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Unusual Reagent Control of Diastereoselectivity in the 1,2-Addition of Hard Carbon Nucleophiles to C_6-Heteroatom Substituted Cyclohexenones

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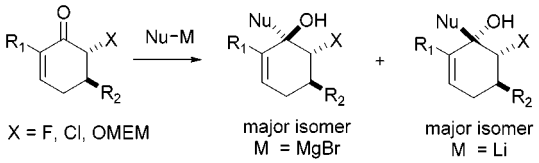
ABSTRACT



A surprising and synthetically useful counterion-dependent reversal of diastereoselectivity was found in 1,2-additions of hard carbon nucleophiles to C_6-heterosubstituted cyclohexenones. In general, Grignard reagents added *syn* to the C_6-substituent and Li reagents added *anti*, although some exceptions were found. Selectivities could be increased in some cases by appropriate choice of solvent and/or cosolvent.

The addition of carbon nucleophiles to aldehydes and ketones is one of the fundamental reactions in organic synthesis.[1] Such additions to cyclohexenones afford tertiary allylic cyclohexenols, which are common functional groups in natural products (Figure 1)[2] as well as useful intermediates in a variety of reactions.[3]

In 1,2-additions to cyclohexanones and cyclohexenones, the intrinsic stereoelectronic preference for axial addition of small nucleophiles and the propensity of larger nucleophiles to give higher proportions of equatorial addition products have been demonstrated both experimentally[4−9] and computationally.[5] However, it is clear from results in our laboratories that these simple guidelines do not generally predict the stereochemical outcome in additions to C_6-heteroatom substituted cyclohexenones.[10,11]

In the context of ongoing studies in our laboratories, we required stereoselective syntheses of a series of vinyl and

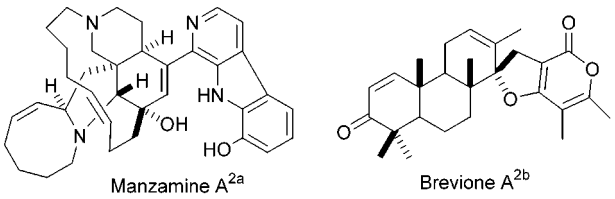


Figure 1. Natural products containing tertiary allylic alcohols or derivatives thereof.

[†] Author to whom correspondence regarding X-ray crystallographic analyses should be addressed.

(1) (a) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521−546. (b) Eliel, E. L. in *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, pp 125−155. (c) Holm, T.; Crossland, I. in *Grignard Reagents: New Developments*; Richey, H. G., Ed.; Wiley: New York, 2000, pp 1−26. (d) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: San Diego, 1995. (e) Eicher, T. In *The Chemistry of the Carbonyl Group*; Patai, S., Ed.; Interscience: New York, 1991; Vol. 1, pp 621−693. (f) Huryn, D. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 1, pp 49−75 and references therein.

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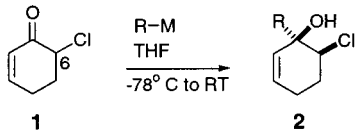
Table 1. 1,2 Additions to 6-chlorocyclohexenone



1 2

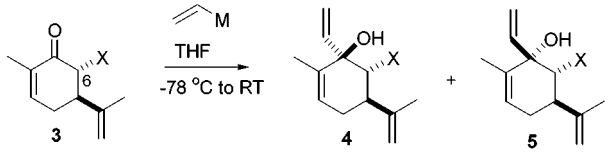
entry	R	M	product (yield)
1	≡–	MgBr	**2a** (56)
2	TMS–≡–	Li	**2a** (43)[a]
3		MgBr	**2b** (47)[b]
4		Li	**2b** (51)

[a] Yield after desilylation. [b] 10% 1,4-addition products also isolated.

