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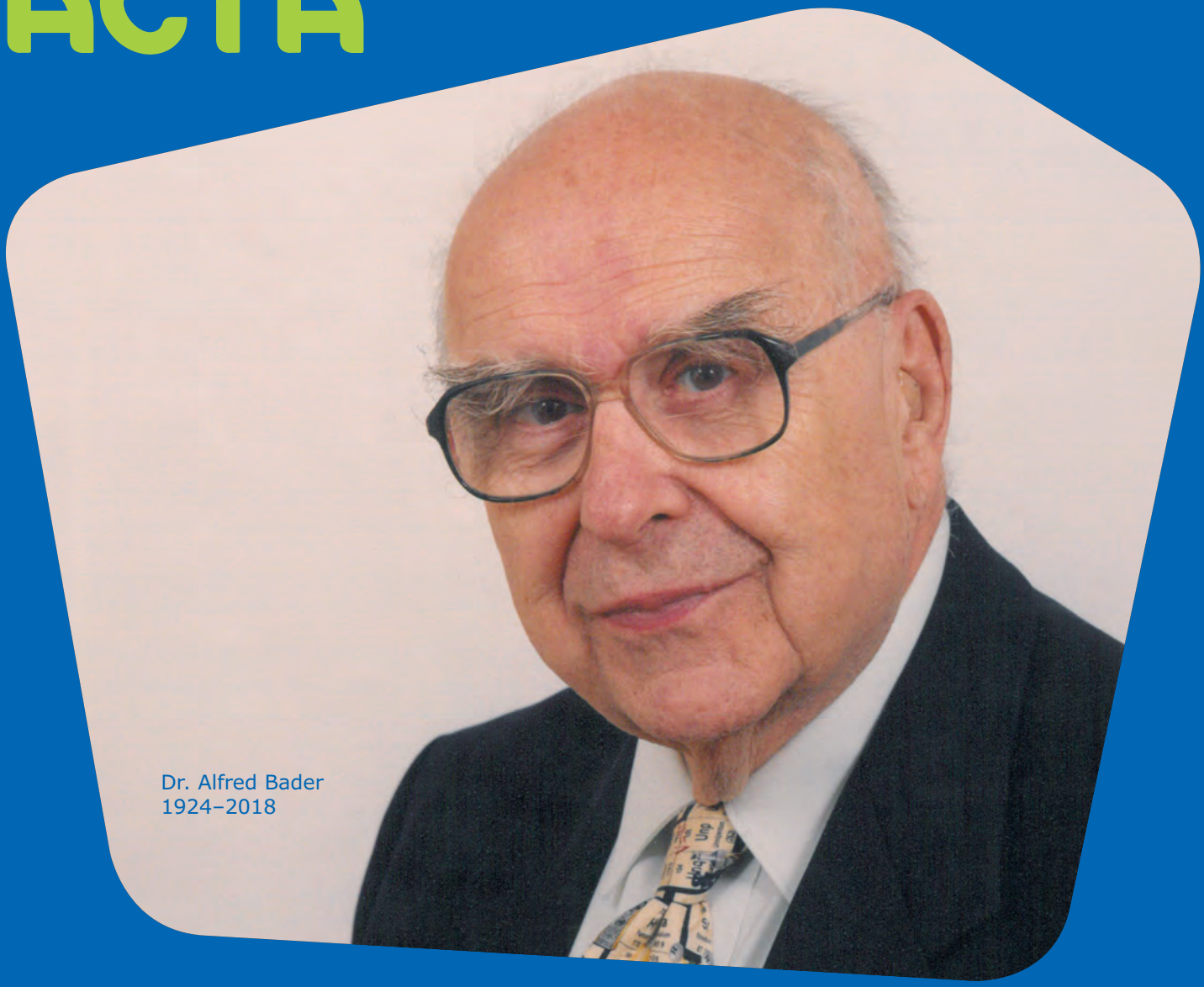
ALDRICHIMICA ACTA



Dr. Alfred Bader
1924–2018

Remembering Dr. Alfred R. Bader (1924–2018)

Phenothiazines, Dihydrophenazines, and Phenoxazines: Sustainable Alternatives to Precious-Metal-Based Photoredox Catalysts

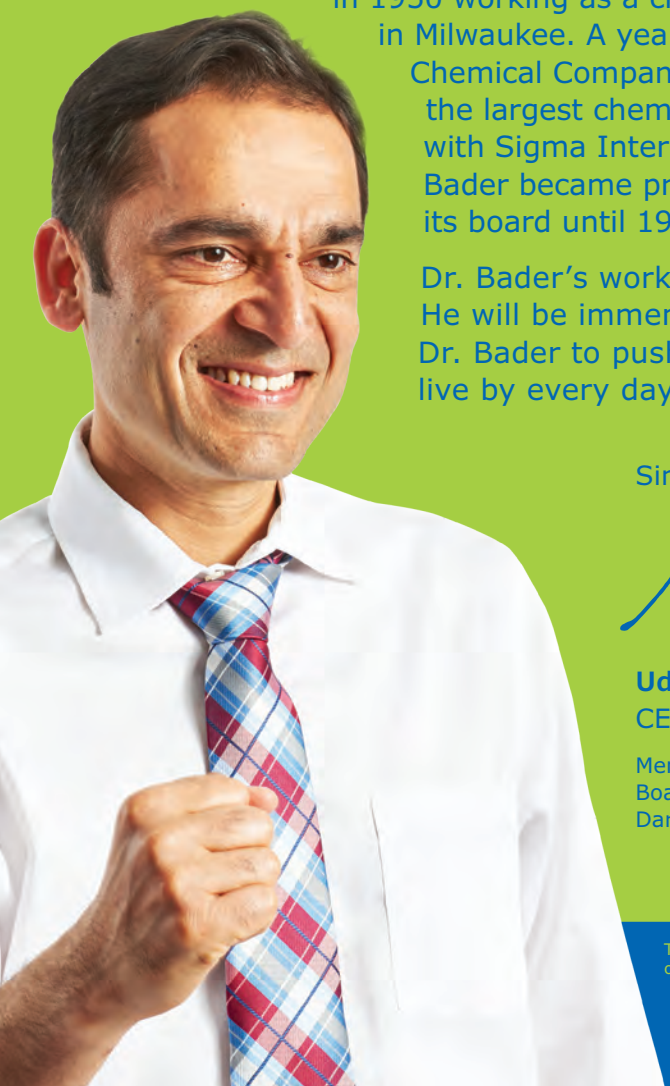
Titanium Salalen Catalysts for the Asymmetric Epoxidation of Terminal (and Other Unactivated) Olefins with Hydrogen Peroxide

Remembering Dr. Alfred Bader

Alfred Bader, a pioneer in the field of chemistry and co-founder of Aldrich Chemical Company, now a part of the Life Science business of Merck KGaA, Darmstadt, Germany, passed away on December 23, 2018, at the age of 94.

Scientists from around the world grew up using Aldrich Chemical products in their labs, referencing the Aldrich Catalog and Handbook, and appreciating the oft-used request to "Please Bother Us."— a request for customers to call at any time with any question or idea. Bader's commitment to his customers and to the broader scientific community could be felt in all aspects of his work.

Bader's remarkable story began in 1938, when at age 14, he fled his native Vienna during the rise of Nazism. He would eventually complete a chemistry degree at Queen's University in Kingston, Ontario, and later a Ph.D. in organic chemistry at Harvard. Bader was an entrepreneur at heart. He began his career in 1950 working as a chemist for the Pittsburgh Plate Glass Company in Milwaukee. A year later, he and Jack Eisendrath founded Aldrich Chemical Company, which would eventually grow to become one of the largest chemical companies in the world. Aldrich later merged with Sigma International, Ltd., to form Sigma-Aldrich Corporation. Bader became president of Sigma-Aldrich Corp. and then served on its board until 1992, when he left to focus on philanthropic efforts.



Dr. Bader's work and legacy have left a lasting impact on science. He will be immensely missed. Passion and curiosity drove Dr. Bader to push the boundaries of chemistry, something we live by every day.

Sincerely yours,

Udit Batra, Ph.D.
CEO, Life Science

Member of the Executive Board, Merck KGaA, Darmstadt, Germany

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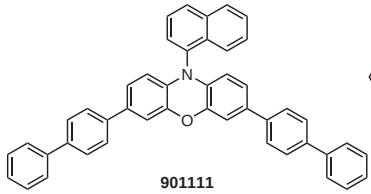
"PLEASE BOTHER US."

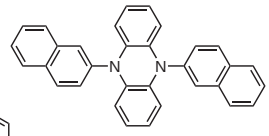
Dear Fellow Chemists,

Professor Garret M. Miyake of the Department of Chemistry at Colorado State University kindly suggested that we offer PhenO_1Naph_Biph (**901111**) and PhenN_2Naph (**901112**) as sustainable alternatives to precious-metal-based photoredox catalysts, such as the Ir- and Ru-based ones. These organic photoredox catalysts act as strong excited-state reductants, and have proven effective in controlling atom-transfer radical polymerizations (ATRPs).[1] They have also proven very valuable in small-molecule organic synthesis by efficiently catalyzing carbon–carbon and carbon–heteroatom bond formations,[2] and enabling transformations not previously accessible with precious-metal catalysts.[3]

(1) Theriot, J. C.; Lim, C.-H.; Yang, H.; Ryan, M. D.; Musgrave, C. B.; Miyake, G. M. *Science* **2016**, *352*, 1082. (2) Du, Y.; Pearson, R. M.; Lim, C.-H.; Sartor, S. M.; Ryan, M. D.; Yang, H.; Damrauer, N. H.; Miyake, G. M. *Chem.—Eur. J.* **2017**, *23*, 10962. (3) For a fuller discussion of the chemistry of these and other organic photoredox catalysts, see Professor Miyake's review in this issue (pp 7–21).



901111
PhenO_1Naph_Biph



901112
PhenN_2Naph

901111	PhenO_1Naph_Biph, ≥97%	100 mg
901112	PhenN_2Naph, ≥97%	100 mg

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Udit Batra, Ph.D.
CEO, Life Science

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ABOUT OUR COVER

Dr. Alfred Robert Bader—co-founder of Aldrich Chemical Co. and Sigma-Aldrich Corp. (today a part of the Life Science business of Merck KGaA, Darmstadt, Germany) and one of the most influential men in the chemical industry* since the mid-twentieth century—passed away peacefully on December 23, 2018, at the age of 94.

Dr. Bader founded and launched the *Aldrichimica Acta* in 1968. For about the first 24 years of its existence, the *Acta* cover featured paintings from Dr. Bader's private collection, and he often wrote the "About Our Cover" commentary about the featured painting. A Harvard chemistry graduate, Alfred was also a renowned art connoisseur and avid art collector, who acquired the nickname *The Chemist Collector*. Until the end, Dr. Bader was a most enthusiastic supporter of, and advocate for, the *Acta*: He believed strongly in its value, eagerly anticipated each issue, requested copies of each, and distributed them to his visitors. He promoted the *Acta* wherever he went and whenever he could. He will be missed.

Alfred perusing his favorite publication (April 2014).

* *To find out more about Dr. Bader's enduring legacy to chemistry and the art world, visit* ***SigmaAldrich.com/Acta***

Remembering Dr. Alfred R. Bader (1924–2018)[1,2]

Dr. S. J. Firsan

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Outline

1. Introduction

Dr. Alfred Robert Bader—co-founder of Aldrich Chemical Co. and Sigma-Aldrich Corp. (today a part of the Life Science business of Merck KGaA, Darmstadt, Germany)—passed away peacefully on December 23, 2018, at the age of 94. He is survived by his wife, Isabel, his two sons, David and Daniel, and several grandchildren.[3]

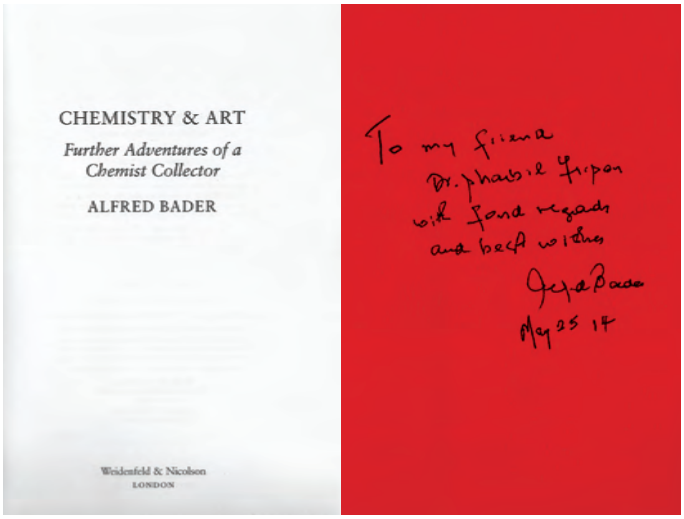
When I began writing this personal account as a tribute to Alfred, whom I had the honor of knowing and working with for more than 20 years, I approached the task with a good deal of concern about how to properly cover in just a few pages a life so rich in accomplishments. With this in mind, this piece constitutes a look through a narrow window at a man who was very closely associated with, and has heavily impacted, the business and science of chemistry for over a half century.[4] A more complete picture of a man as influential and complex as Alfred was awaits a future biographer.[5,6]

I first saw and heard Alfred while still in graduate school at the University of Illinois in Urbana-Champaign. Sometime in the early 1980s, Alfred came to the UI to give a lecture on the intersection of art and chemistry and on playing detective with unattributed or misattributed works of art by using various scientific techniques. It was an engaging lecture, and while it was not about Aldrich Chemical Co., it still indirectly served as a powerful advertisement for the relatively young company.

Dr. Bader as the Guest Speaker at the ACS Milwaukee Section Meeting (September 2001).

Although Alfred no longer had official ties to the company, he still liked to meet new employees whom he perceived could have some impact on the business—after all, he was still the largest individual shareholder and had a vested interest in how well the company was performing. In my case, I met Alfred not long after I joined Aldrich in January of 1996 at one of the regular meetings of the ACS Milwaukee Section. Alfred cared a great deal about the *Aldrichimica Acta* throughout his life and liked to see it in capable hands. Therefore, when he found out that, among other things, I had responsibility for the *Acta*, he naturally took a keen interest in me. Thus, began our professional and personal relationship that continued almost until his death.

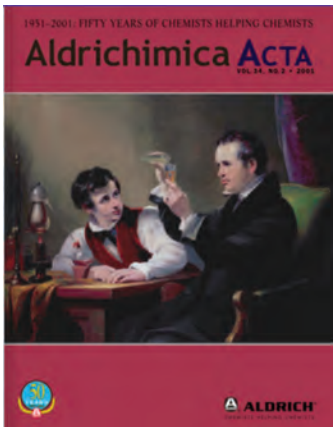
The *Acta* was but one of our mutual interests. With Alfred having a strong interest in Middle Eastern affairs and I being originally from Lebanon, he was naturally curious to hear my perspective on current happenings in the region. Whenever we met, Alfred would often initiate a conversation about the Middle East. He was especially proud that his ancestors were from the region and that his last name meant "full-moon-faced". He would



often tell me fondly and proudly about his paternal grandfather—born in Moravia of the Czech Republic and a graduate of the prestigious French civil engineering school, L'École des Ponts et Chaussées in Paris—who had worked with Ferdinand Marie de Lesseps on the construction of the Suez Canal in the mid-1800s.[7] In subsequent years, I would meet with Alfred mostly at his request a few times a year.[8] As I pointed out in my editorial in early 2009 on the occasion of his 85th birthday,[9] Alfred had primarily four pursuits in life that he was passionate about (what he called his **ABC**s): **A**rt (the appreciation and collection of), **B**ible (the study and teaching of), **C**hemistry (the science and business of), and, later in life, **P**hilanthropy. One other lesser known, but nonetheless very early interest he had, was collecting stamps.

