http://dx.doi.org/10.5012/bkcs.2013.34.8.2335

Relative Reactivity of Various *Al*-substituted-dialkylalans in Reduction of Carbonyl Compounds; A Theoretical Study on Substituent Effect

Keepyung Nahm* and Jin Soon Cha

*Department of Chemistry, Yeungnam University, Kyungbuk 712-749, Korea. *E-mail: kpnahm@yu.ac.kr*
Received April 25, 2013, Accepted May 13, 2013

Relative reactivity of various *Al*-substituted dialkylalans ($AlR_2(X)$) in reduction of acetone has been studied with density functional theory and MP2 method. Formation of the alan dimers and the alan-acetone adduct, and the transition state for the Meerwein-Ponndorf-Verley (MPV) type reduction of the adduct were calculated to figure out the energy profile. Formation of dimeric alans is highly exothermic. Both the relative free energies for acetone-alan adduct formation and the TS barriers for the MPV type reduction with respect to alan dimers and acetone were calculated and they show the same trend. Based on these energetic data, relative reactivity of alans is expected to be; $AlR_2(Cl)$ > $AlR_2(OTf)$ > $AlR_2(O_2CCF_3)$ > $AlR_2(F)$ > $AlR_2(OMs)$ > $AlR_2(OAc)$ > $AlR_2(OMe)$ > $AlR_2(NMe_2)$. The energy profile is relatively well correlated with the experimental order of the reactivity of *Al*-substituted dialkylalans. It is noted that the substituents of alans have initial effects on the relative free energies for the carbonyl-adduct formation. Therefore, an $AlR_2(X)$ which forms a more stable carbonyl-adduct is more reactive in carbonyl reduction.

Key Words : *Al*-substituted-dialkylalan, MPV reduction, Relative reactivity, DFT, TS barrier

Introduction

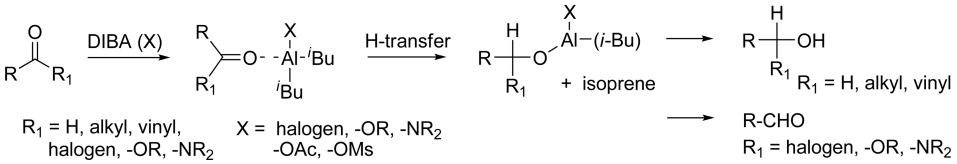
DIBALH (diisobutylaluminum hydride) is widely used in the reduction of many functional groups basically with highly active Al-H, such as, aldehydes, ketones, acids, esters, acid chlorides, epoxides to the corresponding alcohols and amides to amines, nitriles to imines, nitros to hydroxyamines, and disulfides to thiols, *etc*.[1,2] *Al*-substituted diisobutylalans (DIBAL(X)) are easily derived from DIBALH and HX.[3,4] Introduction of electronegative substituent X groups to DIBALH changes the reactivity and selectivity in the reduction. DIBALH has two hydride sources; the hydride attached to Al and another hydride at isobutyl group,[5-7] whereas DIBAL(X) has only the latter hydride and behaves as MPV (Meerwein-Ponndorf-Verley) type reagent.[8-11] Generally the reactivity of DIBAL(X) becomes lower and the selectivity increases.

With *iso*-butyl hydride, DIBAL(X) reduces mainly aldehydes, ketones and epoxides, but not carboxylic acid and it derivatives. We have intensively studied the carbonyl reduction by DIBAL(X) such as DIBAL(F), DIBAL(Cl), DIBAL(OR), DIBAL(OAc), DIBAL(OMs) and DIBAL(NR_2).[12-17] In comparison of the reactivity of various alans, DIBAL(X), it appears that the experimental order of reactivity is as follows; DIBAL(Cl) ≥ DIBAL(F) > DIBAL(OMs) > DIBAL(OR) ≥ DIBAL(NR_2) ≥ DIBAL(OAc).[3,4] (Table 1) Apparently, when the conjugate acid HX is more acidic, DIBAL(X) seems more reactive. For examples, DIBAL(Cl) is more reactive than DIBAL(F), and DIBAL(O_2CCF_3) is more reactive than DIBAL(OAc), *etc.* Acidity of HX would be a factor involved in the reactivity of DIBAL(X). However, when this assumption is applied to different types of acids, such as HCl ($pK_a = -7$), $HOS(O_2)CH_3$ ($pK_a = -1.9$), HF ($pK_a = 3.2$), HOAc ($pK_a = 4.8$), HOR ($pK_a = 15.5$) and HNR_2 ($pK_a = 35$),[18] the order of reactivity is not correlated with the acidity order.

