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Combined Experimental and Theoretical Mechanistic Investigation of the Barbier Allylation in Aqueous Media

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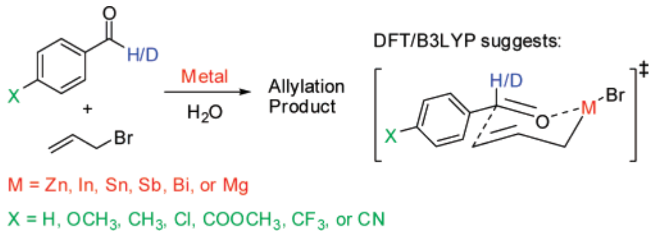

The Barbier allylation of a series of para-substituted benzaldehydes with allylbromide in the presence of Zn, In, Sn, Sb, Bi, and Mg was investigated using competition experiments. In all cases, the slope of the Hammett plots indicated a build-up of negative charge in the selectivity-determining step. For Zn, In, Sn, Sb, and Bi, an inverse secondary kinetic isotope effect was found ($k_H/k_D = 0.75-0.95$), which was compatible with the formation of a discrete organometallic species prior to allylation via a closed six-membered transition state. With Mg, a significantly larger build-up of negative charge along with a small positive secondary kinetic isotope effect ($k_H/k_D = 1.06$) indicated that the selectivity-determining step was the generation of the radical anion of benzaldehyde. The reaction through a six-membered transition state was modeled using density functional theory with the effect of solvent described by a polarized continuum model. The calculated secondary deuterium isotope effects based on this mechanism were found to be in good agreement with experimental values, thus adding further support to this mechanistic scenario.

Introduction

The chemistry of organometallic nucleophiles began in the middle of the 18th century with the synthesis of diethylzinc[1] and the subsequent reaction with carbonyl groups.[2] At the turn of the century, Barbier described a one-pot reaction between a ketone and an alkyl halide in the presence of magnesium metal.[3] One year later, Grignard turned this reaction into a two-step procedure by forming the organomagnesium reagent prior to reaction with the carbonyl compound.[4] This stepwise protocol became the preferred method, and the Grignard reaction has been one of the most important methods in organic chemistry for forming a carbon−carbon bond.[5] In the past two decades, however, the one-pot Barbier procedure has gained renewed interest, especially for coupling of the more reactive allylhalides.[6] Contrary to the Grignard reaction, the Barbier procedure does not require strictly anhydrous solvents but can be performed very effectively in aqueous media. In fact, the allylation of aldehydes and ketones under the Barbier conditions usually occurs faster and gives rise to a higher yield when water is used as a (co)solvent.[7] Furthermore, a number of metals are known to participate in the coupling reaction in aqueous media including zinc, indium, tin, manganese, antimony, bismuth, and magnesium.[8] Among these, the most widely used metals are zinc and indium.[7,9]

In spite of the many applications, the mechanism of the Barbier reaction in aqueous media is not well-understood. In the literature, it has been speculated as to whether the mechanism follows a radical pathway or proceeds via a discrete allylmetal

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species.[8] It is known that the Barbier allylation in aprotic solvents proceeds through a direct nucleophilic addition reaction with zinc and tin,[10] while allylmagnesium bromide reacts by a single electron-transfer process.[11] A recent computational study has shown that allylzinc, -indium, -tin, -antimony, and -bismuth species are more reactive toward the allylation of carbonyl compounds than toward hydrolysis, while allylmagnesium bromide shows a similar reactivity in the two reactions.[12] Secondary deuterium kinetic isotope effect studies on the allylation of benzaldehyde in aqueous media have indicated that the reaction with zinc, indium, and tin proceeds through a rate-determining polar addition with the allylmetal species, while the allylation with magnesium and antimony follows a single electron-transfer pathway on the metal surface in the magnesium case and between the allylmetal and the aldehyde in the antimony case.[13] Further experimental evidence comes from NMR studies that have shown that indium, tin, and antimony react with allylbromide in water to form allylmetal intermediates.[14] However, for the different metals, there are still a number of unanswered questions with regard to the nature of the allylmetal species and the involvement of single electron-transfer processes. Therefore, we decided to perform a more systematic study of the mechanism for the Barbier allylation in aqueous media in the presence of various metals. Herein, we describe a combined experimental and theoretical study with six metals where we employed Hammett studies and isotopic labeling experiments in combination with high-level computational modeling.

Results and Discussion

Hammett Studies. We recently used a combination of Hammett correlations and computational studies to investigate the mechanism for the addition of functionalized organozinc reagents to a series of para-substituted benzaldimines and found that the rate-determining step most likely did not involve free radicals.[15] Prompted by this study, we chose to investigate the Barbier reaction by allylating para-substituted benzaldehydes with allylbromide (Scheme 1). Zinc, indium, tin, antimony, bismuth, and magnesium were selected as the metals since they display vastly different reactivities in aqueous media and may react by different mechanisms.

