Final Technical Report Cover Page

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1.0 Executive Summary

Strategies that explore/evaluate alternative energy streams, including the bio-renewable feedstocks that can be transformed into fuels or value-added chemicals, will facilitate and secure U.S. leadership in alternative-energy technologies and advance U.S. competitiveness. Development of catalytic hydrogen transfer reactions through the design of metal-ligand complexes is an enabling technology for processing bio-derived alcohols into chemical building block synthons. The goal of this DOE-funded project was to investigate the fundamental science related to the development of homogeneous (de)hydrogenation catalysts in order to enable energy-relevant transformations of bio-relevant chemical feedstocks including ethanol. The primary focus was to improve the activity of ethanol upgrading catalysts, specifically informed through mechanistic studies, in order to enable rational design optimization strategies. Following in depth mechanistic studies, targeted reaction optimization approaches included: 1) ligand redesign to improve catalyst stability, 2) development of new carbon-carbon bond forming reactions using ethanol as a precursor, and 3) examination of photochemically-mediated reactions, ultimately to facilitate integration within other reactor designs such as continuous flow reactors. These new approaches to study such transformations are directly relevant to DOE's missions, which include C-H-O activation for selective reduction and oxidation of fossil- and biomass-related conversions that can be adapted for energy generation and storage.

The methods used in this proposal were largely mechanism-driven and relied on in situ and ex situ studies. These analyses served to identify the operative pathways and activity-dependent steps so that higher efficiency catalysts could be re-engineered. Iterative catalytic reaction sequences were used to directly process alcohols into useful chemical building block synthons. Photochemical strategies also provided a new avenue to improve reaction conditions. The high modularity of the catalyst components (ligands) has enabled the preparation and analyses of multiple catalyst precursors that vary in their electronic and steric characteristics. These studies uncovered an unexpectedly beneficial substitution pattern of the ligand structure. A key outcome of the DOE project was the development of new catalysts that are the best in class for upgrading ethanol to butanol with a turnover number of 155,890 and a turnover frequency of 12,690 h^{-1}. In addition to upgrading ethanol to butanol, cascade reaction sequences were developed to form new C-C bonds using ethanol as a bio-relevant feedstock, providing access to platform chemicals from renewable sources. As part of the reaction discovery process, new mechanistic details were uncovered that provided insights into: a) catalyst speciation, b) decomposition pathways, c) carbon monoxide releasing pathways, and d) carbon-carbon and carbon hydrogen bond breaking pathways. Most of these outcomes were previously not known; however, they provided important directions for new catalyst design strategies. Finally, use of high throughput and in situ photochemical reaction analyses enabled detailed studies into changes to the catalyst structure upon irradiation. Irradiation was found to improve hydrogen transfer catalysis by promoting a ligand dissociation event.

Homogeneous catalysts can serve a unique role toward the development of processes for converting renewable feedstocks derived from non-edible biomass into value-added fuels and/or chemical building blocks. In this context, efficient catalytic systems to convert renewables to useful fuels or platform chemicals are critically needed for their sustained use. The funded DOE-supported research efforts impact the efficiency of conversion of matter into fuels, chemicals, and materials, while minimizing the impact to the environment. This project contributed to a broader goal of securing energy independence by providing a means to utilize renewable feedstocks to produce biofuels and chemical precursors, ultimately to displace a share of petroleum-derived fuels and encourage a domestic bioenergy industry.

2.0 Background

The PI and co-PI are chemistry professors at the University of Michigan and have complementary expertise ranging from ligand design, inorganic structure/bonding, homogenous catalysis, photochemical transformations, continuous processing chemistry, and organic methodology. These scientific backgrounds afforded a unique a synergy to achieve the project goals. Long-term goals of both research groups are to develop new chemical reactions that transform renewable feedstocks into value added fuels and platform chemicals.

3.0 Project Objectives

The objectives of the proposal were to develop new strategies to use coordination complexes to transform biorenewable feedstocks into fuels, chemicals, and materials. Emphasis was placed on mechanistic inquiry to guide catalyst (re)design for hydrogen transfer (Objective 1), enhance reactivity with photochemistry (Objective 2), and investigate flow-processes for valorization of reactive intermediates (Objective 3). Several substrate and catalyst classes were canvassed to enable selective and efficient upgrading of biorenewable feedstocks, such as ethanol, to drop-in gasoline additives and useable chemicals. The workflow used structure/function relationships to optimize catalysts, followed by photochemical strategies to further improve catalyst activity. These efforts were envisaged to interface with alternative reactor designs such as continuous flow processing to control reaction selectivity and ultimately provide an avenue for the synthesis of myriad platform chemicals derived from ethanol upgrading (Objective 3).

Project Goals:

1) Establish catalyst design principles to enable catalytic upgrading of biomass-relevant alcohols.
2) Develop photochemical strategies to enhance activity of hydrogen transfer catalysts.
3) Exploit continuous flow reactors to control and improve reaction selectivity and provide diversified products.

4.0 Description of Activities Performed

The goals of the research performed during the last grant period were to uncover catalyst design principles to enable upgrading of ethanol to higher order fuels and platform chemicals. Effort was placed on developing: 1) tandem catalytic upgrading reactions to further diversify higher order products derived from ethanol, 2) mechanistic understanding to enable the preparation of highly active ruthenium catalysts, and 3) low temperature and photo-driven hydrogen transfer reactions. Note that the majority of this project was active during the COVID era, which impacted project continuity, continuous staffing, and publication output.

1) Optimization of catalysis

To provide new routes to platform chemicals from EtOH, we targeted a single pot cascade reaction sequence to intercept the products of the initial Guerbet reaction (ethanol to 1-butanol) using Ru(BPI)(PPh_3)$_2$Cl (BPI = 1,3-bis(2'-pyridylimino)isoindolate). To increase the value of ethanol-derived products, we evaluated carbon-carbon bond forming reactions using carbon pronucleophiles or ylides. The critical challenge to overcome for these reactions was to minimize the amount of ethanol present prior to the addition of the carbon pronucleophile to maximize the amount of higher-order alkyl group (Bu, Hex, etc) incorporation. Our initial results for ethanol

upgrading were performed in neat ethanol, and an extensive solvent screen revealed that use of co-solvents has a large impact on the ratio of ethanol to 1-butanol formed, ranging from 180 : 1 (DMF) to 1 : 2 (mesitylene). We probed numerous hypothesized selectivity-determining steps and uncovered an important result that the base counter cation plays a large role to influence the Guerbet reaction. Our initial experiments used alkali metal O^{t}Bu bases. To introduce alkali metals without dramatically changing their solubility in mesitylene, we used a combination of an organic superbase (phosphazene P$_4$-^{t}Bu) with metal BArF$_{24}$ (ArF$_{24}$ = 3,5-trifluoromethylphenyl) salts. We uncovered a correlation between the formation of carboxylate salts (via a Cannizzaro pathway) and the counter cation: lithium minimized carboxylate formation while potassium maximized carboxylate formation. Interestingly, sodium provided the highest yield of Guerbet alcohols, and likely reflects an intermediate reactivity regime, providing an appropriate balance of acidity and reactivity.