Table 1. Various DIBAL(X) and their reactivities in reduction

DIBAL(X)	pK_a (HX)[b]	Ketones, Rxn time[a]		ref
		CH_3CH=CH-CHO	Chalcone	
DIBAL(F)	3.2	1.5[d] (3)[c]	24[e]	12
DIBAL(Cl)	−7.0	0.75[d] (1.5)[c]	72	3
DIBAL(OEt)	15.5	6	168	13
DIBAL(NEt_2)	35.0	12	240	14
DIBAL(OAc)	4.8	24 (72)[c]		15
DIBAL(O_2CCF_3)	0.23	3 (6)[c]		16
DIBAL(O_3SMe)	−1.9	6 (12)[c]	120	15
DIBAL(O_3SCF_3)	−15.0	1.5 (6)[c]	24	17

[a]For ~100% conversion, in hour, and reaction mixtures contained 2.0 eq alans in Et_2O and the products are the corresponding alcohols. [b]From ref 18. [c]1.1 eq reagents. [d]Estimated as a half of the reaction time at 1.1 eq of reagents. [e]10% conversion.



Scheme 1

There would be some other factors involved in the relative reactivity of DIBAL(X). Aluminum alkoxides ($Al(OR)_3$) are known to form aggregates and the carbonyl substrates have to be inserted to the aggregate to form complexes with Al in the reduction process.[19] In the same sense, DIBAL(X) may form dimers or higher aggregates with bridging X. And one can consider a role of electrophilic aluminum of DIBAL(X), which forms either dimers or adducts with carbonyl compounds.

To rationalize the reactivity of DIBAL(X), here we performed a computational study of the reduction of a carbonyl compound by various models of DIBAL(X) and tried to figure out the relative reactivity of various DIBAL(X) depending on the substituent X.

Calculation Methods

We selected a simple alan model of $Al(X)(CH_2CH_3)(CH_3)$, where two *iso*-butyls of DIBAL(X) were trimmed to an ethyl and a methyl group for saving calculation time. The substituent X is either a hydrogen (H) or a halide (F, Cl) or an alkoxy (OCH_3) or an amino $N(CH_3)_2$ or acetate or mesylate; Al(H)(Et)(Me) (**Alan(H)**), Al(F)(Et)(Me) (**Alan(F)**), Al(Cl)(Et)(Me) (**Alan(Cl)**), Al(OMe)(Et)(Me) (**Alan(OMe)**), and $Al(NMe_2)(Et)(Me)$ (**Alan(NMe$_2$)**), $Al(O_2CMe)(Et)(Me)$ (**Alan6(OAc)**) and $Al(OSO_2Me)(Et)(Me)$ (**Alan(OMs)**). Acetone was a model carbonyl compound. And the adducts of alans and acetone, **Add(X)**, were calculated. The transition states, **TS(X)**, for the hydride-transfer from the ethyl group were also located. **Alan(H)** has two hydride sources of Et-H and more reactive Al-H, but only the hydride of Et-H was considered as a hydride source, and Al-H was considered just as a substituent for comparison with other substituent X.

All calculations were performed with GAUSSIAN 09 package.[20] Most of the calculations were carried out by using the Becke3LYP hybrid functional and the 6-31+G(d) basis sets.[21-25] Frequency calculations have been carried out to determine all minima and transition states. Zero-point energies and thermal corrections were taken from frequency calculations and are not scaled.[21,24] Single-point energies were calculated at the M06-2X/6-31+G(d) level[26,27] with the geometries optimized at B3LYP/6-31+G(d) level. For M06-2X free energies, the B3LYP zero-point and thermochemical corrections were added to the M06-2X electronic energies.

And the MP2/6-31+G(d) levels of theory was applied to evaluate the appropriate calculation level.[28] The calculation data from MP2 functional show the same trend and are very similar to those from M06-2X//B3LYP. Therefore the calculation results from 6-31+G(d) using M06-2X//B3LYP functional were described mainly.

For the solvent effects, the self-consistent reaction field (SCRF) technique with Thomasi's polarized continuum model using the polarizable conductor calculation model [SCRF-(CPCM)][29] for diethyl ether ($\varepsilon = 4.24$) was used at M06-2X/6-31+G(d)//B3LYP/6-31+G(d) level. Free energies are quoted at 298.15 K and 1 atm.

Results and Discussion

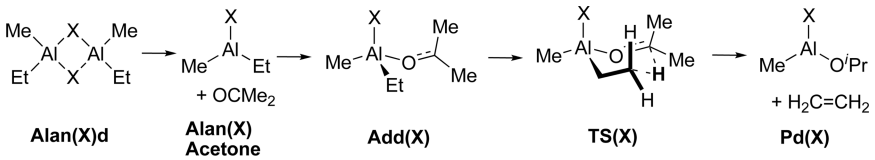
Since the alans are known to form stable dimers,[11,19] our model reaction describes the alan dimer formation first, then the ketone adduct formation. The ketone-alan adducts are assumed to be formed with monomeric alans which are dissociated from the alan dimers.

Formation of Dimeric Alans. We calculated dimers of model alans, (**Alan(H)d**, **Alan(F)d**, **Alan(Cl)d**, **Alan(OMe)d**, **Alan(NMe$_2$)d**, **Alan6(OAc)d** and **Alan(OMs)d**). Dimer formation is exothermic in all model alans. In comparison of the formation energies, their ΔG_f values (eq. (1), in kcal/mol) are the following order; **Alan(Cl)d** (−15.7) > **Alan(OAc)d** (−18.0) > **Alan(H)d** (−20.3) > **Alan(OMs)d** (−24.3) > **Alan(F)d** (−33.4) > **Alan(NMe$_2$)d** (−38.6) > **Alan(OMe)d** (−46.2). (Table 2).

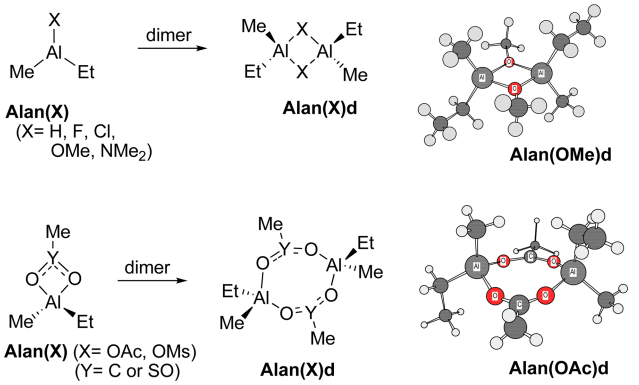
$$\Delta G_{f,dimer} = (\Delta G_{dimer}) - 2\,(\Delta G_{alan}) \quad (1)$$

The dimers have four-membered rings with the bridging halogens or oxygens or nitrogens, except **Alan6(OAc)d** and **Alan(OMs)d**). Alans with X = NMe_2, OMe and F are highly favored in dimerization. Dimeric **Alan(Cl)d**, **Alan(OAc)d** and **Alan(H)d** are moderately favored. For **Alan(OAc)** and **Alan(OMs)**, the monomer alans have internal four-membered rings with the bidentate substituents of acetate and mesylate. Their dimers would have either 4-membered or 8-membered rings, and the 8-membered dimers are calculated to be more stable than 4-membered dimers by 11.8 and 18.5 kcal/mol, respectively.[30]

One would expect that the more tightly bound dimers are less reactive in the reduction, since the dissociation of dimer is necessary in the acetone adduct formation. However the order of the free energy for dimer formation is not well correlated with the experimental order of reactivity in the reduction. **Alan(OAc)d** has a relatively lower formation energy and would have high reactivity, but in the experiment it is not so reactive. And **Alan(F)** has lower dimerization energy than **Alan(OAc)** and **Alan(OMs)**, but **Alan(F)** is more reactive in experiment. Therefore the formation energy of dimer cannot be considered to be main factor in deter-



Scheme 3



Scheme 3

mining the reactivity of *Al*-substituted dialkylalans.

Formation of the Acetone-Alan Adducts. In experiment, it has been assumed that a monomeric alan or a terminal alan in the dimeric or polymeric alans is active in the reduction.[11] In our model, the alan dimers will be dissociated to two alans, which will participated in the formation of acetone adducts. Therefore, the energy of a monomer alan is considered to be a half energy of an alan dimer (1/2 ΔG_{dimer} from Eq. (1)). The free energy for the adduct formation ($\Delta G_{f,Add}$) with a monomer alan is calculated as in Eq. (2). And TS barriers with respect to an alan and ketone (Eq. (3)) or the adduct (Eq. (4)) will be calculated as follows;

$$\Delta G_{f,Add} = (\Delta G_{adduct}) - (\Delta G_{ketone} + 1/2\ \Delta G_{dimer}) \quad (2)$$

$$\Delta G_{(TS/(Alan+keto))} = (\Delta G_{TS}) - (\Delta G_{ketone} + 1/2\ \Delta G_{dimer}) \quad (3)$$

$$\Delta G_{(TS/Add)} = (\Delta G_{TS}) - (\Delta G_{adduct}) \quad (4)$$

Acetone adduct models are Al(X)(Et)(Me)(O=CMe$_2$), **Add(X)**. All adducts have tetravalent aluminums. In **Add (OAc)** and **Alan(OMs)**, the substituents (acetate and mesylate) are bound mono-dentately to Al and also form the tetravalent adducts as in the other adducts.

The acetone adducts can be arranged in the order of increasing formation energy ($\Delta G_{f,Add}$, Eq. (2), in kcal/mol); **Add(Cl)** (–3.79) < **Add(H)** (0.75) < **Add(F)** (4.94) < **Add(OMs)** (6.49) < **Add(OAc)** (8.93) < **Add(OMe)** (13.7) < **Add(NMe$_2$)** (14.9) (Table 2).

Alan(OMe) and **Alan(NMe$_2$)** which form very tight dimers are least favored in the acetone adduct formation.[11,19] On the other hand, **Alan(Cl)** forms a relatively loose dimer and forms a favored acetone adduct. **Alan(F)d** has a high dimerization energy ($\Delta G_{f,dimer}$ = –33.4 kcal/mol), but its acetone adduct **Add(F)** is moderately favored ($\Delta G_{f,adduct}$ = 4.94 kcal/mol).

Hydride Transfer of the Acetone-Alan Adducts. The acetone-alan adduct undergoes MPV-type hydride transfer from an ethyl to a carbonyl carbon. The product *iso*-propyl-

Table 2. Relative free energies for the reduction of acetone by various Alans (in kcal/mol)

Alan(X)[a]	ΔG for formation		Energy barrier (TS(X))[b]		ΔG for Pd(X)
	Alan(X)d	Add(X)	*vs.* Add(X)	*vs.* (acetone + 1/2Alan(X)d)	*vs.* (ethane + Al(X)(Me)(OPr))
Alan(H)	–20.25 (–16.02)	0.75 (1.90)	22.42 (22.80)	23.17 [23.60] (24.70)	–3.99 (–7.10)
Alan(F)	–33.37 (–33.67)	4.94 (5.39)	22.60 (24.53)	27.54 [26.19] (29.92)	3.35 (0.65)
Alan(Cl)	–15.69 (–15.05)	–3.79 (–1.41)	22.56 (23.13)	18.77 [18.01] (21.72)	–4.93 (–5.29)
Alan(OMe)	–46.16 (–47.35)	13.72 (15.68)	22.78 (23.75)	36.50 [37.24] (39.43)	9.75 (9.83)
Alan(NMe$_2$)	–38.63 (–42.01)	14.86 (17.48)	24.57 (26.21)	39.43 [40.01] (43.69)	7.89 (7.91)
Alan(OAc)	–18.02 (–17.11)	8.93 (10.94)	23.57 (24.12)	32.50 [32.52] (35.06)	–2.62 (–6.49)
Alan(OMs)	–24.32 (–23.35)	6.49 (8.00)	24.50 (25.23)	30.99 [30.72] (33.23)	–0.91 (–1.22)
Alan(TFA)	–23.07	2.29	24.15	26.44	–0.76
Alan(OTf)	–23.70	0.00	25.34	25.33	–0.96

[a]numbers are calculated at M06-2X//B3LYP/6-31+G(d), and values in parenthesis are obtained at MP2/6-31+G(d). [b]values in bracket are calculated from CPCM-SCRF (diethyl ether) at M06-2X//B3LYP/6-31+G(d).

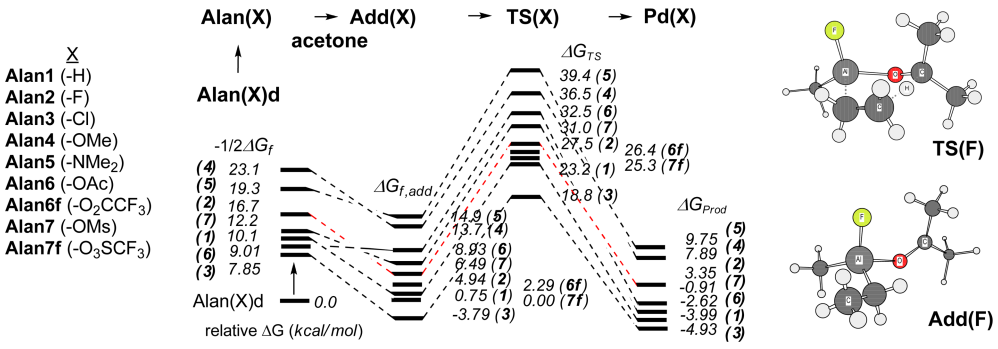


Figure 1. Energy profiles with respect to alan dimers and acetone for the reduction of acetone by various Alan(X).

oxide remains at Al but an ethylene will be liberated from the alan.

All TS(X)s for the MPV-type hydride transfer have half-chaired 6-membered rings including the hydride, and a substituent X is at axial position. For **Alan(H)**, the real TS will undergo Al-Hydride transfer, therefore **TS(H)** of MPV-type TS was not further discussed.

The TS barriers can be estimated with respect to either the reactants of alan and ketone or the adducts. When the TS barriers are calculated from the alan dimers and acetone (Eq. (3)), the TS barriers are in the range of 18.8-39.4 kcal/mol; **TS(Cl)** (18.8) < **TS(F)** (27.5) < **TS(OMs)** (31.0) < **TS(OAc)** (32.5) < **TS(OMe)** (36.5) < **TS(NMe$_2$)** (39.4). This order is in good match with that of the adduct formation energy. It predicts the relative reactivity of DIBAL(X) as follows; Alan(Cl) ≥ Alan(F) > Alan(OMs) > Alan(OAc) ≥ Alan(OMe) > Alan(NMe$_2$). And this order is quite well correlated with the experimental reactivity of DIBAL(X) except Alan(OAc); experimental order is; Alan(Cl) ≥ Alan(OMs) > Alan(F) > Alan(OMe) ≥ Alan(NMe$_2$) ≥ Alan(OAc).

On the other hand, when the TS barriers are calculated with respect to the adducts (Eq. (4)), the barriers are near the same in the range of 22.56-24.57 kcal/mol (Table 2). It is interesting that variation of the substituent X gives impact mainly in the formation of carbonyl adduct, but gives only a little influence in the TS energy. Therefore, the relative reactivity would be determined by the relative free energy for the adduct formation.

In correlation of the relative TS barriers with experimental reactivity in reduction, **Alan(OAc)** is not matched well and **Alan(OMs)** also shows a slight discrepancy. In our calculations, **Alan(OAc)** and **Alan(OMs)** have bidentate substituents and they form 8-membered ring dimers,[30] which is different from the other alans. To verify those substituents in details, further study has been done with fluorinated derivatives, Alan(O_2CCF_3) and Alan(OSO_2CF_3) (**Alan(TFA)** and **Alan(OTf)**). Experimentally the trifluoroacetate (TFA) alan and the trifluorinated mesylate (OTf) alan show higher reactivity in reduction than the acetate and mesylate alans.

Our calculation shows that the fluorinated dimers also have 8-membered ring structures and their dimerization energies are −23.07 and −23.70 kcal/mol for **Alan(TFA)d** and **Alan(OTf)d**, respectively. The calculated free energies for acetone-adduct formation (**Add(TFA)** and **Add(OTf)**) are 2.29 and 0.00 kcal/mol, which are lower by ~6.5 kcal/mol than those of nonfluorinated **Add(OAc)** and **Add(OMs)**. And the TS barriers with respect to reactants are 26.44 and 25.33 kcal/mol for **TS(TFA)** and **TS(OTf)**, respectively. Those TS barriers are lower than those from **TS(OAc)** and **TS(OMs)** by ~6 kcal/mol. The TS barriers calculated from the adducts, **Add(TFA)** and **Add(OTf)**, are 24.15 and 25.34 kcal/mol and these are similar to those from other adducts. With those all TS barriers included, the relative reactivity of Alan(X) in MPV-type reduction is expected to be in the following order; **Alan(Cl) Alan(OTf)** > **Alan(TFA)** > **Alan(F)** > **Alan(OMs)** > **Alan(OAc) Alan(OMe)** > **Alan(NMe$_2$)**. In Figure 2, the calculated TS barriers for reduction with various Alan(X)s are plotted in increasing orders, and the experimental reaction times of the corresponding DIBAL(X) from Table 1 are plotted. They show reasonable correlation between TS barriers and the reaction times, except Alan (OAc).

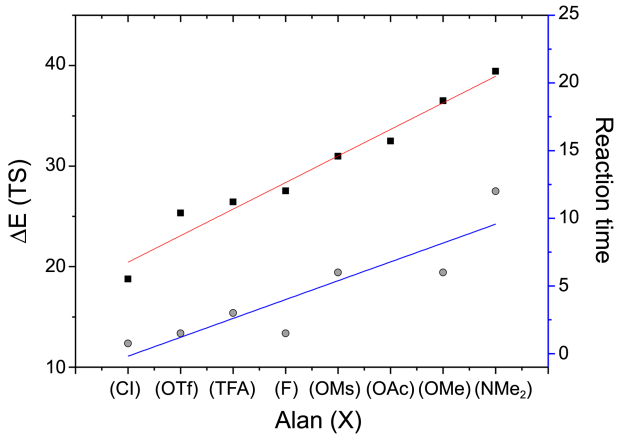


Figure 2. Plot of relative TS barriers (■; ΔE(TS) in kcal/mol) of Alan(X) from Table 2, and reaction times (●; in hr, ~100% conversion) of reduction of crotonaldehyde by DIBAL(X) from Table 1. (DIBAL(OAc) data was omitted. See the text.)

In summary, *Al*-substituted dialkylalans are expected to form stable dimers. And the relative reactivity of DIBAL(X) in MPV type reduction has been estimated from the TS barriers with respect to the alan dimers and a carbonyl compound; DIBAL(Cl) ≥ DIBAL(OTf) > DIBAL(O_2CCF_3) > DIBAL(F) > DIBAL(OMs) > DIBAL(OAc) ≥ DIBAL (OMe) > DIBAL(NMe$_2$), which is well correlated with the experimental order of the reactivity of DIBAL(X) except DIBAL(OAc). It is noted that the transition state barriers with respect to the carbonyl-adducts are near the same regardless of the substituent X in alans. Therefore, a substituent in DIBAL(X) gives impact to the formation energy of a carbonyl-adduct, but less influence to the TS energy. DIBAL(X) which forms a more stable carbonyl-adduct will have higher reactivity in MPV type reduction.

Acknowledgments. This research was supported by the Yeungnam University research grants.

Supporting Information. Cartesian coordinates for the calculated structures and ZPE-corrected free energies of Alan(X), Alan(X)-dimers and TS(X) from DFT calculations are available via the Internet at http://journal.kcsnet.or.kr.

References

1. Winterfeldt, E. *Synthesis* **1975**, 617.
2. Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry*: Part B, 5th ed.; Plenum: 2007; p 396
3. Cha, J. S. *Org. Process Res. Dev.* **2006**, *10*, 1032.
4. Cha, J. S.; Kwon, O. O.; Kwon, S. Y. *Bull. Korean Chem. Soc.* **2007**, *28*, 2162.
5. Miller, A. E. G.; Bliss, J. W.; Schwatzman, L. H. *J. Org. Chem.* **1959**, *24*, 627.

6. Ziegler, K.; Schneider, K.; Schneider, J. *Justus Liebig's Ann. Chem.* **1959**, *623*, 9.
7. Ziegler, K.; Martin, H.; Krupp, F. *Justus Liebig's Ann. Chem.* **1960**, *629*, 14.
8. Meerwein, H.; Schmidt, R. *Liebigs Ann. Chem*. **1925**, *444*, 221.
9. Ponndorf, W. Z. *Angew. Chem*. **1926**, *39*, 138.
10. Verley, M. *Bull. Soc. Chim. Fr.* **1925**, *37*, 871-874.
11. Nguyen, S. T. *Tetrahedron: Asymmetry* **2005**, *16*, 3460.
12. Cha, J. S.; Kwon, O. O.; Kwon, S. Y. *Bull. Korean Chem. Soc.* **1995**, *16*, 1009.
13. Cha, J. S.; Kwon, O. O.; Kwon, S. Y. *Org. Prep. Proced. Int.* **1996**, *28*, 355.
14. Cha, J. S.; Kwon, S. Y.; Kwon, O. O.; Kim, J. M.; Song, H. *Bull. Korean Chem. Soc.* **1996**, *17*, 900.
15. Cha, J. S.; Yi, J. E. *J. Incl. Phenom. Macrocycl. Chem.* **2009**, *65*, 15.
16. Cha, J. S.; Noh, M. *Bull. Korean Chem. Soc*. **2010**, *31*, 840.
17. Cha, J. S. *Bull. Korean Chem. Soc.* **2011**, *32*, 219.
18. Smith, M. B.; March, J. In *March's Advanced Org. Chem.*, 6th ed.; Wiley: 2007; p 359.
19. Kow, R.; Nygren, R.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 826.
20. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A. *et al. Gaussian 09*, Revision C.01; Gaussian, Inc.: Wallingford, CT, 2010.
21. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
22. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372-1377.
23. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652.
24. Bauschlicher, C. W., Jr.; Partridge, H. *J. Chem. Phys.* **1995**, *103*, 1788.
25. Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.
26. Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc*. **2008**, *120*, 215.
27. Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res*. **2008**, *41*, 157.
28. Head-Gordon, M.; Head-Gordon, T. *Chem. Phys. Lett.* **1994**, *220*, 122.
29. Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995-2001.
30. Florjanczyk, Z.; Bury, W.; Zygadzo-Monikowska, E.; Justyniak, I.; Balawender, R.; Lewinski, J. *Inorg. Chem*. **2009**, *48*, 10892.