alkynyl cyclohexenols such as **2a**,**b** (Table 1). Additions of vinyl and ethynyl nucleophiles to 6-chlorocyclohexenone (**1**)[3b,12] gave the expected *anti* alcohols **2a**,**b** with greater than 25:1 diastereoselectivity with either alkynyl- or vinyl-Li or -MgBr. The reactions presumably proceeded via a Felkin–Anh transition state[13] with addition occurring *anti* to the axial C_6-chloro substituent (vide infra).[14]

By contrast, vinylmetal additions to *trans*-6-chlorocarvone **3a**[12] demonstrated an unusual counterion-dependent reversal of diastereoselectivity (Table 2, entries 1 and 2). VinylMgBr produced predominately equatorial alcohol **4a** via addition *syn* to the C_6-chloride. VinylLi addition produced axial alcohol **5a** as the major product via *anti* addition. The relative stereochemistry of alcohols **4a** and **5a** was determined by ^{13}C NMR analysis of the two diastereomers.[15] A few scattered examples of counterion-dependent reversal of selectivity have appeared in the literature,[16] although to our knowledge no systematic investigation of this phenomenon has been conducted.

Table 2. Vinyl Additions to *trans*-6-Halocarvone



3 4 5

entry	compd	X	M	**4**:**5**	yield[a]
1	**a**	Cl	MgBr	4:1	65
2	**a**	Cl	Li	1:5	70
3	**b**	F	MgBr	2:1	36
4	**b**	F	Li	1:3	56

[a] Isolated yield of major isomer.

In an effort to probe steric versus electronic effects of the C_6-heteroatom on diastereoselection, vinylmetal additions to *trans*-6-fluorocarvone **3b**[17] were examined (Table 2, entries 3 and 4).[18] In the case of vinylmetal additions to fluorocarvone **3b**, we again observed a reversal of diastereoselec-

(2) For examples of natural products containing tertiary allylic alcohols, see: (a) Sakai, R.; Higa, T. *J. Am. Chem. Soc.* **1986**, *108*, 6404–6405. (b) Macias, F. A.; Varela, R. M.; Simonet, A. M.; Cutler, H. G.; Cutler, S. J.; Dugan, F. M.; Hill, R. A. *J. Org. Chem.* **2000**, *65*, 9039–9046. (c) Fraga, B. M.; Terrero, D.; Gutierrez, C.; Gonzalez-Coloma, A. *Phytochemistry* **2001**, *56*, 315–320. (d) Collins, D. O.; Gallimore, W. A.; Reynolds, W. F.; Williams, L. A. D.; Reese, P. B. *J. Nat. Prod.* **2000**, *63*, 1515–1518. (e) Ahmed. A. A. *J. Nat. Prod.* **2000**, *63*, 989–991. (f) Cinel, B.; Roberge, M.; Behrisch, H.; van Ofwegen, L.; Castro, C. B.; Andersen, R. J. *Org. Lett.* **2000**, *2*, 257–260.

(3) See, for example: (a) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4186–4187. (b) Paquette, L. A.; Ross, R. J.; Shi, Y.-J. *J. Org. Chem.* **1990**, *55*, 1589–1598. (c) Zhang, X.; McIntosh, M. C. *Tetrahedron Lett.* **1998**, *39*, 7043–7046. (d) Trost, B. M.; Haffner, C. D.; Jebaratnam, D. J.; Krische, M. J.; Thomas, A. P. *J. Am. Chem. Soc.* **1999**, *121*, 6183–6192.

(4) (a) Trost, B. M.; Florez, J.; Jebaratnam, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 613–615. (b) Trost, B. M.; Florez, J.; Haller, K. J. *J. Org. Chem.* **1988**, *53*, 2394–2396.

(5) (a) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908–910. (b) Wu, Y.-D.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.* **1987**, *109*, 5560–5561. (c) Wu, Y.-D.; Houk, K. N.; Florez, J.; Trost, B. M. *J. Org. Chem.* **1991**, *56*, 3656–3664. (d) Ando, K.; Houk, K. N.; Busch, J.; Menasse, A.; Sequin, U. *J. Org. Chem.* **1998**, *63*, 1761–1766.