Tandem C-C bond forming reactions

Using mixtures that mimic the reaction components after the ethanol upgrading reaction, we evaluated the second (alkylation) step of the reaction sequence with each substrate using 1-butanol as the substrate. Reactions using fluorene, 2-naphthylacetonitrile, and acetophenone provided butylated products in 51, 91, and 20% yields, respectively. We combined the results of both sets of optimization data and evaluated a one-pot tandem reaction sequence to directly upgrade ethanol to butylated and hexylated products using fluorene as a representative substrate. The reaction yields and selectivity profiles were initially highly variable and sensitive to solvent volume and stir rate; these properties necessitated extensive controls and replicate data to ensure batch to batch reproducibility. After optimizing the physical reaction parameters, we evaluated the effects of stoichiometry, temperature, time, base, counter ion, and catalyst identity.We identified four representative substrates amenable to a tandem Guerbet/alkylation reaction: fluorene, 2-naphthylacetonitrile, acetophenone, and a phosphonium ylide. Fluorene underwent alkylation in 98% combined alkylation yield, acetophenone and 2-naphthylacetonitrile underwent alkylation without self-condensation, giving 79% and 84% combined alkylation yield. Finally, this strategy enabled the alkylation of phenyldiacetonitrile (74% alkylation at both nucleophilic positions), an industrially relevant substrate commonly used in condensation/polymerization reactions. Alkylation of such precursors provides subsequent polymers with distinct morphologies and properties. Finally, we developed the first example of a tandem ethanol dehydrogenation/Wittig olefination. Introduction of a phosphonium ylide to the standard Guerbet conditions afforded 76% olefination products in addition to Guerbet alcohols. We found that only the trans styrene formed, which we attribute to Ru-catalyzed olefin isomerization. Overall, these results illustrate ethanol can be valorized with appropriate reaction optimization (Figure 1).

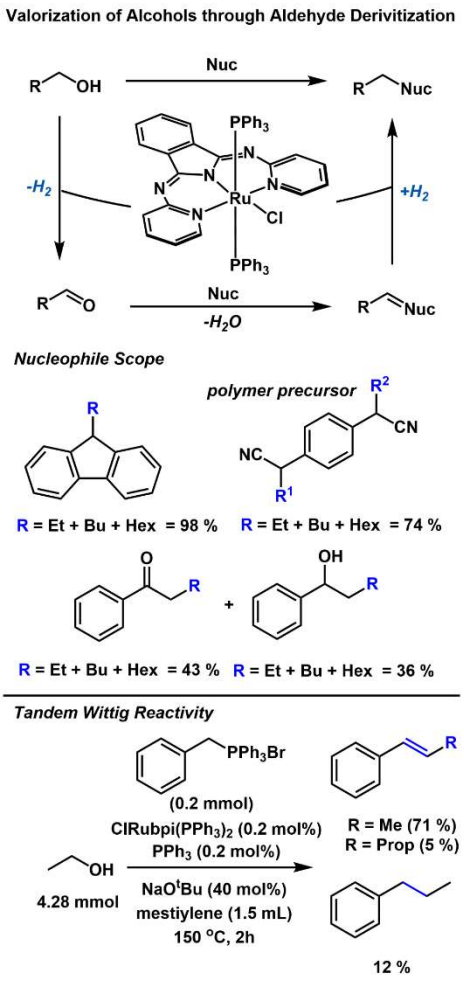


Figure 1. Tandem alcohol dehydrogenation/alkylation.

2) Mechanistic understanding to enable the preparation of highly active ruthenium catalysts

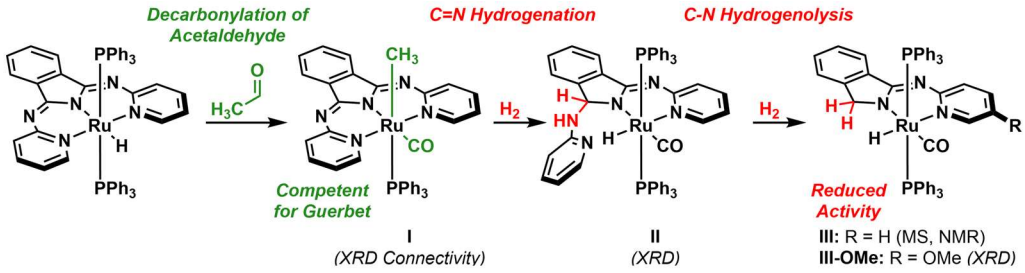


Figure 2. Identification of catalyst decomposition products from the Guerbet reaction.