SCHEME 1. General Scheme for Competitive Allylation of Benzaldehydes

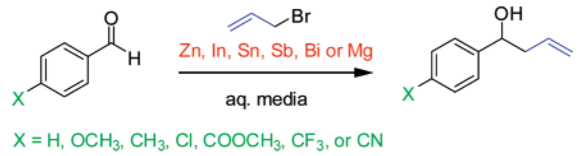

TABLE 1. Yields for Allylations in Scheme 1

		yield[a] (%)					
entry	X	Zn[b]	In[c]	Sn[c]	Sb[d]	Bi[c]	Mg[e]
1	-CN	99 (94[f])	90	94	93	98	
2	-COOMe	98 (93[f])	87 (99[g])	82 (85[g])	95	83 (88[g])	25 (26[g])
3	-CF_3	99 (91[f])	98	99	66 (90[g])	94	60 (65[g])
4	-Cl	96 (90[f])	75 (80[g])	95	87 (92[g])	84 (92[g])	60 (62[g])
5	-H	96 (92[f])	92	94	69	88	49[f]
6	-Me	99 (95[f])	75 (81[g])	82 (93[g])	50 (83[g])	71 (84[g])	14 (79[g])
7	-^{t}Bu	99 (92[f])	56 (81[g])			63 (82[g])	
8	-OMe	76 (82[f])		18 (41[g])		37 (72[g])	
9	-OBu	83 (90[f])					

[a] Yields determined by GC. [b] Performed in 1:1 THF/saturated aqueous NH_4Cl with acid-washed zinc. [c] Performed in 1:1 THF/H_2O. [d] Performed in 7:3 THF/0.5 M HCl with antimony metal prepared from reduction of $SbCl_3$ with $NaBH_4$. [e] Performed with allyliodide in 4:1 DMF/0.1 M NH_4Cl. [f] Isolated yield. [g] Yield based on converted aldehyde.

First, reaction conditions had to be established for each of the six metals. In most cases, THF was used as a cosolvent to dissolve the para-substituted benzaldehydes. With zinc, the highest yield of the homoallylic alcohols was obtained in a 1:1 mixture of THF and aqueous ammonium chloride (Table 1).[8c] This mixture formed a two-phase system consisting of an aqueous THF phase and a saturated ammonium chloride phase. It was shown by GC that the aldehydes and the allylbromide were present in the THF phase, while no compounds could be detected in the ammonium chloride phase. The yields of the homoallylic alcohols were lower when the reactions were performed in a THF/water mixture, and this did not change by using ultrasound. On the other hand, with indium, tin, and bismuth, the THF/water mixture proved to give the best results. All three metals reacted significantly more slowly than zinc, and it was necessary to heat the reactions with tin and bismuth to 60 °C. Antimony and magnesium resulted in a slower reaction than all the other metals. With antimony, it was necessary to use a solvent system of THF and 0.5 M hydrochloric acid.[14c] Furthermore, antimony had to be prepared from antimony(III) chloride and sodium borohydride[16] to give a good conversion, while commercially available antimony powder reacted more sluggishly. It has been reported previously that antimony and bismuth can be activated by potassium fluoride for the allylation of aldehydes,[8h,17] but in our hands, this procedure did not provide a more reactive metal. Magnesium proved to be even more troublesome, and we were unable to reproduce the original conditions with allyliodide in either a THF/water mixture or in a 0.1 M ammonium chloride solution.[8g] In our hands, these reactions did not go to completion and mainly led to pinacol

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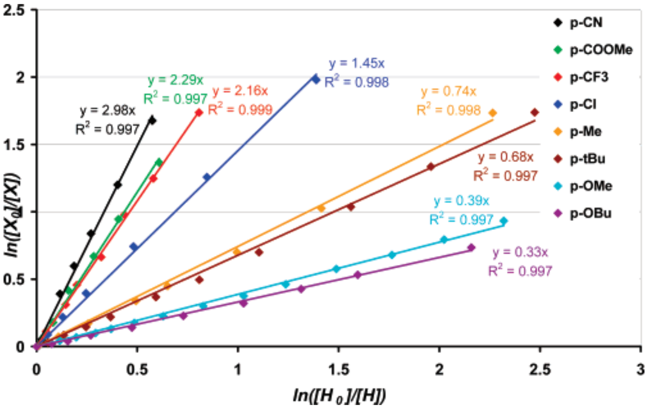

FIGURE 1. Kinetic data for the competitive zinc allylation.

coupling and reduction of the aldehyde even with a variety of different magnesium sources. Other solvent mixtures were investigated, and it was found that 0.1 M ammonium chloride in either ethanol or DMF gave full conversion and fewer byproducts. The best results were obtained in a 4:1 mixture of DMF and 0.1 M ammonium chloride.

The Hammett studies were performed as a series of competition experiments, where the reaction progress was determined by measuring the disappearance of aldehyde using naphthalene as the internal standard.[18] If the reactions were of first order in aldehyde, the concentrations of the aldehydes will follow, for example, eq 1, where the subscript 0 stands for initial concentration, X is the para-substituted aldehyde, and H is benzaldehyde.

$$\ln\left(\frac{X_0}{X}\right) = k_{\mathrm{rel}} \ln\left(\frac{H_0}{H}\right) \tag{1}$$

The competition experiments were carried out with 1 equiv of benzaldehyde, 1 equiv of one of the six different para-substituted benzaldehydes, 1−2 equiv of allylbromide, and 1−2 equiv of the metal. Zinc was the first metal to be investigated, and the experiments were performed by adding zinc in portions of approximately 0.1 equiv because the reaction was otherwise too fast to be adequately monitored. The reaction was also highly exothermic and will lead to extensive formation of byproducts if the temperature is not maintained at room temperature. It was not possible to extend the Hammett plot to include para-nitrobenzaldehyde or -dimethylaminobenzaldehyde since these aldehydes with strongly electron-withdrawing or -donating substituents were resistant to the allylation conditions. In all cases, the correlation coefficient was better than 0.99, when ln(X_0/X) was plotted against ln(H_0/H) (Figure 1).

The obtained k_{rel} values were used to construct the Hammett plot in Figure 2. When applying the regular σ values, a plot with a small positive slope was obtained for the electron-withdrawing substituent (right-hand side in Figure 2). However, this line could not be extended to include the electron-donating substituents, where a significantly steeper line was obtained. Surprisingly, we found a linear correlation when using σ^+ values, in spite of the fact that these values were originally developed for reactions in which a cation was developed.[19] Although this fit to the σ^+ values usually implies the involvement of a cation, the slope of the line is positive for both sets of σ values, indicating that a small negative charge is being developed at the benzylic position. The methoxy and butoxy substituents cause the reaction to proceed more slowly than would be expected from the standard σ values, which suggests that for these substituents, there could be a change in the rate-determining step.[20] In any case, the poor correlation with the $\sigma^\bullet$ values indicates that a radical intermediate is not involved in the allylation reaction.

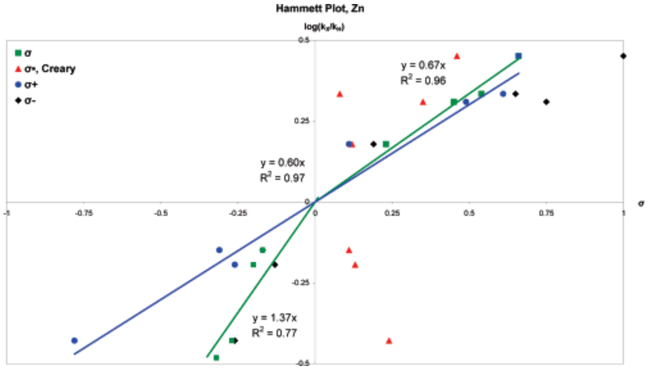

FIGURE 2. Hammett plot for the zinc-mediated allylation of para-substituted benzaldehydes. σ values were obtained from Hansch et al.[21]

The method applied for the zinc allylation also was used in the competitive allylations with indium, tin, antimony, bismuth, and magnesium (i.e., the disappearance of the starting material was monitored during the progress of the reaction). As compared to the zinc allylation, these reactions were all slower and required several hours to reach full conversion. As a result, it was not necessary to add the metals in portions, and the entire portion of metal was therefore added at the beginning of each experiment. For tin and bismuth, the reaction took 1−4 h to initiate and then went to completion in 3−4 h.

The full Hammett plots are included in the Supporting Information. For the four metals (indium, tin, antimony, and bismuth), a good correlation was obtained using ordinary σ values, although the methoxy substituent again deviated from the straight line (Figure 3). The slopes of the lines are positive with a slightly larger ρ value than previously observed with zinc, indicating a higher build-up of negative charge in the selectivity-determining step. The reactions with magnesium only led to the desired allylation product for the para substituents Me, Cl, CF_3, and COOMe, and only in the former three cases were there reasonable GC yields (see Table 1). The Hammett plot for magnesium indicates the build-up of a significant negative charge in the benzylic position and clearly distinguishes this metal from the other five that are all very similar.

The similarity between the first five metals is somewhat surprising when the differences in reaction conditions are taken into account, but this similarity gives a strong indication that a common mechanism is operating. The relatively small slope of the lines indicates that only a partial negative charge is amassed in the transition state, which is what would be expected from a closed, six-membered transition state (TS). For magnesium, the

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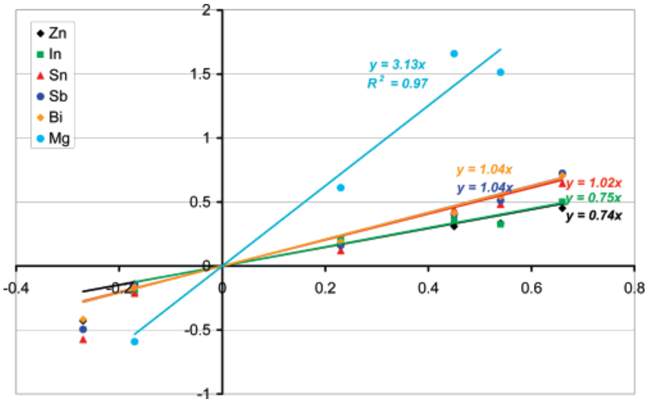