(6) (a) Stork, G.; Stryker, J. M. *Tetrahedron Lett.* **1983**, *24*, 4887–4890. (b) Stork, G.; West, F.; Lee, H. Y.; Isaacs, R. C. A.; Manabe, S. *J. Am. Chem. Soc.* **1996**, *118*, 10660–10661.

(7) Buckwalter, B. L.; Burfitt, I. R.; Felkin, H.; Joly-Goudket, M.; Naemura, K.; Salomon, M. F.; Wenkert, E.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1978**, *100*, 6445–6450.

(8) (a) Tanis, S. P.; McMills, M. C.; Herrinton, P. M. *J. Org. Chem.* **1985**, *50*, 5887–5889. (b) Harnett, J. J.; Alcaraz, L.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D.-S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 2009–2012.

(9) Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Rigby, J. H.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 3080–3087.

(10) For examples of 1,2-additions to epoxyquinones and epoxyquinone monoketals, see: Wipf, P.; Coish, P. D. G. *J. Org. Chem.* **1999**, *64*, 5053–5061. Alcaraz, L.; Macdonald, G.; Ragot, J.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron* **1999**, *55*, 3707–3716 and references therein.

(11) A recent issue of *Chemical Reviews* was devoted to diastereoselection: (a) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1224. (b) Dannenberg, J. J. *Chem. Rev.* **1999**, *99*, 1225–1242. (c) Tomoda, S. *Chem. Rev.* **1999**, *99*, 1243–1264. (d) Cieplak, A. S. *Chem. Rev.* **1999**, *99*, 1265–1336. (e) Ohwada, T. *Chem. Rev.* **1999**, *99*, 1337–1376. (f) Gung, B. W. *Chem. Rev.* **1999**, *99*, 1377–1386. (g) Kaselj, M.; Chung, W.-S.; le Noble, W. J. *Chem. Rev.* **1999**, *99*, 1387–1414. (h) Adcock, W.; Trout, N. A. *Chem. Rev.* **1999**, *99*, 1415–1436. (i) Mehta, G.; Chandrasekhar, J. *Chem. Rev.* **1999**, *99*, 1437–1468. (j) Wipf, P.; Jung, J.-K. *Chem. Rev.* **1999**, *99*, 1469–1480.

(12) (a) Wender, P. A.; Holt, D. A. *J. Am. Chem. Soc.* **1985**, *107*, 7771–7772. (b) Brummond, K. M.; Gesenberg, K. D. *Tetrahedron Lett.* **1999**, *40*, 2231–2234.

(13) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199–2204. (b) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205–2208. (c) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145–161.

(14) Although we were unable to rigorously determine the relative stereochemistries of alcohols **2a** and **2b**, the assignments are based on ample precedent: (a) Hussey, A. S.; Herr, R. R. *J. Org. Chem.* **1959**, *24*, 843–845. (b) Gilchrist, T. L.; Stanford, J. E. *J. Chem. Soc., Perkin Trans. 1* **1987**, 225–230. See also refs 3b and 22.

(15) The ^{13}C NMR shifts for the tertiary carbinol carbon and the terminal carbon of the vinyl substituent of equatorial alcohols **4a**,**b** were downfield relative to those of axial alcohols **5a**,**b**, whereas the shift of the internal carbon of the vinyl substituent of **4a**,**b** was upfield relative to that of **5a**,**b**. See Supporting Information for shift assignments and refs 4a and 7 for relevant examples.

