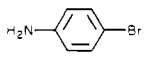
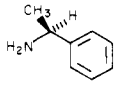
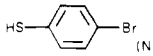
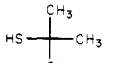
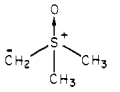
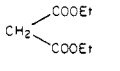
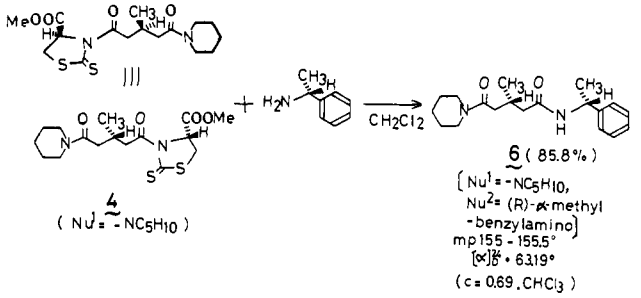
Table I. Treatment of 3 ($Nu^1 = -NC_5H_{10}$) with Several Nucleophiles (Nu^2)

Nu^2	product[a]	mp, °C	$[\alpha]^{25}D$, deg ($CHCl_3$)	yield,[b] %
	5a	124–125	+0.98 (c 1.02)	99.0
	5b	155–155.5	−63.48 (c 0.66)	93.0
	5c[c]	oil	−1.39 (c 1.73)	96.9
	5d	oil	−4.02 (c 1.32)	85.4
	5e[d]	130–131.5	+2.30 (c 1.00)	76.0
	5f[e]	oil	−3.63 (c 2.40)	98.5

[a] Satisfactory spectral and analytical data were obtained in compounds 5: $Nu^1 = -NC_5H_{10}$. [b] Isolated yield. [c] To a suspension of *p*-bromothiophenol (1 mmol) and NaH (1 mmol) in THF (5 mL) was added compound 3 (0.5 mmol) in THF (3 mL) and stirred at room temperature for 10 min in N_2. [d] To an in situ reagent[18] obtained by refluxing trimethylsulfoxonium chloride (2 mmol) and NaH (1.5 mmol) in THF (3 mL) for 2 h in N_2 was added compound 3 (0.5 mmol) in THF (2 mL). The mixture was stirred at room temperature for 10 min. [e] To a suspension of sodium diethylmalonate (ca. 2 mmol) prepared in THF (3 mL) as usual was added compound 3 (1 mmol) in THF (3 mL) and stirred for 1 h. The product 5f is shown to be a mixture of the keto and enol form in a 4:6 ratio (^1H NMR analysis).

Scheme III



chromatography (HPLC). The best result was obtained with piperidine as Nu^1.

As exemplified by the case of piperidine as Nu^1, separation of the diasteromeric mixture [5.9 g, 73.6% yield from **2** (10 g)] on a silica gel column with *n*-hexane–Et_2O–EtOAc (2:2:1) afforded a pure major component **3** [$Nu^1 = -NC_5H_{10}$, 4.3 g, yellow needles from Et_2O, mp 95.5–96 °C, $[\alpha]_D^{25}$ −99.0° (*c* 1.00, EtOAc)] and a pure minor component **4** [$Nu^1 = -NC_5H_{10}$, 0.58 g, yellow oil]. For confirmation of the structure and absolute configuration of compound **3** ($Nu^1 = -NC_5H_{10}$), it was chemically converted into the known (−)-(3*S*)-3-methylvalerolactone[8b] (see Scheme II). Also, the structure and stereochemistry of **5b**, prepared by aminolysis of **3** ($Nu^1 = -NC_5H_{10}$) with (*S*)-(α-methylbenzyl)amine (see Table I), were determined by X-ray analysis.[15]

The stereochemistry of the minor product **4** ($Nu^1 = -NC_5H_{10}$) was also established by its transformation into compound **6** [$Nu^1 = -NC_5H_{10}$, Nu^2 = (*R*)-(α-methylbenzyl)amino], the enantiomer of compound **5b** (see Scheme III and Table I).

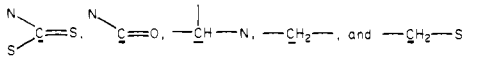
Finally, compound **3** ($Nu^1 = -NC_5H_{10}$) was subjected to "the monitored reaction" employing several nucleophiles "Nu^2" and gave optically pure acyclic products **5a–f** in high yields (Table I). These products should be useful as synthons for the total synthesis of natural products.

