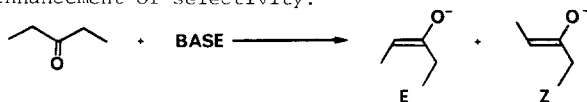


lithium amide. Identical product ratios were obtained under either conditions. The efficacy of this internal quench methodology as compared to the two step procedure of House is shown in the accompanying table.⁴ In addition to the increased selectivity of the highly hindered amide as compared to LDA the yield of enol ethers in all internal quench reactions was quantitative; no condensation products were observed.

SUBSTRATE	ENOL ETHER		A:B ^a (A:B) ^b	
	A	B	LDA	LOBA
			95:5 (86:14)	97.5:2.5 (86:14)
			95:5 (94:6) ⁵	97.5:2.5
			95:5	>97.5:<2.5
			90:10 (85:15) ⁶	97:3 (95:5)
			50:50 (0:100)	50:50

a) Internal quench
b) Two step procedure

The use of a highly hindered lithium dialkylamide would be expected to yield preferentially the E rather than the Z enolate in the reaction with a ketone or ester. Ireland⁷ reported that the reaction of 3-pentanone with LDA followed by quenching with t-butyldimethylsilyl chloride (TBDMSCl) gave the E and Z silyl enol ethers in a ratio of 77:23, respectively. Kuwajima⁸ reported an E:Z ratio of 86:14 using lithium 2,2,6,6-tetramethylpiperidide (LiTMP) as the base. We have found that whereas the internally trapped reaction of LDA (TMSCl) gave an E:Z ratio of 77:23, the use of LOBA led to a 98:2 ratio of the E and Z enol ethers, demonstrating a major enhancement of selectivity.



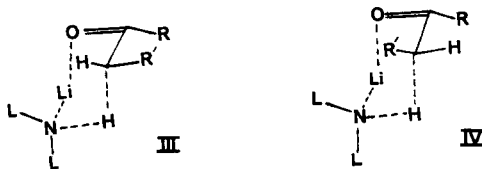
These results can be rationalized by consideration of steric interactions in the assumed pericyclic transition states I and II. For a lithium dialkylamide with an extremely bulky substituent L, the large repulsion of L and R' in II dominates and causes this pathway



to be disfavored relative to transition state I which leads to the E enolate. The increased selectivity for the formation of E enolates with LOBA as compared to LDA is demonstrated by the following results.⁹

SUBSTRATE	TMS KETENE ACETAL		E:Z	
	<u>E</u>	<u>Z</u>	LDA	LOBA
<chem>CC(=O)C</chem>			91:9	>95:<5
<chem>CCC(=O)CC</chem>			80:20	95:5

The reaction of LDA with 3-pentanone in 23% hexamethylphosphoric triamide (HMPA)/THF afforded an E:Z enol ether ratio of 5:95, respectively.⁷ Ireland assumed that this selectivity was kinetically determined. He proposed that in the absence of HMPA lithium is strongly coordinated to the carbonyl oxygen thus making it effectively bulkier than R leading to the



predominance of III and therefore the E enolate. In the presence of HMPA this coordination is absent and the sterically favored transition state is IV leading to the Z enolate.¹⁰ The use of TMSCl as an in situ trapping agent afforded a unique probe to determine whether the stereochemical result of the reaction in the presence of HMPA is under kinetic or thermodynamic control.^{11,12}



internal quench	THF	98	:	2
internal quench (8 equiv TMSCl)	HMPA:THF	37	:	63
internal quench (17 equiv TMSCl)	HMPA:THF	46	:	54
two step procedure	HMPA:THF	18	:	82

The results shown in the table above clearly indicate that the selectivity in the presence of HMPA is the result of equilibration to the more thermodynamically stable Z isomer. In situ trapping results in greater amounts of E isomer as compared to that obtained with the two step procedure. Greater concentrations of trapping reagent increase the amount of E isomer.

General in situ trapping procedure: Into a dry 25 ml. flask under N_2 was placed the lithium dialkylamide (1.1 mmol) in 2 ml. of THF at -78° . A solution of TMSCl (5-10 mmol) in 2 ml. of THF at -78° was added followed by dropwise addition of the substrate (1.0 mmol) in 2 ml. of THF. After 1 minute 2 ml. of dry triethylamine was added followed by quenching with saturated aqueous sodium bicarbonate solution. The product was extracted into petroleum ether and the ether extracts were washed first with water and then with 0.1N citric acid. Drying over sodium sulfate and concentration gave the silyl enol ethers.¹³

References and Notes

1. The synthesis of di-*t*-alkylamines is described in the accompanying paper; see also A. W. Gross, Ph.D. dissertation Harvard University, August 1983.
2. J. d'Angelo, Tet., 32, 2979 (1976); H. O. House, M. Gall, and H. D. Olmstead, J. Org. Chem., 36, 2361 (1971); H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, J. Org. Chem., 34, 2324 (1969).
3. After completion of this work the TMSCl in situ trapping of α -lithiated cyanobenzene was reported. T. D. Krizan and J. C. Martin, J. Am. Chem. Soc., 105, 6155 (1983).
4. All product ratios were determined by VPC and comparison with authentic samples.
5. R. D. Clark and C. H. Heathcock, Tet. Lett., 2027 (1974); R. D. Clark and C. H. Heathcock, J. Org. Chem., 41, 1369 (1976). While exclusive formation of the KC enolate in the reaction of LDA with 2-octanone is reported, only a 54% yield was obtained. Attempts to repeat this work gave a 94:6 ratio of the kinetically and thermodynamically controlled enol ethers in ca. 50% yield.
6. G. H. Posner and C. M. Lentz, J. Am. Chem. Soc., 104, 934 (1979).
7. R. E. Ireland, R. M. Mueller, and A. K. Willard, J. Am. Chem. Soc., 98, 2868 (1976).
8. E. Nakamura, K. Hashimoto, and I. Kuwajima, Tet. Lett., 2079 (1978).
9. The ratios of the labile trimethylsilyl ketene acetals was determined by NMR analysis. The reactions were simply concentrated in vacuo, resuspended in acid free $CDCl_3$, and filtered into an NMR tube.
10. This argument ignores the repulsion of L and R' in IV. The presence of the pericyclic transition states in the presence of HMPA is also in question.
11. Rathke has suggested that enolate formation in the presence of HMPA was thermodynamically controlled on the basis that high base to ketone ratios gave increased amounts of the E enolate. Z. A. Fataftah, I. E. Kopka, and M. W. Rathke, J. Am. Chem. Soc., 102, 3960 (1980).
12. The reactions were performed by adding LOBA to the ketone and a 10-fold excess of TMSCl in 23% HMPA/THF at -78° . Therefore, the occurrence of some equilibration prior to trapping is possible. The preferred mode of addition, ketone added to LOBA and TMSCl, was not feasible since LOBA reacts with TMSCl at -78° in the presence of HMPA.
13. This research was assisted financially by a grant from the National Science Foundation.

(Received in USA 7 November 1983)