(16) (a) Miyashita, K.; Tanaka, A.; Shintaku, H.; Iwata, C. *Tetrahedron* **1998**, *54*, 1395–1406. (b) Ireland, R. E.; Courtney, L.; Fitzsimmons, B. J. *J. Org. Chem.* **1983**, *48*, 5189–5198. (c) See also Tagamose, T. M.; Bols, M. *Chem. Eur. J.* **1997**, *3*, 456–462. Nicotra, F.; Panza, L.; Ronchetti, F.; Russo, G. *Gazz. Chim. Ital.* **1989**, *119*, 577–579. (d) There was apparently no reversal of diastereoselectivity in 1,2-additions of vinylMgBr and vinylLi to 2-chlorocyclohexanone: Holt, D. A. *Tetrahedron Lett.* **1981**, *22*, 2243–2246.

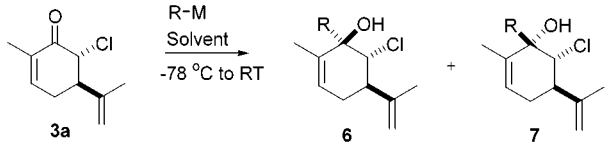
(17) *trans*-6-Fluorocarvone **3b** was prepared by fluorination of the Li enolate of (*S*)-(+)-carvone using the procedure of Davis: Davis, F. A.; Han, W. *Tetrahedron Lett.* **1992**, *33*, 1153–1156.

tivity,[15] although the magnitude decreased slightly in both additions.

The diastereoselectivity of additions of several other hard carbon nucleophiles to *trans*-6-chlorocarvone **3a** was investigated (Table 3). Counterion-dependent reversal of selectivity was evident for all sets of nucleophiles, with Grignard reagents giving good to excellent *syn* selectivity (entries 1, 3, and 5) and alkynyl, alkyl, and aryllithium reagents all exhibiting good *anti* selectivity (entries 2, 4, and 6).[15]

However, when *cis*-6-chlorocarvone **8**,[21] was treated with either vinylMgBr or vinylLi, *anti* diastereomer **9** was produced as the sole detectable product by ^{1}H NMR analysis (Scheme 1).[22]

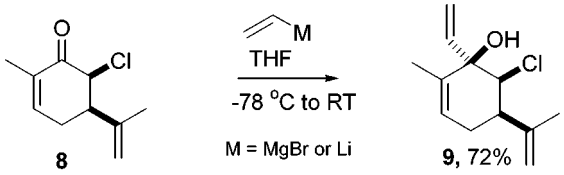
Table 3. Diastereoselectivity in Additions to *trans*-6-Chlorocarvone



entry[a]	R	M	solvent	compd	**6**:**7**[b]	yield[c]
1	HCC	MgBr	THF	**a**	5:1	78
2	TBSCC	Li	ether	**a**	1:6	71[d]
3	^{n}Bu	MgBr	ether	**b**	25:1	59
4	^{n}Bu	Li	THF	**b**	1:6[19]	58[e]
5	Ph	MgBr	ether	**c**	12:1	52
6	Ph	Li	ether	**c**	1:7[20]	51

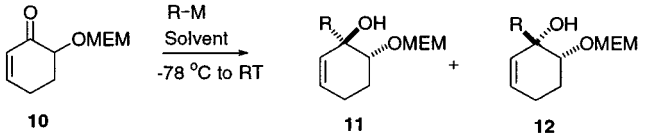
[a] All additions except entry 2 were performed on substrates derived from the (*R*)-enantiomer of carvone. [b] Ratio determined by ^{1}H NMR integration of C_6-protons. [c] Isolated yield of major isomer. [d] Yield after desilylation. [e] Inseparable mixture of diastereomers.