This novel nonenzymatic asymmetric synthesis is not only useful as a practical synthetic tool but also as an aid in the elucidation of the action of enzymes such as α-chymotrypsin[8c] and pig liver esterase.[8a,d] Thus we have established a new concept that the introduction of the two same chiral ligands, e.g., two 4(*R*)-MCTT groups, into a symmetrical molecule having a prochiral center changes its original symmetrical nature (environment) into the unsymmetrical nature (environment).[19] This new concept can be widely applied to other similar reactions (e.g., differentiation between enantiotopic groups in meso compounds), and such studies are now in progress.

Registry No. 1, 626-51-7; 2, 80963-69-5; 3, 80963-70-8; 4, 80963-71-9; 5a, 80963-72-0; 5b, 80963-73-1; 5c, 80963-74-2; 5d, 80963-75-3; 5e, 80963-76-4; 5f, keto form, 80963-77-5; 5e, enol form, 80963-78-6; 6, 80963-79-7; H_2N-*p*-C_6H_4Br, 106-40-1; $PhCHMeNH_2$, 3886-69-9; Br-*p*-C_6H_4SH, 106-53-6; Me_3CSH, 75-66-1; $Me_2S(O):CH_2$, 5367-24-8; $CH(CO_2Et)_2$, 105-53-3; 4(*R*)-methoxycarbonyl-1,3-thiazolidine-2-thione, 80963-80-0.

Supplementary Material Available: Crystallographic details, tables of atomic positional and thermal parameters, and perspective views for **2** and **5b** (11 pages). Ordering information is given on any current masthead page.

(19) On the ^{13}C NMR (JEOL FX270) chart of diamide **2** in $CDCl_3$ solution, duplicte signals assignable to the following carbon atoms were observed:



We express our thanks to Dr. K. Matsushita (JEOL Co., Ltd.) for the determination of the ^{13}C NMR spectra.

Remarkably High Regioselective Deprotonation and Alkylation of Unsymmetrical Imines at the More Substituted α-Carbon Atom

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Received October 13, 1981

After the pioneering work of Stork[1a] and Wittig[1b] in 1963, studies showing that metalation of imines and their subsequent alkylation occur selectively syn to the substituent of the sp^2-hybridized nitrogen atom regardless of either symmetrical or unsymmetrical substitution of the imines have proved to be extremely useful for synthetic organic chemistry.[2,3] Theoretical and ex-

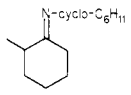
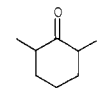
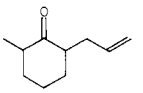
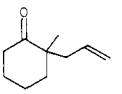
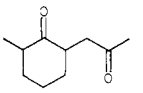
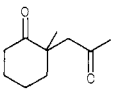
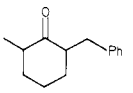
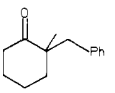
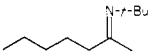
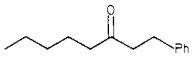
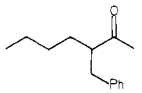
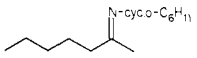
(1) (a) Stork, G.; Dowd, S. *J. Am. Chem. Soc.* **1963**, *85*, 2178–2180. (b) Wittig, G.; Frommeld, H. D.; Suchanek, P. *Angew. Chem.* **1963**, *75*, 978–979.

(2) (a) Wittig, G.; Frommeld, H. D. *Chem. Ber.* **1964**, *97*, 3548–3559. (b) Wittig, G.; Reiff, H. *Angew. Chem.* **1968**, *80*, 8–15. (c) Larcheveque, M.; Valette, G.; Cuvigny, T.; Normant, H. *Synthesis* **1975**, 256–259. (d) Cuvigny, T.; Larcheveque, M.; Normant, H. *Justus Liebigs Ann. Chem.* **1975**, 719–730. (e) Harvey, W. E.; Tarbell, D. S. *J. Org. Chem.* **1967**, *32*, 1679–1681. (f) Nagata, W.; Hayase, Y. *J. Chem. Soc. C* **1969**, 460–466. (g) Evans, D. *J. Am. Chem. Soc.* **1970**, *92*, 7593–7595. (h) Stork, G.; Benaim, J. *Ibid.* **1971**, *93*, 5938–5939. (i) Wittig, G.; Fischer, S.; Tanaka, M. *Justus Liebigs Ann. Chem.* **1973**, 1075–1081. (j) House, J. O.; Liang, W. C.; Weeks, P. D. *J. Org. Chem.* **1974**, *39*, 3102–3107. (k) Jacobsen, R. M.; Raths, R. A.; McDonald, J. H. *Ibid.* **1977**, *42*, 2545–2549. (l) Meyers, A. I.; Williams, D. R.; Druelinger, M. *J. Am. Chem. Soc.* **1976**, *98*, 3032–3033. (m) Whitesell, J. K.; Whitesell, M. A. *J. Org. Chem.* **1977**, *42*, 377–378. (n) Kitamoto, M.; Hiroi, K.; Terashima, S. *Chem. Pharm. Bull.* **1974**, *22*, 459–464 and references therein.

