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Reaction of Metalated Nitriles with Enones

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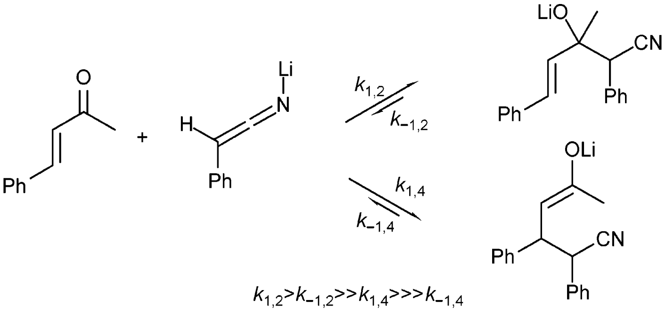
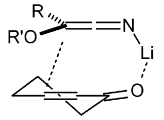


There have been a number of reports of the kinetic conjugate (1,4) addition of metalated arylacetonitriles to enones. Several proposals have been made to explain this behavior based on nucleophile structure or aggregation state or on the HSAB properties of the reactants. A reexamination of these studies showed that in each case the 1,4 adducts resulted from equilibration of the kinetically formed 1,2 adducts to the more stable 1,4 adducts. Thus, no conclusions about the origins of 1,4 selectivity can be drawn from these experiments. The 1,2 addition, retro-1,2 addition, 1,4 addition, and retro-1,4 addition of lithiophenylacetonitrile to benzylideneacetone were examined, and a free energy level diagram was constructed for the reaction.

The addition of organolithium reagents to α,β-unsaturated carbonyl compounds can have synthetic utility only if regioselectivity (1,2 vs 1,4 addition) can be controlled. We have been interested in trying to understand the mechanistic features that control selectivity[1] and report here our studies of the regioselectivity of addition of metalated phenylacetonitriles to enones.



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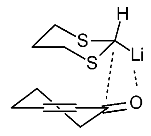

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Stork and Maldonado[2] made the synthetically valuable observation in 1974 that metalated nitriles (protected cyanohydrins) tend to give a larger proportion of 1,4 adduct than other acyl anion equivalents such as lithiodithianes or metalated vinyl ethers.[3a,4] The factors controlling this regioselectivity have been a matter of debate ever since. Several distinct mechanistic rationales were evoked to account for this uncommon regioselectivity. Stork and Maldonado proposed that the linear N−Li structure of lithionitriles permitted an extended transition state (**1**) leading to 1,4 addition, whereas C-lithiated reagents favored a more compact four-membered cyclic transition state (**2**) which leads to 1,2 addition.

Aggregation Control of 1,2 vs 1,4 Addition. Recently, 1,2 vs 1,4 regioselectivity of lithiophenylacetonitrile has been correlated to the aggregation state of the anion solution structures[5a,b] using integrated IR bands to determine dimer and monomer concentrations in various solvents. The monomer concentration showed linear correlation to the 1,2 adduct with benzylideneacetone, and the dimer concentration correlated to the 1,4 adduct in THF and THF−toluene solutions (Figure 1). The authors proposed transition states analogous to those proposed by Stork, with the additional refinement that the linear N−Li four-center bonded dimer[6a,7a] led to 1,4 addition, whereas the monomer, suggested by ab initio calculations (3-21+G* basis set) to have a C-

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[1] Reich, H. J.; Sikorski, W. H. *J. Org. Chem.* **1999**, *64*, 14−15. Sikorski, W. H.; Reich, H. J. *J. Am. Chem. Soc.* **2001**, *123*, 6527−6535.

[2] Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1974**, *96*, 5272−5274.

[3] (a) Seebach, D. *Synthesis* **1969**, 17−36. (b) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271−90.

[4] Baldwin, J. E.; Höfle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125−7127.

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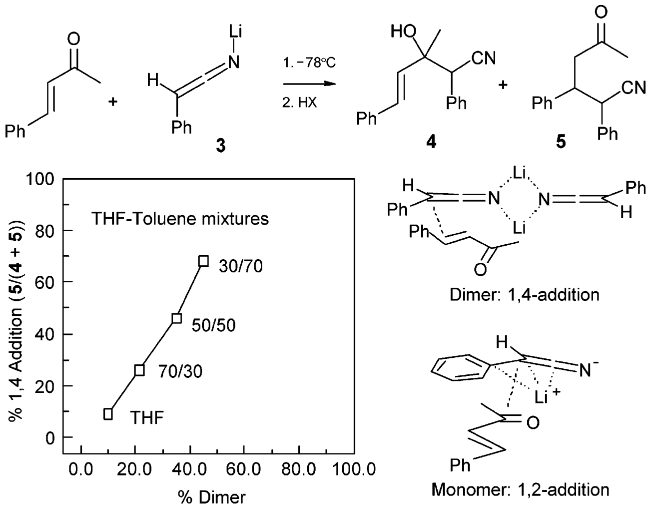
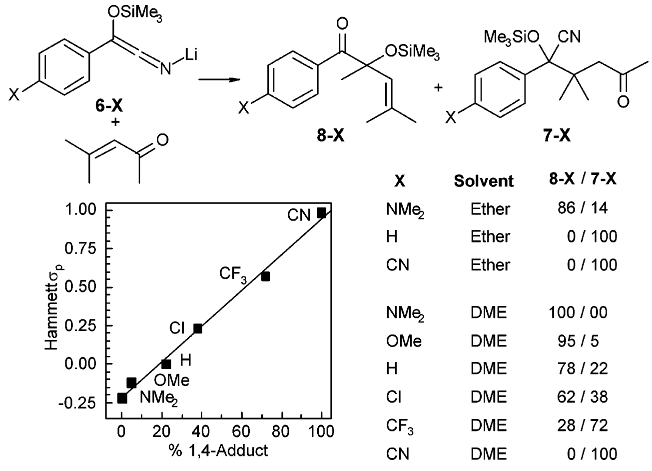


FIGURE 1. Correlation between aggregation state and 1,4 addition for **3** and benzylideneacetone.[5a] Proposal for aggregation control of regioselectivity.



X	Solvent	8-X / 7-X
NMe$_2$	Ether	86 / 14
H	Ether	0 / 100
CN	Ether	0 / 100
NMe$_2$	DME	100 / 00
OMe	DME	95 / 5
H	DME	78 / 22
Cl	DME	62 / 38
CF$_3$	DME	28 / 72
CN	DME	0 / 100

FIGURE 2. Effect of para substituents and solvent on the ratio of 1,2 to 1,4 addition of benzaldehyde *O*-trimethylsilylcyanohydrins in ether and DME.[9a,b]

metalated structure,[5c,6b] underwent 1,2 addition. Higher level calculations, including solvent molecules, predicted that an N-metalated structure would be more favorable for the monomer as well.[14d]

HSAB Control of 1,2 vs 1,4 Addition. Several arguments rationalizing 1,2 vs 1,4 addition propensities have been made on the basis of frontier molecular orbital arguments and the HSAB (hard and soft acid–base[8]) properties of electrophiles and nucleophiles. Ahn, Deschamps, and Seyden-Penne suggested that 1,2 additions should be more charge controlled (harder electrophile) and 1,4 addition more orbital controlled (softer electrophile).[5d] Solvent effects on regioselectivity have been interpreted in terms of ion-pairing effects.[9a] The metalated benzaldehyde cyanohydrin **6-H** is reported to form the 1,4 adduct **7** in ether, whereas the silyl-shifted 1,2 adduct **8** is formed in THF or more polar solvent combinations such as DME or HMPA (Figure 2). It was reasoned that in ether the "softer" contact ion pair or an aggregate of it is the reactive species, yielding the 1,4 product, whereas in more polar solvents the "harder" solvent separated ion pair was responsible for 1,2 addition.