Scheme 1. Vinyl Additions to *cis*-6-Chlorocarvone



To determine whether these findings were generalizable to other C_6-substituted cyclohexenones, we examined additions to methoxyethoxymethyl (MEM) protected 6-hydroxycyclohexenone **10**.[23] A reversal of diastereoselectivity was again observed as a function of the counterion (entries 1 and 3, Table 4).[24] Some notable solvent effects were observed in the additions. When DMPU was used in the Grignard additions (entries 2 and 7), selectivity increased from 2:1 to 3:1 for ethynylMgBr and from 2:1 to 4:1 for vinylMgBr. In the Li acetylide additions, changing the solvent from THF to ether improved selectivity from 1:3 to 1:7 (entries 3 and 4). Adding NEt_3 as a cosolvent further improved the selectivity to 1:13 (entry 5).[25] No such solvent-related improvements were found for the addition of vinyllithium,

Table 4. Solvent Effects in Alkyl MgBr and Alkyl Li Additions to 6-OMEM-cyclohexenone



entry	R	M	solvent/ co-solvent	cmpd	**11**:**12**[24]	yield[a]
1	≡-~	MgBr	THF	**a**	2:1	63
2	≡-~	MgBr	THF/ DMPU (10 eq)	**a**	3:1	48
3	TMS-≡-~	Li	THF	**b**	1:2	70
4	TMS-≡-~	Li	ether	**b**	1:7	69
5	TMS-≡-~	Li	ether/ TEA (2:1)	**b**	1:13	67
6	~	MgBr	THF	**c**	2:1	31
7	~	MgBr	THF/ DMPU (10 eq)	**c**	4:1	48
8	~	Li	THF	**c**	1:2	69

[a] Isolated yield of major isomer.

(18) It has been reported that the proportion of equatorial reduction of *cis*-2-fluoro-4-*tert*-butyl-cyclohexanone increased slightly relative to the 2-chloro analog: Rosenberg, R. E.; Abel, R. L.; Drake, M. D.; Fox, D. J.; Ignatz, A. K.; Kwiat, D. M.; Schaal, K. M.; Virkler, P. R. *J. Org. Chem.* **2001**, *66*, 1694−1700.

(19) ^{n}BuLi addition to **3a** was performed at room temperature, and the reaction mixture was quenched with HOAc after 5 min. In the absence of an HOAc quench, selective decomposition of the minor product **6b** occurred upon prolonged (ca. 90 min) stirring of the reaction mixture at room temperature. Presumably the minor isomer **6b**, in which the alkoxide is *trans* to the chloride, decomposed via formation of the corresponding epoxide. In this case, an apparent selectivity of >1:20 was observed. See Supporting Information for details.

(20) X-ray crystallographic analysis of alcohol **7c** confirmed stereochemical assignments. See Supporting Information for details.

(21) Kinetic epimerization of *trans*-6-chlorocarvone **3a** was achieved by adding **3a** to a solution of LDA at −78 °C followed by addition of a THF solution of camphor sulfonic acid. A 3:1 ratio of **8**:**3a** was obtained with *cis*-6-chlorocarvone **8** isolated in 64% yield.

(22) X-ray crystallographic analysis of an (*S*)-*O*-benzyl lactate ester derived from **9** confirmed stereochemical assignments. See Supporting Information for details.

(23) MEM-protected 6-hydroxycyclohexenone **11** was available from Rubottom oxidation and protection of 2-cyclohexen-1-one. (a) Oxidation: Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599−1602. (b) Protection: Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809−812.

(24) Relative stereochemistries for alcohols **11** and **12** were assigned by correlation to the free diol derived from propargyl alcohol **11a**. The structure of the diol was unambiguously determined by X-ray crystallography (see Supporting Information for full details).