We performed a series of mechanistic studies for the $Ru(BPI)(PPh_3)_2Cl$-catalyzed Guerbet reaction by employing both *in situ* IR and *ex situ* NMR/ESI-MS experiments to examine the time profile for catalytic intermediates as well as the terminal Ru-complexes. We identified two important pathways: 1) rapid generation of Ru carbonyl species (via the decarbonylation of ethanol), and 2) hydrogenolysis of the BPI ligand backbone. In situ reactIR analyses of the Guerbet reaction indicated the rapid growth of a ruthenium carbonyl species at 1909 cm^{-1} for 14 minutes, followed by gradually conversion to a second carbonyl species at 1918 cm^{-1}. NMR, ESI-MS, and XRD analyses of the ruthenium complexes as the reaction progressed revealed the generation of series ruthenium carbonyl species. The methyl carbonyl species **I** was formed within the first 15 minutes (via acetaldehyde decarbonylation). Over the remaining two hours, two bidentate complexes **II** and **III** formed, via hydrogenation and hydrogenolysis of the bpi C=N bond, respectively. Although **I** was competent for Guerbet (56% yield in 2 h) reactivity, a variant of **III** that could be independently prepared (**III-OMe**) showed reduced activity (29% in 4 h). These results indicate two key steps in the degradation of the catalyst: 1) decarbonylation of aldehydes, and 2) hydrogenation of the N=C bond.

Decarbonylation Pathway:

Although decarbonylation of aldehydes and alcohols most often generates carbonyl hydrides,[33-36] alkyl carbonyl complexes can also be generated.[37,38] During the Guerbet reaction, $Ru(BPI)(PPh_3)_2Cl$ was converted into the methyl carbonyl complex **I**; surprisingly, the analogous carbonyl hydride was not observed. DFT analyses (B3LYP-D3(BJ)/def2-TZVP//PCM(mesitylene)) established that the carbonyl hydride complex is 17.7 kcal/mol lower in energy than the formation of **I** with release of H_2 (Figure 3). These DFT results indicate that decarbonylation by the $Ru(BPI)(PPh_3)_2Cl$ precatalyst affords the kinetic (**I**), rather than thermodynamic product.

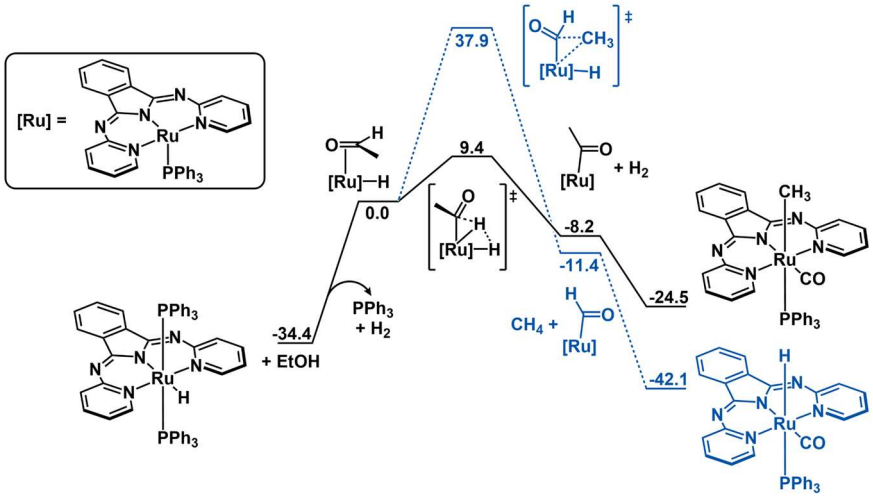


Figure 3. Identification of catalyst decomposition products from the Guerbet reaction.

The reaction sequence to form **I** proceeds through a Ru-acetyl intermediate via α C-H bond cleavage followed by H_2 release. We found that an analogous sequence that cleaves the C-C, rather than the C-H bond of acetaldehyde, in the first step has a barrier for C-C bond cleavage that is

28.5 kcal/mol higher than that for C-H bond cleavage. This result is consistent with distinct orbital requirements needed for C-H vs. C-C bond cleavage, which causes scission of the C-H bond to be kinetically favorable.[40,41]

Following these observations, we undertook independent syntheses of these intermediates to assess which of these two pathways (if any) impart decreased catalytic activity. These syntheses required unique synthetic approaches to generate partially deconstructed ligands. We note that some of these bidentate ligands (e.g. 1-(2-pyridylimino)-isoindoline (pi)) have not been previously reported, and thus we disclosed the first synthesis of such metal complexes. After preparing these complexes, we evaluated their catalytic competence and found an important, unexpected result: the primary degradation pathway is ligand hydrogenolysis.