HSAB theory has also been invoked to account for substituent effects on the regioselectivity of lithiated nitriles. A series of para-substituted trimethylsilyl benzaldehyde cyanohydrins **6-X** gave a linear correlation between the Hammet σ_p constants and the percent of 1,4 addition to mesityl oxide (Figure 2).[9b] It was argued that the *p*-cyano anion is extensively delocalized and thus a softer nucleophile which prefers to add 1,4, whereas the charge is more localized on the carbanion carbon in the *p*-NMe$_2$ compound, which then reacts at the harder carbonyl position. A related paper on the addition of lithioarylacetonitriles to mesityl oxide suggested that the 1,4 addition of the parent (**3**) was probably not kinetically controlled but that of the *p*-methoxy analogue was.[5e] A rationale for the different behavior of *p*-methoxyphenyl-

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(5) (a) Strzalko, T.; Seyden-Penne, J.; Wartski, L.; Corset, J.; Castella-Ventura, M.; Froment, F. *J. Org. Chem.* **1998**, *63*, 3295–3301. Strzalko, T.; Seyden-Penne, J.; Wartski, L.; Froment, F.; Corset, J. *Tetrahedron Lett.* **1994**, *35*, 3935–3936. (b) Croisat, D.; Seyden-Penne, J.; Strzalko, T.; Wartski, L.; Corset, J.; Froment, F. *J. Org. Chem.* **1992**, *57*, 6435–6447. Corset, J.; Castella-Ventura, M.; Froment, F.; Strzalko, T.; Wartski, L. *J. Org. Chem.* **2003**, *68*, 3902–3911. (c) Strzalko, T.; Seyden-Penne, J.; Wartski, L.; Corset, J.; Castella-Ventura, M.; Froment, F. *J. Org. Chem.* **1998**, *63*, 3287–3294. (d) Deschamps, B.; Anh, N. T.; Seyden-Penne, J. *Tetrahedron Lett.* **1973**, *14*, 527–530. Sauvetre, R.; Roux-Schmitt, M.-C.; Seyden-Penne, J. *Tetrahedron* **1978**, *34*, 2135–2140. (e) Roux-Schmitt, M.-C.; Wartski, L.; Seyden-Penne, J. *J. Chem. Res (S)* **1980**, 346; Roux-Schmitt, M.-C.; Wartski, L.; Seyden-Penne, J. *J. Chem. Res (M)* **1980**, 4141–4153. (f) Wartski, L.; El Bouz, M.; Seyden-Penne, J.; Dumont, W.; Krief, A. *Tetrahedron Lett.* **1979**, *20*, 1543–1546. (g) Roux, M. C.; Wartski, L.; Seyden-Penne, J. *Tetrahedron* **1981**, *37*, 1927–34. (h) Wartski, L.; El-Bouz, M.; Seyden-Penne, J. *J. Organomet. Chem.* **1979**, *177*, 17–26.

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(7) (a) Carlier, P. R.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 11602–11603. (b) Galiano-Roth, A. S.; Kim, Y.-J.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5053–5055. Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9198–9202. (c) 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. Briggs, T. F.; Winemiller, M. D.; Xiang, B.; Collum D. B. *J. Org. Chem.* **2001**, *66*, 6291–6298. (d) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2459–2463. (e) DePue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5518–5524.

(8) Ho, T.-L. *Chem. Rev.* **1975**, *75*, 1–20.

(9) (a) Hünig, S.; Wehner, G. *Chem. Ber.* **1980**, *113*, 302–323. (b) Hünig, S.; Wehner, G. *Chem. Ber.* **1980**, *113*, 324–332 (c) Hünig, S.; Schäfer, M.; Schweeberg, W. *Chem. Ber.* **1993**, *126*, 205–210.

(10) Dolak, T. M.; Bryson, T. A. *Tetrahedron Lett.* **1977**, 1961–64. Brown, C. A.; Yamaichi, A. *J. Chem. Soc., Chem. Commun.* **1979**, 100–101. Cohen, T.; Abraham, W. D.; Myers, M. *J. Am. Chem. Soc.* **1987**, *109*, 7923–24.

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(12) There has been considerable published work on the structure of lithiophenylacetonitrile and analogues, including spectroscopic studies by NMR[5b, 7a, 13, 14a] and IR spectroscopy.[5b] X-ray crystal structures have been reported,[6a] and the effect of polar cosolvents such as TMEDA[7a] and HMPA has been studied.[5 g, 14a] The reactivity has also been studied in several contexts, including the aldol condensation.[5, 14b] There have been computational studies of metalated nitrile structure and reactivity.[5c, 14d, 15, 16]

(13) Abbotto, A.; Bradamante, S.; Pagani, G. A. *J. Org. Chem.* **1993**, *58*, 449–455.

(14) (a) Carlier, P. R.; Lo, C. W.-S. *J. Am. Chem. Soc.* **2000**, *122*, 12819–12823. (b) Carlier, P. R.; Lo, K.-M. *J. Org. Chem.* **1994**, *59*, 4053–4055. Carlier, P. R.; Lo, K.-M.; Lo, M. M.-C.; Williams, I. D. *J. Org. Chem.* **1995**, *60*, 7511–7517. (c) Carlier, P. R.; Lo, C. W.-S.; Lo, M. M.-C.; Wan, N. C.; Williams, I. D. *Org. Lett.* **2000**, *2*, 2443–2445. (d) Carlier, P. R.; Madura, J. D. *J. Org. Chem.* **2002**, *67*, 3832–3840.

acetonitrile and **6-OMe** (which gives mostly 1,2 addition) was suggested based on the possibly more pyramidal structure of the siloxy substituted carbanion center in **6-OMe**.

We became interested in this question, and particularly the aggregation hypothesis of Figure 1,[5a] as a follow up on our studies of the effect of polar cosolvents such as HMPA and DMPU on the 1,2/1,4 dichotomy in the reaction of sulfur-substituted organolithium reagents with enones and enals.[1] In this work we provided support for the notion[5f,10] that ion-pair status (contact vs separated ion pairs) and lithium solvation levels were major determinants of the propensity for 1,4 addition. The direct correlation between dimer concentration and 1,4 addition for the lithiophenylacetonitrile reactions represents a rare case where selectivity could be directly attributed to aggregate structure, a concept frequently invoked to rationalize selectivity changes in synthetically useful reactions.[11] This observation implies strongly that the Curtin−Hammett principle does not apply, i.e., that the rate of reaction is faster than the rate of aggregate interconversion, an effect possibly subject to direct experimental test.

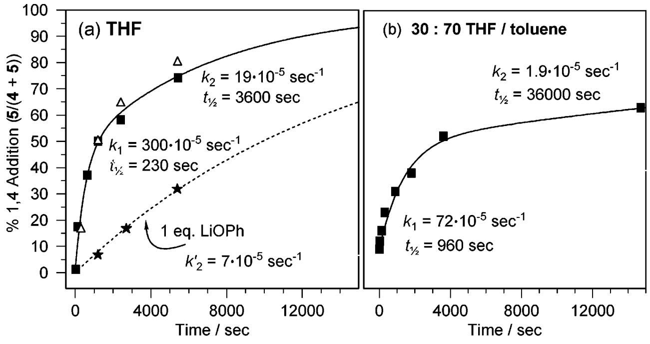
Implicit in the aforementioned proposals is the presumption that products were formed under kinetic control, since product ratios formed under thermodynamic control provide no information as to the nature of transition states. Indeed, all of the workers in the area recognized the possibility that the 1,4 adduct, which is usually thermodynamically more stable than the 1,2 adduct, could arise simply by equilibration if the addition were reversible. The isomerization of 1,2 to 1,4 adducts in aldol additions to enones has been detected many times, including during the additions of lithioacetonitriles.[5d,h,9c] We report here that in all of the above cited cases, each of which implied or explicitly claimed kinetic formation of 1,4 -addition products, these arise not from any special transition state effects, but from equilibration of the kinetically formed 1,2 adducts to the thermodynamically favored 1,4 adducts.

Results and Discussion

Aggregation Control. Our examination of the reaction of lithiophenylacetonitrile (**3**)[12] with benzylideneacetone gave quite different results from those reported in Figure 1.[5a] We observed a time dependence on the product ratios, with high ratios of 1,2 to 1,4 adduct if reaction times were short (<30 s) and an effective quench was used (Figure 3). At longer times, 1,4 products increasingly predominated, with eventual complete conversion to the 1,4 adduct.

This behavior can be explained with the hypothesis shown in Scheme 1. The lithiophenylacetonitrile adds quickly and reversibly at the carbonyl carbon to afford the 1,2 adduct. Upon retro 1,2 addition, a slower conjugate addition affords the 1,4 adduct. We set out to estimate values for the rate constants with the goal of constructing an approximate free energy diagram for this scheme.

The 1,2 Addition (Aldol, $k_{1,2}$). The rate of 1,2 addition was too fast to measure at −78 °C at the concentrations usually used (0.08 M). Typical experiments involve an excess of the benzylideneacetone and quench with a mixture of propionic acid and benzaldehyde, the latter to establish that there was some free lithiophenylacetonitrile left. Such an experiment at −98 °C with an 8 s reaction time gave 94% conversion to **4**, corresponding to $k_{1,2} = 80\ \mathrm{M^{-1}\ s^{-1}}$, $\Delta G^{\ddagger} = 8.5$ kcal/mol. A high dilution experiment (0.001 M) at −78 °C gave 83% conversion in 3 s, corresponding to $k_{1,2} = 400\ \mathrm{M^{-1}\ s^{-1}}$, $\Delta G^{\ddagger} = 8.9$ kcal/mol. The diastereomer ratio of the 1,2 addition products **4A** and **4B** (relative stereochemistry was not assigned) in these experiments varied slightly depending on conditions. At the shortest reaction times (<10 s), where the diastereomer ratio is close to kinetically controlled, ratios as high as 67/33 were observed. Later in the reaction (10−120 min), when substantial product had built up, the ratio became close to 1:1. Since the 1,2-adducts must be at equilibrium on any time scale greater than 1 min or so, the small drift in ratios observed as the isomerization of **9** to **10** proceeded can be attributed to changes in the equilibrium ratio as various mixed aggregates between **9** and **10** are formed.

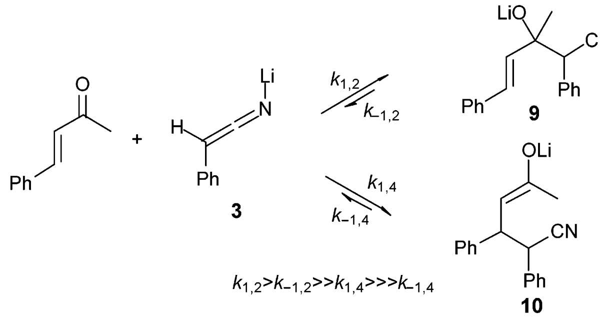


Simulation model: $(\mathbf{9})_2 \xrightarrow{k_1} \mathbf{9}\cdot\mathbf{10} \xrightarrow{k_2} (\mathbf{10})_2$

	$k_1 \cdot 10^5$	$k_2 \cdot 10^5$	k_1 / k_2
THF	300	19	16
30 : 70 THF/toluene	72	1.9	37

FIGURE 3. Isomerization of **9** to **10** in (a) THF and (b) 30:70 THF/toluene at −78 °C. Each point is a separate experiment: ■, 1,2 adduct **9** formed by reaction of **3** with benzylideneacetone (the solid lines are best fit kinetic simulations of these points using the bimodal scheme and rate constants shown); △, 1,2 adduct formed by deprotonation of **4**. ★ 1,2 to 1,4 isomerization in THF in the presence of 1 equiv of LiOPh (the dashed line (k'_2) corresponds to first-order conversion).

SCHEME 1



The Retro-1,2 Addition (Retro-Aldol, $k_{-1,2}$). The alkoxide **9** formed by deprotonation of the 1,2 adduct **4** with LDA was converted to the 1,4 adduct **10** at −78 °C in THF at a rate comparable to reaction of **3** with benzylideneacetone (Figure 3). This alone does not establish that the retro-aldol process was occurring, since

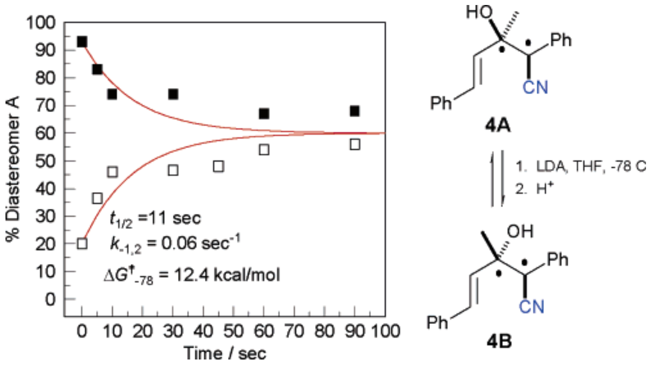
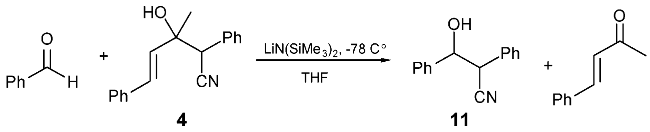


FIGURE 4. Interconversion of the diastereomers of **4** in THF at −78 °C (relative stereochemistry was not assigned). The lines are calculated for first-order conversion of each isomer to the equilibrium 60/40 mixture with $k = 0.06$ s^{-1}.

a 1,3-sigmatropic rearrangement mechanism is conceivable. We performed two types of experiments to estimate the actual rate of the retro-aldol process: interconversion of the 1,2 adduct diastereomers and external trapping of lithionitrile **3**.

