

Switchable Solvents: A Combination of Reaction & Separations

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A switchable solvent is a solvent capable of reversing its properties between a non-ionic liquid to an ionic liquid which is highly polar and viscous. Switchable solvents have applications for the Heck reaction, which is the chemical reaction of an unsaturated halide with an alkene in the presence of a palladium catalyst to form a substituted alkene. The objective of this research was to apply a switchable solvent system to the Heck reaction in order to optimize reaction and separations by eliminating multiple reaction steps. Switchable solvents reduce the need to add and remove multiple solvents because they are capable of switching properties and dissolving both the inorganic and organic components of the reaction. This reversal of chemical properties by a switchable solvent provides for easier separation of the product, minimizes the cost by eliminating the need for multiple solvents, and reduces the overall environmental impact of the industrial process. Specifically, the cost is lowered by the ability of the catalyst and solvent to be recycled from the system. In addition, the “switch” that initiates the formation of the ionic liquid switchable solvent is carbon dioxide, which is cheap and nontoxic. In conclusion, we were able to use a switchable solvent system to obtain good product yields of E-Stilbene, the desired product of the Heck reaction, and recycle the remaining catalyst + solvent which also produced good product yields at a lower economic and environmental cost.

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INTRODUCTION

A common problem for chemical synthesis is the reaction of an inorganic salt with an organic substrate, which is an important reaction in the production of many industrial chemicals and pharmaceutical products. Typically, a phase transfer catalyst (PTC), such as a quaternary ammonium salt, is used and must subsequently be separated from the product after the reaction has proceeded. However, the separation of a PTC from the product is very difficult. In fact, solvents such as dimethyl sulfoxide (DMSO) or ionic liquids, liquid salts at or near room temperature, that are capable of dissolving both the organic and inorganic components of the reaction still inhibit simple separation of the product from the catalyst. (Heldebrant et al., 2005)

Now imagine a smart solvent that can reversibly change its properties on command through a built in “switch”. Our goal in designing such a solvent is to minimize the economic and environmental impact of such industrial processes while creating a solvent that remains highly polar. These solvents are able to dissolve both the organic and inorganic components of the reaction while highly polar and then change properties for easier separation and effective product isolation after the reaction is complete.

Switchable solvent systems are capable of doing just that. These systems involve a non-ionic liquid, an alcohol and amine base, which can be converted to an ionic liquid upon exposure to a “switch”. The switch chosen to induce this change in solvent properties is carbon dioxide. CO₂ reacts with the alcohol-amine mixture to form an ammonium carbonate. Furthermore, it is cheap, readily available, benign, and easily removed by heating and purging with nitrogen or argon. Switchable solvent systems therefore should facilitate chemical syntheses involving reactions of inorganic salts and organic substrates by eliminating the need to add and remove different solvents after each synthetic step in order to

achieve different solvent properties (Heldebrant et al., 2005; Phan et al., 2007).

Industrial chemical production usually requires multiple reaction and separation steps, each of which usually requires the addition and subsequent removal of a different solvent for each step. For example, the synthesis of Vitamin B12 is achieved in 45 steps. The application of switchable solvent systems to industrial production processes of major chemicals and pharmaceuticals would significantly lower the associated pollution and cost of these processes by eliminating the need to add and remove multiple solvents for each reaction step. (Heldebrant et al., 2005; Phan et al., 2007).

PROJECT DESCRIPTION

Switchable solvents convert between a non-ionic liquid, which has varying polarity, to an ionic liquid whose properties include higher polarity and higher viscosity. As discussed in previous research, the ideal properties of the solvent as a reaction medium include a usable liquid range, chemical stability, and the ability to dissolve both organic species and inorganic salts. In terms of the solvent's role in separations, the solvent should be decomposable at moderate conditions with a reasonable reaction rate, the decomposition products should have very high or very low vapor pressures, and recombination to form solvent should be relatively easy. Our principle aims in designing a switchable solvent system to optimize reactions and separations were to eliminate multiple reaction steps, reverse solvent properties to facilitate better separations, and minimize the cost and environmental impact by optimizing catalyst and solvent recycle. (Heldebrant et al., 2005; Xiao, Twamley, & Shreeve, 2004; Phan et al, 2007).