2. If at First You Don't Succeed, …

My interactions with Alfred followed mostly from my responsibilities at Aldrich, and revolved principally around two of Alfred's four pursuits, **C**hemistry and **A**rt: **C**hemistry in terms of suggestions for review articles and new products, and **A**rt in terms of paintings that Alfred owned and that he passionately wanted used on the covers of the *Aldrichimica Acta*. In this second regard, Alfred was anything if not persistent. He pushed very hard, *and often*, to have paintings in his collection[10] be featured on the cover. His persistence paid off, as we eventually featured a painting that Alfred owned[11] on the cover of the second issue of the *Acta* of 2001, after a hiatus of about 10 years. Thereafter, we featured one of his paintings every now and then.[12]



First of the Paintings in Alfred's Collection to Be Featured on the Cover of the *Aldrichimica Acta* After a 10-Year Hiatus.

3. The Business of Chemistry

Whatever the final verdict on Alfred's lifetime achievements may be, one undisputable fact is the central and critical roles he played in starting, building, and running a robust chemical company—Aldrich and then Sigma-Aldrich, now a part of the Life Science business of Merck KGaA, Darmstadt, Germany—that is still a world leader in the chemistry and life science businesses. In the process, Alfred has (i) helped countless researchers around the world by facilitating and accelerating their research, and thus contributed significantly to the tremendous scientific advances that we have all witnessed over the past half century; and (ii) provided steady employment and a good standard of living for thousands of individuals, their families, and their communities.

3.1. Adversity Stokes the Drive

This accomplishment, however, did not come easily to the young Austrian immigrant, who had fled Vienna as a teenager after the Nazis marched into the city and just before Europe plunged into World War II, and who had to overcome major obstacles along the way. While Alfred grew up in the home of his well-off paternal aunt in Vienna,[13] he suddenly found himself moving around from country to country and place to place as a refugee, sometimes regarded with suspicion as an "enemy" alien by the host country, and having to shine shoes and wash clothes in order to survive.[14] However, Alfred had what it takes to overcome adversity and to succeed: intelligence, drive, persistence, passion, and a business acumen that came naturally to him.

3.2. The Consummate Salesman

Throughout his life, Alfred was a tireless salesman and negotiator. Armed with a first-rate knowledge of chemistry, he crisscrossed North America and Europe in search of new products to list and sell, of business partners, and of customers for the young company he co-founded and ran for decades. Most valuable was his connection to, appreciation of, and repeat visits to chemistry academics who proved to be a tremendous innovation asset for the company. They helped Alfred keep his pulse on what areas were being actively researched and, thus, in need of reagents, starting materials, solvents, and laboratory equipment. *Alfred loved selling.* Whenever I happened to meet him soon after he had sold a painting, large or small, or a copy of one of his books, I would find him beaming. Of course, at that point it was not for the money he made on the sale, but for the sheer joy of making the sale.

3.3. Continued Involvement

Alfred never lost his strong interest in the goings-on at the company to his last days. He frequently explained this to me and others by saying that the company was his "baby" and that he could not let go of it. For this reason, he was not content with the official statements and reports that the company put out, and liked to learn as many additional details as he could. He would often write to, or call, officers of the company to get more information, and would make an effort to attend as many of the company functions that were open to him as he could.

3.4. The Perpetual Entrepreneur

If you were a centimillionaire[15] in your sixties, seventies, or eighties, how would you live your life? Would you aim to enjoy a quiet, carefree retirement? Not Alfred! Until he no longer physically could, he continued to maintain a regular work schedule at his gallery, to travel and give several lectures a year, to do philanthropic work, correspond with an astonishing variety of professionals and, perhaps most importantly for the business of chemistry, to help chemistry startups by investing in them, with mixed results—some succeeding, some failing.[16] Labeling Alfred as a workaholic would not have been an exaggeration.

Alfred Perusing His Favorite Publication (April 2014).

4. Alfred, the Person

Alfred Challenging the Author's Older Son in a Game of Chess (May 2014). Needless to Say That Alfred Quickly Won That Game and Many Others.

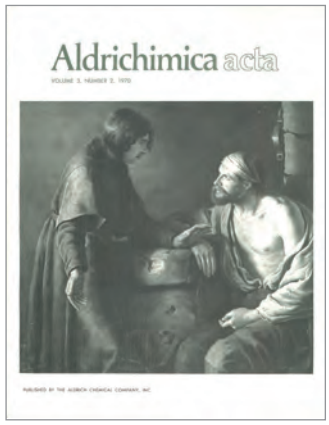
What, then, was Alfred like in person? If you had the opportunity to meet him, the first thing that would strike you about Alfred would be his modesty that was manifested in the clothes he wore, the car he drove, the house he lived in, and in the unassuming manner he carried himself with people of all walks of life.[9] He was consistently soft-spoken, polite, and considerate.

4.1. The Philanthropist

Alfred was a generous donor and was liberal in showing his gratitude to the institutions that helped him as a young refugee. He was also interested in establishing a lasting legacy and in contributing to institutions of higher learning and scientific societies. That he did, abundantly, as his donations to universities (in Canada, in particular Queen's University, and in Britain, the U.S., and the Czech Republic) and chemical societies (ACS, RSC, Czech, and Canadian) attest to. In addition to endowing chairs in chemistry, and setting up scholarships,[17] fellowships, and many other types of assistance to able and/or needy young professionals, Alfred has also contributed generously and consistently to a number of humanitarian efforts around the world.[18] As generous as Alfred was towards universities, scientific societies, and humanitarian organizations, he was exacting with money on a personal level throughout his life to a point that used to astonish his acquaintances and colleagues.

4.2. A Religious Man

Alfred taught, and was deeply interested all his life in, the (Hebrew) Bible and its teachings (the **B** part of his **ABC**). Born to a devout Catholic mother, who could not raise him because she had fallen on hard times, he was raised by his paternal aunt, who instilled in him the love of Judaism. He thus sought all his life to live as much as possible as a committed [his word] and devout Jew, albeit one who was not comfortable with the labels orthodox, conservative, or reformist.[19] Despite that, he still had to be converted to Judaism, *as an adult*, in a ritual ceremony before his first marriage.[20]



Alfred's Favorite Painting, *Joseph and the Baker* by a Rembrandt Student, Was Featured on the Cover of AA **1970**, *3* (2). The Painting Is Now in the Private Collection of David Bader.

4.3. Contrary to Prevailing Wisdom

With regard to diet and exercise, and as far as this author knows, Alfred did not participate in any kind of sport or fitness program most of his life. He also was not particularly mindful of how healthy or unhealthy the foods he ate were. (A lifestyle that reminds me of that of a nonagenarian friend of Alfred, the late Professor H. C. Brown.) Nonetheless, he was in amazingly good health most of his life. Even at 86 years of age, when many of his younger and more physically fit colleagues had passed away, he still had a sharp intellect, good hearing, good eyesight, and still drove his car to and from work. However, as can be expected and as Alfred got older, his recollection of events and their relative importance gradually started to blur, as I discovered when I was researching my article on the history of Aldrich when Alfred was about 77 years old.[4a]

5. Farewell

In all the years I dealt with Alfred, I came to expect a phone call from him on a fairly regular basis, often bright and early in the morning, when he would, among other things, comment favorably

The Author and His Family Enjoying Sunday Brunch with Alfred and Isabel at the Astor Hotel in Milwaukee (August 2007).

or, more often, unfavorably on something he saw in a recent issue of the *Aldrichimica Acta* or in one of our other publications such as the catalog/handbook. After I wrote my 2001 piece about the history of the company on the occasion of the 50th anniversary of Aldrich,[4a] he called and gave me a glowing review of the piece. With Alfred's departure, the *Acta* has lost another staunch and longtime supporter and believer in its mission and value.[21] Until almost the end, Alfred promoted the *Acta* wherever he went and whenever he could.

Farewell, Alfred! Farewell, Friend! Your kindness, humility, and friendship will be missed forever. I offer my sincere condolences to Alfred's widow, Isabel, his two sons, David and Daniel, and their families.

6. References and Notes

(1) The information, views, and opinions expressed in this article are the sole responsibility of the author and do not necessarily reflect those of Merck KGaA, Darmstadt, Germany, its affiliates, or its officers.

(2) I wish to thank my colleagues, Ms. Rachel Bloom Baglin and Dr. Ben Glasspoole, for a critical reading of, and insightful comments on, early drafts of this article.

3) Dr. Bader's obituary and selected related information can be found at: (a) The Goodman-Bensman Whitefish Bay Funeral Home web site at https://www.goodmanbensman.com/obit/dr-alfred-bader/ (accessed Jan 17, 2019). (b) Glauber, B. *The Milwaukee Journal Sentinel* [Online], December 24, 2018. https://www.jsonline.com/story/news/2018/12/24/alfred-bader-chemical-magnate-milwaukee-philanthropist-dies-94/2407962002/. (c) Wang, L. *Chem. Eng. News* [Online], December 25, 2018. https://cen.acs.org/people/obituaries/Alfred-Bader-dies-age-94/96/web/2018/12. (d) Bader Philanthropies, Inc., web site. https://www.bader.org/honoring-life-legacy-dr-alfred-bader/ (accessed Jan 17, 2019).

(4) (a) Firsan, S. J. *Aldrichimica Acta* **2001**, *34*, 35. (b) Alfred Bader. *Wikipedia–The Free Encyclopedia*; Wikimedia Foundation, Inc. https://en.wikipedia.org/wiki/Alfred_Bader (accessed Jan 18, 2019).

(5) Alfred has authored two, relatively short and candid autobiographies. (See reference 6.) However, several topics from his life and work are not adequately covered in them.

(6) (a) Bader, A. *Adventures of a Chemist Collector*; Weidenfeld & Nicolson: London, U.K., 1995. (b) Bader, A. *Chemistry & Art: Further Adventures of a Chemist Collector*; Weidenfeld & Nicolson: London, U.K., 2008.

(7) Reference 6a, p 10.

(8) I last saw Alfred on February 1, 2015, when I visited him at The Eastcastle Place Health and Rehabilitation Center, where he had settled permanently following a series of strokes and consequent falls that began on July 16, 2010, during one of his customary stays at his second home in Bexhill, England. After that visit, Alfred had become too frail, tired easily, and could not receive visitors, except very close family members.

(9) Firsan, S. J. "Please Call Me Alfred." *Aldrichimica Acta* **2009**, *42* (1), IFC.

(10) In 1992, Alfred opened an art gallery, Alfred Bader Fine Arts, at a suite in the historic Astor Hotel on Milwaukee's East Side. (See reference 6a, page 180, last paragraph.)

(11) This famous painting, *Prussian Blue* by Thomas Phillips (London, 1816), was featured on the cover of *Aldrichimica Acta*, Vol. *34*, No. 2, 2001, and is now owned by Alfred's son, Daniel Bader.

(12) In this regard, it is worth noting that Alfred rarely liked paintings featured on the *Acta* cover that were not from his collection. This, in spite of the fact that *Acta* readers, internal and external, enjoyed them a great deal and that many of the paintings he wanted featured (typically dark portraits of dignified old men and women in stoic poses, albeit by renowned artists) no longer appealed to the growing younger generations of readers.

(13) Reference 6a, pp 11–12

(14) Reference 6a, pp 26–30.

(15) Alfred's own description of his wealth during an undated meeting with the author.

(16) (a) Materia Will Build Plant in Singapore. *Chem. Eng. News* **2011**, *89* (12), March 21, p 23. (b) See also reference 6b, pp 16–18.

(17) For an example, see the announcement: Alfred and Isabel Bader Scholars. *Chem. Eng. News* **2010**, *88* (19), May 10, p 47.

(18) For some examples, see reference 6b, Chapter 18.

(19) Reference 6a, pp 66–67.

(20) Reference 6a, p 66, 4th paragraph.

(21) The other was Dr. Jai P. Nagarkatti, former Chairman, CEO, and President of Sigma-Aldrich Corp. See Firsan, S. J. *Aldrichimica Acta* **2010**, *43*, (3) 63.

About the Author

Sharbil J. Firsan is the longtime editor of the *Aldrichimica Acta,* and has been with Sigma-Aldrich Corp.—now a part of the Life Science business of Merck KGaA, Darmstadt, Germany—for over 23 years. He was born and raised in Lebanon, and completed his undergraduate studies at the American University of Beirut. After obtaining his Ph.D. degree in organic chemistry from the University of Illinois at Urbana–Champaign, he did a year of postdoctoral work at the University of Oregon, and then moved to Oklahoma State University to become Research Associate and then Visiting Assistant Professor. With his wife and two sons, Sharbil enjoys reading, outdoor activities, gardening, and travel. The two accomplishments he is most proud of are his two sons, Paul and Patrick.

Phenothiazines, Dihydrophenazines, and Phenoxazines: Sustainable Alternatives to Precious-Metal-Based Photoredox Catalysts


Mr. D. A. Corbin


Dr. C.-H. Lim


Prof. G. M. Miyake

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Keywords. phenothiazines; dihydrophenazines; phenoxazines; organic photoredox catalysis; O-ATRP; strong excited-state reductant; light-driven polymerization; precious-metal-free; oxidative quenching.

Abstract. The application of photoredox catalysis to atom-transfer radical polymerization (ATRP) has resulted in the development of strongly reducing organic photoredox catalysts (PCs) that are some of the most reducing catalysts known. The objectives of this review are to highlight these PCs with regard to their development and applications in polymer and organic synthesis, as well illuminate aspects of these PCs that remain to be studied further.

Outline

1. Introduction

Photoredox catalysis has gained increasing attention because it provides chemists with the ability to perform challenging transformations by harnessing the reactivity of excited state photoredox catalysts (PCs) under mild reaction conditions. This ability is particularly important in synthetic organic chemistry, where photoinduced electron transfer (PET), between a PC and either a donor (reductive quenching) or acceptor (oxidative quenching), and energy transfer have facilitated previously challenging reactions and enabled a myriad of novel transformations.[1–7] Among the best known PCs are those containing precious metals such as ruthenium and iridium.[2,4] However, these PCs present an issue with regards to sustainability,[8] as Ru and Ir are among the rarest metals on earth. To this end, several organic PC families have been reported as alternatives—including anthracenes,[9–11] benzophenones,[12–14] acridiniums,[15–17] xanthene dyes,[18–20] perylene diimides,[21] and many more[3]—that are capable of mediating various synthetic transformations. However, most organic PCs operate through a reductive quenching pathway, and strongly reducing organic PCs are less common.

Given the wide range of transformations to which photoredox catalysis has been applied, it is not surprising that it has also

found use in polymer synthesis.[22] For example, in the free radical polymerization of methacrylates reported in 2011, $Ru(bpy)_3^{2+}$ operated as a PC through a reductive quenching mechanism requiring the use of a sacrificial electron donor.[23] Notably, the controlled radical polymerization of methyl methacrylate (MMA) in the presence of *fac*-[Ir(ppy)$_3$] (**1**) under visible light irradiation was reported a year later.[24] Operating by an atom-transfer radical polymerization (ATRP) mechanism, control in this class of reactions is achieved by reversible deactivation, most commonly with a bromide chain end group, which can be iteratively removed and reinstalled on the polymer chain via reduction and oxidation, respectively. As this process minimizes the number of reactive radicals in solution at any given time, it reduces bimolecular radical termination processes,[25] thus enabling control over the polymerization as evidenced by (1) linear first-order kinetics, (2) linear growth of polymer molecular weight (MW) as a function of monomer conversion, (3) relatively low- to low-molecular-weight dispersity ($Đ$ < 1.2 and $Đ$ < 1.1, respectively), and (4) achievement of initiator efficiency (I^* = $M_{n[theoretical]}/M_{n[experimental]}$; M_n = number average molecular weight) near 100%. Notably, this system efficiently polymerized MMA employing low catalyst loadings (as little as 50 ppm of **1**) while maintaining good control over the polymerization, something that has been challenging even in the traditional ATRP.[26] Moreover, temporal control over the polymerization was demonstrated by cycling the light source on and off, showing that the polymerization could be started and stopped without loss of the bromide end-group functionality.[24]

Despite these achievements, concerns regarding the sustainability of this PC remained, motivating the development of an ATRP method employing organic PCs, or organocatalyzed ATRP (O-ATRP), instead. Furthermore, the purification of polymers presents challenges, and trace contamination by metal residues could impede application of these materials in biomedical devices, electronic applications, and multistep syntheses.[27] Thus, shortly after the seminal paper by Fors and Hawker,[24] O-ATRP was demonstrated in two concurrent reports, polymerizing MMA using perylene (**2**)[28] or 10-phenylphenothiazine (**3**).[29] Of these two catalysts, the superior capability of **3** to mediate a controlled polymerization was evidenced in its ability to synthesize polymers with lower dispersity ($Đ$) compared to **2**. This difference was attributed to **3**'s significantly stronger excited state reduction potential [$E^0(^2PC^{\bullet+}/^3PC^*)$ = –0.6 V for **2**,[30] $E^0(^2PC^{\bullet+}/^1PC^*)$ = –2.1 V for **3**,[29] both vs SCE]. However, **2** could operate using visible light irradiation, whereas **3** required the use of UV light, raising concerns for potential side reactions that might result from UV absorption by the organic molecules in solution.[4] Thus, the development of strongly reducing and visible-light-absorbing organic PCs has been pursued, yielding a variety of PCs based on the phenothiazine (PhenS), dihydrophenazine (PhenN), and phenoxazine (PhenO) scaffolds (**Figures 1 and 2**).