The alkoxide diastereomers **9A** and **9B** are present in a 60:40 ratio at equilibrium.[14b,c] Chromatographically purified alcohol **4** enriched in each of its diastereomers **4A** and **4B** was deprotonated with LDA at −78° C in THF and then quenched with a propionic acid−Et_2O or propionic acid−methanol solution after reaction times of 5−100 s. Less than 8% of 1,4 adduct was formed in these experiments, but 1−11% of benzylideneacetone was formed, suggesting that the retro-aldol was competitive with mixing of the reagents, leading to protonation of the lithiophenylacetonitrile by the alcohol. There was too much scatter in the points to obtain reliable rate constants, presumably because mixing and temperature control is difficult in these very short experiments, but we estimate a half-life of 11 s for the isomerization (Figure 4). The very fast interconversion of diastereomers (about 50 times as fast as regioisomer interconversion) means that kinetic and thermodynamic diastereoselectivity can be misidentified even more easily than regioselectivity.[5g,14b]

To provide a second estimate of the retro-aldol rate we performed a series of experiments which involved trapping of the product **3** with an electrophile. Benzaldehyde was shown to be an effective trap for lithionitrile **3** by adding a 1:1 mixture of benzaldehyde and benzylideneacetone to the lithiophenylacetonitrile and observing a 99/1 ratio of aldols favoring the benzaldehyde adduct **11** (a 80:20 ratio of anti/syn isomers was formed[14b]). When a mixture of **4** and excess benzaldehyde were treated with $LiN(SiMe_3)_2$, **11** was formed rapidly, although these experiments also showed considerable scatter (half-life of 10−30 s). In addition to the short reaction times and mixing problems present in the diastereomer interconversion, there are other potential problems. Addition of $LiN(SiMe_3)_2$ to the benzaldehyde in competition with deprotonation of **4** would lower the concentration of both benzaldehyde and the alkoxide **9**. The concentration of benzaldehyde could also be lowered by addition of **9** to the benzaldehyde to form a lithiohemiacetal, similar to those detected by McGarrity and co-workers in their rapid injection NMR study of the reaction of BuLi with benzaldehyde.[17] With these limitations in mind, the trapping occurs on a comparable time scale to that observed for the diastereomer interconversion. We estimate $\Delta G^{\ddagger}_{-78}$ for the retro-aldol ($k_{-1,2}$) as 12.4 kcal/mol.



The 1,2 to 1,4 Isomerization. Initial 1,2 to 1,4 ratios as high as 98/2 were achieved in THF at −78 °C. In 30:70 THF/toluene the highest ratio observed at −78 °C was 91/9, but ratios as high as 97/3 were observed at −98 °C. We presume that our quenching procedure (addition of a 3 M solution of propionic acid in ether) does not work quite as well in the less polar solvent mixture as in pure THF. This may also be an explanation for the reported increase in the fraction of 1,4 adduct as solvent polarity was decreased (Figure 1). The quenching procedure used (addition of 2 M aqueous HCl) might become increasingly ineffective as the solvent became less polar, resulting in more isomerization before the reaction was stopped.

The 1,2 to 1,4 adduct isomerization showed a distinct bimodal dependence on time. Isomerization was fast up to about 50% conversion, with a half-life of ca. 4 min at −78 °C. The reaction then slowed drastically, with the last half proceeding about 1/20 as fast (Figure 3).[18] It is this two-phase process that can lead to a false impression that the product ratio formed in the first few minutes is the kinetic one. In fact, Strzalko and co-workers used reaction times of 5 and 30 min in their study,[5a] just the interval in which the fast phase is almost completed, and the slow phase has progressed only partially. This problem is exacerbated by the inherent temperature increases caused by addition of the reactant and quenching solutions to the reaction mixture.

One possible explanation for the bimodal kinetics is that the aggregate of the 1,2 adduct **9** isomerizes rapidly, whereas mixed aggregates between **9** and **10**, formed as the reaction proceeds, do the retro-aldol much more slowly. Although the actual aggregation states have not been determined, and our data is not accurate enough to individually define the role of multiple aggregates, the kinetics can be simulated nicely (solid line in Figure 3) by the following simple kinetic model. We assume that initially the 1,2 adduct exists as a dimer $(\mathbf{9})_2$, which isomerizes rapidly to the mixed aggregate **9·10**. This species isomerizes to $(\mathbf{10})_2$ at about 1/20 the rate of the homodimer.[19] To observe this product inhibition the mixed aggregate **9·10** must be thermodynamically favored over the homodimers, although it could also be

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[18] The rates in both phases were independent of concentration within experimental error over a factor of 12 in concentration.

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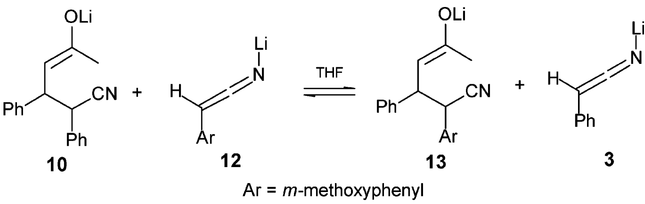
SCHEME 2



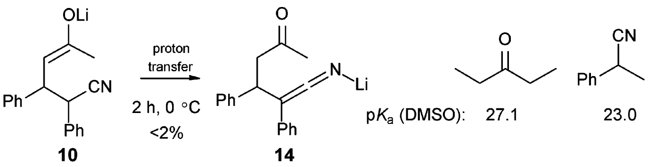
kinetically trapped if interconversion among the aggregates $(\mathbf{9})_2$, $(\mathbf{10})_2$, and **9·10** was slower than isomerization. The rates measured for conversion of 1,2 to 1,4 adduct in THF at −78 °C correspond to $\Delta G^{\ddagger}{}_{-78} = 13.5$ kcal/mol for the initial fast phase and $\Delta G^{\ddagger}{}_{-78} = 14.6$ kcal/mol for the slower second phase. We emphasize that this scheme is a functional kinetic model only. The actual process could involve a series of mixed tetramers with the rate decreasing sharply as alkoxides **9** are replaced byproduct enolates **10** in the aggregates.[20] An equivalent kinetic scheme to the one above would replace dimers $(\mathbf{9})_2$, **9·10**, and $(\mathbf{10})_2$ by the tetramers $(\mathbf{9})_4$, $(\mathbf{9})_2\cdot(\mathbf{10})_2$, and $(\mathbf{10})_2$.

