Metal Catalyzed Transformations
Adrian Burke, Dominique Hebrault, METTLER TOLEDO

Metal Catalyzed Transformations have been a key topic in academic research for a number of years, both for their scientific interest, as well as the large number of reactions that have become important to industry. Some of the major challenges faced by researchers today include the need to accurately determine the start and end point of reactions, as well as gaining sufficient information to fully understand, characterize and optimize chemical reactions. This, combined with the need to complete larger numbers of investigations, with less resource and in shorter time, is leading researchers to look for innovative ways to gain the information they require to complete their work successfully.

In situ IR spectroscopy has been increasingly used in synthetic organic chemistry due to its ability to deliver key pieces of information that enables researchers to elucidate the mechanism, kinetics and pathway of many different reactions. ReactIR™ is a real-time in situ reaction analysis system used by researchers to increase their understanding of organic chemistry using well understood mid-IR spectroscopy. A robust ATR probe is inserted directly into the vessel, providing a “molecular video” of the reaction. The concentration changes of all key reactive and transient species are monitored allowing for mechanism and pathway determination. Accurate kinetic analysis is achieved with the automated collection of a comprehensive data set – analyzed using iC Kinetics™ software which generates a kinetic model in fewer experiments than a traditional approach.

This white paper highlights four examples from academia where ReactIR™ has been used as an enabling tool to uncover key parameters in each investigation. It is not the intent to go into detailed scientific findings. These were documented in each paper, and it is recommended to read the original publications for this purpose. Instead, the authors highlight the context in which ReactIR™ was used and how this helped researchers answer key questions.
1. Heterobimetallic Bi–Rh Paddlewheel Carboxylates as Catalysts for Metal Carbenoid Transformations

Jørn Hansen†, Bo Li‡, Evgeny Dikarev‡, Jochen Autschbach§ and Huw M. L. Davies*†
† Department of Chemistry, Emory University, 440 Atwood Hall, 1515 Dickey Drive, Atlanta, Georgia 30322 ‡ Department of Chemistry, University at Albany, State University of New York, Albany, New York 12222 § Department of Chemistry, University at Buffalo, State University of New York, Buffalo, New York 14260-3000 J. Org. Chem., 2009, 74 (17), pp 6564–6571

Combined Experimental and Computational Studies

This paper reports on work by Huw Davies and colleagues at Emory University in Atlanta, GA. During their work, Professor Davies and his colleagues set out to evaluate the catalytic activity of heterobimetallic Bi–Rh carboxylate complexes in metal carbenoid chemistry, and specifically in cyclopropanation reactions. They also compared the performance of the heterometallic BiRh(O₂CCCF₃)₃(O₂CCCH₃) complex to its homometallic analogue Rh₂(O₂CCCF₃)₃(O₂CCCH₃) in terms of selectivity and reactivity. Figure 1-1 shows the catalytic cycle under investigation.

The diazo reagent is reacted with styrene to form a cyclopropane product (Figure 1-2). In the first instance, the catalyst is the homometallic species Rh₂(O₂CCCF₃)₃(O₂CCCH₃). ReactIR™ in situ spectroscopy was used to follow the reaction of the diazo species, by following disappearance of the diazo stretch frequency at ~2100cm⁻¹. The waterfall plot in Figure 1-3 shows data collected during the reaction. The plot shows wavenumber, plotted against absorbance, plotted against time. It is possible to follow the reduction in absorbance of the diazo stretch frequency over time, which directly relates to a reduction in the concentration of that species in solution.
The waterfall plot in Figure 1-3 shows the reaction is very fast, and is in fact complete in a fraction of the time window shown, which is 56 seconds. 0.2 mol% of catalyst was used, which corresponds to a turnover frequency of approximately 30s\(^{-1}\).