To date, a number of reviews have been published detailing the applications of photoredox catalysis in organic and polymer synthesis.[1–4,22,31,32] However, due to their relatively recent development, reviews of PCs based on PhenS, PhenN, and PhenO are relatively few.[3,30,33] Therefore, this review will focus on these PCs, highlighting their development, reactions, and mechanisms in hope of demonstrating their broad utility in synthetic organic and polymer chemistry. Moreover, this review will discuss future research directions regarding these PCs in the hope of accelerating their development, improvement, and utilization in the coming years.

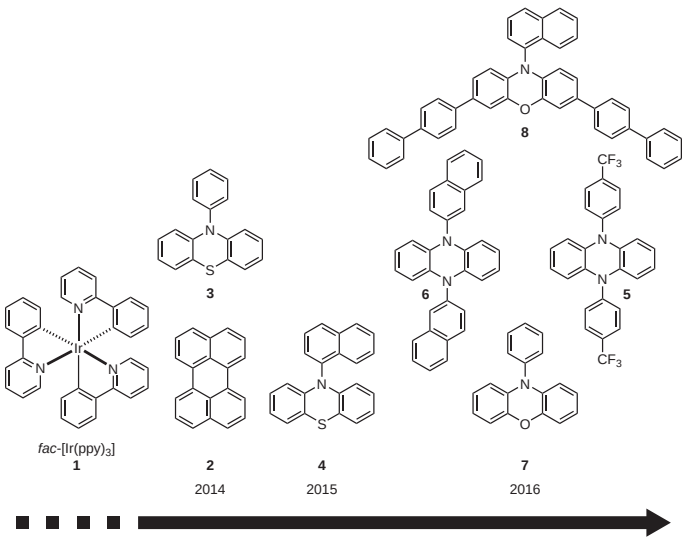


Figure 1. Examples Highlighting the Evolution of Strongly Reducing Organic PCs Based on PhenS, PhenN, and PhenO.

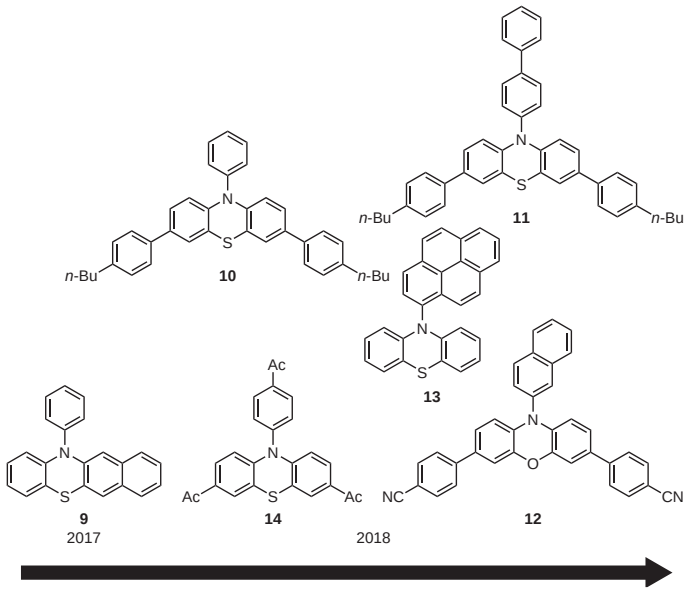
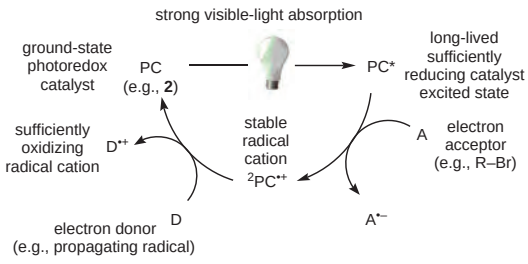


Figure 2. Further Examples Highlighting the Evolution of Strongly Reducing Organic PCs Based on PhenS, PhenN, and PhenO.

2. Development of Strongly Reducing Organic Photoredox Catalysts

While their application scope has since grown, the original motivation for using PhenS, PhenN, and PhenO as strongly reducing organic PCs came from O-ATRP. Inspired by the seminal report on photoredox catalyzed ATRP using **1**,[24] this method was developed as a metal-free variant of ATRP to eliminate metal contamination of polymer products for metal-sensitive applications. Originally, it made use of either **2**[28] or **3**[29] to polymerize methacrylates in a controlled fashion, but differences between these two organic PCs as well as the drawbacks of each soon became apparent, prompting the development of strongly reducing organic PCs that are capable of establishing a high degree of control over polymerizations by using a visible light source so as to avoid possible side reactions caused by UV light.[34]

In the proposed mechanism, the PC operates through oxidative quenching (**Scheme 1**),[28,29] in which the photoexcited PC reduces an electron acceptor to generate the PC radical cation ($^2PC^{\bullet+}$), followed by oxidation of an electron donor by $^2PC^{\bullet+}$ to regenerate the ground state catalyst. In the case of O-ATRP, the acceptor is typically an alkyl bromide initiator or a bromide-capped polymer chain-end, whereas the donor is the propagating radical formed by activation of the C–Br bond. With this mechanism in mind, several desirable characteristics were targeted in the search for new O-ATRP catalysts:[34] (i) Strong visible-light absorption (high molar absorptivity); (ii) long-lived excited state; (iii) sufficiently negative excited state reduction potential [$E^0(^2PC^{\bullet+}/PC^*)$, singlet or triplet excited state] for the reduction of common alkyl bromide ATRP initiators [E^0(C–Br/C–Br$^{\bullet-}$) = –0.6 to –0.8 V vs SCE[35]]; (iv) sufficiently oxidizing $^2PC^{\bullet+}$ [$E^0_{ox} = E^0(^2PC^{\bullet+}/^1PC)$] for oxidation of the propagating radical [E^0(C–Br/C–Br$^{\bullet-}$) = –0.6 to –0.8 V vs SCE]; (v) redox reversibility, i.e., a stable $^2PC^{\bullet+}$ that does not partake in degradative side reactions; (vi) low reorganization energy for the transition from PC* to $^2PC^{\bullet+}$ to ^1PC; and (vii) photoinduced charge-transfer excited states resulting from spatially separated singly occupied molecular orbitals (SOMOs).



Scheme 1. A General, Oxidative Quenching Mechanism by Which Strongly Reducing PCs Operate. First, an Electron Is Donated by the Excited State PC (PC*) to an Acceptor (A), Followed by Extraction of an Electron from an Electron Donor (D) to Regenerate the Ground State PC. *(Ref. 28,29)*

Following these design principles and with guidance from computational methods, two new families of PCs with favorable properties for O-ATRP were discovered: *N,N*-diaryldihydrophenazines (PhenN's) (e.g., **5** and **6**)[34] and *N*-arylphenoxazines (PhenO's) (e.g., **7** and **8**).[36] PhenN's improved upon previous generations of PCs by accessing more reducing triplet excited states [computationally predicted $E^0(^2PC^{\bullet+}/^3PC^*)$ < –2.0 V vs SCE] while maintaining visible light absorption.[34] In turn, polymerizations with PhenN's produced polymers with dispersities (*Đ*) as low as 1.10 (for PC **5**), although with consistently moderate initiator efficiencies, presumably due to side reactions of the PCs with propagating radicals. A major conclusion in this report was that PhenN PCs bearing electron-withdrawing groups (EWGs) or an extended π system on the *N*-aryl substituents appeared to consistently outperform other PCs, prompting an investigation into the cause of these observed differences.

As all of the PCs investigated in this study were sufficiently reducing (as PC*) and oxidizing (as $^2PC^{\bullet+}$) to mediate O-ATRP, density functional theory (DFT) calculations were used to elucidate the differences in their electronic structure that might influence PC performance.[34] These calculations revealed that all of the PC triplet excited states studied featured low-lying SOMOs localized on the PhenN core, whereas the nature of the high-lying SOMOs was dependent on the functionality on the *N*-aryl substituents. Specifically, PCs bearing electronically neutral or donating groups exhibited population of high-lying SOMOs on the PhenN core. In contrast, PCs bearing EWGs or extended π systems on the *N*-aryl substituents showed high-lying SOMOs localized onto the *N*-aryl group, suggesting photoinduced intramolecular charge transfer (CT). With these properties in mind, PC **6** was computationally predicted to contain spatially separated SOMOs and, experimentally, **6** exhibited enhanced performance in O-ATRP, producing polymers with *Đ* as low as 1.03.

More recently, 10-phenylphenoxazine (**7**) was also predicted and demonstrated to have favorable properties for use as an O-ATRP catalyst.[36] While **3** and **7** differ only by their chalcogenide, the difference in size between O and S was hypothesized to have significant impacts on the comparative performance of these PCs, as the ground state structure of **3** is noticeably bent while the ground state structure of **7** is more planar, and computations predict that the radical cation of both compounds is nearly planar. As such, owing to the smaller size of O and more planar core structure, DFT calculations predicted PhenO's would have lower reorganization energies than PhenS when transitioning from the triplet excited state to the radical cation and back to the ground state. As these PCs have been proposed to operate via an outer-sphere electron-transfer mechanism, this lower penalty for structural reorganization was hypothesized to result in enhanced PC performance due to more favorable electron-transfer processes.

To investigate whether photoinduced intramolecular CT might also be accessible in PhenO's, derivatives possessing different *N*-aryl substituents were synthesized and investigated in

O-ATRP.[36] Computations predicted that PhenO's possessing either a 1- or 2-naphthyl substitution at the *N*-aryl position could access photoinduced CT excited states, and experimentally these PCs were observed to produce, under UV irradiation, polymers with $Đ$ < 1.3. While these studies were useful in determining structural influences on PC properties, and these PCs were successful in O-ATRP, neither **7** nor the *N*-naphthylphenoxazines absorb light in the visible spectrum. Therefore, structural modifications of 1-naphthylphenoxazine were undertaken to red-shift its absorption while maintaining a strong excited state reduction potential as well as CT character. Thus, **8** was introduced, bearing biphenyl core-substituents that effectively red-shifted the absorption into the visible range as well as increased the molar extinction coefficient to 26,600 $M^{-1}cm^{-1}$ (**Table 1**).[35,36] It should be noted that although the wavelength of maximum absorption of **8** is still in the UV range (λ_{max} = 388 nm), its absorption tails significantly into the visible range, resulting nonetheless in strong visible light absorption. Gratifyingly, the use of **8** in the polymerization of MMA under white light irradiation resulted in polymers possessing relatively low $Đ$'s ($Đ$ = 1.13) and achieving nearly quantitative I*. With regards to PhenS's, similar efforts have been made to red-shift their absorption. For example, *N*-phenylbenzo[*b*]phenothiazine (**9**) has been reported, which featured a nearly 50 nm red-shifted absorption relative to **3**, allowing it to absorb in the visible region.[37] Additionally, methods to synthesize visible-light-absorbing PhenS derivatives by substitution of the PhenS core with 4-*n*-butylphenyl groups (PCs **10** and **11**) have been reported.[38,39]

The tunability of PhenO-based PCs has also been demonstrated,[35] as synthetic variations have been systematically made to tune PC absorption, CT in the excited state, and redox properties. While the former two have already been discussed in the context of various PCs, of more interest is the latter, which expanded on previous findings[34] and yielded a library of PhenO PCs with DFT-predicted $E^0(^2PC^{\bullet+}/^3PC^*)$ values spanning −1.42 V (for PC **12**) to −2.11 V (for PC **7**) and $E^0(^2PC^{\bullet+}/^1PC)$ spanning 0.30 V to 0.62 V (all vs SCE, Table 1).[35,36] Additionally, some work has also been reported on synthetically tuning the PhenN[34,40–42] and PhenS[38,39,43–45] core structures. In particular, Matyjaszewski and co-workers investigated the influence of a number of *N*-aryl substituents on PC properties and reactivity in O-ATRP for a variety of PhenS-based PCs, such as **4**.[43]

Finally, in an effort to improve PC recyclability, which remains one of the limitations of these PCs, a variant of **3** attached to a polymer support was developed that could be repeatedly added and removed from reaction mixtures simply with a set of tweezers.[46] As a result, the PC could be used in multiple polymerizations (up to 6 times) without any observable loss in performance, thus providing a means of catalyst recycling.

Table 1 Tunable Properties of PhenO's through Facile Synthetic Modifications of the Core Structure *(Ref. 35,36)*

PC	**7**	**8**	**12**
$E^0(^2PC^{\bullet+}/^3PC^*)$[a]	−2.11 (−2.48)[d]	−1.70 (−1.80)[d]	−1.42 (−1.75)[d]
$E^0(^2PC^{\bullet+}/^1PC)$[a]	0.58 (0.68)[e]	0.42 (0.65)[e]	0.62 (0.69)[e]
$\lambda_{max,abs}$[b]	324 nm	388 nm	411 nm
$\varepsilon_{max,abs}$[c]	7,700 $M^{-1}cm^{-1}$	26,600 $M^{-1}cm^{-1}$	22,300 $M^{-1}cm^{-1}$

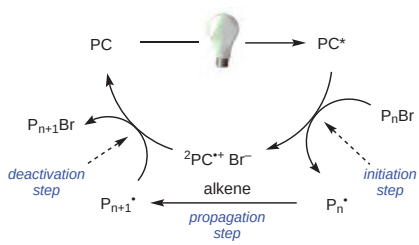
[a] DFT-predicted redox potentials reported in V vs SCE. [b] Maximum absorption wavelengths. [c] Molar absorptivities at λ_{max}. [d] Values in parentheses are experimental $E^0(^2PC^{\bullet+}/^1PC^*)$ values (V vs SCE), where the lowest excited singlet energies were estimated from the maximum wavelength of emission. [e] Values in parentheses are experimental $E_{1/2}$ values (V vs SCE) determined using cyclic voltammetry.

3. Applications in Polymerization Reactions

3.1. O-ATRP

Broadly speaking, O-ATRP occurs by a mechanism similar to that of traditional ATRP, in that a catalyst mediates an equilibrium between "active" ($P_n^{\bullet}$) and "dormant" (P_nBr) polymer chains, repeatedly activating and deactivating polymers by reversible removal and addition of a halide end group, often a bromide (**Scheme 2**). Key to this process is that deactivation is favored over activation and propagation, thus maintaining a low concentration of reactive radicals in solution to minimize bimolecular coupling and other termination reactions.[25] In thermally driven ATRP, activation occurs via an inner sphere electron-transfer (ISET) mechanism, in which the halide is transferred from the polymer chain-end (or alkyl halide initiator) to the catalyst species at the same time as electron transfer. By contrast, activation in O-ATRP occurs through an outer sphere electron-transfer (OSET) mechanism, where an excited state PC (PC*) directly reduces an alkyl bromide (either an initiator or a polymer chain-end) to generate Br^-, $^2PC^{\bullet+}$, and an active, propagating radical. $^2PC^{\bullet+}$ may subsequently associate with Br^- to form the ion pair $^2PC^{\bullet+}Br^-$.[40] Upon deactivation, $^2PC^{\bullet+}Br^-$ oxidizes the radical chain-end and reinstalls the bromide to re-form the dormant polymer species and regenerate the ground state PC. While specific mechanistic details are still under investigation and may vary between individual PCs, the current understanding of this mechanism will be discussed in greater detail in a later section (see Section 5).

