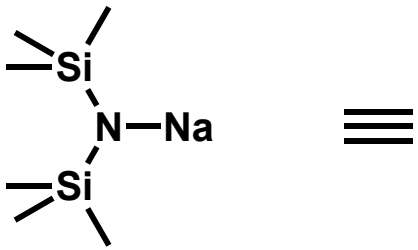
Enolization using NaHMDS

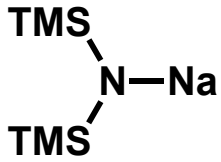
2022.4.9. Literature Seminar
M2 Hibiki Asai

Contents

NaHMDS



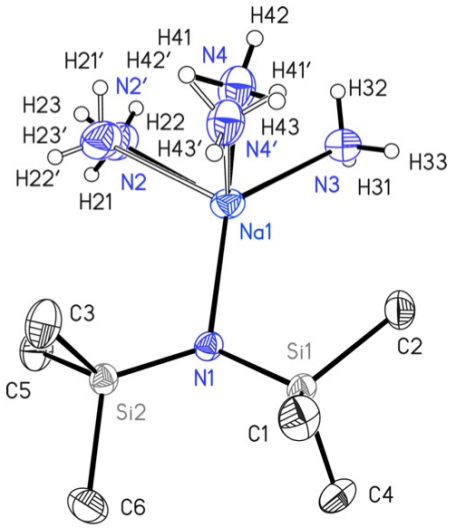
≡

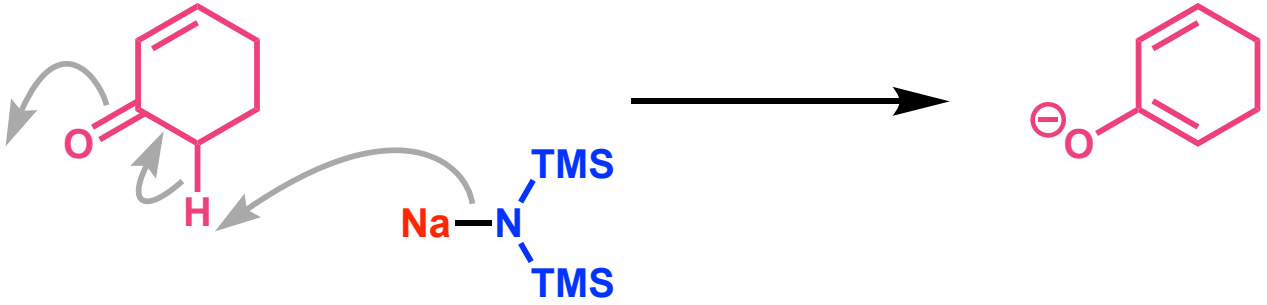


≡ NaHMDS

pKa = 29.5 [1)]
melting point: 165~167 °C [2)]
boiling point: 202 °C (1.5 mmHg) [2)]

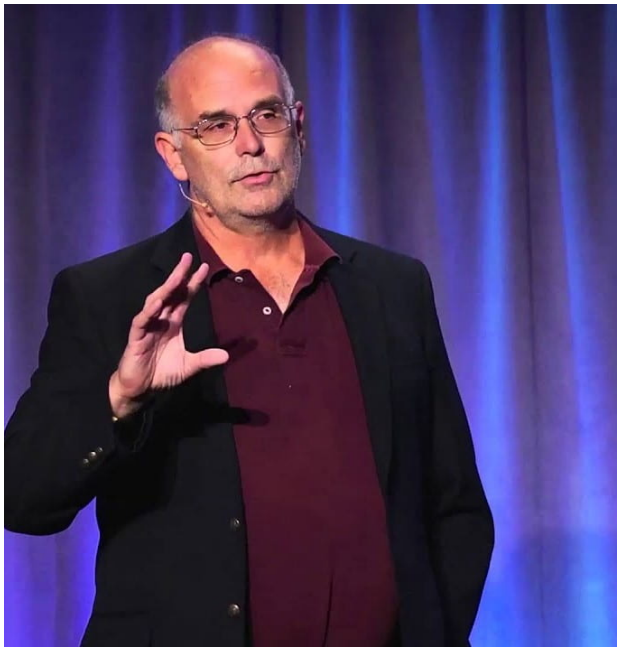
$(Et_3N)_3NaN(SiMe_3)_3$ [3)]





1) Shinkai, S.; Inuzuka, K.; Miyazaki, O.; Manabe, O. *J. Org. Chem.* **1984**, *49,* 3442. 2) Wannagat, U. Zeitschrift fuer Anorganische und Allgemeine Chemie, **1964**, *326*, 309. 3) Neufeld, R.; Michel, R.; Herbst-Irmer, R.; Schöne, R.; Stalke, D. *Chem. Eur. J.* **2016**, *22*, 12340.

Introduction of Prof. Collum



Prof. David B Collum
1977 B.S. @ Cornell University
1980 Ph.D @ Columbia University (Prof. W. Clark Still)

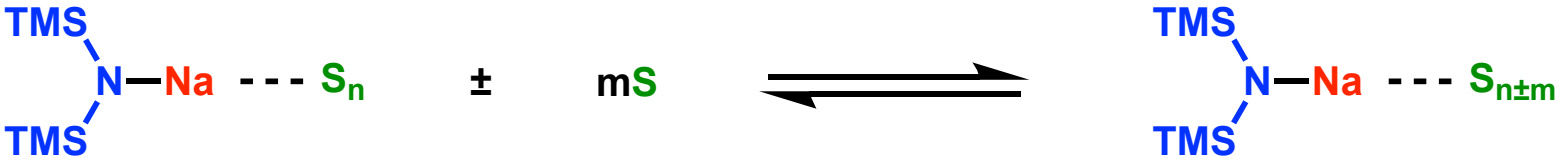
Professor @ Cornell University

Research topic: physical organic chemistry, organolithium chemistry, organosodium chemistry, kinetics and reaction mechanism

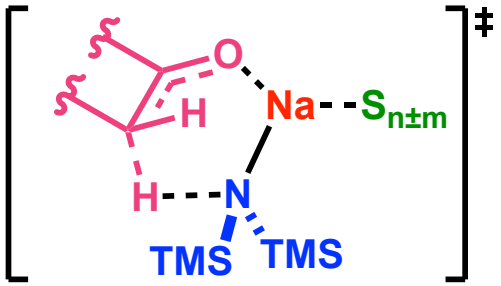
Contents

Mechanism A: Monomer to Monomer

S: solvent

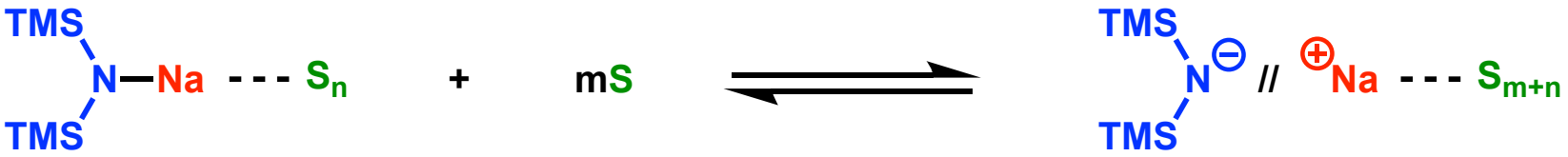


$$-\frac{d}{dt}[ketone] \propto [(TMS)_2NNaS_n]^{1}[ketone]^{1}[S]^{\pm m}$$

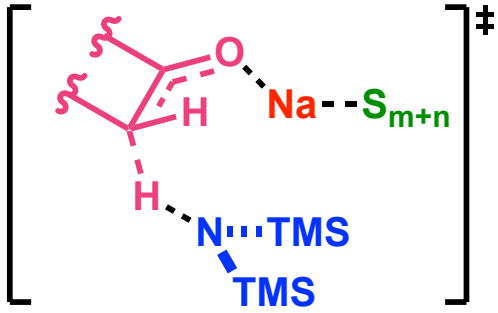


Mechanism B: Monomer to Ion Pair

S: solvent

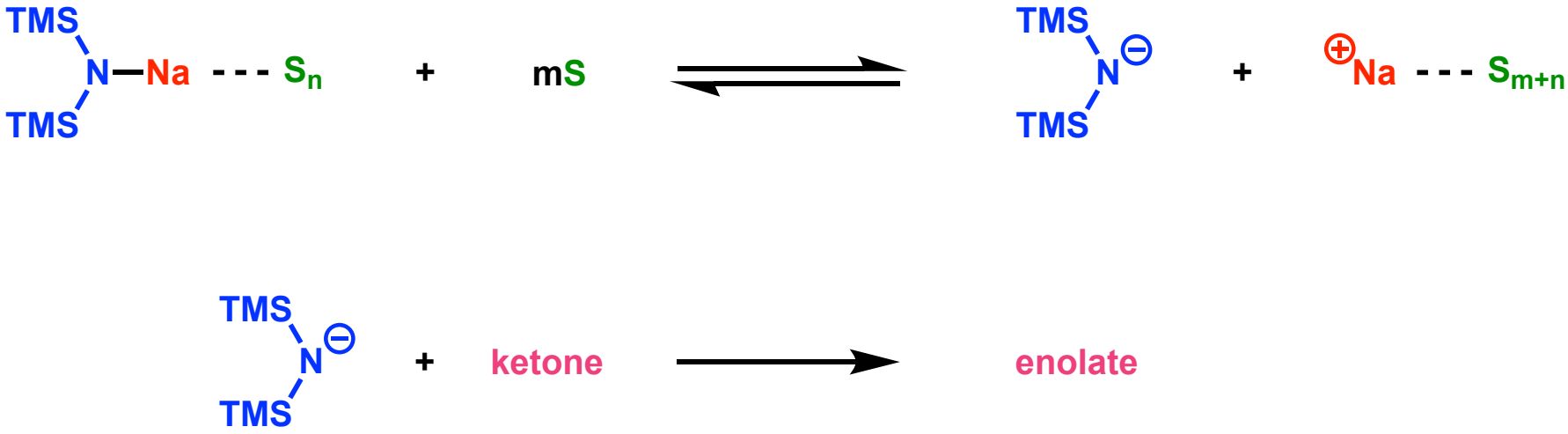


$$-\frac{d}{dt}[ketone] \propto [(TMS)_2NNaS_n]^{1}[ketone]^{1}[S]^{m}$$

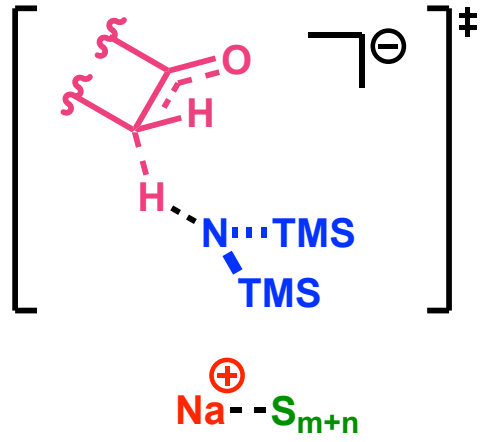


Mechanism C: Monomer to Free Ion

S: solvent

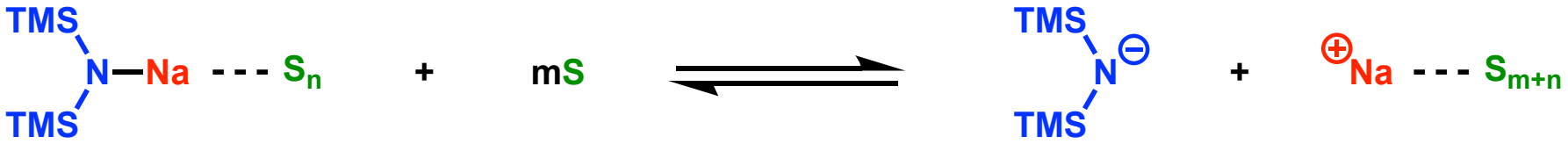


$$-\frac{d}{dt}[ketone] \propto [(TMS)_2NNaS_n]^{\frac{1}{2}}[ketone]^1[S]^{\frac{m}{2}}$$



Mechanism C: Monomer to Free Ion

S: solvent



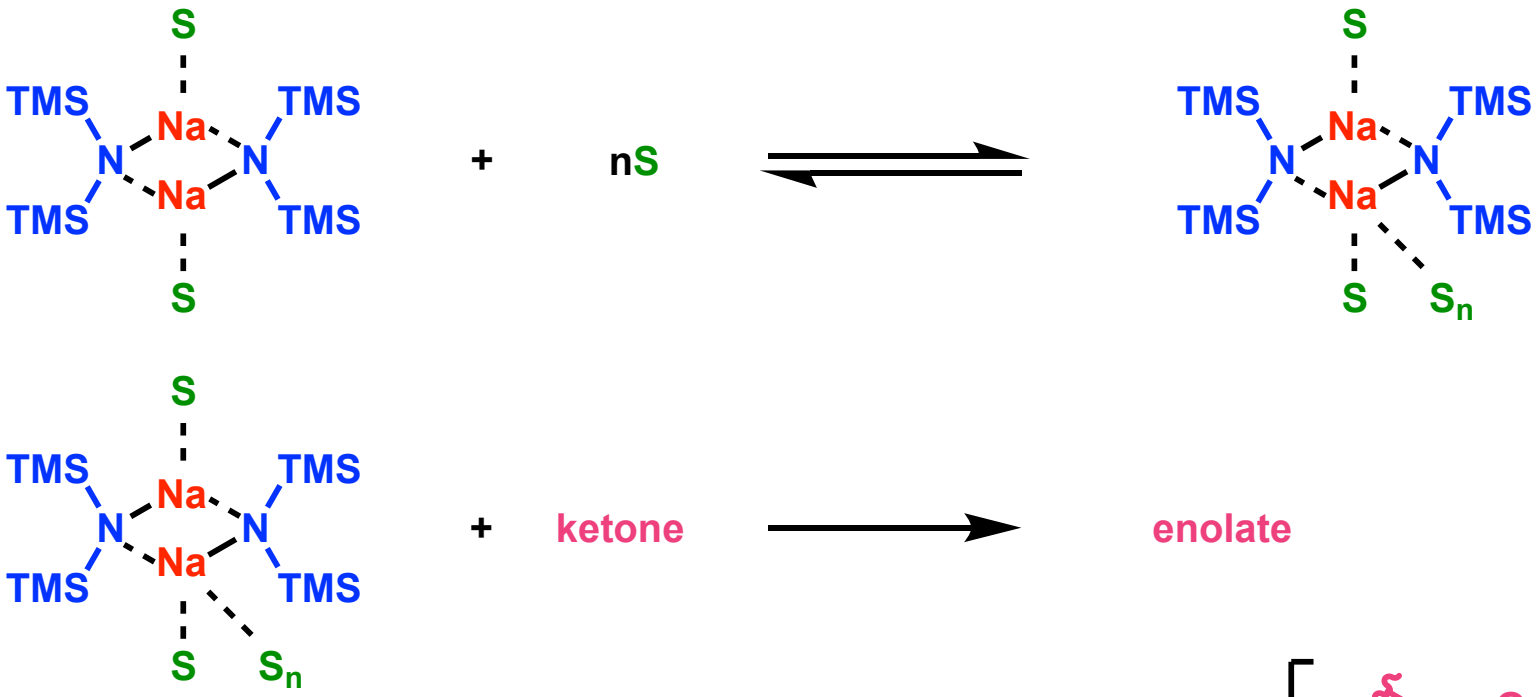
$$\begin{cases} K_{eq} = \dfrac{[(TMS)_2N^-][Na^+S_{m+n}]}{[(TMS)_2NNaS_n][S]^m} \\ [(TMS)_2N^-] = [Na^+S_{m+n}] \end{cases}$$

$$\therefore\ K_{eq} = \frac{[(TMS)_2N^-]^2}{[(TMS)_2NNaS_n][S]^m}, \qquad [(TMS)_2N^-] = K_{eq}^{\frac{1}{2}}[(TMS)_2NNaS_n]^{\frac{1}{2}}[S]^{\frac{m}{2}}$$

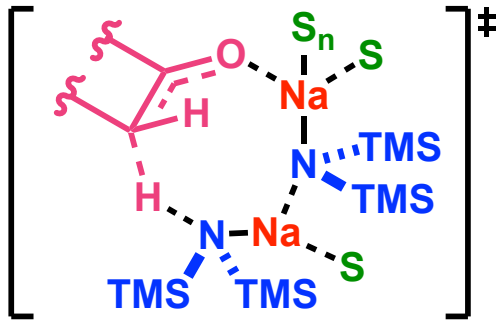
$$-\frac{d}{dt}[ketone] \propto [(TMS)_2N^-]\,[ketone] = [(TMS)_2NNaS_n]^{\frac{1}{2}}[ketone]^1[S]^{\frac{m}{2}}$$

Mechanism D: Dimer to Dimer

S: solvent

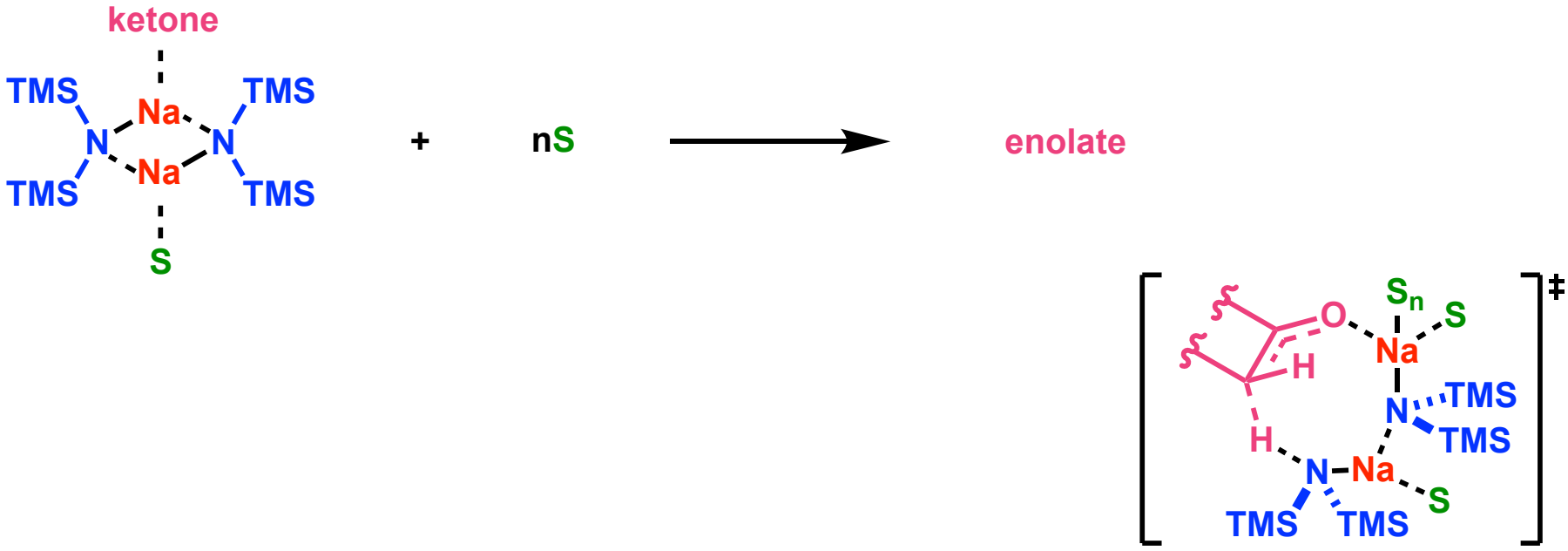


$$-\frac{d}{dt}[ketone] \propto [((TMS)_2N)_2Na_2S_2]^{1}[ketone]^{1}[S]^{n}$$



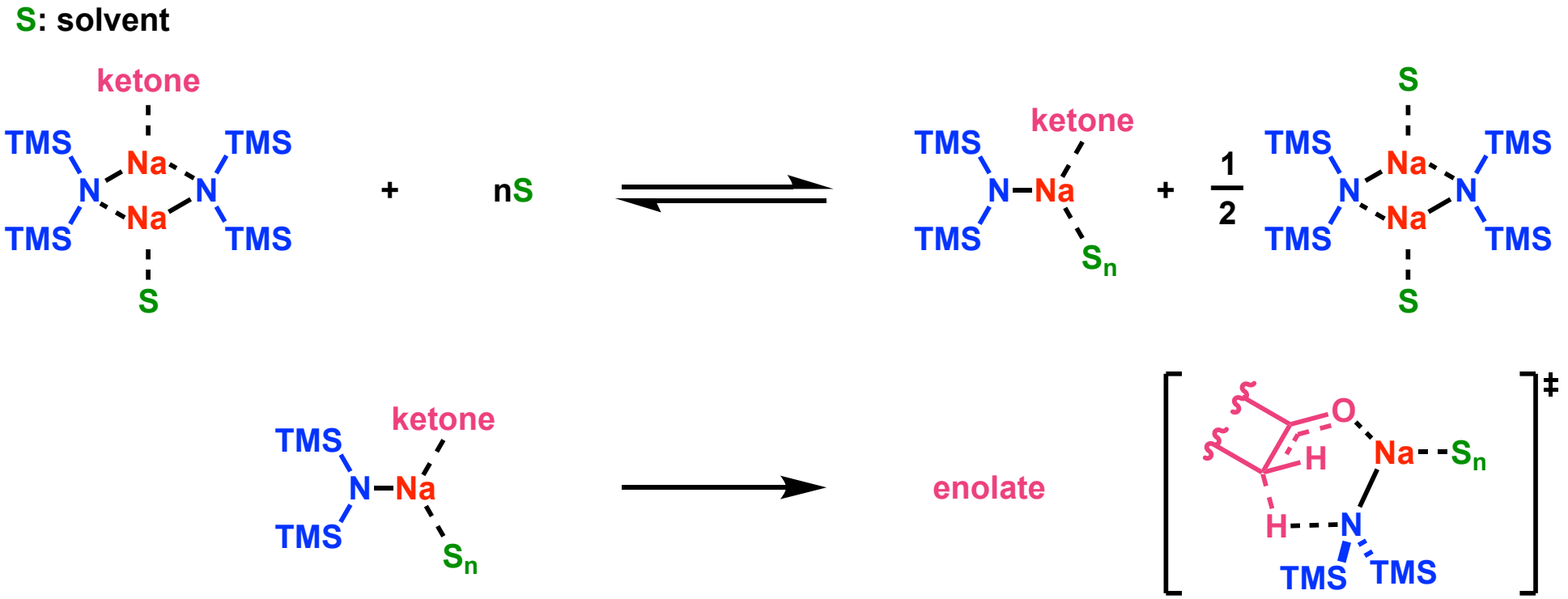
Mechanism E: Complexed Dimer to Dimer

S: solvent



$$-\frac{d}{dt}[ketone] \propto [((TMS)_2N)_2Na_2Sketone]^{1}[((TMS)_2N)_2Na_2S_2]^{0}[S]^{n}$$

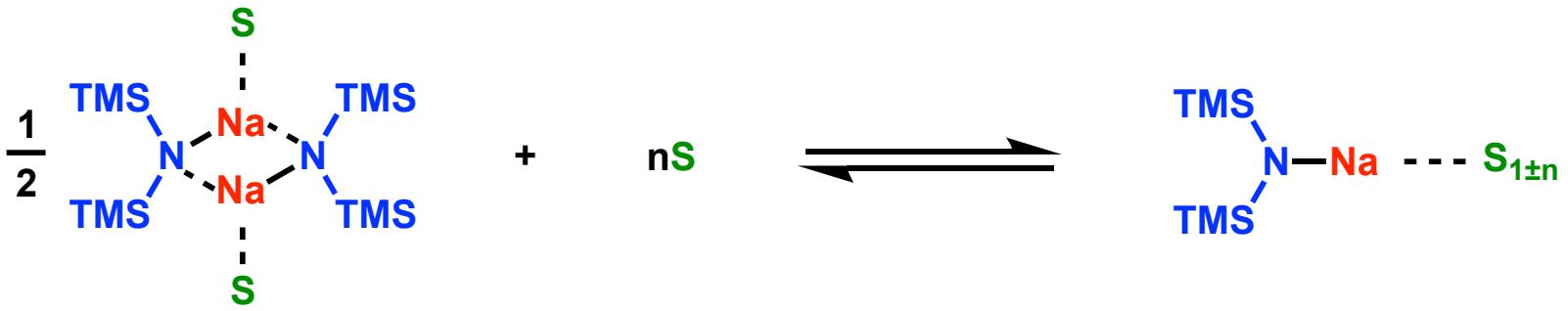
Mechanism F: Complexed Dimer to Monomer



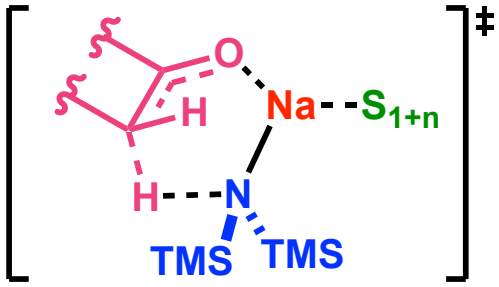
$$-\frac{d}{dt}[ketone] \propto [((TMS)_2N)_2Na_2Sketone]^{1}[((TMS)_2N)_2Na_2S_2]^{-\frac{1}{2}}[S]^{n}$$

Mechanism G: Dimer to Monomer

S: solvent

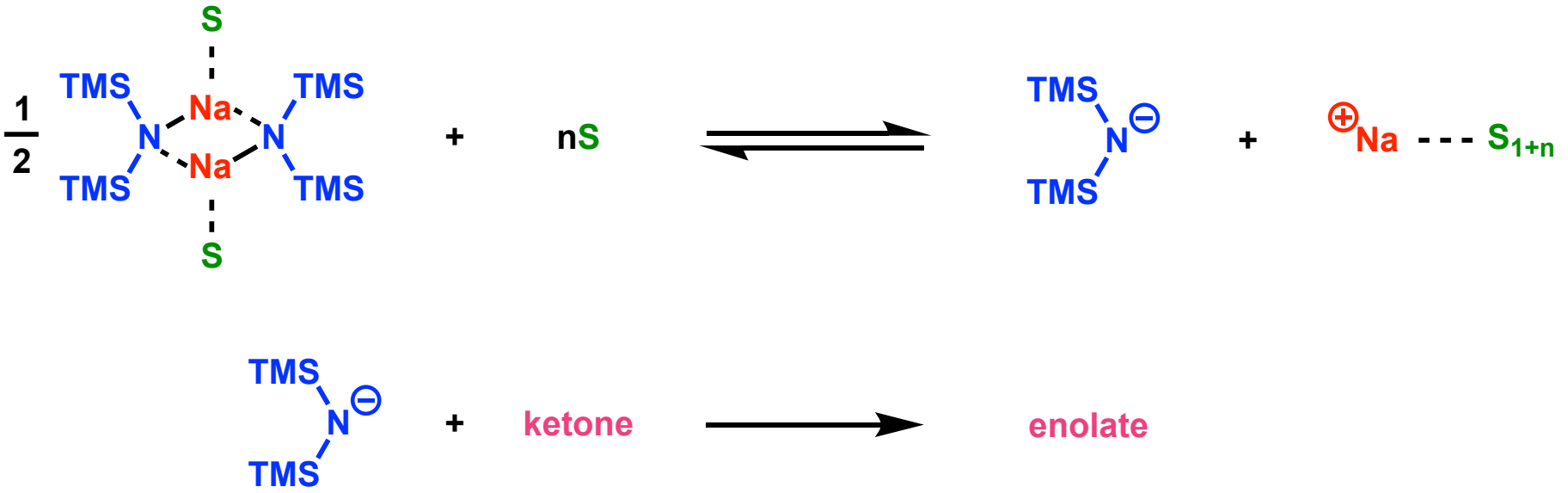


$$-\frac{d}{dt}[ketone] \propto [((TMS)_2N)_2Na_2S_2]^{\frac{1}{2}}[ketone]^1[S]^n$$

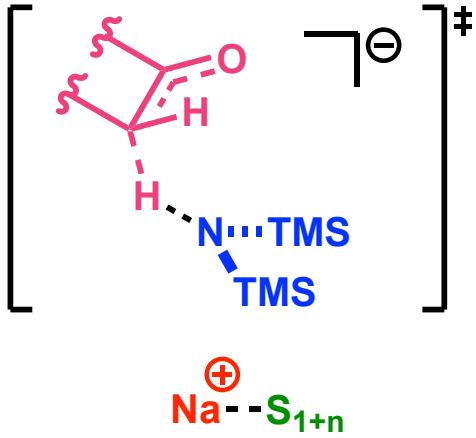


Mechanism H: Dimer to Free Ion

S: solvent

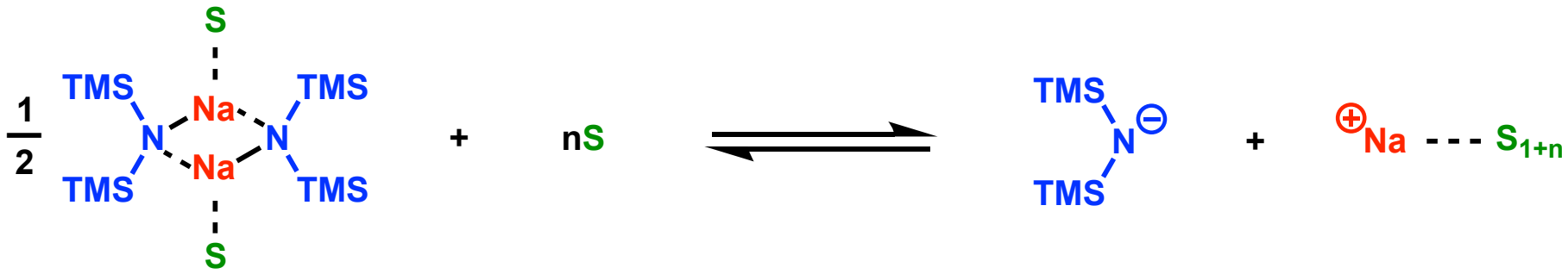


$$-\frac{d}{dt}[ketone] \propto [((TMS)_2N)_2Na_2S_2]^{\frac{1}{4}}[ketone]^1[S]^{\frac{n}{2}}$$



Mechanism H: Dimer to Free Ion

S: solvent



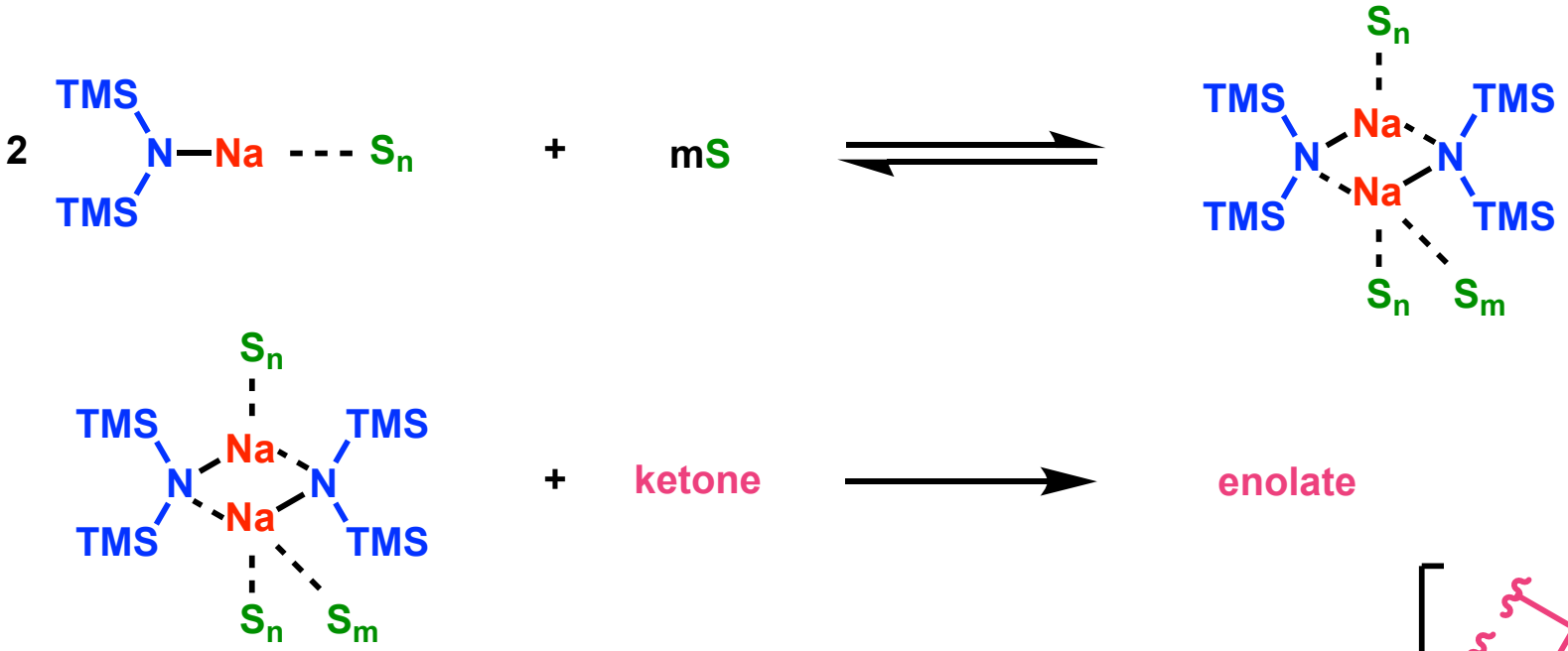
$$\begin{cases} K_{eq} = \dfrac{[(TMS)_2N^-][Na^+S_{1+n}]}{[((TMS)_2N)_2Na_2S_2]^{\frac{1}{2}}[S]^n} \\ [(TMS)_2N^-] = [Na^+S_{1+n}] \end{cases}$$

$$\therefore\ K_{eq} = \frac{[(TMS)_2N^-]^2}{[((TMS)_2N)_2Na_2S_2]^{\frac{1}{2}}[S]^n}, \qquad [(TMS)_2N^-] = K_{eq}^{\frac{1}{2}}[((TMS)_2N)_2Na_2S_2]^{\frac{1}{4}}[S]^{\frac{n}{2}}$$

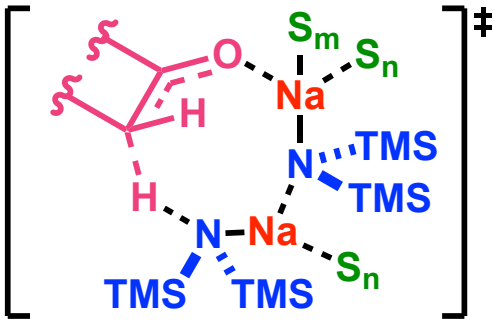
$$-\frac{d}{dt}[ketone] \propto [(TMS)_2N^-]\,[ketone] = [((TMS)_2N)_2Na_2S_2]^{\frac{1}{4}}[ketone]^1[S]^{\frac{n}{2}}$$

Mechanism I: Monomer to Dimer

S: solvent

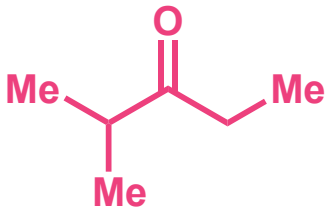


$$-\frac{d}{dt}[ketone] \propto [(TMS)_2NNaS_n]^{2}[ketone]^{1}[S]^{m}$$



Contents

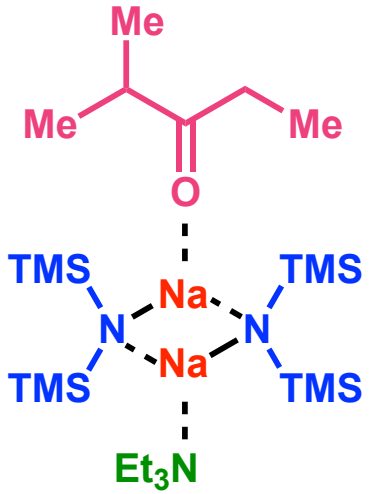
Toluene/Et_3N: Complexed Dimer



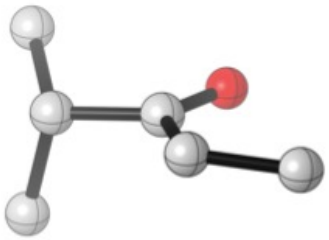
1719 cm^{-1}

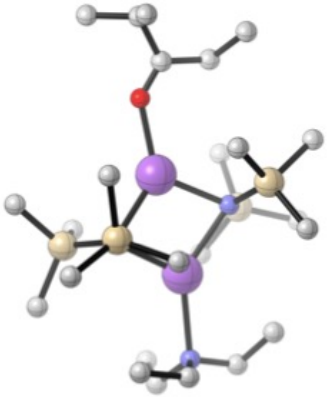
NaHMDS (toluene/Et_3N solution)

–78 °C

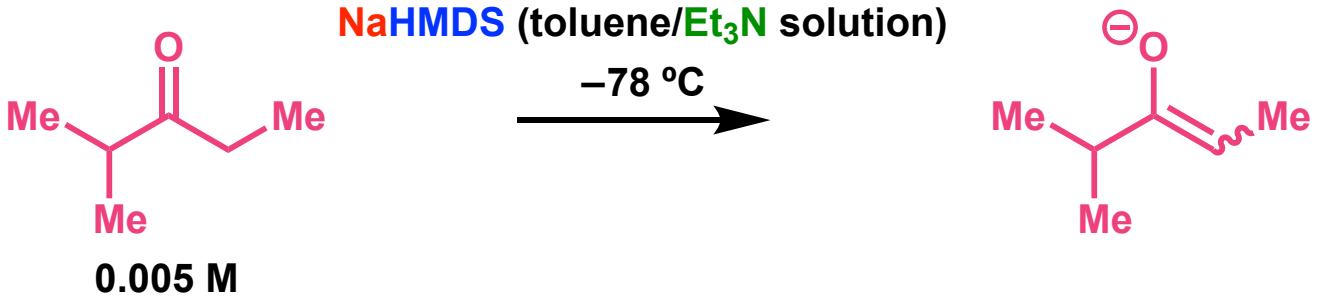


1712 cm^{-1}





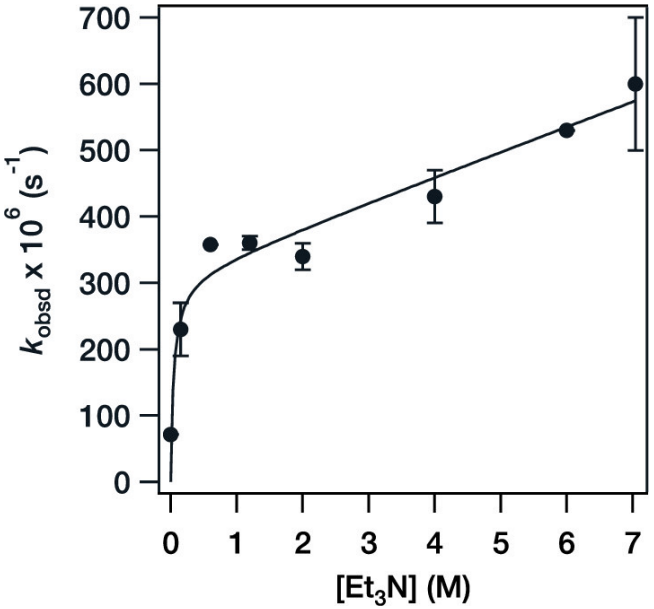
Toluene/Et_3N: In situ IR Spectroscopy



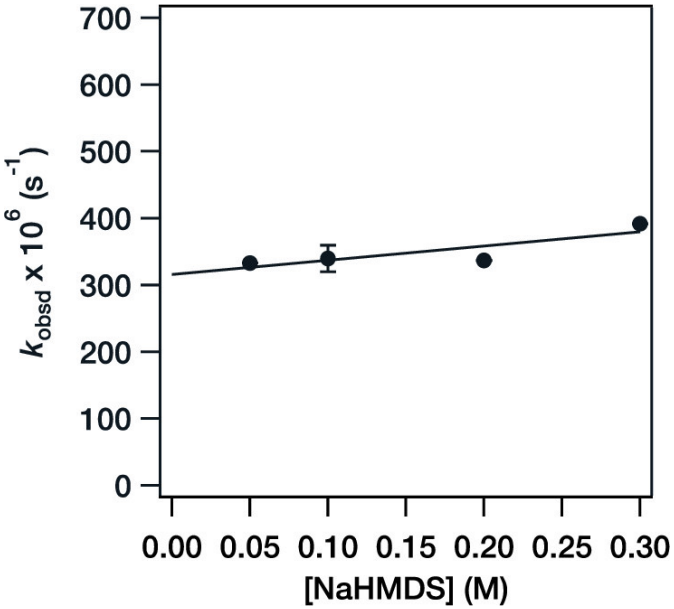
0.005 M

(1712 cm^{-1})

(1599~1610 cm^{-1})

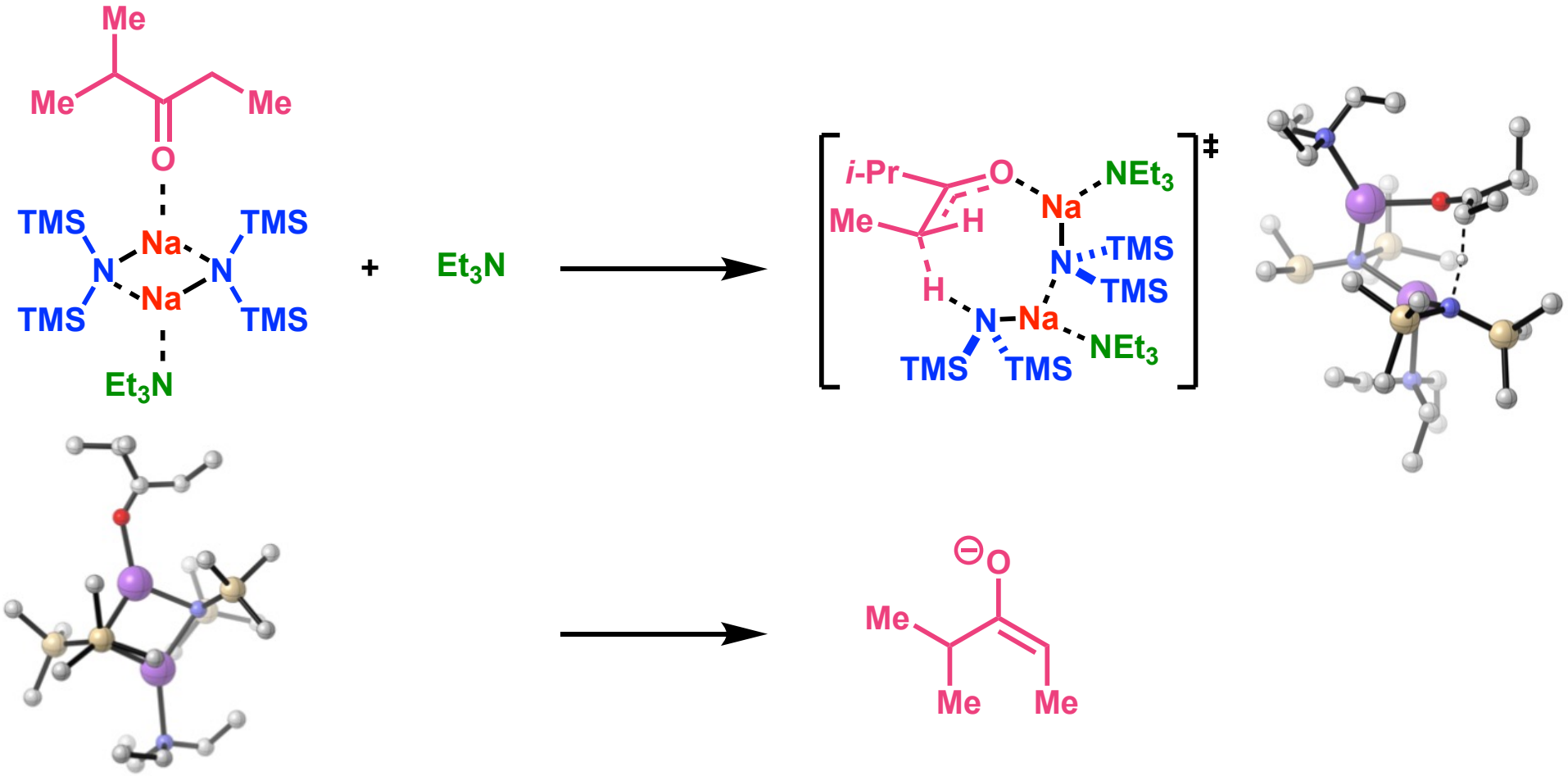


NaHMDS (0.10 M in toluene/Et_3N)



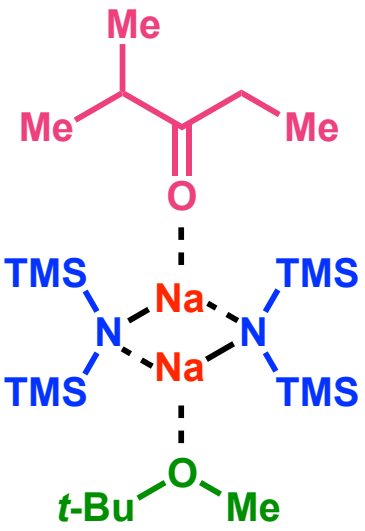
Et_3N (2 M in toluene)

Toluene/Et_3N: Mechanism E



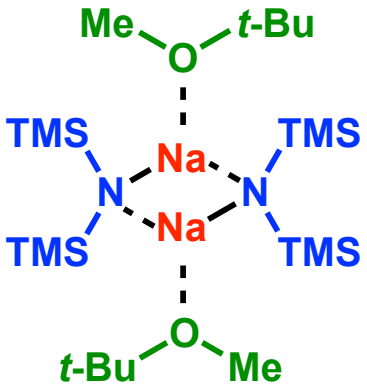
$$-\frac{d}{dt}[ketone] \propto [((TMS)_2N)_2Na_2(NEt_3)_2]^0[NEt_3]^1$$

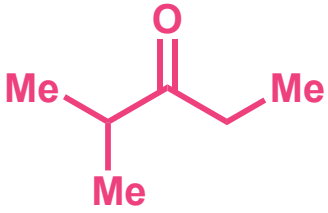
Toluene/*t*-BuOMe: Complexed Dimer



1712 cm^{-1}

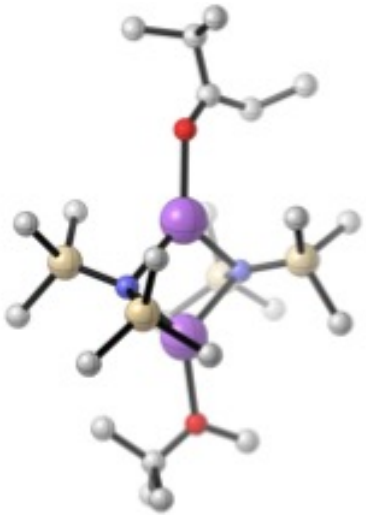
t-BuOMe



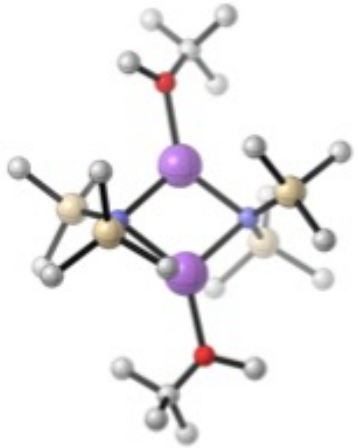


1718 cm^{-1}

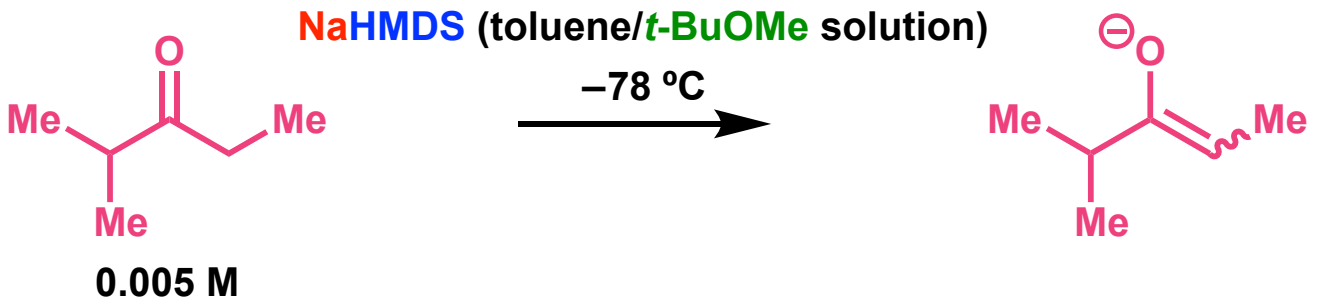
2.0 M > *t*-BuOMe

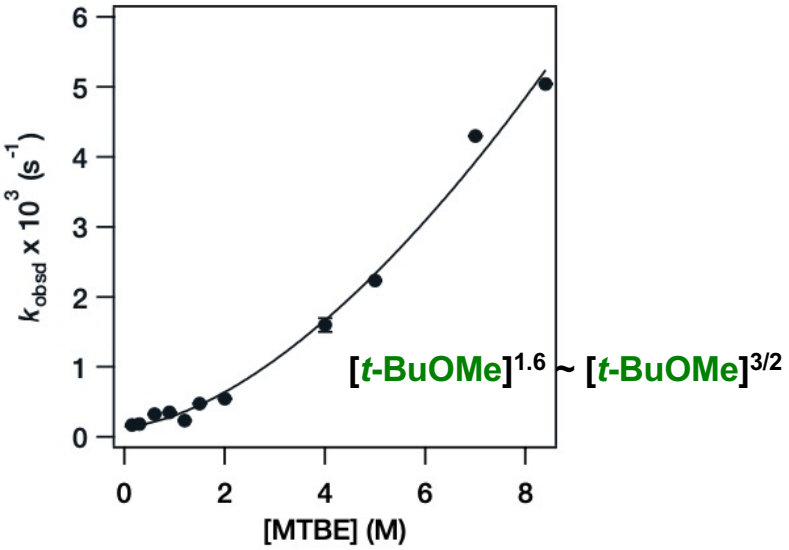


2.0 M < *t*-BuOMe

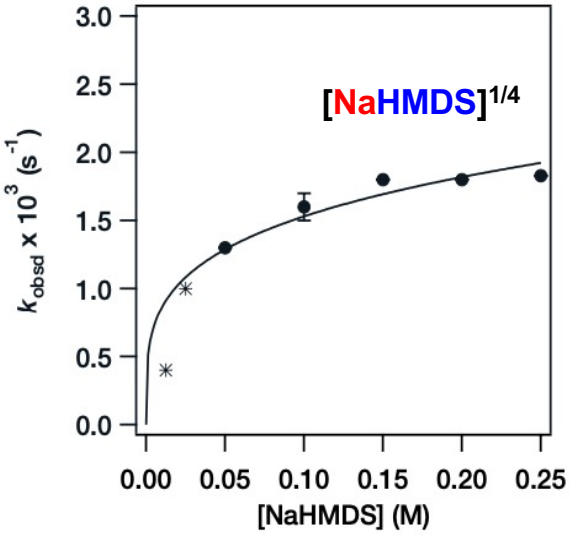


Toluene/*t*-BuOMe: In situ IR Spectroscopy



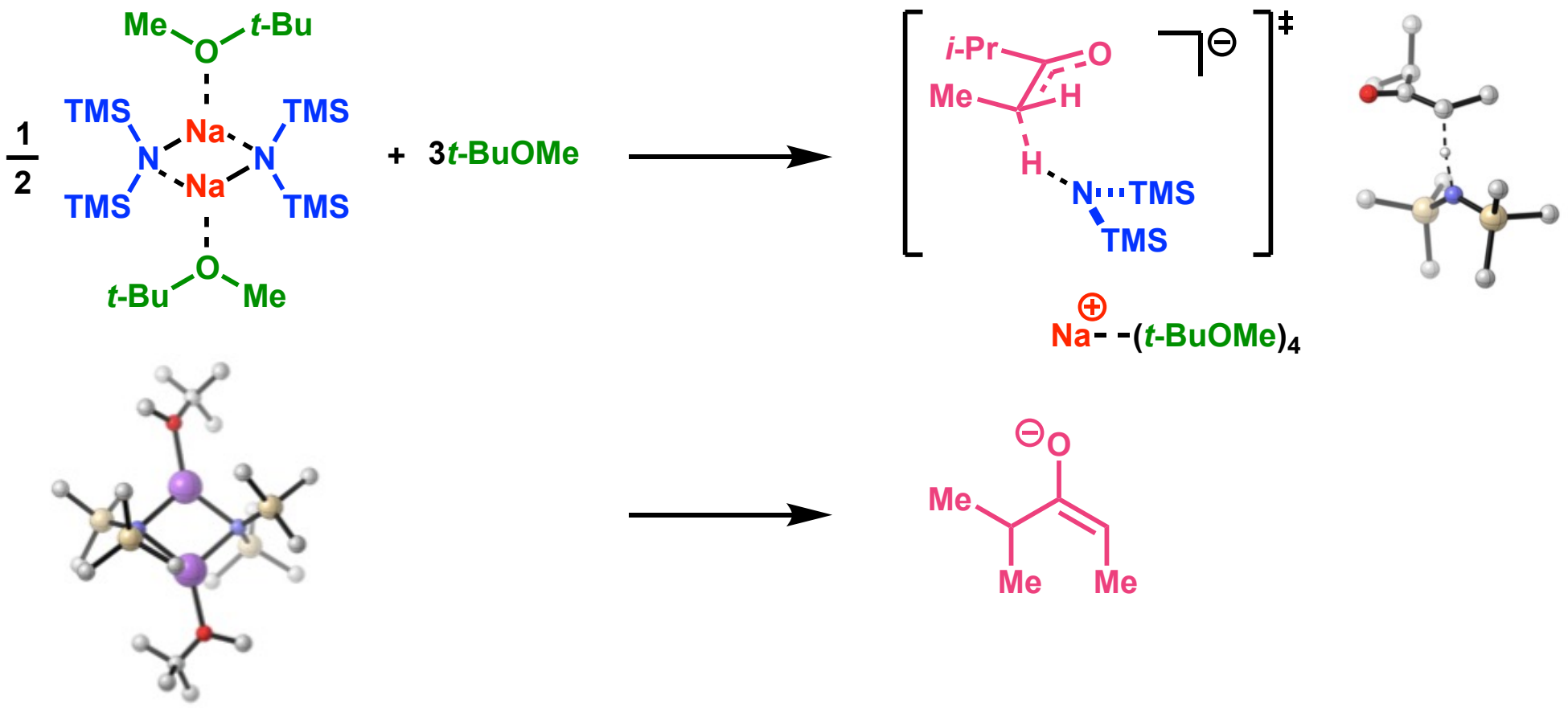


NaHMDS (0.10 M in toluene/*t*-BuOMe)



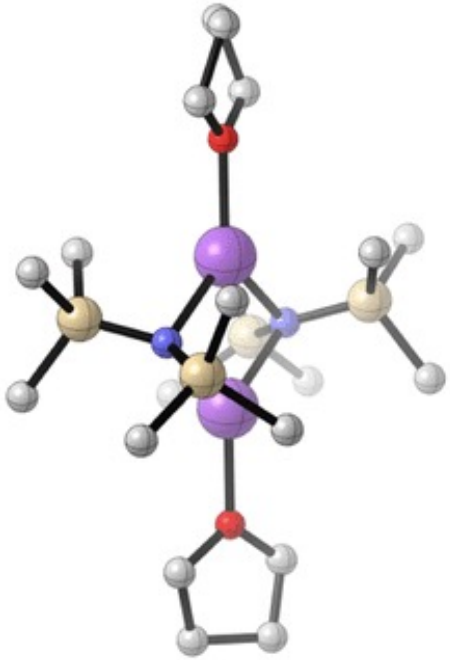
t-BuOMe (4 M in toluene)

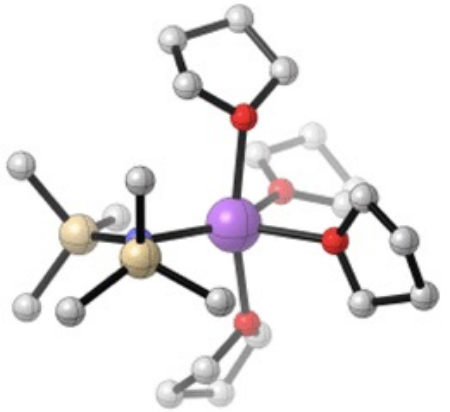
Toluene/*t*-BuOMe: Mechanism H



$$-\frac{d}{dt}[ketone] \propto [((TMS)_2N)_2Na_2(tBuOMe)_2]^{\frac{1}{4}}[tBuOMe]^{\frac{3}{2}}$$

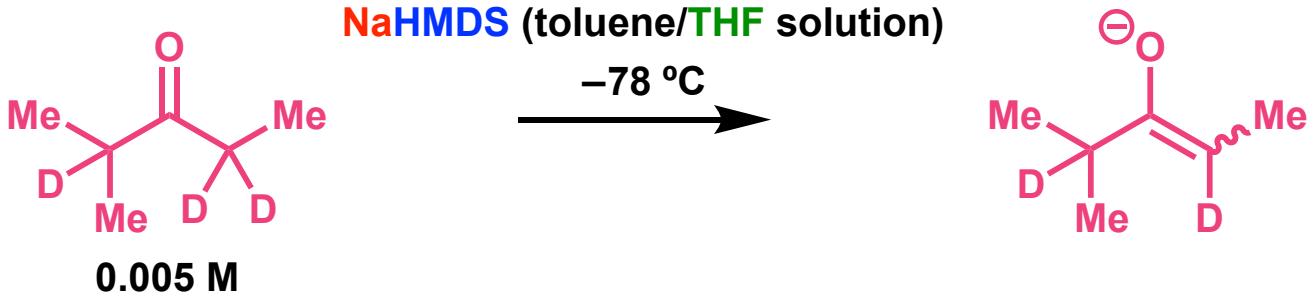
Toluene/THF: Dimer to Monomer



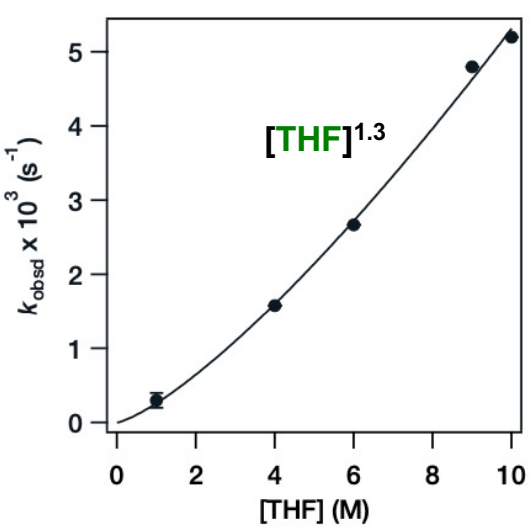


1) Woltornist, R. A.; Collum, D. B. *J. Am. Chem. Soc.* **2021**, *143*, 17452. 2) Woltornist, R. A.; Collum, D. B.*J. Org. Chem.* **2021**, *86*, 2406.

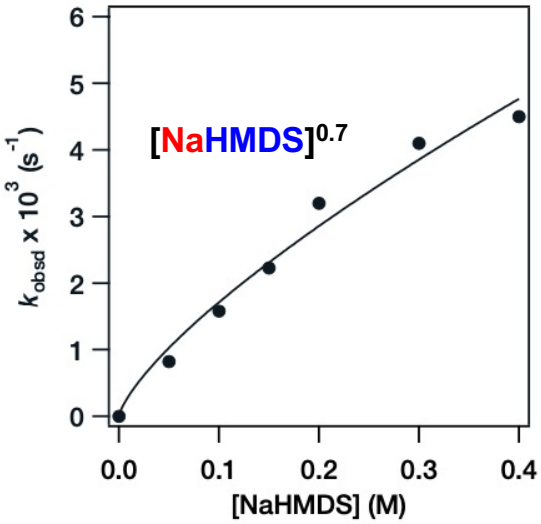
Toluene/THF: In situ IR Spectroscopy



0.005 M

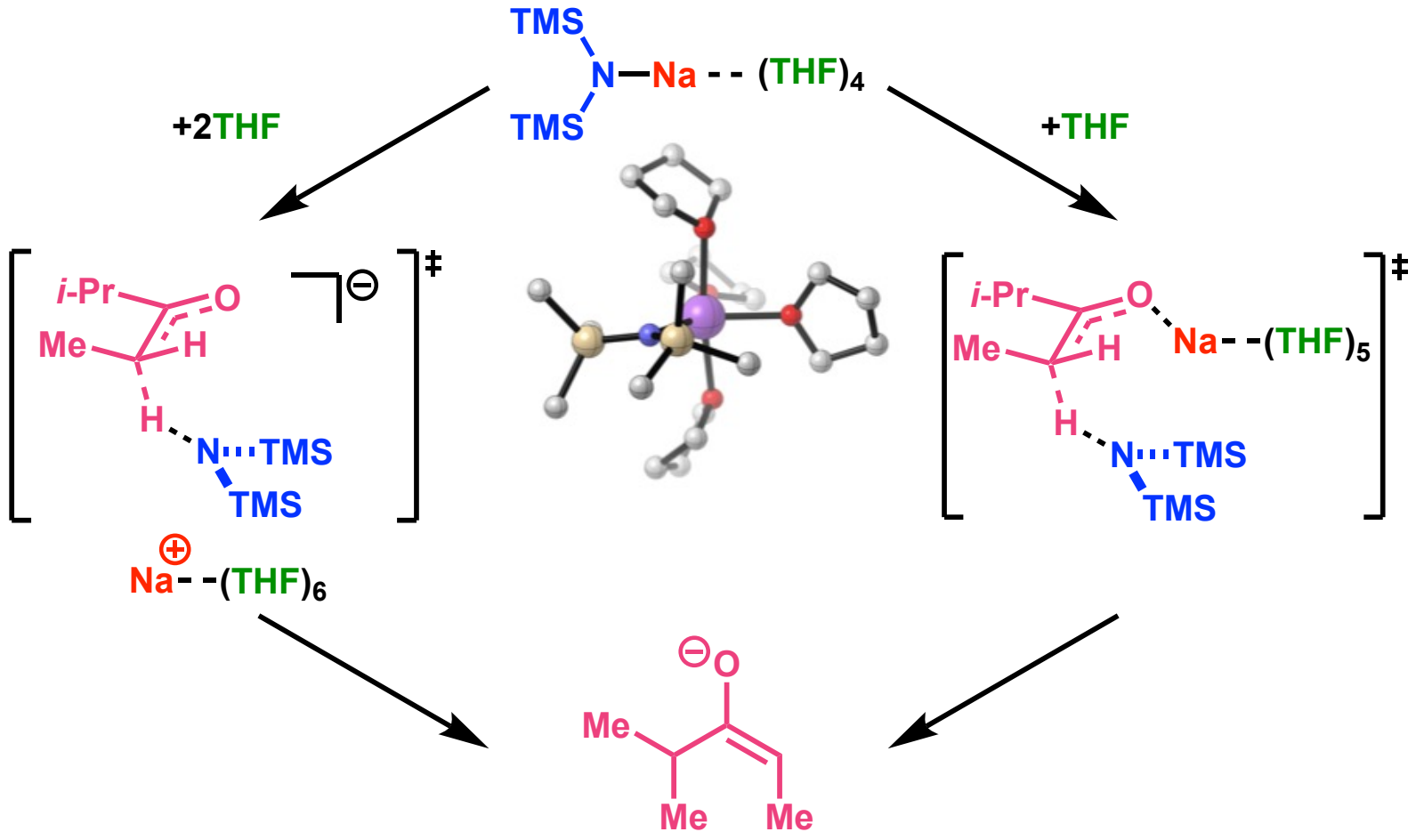


NaHMDS (0.10 M in toluene/THF)



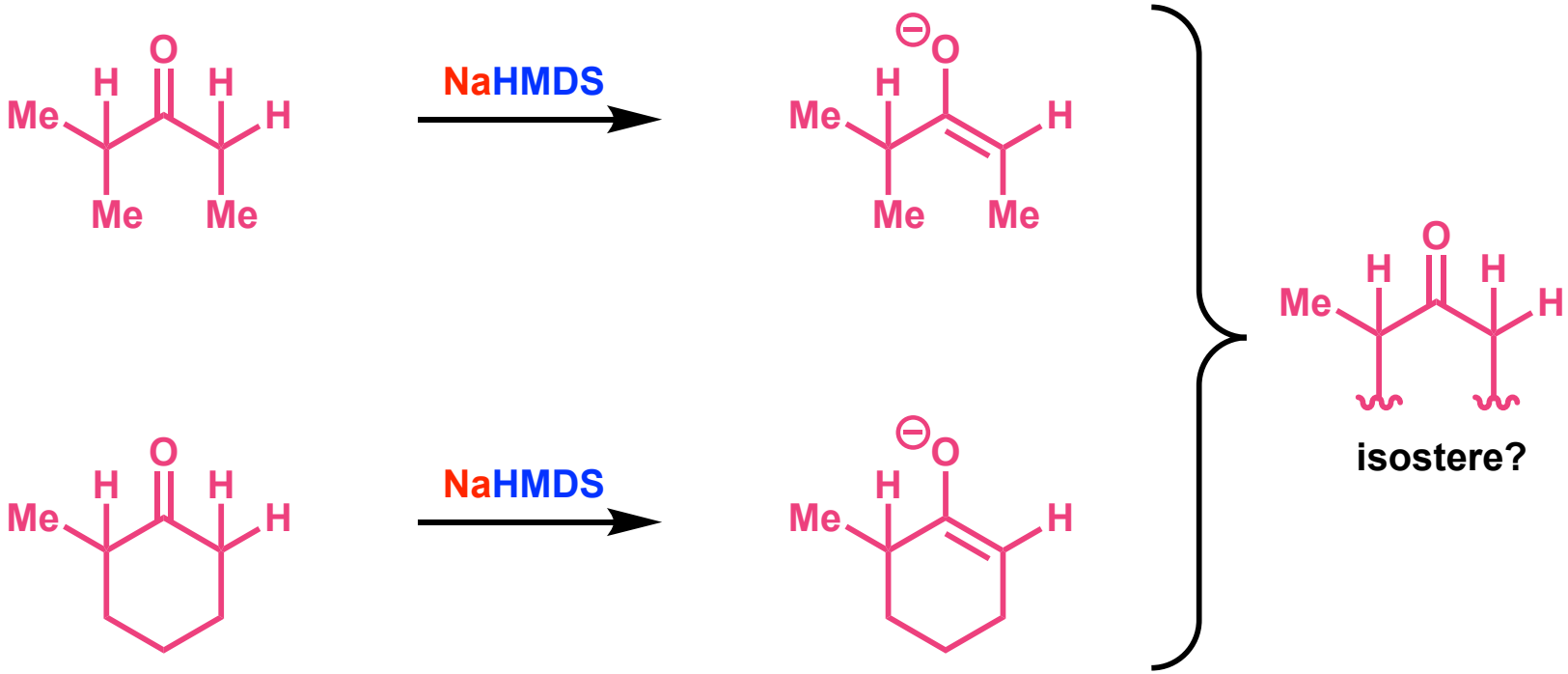
THF (4 M in toluene)

Toluene/THF: Mechanism B and C

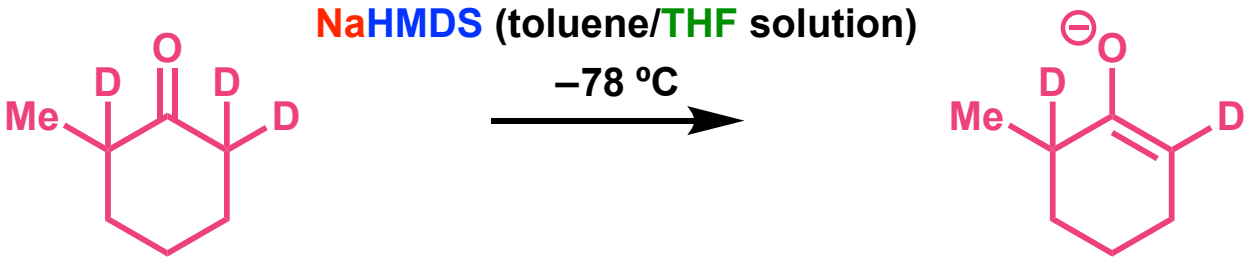


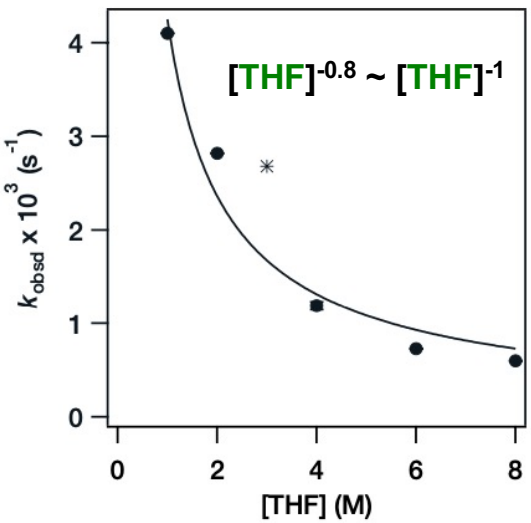
$$-\frac{d}{dt}[ketone] \propto A\left([(TMS)_2NNaS_n]^{1}[THF]^{1}\right) + B([(TMS)_2NNaS_n]^{\frac{1}{2}}[THF]^{1})$$

Toluene/THF: 2-Methylcyclohexanone

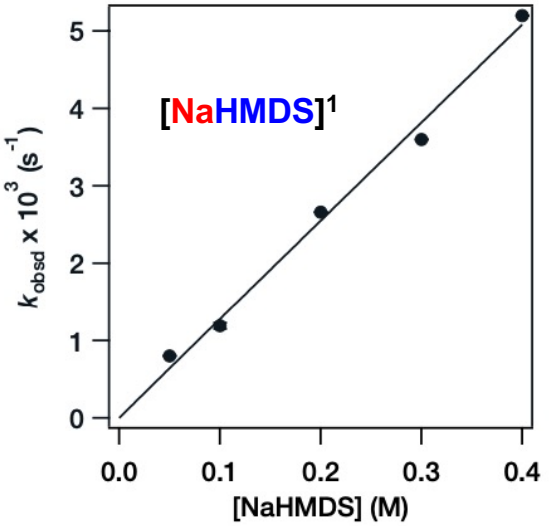


Toluene/THF: In situ IR Spectroscopy



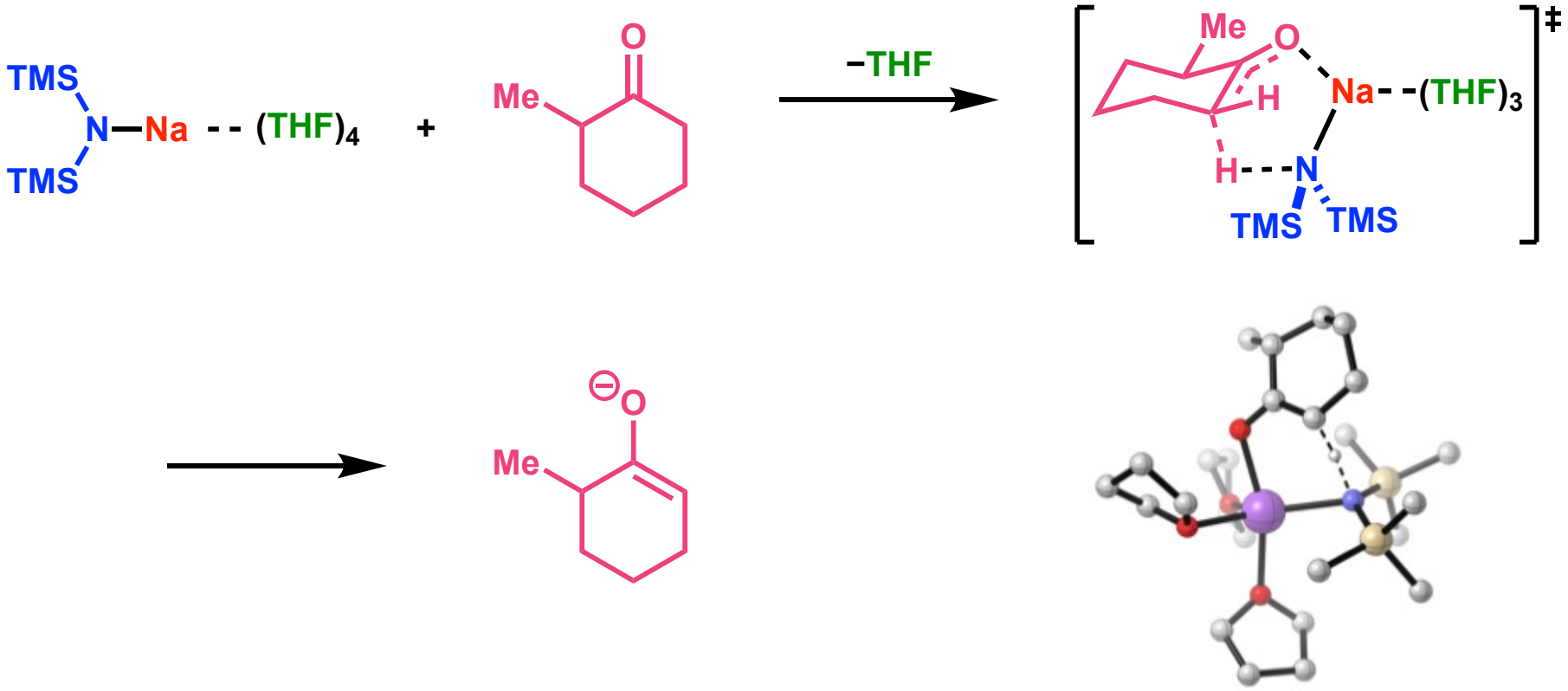


NaHMDS (0.10 M in toluene/THF)



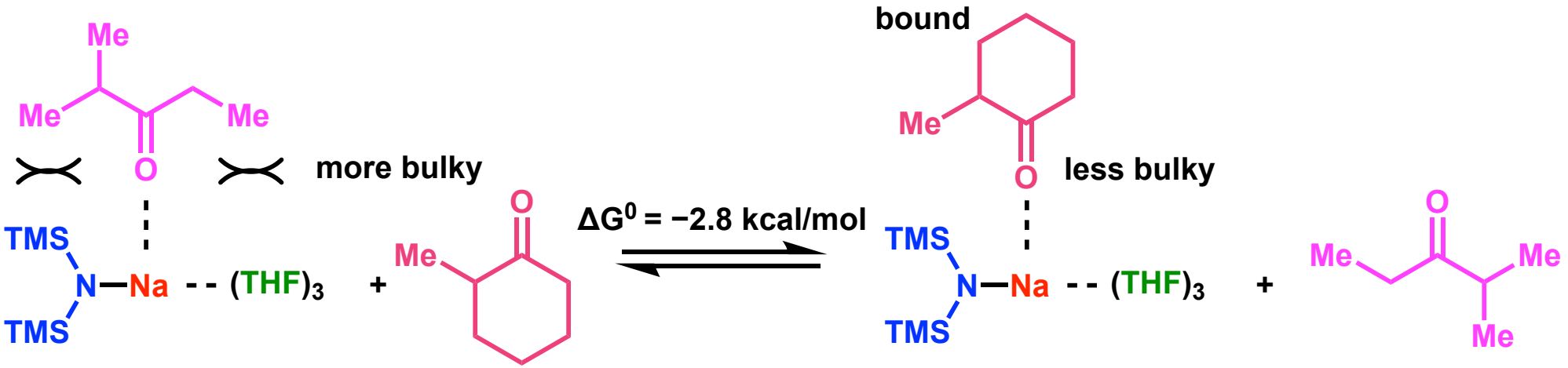
THF (4 M in toluene)

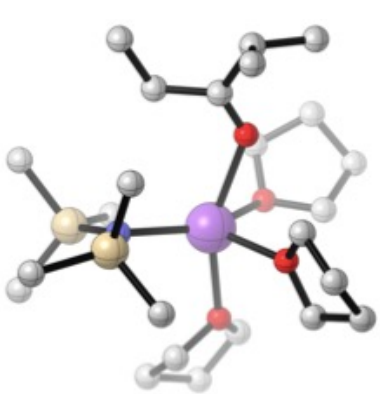
Toluene/THF: Mechanism A

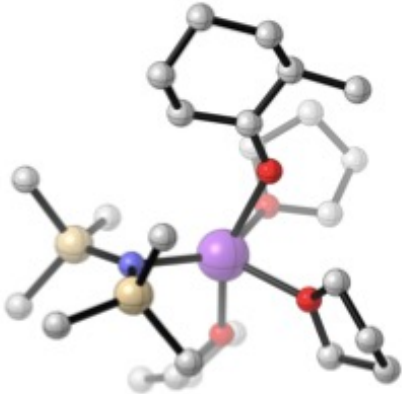


$$-\frac{d}{dt}[ketone] \propto [(TMS)_2NNa(THF)_4]^{1}[THF]^{-1}$$

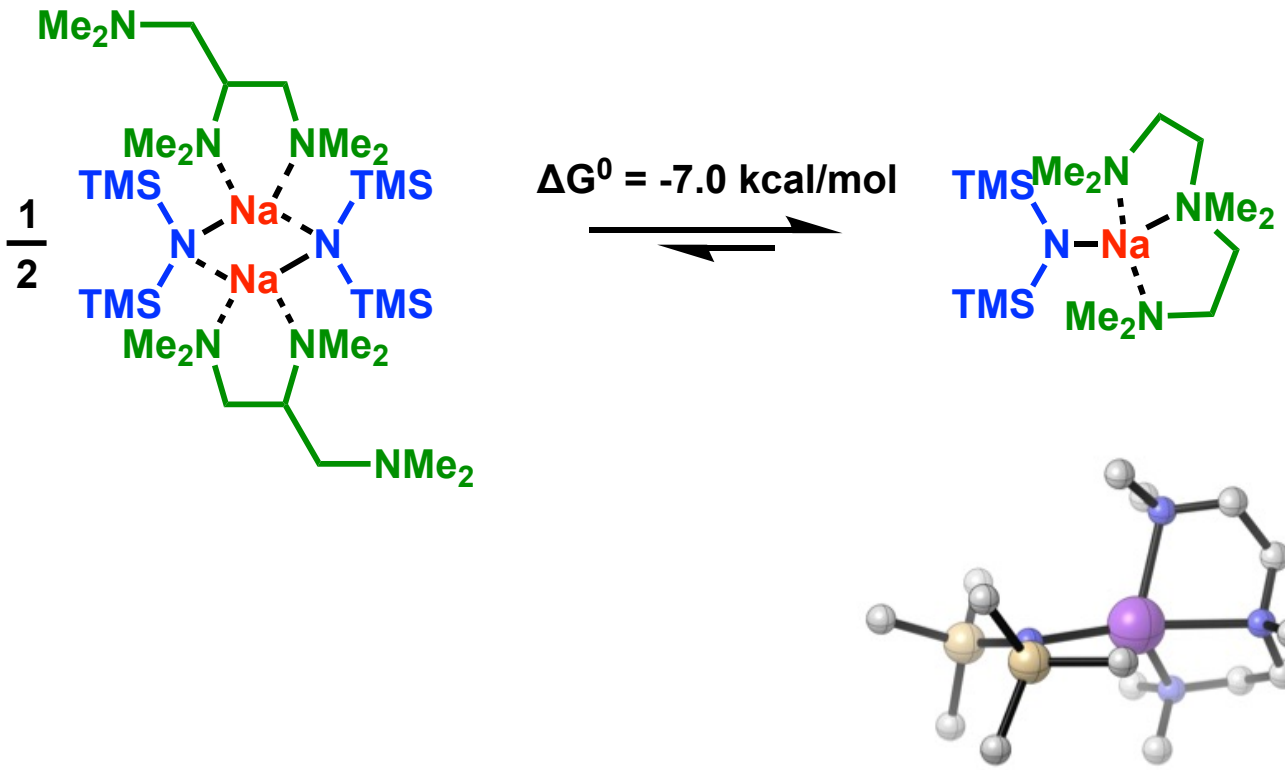
Toluene/THF: Difference between Substrates





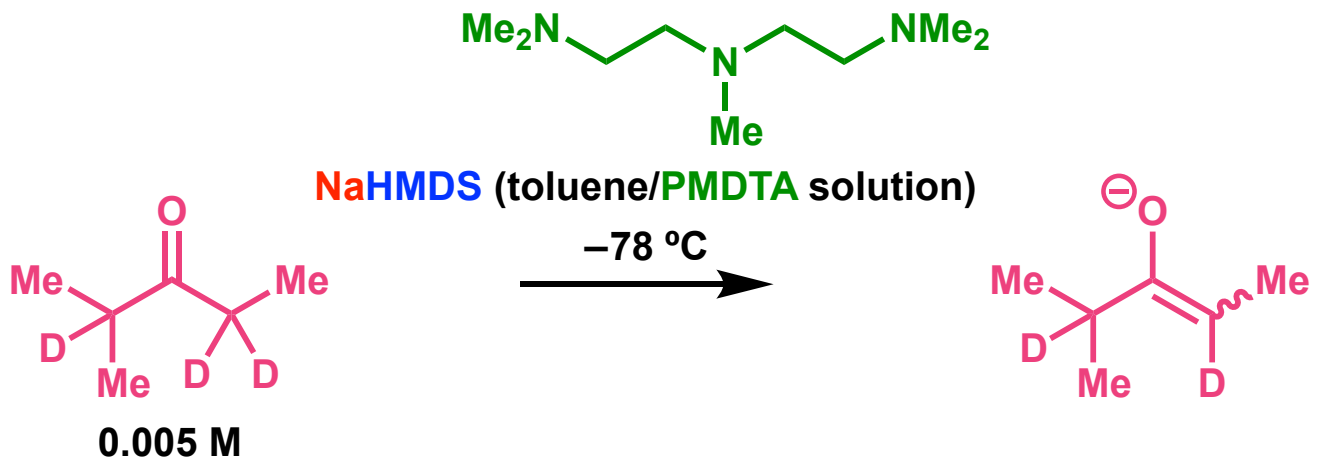


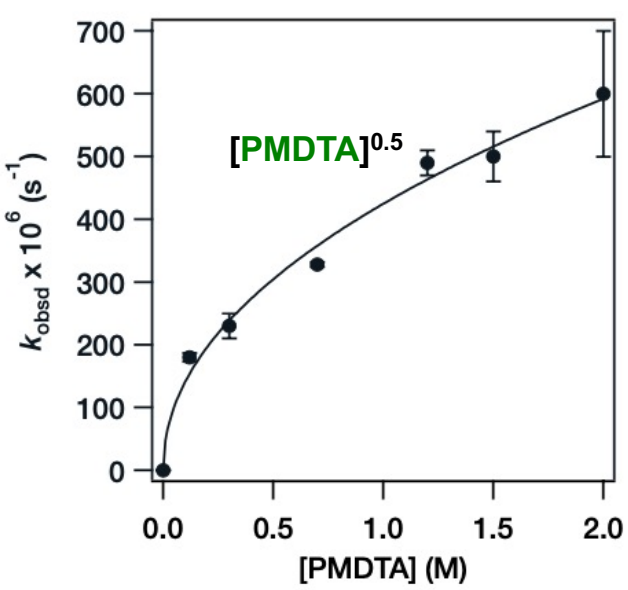
Toluene/PMDTA: Dimer to Monomer



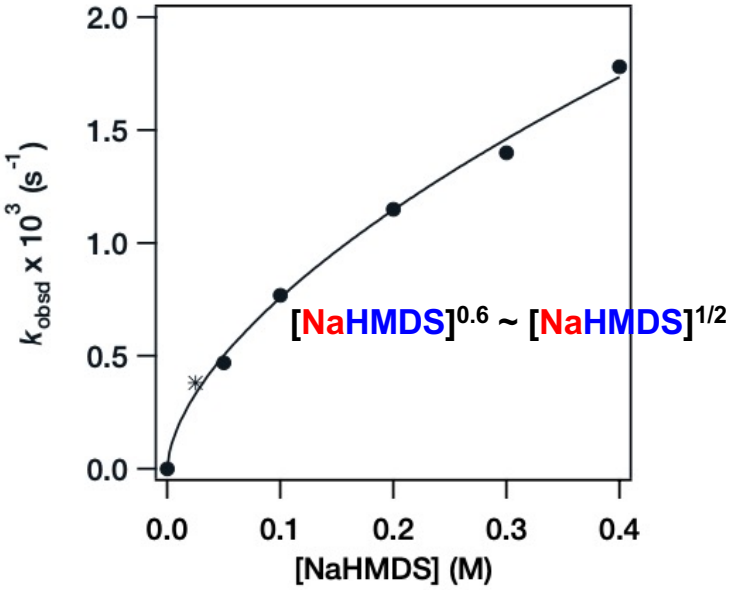
1) Woltornist, R. A.; Collum, D. B. *J. Am. Chem. Soc.* **2021**, *143*, 17452. 2) Woltornist, R. A.; Collum, D. B.*J. Org. Chem.* **2021**, *86*, 2406.

Toluene/PMDTA: In situ IR Spectroscopy



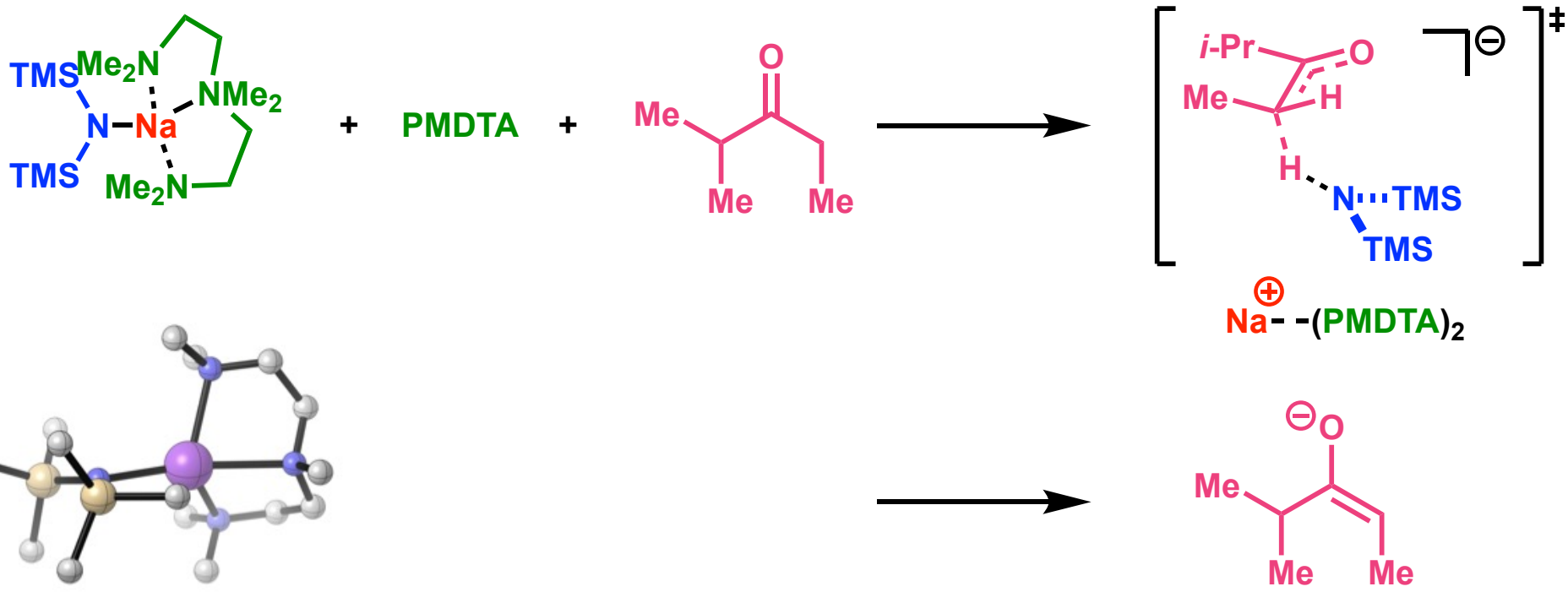


NaHMDS (0.10 M in toluene/PMDTA)



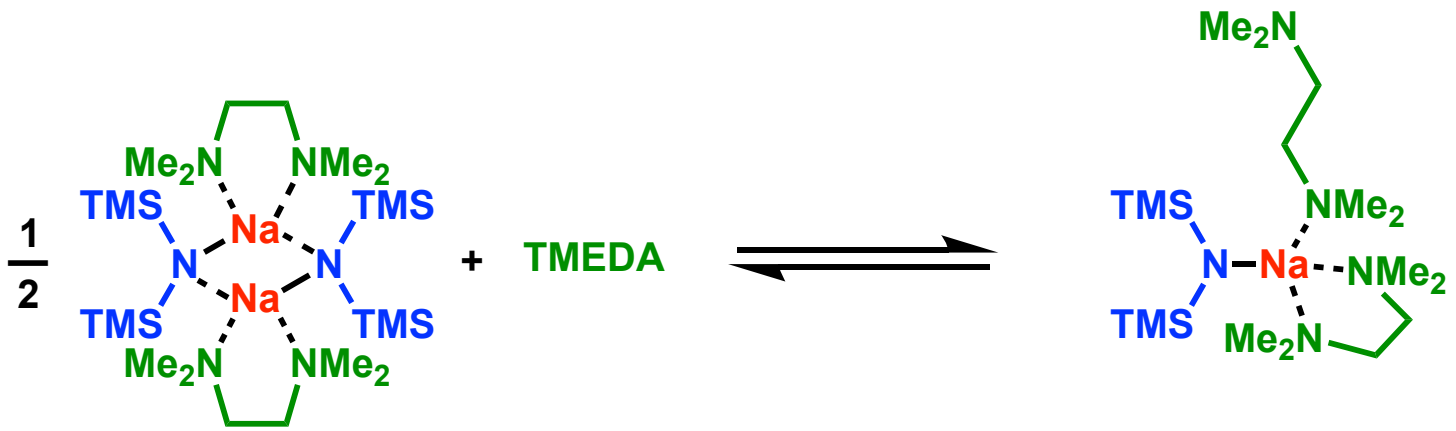
PMDTA (2 M in toluene)

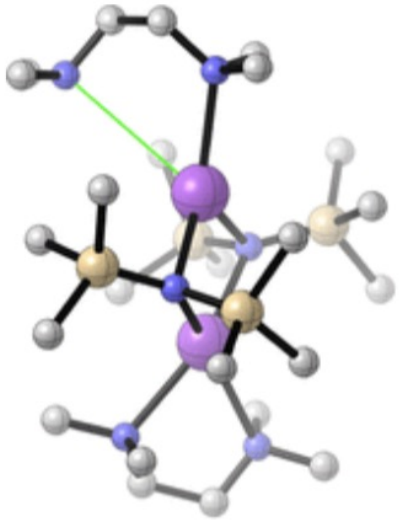
Toluene/PMDTA: Mechanism C

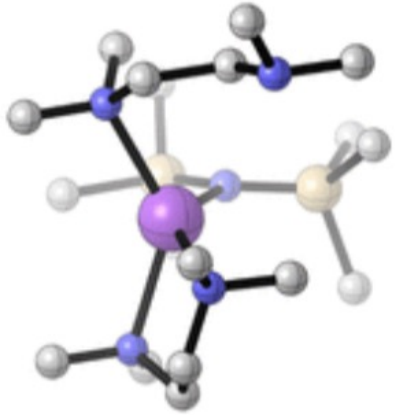


$$-\frac{d}{dt}[ketone] \propto [(TMS)_2NNaPMDTA]^{\frac{1}{2}}[PMDTA]^{\frac{1}{2}}$$

Toluene/TMEDA: Dimer to Monomer

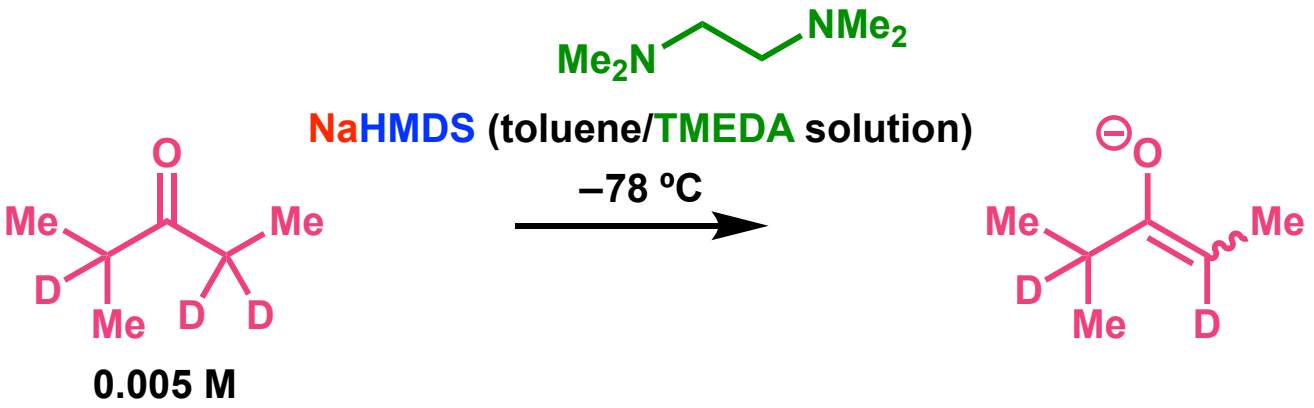


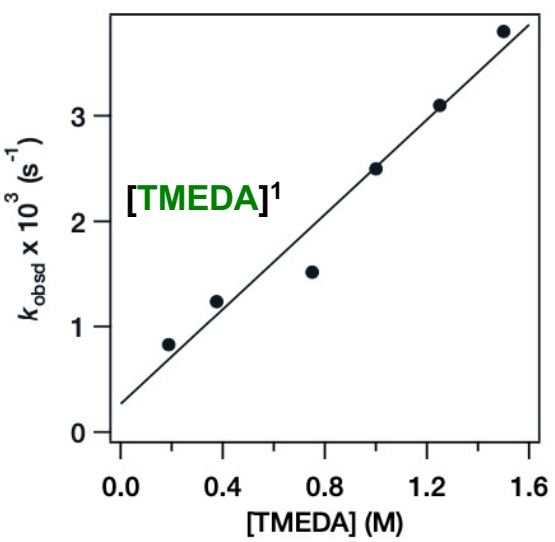




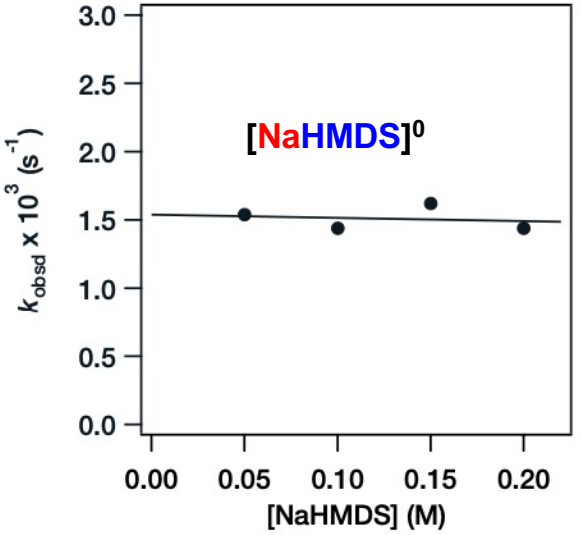
1) Woltornist, R. A.; Collum, D. B. *J. Am. Chem. Soc.* **2021**, *143*, 17452. 2) Woltornist, R. A.; Collum, D. B.*J. Org. Chem.* **2021**, *86*, 2406.

Toluene/TMEDA: In situ IR Spectroscopy





NaHMDS (0.10 M in toluene/TMEDA)



TMEDA (0.75 M in toluene)

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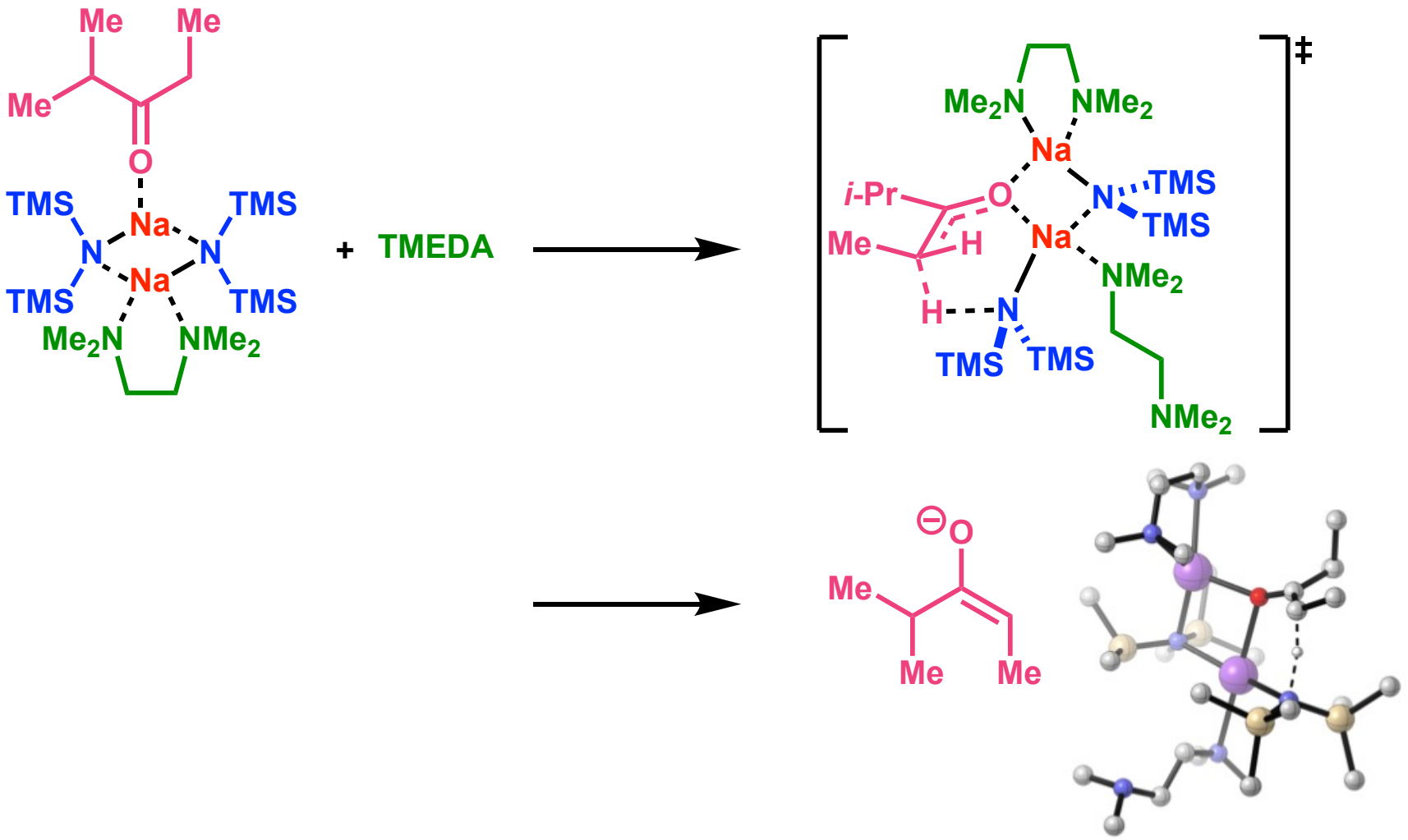
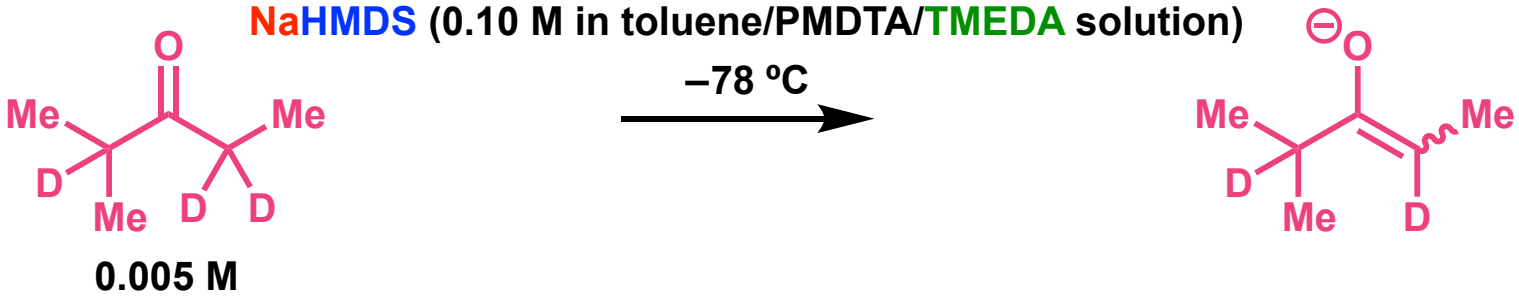
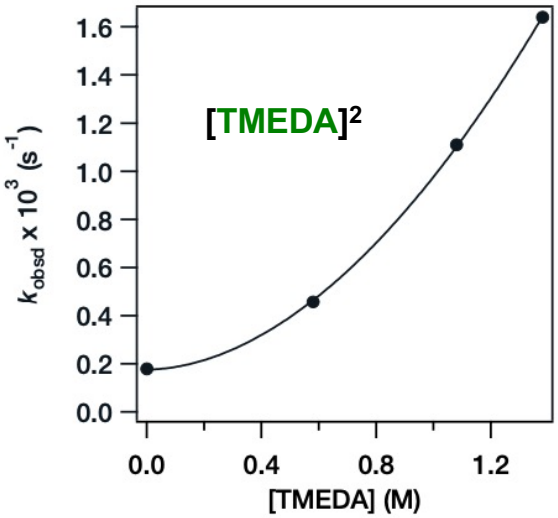
Toluene/TMEDA: Mechanism E



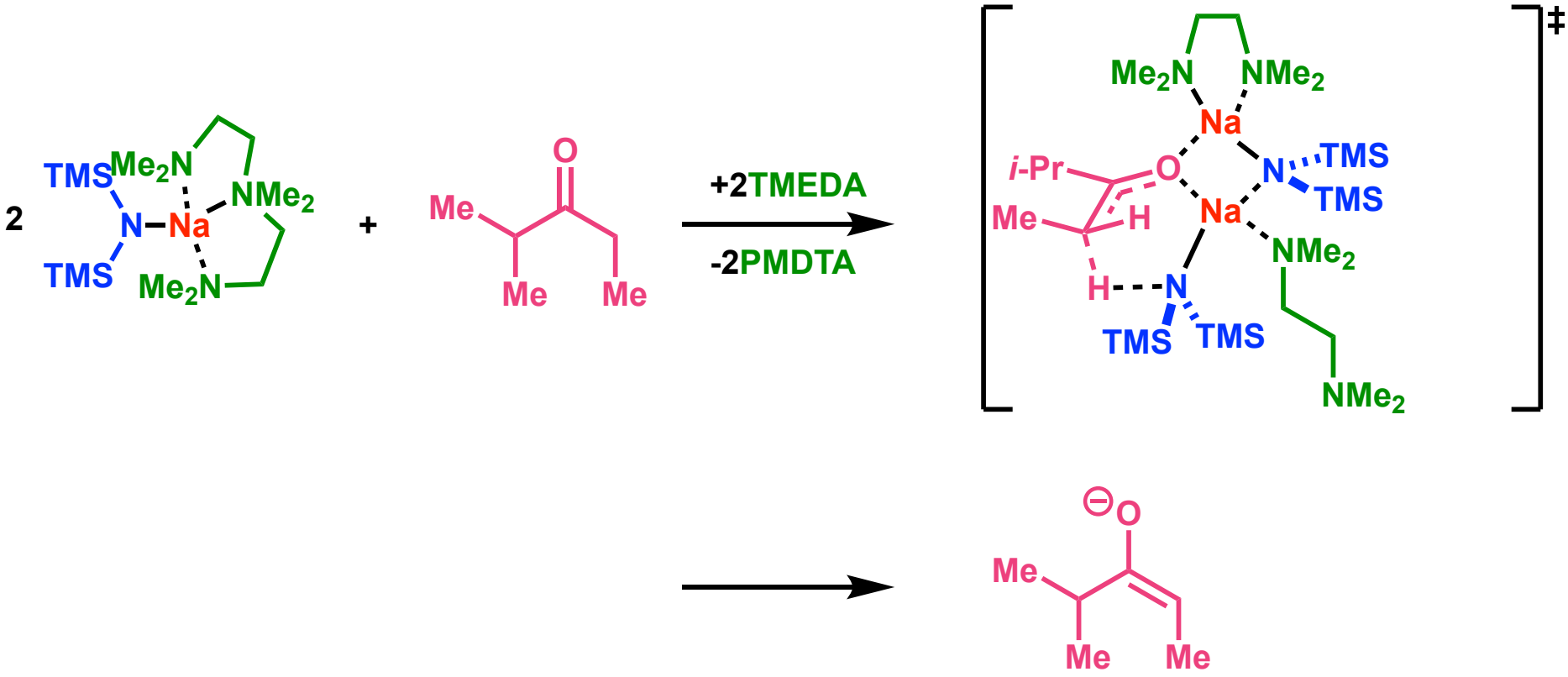
$$-\frac{d}{dt}[ketone] \propto [((TMS)_2N)_2Na_2(TMEDA)_2]^0[TMEDA]^1$$

Toluene/PMDTA/TMEDA: In situ IR Spectroscopy





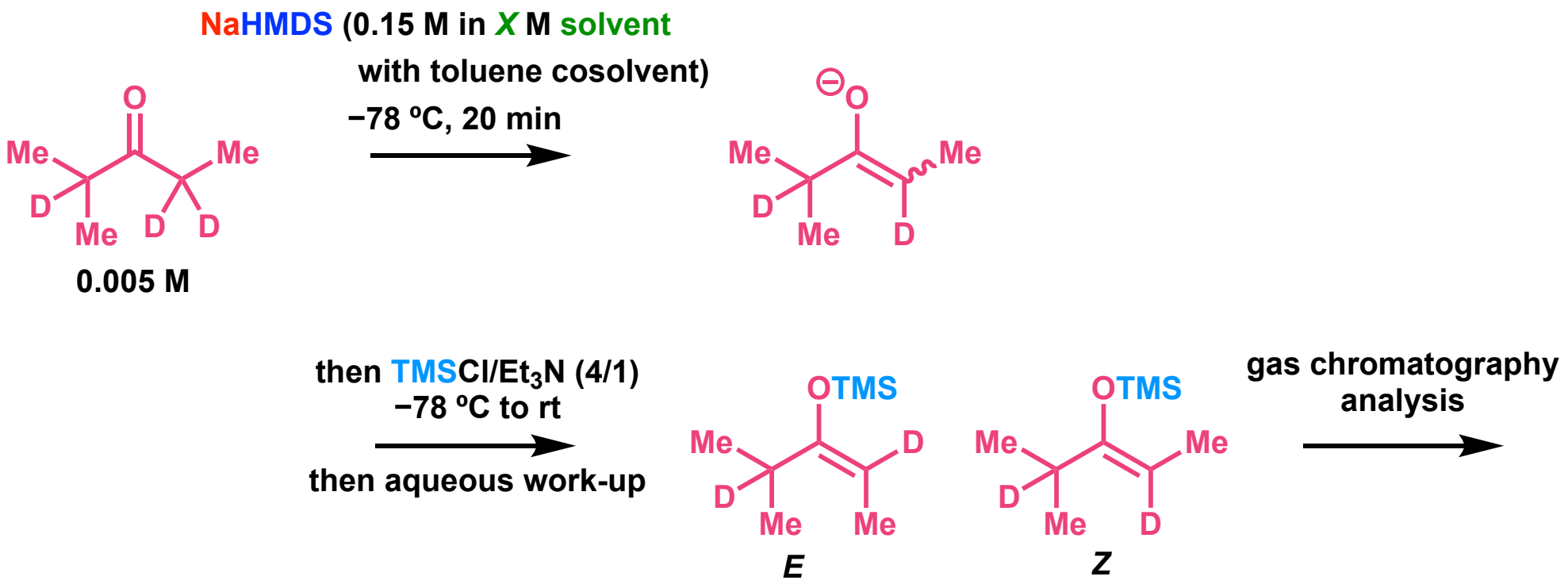
Toluene/PMDTA/TMEDA: Mechanism I



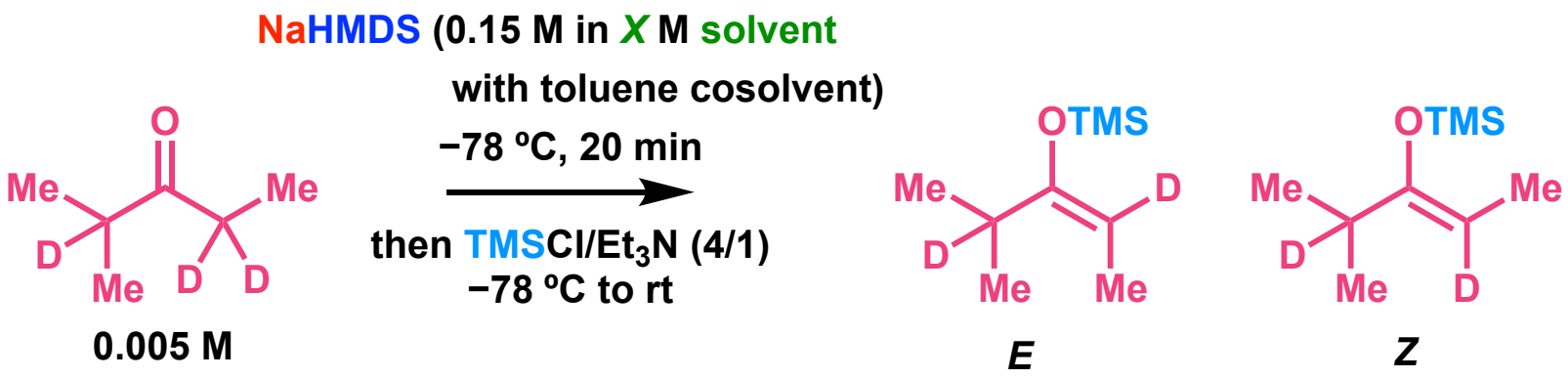
$$-\frac{d}{dt}[ketone] \propto [TMEDA]^2$$

Contents

Experimental Procedure



E/*Z* Selectivity



entry	solvent	X	*E*/*Z*	k_{rel}	mechanism
1	Et_3N	4.00	20:1	1	E
2	*t*-BuOMe	6.00	10:1	10	H
3	PMDTA	1.50	8:1	15	C
4	TMEDA	1.50	4:1	113	E
5	THF	9.00	1:90	137	B and C

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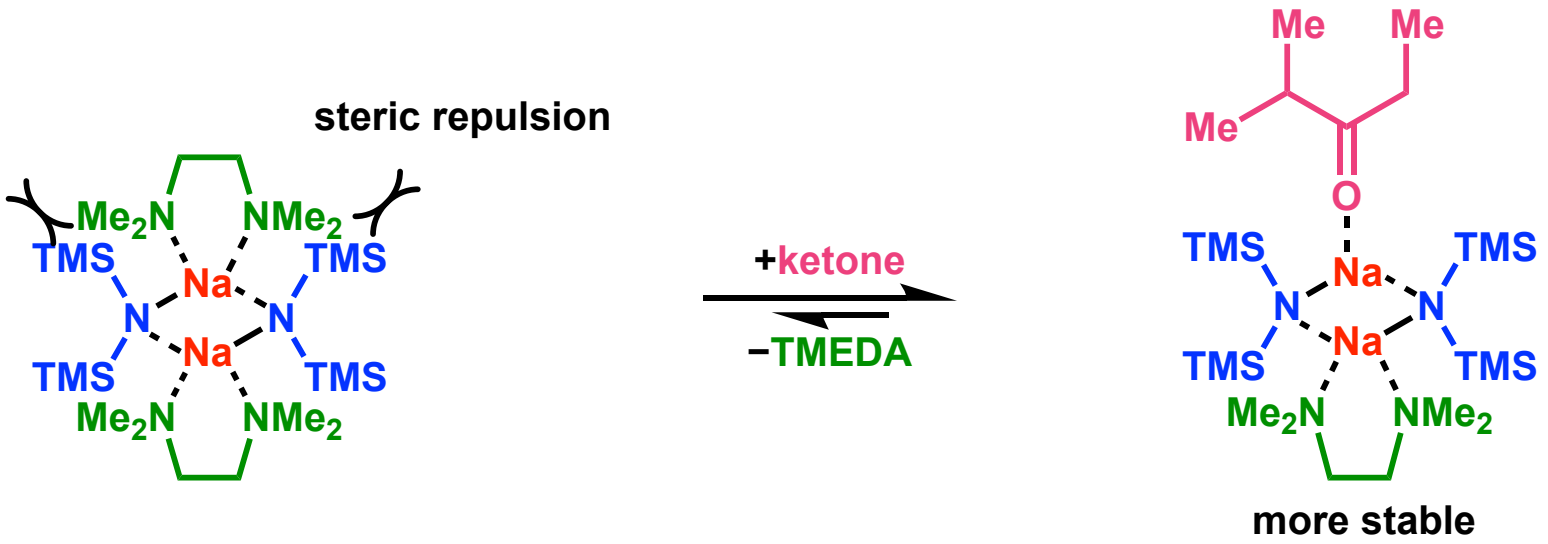
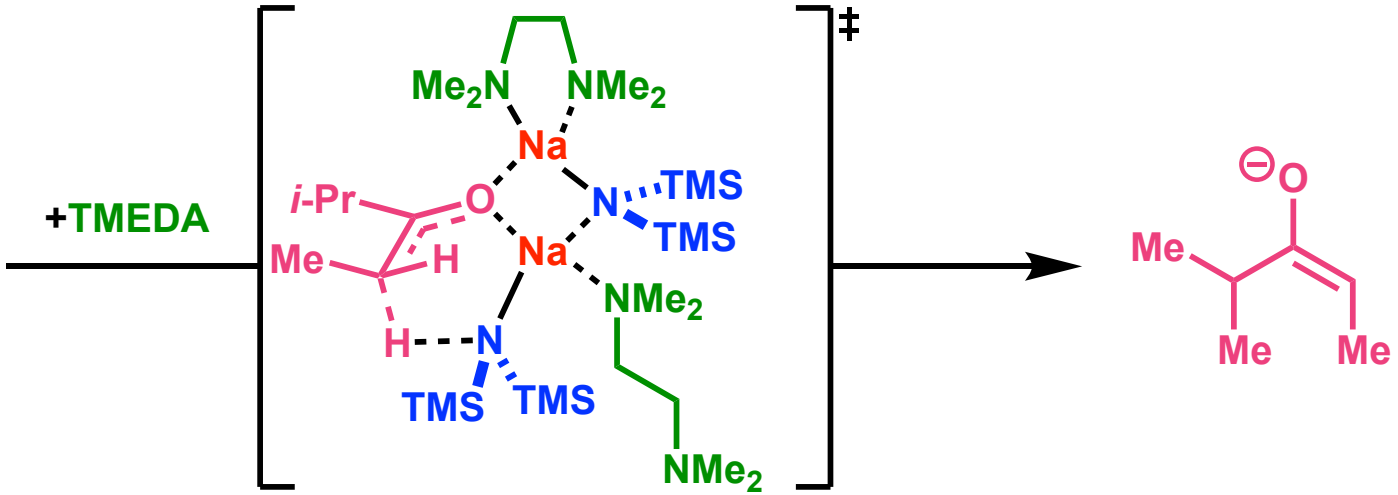
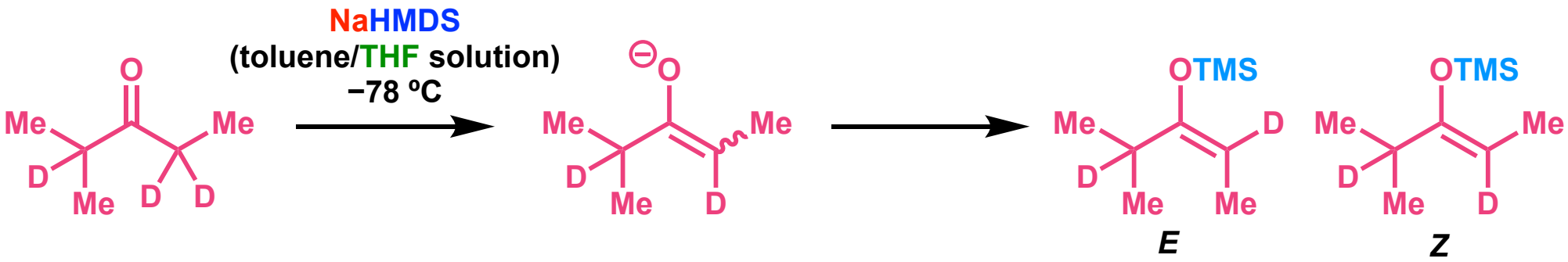
High Reactivity in TMEDA





Z-Selectivity in THF: *E*/*Z* Isomerization

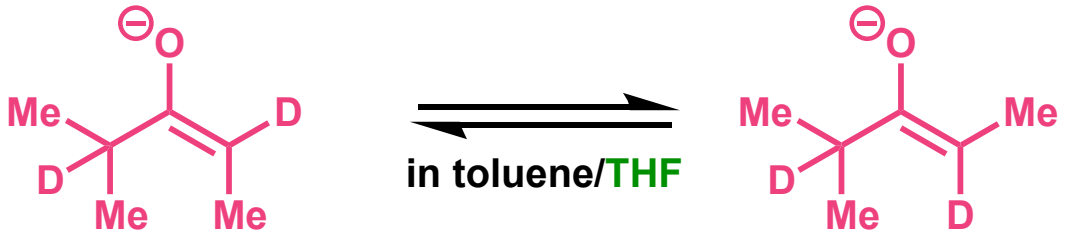


then TMSCl/Et_3N (4/1)
−78 °C (silylation half time ~ 20 min)

E/*Z* = 1:90

then TMSOTf
−78 °C (silylation half time < 5 sec)

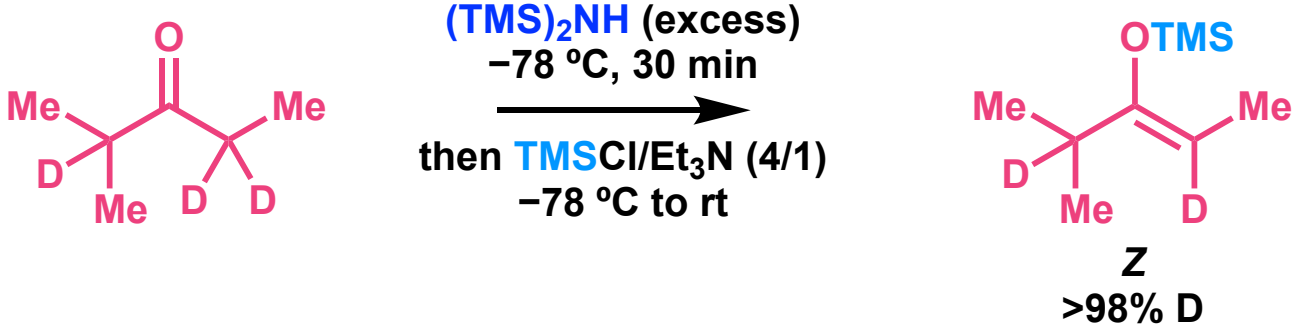
E/*Z* = 1:4



Was enolate isomerized in THF?

1) Woltornist, R. A.; Collum, D. B. *J. Am. Chem. Soc.* **2021**, *143*, 17452.

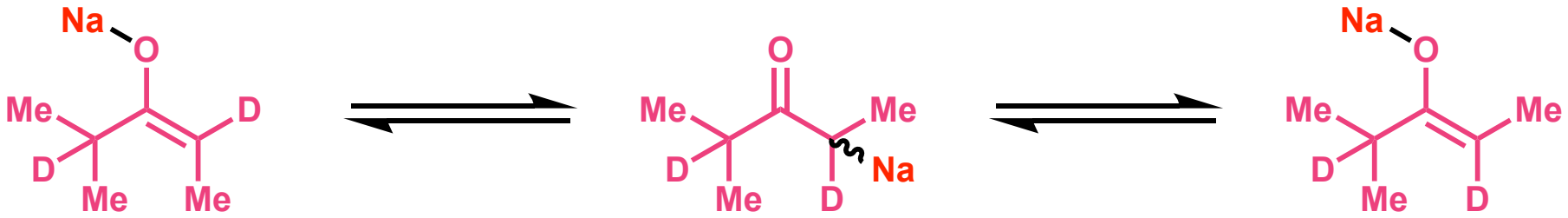
Z-Selectivity in THF: *E*/*Z* Isomerization



Z
>98% D

→Enolate was not isomerised through the medium of proton.

Therefore, enolate might be isomerised via C-Na enolate.



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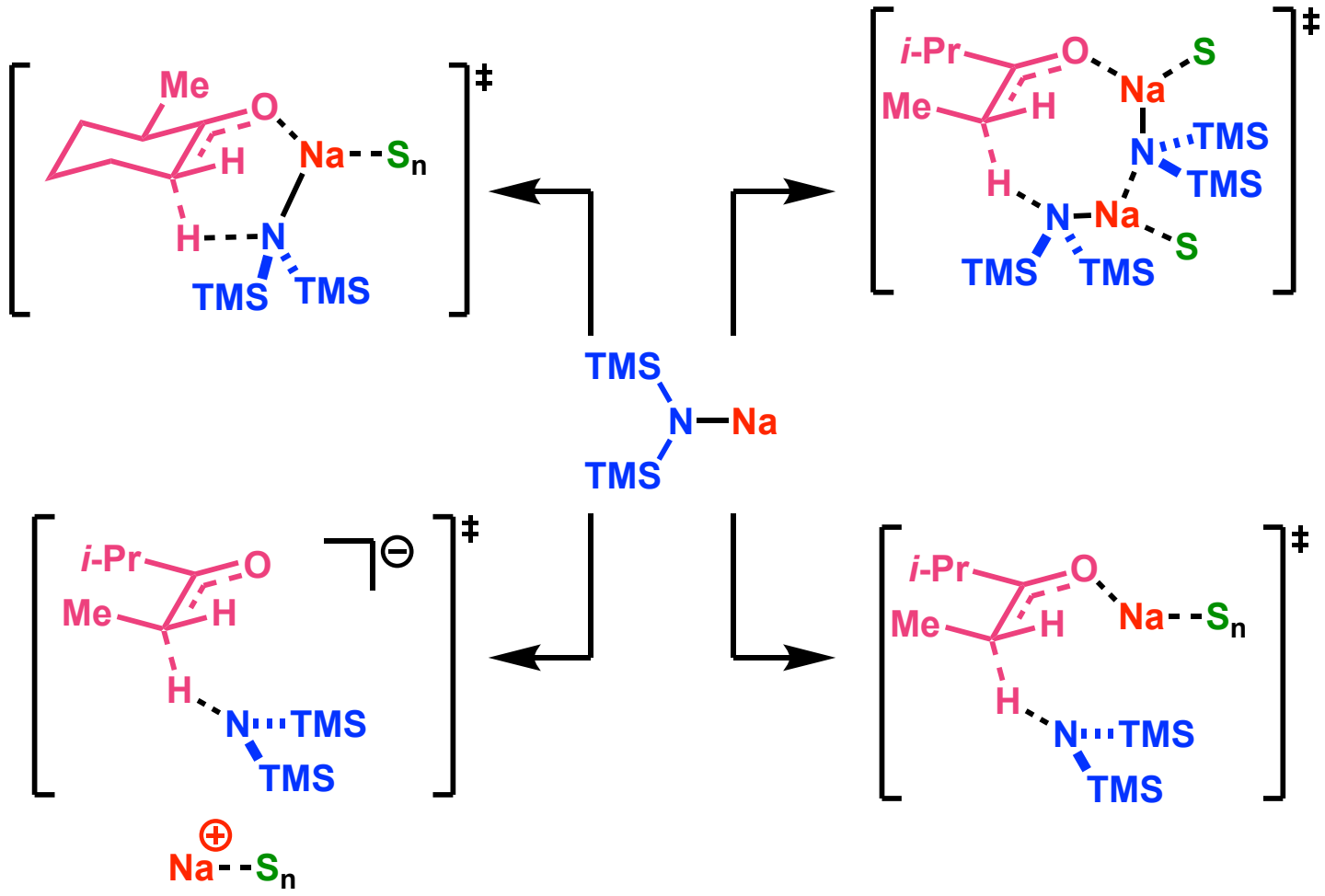
Summary



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