By comparison, Figure 1-4 shows the heterometallic BiRh\((O_2CCF_3)_3(O_2CCH_3)\) complex used as the catalyst. Here the data shows that, under similar conditions, the reaction completes substantially slower when compared to using the homometallic species Rh\(_2\)(O\(_2CCF_3\))\(_3\)(O\(_2CCH_3\)) as the catalyst. In fact, the reaction takes around 45 minutes to complete, meaning a turnover frequency of approximately 0.019s\(^{-1}\).

The data allows for a direct comparison of the relative reactivities of the two catalysts. The homometallic species Rh\(_2\)(O\(_2CCF_3\))\(_3\)(O\(_2CCH_3\)) is approximately 1600 times more reactive than the heterometallic BiRh\((O_2CCF_3)_3(O_2CCH_3)\) species. This confirmed the results expected from calculated models.

This work shows how easy it is to use ReactIR™ \textit{in situ} reaction analysis to calculate the time taken to reaction completion. In this case, it was achieved by immersing a ReactIR™ probe directly into the reaction mixture, and monitoring the rate of disappearance of the diazo compound. Figures 1-3 and 1-4 show the very simple visualization of concentration decrease, and enabled the reaction completion times to be calculated at 16 seconds and 45 minutes respectively. ReactIR™ can be used in a fast scan mode to collect a spectrum every second, making it a unique tool to follow the progress of fast reactions.
Structure, Configurational Stability and Stereodynamics in Solution

This work is a great example of how in situ spectroscopy can be used not only to monitor a chemical reaction, but also to gather key information which can be used to deduce the structure of reaction intermediates. During this work, Vito Capriati, Saverio Florio and colleagues at the University of Bari in Italy used in situ IR and NMR spectroscopy together to give them a better insight into the stability of the lithium salt shown in Figure 2-1. Previous studies had shown seemingly conflicting results. On the one hand, the salt would racemize extremely quickly at very cold temperatures, which was corroborated from computer modeling. On the other hand, the same molecule was observed to be stable at -78°C for hours during a deuteration experiment.

Figure 2-2 shows the formation of the lithium salt Li-1, which is obtained from reacting structure 1 with a strong base in THF at -100°C.

The key question the researchers wanted to answer was, “Is the lithium salt more like an organolithium or is it more like an azaenolate?” (Figure 2-3).
In situ IR spectroscopy produced some interesting clues. As the deprotonation occurred, the 2 bands corresponding to the starting oxazolinyl species at 1660 and 1678 cm\(^{-1}\) disappeared while a band at 1600 cm\(^{-1}\) emerged (Figure 2.4).

Based on literature data, an alkylidene epoxide like the structure in Figure 2-3 would be expected to produce a band more in the 1750-1800 cm\(^{-1}\) region. In other words, having a shift of only 60 cm\(^{-1}\) or so indicates that what’s happening is more consistent with the formation of the organolithium derivative Li-1.

As in the previous example from Huw Davies and colleagues, this is a very fast reaction. All of compound 1 is reacted within one minute, which can be seen by profiling the bands corresponding to compound 1 and its lithiated equivalent against time (Figure 2.5).

Due to its functional group specificity, in situ mid-IR spectroscopy enabled the collection of key information that could be used to suggest the formation of species Li-1 rather than a suspected azenolate. \(^{13}\)C and \(^{7}\)Li NMR were also used to further investigate the reaction intermediates and confirm the findings of the group.
3. Efficient Palladium-Catalyzed C(sp)−C(sp) Cross-Coupling Reaction Using Phosphine–Olefin Ligand

Wei Shi†, Yingdong Luo†, Xiancai Luo†, Lei Chao†, Heng Zhang†, Jian Wang‡ and Aiwen Lei*†
College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, Hubei 430072, P. R. China, and Mettler-Toledo AutoChem, 7075 Samuel Morse Drive, Columbia, Maryland 21046; J. Am. Chem. Soc., 2008, 130 (44), pp 14713–14720; † Wuhan University, ‡ Mettler-Toledo AutoChem, Inc.