We have performed a test for this behavior by preparing **9** in the presence of 1 equiv of lithium phenoxide, an unreactive surrogate for the enolate **10**. We hypothesized that formation of mixed aggregates between **9** and LiOPh might inhibit the isomerization of **9** to **10** similarly to that provided by mixed aggregates between **9** and **10**.[21a] In fact, with lithium phenoxide present there is little or no "fast phase" for the isomerization (Figure 3); the entire isomerization now proceeds at a rate comparable to that of the slow phase in the absence of phenoxide.[22]

The rate of 1,2 addition must be 50 times as fast as that of 1,4 addition ($k_{1,2}/k_{1,4}$ Scheme 1), since we have observed kinetic 1,2 to 1,4 ratios as high as 50:1. Thus, the rate of isomer interconversion (essentially $k_{-1,2}$) should be 50× as fast as the fast initial phase of the 1,2 to 1,4 isomerization. The observed value is a factor of 20. These numbers are probably within experimental error.

The Retro 1,4 Addition (Retro-Michael, $k_{-1,4}$). A series of crossover experiments were performed to determine the rate of retro-1,4 addition of **10** (Scheme 2). A solution of **10** was prepared in situ by the reaction of lithiophenylacetonitrile with benzylideneacetone and warming to 0 °C to complete the isomerization. This solution was then treated with a 2-fold excess of lithio-*m*-methoxyphenylacetonitrile **12**, and the crossover product **13**, formed by reaction of **12** with the benzylideneacetone released in the retro 1,4 addition, was monitored. The formation of **13** was readily detected at −25 °C or higher. The rate of conversion followed reasonable first-order kinetics, and the rate was unaffected after dilution by a factor of 4. There was no significant substituent effect on the equilibration, a 1:1 ratio of either **10** and **12** or **13** and **3** each went to a 1:1 ratio of **10** and **13** at comparable rates. Rates were measured at eight temperatures between −20 and 20 °C. An Eyring plot gave $\Delta H^{\ddagger} = 15.1 \pm 1.0$ kcal/mol, $\Delta S^{\ddagger} = -19 \pm 4$ eu. Extrapolation of the rates to −78 °C gave $\Delta G^{\ddagger}{}_{-78} = 18.7$ kcal/mol. A long-term experiment at −78 °C (120.5 h) gave a barely detected amount of crossover product (0.4%) which corresponds to a $k_{-1,4}$ of $9.2 \times 10-9$ s^{-1}, ($\Delta G^{\ddagger} = 18.4$ kcal/mol), in good agreement with the results extrapolated from higher temperatures.

SCHEME 3



We observed a downward drift of the infinity point (from the expected value of 67% conversion) in some of the kinetic runs of Scheme 2. A potential explanation for this observation is that the 1,4 adduct enolates (**10** and **13**) are probably more basic than the metalated nitrile **14** and its *m*-methoxy analogue, judging from the pK_a (DMSO) of diethyl ketone (27.1[27a]) and α-phenylpropionitrile (23.1[27b]), so that rearrangement of **10** to **14** could occur. We performed a control experiment by treating benzylideneacetone with 3 equiv of **3** to mimic the presence of 2 equiv of **12** in the experiment of Scheme 2. After reaction time long enough for >80% conversion (2 h at 0 °C) the reaction was quenched with DOAc. Analysis by ^{1}H and ^{2}H NMR spectroscopy showed 84% deuteration α to the ketone and only 2% deuteration at the benzylic nitrile position (Scheme 3). Thus, enolate equilibration was insignificant during this particular experiment.

From these data, a rough energy diagram of the reaction between α-lithiophenylacetonitrile and benzylideneacetone in THF can be constructed (Figure 5). The highest selectivity for 1,2 vs 1,4 addition that we have measured is about 50/1, corresponding to $\Delta\Delta G^{\ddagger} = 1.5$ kcal/mol, whereas the same selectivity measured from the kinetic data was 1.1 kcal/mol (factor of 20), which we consider good agreement. From the energy diagram we can determine that the free energy difference favoring the 1,4 adduct is about 4.9 kcal/mol. The exothermicity of the 1,2 addition is >3.5 kcal/mol, and the exothermicity of the 1,4 addition is >8 kcal/mol.

The HSAB Hypothesis. Interpretation of the linear correlation between σ_{para} and the ratio of 1,2 to 1,4

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[20] Lithium *tert*-butoxide, lithium phenoxide and the lithium enolate of acetophenone are all approximately tetrameric in THF: Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 7288−7293.

[21] (a) For studies of Lithium phenoxides as enolate surrogates see: Jackman, L. M.; Smith, B. D. *J. Am. Chem. Soc*. **1988**, *110*, 3829−3835. Jackman, L. M.; Chen, X. *J. Am. Chem. Soc.* **1992**, *114*, 403−411. Jackman, L. M.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 8681−8684. (b) Jackman, L. M.; Dunne, T. S. *J. Am. Chem. Soc.* **1985**, *107*, 2805−2806. Jackman, L. M.; Lange, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 4494−4499.

[22] The role of alkoxide and amide mixed aggregates has been explored in a variety of contexts: lithium enolate/LiX,[7b, 19a, 21b] BuLi/BuOLi,[17] RLi/LiNR$_2$,[23a, 24] lithium acetylide/ROLi,[7c] lithium enolate/LiNR^2,[3b, 7d, 25] R$_2$NLi/LiX,[7e, 26] lithionitrile/LiNR$_2$.[6a, 7a, 23b]

[23] (a) Hilmersson, G.; Malmros, B. *Chem. Europ. J.* **2001**, *7*, 337−341. (b) Sott, R.; Granander, J.; Hilmersson, G. *Chem. Europ. J.* **2002**, *8*, 2081−2087.

[24] Corruble, A.; Davoust, D.; Desjardins, S.; Fressigne, C.; Giessner-Prettre, C.; Harrison-Marchand, A.; Houte, H.; Lasne, M.-C.; Maddaluno, J.; Oulyadi, H.; Valnot, J.-Y. *J. Am. Chem. Soc.* **2002**, *124*, 15267−15279.

[25] Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8602−8604.

[26] Sugasawa, K.; Shindo, M.; Noguchi, H.; Koga, K. *Tetrahedron Lett.* **1996**, *37*, 7377−7380.

[27] (a) Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006−7014. (b) Bordwell, F. G.; Cheng, J.-P.; Bausch, M. J.; Bares, J. E. *J. Phys. Org. Chem.* **1988**, *1*, 209−223.