(25) Carreira, E. M.; Du Bois, J. *Tetrahedon Lett.* **1995**, *36*, 1209−1212.

with the highest selectivity being only 1:2 in THF (entry 8).[26]

Several models for carbonyl addition have been proposed to rationalize diastereoselectivity in the addition of nucleophiles to cyclohexanones and cyclohexenones. These include Cram chelation,[1a,27,28] Felkin−Anh,[13] electrostatic repulsion,[18] and delivery[28,29] models. In the examples reported herein, four reaction pathways are in principle possible: axial or equatorial addition to either half-chair conformation of the cyclohexenone substrate (**i** or **ii**, Figure 2). In the case of

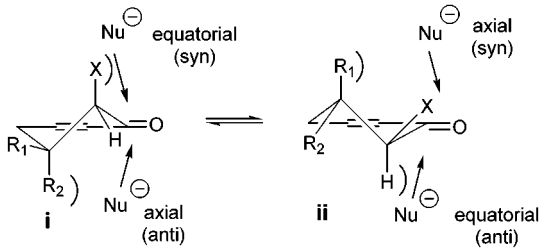


Figure 2. Four possible reaction pathways for additions to C_6-substituted cyclohexenones.

6-chlorocyclohexenone and *cis*-6-chlorocarvone, (cf. Table 1 and Scheme 1), excellent diastereoselectivity was observed and the same product was formed regardless of the nucleophile counterion. These results imply the operation of a single Felkin−Anh pathway, in which axial attack of the nucleophile occurs via the half-chair conformation **i**.

However, the observation of counterion-dependent reversal of diastereoselectivity is indicative of the operation of at least two reaction pathways.[30] Similarly, the modest diastereoselectivities observed in additions to 6-OMEM cyclohexenone imply that Cram chelation and/or Felkin−Anh pathways are not the sole modes of addition. Given the relatively modest energy differences necessary to reverse the diastereoselection (e.g., from 1:5 to 5:1), extricating the individual contributions of solvent, metal, R-group, and C_6-heteroatom substituent may prove challenging.[31] Further efforts toward optimizing the diastereoselectivity, probing the generality of the reversal and examining a wider variety of counterions are underway.

In summary, we have found that diastereoselectivity in the addition of hard carbon nucleophiles to C_6-substituted cyclohexenones may in some cases be controlled by the counterion of the nucleophile, with Grignard reagents generally adding *syn* and lithium reagents adding *anti* to the C_6-substituent. Further, this selectivity may be optimized by use of an appropriate solvent and/or cosolvent in the addition reaction.

Acknowledgment. Support for this work was provided by the National Institutes of Health (GM-59406). M.C.M. is a Cottrell Scholar of Research Corporation. We thank Frank R. Fronczek, Louisiana State University, for assistance with X-ray crystallographic analysis. Thanks to Andrew Poss, Honeywell International, Inc., for a generous gift of *N*-fluorobenzenesulfonimide.

Supporting Information Available: Representative experimental procedures, characterization data for compounds **2**−**9**, **11a**,**c**, and **12b**,**c**; lactate ester of **9**, ORTEPs of **7c**, the (*S*)-*O*-benzyl lactate ester of **9**, and the free diol derived from **11a**; structure proof of alcohols **11a** and **11c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Ancillary studies using various protecting groups for the C_6 alcohol yielded similar results.

(27) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031−1034.

(28) Paquette, L. A.; Lobben, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 1917−1930.

(29) Allen, J. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 351−352.

(30) Computational studies have examined the role of polar substituents in diastereoselective carbonyl addition reactions: (a) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1990**, 456−458. (b) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018−5027. (c) Shi, Z.; Boyd, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 9614−9619. Other theoretical studies have investigated selectivity in additions involving Grignard, organolithium, organoaluminum and/or organopotassium reagents: Yadav, V. K.; Sriramurthy, V. *Tetrahedron* **2001**, *57*, 3987−3995. See also refs 5c−d.

(31) A further complicating factor is the aggregation state of the nucleophile. A number of studies indicate that the molecular aggregation of organolithium and Grignard reagents is dependent upon solvent and the R group and that aggregation affects the reactivity of the nucleophile as well as the mechanism and the stereoselectivity of the addition. (a) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028−2038. (b) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1984**, *107*, 1805−1815. (c) Haeffner, F.; Sun, C.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 12342−12348. See also refs 1a, c, d.