Ionic liquids have gained popularity in their technological applications as electrolytes in batteries, photoelectrochemical cells, and many other wet electrochemical

devices. They are particularly attractive solvents because of dramatic changes in properties such as polarity, which may be elicited through a “switch”. On the other hand, changes in conditions such as temperature and pressure usually can only elicit negligible to moderate changes in a conventional solvent’s properties making the use of multiple solvents for a single process necessary. In addition, ionic liquids have low vapor pressures essentially eliminating the risk of inhalation. In particular, guanidinium-based ionic liquids have low melting points and good thermal stability, properties which make these high nitrogen materials attractive alternatives for energetic materials. (Xiao, Twamley, & Shreeve, 2004; Gao, Arritt, Twamley, & Shreeve, 2005).

Our research focused on the application of switchable solvents for the Heck reaction in order to optimize the reaction and separation. Specifically, we studied the reaction of bromobenzene and styrene in the presence of a palladium catalyst ($\text{PdCl}_2(\text{TPP})_2$) and base to form E-stilbene, an important pharmaceutical intermediate in the production of many anti-inflammatories. (Heldebrant, Jessop, Thomas, Eckert, Liotta, 2005; Xiao, Twamley, & Shreeve, 2004).

As illustrated in Figure 3, the nonionic liquid can be “switched” to an ionic liquid by exposure to carbon dioxide and reversed back to a non-ionic liquid by exposure to argon or nitrogen. The reaction of bromobenzene and styrene in the presence of palladium catalyst is run in the highly polar ionic liquid which is able to dissolve both the organic and inorganic components of this system. The ionic liquid is a particularly effective media for this reaction in that it is able to immobilize the palladium catalyst while preserving the overall product yield. In addition, ionic liquids are nonvolatile, inflammable, and thermally stable making them an attractive replacement for volatile, toxic organic solvents. (Heldebrant, Jessop, Thomas, Eckert, Liotta, 2005; Xiao, Twamley, & Shreeve, 2004; Phan et al., 2007).

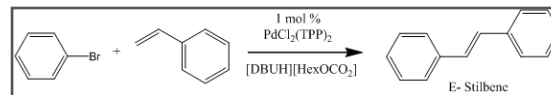


Figure 1. The Heck reaction of bromobenzene and styrene in the presence of palladium catalyst and ionic liquid.

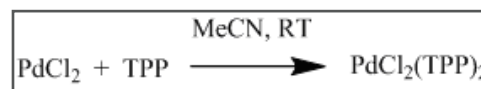


Figure 2. Synthesis of the palladium catalyst used in the Heck Reaction (Figure 1).

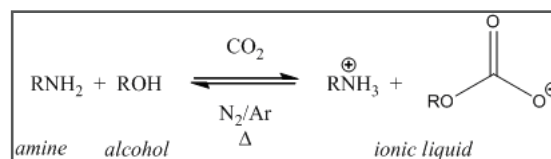


Figure 3. Ionic liquid formation; note the reversibility of this reaction under Argon.

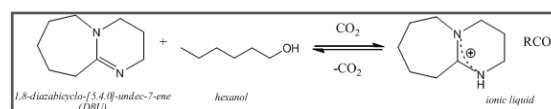


Figure 4. Switchable solvent system comprised of 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU) and hexanol.

In a previous study, a guanidine acid-base ionic liquid was determined to be an effective media for the palladium catalyzed Heck reaction of bromobenzene and styrene [4]. The guanidine acid-base ionic liquid was used as both the solvent, ligand, and base in this reaction with the guanidine acting as a strong organic base able to complex with the Pd(II)salt and as a replacement for a phosphine ligand. High activity, selectivity, and reusability were all observed under moderate conditions and thus we expect our system to function best at similar conditions. (Li, Lin, Xie, Zhang, Xu, 2006; Gao, Arritt, Twamley, & Shreeve, 2005).

PROJECT DESCRIPTION

Once the reaction is run in the ionic liquid, the homogeneous product-ionic liquid solution is extracted and separated into a two phase product, catalyst/ionic liquid system. After the product is removed by extraction with heptane, the system is exposed to argon and the ionic liquid is reversibly switched back to a nonionic liquid where the system again separates into a two phase salt precipitate byproduct/catalyst and nonionic liquid solution system. In this final stage the catalyst and solvent may be removed and recycled back into the process.

Our studies of the palladium catalyzed Heck reaction of bromobenzene and styrene were performed in a

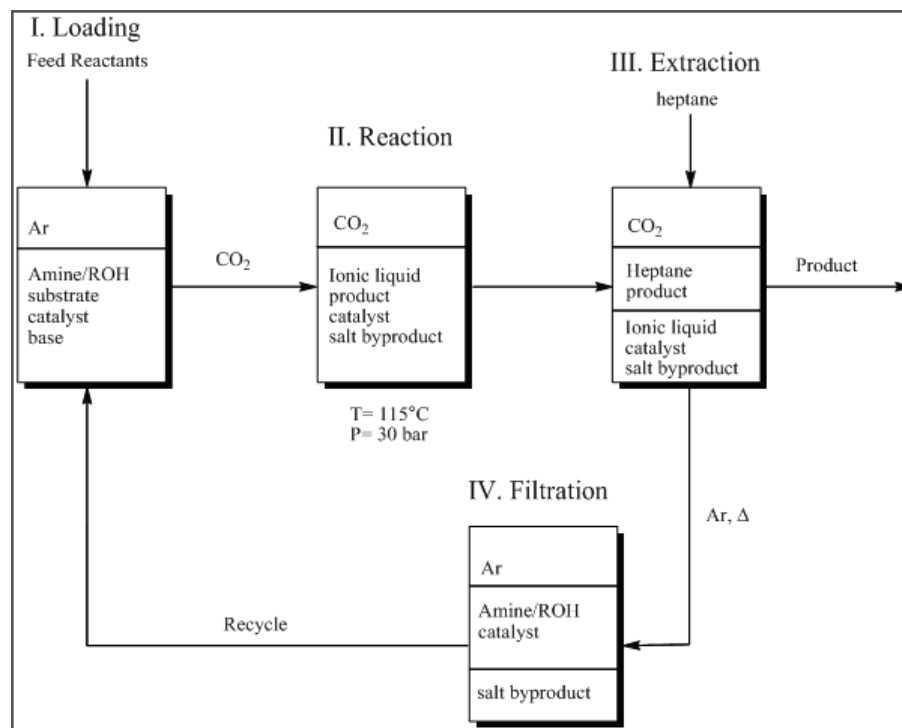
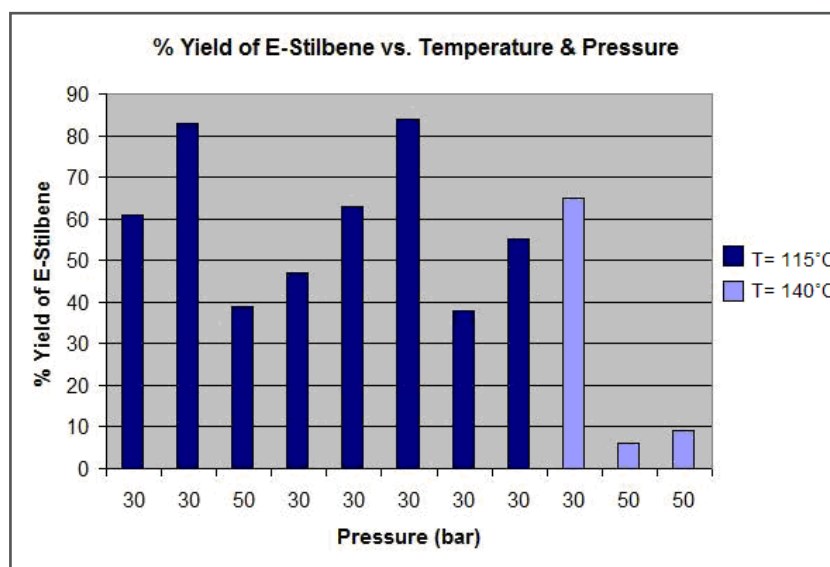


Figure 5. Process Diagram for the Heck reaction performed in a switchable solvent system.

10ml window autoclave. First the catalyst solution was added and the solvent vacuumed out. Next the ionic liquid, bromobenzene, and styrene were added, and the system was pressurized. The autoclave was then left stirring and heating for three days until the reaction was completed. After three days, the autoclave was allowed to cool down and depressurize. Once the system was back to room temperature and atmospheric pressure, the homogeneous ionic liquid/product/catalyst solution was extracted from the autoclave with heptane under carbon dioxide in order to sustain the formation of the ionic liquid. The product in heptane phase was then removed and the remaining ionic liquid/catalyst phase was exposed to argon and heat. After exposure to argon and heating, the byproduct salt precipitated out of the catalyst/reversed non-ionic solvent solution. The catalyst and solution was then removed from the salt byproduct and recycled. Any remaining product left in the autoclave from the extraction with heptane was then extracted with dichloromethane (DCM) for later mass balance calculations.

Figure 6. Palladium (PdCl₂(TPP)₂) catalyzed Heck reaction of bromobenzene and styrene in a switchable ionic liquid system. The catalyst and ionic liquid solution used in the reaction run at T=115°C and P=30 bar, which had 55% yield, was recycled from the reaction run at T=115°C and P=30 bar, which had 83% yield, demonstrating that the catalyst in ionic liquid remained active in the reaction and that was good recycle.



RESULTS AND CONCLUSIONS

The Heck reaction was optimized by running at various temperature and pressure conditions. In order to assess the success of each system, the conversion percentages were compared.

Based on Figure 4, the optimal conditions for product formation and catalyst + solvent recovery were a temperature of 115°C and a pressure of 30 bar. The reactions run at these conditions show very acceptable and repeatable results, such as an 83% and an 84% yield, the highest observed percent yields. However, the high variability of the product yield results at these conditions can be explained by the poor extraction methods for this system. Extracting with large amounts of heptane (greater than 50mL) led to higher product yields (greater than 60%) whereas extracting with less heptane (10-50mL) led to lower product yields at these conditions due to product loss in the system. Therefore, there was a tradeoff between the amount of heptane used in the extraction to recover the product, which adds to the

overall cost of the process, and the amount of product we were able to recover from the system.

The catalyst in solvent was also extracted from the reaction which had an 83% product yield and recycled for a second reaction performed at the same conditions. Observed yield of 55% from the recycle reaction demonstrates that the recycled catalyst activity was preserved and that the solvent was able to “switch” back to an ionic liquid a second time to run the reaction successfully. In general, the reactions which experienced lower percent yields did so as a result of too harsh reaction conditions, such as too high temperatures and/or pressures. We predict that the palladium catalyst loses activity and perhaps decomposes at higher temperatures and pressures which accounts for the lower yields at harsher conditions. In the reactions with higher percent yields the ionic liquid and catalyst extracted from the system were usually light yellow in color, whereas the reactions with lower percent yields were brown or black indicating catalyst decomposition. In particular, two of the reactions run at $T=140^{\circ}\text{C}$ and $P=50$ bar which had product yields of 6% and 9% respectively contained black particles within the catalyst and solvent mixture. In addition to the extremely low percent yield, we believe the palladium catalyst complex decomposed, and the black particles were possibly palladium nanoparticles (palladium black).

In order to improve this system, further investigations into the extraction methods should be performed in order to find a work-up method which minimizes product loss by maximizing the amount of product that can be washed out of the product phase. The variability of the product yield results are a reflection of this difficult extraction procedure. In our work, we extracted with heptane (between 10 and 50mL) because of its low boiling point, which made it easy to remove the leftover heptane in the system after the product had been extracted by heating. In order to improve the extraction

method, different solvents could also be tried in this extraction. In addition, it was often difficult to extract all of the products and reactants from the autoclave due to the viscosity of the ionic liquid. A better extraction solvent would facilitate this step and minimize product, catalyst, and solvent loss. Another difficulty we encountered with our system was evaporating the solvent out of the catalyst solution before adding the other reactants. Changing the solvent from chloroform to toluene was attempted, but toluene was even more difficult to evaporate from the system. The solution we found was to dissolve the catalyst directly into 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU) and then, after the catalyst and DBU solution was completely homogeneous, add hexanol and expose to carbon dioxide in order to convert it to an ionic liquid and then added it to the system directly. NMR samples of the catalyst in DBU and hexanol were taken to test that the activity of the catalyst was preserved in this solution by confirming the catalyst's molecular structure remained unchanged. In addition, the percent yields of the reactions run with this method confirm that the palladium catalyst retains its activity in the DBU-hexanol solution. This method also eliminates the addition of an extra solvent and its difficult removal from the system.

In conclusion, the application of switchable solvents to the Heck reaction of bromobenzene and styrene was successful in optimizing product (E-Stilbene) yield and catalyst + solvent recovery for a good recyclable system. E-Stilbene is an important intermediate in the synthesis of some pharmaceuticals such as anti-inflammatories and is used in the manufacture of dyes and optical brighteners. A switchable solvent system could therefore be implemented for chemical synthesis of Heck reaction products in order to reduce the economic and environmental impact of this industrial process. (Heldebrant, Jessop, Thomas, Eckert, Liotta, 2005; Heldebrant et al., 2005).

REFERENCES

Heldebrant, D.J.; Jessop, Philip G; Thomas, Colin A.; Eckert, Charles A.; Liotta, Charles L. J. The Reaction of 1,8-Diazobicyclo[5.4.0]undec-7-ene (DBU) with Carbon Dioxide. *Organic Chemistry* 2005, 70, 5335-5338.

Heldebrant, D.J.; Jessop, Philip G; Li, Xiaowang; Eckert, Charles A.; Liotta, Charles L. Green Chemistry-Reversible nonpolar-to-polar solvents. *Nature* 2005, Vol. 436, 1102.

Xiao, Ji-Chang; Twamley, Brendan; Shreeve, Jean'ne M. An Ionic Liquid-Coordinated Palladium Complex: A Highly Efficient and Recyclable Catalyst for the Heck Reaction. *Organic Letters* 2004, Vol. 6, No. 21, 3845-3847.

Li, Shenghai; Lin, Yingjie; Xie, Haibo; Zhang, Suobo; Xu, Jianing. Brønsted Guanidine Acid-Base Ionic Liquids: Novel Reaction Media for the Palladium-Catalyzed Heck Reaction. *Organic Letters* 2006, Vol. 8, No. 3, 391-394.

Phan, Lam; Chiu, Daniel; Heldebrant, David J.; Huttenhower, Hillary; John, Ejae; Li, Xiaowang; Pollet, Pamela; Wang, Ruiyao; Eckert, Charles A.; Liotta, Charles L.; Jessop, Phillip G. Switchable Solvents Consisting of Amidine/Alcohol or Guanidine/Alcohol Mixtures. *American Chemical Society* 2007.

Gao, Ye; Arrit, Sean W.; Twamley, Brendan; Shreeve, Jean'ne M. Guanidinium-Based Ionic Liquids. *Inorganic Chemistry* 2005, Vol. 44, No. 6, 1704-1712.