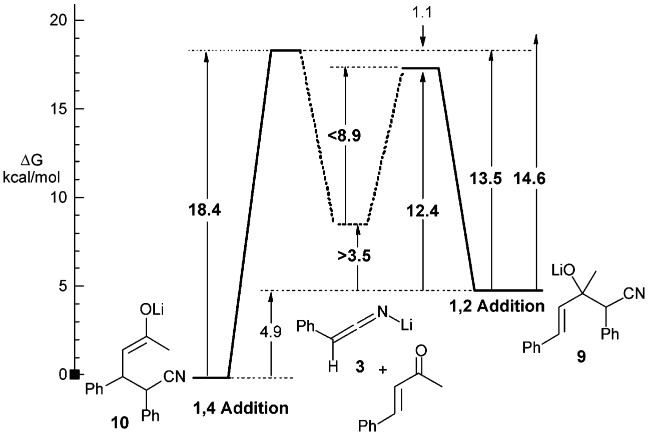
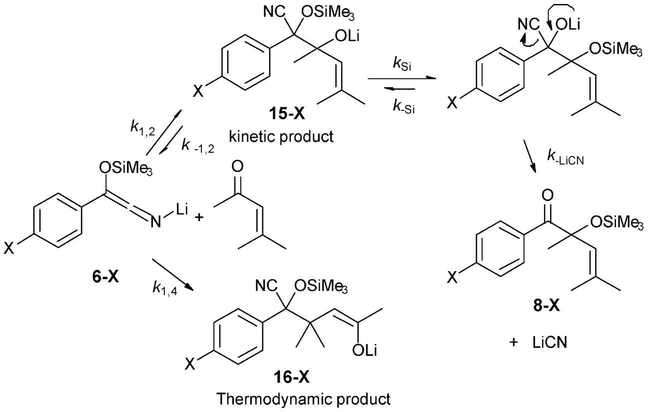
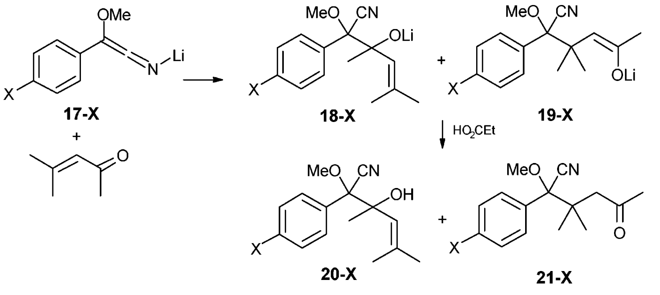


FIGURE 5. Energy diagram for the **3/9/10** system at −78 °C in THF.

SCHEME 4



SCHEME 5



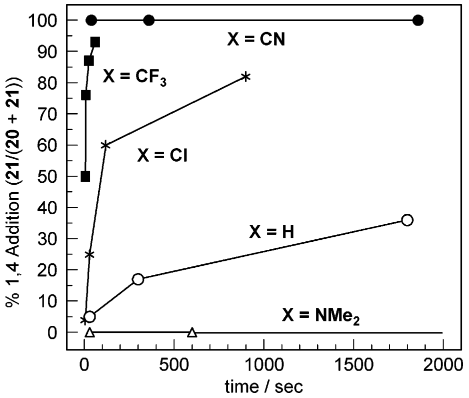


FIGURE 6. Time course of the fraction of 1,4 adduct in the reaction of **17-X** with mesityl oxide in THF at −78 °C to form **20-X** and **21-X**.

addition reported by Hünig and Wehner (Figure 2)[9b] is complicated by the O to O silyl migration of the initial 1,2 adduct **15-X**, which irreversibly leads to formation of the ketone **8-X**. An alternative explanation of their results is that silyl shift (k_{Si}) proceeds at a relatively constant rate for the various *p*-substituents, whereas the retro-aldol rate($k_{-1,2}$), and hence, the rate of the isomerization of the 1,2 to the 1,4 adduct increases in the series from *p*-NMe$_2$ to *p*-CN as the anion becomes increasingly stabilized (Scheme 4). The correlation between 1,4 addition and σ_{para} in Figure 2 is then the result of competition between the silyl shift and the retro-1,2 addition (k_{Si} and $k_{-1,2}$) and not due to any inherent HSAB properties of the lithium reagents.

To avoid this problem, we have investigated a series of *O*-methyl cyanohydrins (**17-X**, X = NMe$_2$, H, Cl, Br, CF$_3$, CN)[28] which should be electronically similar to the *O*-trimethylsilyl analogues **6-X** (Scheme 5).

The results obtained for the *p*-NMe$_2$ (**17-NMe$_2$**) compound in THF parallel those reported for the silyl analogue **6-NMe$_2$** in DME, giving only 1,2 adduct in high yield at −78 °C even after reaction times of several hours (Figure 6). Only at much longer reaction times or when the temperature was raised well above −78 °C or when the polar cosolvent HMPA was added was isomerization to the 1,4 adduct observed. HMPA is known to facilitate retroaldol reactions of lithionitriles with aldehydes.[14c]

With compounds **17-Cl** and **17-H** our results were quite different than Hünig's results for **6-Cl** and **6-H**. For each we were able to observe >95% 1,2 addition at short reaction times (5−20 s). Thus, here, as for all the systems studied except **17-CN** and **17-CF$_3$**, the kinetic product is almost completely the 1,2 adduct. Our experiments were done in THF, whereas Hünig's were done in DME, so we have performed an experiment with **17-Cl** in DME, and found that 1,2 adduct was also the kinetically formed product at short reaction times.

Compound **17-CN**, on the other hand, gave only the 1,4 adduct under all conditions tried, like that reported for **6-CN**. With short reaction times (40 s at −78 °C) only 30% conversion to products was observed, showing that the 1,4 adduct was a true kinetic product. A reasonable explanation for this observation is that the 1,2 addition has become endothermic ($k_{-1,2} > k_{1,2}$ in Scheme 4) for the strongly stabilized *p*-CN lithionitrile. We estimated above that the benzylideneacetone−lithiophenylacetonitrile 1,2 addition was around 4 kcal/mol exothermic (Figure 5). In DMSO the additional anion stabilization provided by the *p*-CN group in phenylacetonitrile is about 8 kcal/mol (the pK_a of phenylacetonitrile in DMSO is 21.9, for the *p*-cyano it is 16.0[27b]). Although this energy difference would be considerably smaller under the ion-paired and aggregated conditions of our experiments in THF, it could easily be enough to invert the stability of 1,2 adduct vs lithionitrile and enone. It is not unusual for aldols with ketone acceptors to be thermodynamically unfavorable.[29]

The *p*-CF$_3$ compound showed behavior intermediate between that of **17-CN** and **17-Cl**. The addition was slow

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[28] Utimoto, K.; Wakabayashi, Y.; Shishiyama, Y.; Inoue, M.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4279−4280.

[29] Conant, J. N.; Tuttle, N. *Org. Synth. Coll. Vol I*, **1932**, 199−202.

enough at −78 °C that the progress of the reaction could be observed (half-life ca. 20 s), but the 1,2 adduct never built up to more than 10% of the product. Here the rate of retro-aldol ($k_{-1,2}$ of Scheme 4) has become comparable to the addition rate $k_{1,2}$ (i.e., the free energy of 1,2 adduct **18-CF$_3$** is similar to that of **17-CF$_3$** and mesityl oxide).

