.; Ecabert, R.; Stihle, M.; Gsell, B.; Thoma, R.; Diez, J.; Benz, J.; Plancher, J.-M.; Hartmann, G.; Banner, D. W.; Haap, W.; Diederich, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 314–318.
- (214) Matter, H.; Nazaré, M.; Güssregen, S.; Will, D. W.; Schreuder, H.; Bauer, A.; Urmann, M.; Ritter, K.; Wagner, M.; Wehner, V. *Angew. Chem. Int. Ed.* **2009**, *48*, 2911–2916.
- (215) Fieser, L. F. *J. Am. Chem. Soc.* **1953**, *75*, 5421–5422.
- (216) Song, H.; Liu, Y.; Wang, Q. *Org. Lett.* **2013**, *15*, 3274–3277.
- (217) Birman, V. B.; L. Rheingold, A.; Lam, K.-C. *Tetrahedron Asymmetry* **1999**, *10*, 125–131.
- (218) Haibach, M. C.; Stoltz, B. M.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 15123–15126.
- (219) Nguyen, J. D.; D’Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem.* **2012**, *4*, 854–859.
- (220) Discekici, E. H.; Treat, N. J.; Poelma, S. O.; Mattson, K. M.; Hudson, Z. M.; Luo, Y.; Hawker, C. J.; de Alaniz, J. R. *Chem. Commun.* **2015**, *51*, 11705–11708.
- (221) Smith, J. D.; Jamhawi, A. M.; Jasinski, J. B.; Gallou, F.; Ge, J.; Advincula, R.; Liu, J.; Handa, S. *Nat. Commun.* **2019**, *10*, 1837.
- (222) Balashova, I. M.; Danner, R. P.; Puri, P. S.; Duda, J. L. *Ind. Eng. Chem. Res.* **2001**, *40*, 3058–3064.
- (223) Snyder, L. R. *J. Chromatogr. Sci.* **1978**, *16*, 223–234.
- (224) Freed, B. K.; Biesecker, J.; Middleton, W. *J. Fluor. Chem.* **1990**, *48*, 63–75.
- (225) Ciriminna, R.; Delisi, R.; Xu, Y.-J.; Pagliaro, M. *Org. Process Res. Dev.* **2016**, *20*, 403–408.
- (226) Armarego, W. L. F., *Purification of Laboratory Chemicals*, 7 edition; Butterworth-Heinemann: Amsterdam : London, 2012; 1024 pp.
- (227) Gudipudi, G.; Sagurthi, S. R.; Perugu, S.; Achaiah, G.; David Krupadanam, G. L. *RSC Adv* **2014**, *4*, 56489–56501.
- (228) Okamoto, T.; Kakinami, T.; Nishimura, T.; Hermawan, I.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1731–1733.
- (229) Finck, L.; Brals, J.; Pavuluri, B.; Gallou, F.; Handa, S. *J. Org. Chem.* **2018**, *83*, 7366–7372.
- (230) Stodulski, M.; Goetzinger, A.; Kohlhepp, S. V.; Gulder, T. *Chem Commun* **2014**, *50*, 3435–3438.

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CURRICULUM VITA

Justin D. Smith

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Education

- Ph.D. in Chemistry, University of Louisville, 2020
- B.S. in Chemistry, with distinction, University of Kansas, 2011
- B.S. in Chemistry, University of Regensburg, 2011

Laboratory Experience

- Research Assistant, University of Louisville, Handa Group, 2016–2020
- Research Assistant, University of Kansas, Gehrke Group, 2015–2016
- Research Assistant, UC Santa Barbara, Lipshutz Group, 2013–2015
- Research Assistant, University of Kansas, Gehrke Group, 2010–2012
- Research Assistant, University of Regensburg, Díaz-Díaz Group, 2010
- Undergraduate Researcher, Dublin City University, Regan Group, 2009–2010
- Research Assistant, University of Kansas, KU CMLD Core C, 2009

Employment Overview

- Graduate Teaching/Research Assistant, University of Louisville, 2016–2020
- Graduate Teaching Assistant, UC Santa Barbara, 2013–2015
- Program Assistant, KU Office for Diversity in Science Training, 2012–2013

Graduate Research Support

- Dorothy Gibson Memorial Fellowship (awarded annually to one Chemistry Ph.D. student entering the fourth year of the graduate program at the University of Louisville), 2019–2020

Peer-Reviewed Publications

7. Smith, J. D.; Jamhawi, A. M.; Jasinski, J. B.; Gallou, F.; Ge, J.; Advincula, R.; Liu, J.; Handa, S. “Organopolymer with Dual Chromophores and Fast Charge-Transfer Properties for Sustainable Photocatalysis” *Nat. Commun.* **2019**, *10*, 1837

