Synergy between experimental and computational approaches to homogeneous photoredox catalysis

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In this Frontiers article, we highlight how state-of-the-art density functional theory calculations can contribute to the field of homogeneous photoredox catalysis. We discuss challenges in the fields and potential solutions to be found at the interface between theory and experiment. The exciting opportunities and insights that can arise through such an interdisciplinary approach are highlighted.

Introduction

Homogeneous photoredox catalysis has emerged as a powerful activation mode for chemical synthesis.1–3 Although the underlying principles have been known for several decades, the current widespread applications in organic synthesis originated from a renaissance of the field in 2008.4,5 These seminal works demonstrated how visible-light photoredox catalysis could enable elusive and selective transformations of high value for molecular construction. Since then, the field has virtually exploded and photoredox catalysis has proved its utility in complex molecule synthesis.3,4,6–9 Most impressively, photoredox catalytic methods enable a highly attractive strategy for late-stage functionalization of complex molecules (Fig. 1).10

Density functional theory (DFT) is one of the most widely used theoretical methods for studying catalytic processes.11–14 Its dependence on electron density allows DFT to be computationally efficient and affordable when compared to the most accurate coupled-cluster approaches.15,16 Even though the latter are accurate in non-relativistic theory, their utility is limited for realistic systems because too many atoms are usually involved. In contrast, DFT can be used in calculations involving realistic molecular models with reasonable computational cost and accuracy.15,16 There have also been improvements in DFT-techniques in recent years when it comes to solvent effects and relativistic corrections. Therefore, it remains a powerful computational approach for achieving reasonable theoretical results.

In this Frontiers article, we would like to highlight an area in which homogeneous photoredox catalysis can have

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enable prediction of absorption properties as well. The
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potent photocatalysts for given reaction systems. Furthermore,
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strate–catalyst and ligand–metal combinations when designing
potent photocatalysts for given reaction systems. Furthermore,
UV/Vis-absorption wavelength ranges for photocatalysts can
be estimated using time-dependent (TD)-DFT, which would
enable prediction of absorption properties as well. The
approach has also been used to accurately calculate the electro-
chemical potentials of various organic molecules. Overall,
a range of interesting parameters can be computed using
DFT, however, proper validation of such computations by
comparison with experimental data is essential.

The photocatalytic cycle harvests photon energy to fuel the
chemical reaction in question (Fig. 1). It does not directly
involve bond-breaking and bond-forming events (as known to
date). As such, it is of broad interest to develop multifunc-
tional catalytic systems, capable of catalyzing bond-rearranging
events in addition to the light harvesting process. A few
examples exist of such catalytic systems and this field is
growing rapidly. This is also an area in which DFT could
be utilized for design, studies of properties and development
of predictive tools, particularly considering that preparation
of complex catalyst systems could be highly resource and time
consuming.

Catalysts, mechanism and properties

Although widely used in transition metal catalysis, DFT
has not been employed actively in the field of homogeneous
photoredox catalysis. This is surprising, since DFT can offer
insights through estimations and modelling of a range of
molecular properties and reaction parameters of relevance.
Experimental mechanistic studies of visible-light photo-
catalyzed transformations have become the subject of intense
efforts in several research groups. Although many
experimental tools exist to investigate the mechanistic
phenomena of such reactions, computational techniques can
offer a range of supporting and complementary insights. DFT
is particularly useful for studying mechanistic details unattain-
able by any other means.

A recent study showed how DFT can be employed to calcula-
ted a broad range of transition metal photocatalysts with good
accuracy. Obtaining experimental excited-state redox potentials is
not straightforward, and the study demonstrates that DFT can
be a powerful tool for property predictions and catalyst design
in this area (Fig. 2). Such methods can potentially assist the
ongoing efforts in designing new catalysts with considerably
minimized costs. Moreover, DFT could suggest suitable sub-
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Late-stage functionalization

The purpose of late-stage functionalization can be two-fold.
Either one wishes to (1) install a specific functional group in
the desired position of a molecular scaffold if the objective is
target synthesis or (2) install a variety of groups in different
positions if the objective is chemical library diversification.
In both cases it would be advantageous to have at one’s dis-
posal diverse structural elements to introduce in a selective
manner. As such, an important area within late-stage photo-
catalytic C–H functionalization will be to develop a broad
range of versatile precursors capable of activation in a given
catalytic system. A recent important example is the late-stage
methylation of voriconazole (Scheme 1). The introduction of
small alkyl groups in selected positions of drug candidates is
of high interest in medicinal chemistry. Such groups can
potentially fine-tune properties related to bioavailability and
stability. New peroxide-based reagents were developed
capable of selectively delivering small alkyl groups via photo-
redox catalysis. This was thoroughly demonstrated in site-

![Fig. 1](image1.png)

**Fig. 1** Basic principles of photoredox catalysis in organic synthesis. The photocatalyst harvests photon energy and transforms it into chemical potential that can be exploited for selective complex molecule construction. Radicals can be generated in both the reductive and oxidative quenching cycles and can then undergo the desired functionalizations of complex molecules.

![Fig. 2](image2.png)

**Fig. 2** Redox properties can be predicted with reasonable accuracy for a range of transition metal photocatalysts. The figure shows the correlation between experimental and predicted redox potentials for a range of common photocatalysts, adapted from ref. 25.
selective methylation of several complex drug molecules. The specific catalyst needed was obtained through robotically assisted screening. Clearly, a multitude of interrelated problems must be considered when designing a desired functionalization strategy, including the stability, versatility and redox properties of the radical precursor and catalyst, in addition to understanding and predicting the site selectivity of the ensuing functionalization process.

