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*Understanding and Controlling the Reactivity of Allylmagnesium Reagents in Stereoselective Synthesis*

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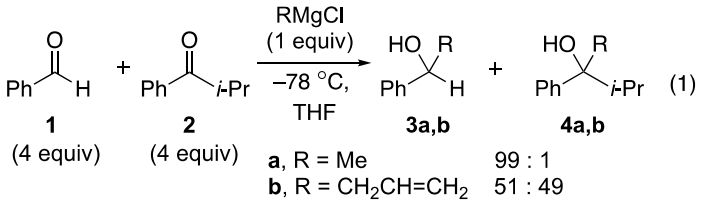
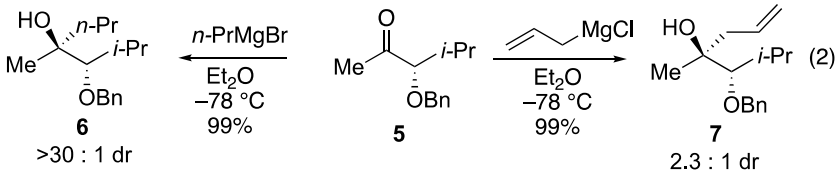
**Narrative Progress Report**

Our laboratory has focused on developing models to understand the origins of stereocontrol of carbon–carbon bond forming reactions. Previous studies centered on reactions involving oxocarbenium ions, which are highly reactive electrophiles, with alkene and alcohol nucleophiles. Those studies revealed that stereoselectivity is observed with relatively weak nucleophiles (such as $CF_3CH_2OH$) but when a nucleophile is sufficiently reactive (such as $CH_3CH_2OH$), the stereochemistry-determining step becomes diffusion. As a result, addition reactions are not stereoselective. Our experiments in the present project have revealed that the opposite scenario is true: when a highly reactive nucleophile reacts with a relatively weak electrophile (an aldehyde or ketone), stereoselectivity can also be controlled by diffusion.

Our first experiments focused on identifying the appropriate nucleophile that would be particularly reactive. We quickly realized that allylmagnesium halides, which are frequently used reagents in synthetic organic chemistry, are much more reactive than other Grignard reagents. This difference in reactivity is illustrated by competition experiments. When excesses of an aldehyde and a hindered ketone were treated with MeMgCl, addition occurred selectively to the aldehyde (eq 1). On the other hand, allylmagnesium chloride added without chemoselectivity. This result suggests that the chemoselectivity-controlling step is diffusion of the reagent to the carbonyl compound, a step that should occur with no selectivity. Subsequent carbon–carbon bond formation must be so fast that once the components have encountered each other, bond formation is faster than separation of the reactive partners.

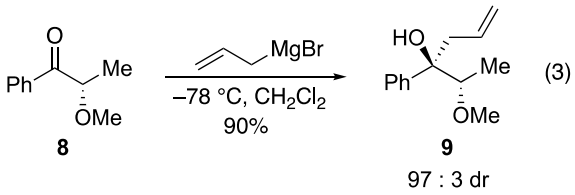



If carbon–carbon bond formation were faster than separation of the reactive partners, then diastereoselectivity, like chemoselectivity, should be low for allylmagnesium chloride. This trend was supported by experiments. While alkylmagnesium reagents follow expected stereochemical models like the chelation-control model, allylmagnesium reagents do not (eq 2). Experiments showed that, unlike other Grignard reagents, allylmagnesium halides also do not conform to a central requirement of the chelation-control model. The model requires that the chelated complex must be the most reactive species in solution, considering that it is not the most populated. This requirement cannot be met if every encounter between the reagents leads to product, as noted above.

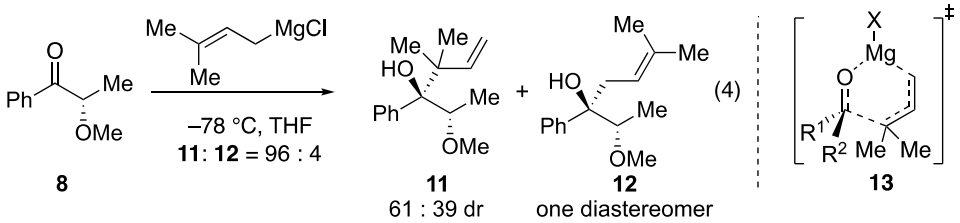



This explanation suggested that under the appropriate reaction conditions, these reactions could be highly stereoselective. If the chelate were the dominant species in solution, then the addition reaction could occur stereoselectively. That expectation was supported by experiments using $CH_2Cl_2$ as solvent in place of $Et_2O$ or THF (eq 3). In $CH_2Cl_2$, the chelate should be more populated considering that the chiral ketone is not competing with the ethereal solvent for the magnesium atom. Competition experiments and

in situ spectroscopic experiments suggest that the chelate does predominate and that kinetic acceleration is not required to observe selectivity. Consequently, this study represented a revision to the chelation-control model.




We recently reported experiments that provide insight into the reaction mechanism of additions of allylmagnesium halides to ketones. Several mechanisms have been proposed to explain the mechanism of reaction of allylmagnesium reagents, as we summarized in a recent review article. We later reported that a substituted allylmagnesium reagent can be used to differentiate among the possible mechanisms. The low diastereoselectivity observed for formation of alcohol **11** likely results from a rapid addition through a cyclic transition state **13** (eq 4). The alternative regioisomer **12**, however, must be formed by the types of mechanisms observed for any organomagnesium reagent, and thus this product was formed with high diastereoselectivity, just as it was for those other Grignard reagents.




This project has significantly influenced the careers of those of us involved. One student received her Ph.D. degree based upon her work on this project. A second student recently advanced to Ph.D. candidacy for her studies of organomagnesium reagents. A former postdoctoral researcher, who is currently in a tenure-track academic position, also participated in this project, and she is a co-author on a recent review. Her work will also appear in two future papers. In addition, two high school girls contributed to the project through summer programs at NYU, and they will be co-authors on an upcoming manuscript. I have benefited from this project because it has allowed me to develop expertise in an area that is new for me.