FIGURE 3. Hammett plots for the allylations with zinc, indium, tin, antimony, bismuth, and magnesium.

significantly larger slope indicates that a significant negative charge is present in the selectivity-determining step. This would be expected, for instance, if the generation of a radical anion in the benzylic position is the selectivity-determining step as was suggested previously,[8g] which is then followed by a fast allylation reaction. This mechanism is supported by two earlier Hammett studies where substituted benzophenones were reacted with *t*-butylmagnesium chloride[21] and allylmagnesium bromide,[22] respectively. When *t*-butylmagnesium chloride was employed, a Hammett ρ value of 3.0 was found, which is similar to the result in the current study and in line with the formation of a radical anion by electron transfer from the Grignard reagent. On the contrary, when preformed allylmagnesium chloride was used, the reaction rate was completely unaffected by the nature of the para substituents, which gave a slope of zero in the Hammett plot.[23] The results obtained in the current study indicate that under Barbier conditions, the radical anion of benzaldehyde is generated first, as indicated by the high ρ value, and that the following allylation is neither rate- nor selectivity-determining.

Secondary Deuterium Kinetic Isotope Effect (SDKIE). To add further mechanistic support to the closed, six-membered TS, a study of the SDKIE was undertaken. An inverse SDKIE ($k_H/k_D < 1$) value is a strong indication of a polar addition as the rate-determining step,[11,13] whereas a normal SDKIE ($k_H/k_D > 1$) value would be compatible with the formation of a radical species. By means of two separate competition experiments, the relative rate of allylation for benzaldehyde and *d*-benzaldehyde could be determined relative to *p*-tolualdehyde. The comparison of the rates was carried out indirectly since standard GC is unable to differentiate between *d*-benzaldehyde and benzaldehyde. With zinc, the SDKIE was determined to be as large as 0.83, which suggests a relatively late TS. With tin, antimony, and bismuth, almost equally large values were determined (k_H/k_D = 0.85 (Sn), 0.75 (Sb), and 0.85 (Bi), respectively), whereas the use of indium resulted in only a minor effect (k_H/k_D = 0.95), suggesting that a much earlier TS is operating for this metal. In a related study by Lucas et al.,[13b] a significantly lower SDKIE was found for indium (k_H/k_D = 0.82), and due to the obvious disagreement, we decided also to perform a direct determination of the SDKIE for indium with GC-MS. Using selected ion monitoring (SIM) for the molecular ions of both benzaldehyde and *d*-benzaldehyde (m/z = 106 and 107, respectively), it was possible to quantify the disappearance of these aldehydes relative to the molecular ion of the internal standard (naphthalene, m/z =128). This experiment gave a SDKIE value of 0.92, which corroborates the slightly higher value (0.95) obtained in the indirect competition experiment. Also, for antimony, there are significant differences in the SDKIE value determined here (0.75) and the one reported earlier by Lucas et al. (1.07).[13b] However, in their case, a 2 M potassium fluoride solution was used, whereas we used a 0.5 M solution of hydrochloric acid, which may significantly alter the pathway of the reaction.

In contrast to the other five metals, the use of magnesium resulted in a normal rather than an inverse SDKIE value. The exact value was 1.04, which is very close to the value obtained by Lucas et al. (1.06).[13b] The finding of a normal SDKIE can be taken as an indication that a radical anion forms in the selectivity-determining step, in sharp contrast to all the previously investigated metals where the SDKIE value below 1 clearly indicates that C−C bond formation is rate-limiting.

Computational Study. In conjunction with the experimental study, we performed a computational study in an attempt to increase our understanding of this fundamental reaction. Although the metal-mediated allylation reaction is one of the basic transformations in organic synthesis, it is only recently that it has attracted interest from the theoretical community.[24] In general, allylmetal species can be considered to be highly fluxional, and there are several different equilibria that may be operating, including the well-known equilibrium between η^1- and η^3-coordination modes. The most well-studied of these equilibria is undoubtedly the Schlenk equilibrium for Grignard reagents,[25] but in addition to this, several different monomeric, oligomeric, or even polymeric complexes have been suggested, in particular, for indium.[14a]

In the present study, we limited ourselves to the mono-allyl species, which can be considered to be the simplest possible model for the previously mentioned complexes. As to whether this mono-allyl species is indeed the molecular entity responsible for the observed reaction is beyond the scope of the current study, but it is possible that such coordinatively unsaturated species can allow for a facile pre-coordination of the substrate.