- Selected to be a Nature Communications Editors' Highlights article for Energy Materials
6. Bihani, M.; Ansari, T.; Smith, J. D.; Handa, S. "The Magical but Endangered Metal: Searching for Sustainable Palladium Catalysis" *Curr. Opin. Green Sustainable Chem.* **2018**, *11*, 45
 5. Smith, J. D.; Ansari, T. N.; Andersson, M. P.; Dongari, Y.; Ibrahim, F.; Liang, S.; Hammond, G. B.; Gallou, F.; Handa, S. "Micelle-Enabled Clean and Selective Sulfonylation of Polyfluoroarenes in Water Under Mild Conditions" *Green Chem.* **2018**, *20*, 1784
- Selected as the issue 8 back cover article
4. Handa, S.; Smith, J. D.; Zhang, Y.; Takale, B. S.; Gallou, F.; Lipshutz, B. H. "Sustainable HandaPhos-ppm Palladium Technology for Copper-Free Sonogashira Couplings in Water Under Mild Conditions" *Org. Lett.* **2018**, *20*, 542
 3. Brals, J.; Smith, J. D.; Ibrahim, F.; Gallou, F.; Handa, S. "Micelle-Enabled Palladium Catalysis for Convenient sp²-sp³ Coupling of Nitroalkanes with Aryl Bromides in Water Under Mild Conditions" *ACS Catal.* **2017**, *7*, 7245
- Co-first author with equal contribution
2. Smith, J. D.; Gallou, F.; Handa, S. "Organometallic Catalysis and Sustainability: From Origin to Date" *Johnson Matthey Technol. Rev.* **2017**, *61*, 231
 1. Handa, S.; Smith, J. D.; Hageman, M. S.; Gonzalez, M.; Lipshutz, B. H. "Synergistic and Selective Copper/ppm Pd-Catalyzed Suzuki-Miyaura Couplings: In Water, Mild Conditions, with Recycling" *ACS Catal.* **2016**, *6*, 9179

Theses and Dissertations

2. (Pseudo)phase tuning in the service of synthesis: technologies for sustainable catalysis, Ph.D. dissertation, University of Louisville, 2020
1. Studies in Several Gel-Related Projects: Catalytic Hydrogel Beads, Gel-Phase Photo Chemistry, and Orthogonally Synthesized Biopolymer Matrices for Pollutant Removal, B.S. thesis, University of Regensburg, 2010

Presentations

2. "Tuning of polymeric organophotoredox catalyst properties for backside irradiation applications," poster presentation, Physical Organic Chemistry Gordon Research Conference, Holderness, NH, 6/25/2019
1. "Selective sulfonylation of polyfluoroarenes using mild, sustainable photocatalytic conditions," oral presentation, Southeastern Regional Meeting of the American Chemical Society, Charlotte, NC, 11/11/2017

Research Mentorship

Mentored four undergraduate students at the University of Louisville in independent research projects, 2017–2018

- Provided training in relevant synthetic and analytical techniques
- Planned and managed student projects; each student was given an individual project (photocatalytic sulfonylation, copper-based photocatalyst development, photocatalytic decarbonylation, and photocatalytic surfactant development) which was separate from the mentor's own primary research activities
- Ensured that research progress was adequate for the two students who were participants in the University of Louisville's Summer Research Opportunity Program (SROP) for successful program completion; both students successfully presented research posters at the end of the program and both were accepted into medical school

Honors and Awards

- Dorothy Gibson Memorial Fellowship, 2019
- Dual Bachelor of Science in chemistry from the University of Regensburg for completion of honors thesis and EU Atlantis Program requirements, 2011
- Graduation with Distinction, 2011
- Graduation with University Honors, over 40 hours of honors coursework taken at KU (3.93 GPA), 2011
- University of Kansas Undergraduate Research Award, 2011
- Fassnacht Scholarship from the University of Kansas Department of Chemistry "for an advanced student with a major in chemistry," 2010
- University of Regensburg Summer Fellowship, 2010
- University of Kansas Honors Program Development Grant, 2009–2010
- Honors Research Development Program, a three-week intensive immersion in research methodology, 2008
- Ilus W. Davis Award from the University of Kansas Department of English for the best undergraduate essay submitted in fulfillment of a regular class assignment, 2008
- National Merit Scholarship from the University of Kansas, 2007
- National Merit Scholarship from the National Merit Scholarship Corporation, 2007