Catalyst Redesign

Catalyst redesign efforts have focused on preventing the N=C hydrogenation reaction, which we found is the most important feature in the decomposition product that prevents catalysis (Figure 6). During the grant period, we developed the most active catalysts for upgrading ethanol to higher order alcohols. Through systematic ligand modifications, we uncovered that catalysts substituted at the 5-position of the pyridine rings exhibit the highest activity among substitution patterns at the 4, 5, and 6-positions. Analysis of the reaction profile kinetics revealed that the higher activity is due to improved stability. The catalyst containing methyl groups at the 5-position provided the highest TON (155,890) and TOF (12,690 h^{-1}) values reported to date for a single site homogeneous catalyst that converts ethanol to higher-order alcohols (C_4–C_8). We used this empirical result, coupled with analyses of catalyst decomposition pathways, to identify design strategies that further enhance catalyst stability. The key strategy was to introduce electron-donating groups at the 5-position of the pyridine rings to prevent C=N bond hydrogenation. Incorporation of C5-isopropyl, C5-tert-butyl, and C5-methoxy groups similarly improved catalytic activity, a result we attribute to either an electronic effect of deactivating the N=C bond, or alternatively, a steric effect that warrants additional investigation. The net result of our mechanism-guided catalyst redesign is that we have discovered a strategy to modify the catalyst structure to obtain the most active homogeneous catalysts for ethanol upgrading to higher order alcohols.[1]

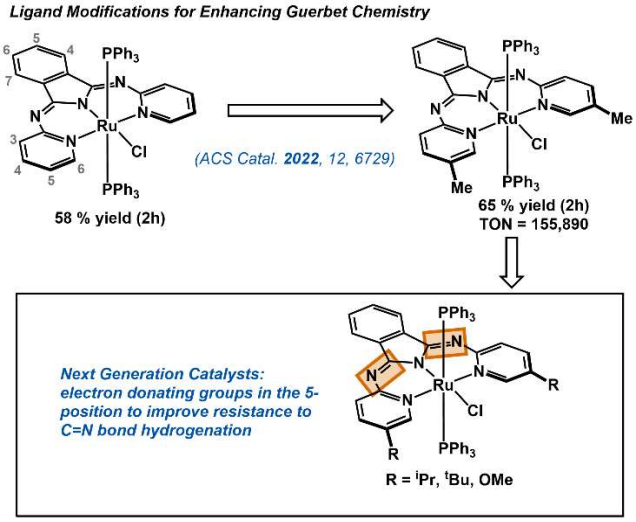


Figure 4. Our data showing formation of >C4 alcohols from ethanol using Guerbet chemistry.

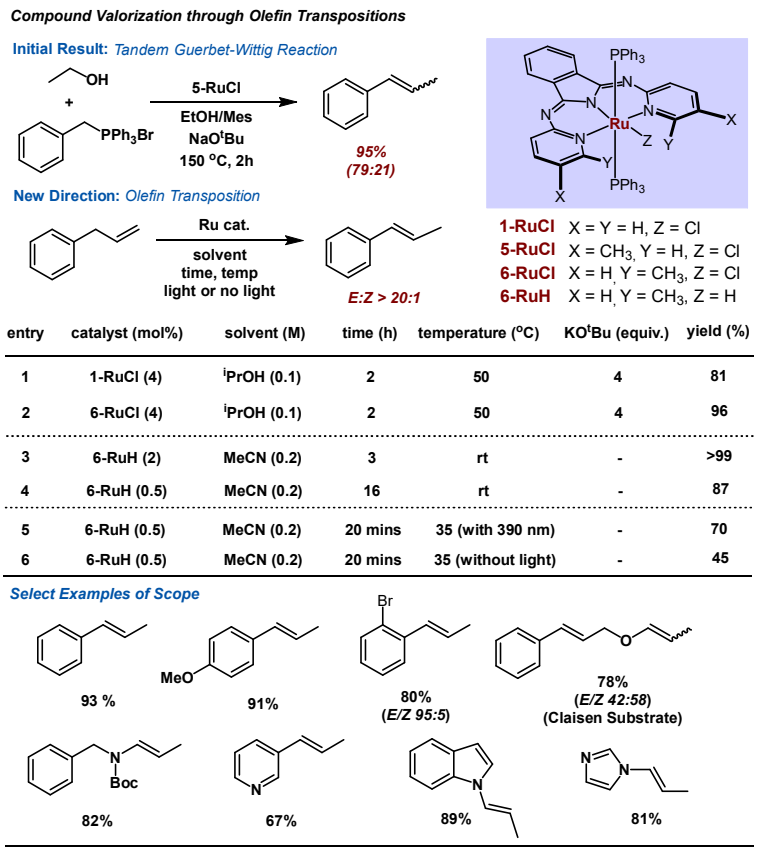
Olefin Transposition and photo-driven hydrogen transfer reactions

During the tandem Guerbet/Wittig alcohol coupling reactions in Figure 1, we identified that only the trans-methyl styrene product formed from reactions between ethanol and the phosphonium ylide. We uncovered that the Ru(BPI)$(PPh_3)_2$H catalyst is highly active for cis/trans olefin isomerization, a reaction not previously explored for this catalyst class.[174] We recognized the potential to exploit this previously unobserved reactivity for the development of mild olefin transposition reactions driven by reversible insertion/elimination. Accordingly, we developed a Ru-catalyzed chain walking reaction of terminal to internal olefins (Figure 5). When allylbenzene was heated to 50 °C in the presence of isopropanol and Na^{t}OBu, the 1,3-olefin transposition product, β–methyl styrene, formed in 81% yield after 2h (4 mol % of Ru(BPI)$(PPh_3)_2$Cl). We found that the yield could be improved (96%) when incorporating –CH_3 groups in the 6 position of the pyridine rings. The use of a pre-formed Ru-H precatalyst enabled additive-free reactions in near quantitative yield. When the catalyst loading was decreased

<1%, long times (>16 h) were required to achieve ~90% yield. We applied these conditions to a variety of olefins including, allylic, homoallylic, and longer chain terminal olefins, and all afforded transposition products in high yields.[2] Allyl protected imidazole, indole, and benzylamine substrates gave access to valuable enamine products, while an allyl pyridine derivative was successfully converted to its vinyl product. O-allyl protected cinnamyl ether converted to a mixture of the corresponding E and Z vinyl ethers, giving access to a substrate for a Claisen rearrangement. Additionally, halogen-containing compounds are also tolerated which contrasts similar strategies that employ palladium.[3]

In another direction to exploit photochemically-driven reactivity, we targeted ligand-redesign strategies as well as chemical reactivity studies. Due to the inherent competition between photoexcited reactivity and excited-state decay, we sought to modify the excited state properties of Ru complexes by fine-tuning of the catalyst structure and used two approaches: 1) extending π-conjugation and, 2) substitution with donor and/or acceptor groups. We developed a new ligand, **L_1**, featuring annulation of the aromatic pyridine arms; a feature we anticipated would provide a red shift of the absorption features, and thus, increase photohydricity. In another approach, we prepared three new ligands with electron withdrawing groups and electron donating groups on the opposite sides of the ligand, to induce a molecular dipole, **L_2**, **L_3**, and **L_4**. We anticipated these electronic effects will decrease the HOMO-LUMO gap, increasing photoacidity. Characterization of the ligands' absorption spectra indicated profiles that are dependent on substitution pattern, validating our approach.