(3) (a) Fraser, R. R.; Banville, J.; Dhawan, K. L. *J. Am. Chem. Soc.* **1978**, *100*, 7999–8001. (b) Fraser, R. R.; Banville, J. *J. Chem. Soc., Chem. Commun.* **1979**, 47–48. (c) Houk, K. N.; Strozier, R. W.; Rondan, N. G.; Fraser, R. R.; Chuaqui-Offermanns, N. *J. Am. Chem. Soc.* **1980**, *102*, 1426–1429.

0002-7863/82/1504-2081$01.25/0

Table I. Methylation and Alkylation of Unsymmetrically Substituted Imines (2 and 6)

entry	imine	base[a]	alkyl halide[b]	products	% yield[c]	4:5 or 7:8[d]
1	 2a	*s*-BuLi 1b	CH_3I 3a	 4a  5a	56	10:90
2	2a	1b	CH_2=$CHCH_2Cl$ 3b	 4b  5b	76	10:90
3	2a	1b	CH_2=$C(OSiMe_3)CH_2Cl$ 3c	 4c  5c	71	11:89
4	2a	*n*-BuLi 1a	$PhCH_2Cl$ 3d	 4d  5d	53	13:87
5	2a	1a/TMEDA	3d	4d	5d	60[e]	16:84
6	2a	1b	3d	4d	5d	86	10:90
7	2a	1b[f]	3d	4d	5d	74	13:87
8	2a	1b[g]	3d	4d	5d	69	10:90
9	2a	1b[h]	3d	4d	5d	68	10:90
10	2a	1b/TMEDA	3d	4d	5d	57	16:84
11	2a	*t*-BuLi (1c)	3d	4d	5d	85	15:85
12	2a	1c/TMEDA	3d	4d	5d	53	14:86
13	 2b	1b	3d	4d		97	100:0
14	 6a	1b	3d	 7  8		41	53:47
15	6a	1b/HMPA	3d	7		61	100:0
16	6a	1c	3d	7	8	40	44:56
17	 6b	1b	3d	7	8	49	74:26
18	6b	1b/HMPA	3d	7		62	100:0
19	6b	1c	3d	7	8	64	78:22
20	6b	1b/HMPA[i]	3d	7		48	100:0

[a] α-Lithiated imines were prepared by the procedure shown in ref 6 unless otherwise noted. [b] All alkylations were carried out at room temperature for 1.5-2 h. [c] Yields after isolation. [d] Determined by HPLC, GLC, or isolation. [e] Determined by GLC. [f] *s*-BuLi (1b) was added slowly to the THF solution of 2a. [g] Metalation was carried out at −30 °C for 2.5 h and alkylation was conducted at −30 °C. [h] Metalation was conducted at 0 °C for 2 h. [i] Metalation was conducted at −78 °C for 2 h.

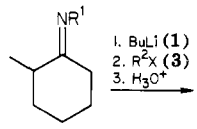
perimental investigations attributed the origin of the regiocontrol to a minimization of dipole–dipole electrostatic interaction between nitrogen lone-pair electrons and a carbanion.[3c] We report here that the alkylation site depends dramatically upon the nature of the base, the substituent on the imine nitrogen, and the solvent. Selective alkylation takes place preferentially at the more substituted α-carbon atom when butyllithium (**1**) is used as a base for deprotonation of the *N*-cyclohexylimine of 2-methylcyclohexanone (**2a**). To our knowledge, this is the first example of a case where deprotonation of simple imines and subsequent alkylation do not necessarily occur predominantly at the less substituted α site.[4] The results are summarized in Table I.

In sharp contrast to alkylation of α-metalated imines derived from unsymmetrically substituted imines by using conventional deprotonation procedures,[1,2] deprotonation of the *N*-cyclohexylimine of 2-methylcyclohexanone (**2a**) with *n*-, *sec*-, and *tert*-butyllithium (**1a**, **1b**, and **1c**, respectively) and subsequent alkylation with alkyl halides gave, in every case, an approximately 90:10 isomeric mixture of the corresponding α-alkylated 2-methylcyclohexanones in which **5**, resulting from alkylation at the more substituted site, predominated over **4**,[5] alkylated at the less substituted site[6] (eq 1). Each isomer was separated and the ratio was determined with high performance liquid chromatography (HPLC) by using hexane/ether (3:1) with calibration by an authentic mixture of isomers.