Another unusual regioselectivity reported was that the addition of **6-H** to mesityl oxide in ether produced only 1,4 adduct, whereas the reaction in DME or THF gave largely 1,2 adduct (Figure 2).[9a] This was also rationalized in HSAB terms, with the softer contact ion pair in ether undergoing 1,4 addition, whereas the harder solvent separated ion pair (SIP) in THF and DME gave 1,2 addition. Here the experiment may be complicated by the fact that **6-H** was insoluble in ether, and an aqueous NH_4Cl quench was used, which may not have reacted at −78 °C. We have performed an experiment with **17-H** and mesityl oxide in ether and find that 98% of 1,2 adduct was formed (<2% of unreacted starting materials, 80% yield) at −78 °C after 12 s reaction time. We thus suggest that none of the product ratios in ether summarized in Figure 2 represent kinetic product ratios, and these results permit no conclusions about the nature of interactions at the transition state.

We also reinvestigated the report that lithio-*p*-methoxyphenylacetonitrile underwent kinetically controlled 1,4 addition to mesityl oxide in THF.[5e] This report is also in error. We find that >99% of the product was the 1,2 adduct (7 s at −78 °C), which isomerized to 48% 1,4 adduct in 19 min and 93% after 2 h.

Summary. We have reexamined the experimental evidence supporting several widely held and appealing hypotheses to explain the course of addition of metalated nitriles to α,β-unsaturated ketones: that soft anions prefer 1,4 additions, whereas hard anions prefer 1,2 additions, and that the *N*-metalated linear structures of dimeric lithioacetonitriles favor 1,4 additions whereas monomers or SIPs form 1,2 adducts. For the specific cases of the addition of **3** to benzylideneacetone and addition of **17-H**, **-Cl**, and **-NMe$_2$** (and by extension to **6** analogues) to mesityl oxide, we find that the experimental evidence does not support an interpretation in terms of these hypotheses, but that in each case the 1,4 products are formed under thermodynamic control by isomerization of the kinetically favored 1,2 adducts. That is not to say that these effects do not exist, but in these systems they do not overwhelm the high kinetic preference for 1,2 addition. The special cases of **17-CF$_3$** and **17-CN** with mesityl oxide can be rationalized on the basis that the 1,2 addition has become endothermic, so the 1,2 adduct **18-X** cannot build up in the reaction mixture.

Experimental Section

General Methods. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl before use. All glassware was placed in an oven at 110 °C overnight or flame-dried prior to use. *n*-BuLi was titrated with *n*-propanol in THF at −78 °C with 1,10-phenanthroline as an indicator. Dry ice/acetone slurry was used to achieve −78 °C temperature baths and N_2(l)/ethanol to attain −100 °C baths. The phenylmethoxyacetonitriles were prepared by reaction of benzaldehyde dimethylacetals[30] with Me_3SiCN.[28]

Sample Reaction of 3 with Benzylideneacetone. Phenylacetonitrile (29 μL, 0.25 mmol) was added to a nitrogen-purged 5 mL, long-necked (5 cm, to minimize warming by conduction of heat) round-bottom flask. To this was added 3 mL of dry THF, the system was cooled to −78 °C under positive nitrogen pressure, and 120 μL (0.25 mmol) of 2.08 M *n*-BuLi was added. The nitrogen inlet needle was removed, the puncture septum was greased to prevent quenching, lithiation was continued for 20 min, and 100 μL of 2.5 M benzylideneacetone solution was injected into the flask. The solution was stirred for the appropriate time and quenched with 200 μL of 3 M propionic acid in diethyl ether. The solution was taken up in 1:1 hexanes/diethyl ether, washed once with saturated $NaHCO_3$ solution, twice with water, and once with brine, dried with anhydrous $MgSO_4$, and rotary evaporated. To this was added pentachloroethane, (15 μL, 0.125 mmol) as an internal NMR standard, and the solution was mixed thoroughly with deuterated chloroform with 0.03% tetramethylsilane. Spectra were taken on a 300 MHz NMR spectrometer. Data are displayed in Figure 3 and in Table S-1.[31]

High-Dilution Experiment. The high-dilution experiment to measure $k_{1,2}$ was performed as above with the following changes: phenylacetonitrile (22 μL, 0.19 mmol) was added to a nitrogen-purged 250 mL RBF containing 90 mL of THF metalated with 75 μL (0.19 mmol) of 2.6 M *n*-BuLi, and 100 μL of 0.95 M benzylideneacetone solution was injected into the flask. The solution was stirred for 3 s and quenched with a mixture of 50 μL of benzaldehyde and 100 μL of 3 M propionic acid in diethyl ether.

Test for Unreactive Mixed Aggregate with LiOPh. The same conditions were used as above with the following changes: phenol (24 mg, 0.25 mmol) was added to the flask before purging with nitrogen, 200 μL (0.50 mmol) of 2.5 M *n*-BuLi was added, and the reactions were quenched with 400 μL of 3 M propionic acid in diethyl ether. Data are displayed in Figure 3 and in Table S-2.[31]

Preparation of 4A and 4B. The same reaction conditions were used as for **3** reacting with benzylideneacetone, except that the scale was increased to 2 mmol, the temperature decreased to −100 °C to suppress formation of **5**, the reaction time was 5 s, and products were purified on a silica gel column eluted with 2:1 hex/Et_2O to separate diastereomers. **4A**: R_f = 0.19. **4B**: R_f = 0.10. 3-Hydroxy-2,5-diphenyl-3-methylpent-4-enenitrile (**4A**): ^1H NMR (300 MHz, $CDCl_3$) δ 7.4−7.2 (m, 10H), 6.62 (d, *J* = 16.0 Hz, 1H), 6.28 (d, *J* = 16.0 Hz, 1 H), 3.95 (s, 1H), 2.27 (s, OH), 1.49 (s, 3H). (**4B**): δ 7.4−7.2 (m, 10H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.27 (d, *J* = 16.0 Hz, 1H), 3.92 (s, 1H), 2.25 (s, OH), 1.52 (s, 3H). Full characterization data can be found in the Supporting Information.[5d]

Sample Reaction of 1,2 Adduct (4) Rearranging to 1,4 Adduct (5). Chromatographically purified (2:1 hex/Et_2O, silica gel) **4** (33 mg, 0.125 mmol) was added to a 5 mL long-necked RBF, the flask was purged with nitrogen, 3 mL of dry THF was added, the system was cooled to −78 °C under positive nitrogen pressure, and 125 μL of 1.0 M LDA (0.25 mmol) was added. The resulting solution was stirred for the appropriate time and quenched with 100 μL of 3 M propionic acid in diethyl ether. The solution was worked up as in reaction of **3** with benzylideneacetone. Data are presented in Figure 3 and tabulated in Table S-3.[31]

Diastereomer Interconversion Studies: Retro-Aldol. Chromatographically purified (2:1 hex/Et_2O, silica gel) **4** (44 mg, 0.16 mmol) enriched in the minor diastereomer (**4A/4B** = 20:80) was added to a 5 mL long-necked RBF. The flask was purged with nitrogen, 2 mL of THF was added, and this was

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[30] The dimethyl acetals were prepared using the procedure reported by: Creary, X.; Aldridge, T. *J. Org. Chem.* **1991**, *56*, 4280−4285. All are known compounds. *p*-H, *p*-Cl, *p*-NMe$_2$ were reported by: Hassner, A.; Wiederkehr, R.; Kascheres, A. J. *J. Org. Chem.* **1970**, *35*, 1962−1964, among others and *p*-CN and *p*-CF$_3$ were reported by Mueller, K.; Guerster, D.; Piwek, S.; Wiegrebe, W. *J. Med. Chem.* **1993**, *36*, 4099−4107.

