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Mechanism for the Regioselective Asymmetric Addition of Grignard Reagents to Malimides: A Computational Exploration[||]

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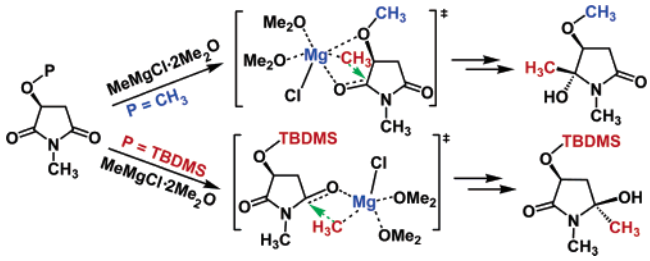
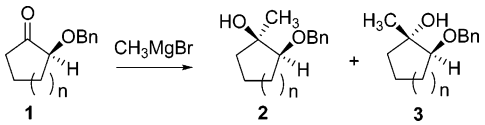


We present a systematic theoretical investigation on the addition reaction of Grignard reagents to malimides to understand its mechanism as well as the origin of its regio- and diastereo-selectivity. The computations carried out at a hybrid density functional B3LYP/6-31G* level of theory reveal that (i) the addition of Grignard reagents with *N*,*O*-dimethylmalimide (1-methyl-3-methoxypyrrolidine-2,5-dione) occurs regioselectively at the α-carbonyl (C1) by passing through a *cis*-α-chelated precursor and affords stereoselectively *cis*-addition product, in qualitative agreement with the previous experimental observations; (ii) such regioselectivity is ascribed to the preferential chelation of Grignard reagent to the α-carbonyl (C1) over the coordination to the α′-carbonyl (C4); (iii) its unusual *trans*-addition, in sharp contrast to the Cram chelation-type stereoselectivity for the reaction of aliphatic α- or *β*-alkoxy carbonyl compounds, is due primarily to the rigidity of the five-membered ring skeleton of the malimide that favors the formation of the *cis*-α-chelated precursor; and (iv) poor regioselectivity is predicted for the reaction of *O*-TBDMS-protected malimide (1-benzyl-3-(*tert*-butyldimethylsilyloxy)pyrrolidine-2,5-dione) with Grignard reagent and can be ascribed to the large steric repulsion of the bulky TBDMS group and the electronic effects of the silyl group that remarkably destabilizes the α-chelated precursors and the corresponding transition states.

1. Introduction

Stereoselective and regioselective C−C bond formation is an important goal in organic synthesis. One of the most important stereoselective C−C bond-formation reactions is the 1,2- or 1,3-asymmetric induction reaction of Grignard reagents (RMgX) with chiral α- or *β*-alkoxy carbonyl compounds.[1] For example, it has been shown that the asymmetric addition of cyclic α-alkoxy ketones **1** with RMgX afforded predominantly the *trans*-addition product, namely, the *cis*-diastereoisomer **2** (Scheme 1).[2]

SCHEME 1. Stereoselective Addition of Cyclic α-Alkoxy Ketones with Grignard Reagents (ref 2)



The mechanism of the stereoselective Grignard reagents (RMgX) addition with chiral α- and *β*-alkoxy carbonyl compounds has been the subject of extensive experimental[1,3] and theoretical[4] investigations, and the Cram chelation model[3a−c] has been used most frequently to predict or to account for the sense of asymmetric induction. According to the Cram chelation model (Scheme 2A), a five-membered ring complex intermedi-

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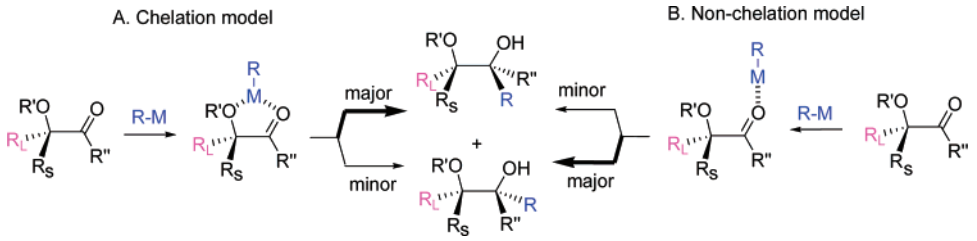
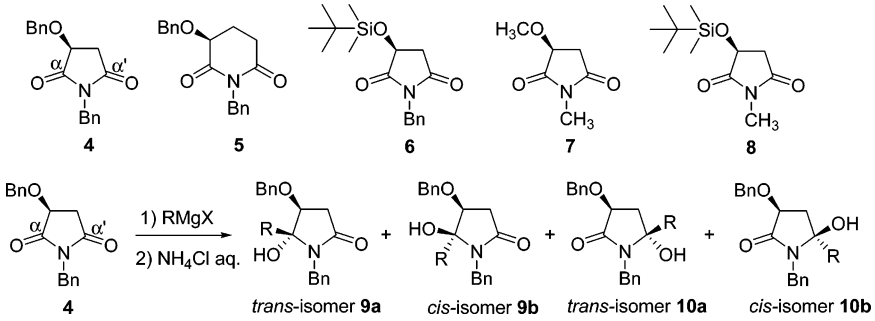
SCHEME 2. Chelation (A) and Nonchelation (B) Mechanisms for the Stereoselective Addition of α-Alkoxy Carbonyl Compounds with Organometallic Compounds



SCHEME 3. Reactions of RMgX with Malimides and 3-Benzyloxyglutarimide



ate is first formed by chelation of the Lewis acidic M atom of the organometallic reagent with the two oxygen atoms of the substrate, followed by migration of the nucleophilic alkyl group (R^-) to the carbonyl group preferentially from the sterically less hindered side, i.e., opposite to the larger group R_L. The Cram chelation model was supported by a number of quantum chemical calculations.[4] For instance, the MP2(FC)/6-31+G*//HF/6-31G* calculations by Morokuma et al.[4i,j] have shown that the reactions of acyclic α- and *β*-alkoxy carbonyl compounds with Me_2Mg are initiated by chelation of the organometallic reagent with the alkoxy carbonyl compounds, and α-chelation is kinetically favorable over *β*-chelation. However, exceptions to the Cram chelation model of stereoselectivity can be found when the organometallic compound is incapable of chelation.[1a] For such a case, the Felkin−Anh model **B** (Scheme 2B) was put forward,[3d−f] in which the stereoselective approach of the nucleophile is governed by stereoelectronic and/or steric factors with the resulting diastereoselection being opposite to that of the Cram chelation model.

Among the various addition reactions of α- and *β*-alkoxy carbonyl compounds concerned thus far, of particular interest is the regioselective reaction of malimide **4** (or 3-benzyloxyglutarimide **5**) with Grignard reagents RMgX that affords α-hydroxylactams **9a** and **9b** (or their higher homologues, not shown), which have been proven to be a key step in the recently developed methodology for efficient and flexible synthesis of bioactive pyrrolidine (or piperidine) alkaloids and *γ*-amino acids (or *δ*-amino acids).[5] The two inequivalent carbonyl groups in malimide **4** (or 3-benzyloxyglutarimide **5**) are as highly electrophilic toward organometallic reagents as that of a ketone.[6] However, it has been interestingly shown that at low temperature Grignard reagents prefer to react with the more hindered α-carbonyl of malimide **4** (or 3-benzyloxyglutarimide **5**), leading smoothly to α-hydroxylactam **9a** and **9b** (or their higher homologues, no shown) with a high regioselectivity (regioselectivity **9**:**10** > 94%, Scheme 3).[5] The regioselective reaction of malimides shows remarkable substituent effect; low regioselectivity was observed in the reaction of RMgX with malimide **6** bearing a bulky substituent, TBDMS (*tert*-butyldimethylsilyl), at the O2 site.[5e] The observed substituent-dependent regioselectivity was attributed to the complex-induced proximity effects (CIPE).[5d−f,7] That is, the Grignard reagent is first coordinated

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with its magnesium atom to the oxygen atom of the alkoxy group at C2, which in turn favors delivering the alkyl group to the nearest C1 carbonyl group. Similar CIPE effects had been used by Speckamp et al.[7] to account for the regioselectivity observed in the reduction of *gem*-disubstituted succinimides.

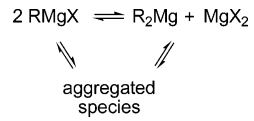
In addition to its remarkable regioselectivity, the reaction of malimide **4** with RMgX displays moderate stereoselectivity in the regioselective formation of **9** with a diastereoselectivity of 6:1 to 8:1 (*trans*-isomer **9a** vs *cis*-isomer **9b**).[5f,8] Such a stereoselectivity is in sharp contrast to that observed for the analogous reactions of α- and *β*-alkoxy cyclic ketones **1** (Scheme 1), where the observed diastereoselectivity faithfully obeys the Cram chelation rule with the *anti*-addition diastereomers **2** being the major products (Scheme 2A).[2] Analogously, the stereoselective reaction of malimide **4** with the Grignard reagent also does not obey the widely accepted Cram chelation rule, despite that the Grignard reagent used in the reaction is obviously subjected to bidentate complexation (chelation) with the substrate. Unfortunately, the mechanism for such an unusual chelation-controlled, "anti-Cram chelation rule" addition reaction remains unclear.

To unravel the mechanism of the aforementioned anti-Cram chelation rule reaction and to understand the origin of its regio- and stereo-selectivities, we have performed quantum mechanical calculations at the B3LYP/6-31G* level on a series of model reaction systems and report the results herein.

2. Computational Methods and Models

All calculations were performed with the GAUSSIAN 98 package.[9] The hybrid density functional method including Becke's three-parameter non-local-exchange functional[10] with the correlation functional of Lee−Yang−Parr[11] (B3LYP) was employed. This method has been widely used in the theoretical investigations of chemical processes involving Grignard reagents.[4m,12] The basis set used is the standard all-electron split-valence basis set 6-31G* including the polarization d-function on non-hydrogen atoms.[13] Geometry optimizations and vibrational analyses were performed without any constraint. All transition structures were characterized by one imaginary frequency. Reported energies are ZPE (zero-point energy)-corrected, unless otherwise specified. To evaluate the solvent effects, single-point B3LYP/6-31G* calculations using the conductor polarized continumm model (CPCM)[14] and B3LYP/6-31+G** calculations using the isodensity polarized continumm model (IPCM)[15] were performed on the gas-phase optimized structures.

SCHEME 4. Schlenk Equilibrium



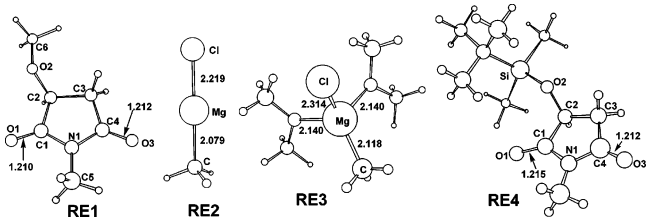


FIGURE 1. B3LYP/6-31G*-optimized geometry of malimide **7** (**RE1**), CH_3MgCl (**RE2**), $CH_3MgCl{\cdot}2Me_2O$ (**RE3**), and malimide **8** (**RE4**).

To reduce computational cost, a model system maintaining the fundamental characters of the real reaction system has been chosen. At first, the simple model compounds **7**, **8**, CH_3MgCl, and Me_2O were used to replace the compounds **4**, **6**, CH_3MgI, and Et_2O, respectively, in actual reactions. Though a Grignard reagent is generally expressed as RMgX (e.g., aforementioned CH_3MgCl), its composition in a real solution is far more complex. In polar solvents, its complex compositions can be described by the revised Schlenk equilibrium (Scheme 4);[16] the ratio of these compositions strongly depends on the solvent used, the concentration, and the halide of Grignard reagents (RMgX).[17] For example, it has been shown experimentally that CH_3MgI is monomeric in either THF solvent within 0.1−3.5 M range or Et_2O at less than 0.1 M, whereas the major species is a dimer in Et_2O within the concentration range

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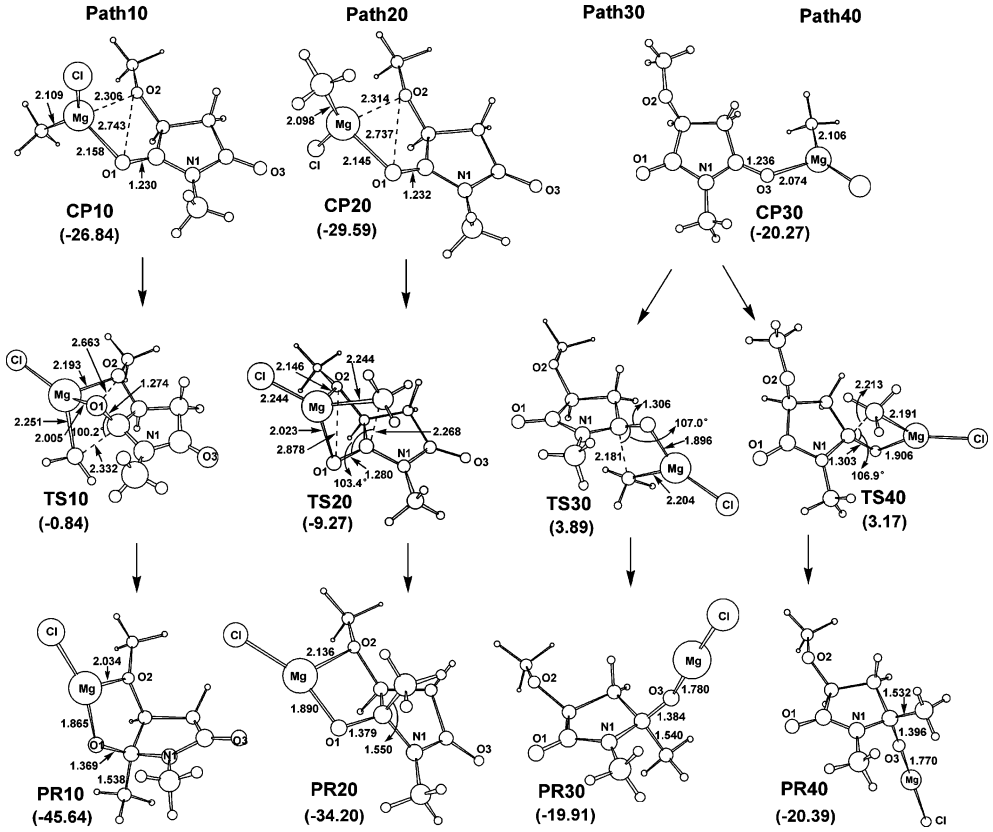

FIGURE 2. B3LYP/6-31G*-optimized geometries of precursors (**CPn0**), transition state (**TSn0**), and products (**PRn0**) for the gas-phase reaction of CH_3MgCl addition to malimide **7**. The ZPE-corrected energies (kcal/mol) relative to the isolated reactants **RE1** and **RE2** are given in parentheses.

of 0.5−1.0 M.[17b,c] A series of theoretical investigations also confirmed that the monomeric $RMgX{\cdot}2Et_2O$ is one of the most favorable forms of RMgX in Et_2O.[17b,18] Hence, we chose $CH_3MgCl{\cdot}2Me_2O$ as a simple model of the real Grignard reagent in Et_2O solvent. Figure 1 depicts the optimized geometries of malimide **7** (**RE1**), CH_3MgCl (**RE2**), $CH_3MgCl{\cdot}2Me_2O$ (**RE3**), and malimide **8** (**RE4**) (Figure 1).

3. Results and Discussion

3.1. Addition of Grignard Reagents to Malimide 7. 3.1.1. Gas-Phase Reaction of Malimide 7 with CH_3MgCl. At first, the gas-phase reaction of malimide **7** (**RE1**) with CH_3MgCl (**RE2**) was considered as the simplest model of the title reactions. Similar model reactions were investigated theoretically by Morokuma[4i,j] and Safont.[4e] As depicted in Figure 2, the Grignard reagent CH_3MgCl may regioselectively and stereoselectively attack the α-carbonyl (C1) or the α′-carbonyl (C4) of malimide **7**, giving rise to four competing reaction pathways **Path10**−**Path40**.

For the attack of CH_3MgCl to the α-carbonyl (C1) of malimide **7** (**Path10** and **Path20**), the first step is the formation of two chelating complexes, *trans*-α-chelated **CP10** and *cis*-α-chelated **CP20**. Such chelations are predicted to be exothermic by 26.8 kcal/mol for **CP10** and 29.6 kcal/mol for **CP20**. The formation of these chelating precursors are followed by migration of the methyl group from the chelated CH_3MgCl to the α-carbonyl (C1) via the puckered five-member ring transition states **TS10** and **TS20**, leading eventually to the addition products **PR10** and **PR20**, respectively. The whole addition processes are exothermic by 45.6 kcal/mol for **path10** and 34.2 kcal/mol for **path20**. Remarkably, the transition state **TS10** is by 8.4 kcal/mol higher in energy than **TS20**. As a result, **path20** is kinetically more favorable over **path10**, despite that **path20** is less exothermic than **path10**. Thus, the addition of the Grignard reagent CH_3MgCl to the α-carbonyl (C1) of malimide **7** is highly stereoselective, giving preferentially rise to the *cis*-addition product **PR20**.

For the attack of CH_3MgCl to the α′-carbonyl (C4) of malimide **7** (**Path30** and **Path40**), no α′-chelation complex could be formed between CH_3MgCl and the O2 and O3 atoms of malimide **6** due to the rigid structure of the pyrrolidinedione ring in malimide **7**. Instead, a tricoordinated Mg complex **CP30** (Figure 2) was located with a computed formation energy of 20.3 kcal/mol. Starting from **CP30**, migration of the methyl group from the monocoordinated CH_3MgCl to the C4 carbonyl can proceed through the four-member ring transition states **TS30** and **TS40**, leading to the products **PR30** and **PR40**, respectively. However, such migration processes are nearly thermoneutral with respect to the precursor **CP30**. Moreover, the transition states **TS30** and **TS40** for the methyl migration to the C4 carbonyl are by ∼13 and ∼3 kcal/mol higher in energy than the transition states **TS20** and **TS10** for the methyl-migration to the C1 carbonyl, respectively, demonstrating that the simplest model reaction of CH_3MgCl with malimide **7** is not only highly regioselective, but also highly stereoselective by following the

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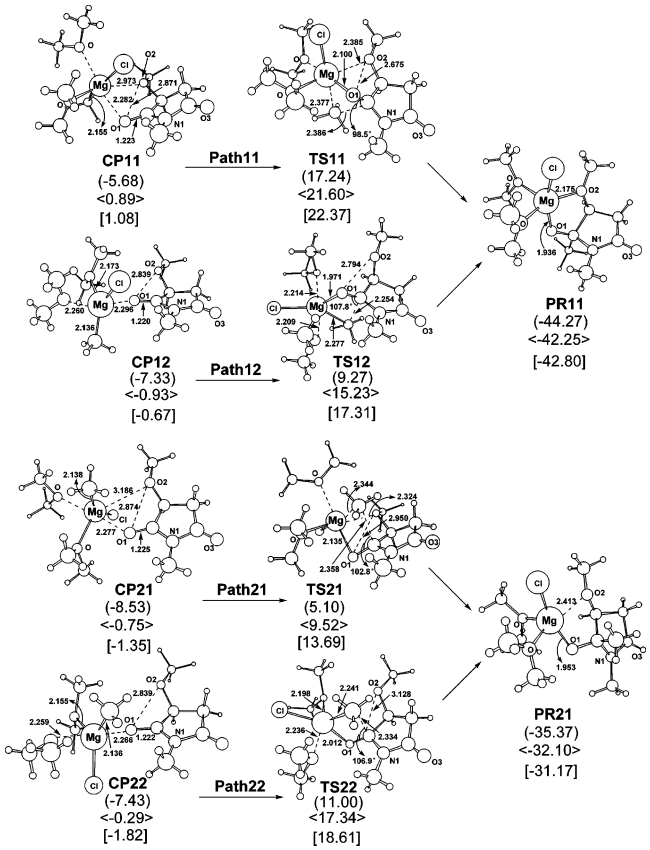

FIGURE 3. B3LYP/6-31G*-optimized geometries of precursors, transition states, and products for the reaction of $CH_3MgCl{\cdot}2Me_2O$ with the α-carbonyl (C1) of malimide **7**. The ZPE-corrected energies (kcal/mol) relative to isolated reactants **RE1** and **RE3** are given in parentheses. The relative energies (kcal/mol) corrected by solvation energies for the stationary points in CH_2Cl_2 solution using CPCM-B3LYP/6-31G* are given in brackets, and those using IPCM-B3LYP/6-31+G** are given in square brackets.

kinetically preferential **path20**, giving rise to the *trans*-isomer **PR20**.

It is interesting that the predicted regioselectivity and stereoselectivity for the simplest model reaction is in qualitative agreement with that observed experimentally for the reaction of Grignard reagent CH_3MgI (in Et_2O solvent) with malimide **4**,[5] despite that such factors as the ligand effect (due to coordination of solvent molecule to the Grignard reagent) and solvent effects are not involved in the simplest model reactions at all. We shall consider the ligand effect and solvent effects in the following subsections.

3.1.2. Reaction of Malimide 7 with $CH_3MgCl{\cdot}2Me_2O$: Ligand Effect. To account for the ligand effect, the Grignard reagent $CH_3MgCl{\cdot}2Me_2O$ (**RE3**) with two Me_2O molecules as ligands have been used. For the reaction of **RE3** with the α-carbonyl (C1) of malimide **7** (Figure 3), four complexes (**CP11**, **CP12**, **CP21**, and **CP22**) were located as precursors for further methyl migration. The $CH_3MgCl{\cdot}2Me_2O$ component is chelated in **CP11** and **CP21** but monocoordinated to the O1 of α-carbonyl in **CP12** and **CP22**. The predicted formation energy for these complexes ranges from 5.7 kcal/mol for **CP11** to 8.5 kcal/mol for **CP21**, which are much lower than those (>26.8 kcal/mol) predicted for the ligand-free cases (**CP10** and **CP20** in Figure 2). Such a prediction calibrates the importance

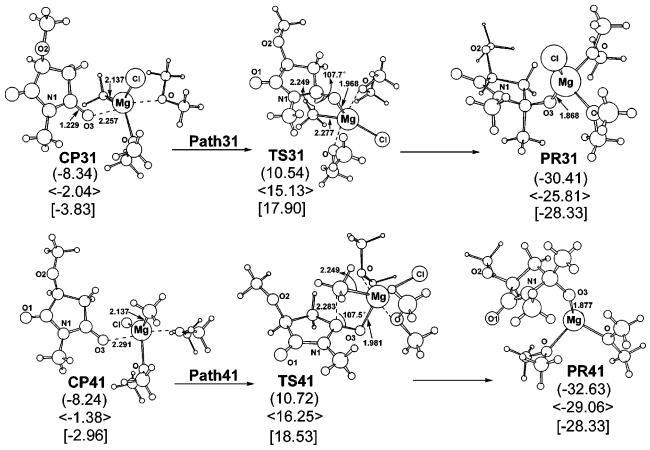

FIGURE 4. B3LYP/6-31G*-optimized geometries of precursors, transition states, and products for the reaction of $CH_3MgCl{\cdot}2Me_2O$ with the α′-carbonyl (C4) of malimide **7**. The ZPE-corrected energies (kcal/mol) relative to isolated reactants **RE1** and **RE3** are given in parentheses. The relative energies (kcal/mol) corrected by solvation energies for the stationary points in CH_2Cl_2 solution using CPCM-B3LYP/6-31G* are given in brackets, and those using IPCM-B3LYP/6-31+G** are given in square brackets.

of the ligand effect of such coordinating solvents as THF and ethers. Starting from these precursors, four transition states **TS11**−**TS22** were found to be responsible for the migration of methyl group from the coordinated Grignard reagent to the C1 carbonyl as well as the formation of the *trans*-addition product **PR11** and *cis*-addition product **PR21**. The predicted formation energy with respect to the isolated reactions **RE1** and **RE3** is 44.3 and 35.4 kcal/mol for **PR11** and **PR21**, respectively. The predicted order of energy for the transition states is **TS21** (5.1) < **TS12** (9.3) < **TS22** (11.0) < **TS11** (17.2). Accordingly, for the formation of *cis*-addition product **PR21**, the most favorable pathway is **path21** that passes through the *cis*-α-chelated precursor **CP21** and transition state **TS21**. For the formation of the *trans*-addition isomer **PR11**, the pathway **path12** via the monocoordinated precursor **CP12** and transition state **TS12** is favorable over **path11**. Moreover, since **TS21** is by 4.2 kcal/mol lower than **TS12** in energy, the reaction of $CH_3MgCl{\cdot}2Me_2O$ with the α-carbonyl of malimide **7** is highly stereoselective and preferentially affords the *cis*-addition product **PR21** by following **path21** (Figure 3).

For the reaction of **RE3** with the α′-carbonyl (C4) of malimide **6**, two pathways (**path31** and **path41**) have been revealed, as shown in Figure 4. The reactions are initiated by the formation of monocoordinated precursors **CP31** and **CP41**, in which the $CH_3MgCl{\cdot}2Me_2O$ component is monocoordinated to the O3 atom of the α′-carbonyl group of malimide **7**. The predicted formation energy with respect to isolated reactants **RE1** and **RE3** is ∼8.3 kcal/mol for both **CP31** and **CP41**. The predicted activation energy for the formation of *trans*- and *cis*-addition products **PR31** and **PR41** is around 10.6 kcal/mol at the transition states **TS31** and **TS41**, by 5.5 kcal/mol higher than that (5.1 kcal/mol at **TS21** for **path21**) predicted for the reaction of **RE3** with the α-carbonyl (C1) of malimide **7**. Accordingly, the reaction of the Grignard reagent **RE3** with malimide **7** occurs regioselectively at the α-carbonyl site and, meanwhile, affords stereoselectively the *cis*-addition product **PR21**. The overall activation energy for such a regio- and stereo-selective addition reaction is thus 5.1 kcal/mol at **TS21**.

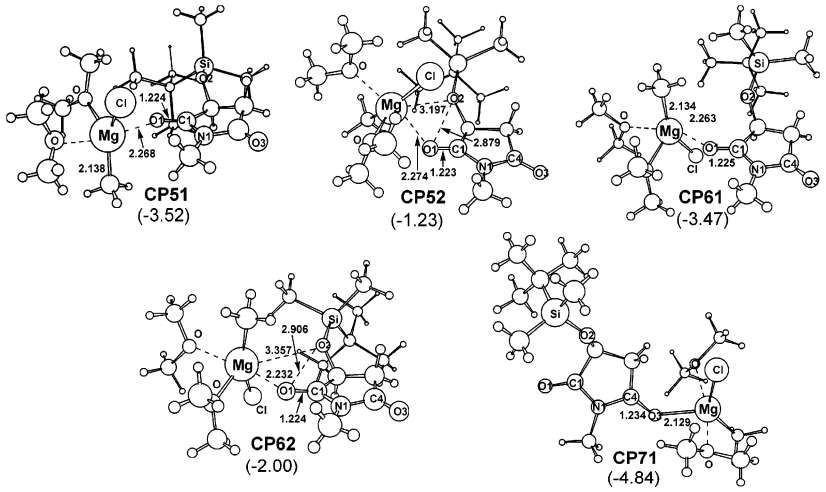

FIGURE 5. Optimized geometries of molecular complexes formed from $CH_3MgCl{\cdot}2Me_2O$ and malimide **8**. The reported ZPE-corrected energies (kcal/mol) relative to the isolated reactants are given in parentheses.

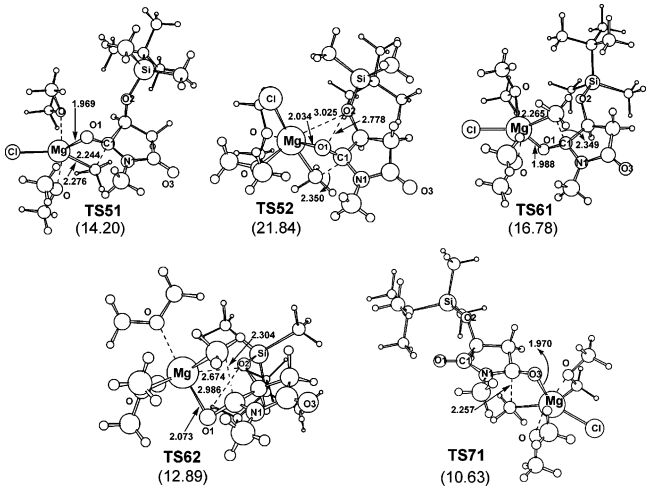

FIGURE 6. Optimized geometries of transition states for the migration of methyl group from $CH_3MgCl{\cdot}2Me_2O$ to malimide **8**. The reported ZPE-corrected energies (kcal/mol) relative to the isolated reactants are given in parentheses.

3.1.3. Solvent Effects in the Reaction of Malimide 7 with $CH_3MgCl{\cdot}2Me_2O$. In typical experiments, the addition of Grignard reagent CH_3MgI (prepared in Et_2O) to compound **4** were carried out in CH_2Cl_2 or THF (tetrahydrofuran) solution.[5] Despite that the affinity of THF to organomagnesium compounds is higher than Et_2O,[19] the difference in the observed regioselectivity and diastereoselectivity was trivial for the reactions in THF and CH_2Cl_2 solutions.[5] To unravel the solvent effects on the predicted energetics and selectivity, we have computed the energies of the stationary points for the reaction of **RE3** and malimide **7** in CH_2Cl_2 solution. The dielectric constant of 8.93 for CH_2Cl_2 solvent was used in the single-point CPCM-B3LYP/6-31G* calculations. The predicted energies for the reactions in the CH_2Cl_2 solvent are also given in Figures 3 and 4.

From Figures 3 and 4, it is obvious that the solvent effects do not change the regioselectivity and stereoselectivity for the reaction of **RE3** with malimide **7**. The most favorable pathway in the CH_2Cl_2 solvent is also **path21** that the addition of **RE3** occurs regioselectively to the α-carbonyl site and affords stereoselectively the *cis*-addition product **PR21**. For the regioselective and stereoselective formation of **PR21**, the predicted activation energy is 9.5 kcal/mol in the CH_2Cl_2 solvent versus 5.1 kcal/mol in the gas phase, whereas the predicted exothermicity is 32.1 kcal/mol in the CH_2Cl_2 solvent versus 35.4 kcal/mol in the gas phase. So the reaction in the CH_2Cl_2 solution is less exothermic (with higher activation energy) than the corresponding gas phase reaction. Nevertheless, the predicted regioselectivity and stereoselectivity for the model reaction of **RE3** with malimide **7** in either the gas phase or CH_2Cl_2 solvent is in good agreement with the previous experimental observations.[5f]

The energetics predicted by IPCM-B3LYP/6-31+G** calculations for the reactions in the CH_2Cl_2 solvent are also given in Figures 3 and 4. The isodensity value of 0.0004 suggest by Frisch[15] and Wiberg[20] was used in these IPCM calculations. The predicted energies conform to the conclusions drawn above.

3.1.4. Origin of the Regioselectivity and Stereoselectivity for the Addition Reactions of Grignard Reagents with Malimide 7. The computational results reported above clearly demonstrate that the vicinal alkoxy group of the α-carbonyl (C1) plays an important role in affording high regioselectivity for the addition reaction of Grignard reagents with malimide **7**. Owing to the presence of the vicinal alkoxy group, the chelation of Grignard reagent to the α-carbonyl (C1) is preferential over the coordination to the α′-carbonyl (C4). Furthermore, the chelation further facilitates the migration of the alkyl group from the Grignard reagent to the α-carbonyl (C1) by stabilizing the corresponding transition state (**TS21**), offering a high regioselection at the α-carbonyl. In this regard, the regioselectivity of the addition reaction could be lowered or even reversed when methoxyl substituent at the C2 site of malimide is replaced by simply a methyl group or a bulky alkoxyl to prevent the Grignard reagent from chelation. Indeed, previous experiments showed that a very low regioselectivity was observed for the addition reaction of Grignard reagent to malimide **6** (Scheme 3) that has a bulky TBDMS (*tert*-butyldimethyl silyl) substituent.[5e] Such a substituent effect on the regioselectivity shall be discussed in the following subsection.

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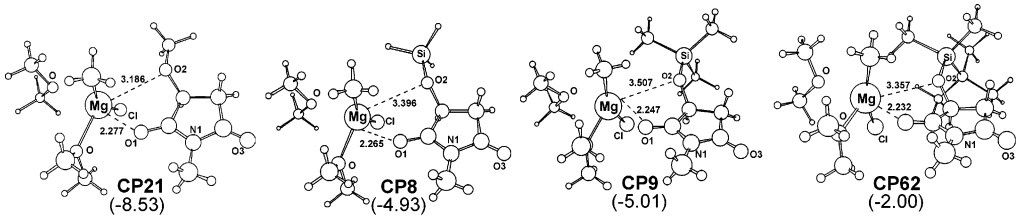

FIGURE 7. Optimized geometries and formation energies of *cis*-chelation complexes derived from the CH_3-, SiH_3-, $Si(CH_3)_3$-, and TBDMS-substituted malimides. The formation energies (kcal/mol) are ZPE-corrected.

In addition to the regioselectivity pertaining to the α-carbonyl (C1) of malimide **7**, the *cis* stereoselectivity of the addition reaction (Figure 3) is not only related to the chelation of Grignard reagent, but also due primarily to the rigidity of the five-membered ring skeleton of malimide **7**, which hinders rotation of the MeO-C2 around the C1−C2 bond. It is the delocalization of π-electrons of the amide group that results in a C1-N-C4 plane, which in turn gives rise to the rigidity of the five-membered ring skeleton of the malimide. Note that the dihedral angle ∠O1−C1−C2−O2 decreases little from 49.08° for the reactant **RE1**, to 46.45° for the *cis*-chelation precursor **CP21**, and 44.68° for the *trans*-chelation precursor **CP11**. Meanwhile, the distance between the methyl group of Grignard reagent and the carbonyl C1 atom is much longer in the *trans*-chelation precursor **CP11** than in the *cis*-chelation precursor **CP21**. Accordingly, the steric constraint pertaining to the MeO−C2 bond favors the *cis*-addition pathway (**path21**) over the *trans*-addition pathway (**path11**) for migration of the methyl group from the chelated Grignard reagent (**CP11** and **CP21**) to α-carbonyl (C1). This is different from the addition reaction of Grignard reagent with the cyclic α-alkoxy ketones (Scheme 1) or with aliphatic α- or β-alkoxy carbonyl compounds, in which the free rotation of C−O (alkoxy) bond allows the chelated Grignard reagent to choose always the sterically less hindered side to transfer its alkyl group to the carbonyl and, thus, results in the Cram chelation-type stereoselectivity.[4e,l]

3.2. Reaction of Malimide 8 with $CH_3MgCl·2Me_2O$: Substituent Effect. TBDMS (*tert*-butyldimethyl silyl) is a protecting group widely used in organic synthesis.[21] It was found that the addition reaction of Grignard reagents to the TBDMS-substituted malimide **6** shows low regioselectivity, in sharp contrast to the high regioselectivity observed for addition reaction of malimide **4** having a smaller Bn (benzyl) protecting group at the O2 site.[5e] To mimic such a substituent effect on the regioselectivity of the aforementioned alkyl-migration reactions, we took the TBDMS-substituted malimide **8** as a model of the TBDMS-substituted malimide **6** and computed the precursors (Figure 5) and transitions states (Figure 6) for the addition reaction of **RE3** with malimide **8** at the B3LYP/6-31G* level of theory.

As depicted in Figure 5, four coordinated complexes (**CP51**, **CP52**, **CP61**, and **CP62**) were located as precursors for the addition reaction of $CH_3MgCl·2Me_2O$ with the α-carbonyl of milimide **8**. Among them, **CP51** and **CP61** are monocoordinated, whereas **CP52** and **CP62** are chelated. Their formation energies ranging from 1.2 to 3.5 kcal/mol are substantially lower than the predicted formation energies (5.7−8.5 kcal/mol) for the coordinated complexes (**CP11**, **CP21**, **CP12**, **CP22**) formed from $CH_3MgCl·2Me_2O$ + malimide **7**. Furthermore, the formation energies of the monocoordinated complexes **CP51** and **CP61** are larger than that of the chelated ones (**CP52** and **CP62**). These computational results indicate the larger steric repulsion exerted by the bulky TBDMS group to the chelated Grignard reagent.[1g,22] Similarly, the large steric repulsion of the bulky TBDMS group destabilizes the transition states (**TS51, TS61, TS52**, and **TS62**) for migration of the methyl group from the coordinated Grignard reagent to the α-carbonyl (C1) (Figure 6). The smallest activation energy required for methyl-migration to the α-carbonyl is 12.9 kcal/mol (at **TS62**) for the malimide **8** case, much higher than that (5.1 kcal/mol at **TS21**) of the malimide **7** case.

On the contrary, the bulky TBDMS group shows little effect on the addition reaction of Grignard reagent with the remote α′-carbonyl group (C4). As depicted in Figure 6, the predicted activation energy for the *trans*-addition of methyl to the α′-carbonyl of malimide **8** for such an addition reaction is 10.6 kcal/mol (**TS71**), nearly identical to the value (10.5 kcal/mol at **TS31**) predicted for the malimide **7** case. It is noteworthy that for the malimide **8** + **RE3** reaction, the addition at the α′-carbonyl site with an overall activation energy of 10.6 kcal/mol is kinetically favored over the addition at the α-carbonyl (overall activation energy ∼12.9 kcal/mol). Hence the regioselectivity for the malimide **8** + **RE3** reaction is poorer than that of the malimide **7** + **RE3** reaction. Such a prediction is in accordance with the experimental observation.[5e]

It should be noted that the low coordination ability of the silicon-protected β-oxygen site in the TBDMS-substituted malimide **8** was related not only to the aforementioned steric effect (i.e., steric repulsion due to the bulky TBDMS group),[22] but also to the electronic effect.[23] The latter effect was attributed to the electron-backdonation from the lone-pair orbital of the β-oxygen to the empty 3d-orbital of the neighboring silicon, which reduces the basicity and coordination ability of the β-oxygen.[23] To clarify either steric or electronic effect controls the coordination ability of the silicon-protected β-oxygen, we have computed the formation energies for the *cis*-chelation precursors (**CP8** and **CP9**) derived from SiH_3- and $Si(CH_3)_3$-substituted malimides and compared them with those of the CH_3- and TBDMS-substituted *cis*-chelation precursors (**CP21**

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and **CP62**). As shown in shown in Figure 7, the predicted formation energies for the SiH_3- and $Si(CH_3)_3$-substituent *cis*-chelation precursors (**CP8** and **CP9**) are around 5 kcal/mol, which are ~3 kcal/mol higher/lower than that of the CH_3-/TBDMS-substituted one. These results suggest that both steric and electronic effects control jointly the coordination ability of the TBDMS-protected β-oxygen in malimide **8**.

4. Concluding Remarks

The addition reactions of Grignard reagents to malimides have been investigated at the hybrid density functional B3LYP/6-31G* level theory. The reaction mechanism, regio- and diastereoselectivity, and substituent effects on the selectivities have been examined computationally. The computational results can be summarized as follows:

(i) The addition takes place regioselectively at the α-carbonyl (C1) of simple malimide **7** and gives stereoselectively rise to the *cis*-addition product, owing to the preferential chelation of Grignard reagent to the α-carbonyl (C1) over the coordination to the α′-carbonyl (C4). The *trans* stereoselectivity of the addition reaction is different from the Cram chelation-type stereoselectivity of the addition reaction of Grignard reagent with aliphatic α- or β-alkoxy carbonyl compounds, due primarily to the rigidity of the five-membered ring skeleton of malimide that favors the formation of *cis*-α-chelated precursor.

(ii) The substituent effect arising from the bulky TBDMS group at the oxygen atom neighboring the α-carbonyl group leads to poor regioselectivity for the addition reaction. It is the large steric repulsion of the bulky TBDMS group and the electronic effects of the silyl group that destabilizes the α-chelated precursors and the followed transition states, which in turn results in poor regioselectivity.

(iii) The predicted regioselectivity and stereoselectivity for the model reactions are in line with the experimental observations for the reactions of Grignard reagent CH_3MgI (in Et_2O solvent) with malimides **4** and **6**.

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Supporting Information Available: The stereochemistry elucidation of the two diasereoisomers of C-1 addition products, which includes NMR and single-crystal X-ray results; the energies and coordinates of the model systems computed at the B3LYP/6-31G* level of theory. This material is available free of charge via the Internet at http://pubs.acs.org.

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