Concomitant with ligand redesign efforts, we pursued photochemical investigations into hydrogen transfer reactions to a model carbonyl-containing substrates. We observed a dramatic effect when irradiating (390 nm light) the reaction of Ru(BPI)$(PPh_3)_2H$ with acetophenone. In the absence of irradiation, reduction of acetophenone was achieved in moderate yields (50%) in 96 hours. In contrast, when irradiated with 390 nm light, 90% conversion was achieved in only 24 hours. Initially, we hypothesized that photochemical excitation of the catalyst imparted an increased hydridic character that facilitated hydride transfer reactivity. However, through a suite of mechanistic studies, we concluded that illumination at 390 nm promotes a ligand dissociation reaction. Monitoring reactions between the Ru-catalyst and benzaldehyde in C_6H_6 with and without irradiation showed increased consumption of ruthenium hydride catalyst with light. Hydride transfer initially formed a 10:90 mixture of ruthenium hydride catalyst to the benzaldehyde reduction product. After 16 hours without irradiation, this relative ratio had changed from 10:90 to 40:60. In a parallel reaction with 390 nm irradiation, however, after 16 hours there was less than 5% remaining of Ru(BPI)$(PPh_3)_2H$ and only 40% of the alkoxide. The results of these experiments taken together suggested that 390

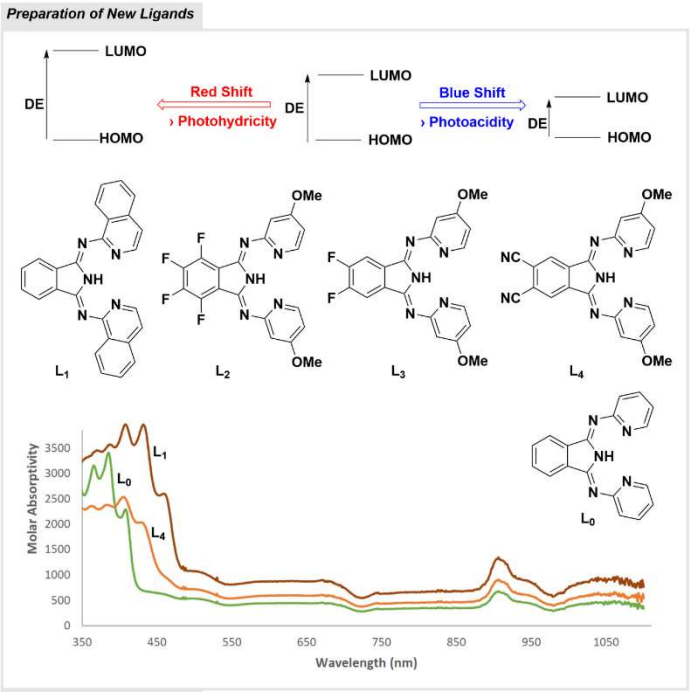


entry	catalyst (mol%)	solvent (M)	time (h)	temperature (°C)	KO^{t}Bu (equiv.)	yield (%)
1	1-RuCl (4)	^{i}PrOH (0.1)	2	50	4	81
2	6-RuCl (4)	^{i}PrOH (0.1)	2	50	4	96
3	6-RuH (2)	MeCN (0.2)	3	rt	-	>99
4	6-RuH (0.5)	MeCN (0.2)	16	rt	-	87
5	6-RuH (0.5)	MeCN (0.2)	20 mins	35 (with 390 nm)	-	70
6	6-RuH (0.5)	MeCN (0.2)	20 mins	35 (without light)	-	45

Figure 5. Our data demonstrating tandem Guerbet-Wittig chemistry (top) and catalytic olefin transposition (bottom).

nm irradiation promoted both Ru–P and Ru–O bond breaking leading to net ligand dissociations in the parent hydride and product alkoxide complexes.