[31] Figures and Tables with an S prefix are in the Supporting Information.

cooled to −78 °C under positive nitrogen pressure and metalated with 100 μL of 1.59 M LDA (0.16 mmol). The solution was stirred for the indicated time (Table S-4) and quenched with 140 μL of 3 M propionic acid in diethyl ether. The solution was worked up as in reaction of **3** with benzylideneacetone. Data are reported in Figure 4 and tabulated in Table S-4.[31]

Benzaldehyde Trapping Studies: Retro-Aldol. To a 5 mL nitrogen-purged long-necked RBF was added 69 mg (0.26 mmol)of **4**, 100 μL of benzaldehyde (1.0 mmol), and 3 mL of THF. The solution was cooled to −78 °C under positive nitrogen pressure and metalated with 260 μL of 1.0 M $LiN(SiMe_3)_2$ (0.26 mmol). The resulting solution was stirred for the appropriate time and quenched with 100 μL of 3 M propionic acid in diethyl ether. The solution was worked up as in reaction of **3** with benzylideneacetone. Data are tabulated in Table S-5.[31]

Benzaldehyde Trapping Studies: Control Experiment. Phenylacetonitrile (29 μL, 0.25 mmol) was added to a nitrogen-purged 5 mL, long-necked, round-bottom flask. Three milliliters of dry THF was added, the system was cooled to −78 °C under positive nitrogen pressure, and 90 μL (0.25 mmol) of 2.83 M *n*-BuLi was added. A mixture of benzaldehyde and benzylideneacetone (0.5 mmol each in 500 μL of THF) was injected into the flask and quenched after 2 min with 200 μL of 3 M propionic acid in diethyl ether. The solution was worked up as in the reaction of **3** with benzylideneacetone. The ratio of **11**/**4** was >99:1, as determined by ^{1}H NMR integration of doublets at δ 4.97−4.93 compared to singlets at δ 3.95 and 3.93.

***m*-Methoxy Crossover Studies: Retro-Michael Trapping.** Phenylacetonitrile (58 μL, 0.50 mmol) and 6 mL of THF were added to a nitrogen-purged flask, the flask was cooled to −78 °C under positive nitrogen pressure, and 0.190 mL (0.5 mmol) of 2.62 M *n*-BuLi was added. The reaction was allowed to stir 20 min to ensure complete metalation, and 200 μL (0.5 mmol) of 2.5 M benzylideneacetone solution in THF was added. The solution was allowed to warm to 0 °C for 1 h to generate **10** in situ. The solution was cooled to the appropriate temperature with an $EtOH/CO_2$ or ice bath, and a solution of **12** (1 mmol in 12 mL of THF) was added via cannula. Samples (3 mL) were withdrawn from the stock solution at various times with a jacketed syringe cooled below the sample temperature and were quenched with 200 μL of 3 M propionic acid (0.6 mmol) in ether. The solution was worked up as in the reaction of **3** with benzylideneacetone. Data are displayed in Figure S-1. The rate constant data and Eyring plot are shown in Figure S-2.

Long-Term Experiment at −78 °C. A similar experiment (3 mL of THF; 29 μL, 0.25 mmol of **3**; 0.100 mL, 0.25 mmol of *n*-BuLi; 0.25 mmol of benzylideneacetone; 0.50 mmol of **12**) was performed in a flask equipped with a stopcock (Schlenk flask) at −78 °C for 120.5 h, and quenched with 60 μL of acetic acid-*d*. The solution was worked up as in the reaction of **3** with benzylideneacetone. Analysis by ^{1}H NMR showed a 78:22 ratio of ***d*-10**:***h*-10** by loss of integration at δ 3.17−2.90, so the reaction mixture had been quenched to the extent of 22%. The level of *m*-methoxy incorporation (**13**) was determined to be 0.4% by line shape simulation of quantitative spectra and integration relative to the ^{13}C satellites of **10** as a standard.

Test for Proton Transfer To Form 14. A solution of phenylacetonitrile (87 μL, 0.75 mmol) in 3 mL of THF in a nitrogen-purged flask was cooled to −78 °C and metalated with 0.29 mL (0.75 mmol) of 2.6 M *n*-BuLi. The reaction was allowed to stir 20 min, 250 μL of 1.0 M (0.25 mmol) of benzylideneacetone solution in THF was added, and the flask was warmed to 0 °C for 2 h to generate **10** in situ and quenched with 50 μL of acetic acid-*d* (DOAc). The solution was worked up as in the reaction of **3** with benzylideneacetone. The ^{1}H NMR spectrum showed 84% deuteration α to the ketone by integration of the AB quartet signals at δ 3.15 and 2.98, and integration of the ^{2}H NMR spectrum showed a ***d*-10**/***d*-14** ratio of >98:2 by integration of peaks at δ 3.15 and 2.98 compared to the α-cyano protons peaks at δ 4.35 and 4.07.

Sample Reaction of 17-H with Mesityl Oxide. Methoxyphenylacetonitrile (37 mg, 0.25 mmol) was added to a 5 mL, long-necked, round-bottom flask, the flask was purged with nitrogen, 3 mL of dry THF was added, and the system was cooled to −78 °C under positive nitrogen pressure. *n*-BuLi (95 μL of 2.65 M, 0.25 mmol) was added, the mixture was stirred for 20 min, and 100 μL of 2.5 M mesityl oxide in THF was injected. The solution was stirred for the indicated time, quenched with 200 μL of 3 M propionic acid in diethyl ether, and worked up as in reaction of **3** with benzylideneacetone. Data are displayed in Figure 6 and in Table S-6.[31]

Acknowledgment. We thank the National Science Foundation (Grant Nos. CHE-0074657 and CHE-0349635) for support of this research. This material is available free of charge via the Internet at http://pubs.acs.org.

Supporting Information Available: Preparation of starting materials, tables of data for the kinetic experiments, characterization data and NMR spectra of reaction products (**4**, **5**, **11**, **20-X**, **21-X**). This material is available free of charge via the Internet at http://pubs.acs.org.

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