In initial reports on O-ATRP using either **2**[28] or **3**[29] in the presence of the initiator ethyl α-bromophenylacetate (EBP), the viability of the method was demonstrated through polymerization of MMA (**eq 1**).[28,29] With the potential of this method established, the homo-polymerizations of several methacrylates were demonstrated, including benzyl methacrylate,[29,34,36] *tert*-



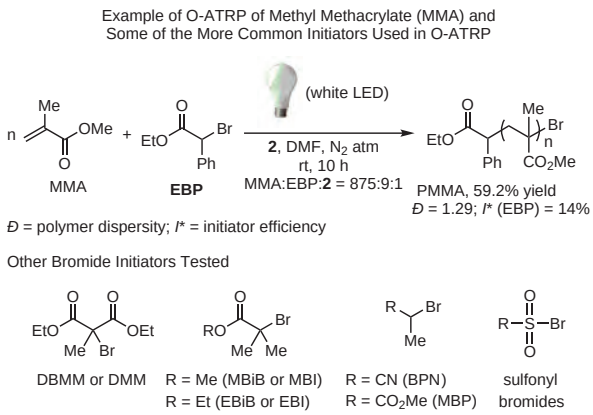
Scheme 2. Proposed O-ATRP Mechanism. *(Ref. 40)*

butyl methacrylate,[29] isobutyl methacrylate,[36] isodecyl methacrylate,[36] trimethylsilylhydroxyethyl methacrylate,[34] 2,2,2-trifluoroethyl methacrylate,[34] and di(ethylene glycol) methacrylate (**Figure 3**).[34] Notably, the polymerization of 2-(dimethylamino)ethyl methacrylate to produce polymers with relatively low *Đ*'s was unsuccessful using **1**, but was realized with PhenS catalysts.[29] In subsequent reports, the monomer scope of these PCs was expanded to methacrylates bearing long alkyl chains,[37,47] extended aromatic groups,[45] and heterocyclic functionalities.[45]

In addition to these more traditional monomers, the polymerizations of biomass-derived methacrylate monomers using PC **3** have also been reported, demonstrating that both homo- and co-polymers of these monomers could be achieved via O-ATRP.[48] The polymerization of acrylonitrile by O-ATRP using **3** and other PhenS catalysts, albeit with relatively high *Đ* (*Đ* = 1.42) compared to traditional ATRP (*Đ* = 1.04), has also been reported.[49,50] While methacrylic acid has been polymerized using **3**,[51] control over this polymerization was not evaluated, necessitating further future studies. Very interestingly, the polymerization of methacrylates with pendant furan-protected maleimides using **5** has also been reported.[52] This report not only provides a strategy for post-polymerization modification, but also demonstrates that these PCs tolerate a wide array of functionalities. However, despite various efforts, the monomer scope of O-ATRP beyond methacrylates remains largely unestablished and, as such, an important future direction of O-ATRP is to define the monomer scope and capabilities of this polymerization platform.

In all ATRP methods, the choice of initiator can also play an influential role in controlling a given polymerization. Thus, various initiators have been investigated for use with all three PC families (see eq 1), especially traditional alkyl bromides such as EBP,[29,34,36,49] diethyl 2-bromo-2-methyl malonate (DBMM),[36] methyl α-bromoisobutyrate (MBiB),[34,36,43] ethyl α-bromoisobutyrate (EBiB),[29] methyl 2-bromopropionate (MBP),[34,36] and 2-bromopropionitrile (BPN).[34,49] In addition, several alkyl chloride initiators have been investigated with PhenS catalysts, though with less success.[43] Although these PCs are capable of activating alkyl chlorides due to their strong excited state reduction potentials, they seem to be inefficient at deactivating the propagating radicals in conjunction with chloride initiators, resulting in less control during polymerizations. Perhaps the most interesting development in O-ATRP initiators thus far has been the introduction of aromatic sulfonyl halides by Chen and co-workers.[39] In their report, nearly 20 sulfonyl bromides were investigated in polymerizations mediated by **11**, achieving *Đ*'s as low as 1.21 in the polymerization of MMA, and in polymerizations of several other methacrylates and acrylates with varying levels of control. Of particular note is that this new initiating system allows for the post-polymerization modification of polystyrene (PS) via O-ATRP, as sulfonyl chlorides can be installed on the aromatic rings of PS to initiate an O-ATRP for *grafting-from* brush synthesis (see Section 3.3).

One drawback of general photoredox catalysis is the difficulty of scaling photochemical reactions,[53,54] as reactions in batch reactors must be performed on a small scale to ensure uniform irradiation throughout the reaction vessel. To overcome this obstacle, flow reactors have been implemented, in which a reaction mixture is pumped through a transparent, narrow tube wrapped around a light source to achieve both uniform irradiation as well as facile scalability.[53] In an effort to extend these benefits to O-ATRP, the polymerizations of various methacrylates using PCs **5**, **6**, and **8** were undertaken in a flow setup, resulting in the ability to synthesize the polymers on a gram scale while maintaining relatively low *Đ*.[48] Moreover, due to the improved irradiation conditions offered by continuous flow, enhanced PC performance was observed, allowing for a tenfold reduction in catalyst loading without significant loss of performance.



eq 1 *(Ref. 28,29,34,36,39,43,49)*

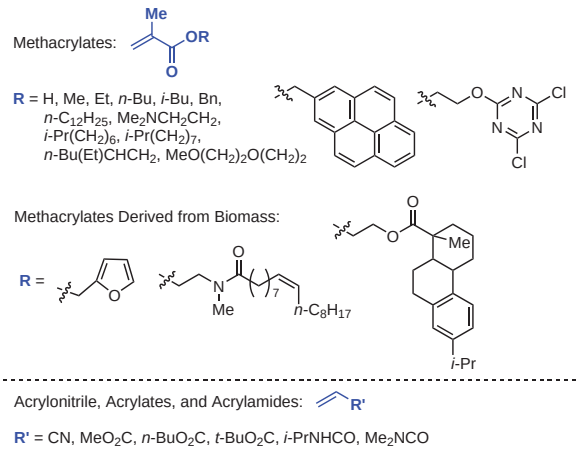
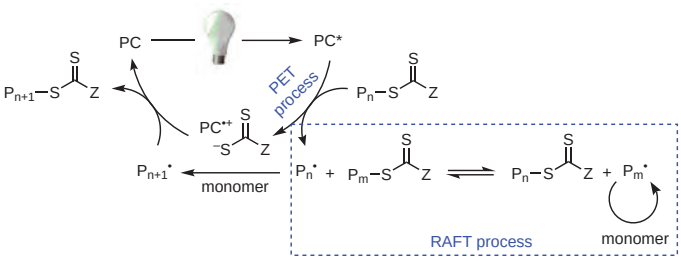


Figure 3. Monomers Successfully Polymerized via O-ATRP by Using PhenS, PhenN, and PhenO Photoredox Catalysts. *(Ref. 29,34,36,45,47–49,51)*

3.2. PET-RAFT

Although the primary application of PhenS, PhenN, and PhenO catalysts has been in O-ATRP, some applications of these PCs to PET-RAFT (photo-induced electron/energy transfer-reversible addition fragmentation chain-transfer) polymerizations have been reported.[55–59] Much like traditional RAFT, PET-RAFT makes use of a chain-transfer agent (CTA), often a thiocarbonylthio compound, to mediate a controlled radical polymerization (**Scheme 3**).[55–58] However, where traditional RAFT commonly utilizes thermal initiators, PET-RAFT makes use of a PC to mediate this process,[55–58] minimizing the formation of dead chains from the reaction of initiator radicals with active polymers.[59] Similar to what is seen in O-ATRP, PC* activates a dormant polymer-CTA bond, generating a radical that can engage in polymerization



For example: Z = PhS or *n*-BuS; P_n = $MeCHCO_2H$ or $MeC(CN)(CH_2)_2CO_2H$

Scheme 3. Xu and Boyer's Proposed Mechanism of PET-RAFT. *(Ref. 55–58)*

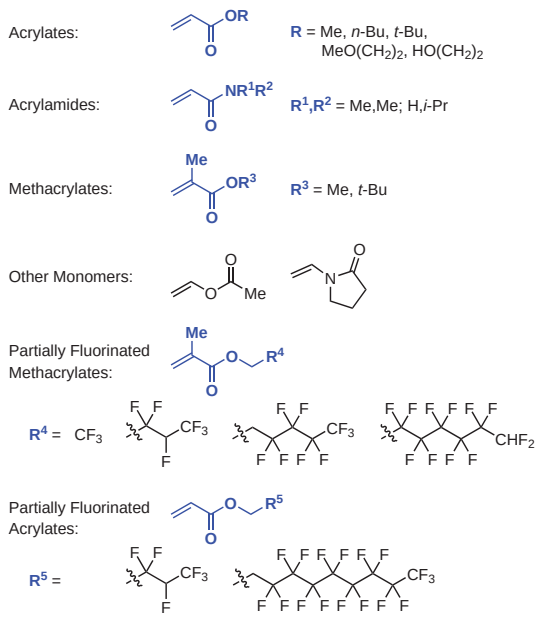


Figure 4. Monomers Polymerized via PET-RAFT by Using PhenN and PhenS Catalysts. *(Ref. 38,46,59)*

($P_n^{\bullet}$), $^2PC^{\bullet+}$, and the respective thiocarbonylthiolate (in the case of a thiocarbonylthio CTA). The active $P_n^{\bullet}$ radical can either propagate or undergo reversible deactivation by one of two pathways: in the first, the radical reacts with $^2PC^{\bullet+}$ to undergo oxidation and reinstallation of the CTA end group. In the second, the active radical can undergo chain-transfer with another CTA-capped polymer, resulting in the deactivation of one chain and the activation of another chain (Scheme 3).

Although originally reported using iridium PC **1**,[60] PET-RAFT was later expanded to PhenS, when **3** was employed to polymerize *N*-isopropylacrylamide, *N,N*-dimethylacrylamide, *tert*-butyl acrylate, and ethylene glycol methyl ether acrylate (**Figure 4**) with relatively low to low *Đ*'s and temporal control.[59] This monomer scope was recently extended to various other acrylates and methacrylates while also introducing a method for catalyst recycling by using a polymer-supported PC that is based on **3**.[46] Finally, the ability of PhenS catalysts to polymerize partially fluorinated monomers has also been demonstrated, producing a variety of partially fluorinated polymers with generally low *Đ*'s.[38]

To demonstrate the utility of PET-RAFT in materials manufacturing, existing polymer-based gels were homogeneously modified in an example of living additive manufacturing.[61] Since the gels consisted of polymer networks with trithiocarbonate iniferters embedded in the polymer backbone, chain extensions could be achieved upon irradiation by infiltrating the gels with *N*-isopropylacrylamide and **3**. Importantly, since this method involved modification of the existing polymer network, the resulting material was homogeneous in nature in contrast to the heterogeneous materials obtained by simply growing one material on another using previous methods.

Moreover, as these PCs have displayed the ability to mediate polymerizations both via O-ATRP and PET-RAFT, some work has combined these two reaction manifolds into a stepwise synthesis of copolymers of acrylates and methacrylates using **5**.[62] Capitalizing on the strengths (and weaknesses) of both methods, a multifunctional initiator bearing a trithiocarbonate moiety and an alkyl bromide moiety was synthesized, in which the former functional group would only react during PET-RAFT and the latter during O-ATRP. Thus, the polymerization of methyl acrylate was achieved via PET-RAFT, followed by the polymerization of methyl methacrylate via O-ATRP, resulting in a block copolymer that otherwise would have been challenging to prepare by either method alone.

3.3. Complex Polymer Architectures

One of the hallmarks of a controlled polymerization is the ability to synthesize complex polymer architectures.[63–65] For the methods described above, this ability has been demonstrated at various levels, through the synthesis of linear block-copolymers,[29,34,36,45,62,66] brushes,[39,67] and even star[68] polymers (**Figure 5**). For example, all three original reports on O-ATRP mediated by PhenS, PhenN, and PhenO catalysts showed that PMMA synthesized with these PCs could be isolated and used as a macroinitiator for the synthesis

of various block copolymers.[29,34,36] Moreover, a report by Xu et al. made use of **5** to synthesize block copolymers of *N*-isopropylacrylamide and *tert*-butyl methacrylate, albeit with poor control over *Đ*.[69] Notably, in addition to chain-extending polymers synthesized via O-ATRP, polymers synthesized by other methods can be synthetically modified for use as O-ATRP macroinitiators. Thus, block copolymers containing poly(3-hexylthiophene)[45] and poly(ethylene glycol)[66] have also been realized, demonstrating the ability of these PCs to tolerate a wide range of functional groups.

Expanding on this notion of modifying existing polymers, several methods have been reported for synthesizing brush polymers from existing linear homopolymers. One approach that has already been discussed to some extent is that in which sulfonyl halides were installed on the phenyl groups of polystyrene to enable grafting of poly(methyl acrylate) chains.[39] Furthermore, fluorinated polymers with chloride-functionalized backbones have been modified using PC **3** to synthesize macromolecules with interesting dielectric properties for electronics applications (**eq 2**).[67,70] Capitalizing on the presence of a chloride moiety in poly(vinylidene fluoride-*co*-chlorotrifluoroethylene) [P(VDF-*co*-CTFE)],[71] grafting of various acrylates and methacrylates onto P(VDF-*co*-CTFE) was achieved while also avoiding metal contamination that occurs in traditional ATRP methods.[70] The impact of this reduced metal contamination was also evaluated and will be discussed further in a later section (see Section 3.4).[67] Finally, the ability of these PCs to synthesize star polymers in the presence of multifunctional initiators was investigated, yielding a range of complex star architectures with up to 8 arms that are composed of either homo- or block-copolymers.[68]

Thus, a variety of polymeric architectures have become accessible by using PhenS, PhenN, and PhenO photoredox catalysts. In particular, something that should be emphasized is the number of methods using these PCs to modify existing polymer structures and yield increasingly complex architectures. While a single method to polymerize any monomer is ideal, the reality is that most methods have associated strengths and weaknesses. However, the ability of PhenS, PhenN, and PhenO photoredox catalysts to tolerate various functional groups allows methods with complementary strengths to be combined, whether it be in a one-pot synthesis[62] or in a multiple–step synthetic sequence, giving rise to polymer architectures that might not be possible by any of these methods alone.

3.4. Avoiding Metal Contamination for Sensitive Applications

Often cited as one of the major advantages of O-ATRP,[28,29,34,36] is the use of PhenS's, PhenN's, and PhenO's for the synthesis of polymers without the metal contamination associated with traditional ATRP. Although significant advances have been made toward reducing catalyst loadings[72–74] and purifying polymers synthesized by traditional ATRP,[75–78] even trace metal contamination remains problematic in polymers for electronics applications.[67,70,71] In particular, grafting insulators, such as PMMA, to poly(vinylidene fluoride)-based polymers (PVDF) has shown promise to yield materials suitable for high-pulse capacitors, whereas residual metal ions from traditional ATRP can result in significant dielectric loss.[79] As this loss has been attributed to ion migration under an applied electric field, using an organic PC to mediate the grafting process can eliminate this issue, since any catalyst remaining in the polymer should be in the ground state and would thus not be influenced by an applied field.

In this regard, the method developed for the modification of P(VDF-*co*-CTFE) using **3** (see eq 2) was shown to be capable of activating the C–Cl bond toward hydrogenation[71] as well as O-ATRP.[70] In a later report, the impact of employing an organic PC versus a traditional copper catalyst was evaluated, demonstrating that polymers prepared via O-ATRP exhibited a far reduced ion mobility compared to polymers prepared using traditional ATRP.[67] Moreover, when comparing the materials properties of these two samples, the former exhibited both enhanced discharge energy density and discharge efficiency over a range of applied electric fields, suggesting that **3** can yield these desirable materials with reduced impact on their performance.