The low ρ value determined in the Hammett studies indicates that only a slight build-up of negative charge takes place in the TS, which is in line with a closed Zimmermann−Traxler transition state.[26,27] Furthermore, as the Hammett correlations were not linear with the $\sigma^{\bullet}$ values, the involvement of radicals in the selectivity-determining step can be ruled out. As a consequence, we limited the computational investigation to molecules that exist as closed-shell singlets. The oxidation state for each of the metals, which is a necessary prerequisite to obtain

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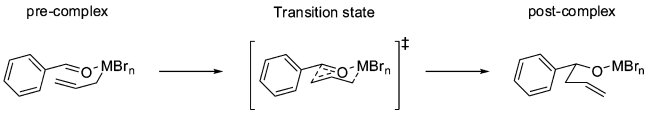
TABLE 2. Characteristic Distances and Imaginary Eigenfrequencies for Six-Membered Transition States (Gas Phase)

entry	metal (oxidn state)	no. of Br$^-$	C−C distance (Å)	M−C distance (Å)	imaginary eigenfrequency (cm^{-}1)
1	Zn(II)	1	2.18	2.16	270*i*
2	In(III)	2	2.10	2.28	309*i*
3	Sn(II)	1	2.28	2.39	240*i*
4	Sn(IV)	3	1.95	2.33	366*i*
5	Sb(III)	2	2.03	2.33	327*i*
6	Bi(III)	2	2.04	2.41	333*i*

SCHEME 2. General Outline of Structures Included in the Computational Study



meaningful results, was not known a priori; thus, we decided to investigate several different possibilities, including zinc(II), indium(I), indium(III), tin(II), tin(IV), antimony(III), and bismuth(III). As the experimental studies clearly indicate that the reaction with magnesium proceeds through an entirely different mechanism, we have not attempted to include this metal in the modeling study.[28]

Two conformations (chair or boat) are possible for the cyclic TS, but previous work on related systems revealed the chair conformation as being energetically favored,[15] which prompted us to exclude the boat conformations in the current study. With benzaldehyde as the substrate, the phenyl moiety can occupy either pseudo-axial or pseudo-equatorial positions in the six-membered cyclic transition state, and not surprisingly, we found the pseudo-equatorial position to be favored. To obtain an overall neutral model system, auxiliary bromide atoms were used as ligands for the metal atom (Scheme 2).[29]

With zinc as the metal, the formation of a pre-reactive complex from benzaldehyde and an σ-allylzinc fragment was exothermic by 68 kJ/mol (gas phase), but the inclusion of entropic contributions (Gibbs free energy, 298 K) reduced this to 16 kJ/mol due to the reduction in molecularity. The use of a polarized continuum solvation model (THF) reduced the exothermicity for the coordination to 18 kJ/mol (SCF energy), whereas by including the gas-phase entropic contributions, the coordination was endergonic by 34 kJ/mol. The pre-complex can undergo C−C bond formation through a six-membered cyclic TS with a C−C bond length of 2.19 Å and a Zn−C bond length of 2.16 Å (Table 2, entry 1). The structure of the six-membered ring remains essentially unchanged upon introduction of implicit solvation (parameters for THF), with the only noticeable change being the movement of the coordinating bromine atom into a pseudo-axial position. The energy profiles for the allylation reaction with zinc are plotted in Figure 4, with the isolated σ-allylzinc species and benzaldehyde as references.

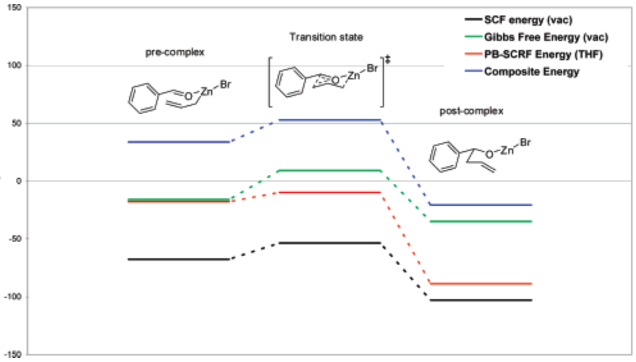


FIGURE 4. Energy profiles for allylation in the presence of zinc(II). All energies are relative to the isolated reactants (Zn-allyl complex and benzaldehyde).

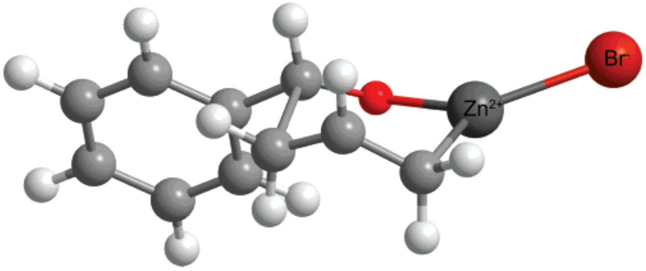


FIGURE 5. Illustration of the cyclic, six-membered TS for the allylation of benzaldehyde with zinc (gas phase).

The solvation model selectively stabilizes the post-complex (product) due to the formation of more localized charges on both zinc and oxygen, and this effect is also present to some degree in the TS. The locked six-membered TS has fewer degrees of freedom than both reactant and product (Figure 5), resulting in a higher Gibbs free energy, but the overall transformation is energetically favored in all cases.

On the basis of the similarity of the Hammett plots, we also desired to find similarities between the different metals in the computational study. With metallic zinc, the oxidative addition was expected to give exclusively the zinc(II) oxidation state, whereas for indium, both indium(I) and indium(III) oxidation states must be considered. Initially, we decided to characterize the reaction with indium(III). However, this resulted in a pre-complex and a post-complex with virtually identical energies (In(III), Figure 7). The TS could be located in the gas phase and by using the solvation model and was found to have a structure similar to that found for zinc, albeit with slightly different bond distances (In−C: 2.28 Å and C−C: 2.10 Å, Figure 6 and Table 2, entry 2). Although indium(III) is frequently employed in allylation reactions, NMR studies of the Barbier allylation in water have suggested that the initially formed allylindium(I) complex reacts directly with the aldehyde instead of participating in further oxidative addition reactions.[14a] As a result, we decided also to characterize the In(I)-mediated pathway.

Unfortunately, all attempts to locate a TS for the indium(I)-mediated pathway were unsuccessful. Instead, we performed a

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(28) For a DFT investigation on the addition of Grignard reagents to carbonyl compounds, see: Yamazaki, S.; Yamabe, S. *J. Org. Chem.* **2002**, *67*, 9346−9353.

(29) To estimate the influence of the ligands on zinc, we also performed an investigation of the Zn-mediated allylation with two water molecules as ligands. In addition, the entire system was embedded in the PCM solvation model for water. The structures of the transition states were found to be very similar, documenting that the models investigated here indeed are relevant for the reactions carried out in aqueous media (*XYZ* data and solvation energies are included in the Supporting Information).

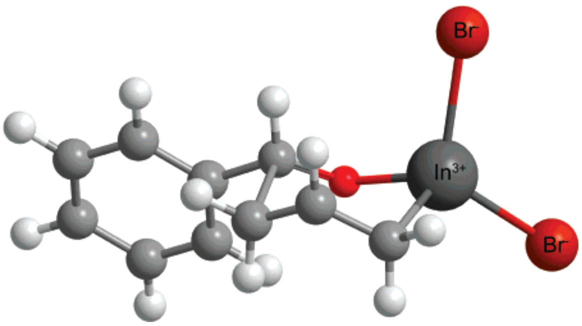

FIGURE 6. Structure of the TS with In(III) and two auxiliary bromide atoms.

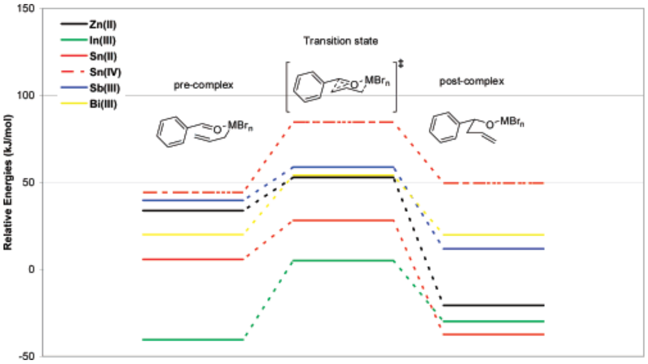

FIGURE 7. Energy profiles for the C−C bond formation via a six-membered TS. All energies are composite energies.

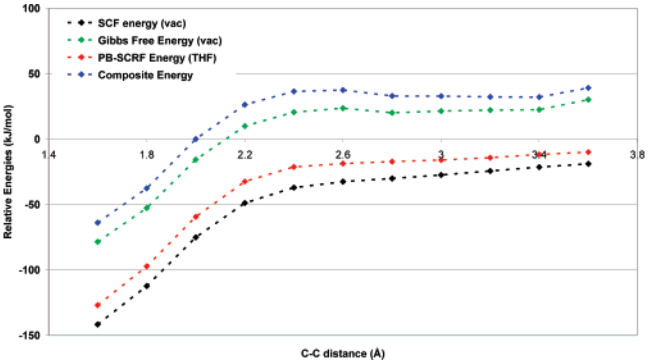

FIGURE 8. Energy profiles calculated for the indium(I)-mediated allylation. Each data point represents a fully minimized structure having that particular C−C bond length fixed.

series of energy minimizations with the C−C bond length fixed between 3.6 and 1.6 Å in intervals of 0.2 Å (Figure 8).

On the basis of the composite energies, it seems that a pre-reactive complex was formed with a C−C distance of approximately 3.2 Å, which undergoes allylation through a TS situated at a C−C distance of about 2.4 Å with a very low activation energy of only 5 kJ/mol. This clearly illustrates the high reactivity of this very electron-rich In(I)-allyl species, which is in accordance with the scenario outlined previously, where the formation of the In(I)-allyl species is slow but the following reaction with aldehyde takes place almost instantaneously.

With tin, we investigated both a tin(II)- and a tin(IV)-mediated allylation pathway since NMR studies have shown that both may operate in aqueous solution.[14b] Also, here, the lower oxidation state seems to be more reasonable (Sn(II), Figure 7), although the two TS are structurally rather similar. As expected, the TS with the smaller and more highly charged tin(IV) has shorter Sn−C distances, whereas the overall more endergonic tin(II) pathway has an earlier TS with a longer C−C distance (Figure 9 and Table 2, entries 3 and 4).

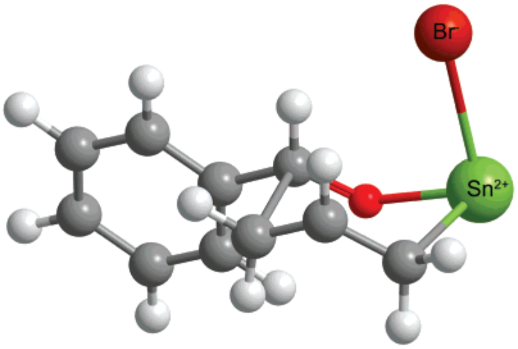

FIGURE 9. Structure of the TS with tin(II) and one bromide.

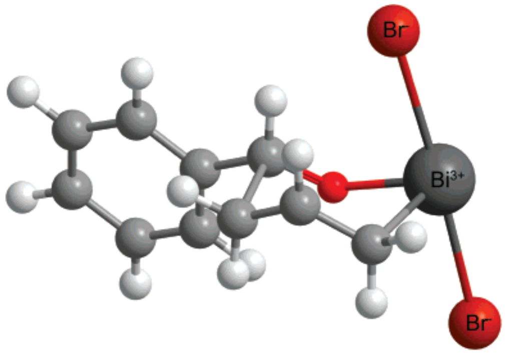

FIGURE 10. Structure of the TS obtained with bismuth in the gas phase. The corresponding TS with antimony is virtually identical, except for a slightly shorter M−C bond length.

Antimony and bismuth are both located in group 15 of the periodic table and would be expected to behave similarly. Indeed, the structures obtained in the computational study were quite similar, and energies were consistently within 5−10 kJ/mol, which prompted us to include only the structure of the TS obtained with bismuth (Figure 10). As expected, for both metals, the overall transformation is exergonic in the gas phase by 36 kJ/mol (Sb) and 30 kJ/mol (Bi), respectively. Inclusion of the solvation model lowered the exergonicity to 10 kJ/mol for antimony, while for bismuth, the reactant and product complexes now had equal energies.

Determination of Kinetic Isotope Effect. All theoretical determinations of kinetic isotope effects are based on the calculated frequencies using analytical gradients in the gas phase. The simplest approach uses only the differences in zero-point energies (ZPEs) and derives a relative speed of reaction for the two isotopomers using a simple Boltzmann-type expression.[30] However, with the current advances in theoretical methods, it has even become possible to evaluate the differences in Gibbs free energies that in addition to the previously mentioned ZPE also account for the differences in all vibrational modes of the molecule. A closed six-membered transition state is expected to be accompanied by an inverse KIE due to the increased sp^3-character of the carbonyl carbon atom, which results in a weakening of the bending vibrations for the attached hydrogen or deuterium. In all cases, the analysis was based on

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[30] Westheimer, F. H. *Chem. Rev.* **1961**, *61*, 265−273.

the calculated differences in Gibbs free energies upon going from the pre-reactive complex to the TS, which were derived from the analytical frequency calculations in the gas phase. Data for the deuterated analogues were obtained using the Hessian from the non-deuterated analogue by simply changing the hydrogen isotope ($^1H \rightarrow ^2H$).

For zinc, the SDKIE value was calculated to be 0.91 (at 298 K), which is slightly higher than the experimental value derived from the competition experiments (0.86). For indium(III), the calculated SDKIE value was determined to be 0.89, which is relatively close to the theoretical value determined for zinc but significantly lower than the experimental value determined for indium (0.95). However, since we were only able to locate the TS for the indium(III)-mediated reaction, this discrepancy between experiment and theory indicates the involvement of an indium(I)-mediated pathway as suggested by NMR studies.[14a] With a more electron-rich In(I)-allyl species, the C−C bond formation process could be extremely facile, and the corresponding TS would then have significant early character, which is expected to result in a very small SDKIE value. With tin as the metal, reaction pathways for both tin(II)- and tin(IV)-mediated reactions were characterized. The agreement with experiment ($k_H/k_D = 0.85$) was better for the tin(IV)-mediated pathway, where the calculated SDKIE value was indeed 0.85 ($T = 60$ °C), whereas for the tin(II)-mediated pathway, the calculated SDKIE value was slightly higher, 0.93 ($T = 60$ °C). This is an indication that the tin(IV)-mediated pathway is operating in these reactions, although we cannot rule out the involvement of a parallel tin(II)-mediated pathway as suggested earlier.[14b] For antimony and bismuth, only the M(III) oxidation states were characterized, which were the only oxidation states that were deemed plausible, and in addition, this is also in line with previous investigations using NMR spectroscopy.[14c] With antimony, the SDKIE value was calculated to be 0.77 at 298 K, which is in good agreement with the experimental value (0.75). For bismuth, the experiments were conducted at 60 °C ($k_H/k_D = 0.85$), and when this temperature was used in the Boltzmann expression, the theoretical value was 0.89, which is only slightly higher than the experimental value. It is particularly noteworthy that the SDKIE value for antimony is in good agreement with the experimental value, and we see no indication of a radical pathway in this reaction as suggested earlier.[13b] Since the experiments with magnesium point to the formation of a radical anion of benzaldehyde as the initial, selectivity-determining event, we also attempted to calculate the resulting theoretical SDKIE value for this transformation. Consequently, the radical anion of benzaldehyde was optimized, and frequencies were calculated for both isotopomers. The SDKIE value was calculated here to be 1.11 (298 K), in semiquantitative agreement with the experimental value, thus further supporting the formation of a radical anion when this metal is employed.