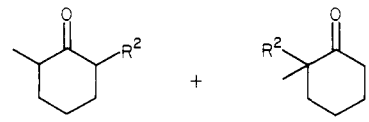
Variations in alkyl halides such as methyl iodide (**3a**) and allyl

(4) Recent papers describing the regiospecific generation of the α-lithiated imines by nucleophilic addition to 2-azadienes contain references to numerous examples of their ability. See: (a) Wender, P. A.; Schans, J. M. *J. Org. Chem.* **1978**, *43*, 782–784. (b) Martin, S. F.; Phillips, G. W. *Ibid.* **1978**, *43*, 3792–3794. (c) Wender, P. A.; Essenstat, M. A. *J. Am. Chem. Soc.* **1978**, *100*, 292–294.

(5) The product **4** resulting from alkylation at the less substituted site was obtained as a mixture of cis and trans derivatives, presumably due to isomerization during hydrolysis or isolation by TLC.[3a]



2a, R^1 = cyclo-C_6H_{11}
2b, R^1 = Me_2N



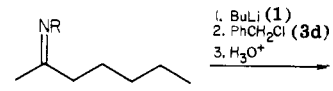
(1)

4a, R^2 = CH_3
4b, R^2 = CH_2=$CHCH_2$
4c, R^2 = CH_3COCH_2
4d, R^2 = $PhCH_2$

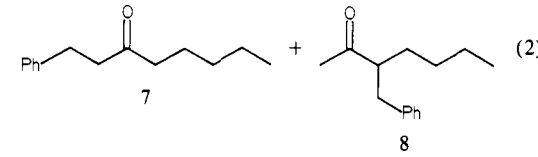
5a, R^2 = CH_3
5b, R^2 = CH_2=$CHCH_2$
5c, R^2 = CH_3COCH_2
5d, R^2 = $PhCH_2$

chloride (**3b**) and in reaction temperature[7] had no effect on the regiochemistry. Addition of tetramethylethylenediamine (TMEDA), however, brought slightly less selective results on the regiochemistry. Apparently butyllithium (**1**) abstracts an anti proton more rapidly than a syn proton of the substituent of the nitrogen atom of the imine (**2a**), which exists mostly in the anti form.[8-10] However, **4d** was obtained exclusively from the benzylation of the dimethylhydrazone of 2-methylcyclohexanone (**2b**), where *sec*-butyllithium (**1b**) was used as a proton-abstracting base, in good accord with the results of the previous experiments.[11]

It is notable that deprotonation with butyllithium (**1**) resulted in the control of regiochemistry of alkylation in a pattern that could be correlated with the steric bulk of the base[12] and the substituent on the imine nitrogen. Another important factor is the basicity of the base used. Butyllithium (**1**) is strong enough to abstract a proton from a tertiary α carbon of the imine (**2a**),



6a, R = *t*-Bu
6b, R = cyclo-C_6H_{11}



7 8

(2)

but lithium diisopropylamide (LDA) and ethylmagnesium bromide, used as a base for syn alkylation,[1a,3a] are too weak. Actually, deprotonation of **2a** with LDA, lithium dicyclohexylamide, and lithium bis(trimethylsilyl)amide in THF was very sluggish, and subsequent benzylation gave no meaningful result.

It is interesting to note that deprotonation of imines of acyclic ketones (**6**) with butyllithium (**1**) occurred similarly at the more substituted α-carbon atom to a considerable extent, in contrast to previous results with lithium diethylamide ($LiNEt_2$)[2c,d] that revealed an exclusively high regioselectivity at the less substituted carbon atom (eq 2). However, the regioselectivity of α-alkylation at the more substituted carbon atom apparently decreases compared to that of the cyclic case, presumably due to decreasing steric hindrance. For example, deprotonation of **6a**[13] with *sec*-butyllithium (**1b**) and subsequent benzylation at room temperature gave **7** and its regioisomer **8** in a ratio of approximately 53:47 after isolation by thin-layer chromatography. Moreover, instead of *N-tert*-butylimine (**6a**), the *N*-cyclohexylimine of 2-heptanone (**6b**) afforded a 74:26 mixture of alkylation products where **7** predominated.

In these cases the effect of hexamethylphosphoric triamide (HMPA) was remarkable in that only one regioisomer, **7**, was obtained exclusively. Thus the origin of the regiocontrol is believed to result not only from the steric effect of the reaction site but also from the exceedingly strong basicity of the organolithiums (**1**). Arguments to account for the regioselectivity of lithiated imines,[3] oxime derivatives,[14] hydrazones,[15] and nitrosoamines[16] that are previously reported appear inapplicable to the present case.[17]

The scope of this reaction as a synthetic procedure is now under examination and further investigation of the origin of the regiocontrol is in progress.

Registry No. 1a, 109-72-8; **1b**, 598-30-1; **1c**, 594-19-4; **2a**, 20007-02-7; **2b**, 5758-08-7; **3a**, 74-88-4; **3b**, 107-05-1; **3c**, 76634-95-2; **3d**, 100-44-7; **4a**, 2816-57-1; **4b**, 36321-95-6; **4c**, 72009-05-3; **4d**, 24785-76-0; **5a**, 1193-47-1; **5b**, 16178-87-3; **5c**, 27943-50-6; **5d**, 1206-21-9; *syn*-**6a**, 81011-82-7; *anti*-**6a**, 81011-83-8; *syn*-**6b**, 81011-84-9; *anti*-**6b**, 81011-85-0; **7**, 6047-99-0; **8**, 29494-51-7.

(6) The following experimental procedure is typical. To a solution of *sec*-butyllithium (**1b**) (2 M in pentane, 1.5 mL, 3 mmol) in dry THF (10 mL), was added **2** (387 mg, 2 mmol) slowly at −78 °C under argon by a syringe with stirring. After being stirred for 1.5–2 h at −78 °C and then 1.5 h at room temperature, benzyl chloride (**3d**) (398 mg, 3.1 mmol) was added and stirred for 2 h, and the reaction mixture was hydrolyzed with 2 M hydrochloric acid for 2.5 h and then washed with ether. The organic solution was concentrated under reduced pressure. The residue was purified by preparative TLC by using hexane/ether (2:1) as an eluent. Pure benzylated 2-methylcyclohexanone (349 mg, 1.72 mmol) was obtained as an isomeric mixture (R_f ca. 0.6) in 86% yield. Each isomer was separated and the ratio was determined by HPLC using hexane/ether (3:1). All compounds obtained in this work gave correct elemental analyses and satisfactory spectral data.

(7) The ratio of **4d**:**5d** did not change in the temperature range −30 to 0 °C. At −78 °C deprotonation was quite slow.

(8) By ^{13}C NMR spectral determination, the syn α carbon and the sp^2-hybridized carbon of the syn form of the imine (**2a**) exhibit approximately 11 ppm higher field and 1 ppm lower field, respectively, in shieldings than those of the anti form,[3a] and the ratio of anti:syn form is approximately 92:8 in a range −78 to 30 °C in THF and 78:22 in $CDCl_3$.

(9) This is the first example of a case where alkylation occurs anti to the substituent of the imine nitrogen[3a] except for a special case such as endocyclic imines.[3c]

(10) By examining time conversion of deprotonation with **1b**, and subsequent benzylation of −30 °C, it has been found that the ratio of **4d** to **5d** slightly decreases as the reaction proceeds, while **4d** and **5d** increase gradually with increasing reaction time. Thus **4d** is mainly derived from deprotonation and subsequent benzylation at the secondary carbon atom of the syn form of **2a** which is kinetically more favorable. Moreover, the choice of the procedure for preparing the α-lithiated imines had no effect upon the ratio of **4d**:**5d** (entry 6 and 7 of Table I). In all cases examined here, therefore, the product regiochemistry appears to be kinetic.

(11) (a) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3–6; (b) *Chem. Ber.* **1978**, *111*, 1337–1361.

(12) Although *tert*-butyllithium (**1c**) appears at first glance to be the sterically most hindered base among **1**, it is not necessarily the case, since it is anticipated that **1c** does not quite aggregate in THF while the degree of aggregation of *n*-butyllithium (**1a**) is to be about 4. Moreover, the aggregation of **1** is almost destroyed by the addition of an equivalent of TMEDA, due to cheletion to lithium metal. See: (a) West, R.; Waack, R. *J. Am. Chem. Soc.* **1967**, *89*, 4395–4399. (b) Mallan, J. M.; Beble, R. L. *Chem. Rev.* **1969**, *69*, 693–755. (c) Settle, F. A.; Haggerty, M.; