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Mechanistic Aspects of the Ligand-Assisted Nucleophilic Addition Reaction

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We demonstrated that the reactions of quinol alkoxides with Grignard reagents yielded 1,4 addition products with complete diastereofacial control (we call this process ligand-assisted nucleophilic addition, LANA).[1] In this paper we report on mechanistic aspects of this reaction.

In a typical LANA reaction (Figure 1) the lithium quinol alkoxide **1** is first prepared in situ, followed by the sequential addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone, DMPU, and a Grignard reagent. The desired syn 1,4 addition adduct **2**, derived from intramolecular delivery of the carbon nucleophile by the hydroxyl oxygen, as well as a cis 1,4-diol **3**, from facially selective intermolecular addition, is produced in varying amounts depending upon conditions. We report herein the results of a systematic study that indicates that the reactive intermediate is not the expected complex of a quinol alkoxide and a Grignard reagent. It is instead a ternary complex composed of a quinol alkoxide, a dialkylmagnesium, and a Lewis acid.

To investigate the importance of the initial transmetalation step on the overall process, we examined the reaction of methylmagnesium chloride (MeMgCl, 3 M; Aldrich) with **1** under conditions that affect aggregation. The baseline 1,4-selectivity was taken to be the reaction of **1** in THF (see Table I). Addition of either 6 equiv of DMPU (entry 2) or 10 equiv *N,N,N′,N′*-tetramethylethylenediamine (TMEDA; entry 3) resulted in a significant increase in selectivity. High selectivity was observed with the crown ether complexing reagent, 15-crown-5 (entry 4); 12-crown-4 (entry 5), a selective lithium chelator, produced only a modest effect. While use of sodium cation gave selectivity similar to our base-line study, use of potassium cation produced the highest selectivity (entries 6 and 7).[2] The use of the tricoordinate chelator solvent, diglyme, resulted only a modest increase in selectivity (entry 8).[3] Thus, although conditions that are known to affect aggregation also affect the outcome of the process, our data suggest no direct cause and effect relationship between them.

Variation of the halide of the Grignard reagent also alters the observed selectivity (see Table II). The highest selectivity resulted from MeMgCl, while the lowest was dimethylmagnesium (Me_2Mg). This trend seems to be independent of the alkyl substituent used.[5] In principle, while many factors might be responsible for this halide dependence (e.g., inherent reactivity differences, aggregation states, etc.), we hypothesize that the origins of the selectivity described above hinge primarily on how the various reaction constituents affect the position of the Schlenk equilibrium (Figure 2). Experiments described below provide the basis for this hypothesis.

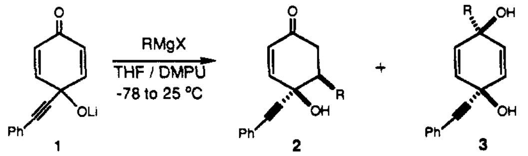

Figure 1. Prototypical LANA reaction.

$$2\,RMgX \rightleftharpoons R_2Mg + MgCl_2$$

Figure 2. Schlenk equilibrium.

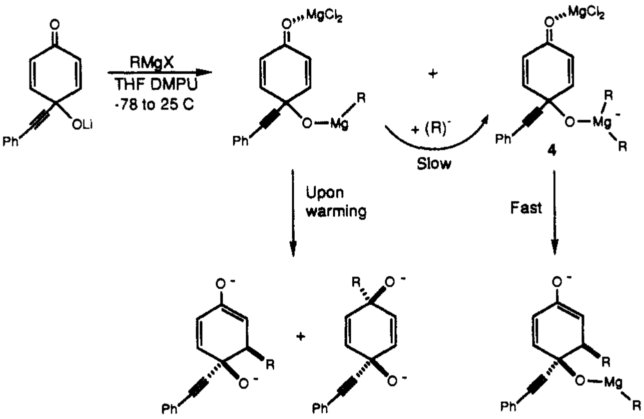

Figure 3. Complex mechanism of LANA.

Table I. Reaction of MeMgCl with **1**: Effect of Counterions[4]

entry	cation	solvent	additive, equiv	selectivity[a]
1	Li	THF		5.4
2	Li	THF	DMPU, 6	13.0
3	Li	THF	TMEDA, 10	10.0
4	Li	THF	15-Cr-5, 1.2	17.0
5	Li	THF	12-Cr-4, 1.2	8.3
6	Na	THF		5.2
7	K	THF		30.0
8	Li	Diglyme		7.0

[a] Selectivity, (1,4-addition)/(1,2-addition).

Table II. Differing Halides and Selectivity[4]

Mg reagent	Mg reagent solvent	selectivity[a]
MeMgMe	ether	5.0
MeMgBr	ether or THF	7.7
MeMgCl	ether or THF	13.0

[a] Selectivity, (1,4-addition)/(1,2-addition).

We followed the progress of the reaction between **1** with MeMgCl at −78 °C over several hours (via HPLC). The reaction proceeded to 40–50% completion with extremely high selectivity (95:1) in 5 min and then completely stopped (no further reaction was observed over a period of 24 h). When the solution was warmed (approximately −25 °C), further reaction occurred, but at a much slower rate and with much lower 1,4-selectivity (5.5:1).

We conclude that *although all of the organomagnesium reagents present in solution may form complexes with the free alkoxide oxygen, only the dialkyl magnesium is reactive enough to transfer an alkyl substituent at −78 °C (Figure 3). Stoichiometric considerations therefore preclude transfer of more than half of the R groups at this temperature. When the solution warms to −25 °C, the remainder of the R groups transfer, but via a different reactive intermediate.*[6]

By manipulation of the Schlenk equilibrium, confirmation of this conclusion can be obtained. As mentioned earlier, reaction of **1** with MeMgCl gave a 14–12:1 selectivity ratio. Pure Me_2Mg, although much more reactive, exhibited only modest selectivity (6–4:1). When we employ a solution of Me_2Mg containing 10%

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[1] Solomon, M.; Jamison, W. C. L.; McCormick, M.; Liotta, D.; Cherry, D. A.; Mills, J. E.; Shah, R. D.; Rodgers, J. D.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 3702. For *o*-quinol acetates and organomagnesium species, see: Miller, B.; Matjeka, E. R.; Haggerty, J. G. *J. Org. Chem.* **1984**, *49*, 3121.

[2] Sodium or potassium metal counterions are of little synthetic utility since retro-acetylide addition processes effectively compete with the desired LANA process.

[3] LANA processes proceed extremely sluggishly in ether. In our hands, dimethoxyethane and THF result in similar selectivities.

[4] See supplementary material.

[5] We have extensively surveyed the effects of alkyl substituents, halides, solvents, and additives on these LANA processes. We will report our findings on this subject in the near future.

[6] Ashby, E. C.; Laemmle, J.; Neumann, H. M. *J. Am. Chem. Soc.* **1972**, *94*, 5421.

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$MgCl_2$, both a high reaction rate and high selectivity (30:1) are observed. Presumably, **1** and Me_2Mg combine to form the "ate" complex **4**, which is further activated by catalytic amounts of a Lewis acid ($MgCl_2$). However, as more $MgCl_2$ is added, the Schlenk equilibrium shifts to that of "normal" Grignard solution and produces the "normal" selectivity.

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Supplementary Material Available: Experimental details for Tables I and II (1 page). Ordering information is available on any current masthead page.

(Z)-1,2-Bis(2,6-diisopropylphenyl)-1,2-dimesityldigermene: Synthesis, Crystal Structure, and π-Bond Energy

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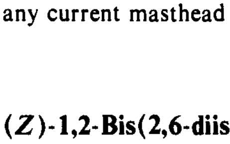
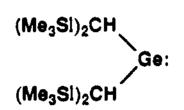
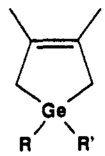
Renewed interest in the digermene (Ge=Ge) system concerns its ground-state geometry and so-called π-bond energy normally equated to the rotational barrier.[1] Since the disclosure of the molecular structure of tetrakis(2,6-diethylphenyl)digermene (**1**),[2] *which retains its structural integrity in solution*, our major efforts have been directed to the investigation of its chemical reactivity[3] and also to the synthesis of a *Z* or *E* stereoisomer of type RR′Ge=GeRR′ (R ≠ R′) which can provide a means of estimating the activation energy required for isomerization. This latter task turns out to be much more involved[4] than expected from the earlier work on similar disilenes,[5] as the judicious selection of R and R′ is now found to be highly crucial. We report herein that (1) our final selection is R = 2,6-diisopropylphenyl and R′ = mesityl, (2) the synthesized and isolated crystalline digermene **2** is the *Z* isomer (*Z*)-**2** rather than the *E* isomer, (3) (*Z*)-**2** is more stable than (*E*)-**2**, and (4) the conformation of (*Z*)-**2** shows a considerable deviation from that of **1**. Findings 3 and 4 are totally unexpected. Furthermore, digermene (*Z*)-**2** provides, for the first time, a set of kinetic parameters for the *Z* ⇄ *E* isomerization of a digermene derivative.



1: M = Ge, R = R′ = 2,6-diethylphenyl
2: M = Ge, R = 2,6-diisopropylphenyl, R′ = Mes (2,4,6-trimethylphenyl)
3: M = Ge, R = R′ = $CH(SiMe_3)_2$
4: M = Ge, R = R′ = H
7: M = Si, R = 2,6-diisopropylphenyl, R′ = Mes
8: M = Si, R = 2,6-diethylphenyl, R′ = Mes



3a



6 : R = 2,6-diisopropylphenyl, R′ = Mes

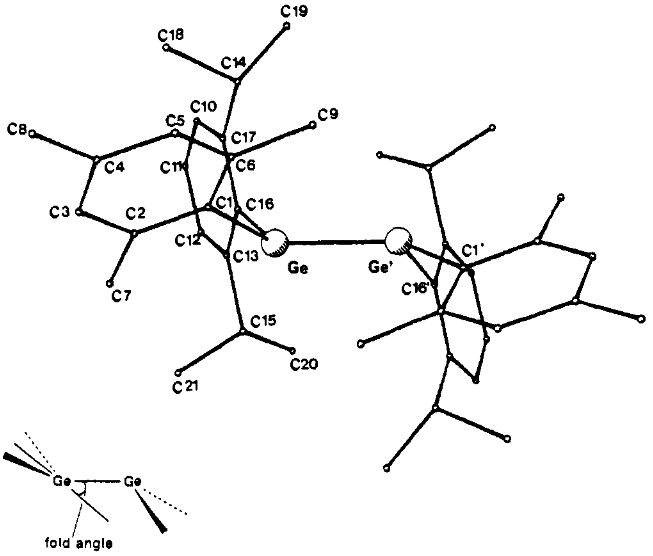


Figure 1. Crystal structure of (*Z*)-**2**. Selected bond lengths (Å) and angles (deg): Ge–Ge, 2.301 (1); Ge–C1, 1.972 (5); Ge–C16, 1.988 (5); Ge–Ge–C1, 124.0 (2); Ge–Ge–C16, 111.6 (2); C1–Ge–C16, 109.9 (2).

Table I. Selected Structural Parameters of Digermenes

compd	*d*(Ge=Ge), Å	fold angle, deg	twist angle, deg	sum of angles around Ge, deg
(*Z*)-**2**	2.301 (1)	36	7	345.5
1	2.213 (2)	12[a]	10[a]	358.4
3	2.347 (2)	32	0	348.5
4	2.27–2.33	34–40	0	

[a] These values are slightly different from the χ_{Ge} and τ used in ref 2.[6]

Synthesis of 2. Exposure of dichloro(2,6-diisopropylphenyl)mesitylgermane to 2 equiv of lithium naphthalenide[3c] led to the formation of two air- and moisture-sensitive digermenes A and B as the major products, as indicated by two sets of ^1H NMR signals assignable to them.[6] A series of fractional recrystallizations of the reaction mixture from THF afforded A as yellow crystals: mass spectrum (EI), *m*/*z* 700–711 (M^+ cluster); UV (methylcyclohexane, room temperature) λ_{max} (log ε) 280 (4.1), 412 nm (4.6). The structure of A was determined as (*Z*)-**2** by X-ray analysis (see below). When (*Z*)-**2** was dissolved in a hydrocarbon or ether solvent, it regenerated B to attain a 2:1 equilibrium mixture favoring (*Z*)-**2**![7] Upon concentration of this mixture, nearly all of (*Z*)-**2** and B crystallized out as pure (*Z*)-**2**. These results show that B is the *E* isomer of (*Z*)-**2**. It should be added that (1) all spectra of (*Z*)-**2** and (*E*)-**2** are consistent with the double-bond formulation[2] and (2) the existence of the corresponding germylene species in solution is excluded to the limit of spectral detection.

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(6) See supplementary material paragraph at the end of this paper.

(7) The more stable isomers of all known disilenes of type RR′Si=SiRR′ have an *E* configuration (ref 5).

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