Although several examples now exist,1 a major advance in photocatalytic late-stage functionalization chemistry was reported by Nicewicz and co-workers in 2015.36 The team achieved selective aryl C–H amination with a range of N–H containing heterocycles using organic photoredox catalysis (Scheme 2). The work is remarkable considering the central role of such heterocycles in both medicinal development and organic materials chemistry. Moreover, since the transformation is achieved at a late-stage on a relatively inert C–H bond, it can enable rapid access to heterogeneous-functionalized chemical libraries. This transformation, and future variants of this kind, are truly enabling chemical technologies and can have tremendous impact in many areas that rely on chemical library development in which heterocyclic structures play a major role.

Understanding mechanistic details in the type of transformation discussed above and being able to predict it would be a central goal for applications of DFT in homogeneous photoredox catalysis.25,37–39 We have recently employed DFT calculations to support a proposed photocatalytic mechanism of the C–H functionalization of indoles based on predicted redox potentials and comparison of various possible mechanistic pathways (Scheme 3).25 Another aspect of the mechanism so far not addressed concerns site-selectivity. Although it would be easy to predict for simple indoles by most chemists, it may not be straightforward in more complex molecules with multiple potential reaction sites. If one could reliably predict sites of late-stage C–H functionalization in complex molecules and suitable catalysts using DFT, this would be an invaluable tool for planning molecular construction and designing chemical libraries using this chemistry. A lot of experimental data is available on radical site selectivity and recent notable studies include those of Baran40 and others.41–43 DFT can be employed to correlate the extensive experimental observations in this area with computed parameters and properties to advance and simplify predictions.37 This would be a highly desirable tool for synthetic planning with late-stage photocatalytic C–H functionalization.

Computational challenges and possibilities

A range of challenges in computational methodologies must be addressed in order to enable accurate predictions and modelling of photochemical events. Considering solvent effects in theoretical studies of chemical reactions is one of the major challenges. Modelling the condensed phase of reactions is often crucial to get reasonable agreement with experiment and to successfully predict reaction mechanisms. There are a few theoretical implicit solvent models that are widely used to model condensed-phase reactions, such as the conductor-like screening model (COSMO),44 the polarizable continuum model (PCM)45 and the solvation model based on density (SMD).46 Explicit solvent models that include discrete solvent molecules distributed around the solute, where specific solvent–solute interactions are taken into account, are other possibilities. The latter models are still too costly for DFT due to the number of solvent molecules needed for a good description. In this aspect, there are continuous efforts to refine and enhance models to incorporate better descriptions. Among these, the hybrid quantum mechanics/molecular mechanics (QM/MM) method,47 which treats the core part of the realistic molecular model using QM and the outer region involving the explicit solvent molecules using MM, and the polarizable embedding (PE)18,49 in which the classical region is rep-
resented by an electrostatic potential with up to octupole moments and induced point dipole moments are notable. These models maintain a very accurate description of the core molecule or reaction center, whilst influences from the larger solvation sphere are still included (Fig. 3).

The most widely used catalysts in photocatalytic synthetic reactions are complexes of transition metals, although organic molecules with the appropriate redox properties are increasingly popular.\(^\text{36}\) In the case of transition metal catalysis, modelling or designing effective catalysts for specific reactions using computational methods involves the treatment of relativistic effects. The computational program packages used to treat relativistic effects available to date are very limited. In many theoretical studies such effects are treated through effective core potentials (ECP), which allow implicit treatment of the core electrons of the metal atoms and include relativistic corrections through parameterization. However, if one aims for accuracy in the calculations involving heavy atoms the use of ECPs may not be enough. In such cases, the use of two-component (e.g. the spin–orbit zero-order-regular approximations (SO-ZORA),\(^\text{50}\) the Douglas–Kroll–Hess (DKH)\(^\text{51}\) or the exact two-component (X2C)\(^\text{52–54}\) and the four-component (Dirac-Coulomb)\(^\text{55}\) relativistic Hamiltonians should be considered. In the latter case, the catalyst size and many other chemical species in the reaction medium limit its use. Tremendous improvements have been made during the last decade in optimizing the program packages based on the two-component relativistic Hamiltonians to be used for such calculations. One good example is the Amsterdam density functional (ADF)\(^\text{56}\) which offers possibilities for ZORA calculations.

Theoretical studies of transition metal photocatalysts using relativistic approaches consider full geometry optimizations and vibrational frequency calculations in both ground and excited states. There are limitations in the latter type of calculations\(^\text{57}\) as there are no implementations for TD-DFT analytical frequency calculations in the most commonly used program packages. However, there is a possibility of calculating the vibrational frequencies numerically. There is a hope that this will be solved very soon.\(^\text{58,59}\) Besides the current limitations, DFT will continue to expand and define its central role as an attractive, state-of-the-art method enabling deep understanding and design of new experiments in catalytic chemistry.

**Future outlook**

As progress continues into an exciting era for homogeneous photoredox catalysis, there is a constant need for deeper understanding of catalyst properties, selectivity and reactivity to refine the chemical methods into enabling technologies. The power of deep understanding lies in its enabling potential as it allows us to predict and streamline chemical synthesis. In particular, a thorough understanding of principles involved in photocatalytic late-stage functionalization would be of paramount importance for molecular design from a synthetic organic chemistry perspective. We can be in a better position to design new chemical reactions and catalysts for the synthetic toolkit through thoughtfully employed quantum chemical calculations. DFT can provide unique and detailed insights into a variety of elementary chemical processes at relatively low cost. The benefits of enlightened, guided and streamlined experimental chemistry are too great to dismiss, and we anticipate that the full potential of photoredox catalysis in organic synthesis will be reached through a synergistic effort of experimental and computational research.

**Acknowledgements**

This work has received support from the Research Council of Norway [grant number 179568/V30] and the Department of Chemistry at UiT The Arctic University of Norway.

**Notes and references**