Application and Mechanistic Aspects
This work, from Aiwen Lei at Wuhan University in Beijing, China, in collaboration with Mettler-Toledo AutoChem, Inc., looks at a Pd catalyzed cross-coupling between a haloalkyne 1 and a terminal alkyne 2 to form diyne 3 (Figure 3-1). In this paper the researchers used in situ IR spectroscopy to measure the reaction rate under various conditions and get an insight into the reaction mechanism. There is also a paper in Organic Letters from the same authors describing a Negishi coupling using the same mechanistic approach5.

This chemistry provides a highly efficient method to synthesize 1,3-diynes. Figure 3-2 shows that the bromoalkyne 1 and the diyne 3 have unique absorbencies at 973 and 955 cm⁻¹ respectively. Figure 3-3 shows that trending these bands against time gives a good picture of reaction evolution for both the starting material and product.
Using Blackmond’s approach to kinetic analysis\textsuperscript{6,7}, the authors then investigated two well defined sets of reaction conditions. Reaction B differs from reaction A by the reactants concentration, the excess of one relative to the other (0.02M) and the catalyst concentration remaining constant.

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Reaction A</th>
<th>Reaction B</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>0.41M</td>
<td>0.29M</td>
</tr>
<tr>
<td>Ph</td>
<td>0.43M</td>
<td>0.31M</td>
</tr>
<tr>
<td>Pd(dbo)\textsubscript{2}</td>
<td>0.006M</td>
<td>0.006M</td>
</tr>
<tr>
<td>Cul</td>
<td>0.003M</td>
<td>0.003M</td>
</tr>
</tbody>
</table>

Figure 3-4a shows the concentration of 3a versus time. Figure 3-4b represents another way of plotting the data, reaction rate versus concentration of bromoalkyne. The perfect overlay of the two trends indicates there is no catalyst deactivation or poisoning.

A third set of experiments was conducted by varying the concentration of bromoalkyne \( 1 \), with everything else remaining unchanged (different excess experiments). As can be seen in Figure 3-5a, this does not affect the initial reaction rate. The reaction also seems to exhibit zero-order profiles. A plot of normalized rate versus adjusted concentration plot confirms this initial observation. The reaction orders that best afford an overlay of straight lines are 0.07 in terminal alkyne and 0.03 in bromoalkyne (Figure 3-5b).
When the implication of these results are considered, in terms of catalytic cycle, it suggests that neither the bromoalkyne nor the terminal alkyne is involved in rate limiting steps.

This leaves two positions in the catalytic cycle where the rate limiting step is to be found – the condensation of intermediates 4 and 5 to give 6, or the reductive elimination yielding the final product 3.

This publication delivers great insight regarding the mechanistic nature of this particular cross-coupling reaction, the data for which is collected using in situ IR spectroscopy and well planned investigation of reaction conditions. After a few more sets of experiments, it was found the rate of the reductive elimination step was limiting and enhanced by the presence of ligand L1.

Webinar Spotlight

Reaction Progress Kinetic Analysis: A Powerful Methodology for Mechanistic Studies of Complex Catalytic Reactions

Professor Donna Blackmond discusses how Reaction Progress Kinetic Analysis (RPKA) methodology simplifies kinetic studies of organic reactions. One advantage of the RPKA approach is that vital kinetic information may be rapidly obtained and extracted even in earliest studies of a new reaction and may help inform the direction of both further reaction optimization and fundamental mechanistic investigation by other methods.

To view this FREE online seminar series visit www.mt.com/iCKinetics
4. Unexpected Formation of a Cyclopentadienylruthenium Alkoxycarbonyl Complex with a Coordinated C=C Bond

Jenny B. Åberg, Madeleine C. Warner and Jan-E. Böckvall*  
Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91  

A Dynamic Kinetic Resolution Catalyzed by Ruthenium Complexes
Even though ruthenium catalysts have been successfully used in combination with lipases to convert racemic secondary alcohols 2 into enantiopure acetates 3, and that is called dynamic kinetic resolution (DKR), the same reaction doesn’t work quite as well when using olefinic alcohol 4. It seems like alcohol 4 racemizes very slowly, possibly because of coordination of its double bond to ruthenium. The paper describes the use of NMR spectroscopy and in situ IR spectroscopy to show evidence for a Ru-olefin complex.

When reacting allylic alcohol and ruthenium complex, two IR bands at 2021 cm⁻¹ and 1964 cm⁻¹ can be seen reducing over time. These correspond to ruthenium complex 1. A new band forming at 1982 cm⁻¹ in the CO region can be seen. Also, a new peak is formed in the acyl region at 1644 cm⁻¹ (Figure 4-1).

2 R=large group (alkyl, aryl)  
3 R=large group (alkyl, aryl)  
4 R=H₂C=CHCH₂CH₂  
5 R=H₂C=CHCH₂CH₂ <50%; no DKR
Trending those peaks (Figure 4-2) allowed Bäckvall and colleagues observe that the rates of disappearance and formation were the same, supporting the hypothesis that diastereomers 10a and 10b are formed (Figure 4-5).

This work provides a great example of the power of combining the structural information offered by the functional specificity of mid-IR with the kinetic information gained from in situ reaction rate monitoring. As a result, in situ IR used in conjunction with 1H and 13C NMR spectroscopy enabled the researchers to identify the formation of diastereomeric ruthenium complexes 10a and 10b. This in turn helped them explain the slow rate of racemization of 4, which makes 4 a poor substrate for dynamic kinetic resolution.
General Conclusions

As stated previously, it was not the intent within this white paper to go into details regarding the scientific findings of the authors. Instead, it is hoped that it has been demonstrated that ReactIR™ in situ spectroscopy, when used either on its own or in conjunction with other techniques, is capable of providing important clues that lead researchers to understanding the kinetics, pathway and mechanisms of chemical reactions.

Specifically, the examples above demonstrate:
- ReactIR™ in situ spectroscopy has been shown to provide valuable, complementary information that enables researchers determine the mechanism and pathway of a number of different types of chemical reactions
- Information collected using ReactIR™ in situ spectroscopy is of a highly complementary nature to other structural data such as NMR
- The combination of ReactIR™ in situ spectroscopy data and iC Kinetics™ software provides a powerful methodology to study the kinetics of a chemical reaction using fewer experiments than more traditional approaches

Our People
METTLER TOLEDO has a global network of Technology and Application Consultants with extensive research and industry experience supporting organic chemistry, chemical development and scale-up.

Email: autochem@mt.com
Phone: 410-910-8500

Website
We are online at the METTLER TOLEDO website (www.mt.com/autochem), where you can find additional detailed information on our products and applications – including an extensive list of upcoming and on-demand webinars.

Blog
Chemical Research, Development and Scale-up is our Blog highlighting the latest publications and providing expert commentary from our own internal experts and from academic and industry professionals.

Customer Community
Our Customer Community Site provides owners and users of our technologies with free access to archived citation lists, application reports, case studies, and extensive training materials – including immediate access to all of our on-demand webinars.

Social Media
Get real-time updates through Facebook and Twitter on the latest developments in chemical synthesis, chemical engineering and scale-up.
Appendix: Citation List


iC Kinetics™ provides a fast, graphical way to describe the characteristics of a chemical reaction and optimize chemistry. The kinetic model created can be used to simulate the effect of concentration and temperature parameters on the performance of the reaction. This data is generated in fewer experiments than a traditional approach, leading to a faster way to optimize chemistry.

www.mt.com/iCKinetics

EasyMax™ enables synthetic and organic chemists to quickly evaluate various potential routes, starting materials, building blocks and reactions conditions to generate the desired quantity of the target compound. Chemists can conduct two completely independent experiments with reactors of different volumes enabling faster and more reliable synthesis.

www.mt.com/EasyMax

Contact us to discuss how these enabling tools can support your investigation.