In addition to electronics applications, biological applications of polymers have also been cited as potentially metal-sensitive to warrant the investigation of PhenS's,[66] PhenN's,[34] and PhenO's.[36] To this end, the ability of **3** to synthesize amphiphilic

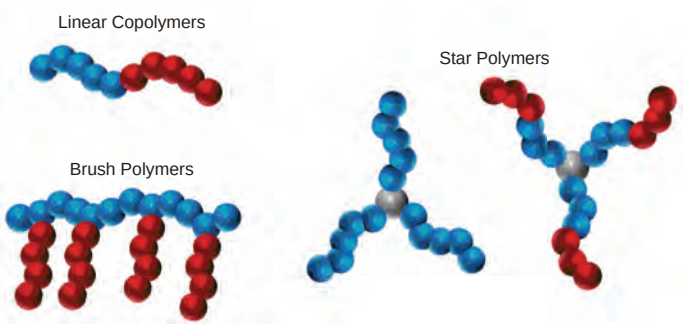
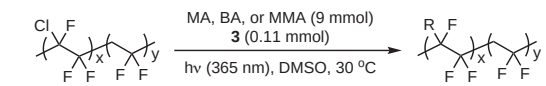


Figure 5. Polymer Architectures Synthesized Using PhenS, PhenN, and PhenO Photoredox Catalysts.

General Approach for the Modification of P(VDF-*co*-CTFE) by Reduction with PhenS Catalysts



poly(vinylidene fluoride-*co*-chlorotrifluoroethylene) [P(VDF-*co*-CTFE)]

VDF:CTFE = 94:6
1.00 g

R = H, PMA, PBA, PMMA

P(VDF-*co*-CTFE)-*g*-PMA
or P(VDF-*co*-CTFE)-*g*-PBA
or P(VDF-*co*-CTFE)-*g*-PMMA

MA = methyl acrylate; BA = *n*-butyl acrylate; MMA = methyl methacrylate

eq 2 *(Ref. 67,70)*

diblock copolymers was investigated,[66] as these materials have attracted attention for drug and gene delivery.[80,81] By modifying poly(ethylene glycol) for use as an ATRP macroinitiator, copolymers of ethylene glycol and glycidyl methacrylate could be obtained, albeit with *Đ* values well above 1.5. It should be noted, however, that organic PCs for biologically relevant polymers may be unnecessary, as copper is vital to human life and copper dietary supplements have even been used to mediate traditional ATRP.[82] Moreover, while these PCs have been shown to be biologically active molecules,[83–90] their toxicity in humans has not been investigated and should warrant further study.

3.5. Surface Modifications

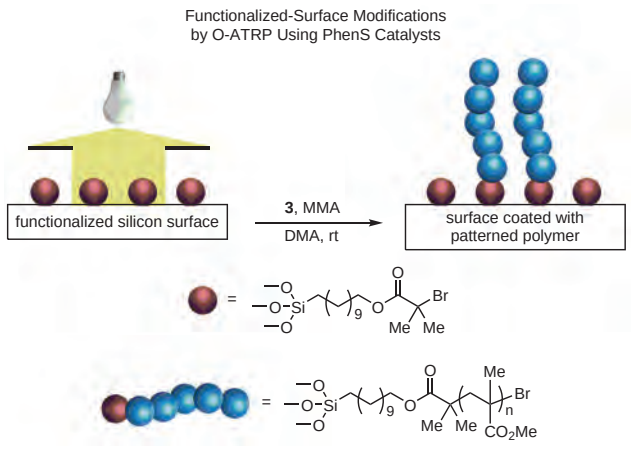
Surface-initiated polymerizations represent a versatile approach for the production of hybrid organic–inorganic materials with interesting surface properties.[91] In particular, surface-initiated ATRP (SI-ATRP) has emerged as an important technique capable of yielding such materials with precisely controlled architectures.[92] However, until recently, the production of patterned surfaces by SI-ATRP remained a challenge, requiring the use of advanced lithographic and printing methods. To overcome this challenge, a method was developed that capitalizes on the spatiotemporal control achieved in O-ATRP and allows the use of binary photomasks to produce patterned polymer coatings on functionalized silicon surfaces in a single step (**eq 3**).[92] Notably, features at even the micron scale could be produced reliably, demonstrating the high level of precision obtainable by this method.

In addition to the modification of flat surfaces, SI-ATRP photocatalyzed by **3** has also been reported using functionalized silica nanoparticles, which were simultaneously used to investigate parameters influencing PC control in the grafting process.[93,94] For example, the effects of various initiating moieties were investigated for both small (16 nm) and large (120 nm) silica nanoparticles, revealing that 2-bromo-2-phenylacetate based tetherable initiators exhibited superior performance to those with 2-bromoisobutyrate moieties.[93] Moreover, this work was extended to determine the impact of the tetherable initiator spacer length on the grafted polymer properties. Thus, it was determined that for O-ATRP, increasing the initiator spacer length results in both lower *Đ* polymer chains and higher grafting density (number of chains per unit of area).[93]

Other work in this area has focused on surfaces of other materials, including iron(III) oxide nanoparticles[95] and europium-doped hydroxyapatite,[96] capitalizing on the ability of these PCs to yield controlled polymer grafts without introduction of unwanted metal ions. Moreover, surface grafting of methacrylic acid onto a silicon wafer has also been achieved,[51] demonstrating compatibility between this monomer and **3**. As controlling the polymerization of methacrylic acid has historically been challenging for ATRP,[97] future work should undoubtedly include investigation of the ability of PhenS's, PhenN's, and PhenO's to yield well-defined poly(methacrylic acid).

3.6. Post-Polymerization Modifications

In addition to the ability to synthesize well-defined polymers for various applications, the ability to alter polymers post-polymerization is also desirable. One such example that has already been discussed is the one in which polystyrene was modified to enable grafting of methyl acrylate chains from the aromatic pendants.[39] In another example, researchers reported on the ability of **3** to remove chloride, bromide, and trithiocarbonate end-groups from various polymers, enhancing their long-term stability by removing these reactive functionalities.[98] Moreover, this method was extended to dehalogenate tethered initiators on functionalized silicon surfaces, allowing for patterns to be prepared on functionalized surfaces prior to use in SI-ATRP. Thus, the utility of these PCs has been demonstrated in a diverse range of polymer-based applications, including polymer synthesis and modification.



eq 3 *(Ref. 92)*

4. Applications in Small-Molecule Transformations

Although the primary application thus far of these strongly reducing organic PCs has been in polymer synthesis, several reports have emerged on their application in small-molecule transformations, demonstrating their broader utility as catalysts for diverse chemical reactions.

4.1. Carbon–Carbon Bond Formations

PhenS catalysts have been reported as PCs in the dehalogenation of various organic molecules (**eq 4**).[44] Much like the activation of alkyl halides in O-ATRP, the dehalogenation of organic halides—including aromatic iodides, aromatic and alkyl bromides, and aromatic chlorides—was demonstrated using PC **3**.[99] While these reactions were originally limited to dehalogenations followed by hydrogenations, the ability of **3** to mediate a radical cyclization provided evidence for a radical mechanism. Thus, this reactivity was later exploited to form C–C bonds with several substrates using PCs **3** and **14**.[44] In addition, by tuning PC reduction potentials [$E^0(^2PC^{\bullet+}/^1PC^*)$ = –2.1 V and –1.5 V vs SCE for **3**

and **14**, respectively], selectivity for certain halides over others was achieved. For example, using PC **14**, iodo functionalities in multi-halide substrates could be targeted. In contrast, and as PC **3** is more reducing, both iodo and bromo functionalities could be targeted while leaving chloro and fluoro groups intact.

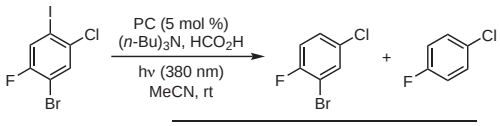
Interestingly, the ability of PhenS catalysts to activate carbon–halogen bonds was also extended to fluorides. Using PC **3** and cyclohexanethiol (CySH) as co-catalyst, C–F bonds in various trifluoromethylarenes were activated for reaction with unactivated alkenes, allowing for the alkylation of several substrates under mild conditions (**eq 5**).[100] Although this activation approaches the thermodynamic limit of PC **3**'s reducing ability [–2.07 V vs SCE for 1,3-bis(trifluoromethyl)-benzene; $E^0(^2PC^{\bullet+}/^1PC^*)$ = –2.1 V vs SCE for **3**], quenching of PC* by 1,3-bis(trifluoromethyl)benzene was demonstrated using Stern–Volmer analysis. Thus, it was proposed that such substrates could be activated to form a radical species capable of mesolytic cleavage of a C–F bond, which would then lead to reaction with alkenes to effect the desired transformations.

Finally, the trifluoromethylation of several aromatic and olefinic compounds has been reported using PC **6** under visible light irradiation of F_3C–I (**eq 6**),[101] as PC **6**'s excited state is sufficiently reducing to directly reduce CF_3I and generate $CF_3^{\bullet}$ for the trifluoromethylation reaction. While such transformations were previously accessible by photoredox catalysis, they required the use of polypyridyl Ru and Ir PCs such as *fac*-[Ir(ppy)$_3$] (**1**),[102–106] as few PCs possess the excited state reduction potentials necessary to mediate these reactions. However, due to the strongly reducing excited states accessible by PhenS's, PhenN's, and PhenO's, transformations such as these have become accessible without the need for these precious metal PCs,[101] demonstrating the potential of these organic PCs as sustainable alternatives to precious metal catalysts.

4.2. Other Coupling Reactions

In addition to the C–C bond formations described above, methodologies for C–N and C–S cross-couplings have also been reported using these strongly reducing organic PCs. For example, through the use of a dual photoredox/nickel catalytic system, the coupling of various primary and secondary amines with aryl bromides was achieved in the presence of PCs **6** or **8** (**eq 7**).[101] Furthermore, using PC **8** at 10 times less catalyst loading than the Ir PC used in the seminal report by Oderinde, Johannes, and co-workers,[107] a similar approach was employed to couple thiols to aryl bromides, yielding a range of products in moderate-to-high yields (**eq 8**).[101] It should be noted that, while similar C–S coupling reactions were reported using aryl iodides with an Ir PC,[107] aryl bromide coupling partners were ineffective in this system. Thus, this reaction (eq 8) represents an example in which these organic PCs have enabled transformations previously inaccessible using precious metals.

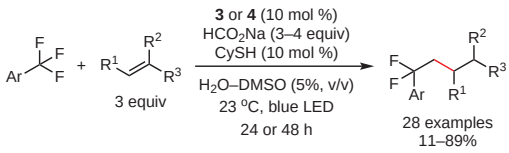
Dehalogenation Selectivity Determined by the Reduction Potential of the Photoredox Catalyst



PC	Rxn Time	Yield	Yield
14	5 h	96%	4%
3	48 h	5%	90%

eq 4 *(Ref. 44)*

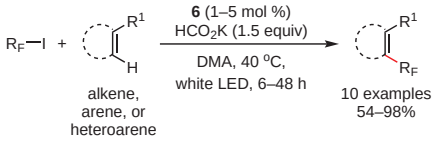
PhenS-Catalyzed Defluorination and C–C coupling of Trifluoromethylated Substrates with Alkenes



Ar = mono- and disubstituted benzene, 2-Pyr; R^1 = H, Me
R^2, R^3 = H, alkyl, terminally functionalized alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl

eq 5 *(Ref. 100)*

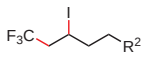
Trifluoroalkylation of Alkenes Catalyzed by Organic Photoredox Catalysts



R_F = CF_3, CF_3CF_2; R^1 = H, Me, MeO

For alkenes, the major substitution product was the trans isomer

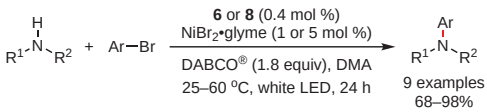
In the absence of HCO_2K, the reaction of F_3C–I with alkenes led to addition products:



R^2 = Ph, *n*-Bu, *n*-Oct, *n*-$C_7H_{14}OH$
42–49%

eq 6 *(Ref. 101)*

Cross-Coupling of Amines with Aryl Bromides by Dual Organic Photoredox–Nickel Catalysis



Ar = 4-XC_6H_4 (X = H, Ph, MeO, CF_3), 2-Np, 2-Pyr
R^1 = H; R^2 = *n*-Pr, Ph, (furan-2-yl)CH_2
NR^1R^2 = pyrrolidinyl, morpholin-4-yl

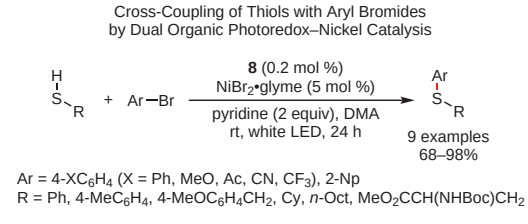
eq 7 *(Ref. 101)*

4.3. Selective Decarboxylative Olefinations

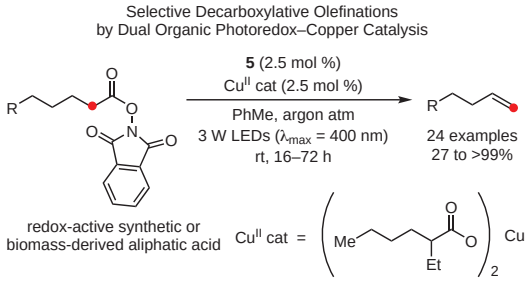
In another example of reactivity enabled by these strongly reducing PCs, PhenN's were employed in visible-light-mediated decarboxylative olefinations to yield terminal alkenes (**eq 9**).[108] The use of **5** in conjunction with a copper catalyst enabled these transformations to be performed with high selectivity (as preventing isomerization to an internal alkene had previously been challenging), under mild conditions and without the use of precious-metal catalysts. Furthermore, this method was demonstrated for a range of activated aliphatic acids, including some derived from biomass feedstocks—showing that the reaction tolerates a variety of functional groups within the substrates.

4.4. Photocatalytic Phosgene Generation for Organic Synthesis

PC **8** can generate fluorophosgene photocatalytically in situ for the synthesis of carbonates, carbamates, and urea derivatives (**Scheme 4**).[109] While the ability of phosgene derivatives to perform such transformations was previously understood, such syntheses required special equipment for handling phosgene due to its severe toxicity.[110,111] Alternatives to this class of reagents do exist, but they tend to be far less effective,[111] requiring one to choose between an effective synthesis and the safety of the associated reagents. As such, the ability of this method to generate a phosgene derivative in situ using photocatalysis is highly attractive, since the phosgene reacts quickly once generated, minimizing the risk of exposure and thus the safety concerns surrounding this reagent.



eq 8 *(Ref. 101)*



eq 9 *(Ref. 108)*

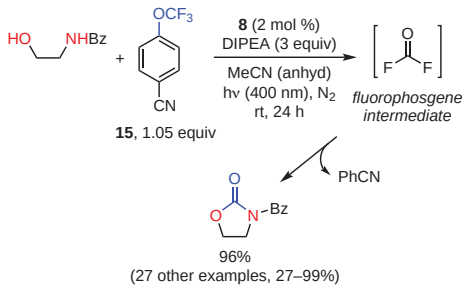
5. Mechanistic Insights Guiding Catalyst Development

Since PCs based on PhenS, PhenN, and PhenO were originally developed for use in O-ATRP, mechanistic work surrounding these PCs has primarily focused on their function in O-ATRP. Thus, mechanistic discussions in this section will be made in the context of this method, although the implications of these discoveries likely extend beyond O-ATRP.

5.1. Photoexcitation, Activation, and Deactivation in O-ATRP

As with any photoredox-catalyzed reaction, the absorption of light is the first important step to the operation of the PC. In the context of O-ATRP, visible-light absorption is preferred over absorption of UV light, as the latter has the potential to initiate undesirable side reactions. To achieve this property, synthetic modifications have been reported for various catalyst families, allowing for the design of strongly reducing but also visible-light absorbing PCs (see Section 2). Since the intensity of a light source can often be tuned with ease, this external stimulus can also be manipulated to influence light absorption by the PC (and thereby the reaction it mediates). This principle was demonstrated by polymerizing MMA in the presence of **8** under various irradiation conditions, where the emission intensity of the light source was modulated.[111,112] As a result of decreasing light intensity, molecular-weight growth during polymerization became less controlled and $Đ$ increased, indicating a loss of control over the polymerization. This result is consistent with a decrease in deactivation efficiency, as decreased light intensity yields less PC* and thereby less $PC^{\bullet+}Br^-$ to deactivate reactive radicals in solution. Significantly, the performance of **8** appeared to be influenced to a lesser extent than that of **2**, suggesting that tolerance to varying reaction conditions can be designed into these PCs.