To probe the light-promoted ligand dissociation further, we examined a ligand exchange reaction and found that tris-(4-OMe-phenyl)phosphine exchanges rapidly with irradiation (<1h), but does not undergo exchange in the absence of irradiation. This result is consistent with a photoinduced ligand dissociative event. Taken altogether, these data suggest a revised mechanistic hypothesis for reactions performed under irradiation: 390 nm light irradiation of *NNN*-Ru-pincer complexes promotes axial ligand dissociation. Leveraging this ligand dissociative behavior upon irradiation could introduce interesting opportunities for catalysis, especially in promoting catalytic turnover by dissociation of strong bonds to Ru.



5.0 Conclusions and Recommendations

This DOE funded project demonstrated the success of using mechanistic studies to not only improve activity of Ru-catalyzed Guerbet reactions, but also enable tandem C-C coupling using ethanol as a C2 synthon, and also olefin isomerization reactions. The results from the in depth mechanistic studies were instrumental in identifying the catalyst decomposition products as well as initial strategies for how to improve catalyst stability during the Guerbet reaction. The critical findings that decarbonylation of an intermediate aldehyde, and hydrogenation of the ligand backbone are key steps in catalyst deactivation provide groundwork for catalyst redesign in order to improve catalyst stability while maintaining high activity and these findings were validated with initial redesign efforts. Finally, light-driven reactions provided an alternative strategy to facilitate ligand dissociation during catalysis, which we note is needed for the precatalyst to enter the catalytic cycle. Collectively, these insights will be used to guide the development of long-lifetime (de)hydrogenation catalysts that upgrade alcohols and related feestocks.

List of publications supported by DOE Award:

1) Farris B. M; Davies, A. M; Stephenson C. R. J;* Szymczak N. K.;* Ethanol Upgrading with *N,N,N*-Pincer-Based Ru Catalysts: Delineating Key Factors Governing Catalyst Evolution and Stability. *ACS Catal.* **2024**, *in revision*.

2) Davies, A. M; Greene, K; Allen, A.; Farris B. M; Stephenson C. R. J;* Szymczak N. K.;* Catalytic Olefin Transpositions Facilitated by Ruthenium N,N,N-Pincer Complexes. *J. Org. Chem*. **2024**, *accepted*. ChemRxiv. DOI: 10.26434/chemrxiv-2022-3c5vp.

51) Davies, A. M.; Li, Z-Y.; Stephenson, C. R. J.;* Szymczak, N. K.* Valorization of Ethanol: Ruthenium-Catalyzed Guerbet and Sequential Functionalization Processes. *ACS Catalysis.* **2022***, 2022, 12, 6729-6736.*

6.0 Lessons Learned

During efforts to develop the Guerbet reactions in continuous flow, we identified a mechanical challenge that is unique to the system. Continuous flow chemistry requires that reaction components are liquid and do not undergo phase changes during the reaction. Thus, one of the main challenges for moving the Guerbet reactions to continuous flow is to maintain solubility of all species during the reaction. During our extensive reaction optimization, we uncovered that the addition of crown ethers maintains solubility of all components without dramatically impacting the reaction activity and selectivity. However, as a result of this challenge, we prioritized efforts to focus more heavily on mechanistic experiments and catalyst redesign and realize that continuous flow reactor design success may be a longer term goal.

During efforts to investigate the photochemical reactions, we found that our initial method of irradiation used a Kessil PR160 LED lamp. Unfortunately, this experimental design does not allow direct analysis of reactions during irradiation, complicating measurements of solution speciation. To overcome this limitation, we acquired an *in situ* fiber optic LED-NMR system to monitor photochemical processes by NMR spectroscopy, and note that an additional challenge is reduced power (110 mW) and photon flux of the *in situ* fiber optic setup, compared to the Kessil lamp (352 mW/cm^2).

During efforts to monitor the catalytic reactions, we found incompatibilities between standard glassware and the temperatures/pressures needed for the Guerbet reaction (150°C, elevated pressure). To enable in situ IR monitoring, we developed a custom glassware setup that enables reaction monitoring by IR and by GC (sample removal by syringe). The apparatus includes a pressure relief disc to rupture if unsafe pressures are generated.