Conclusion

The metal-mediated allylation of aldehydes under Barbier conditions was investigated with both experimental and theoretical methods. For zinc, indium, tin, antimony, and bismuth, linear Hammett plots were obtained with regular σ values, whereas radicals did not seem to be involved in the rate-determining step. A small positive slope was found for the Hammett correlation, which is a strong indication that a discrete organometallic allylmetal species is present in the rate-determining step, which subsequently reacts in a closed, cyclic TS under development of a small negative charge in the benzylic position. A computational study further supported the involvement of a closed, six-membered transition state, and in addition, the calculated SDKIE value based on this mechanism was found to be in good agreement with the experimental values. For indium and tin, both low oxidation states (In^+ and Sn^{2+}) and high oxidation states (In^{3+} and Sn^{4+}) were considered theoretically, and for indium, the lower oxidation state gave the best agreement with the experimental results, whereas for tin, the results indicated that the higher of the two oxidation states was involved. When magnesium was employed, under the Barbier conditions, both experimental and theoretical data supported the formation of a radical anion as the selectivity-determining event. We believe that detailed information on the allylation of aldehydes by the Barbier procedure conveyed in this work may prove to be useful for further improvements of the reaction conditions and thereby stimulate additional applications of this method.

Computational Details

All calculations were performed using density functional theory (B3LYP functional[31]), in combination with the LACVP* basis set as incorporated in the Jaguar program package.[32] The LACVP* basis set used the Los Alamos effective core potential (ECP) and basis set for the description of heavy atoms (Zn, In, Sn, Sb, Bi, and Br),[33] whereas all lighter atoms (H, C, O, and Mg) were described using the 6-31G* basis set.[34] Solvation was described using the Poisson−Boltzmann self-consistent reaction field model (PB-SCRF)[35] with parameters suitable for tetrahydrofuran (dielectric constant: 7.43 and probe radius: 2.524). The difference between the results obtained in the gas phase and those obtained using a solvation model can be large, whereas the difference between two different solvation models is small. The solvation model for water thus was expected to give virtually identical results, which was verified for Zn-allyl addition to benzaldehyde. The PB-SCRF is a continuum solvation model, where the molecule is put into a reaction field consisting of surface charges on a solvent-accessible surface constructed using a hypothetical spherical solvent probe molecule with the indicated radius.[36] The solution-phase structures were fully optimized to allow comparison to gas-phase structures. Vibrational frequencies were calculated for the gas-phase structures using analytical expressions, whereas the corresponding frequencies for the solution phase only were available using numerical derivatives. The numerical frequency calculations are very time-consuming, and in addition, a lower accuracy must be expected; therefore, this approach is intractable. Instead, to obtain an approximate Gibbs free energy in the solution phase (composite energy), we decided to use the solution-phase energy and add the vibrational contribution from the gas phase ($\Delta G_{solv} = \Delta E_{solv} + \Delta G_{gas} - \Delta E_{gas}$). We found that it is advantageous to use the energy for the fully optimized solution-phase

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[31] (a) Lee, C.; Yang, W.: Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785−789. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (c) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372−1377.

[32] *Jaguar*, version 6.5, release 106; Schrodinger, LLC: New York, 2005.

[33] Hay, P. J.; Wadt, R. W. *J. Chem. Phys.* **1985**, *82*, 299−310.

[34] Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257−2261.

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[36] For a discussion of implicit solvation models, see: Cramer, C. J. *Essentials of Computational Chemistry: Theories and Models*; Wiley: New York, 2002.

structures (E_{solv})[37] rather than using single-point solvation energies. For transition states, one single imaginary eigenfrequency was obtained in all cases, which upon visualization was found to correspond to the expected vibration of the forming C−C bonds.

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Supporting Information Available: Experimental procedures, characterization of compounds, and experimental data from kinetic runs. Cartesian coordinates, SCF energies, and Gibbs free energies for structures calculated in the gas phase and PB-SCRF energies for structures calculated using the solvation model. This material is available free of charge via the Internet at http://pubs.acs.org.

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[37] Ahlquist, M.; Fristrup, P.; Tanner, D.; Norrby, P.-O. *Organometallics* **2006**, *25*, 2066−2073.