Once a PC is photoexcited, the lifetime of the desired excited state must be long enough to allow energy or electron transfer to occur with the substrate.[5–7] In the case of PhenO's and PhenN's, activation has been proposed to occur from ^{3}PC*. As such, the lifetime of ^{3}PC* has been measured for some of the PCs in these families, including **6** (4.3 ± 0.5 μs) and **8** (480 ± 50 μs).[101] Interestingly, these lifetimes are competitive with,



Scheme 4. Photocatalytic Generation of Fluorophosgene in Situ for the Synthesis of Carbonates, Carbamates, and Urea Derivatives. *(Ref. 109)*

or even exceed, those of traditional precious-metal-containing PCs (e.g., 1.9 μs for **1**),[113,114] although only **8** has a comparable quantum yield for the triplet excited state (Φ_t = 2% for **6** and Φ_t = 90% for **8**).[101]

However, whether these PCs operate predominately via the ^{1}PC* or ^{3}PC* excited state remains to be determined. Recently, an investigation of electron transfer between photoexcited PhenN's and methyl 2-bromopropionate (MBP) was presented, suggesting ^{1}PC* may be the most important excited state in regards to catalysis for this family of PCs.[115] Similarly, mechanistic investigations related to the dehalogenation of aryl halides have suggested that **3** can operate efficiently from ^{1}PC*.[99] On the other hand, others have argued that these PCs likely operate predominately from ^{3}PC* in O-ATRP, as these states tend to be much longer-lived than ^{1}PC*.[116] Thus, further studies are required regarding which excited state species of the PC is most pertinent to catalysis, something that may prove to be case-specific.

Regardless of the nature of the excited state, the importance of photoexcitation has been demonstrated with **3**.[43] For example, upon irradiation, **3** activates methyl 2-bromoisobutyrate (MBiB) with a rate constant k_{act} = 5.8 x 10^8 M^{-1} s^{-1}, whereas in the absence of irradiation k_{act} = 1.0 x 10^{-14} M^{-1} s^{-1}, demonstrating that ground state **3** is essentially incapable of performing the necessary reduction for activation. Moreover, a comparison of the activation of various initiators suggests similar trends are observable as in traditional ATRP, such as ethyl α-bromophenylacetate (EBP) (k_{act} = 2.0 x 10^{10} M^{-1} s^{-1}) being a faster acting initiator than MBiB, while MCiB (the chloride analogue of MBiB) is a slower acting initiator (k_{act} = 1.5 x 10^6 M^{-1} s^{-1}) than MBiB.

With regard to deactivation, initial reports proposed this step may occur via bimolecular reaction between ^{2}PC$^{\bullet+}$Br$^-$ and the propagating radical, requiring ^{2}PC$^{\bullet+}$ to pre-associate with Br$^-$ prior to deactivation.[28,29,34,36,40] Alternatively, other work has suggested that this process may in fact proceed via a termolecular mechanism.[43] Using derived activation parameters, the rates of various deactivation pathways were calculated according to Marcus theory and compared to the rate of termination for evaluation of their viability. Based on these calculations, a termolecular deactivation was predicted to be more viable than other pathways involving ISET, OSET, and dissociative ET. However, these calculations did not explicitly account for the entropic penalty associated with a three-body collision, which makes termolecular reactions unfavorable,[117] especially considering the species involved are at very low concentrations in O-ATRP. Alternatively, the influence of ion pairing on deactivation in O-ATRP has been reported, supporting a bimolecular mechanism in which PC$^{\bullet+}$ and Br$^-$ form an ion pair prior to deactivation.[40]

5.2. Intramolecular Charge Transfer in the Excited State

During early investigations of PhenN's, it was observed that PCs bearing *N*-aryl substituents with EWGs or extended π systems exhibited noticeably better performance in O-ATRP (especially in regards to producing polymers possessing lower *Đ*'s) than those bearing electron-donating or electron-neutral *N*-aryl substituents.[34] Through the aid of computational chemistry, it was discovered that the electronic properties of these substituents could influence electron density distribution in the ^{3}PC* excited state, giving rise to intramolecular charge transfer (CT) from the PhenN core to the *N*-aryl substituent containing EWGs or extended conjugation. Computationally, this property can be observed by the presence of spatially separated SOMOs in ^{3}PC* (**Figure 6**), as well as by visualizing the shift in electron density upon photoexcitation using electrostatic-potential-mapped electron density diagrams (**Scheme 5**, Part (a)).[40] Experimentally, the effects of CT can be observed (i) visually through the solvatochromism of these PCs, (Scheme 5, Part (b)) and (ii) by using fluorescence spectroscopy for quantitative analysis.[35,40] Notably, this intramolecular CT is analogous to the metal-to-ligand CT,[30] which is observed in many successful metal-based PCs.[118]

After the correlation of these CT properties and their influence on the performance of the PC, several studies have

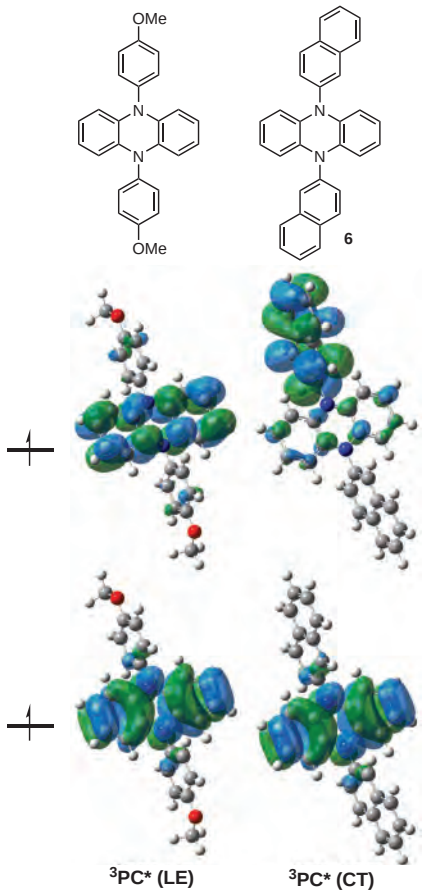


Figure 6. PhenN's Computed to Have Spatially Separated SOMOs (Right) Were Observed to Perform Better as O-ATRP Catalysts than Those That Possessed Localized SOMOs. *(Ref. 40)*

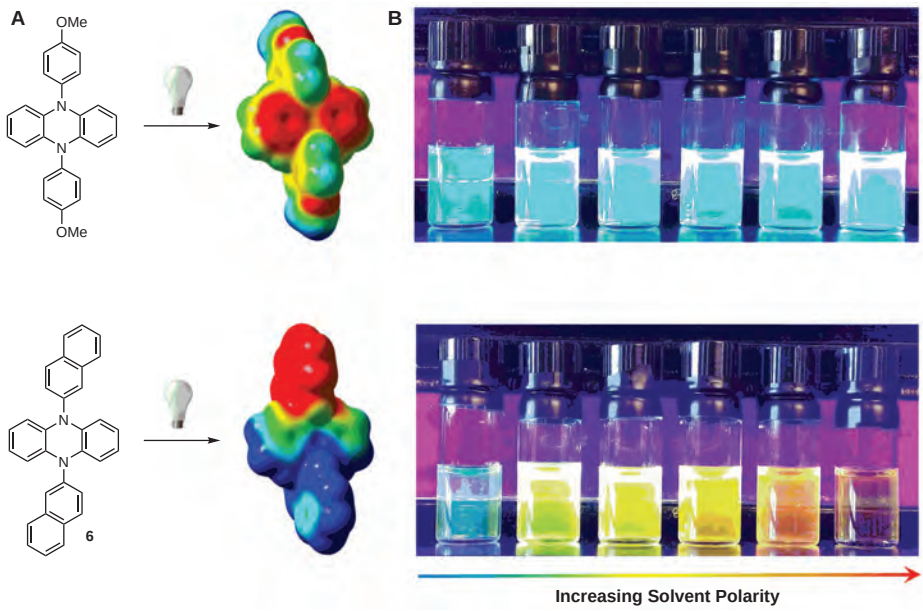
been reported on ways to manipulate CT in favor of improving polymerization control in O-ATRP. For example, following the discovery that PCs with CT character could operate in a range of solvents (whereas non-CT PCs could not), solvent optimization was performed under O-ATRP conditions for a wide range of PCs, including **5** and **6**.[41] As result, it was discovered that switching the solvent from *N,N*-dimethylacetamide (DMA) to ethyl acetate (EtOAc) can yield improved control over the polymerization of MMA, as observed through more linear growth of polymer molecular weight and lower *Đ* (1.08 in EtOAc vs 1.17 in DMA for PC **5**). In addition, a recent investigation into the photophysical properties of PCs with and without CT character has suggested that a CT excited state with perpendicular geometry and appropriate energy (e.g., PC **8**) can aid intersystem crossing (ISC) to the ^{3}PC*,[119] allowing for PCs with favorable photophysical properties to be targeted synthetically. Notably, these findings can be used to explain the observed differences in performance between CT and non-CT PCs, as improved ISC would yield a larger concentration of the active catalytic species in O-ATRP (assuming the PC operates via the ^{3}PC* excited state and not the ^{1}PC*).

5.3. Excimer Formation and Reactivity

The possibility of these PCs forming excimers has also been investigated as a means of understanding their reactivity in thermodynamically challenging reductions.[109] In an attempt to prepare carbonates, carbamates, and urea derivatives, it was observed that PC **8** was capable of reducing 4-(trifluoromethoxy)-benzonitrile (**15**), which was surprising given that this PC should not be thermodynamically capable of reducing this substrate [$E^*_{red}(^2PC^{\bullet+}/^3PC^*) = -1.7$ V whereas $E^0_{red}(\mathbf{15}/\mathbf{15}^{\bullet-}) = -2.1$ V, both vs SCE]. To explain this observation, it was proposed that PC **8** might form excimers under reaction relevant concentrations, leading to the formation of a PC radical anion and radical cation upon photoexcitation. In the absence of an electron donor, these species likely undergo a comproportionation reaction to generate two ground state PC molecules. However, upon addition of an electron donor such as an amine, it was proposed that the PC radical cation could be quenched, resulting in a longer-lived radical anion capable of reducing a substrate. Supporting these hypotheses, quenching of the radical cation upon addition of an amine was observed using transient absorption spectroscopy, and the $E^0_{red}(^1PC/^2PC^{\bullet-})$ of the radical anion of **8** was measured to be about −2.5 V vs SCE, which is sufficient to reduce **15**.[109] Thus, excimers of these PCs may offer a means of enhancing their reducing power to access more challenging transformations in the future.

6. Conclusion and Outlook

Until recently, few PCs with strongly reducing excited states existed, especially organic PCs. Thus, PhenS's, PhenN's, and PhenO's represent a unique subset of molecules that are capable of performing challenging reductions catalytically without the use of precious metals. Capitalizing on their strong excited state reduction potentials, these PC families have been widely applied to the synthesis of polymers with controlled molecular weights, low dispersities, and complex architectures. Furthermore, their ability to operate via several mechanisms



Scheme 5. Comparison of PhenN's without (Top) and with (Bottom) CT Excited States. (A) Computed Electrostatic-Potential-Mapped Electron-Density Diagrams Portraying the Distribution of Electron Density within PCs upon Photoexcitation to an Excited State, with Red Signifying Larger Populations of Electron Density. (B) Charge Transfer PCs Exhibit Large Solvatochromic Shifts in Their Emissions in Solvents of Different Polarity, While Non-CT PCs Do Not. Solvents of Increasing Polarity from Left to Right: 1-Hexene, Benzene, Dioxane, THF, Pyridine, and DMF. *(Ref. 35,40)*

(e.g., O-ATRP and PET-RAFT) has also been demonstrated. Moreover, the ability of these PC families to mediate a variety of small-molecule transformations has been reported, the scope of which will undoubtedly expand in coming years. To promote this expansion, future investigations focusing on the mechanisms of these PCs in a range of applications will be crucial, allowing for their design principles to be refined to target desired, selective transformations. Moreover, these PCs have a unique potential to increase the long-term sustainability of transformations currently mediated by precious metal catalysts. However, the sustainability of these PCs is currently hindered by the fact that all of the PCs discussed herein to date are synthesized via palladium-catalyzed transformations. Thus, future efforts should also include the development of more sustainable PC syntheses that are not dependent on precious metals.

7. Acknowledgments

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Titanium Salalen Catalysts for the Asymmetric Epoxidation of Terminal (and Other Unactivated) Olefins with Hydrogen Peroxide


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Abstract. The epoxidation of terminal, unconjugated olefins with high stereoselectivity has been a long-standing problem in asymmetric catalysis. In this review, we describe the development of titanium salalen catalysts which provide a practical solution to this problem. This type of epoxidation catalyst employs aqueous hydrogen peroxide as terminal oxidant, which makes this method even more attractive from a preparative point of view. The best salalen ligands for this purpose are derived from *cis*-DACH as the chiral building block, and the one such ligand incorporating two 3-(pentafluorophenyl)-salicylic aldehyde moieties (**9c**, "Berkessel ligand") currently affords the most effective and selective titanium catalyst in this regard. In addition to several examples of the recent use of titanium salalen epoxidation in natural product synthesis, practical hints for catalyst preparation and application are presented. Structural and mechanistic aspects of titanium salalens are briefly addressed as well.

Outline

1. Introduction

"If carbonyl compounds have been said to be 'virtually the backbone of organic synthesis', the epoxides correspond to at least 'one of the main muscles'."[1] This famous 1983 statement by Dieter Seebach highlights the fundamental importance of epoxides as building blocks in organic synthesis.[2] At that time, the development of methodology for the preparation of enantiomerically pure epoxides had just taken an enormous leap forward with the discovery of the stoichiometric Sharpless epoxidation of allylic alcohols (SE) in 1980.[3] The catalytic SE followed in 1987,[4a] and served as one of the cornerstones for the conferment of the Nobel Prize in chemistry to K. Barry Sharpless in 2001.[4b] In 1990, Jacobsen[5a] and Katsuki[6] reported independently the first efficient, asymmetric epoxidation of unfunctionalized *E* and *Z* alkenes catalyzed by manganese–

salen complexes such as **1** and **2** (**Figure 1**). More recent developments in the field of metal-based catalytic asymmetric epoxidation include iron complexes of N4-tetradentate ligands such as **3**, as reported by Costas;[7] or bishydroxamic acid ligands such as **4** in combination with vanadium, molybdenum, zirconium, or hafnium, as reported by Yamamoto.[8] In the area of organocatalytic epoxidations, numerous chiral ketone catalysts have been developed,[9] as exemplified by the highly practical Shi catalyst, **5**, first disclosed in 1996, and which is based on readily available D-fructose.[9]

Despite the vigorous development of the field of catalytic asymmetric epoxidation over two decades, one class of olefins had remained largely recalcitrant to efficient catalytic asymmetric epoxidation: terminal, unconjugated olefins ("α-olefins").

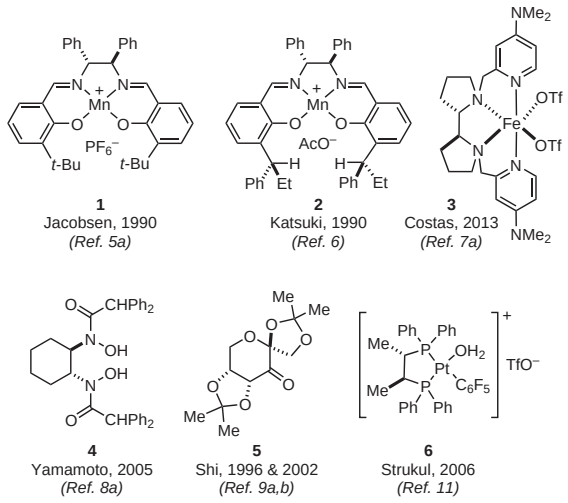
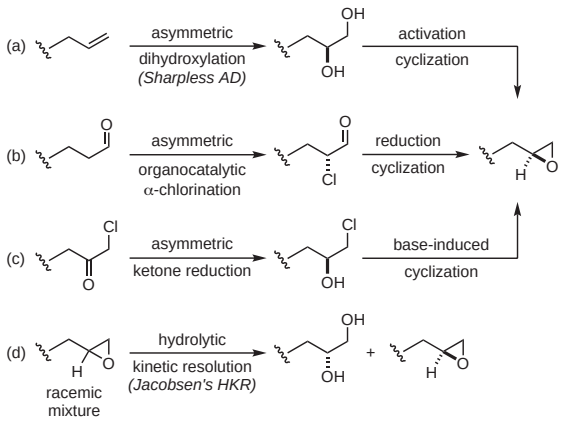


Figure 1. A Selection of Metal Complexes, Ligands, and a Chiral Ketone That Have Been Used in Recent Developments of the Catalytic Asymmetric Epoxidation of Olefins.



Scheme 1. Examples of Indirect Methods for the Preparation of Enantiopure Terminal Epoxides. *(Ref. 13–16)*

In 2000, Eric N. Jacobsen stated: "Perhaps most significant, no useful methods exist for the direct, enantioselective synthesis of terminal epoxides, arguably the most useful subset of these compounds from a synthetic standpoint."[10] For vinylcyclohexane, an α-branched terminal olefin, Shi reported in 2002 a 71% ee for the corresponding epoxide by utilizing a modified chiral ketone catalyst,[9b] and up to 85% ee was reported by Yamamoto in 2006 by employing a molybdenum catalyst.[8b] For α-unbranched terminal olefins such as 1-octene, only Strukul's pentafluorophenylplatinum epoxidation catalyst **6** (Figure 1) had achieved, in 2006, ca. 80% ee, with good yields, and using hydrogen peroxide as oxidant.[11] With this exception, no preparatively relevant method for the direct (i.e., one-step) catalytic transformation of terminal olefins into highly enantioenriched epoxides existed.[12] As a consequence, several "workarounds" were developed for this class of alkenes (**Scheme 1**).[13–16]

A typical two-step procedure consists of the application of the Sharpless dihydroxylation as the stereoselective step, followed by one of the established 1,2-diol-to-epoxide dehydrations (Scheme 1, Part (a)).[13] Alternatively, instead of α-olefins, aldehydes can be used as starting materials that are subjected to asymmetric organocatalytic α-chlorination, followed by reduction/ring closure (Scheme 1, Part (b)).[14] A related procedure involves the enantioselective reduction of α-haloketones to the alcohols, followed by ring closure (Scheme 1, Part (c)).[15] For terminal epoxides that are available as racemates in larger quantities, Jacobsen's hydrolytic kinetic resolution (HKR) is a frequently applied and highly efficient method for obtaining virtually enantiopure terminal epoxides (Scheme 1, Part (d)).[10,16]

2. Discovery of Titanium Salalen Catalyzed Epoxidation with H_2O_2

The situation changed significantly when, in 2005, Katsuki and co-workers reported their most remarkable discovery, namely that the dimeric titanium di-μ-oxo salalen[17] complex **7** is an efficient catalyst for the asymmetric epoxidation of various types of unactivated olefins—including terminal unconjugated 1-octene.[18] A Meerwein–Ponndorf–Verley reduction of the corresponding salen ligand upon treatment with Ti(O*i*-Pr)$_4$ led to salalen complex **7** (**Scheme 2**, Part (a)).[18] Two years later, Katsuki's group disclosed improved reaction conditions that allow the highly enantioselective epoxidation of various terminal and *(Z)*-1,2-disubstituted olefins (Scheme 2, Part (b)).[19] Besides the high yields and enantiomeric excesses, the use of cheap, readily available and environmentally benign aqueous hydrogen peroxide (typically 30%) as the terminal oxidant is another advantage of this new epoxidation method.[20] On the other hand, its drawback and obstacle to broad application in synthesis is the relatively demanding multistep synthesis of catalyst **7**.

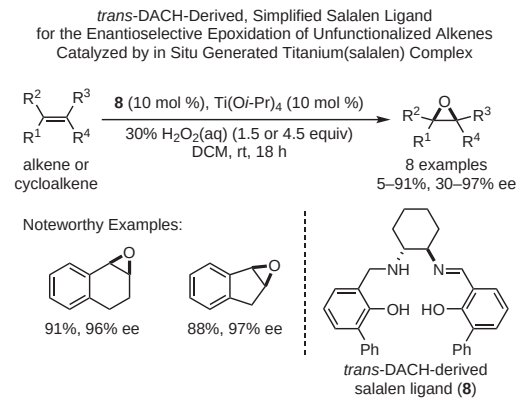
3. Further Development of Titanium Salalen Epoxidation Catalysis

After their seminal discovery in 2005, Katsuki and co-workers mostly focused on titanium salan[17] complexes, which were then

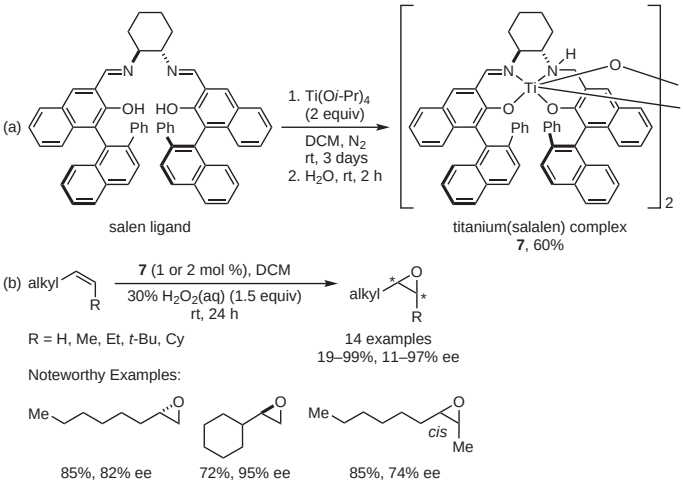
developed within a few years into highly efficient and readily accessible catalysts for the asymmetric epoxidation of *conjugated* olefins with hydrogen peroxide.[21] In contrast, we were mostly interested in the development of practical methodology for the asymmetric epoxidation of *unactivated*, *unconjugated* olefins with hydrogen peroxide, and, therefore, set out to simplify and further improve the original titanium salalen motif. Our earlier work had dealt with the use of salalen complexes for modeling metallo enzymes, and had afforded, inter alia, catalytically active peroxidase models.[22] Methodology for the synthesis of salalen ligands was thus well established in our laboratory, and it was now applied to the titanium systems. In 2007, we presented a series of significantly simplified salalen ligands, derived from *trans*-DACH (DACH = 1,2-diaminocyclohexane).[23] The corresponding titanium complexes have principally the same structure as complex **7**, i.e., they are di-μ-oxo dimers, composed of homochiral halves with cis-β configuration, arranged in the dimer in an anti fashion.[18,19,23] (See also Section 6.) While the epoxidaton of conjugated olefins such as 1,2-dihydronaphthalene or indene proceeded with quite satisfactory yields and enantioselectivities (**eq 1**),[23] the results—in particular the low conversions—for unconjugated olefins were disappointing (1-octene: 6% yield, 60% ee; vinylcyclohexane: 14% yield, 84% ee). We suspected that a competing oxidative catalyst degradation accounted for the low yields when low-reactivity olefin substrates were employed—an assumption that was later corroborated by an in-depth mass spectroscopic study using isotopically labeled ligand **8**.[24]

Our development of simple yet active and selective salalen ligands took a big leap forward in 2013 with the introduction of *cis*-DACH as chiral building block. The *cis*-DACH-derived ligands such as **9a** and **9b** proved highly stable toward oxidative degradation and, for the first time, allowed the efficient and highly enantioselective epoxidation of a variety of unactivated olefins with structurally simple ligands, using hydrogen peroxide as terminal oxidant (**eq 2**).[25,26] Aiming at even higher catalyst stability and activity, we subsequently investigated the effect of introducing fluorine and trifluoromethyl substituents in the salicylic aldehyde moieties of the ligands. This study led to the identification of the current "champion", *cis*-salalen ligand **9c**, which is derived from *cis*-DACH and 3-(pentafluorophenyl)-salicylic aldehyde.[26,27] The corresponding Ti-**9c** complex allowed the highly enantioselective and high-yielding epoxidation of a variety of unactivated olefins.

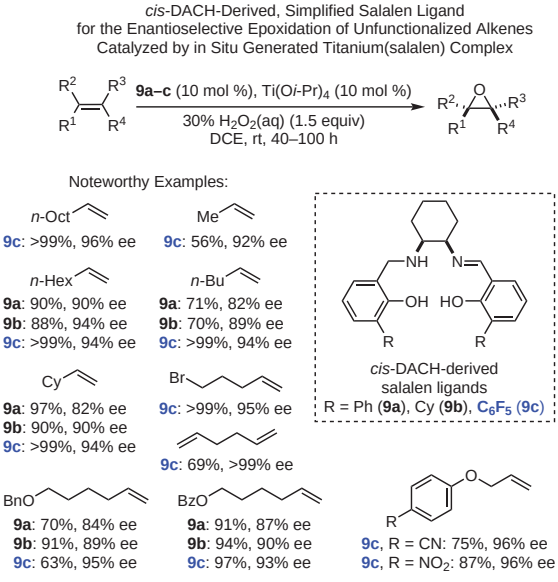
As a rule of thumb, terminal and *(Z)*-1,2-disubstituted olefins are epoxidized at comparable rates and with high



eq 1 *(Ref. 23)*



Scheme 2. (a) Last Step in the Preparation of Dimeric Titanium Di-μ-oxo Salalen Catalyst **7**. (b) Asymmetric Epoxidation of Unactivated Terminal and (*Z*)-1,2-Disubstituted Olefins with Hydrogen Peroxide as the Terminal Oxidant. *(Ref. 18,19)*



eq 2 *(Ref. 25,26)*

enantioselectivity [typically ee's for terminal olefins > ee's for *(Z)*-1,2-disubstituted ones]. Moreover, *(E)*-1,2-disubstituted substrates are epoxidized more slowly, and with low ee's. 2,2-Disubstituted and trisubstituted olefins are converted at best sluggishly and with low enantioselectivities. This reactivity pattern allows, for example, the selective epoxidation of terminal carbon–carbon double bonds in the presence of trisubstituted ones, as exemplified by substrate **10** (**Figure 2**).[28] The catalyst-induced stereoselectivity overrides the intrinsic diastereoselectivity, as shown for substrate **11**: By choosing the proper catalyst enantiomer, both epoxide diastereomers can be prepared with equal selectivity.[28]

3.1. Additive Effects

In the course of our studies, we noticed that both acidic and basic additives can significantly accelerate the epoxidation.[26] From a broader screening of acids and bases as co-catalysts, pentafluorobenzoic acid, tetra-*n*-butylammonium hydrogensulfate (TBAHS), and 2,6-di-*tert*-butylpyridine emerged as the most beneficial additives. While the transformations listed in eq 2 typically required 40–45 h for completion, the reaction time could be reduced to a more convenient 10 h—with reduction of the catalyst loading to 0.5 mol % and no loss in enantioselectivity—by employing one of these co-catalysts (**eq 3**).[26]

Katsuki's titanium salalen catalyst **7** (Scheme 2) was based on (*S*,*S*)-*trans*-DACH and two (a*R*)-binaphthyl salicylic aldehyde moieties, i.e., a total of three chiral building blocks.[18,19] After our discovery of the beneficial effect of *cis*-DACH, we became also interested in studying the combination of Katsuki's binaphthyl salicylic aldehyde motif with our novel diamine building block, and with the 3-phenyl- and 3-cyclohexylsalicylic aldehydes that had proven effective in our ligands **9a** and **9b**, respectively.[29] The structures of the resulting ligands **12**–**14** are displayed in **Figure 3**, and their corresponding titanium complexes were tested in the asymmetric epoxidation of 1-octene and vinyl cyclohexane.[29] In the series **12a**–**12d** (most closely related to Katsuki's complex **7**), up to 94% ee's were obtained for both olefins (with ligand **12c**), but only low conversions and yields were achieved, even after 100 h of reaction time. With ligands **13a**–**13d**, higher conversions and ee's up to 89% were observed. In contrast, ligands **14a**–**14d** gave high conversions and ee's of up to 94% (ligand **14d**) in relatively short reaction times (30–72 h). We could show that, with ligand **14d**, the epoxidation of 1-octene can even be performed in the absence of solvent and with only 0.5 mol % catalyst loading (72%, 96% ee).[29] With the related ligand **14b**, 78% epoxide yield and 92% ee could be achieved at a catalyst loading as low as 0.1 mol %.[29]

4. Applications of the Titanium Salalen Catalyzed Epoxidation in Natural Product Synthesis

The methodology described herein has recently found application in natural product synthesis. In 2017, Costa, Vilarrasa, and co-workers reported a formal total synthesis of the macrolide amphidinolide E, in which the preparation of building block **15**—that ends up as the C10–C17 motif in amphidinolide E—was based on the twofold application of a titanium salalen

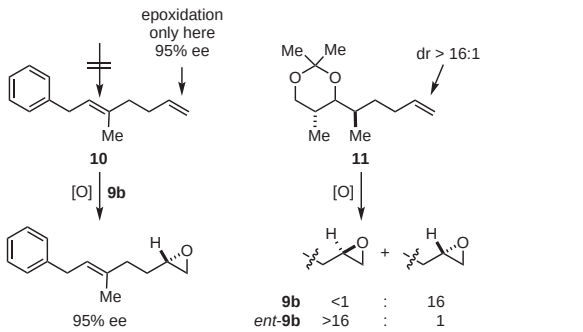
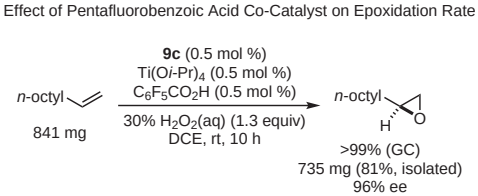


Figure 2. Regio- and Diastereoselective Epoxidations, Exemplified by the Conversion of Olefins **10** and **11**. *(Ref. 28)*



eq 3 *(Ref. 26)*

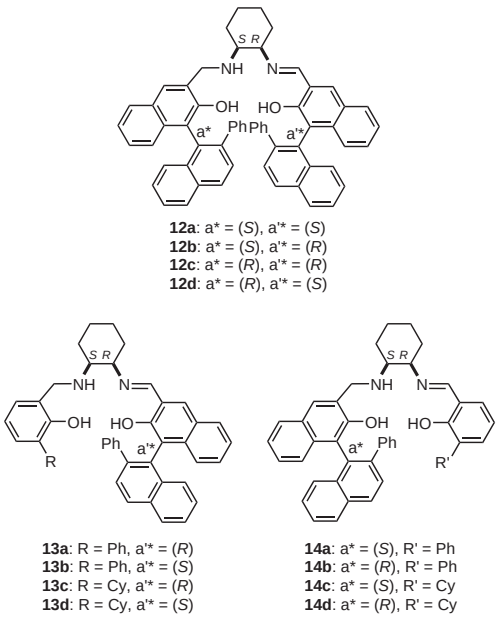
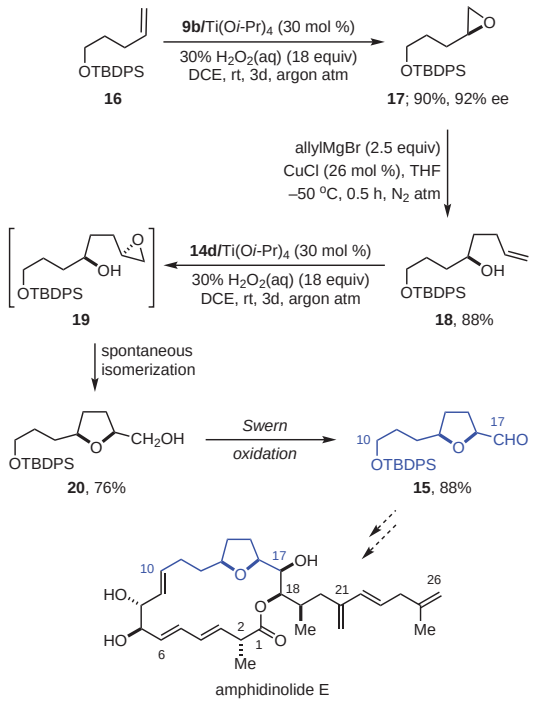


Figure 3. Salalen Ligands Derived from *cis*-DACH and Incorporating Binaphthyl Salicylic Aldehyde Motifs. *(Ref. 29)*

catalyzed asymmetric epoxidation (**Scheme 3**).[30] In the first step, *O*-TBDPS protected 4-penten-1-ol (**16**) was converted into epoxide **17** in 90% yield and 92% ee by using **9b** (see eq 2) as ligand. Epoxide opening with allylGrignard reagent and CuCl gave homoallylic alcohol **18** (88%), which was subjected to epoxidation by employing ligand **14d** (see Figure 3). The resulting hydroxy epoxide **19** isomerized instantaneously to tetrahydrofuran derivative **20**. Swern oxidation of **20** provided the desired building block, **15**.

