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Understanding and Controlling the Reactivity of Allylmagnesium Reagents in Stereoselective Synthesis

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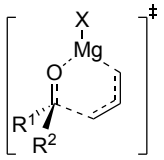
Narrative Progress Report

Our laboratory has focused on developing models to understand the origins of stereocontrol of carbon–carbon bond forming reactions. Our initial studies in this area were focused on reactions involving oxocarbenium ions, which are highly reactive intermediates involved in reactions of importance to synthetic chemists and carbohydrate chemists. These intermediates are such reactive electrophiles that, in the presence of even modest nucleophiles such as alcohols, the reactions occur at rates that are so fast that they cannot be analyzed using stereochemical models. Instead, the rate of diffusion controls the sense of stereoselectivity, leading to outcomes that are neither easily predictable nor explainable.

The present project, a new one in our laboratory, emerged when we asked ourselves whether the same lack of predictability could be observed in other important organic reactions. Carbonyl compounds such as aldehydes and ketones formed a logical family of electrophiles. After some analysis of the literature, we discovered that allylmagnesium halides were such reactive nucleophiles that they should engage in reactions at the rate of diffusion. As we documented in the progress report in 2018, we have discovered that these reactions likely proceed at rates that approach the diffusion rate limit. Furthermore, we provided the first experimental evidence that these reactions likely proceed by a mechanism involving a six-membered ring transition state resembling **1**, and that this mechanistic pathway is much faster than the pathway followed by other organomagnesium reagents.



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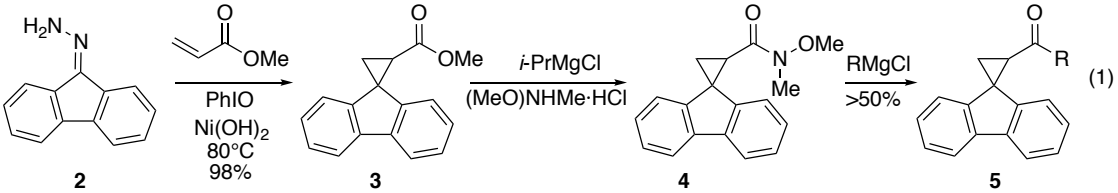
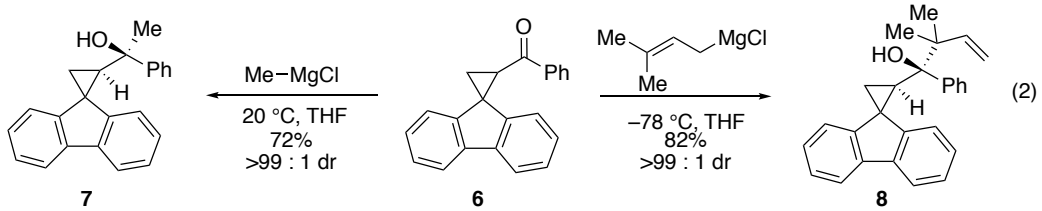
During the last year, we have made significant progress on our studies of this reaction. To address a significant concern regarding the mechanisms of these reactions, we evaluated the mechanisms of additions of organomagnesium reagents to carbonyl compounds. These studies required us to develop a rapid synthesis of a probe compound that possessed a group that would open should radical intermediates be involved (a "radical clock"). We developed a rapid, efficient synthesis of a radical clock based on the fluorenyl group (eq 1), which has been shown to undergo ring opening much faster than the rate of diffusion.



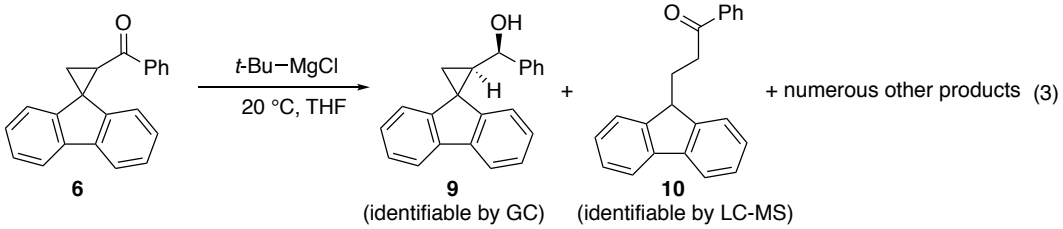
2 **3** **4** **5** (1)

Initial studies showed that most addition reactions of alkylmetal nucleophiles to ketones did not proceed via radical intermediates. For example, additions of alkylmagnesium reagents to the phenyl ketone **6** were slow even at room temperature (eq 2). The products were obtained as a single diastereoisomer (vide infra). Furthermore, it was evident that the reactions with allylmagnesium halides were much faster than reactions with other organomagnesium reagents, as shown for the formation of alcohol **8**. No evidence was observed for ring-opening products even though both the phenyl ketone substrate and the substituted allylic reagent could have undergone a single-electron transfer reaction to form stabilized radical intermediates.

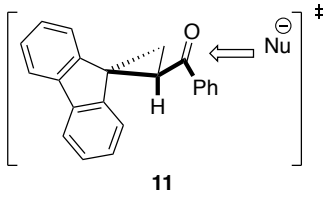


7 **6** **8** (2)

To demonstrate that the radical clock was effective at identifying radical intermediates, it was imperative that a reaction did proceed through these intermediates and that the products could be identified. One example involved the addition of a *tert*-butylmagnesium reagent to the phenyl ketone **6** (eq 3). At least 20 products were formed as determined by HPLC, each in trace quantities. Only two compounds could be identified. One, alcohol **9**, was formed likely by reduction using a β-hydrogen transfer mechanism. The alcohol **10**, which involved opening of the three-membered ring, was identified as a result of a single-electron transfer event. One significant advantage of this fluorenyl-substituted radical clock was the unexpected advantage of a quick visual identification of ring-opening. In all cases where ring-opening products such as **10** were identified, the reaction mixture turned bright orange, likely because of formation of a fluorenyl anion intermediate. Thus, visual inspection of the reaction mixture was sufficient to identify the presence of a single-electron transfer pathway.



It was also noted that these reactions were highly diastereoselective, which provides additional mechanistic information. An X-ray crystal structure of the ketone **6** shows that the COPh side-chain adopts a conformation resembling **11** to maximize favorable orbital overlap of the three-membered ring (as evidenced by alterations of bond lengths within the ring). In this conformation, one face of the carbonyl group is blocked by the fluorenyl group, leaving only one face accessible to nucleophilic attack. Therefore, even reactions of allylic organomagesium reagents, which likely occur at the diffusion rate limit, can only occur to the one face to which the reagent can diffuse. Future studies will address the generality of diffusion-controlled reactions that proceed with high diastereselectivity.



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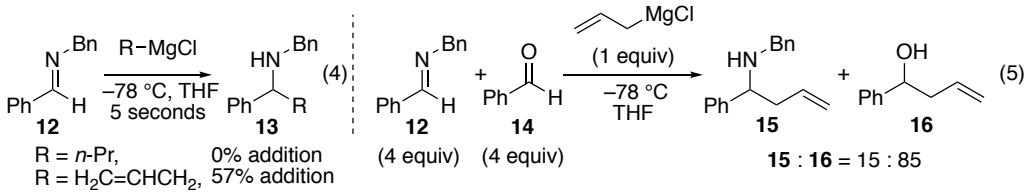
More recent studies have addressed the issues of the mechanism of additions to C=N double bonds. Our preliminary studies suggest that, just as with C=O double bonds, additions occur much faster for allylmagnesium halides than for alkylmagnesium halides, suggesting a similar reaction mechanism (eq 4). These reactions may also, in the case of aldimines, occur near the diffusion rate limit, considering that competition studies show that the imine **15** is almost as reactive as the corresponding aldehyde **16** (eq 5).



This project has significantly influenced the careers of those of us involved. In the last year, one student has published one paper, and she has nearly completed a second paper. In addition, she will be the first author on an invited review in *Chemical Reviews* summarizing the literature in this area. This review, which contains over 600 references and 450 schemes, will be a comprehensive summary of the literature regarding allylmagnesium halide reagents. Another student has made significant progress on her research which we hope will lead to a paper soon. Two high school girls who contributed to the project through summer programs at NYU were co-authors on a manuscript that appeared in early 2019; this paper was the first publication of these two young women, who are now in college. I have benefited from this project because it has allowed me to delve deeply into literature that was previously outside of my area of expertise. That our laboratory has emerged as an important member of this community is reflected in the fact that we were invited to submit a review to *Chemical Reviews*. That manuscript was recently reviewed and we are completing the revisions requested by the Associate Editor.