In 2018, Stadler, Kalesse, and collaborators reported the structure elucidation of the rickiols, novel 20-, 22-, and 24-membered macrolides from the ascomycete *Hypoxylon rickii*, and the total synthesis of 24-membered-ring rickiol E3 (**Scheme 4**).[31] The total synthesis involved early on a titanium salalen catalyzed epoxidation of *O*-benzyl protected 8-nonenol (**21**) to epoxide **22** using ligand **9c** (see eq 2). Linchpin coupling of propylene oxide and epoxide **22** to 2-TBS-1,3-dithiane led to intermediate **23**, which was converted into the "southern fragment" (**24**) of rickiol E3. In this regard, a comparison was made with "workaround d" (see Scheme 1, Part (d)), i.e., the nonstereoselective epoxidation of starting olefin **21** with mCPBA followed by Jacobsen's HKR. In this two-step approach, epoxide **22** was obtained in lower yield (42%) but with virtually identical ee (95%).[31]

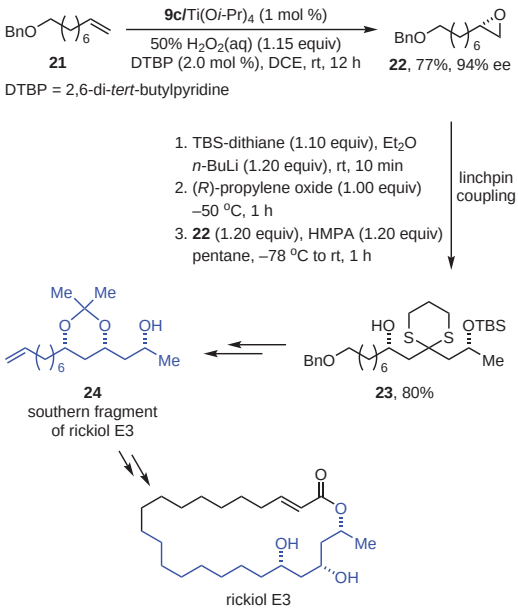


Scheme 3. Formal Total Synthesis of Amphidinolide E by Costa and Vilarrasa Involving Two Titanium Salalen Catalyzed Epoxidations Leading to Key Intermediate **15**. *(Ref. 30)*

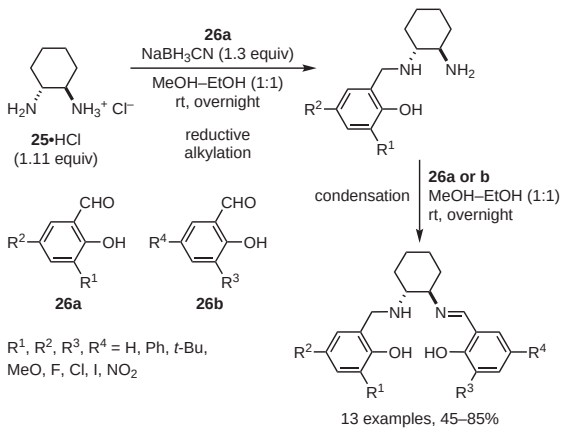
5. Accessing the Salalen Ligands, the Titanium Salalen Catalysts, and the Related Epoxidation

5.1. Salalen Ligands Based on *trans*-DACH

Salalen ligands derived from *trans*-DACH (**25**) have routinely been synthesized in our laboratory by a versatile and practical two-step procedure (**Scheme 5**).[23,24] The first step consists of reductive N-monoalkylation of the diamine, **25**, with a salicylic aldehyde, **26**, in the presence of $NaBH_3CN$ or $NaBH_4$. The monoalkylated product is then condensed with a second



Scheme 4. The Titanium Salalen Catalyzed Epoxidation as the First Step in Stadler and Kalesse's Total Synthesis of Rickiol E3. *(Ref. 31)*



Scheme 5. Synthesis of Salalen Ligands Derived from *trans*-DACH. *(Ref. 23,24)*

equivalent of salicylic aldehyde (same or different) to generate the salalen ligand. Typically, it was sufficient to employ the mono-HCl salt of *trans*-DACH (**25**•HCl) to achieve exclusive monoalkylation of the diamine component.[23,24]

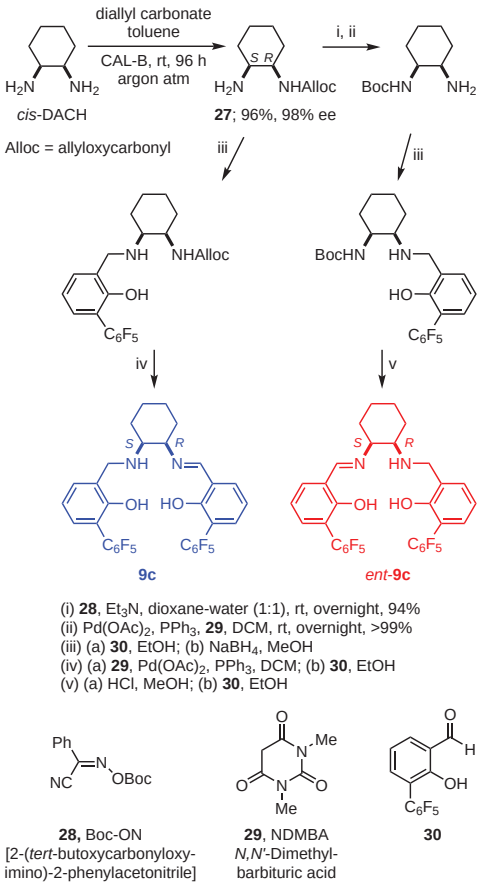
5.2. Salalen Ligands Based on *cis*-DACH

We had reported in 2010 that *cis*-DACH can be desymmetrized in an operationally simple fashion by enantiotopos-differentiating mono-*N*-Alloc protection using diallyl carbonate as the acylating agent in the presence of commercially available *Candida antarctica* lipase B (CAL-B, **Scheme 6**).[32] With enantiopure mono-Alloc *cis*-DACH (**27**) in hand, both enantiomers of the salalen ligands derived from *cis*-DACH were easily prepared, as shown in Scheme 6 for **9c** and its enantiomer *ent*-**9c**.[25,26] Typically, *cis*-DACH salalen ligands such as **9c** are obtained, after a final recrystallization from methanol or ethanol, as analytically pure yellow crystalline materials.

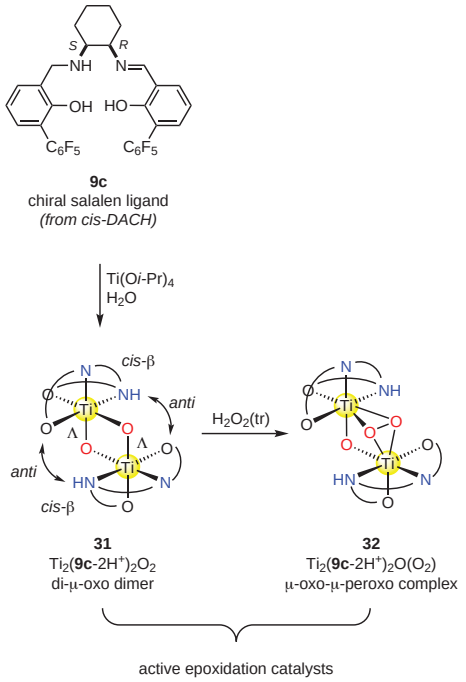
5.3. Titanium Salalen Catalysts

Mixing the salalen ligands derived from either *trans*- or *cis*-DACH with equimolar amounts of Ti(O*i*-Pr)$_4$ in a solvent such as dichloromethane (DCM) and exposing the mixture to traces of moisture (e.g., by simply opening the flask or using nonanhydrous DCM) result in complete conversion into the dimeric di-μ-oxo titanium complexes (**Scheme 7**). The procedure can be run in air, and no inert atmosphere is required. Simple evaporation of the solvent in vacuo is typically sufficient to induce crystallization, whereupon the catalytically active titanium complexes can be collected by filtration in air. A final recrystallization from methanol or ethanol affords analytically pure dimeric di-μ-oxo titanium complexes. These crystalline, yellow to orange materials such as the Berkessel-Katsuki catalyst (**31**) are bench-stable catalysts, and can be stored under air and at room temperature in brown glass containers indefinitely.

As an alternative to the isolation and use of the di-μ-oxo dimers, we have established the so-called "in situ/vac" procedure, for the in situ preparation of the active titanium complexes. For this purpose, equimolar amounts of the ligand and Ti(O*i*-Pr)$_4$ are dissolved in dichloromethane and exposed to traces of water, as described in the preceding paragraph. The solvent is then removed completely, and the remaining yellow to orange solid is dried thoroughly under reduced pressure at room temperature. This "vac" step ensures removal of the isopropyl alcohol byproduct, for which we had earlier observed an inhibitory effect on the subsequent epoxidation reaction.[25] After drying, the solid complex is taken up in the solvent of



Scheme 6. Synthesis of Both Enantiomers of the Salalen Ligand **9c** from *cis*-DACH. *(Ref. 25,26,32)*



Scheme 7. Self-assembly of the Titanium Di-μ-oxo Dimer **31** and Its Further Conversion into the μ-Oxo-μ-peroxo Dimer **32**. *(Ref. 23,25,26,29)*

choice for the epoxidation. In our hands, the "in situ/vac" generated catalysts performed epoxidations in a manner that was equivalent to that of the "isolated" catalysts.

5.4. Practical Considerations for the Titanium Salalen Catalyzed Epoxidations

Due to the better solubility of hydrogen peroxide in them, dichloromethane and in particular 1,2-dichloroethane have typically been employed as solvents for the epoxidations, while acetonitrile and ethyl acetate are viable alternatives. The epoxidations are started by addition of aqueous hydrogen peroxide, typically in one portion, to the solution of catalyst and olefin (and additive if required) in the solvent of choice. In a typical experiment, a 4–6 M solution of the olefin in 0.3–0.5 mL of solvent is prepared and 0.5 mol % of the catalytically active dimer is added. Under "in situ/vac" conditions, the latter is first prepared from 1 mol % each of the ligand and Ti(O*i*-Pr)$_4$. Typically, 1.3–1.5 equivalents of 30% or 50% aqueous H_2O_2 are used, with the latter concentration typically providing higher reaction rates. Vigorous stirring is recommended to ensure efficient mixing of the (typically) biphasic reaction mixture. No inert atmosphere is required, and the epoxidations are typically run at room temperature. Note, however, that increasing the reaction temperature above rt may well have a beneficial effect on *both* rate *and* enantioselectivity. Once reaction monitoring indicates completion, the reaction mixture is passed through a short bed of anhydrous $MgSO_4$–MnO_2 (10:1) mixture, to remove water and to disproportionate excess H_2O_2. The filtrate can then be worked up further in the usual way, ideally by distillation, and workup by column chromatography is possible as well. Under these conditions, the catalyst could be recovered intact in many instances, albeit in the form of the μ-oxo-μ-peroxo dimer. The latter are catalytically just as active as the di-μ-oxo dimers, bench stable, and can therefore be re-used without loss of activity. In our hands, 3–4 runs with the recycled catalyst were possible without significant loss of activity.

As mentioned in Section 3 and eq 3, co-catalysts such as pentafluorobenzoic acid, tetra-*n*-butylammonium hydrogen-sulfate (TBAHS), or 2,6-di-*tert*-butylpyridine (typically employed at the same loading as the catalyst) significantly accelerate the epoxidation.[26] While typical reaction times in the absence of additives are on the order of 40 h at rt (vide supra for temperature effects), the additives allow reduction of the reaction time to ca. 10 h and simultaneous reduction of the catalyst loading by 50%. When exploring epoxidation conditions for a new alkene substrate, testing of the acid/base additives mentioned is strongly recommended.

6. Structural and Mechanistic Aspects of Titanium Salalen Catalysts

All of the salalen ligands investigated by us (trans and cis) coordinate to the titanium ion in a pseudo-octahedral *cis*-β fashion (Scheme 7).[23,25,26,29] The sense of chirality at the metal center is dictated by the ligand: For example, the sense of chirality at the metal center is Λ in the complex with enantiomeric ligand **9c**. This astonishing act of molecular self-assembly is completed by *anti*-selective dimerization of the complex to the di-μ-oxo dimer (e.g., **31**). Upon exposure to hydrogen peroxide, even in very low concentrations, the di-μ-oxo dimer is converted into the μ-oxo-μ-peroxo complex (e.g., **32**) (Scheme 7).[26]

While the μ-oxo-μ-peroxo complex **32** itself does not transfer oxygen to olefins, salalen dimers **31** and **32** show virtually the same activity under the catalytic epoxidation conditions, i.e., in the presence of aqueous hydrogen peroxide. This behavior is in line with earlier observations by Katsuki and co-workers on a titanium di-μ-oxo and μ-oxo-μ-peroxo pair derived from a *salan* ligand,[21c] and we share Katsuki's conclusion that the μ-oxo-μ-peroxo complex serves as a reservoir species that needs to be activated further for oxygen transfer to occur.[21c] The mechanistic details of this activation process for *cis*-DACH derived titanium salalen complexes are currently under investigation in our laboratory.[33]

7. Conclusion

For the synthetic organic chemist, titanium salalen catalysts efficiently close a gap in synthetic methodology, namely the one-step, high-yield, and highly enantioselective epoxidation of unactivated olefins—in particular, terminal, unconjugated ones. As an additional benefit, this type of epoxidation uses aqueous hydrogen peroxide, a readily available, safe, and environmentally benign terminal oxidant. Reported first in 2005 for *trans*-DACH derived complexes by Katsuki and co-workers,[18] our research efforts have since furnished the novel class of *cis*-DACH derived salalen ligands, in particular bis(pentafluorophenyl)salalen ligand **9c**, which exhibits outstanding stability, catalytic activity, and stereoselectivity.

8. References and Notes

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About the Author

Albrecht Berkessel was born in 1955 in Saarlouis, and obtained his Diploma in 1982 at the University of Saarbrücken. For his Ph.D. studies, he moved to the laboratory of Professor Waldemar Adam at the University of Würzburg. In 1985, he obtained his Ph.D. degree (*summa cum laude*) for mechanistic studies on the photochemistry of divinyl ethers. The same year, he joined the research group of Professor Ronald Breslow at Columbia University, New York, as a Lynen Fellow (Alexander von Humboldt Foundation) to work on functionalized cyclodextrins as enzyme models and on the mechanism of biotin action. In 1986, he returned to Germany to start independent research on the mechanisms of nickel enzymes from methanogenic archaea. His "Habilitation" at the Goethe University of Frankfurt/Main, in association with Professor Gerhard Quinkert, was completed in 1990, and he was then appointed "Privatdozent". In 1992, he

became Associate Professor at the University of Heidelberg. Since 1997, he has been Full Professor of Organic Chemistry at the University of Cologne. His current research interests center around mechanistic and preparative aspects of metal-based catalysis, organocatalysis, biocatalysis, and biological/medicinal chemistry.

Professor Berkessel has held visiting professorships at the University of Wisconsin, Madison; the Research School of Chemistry of the Australian National University, Canberra; the National University of Singapore; Chuo University, Tokyo; and, recently, a Distinguished Visiting Professorship at Kyoto University, Japan. His awards include the Young Faculty Award of the Fonds der Chemischen Industrie, and the Award in Chemistry of the Göttingen Academy of Sciences. Professor Berkessel is the recipient of the Horst-Pracejus-Preis 2019 of the German Chemical Society. He has published more than 200 research papers and is one of the two authors of the Wiley-VCH bestseller *Asymmetric Organocatalysis* (2005).

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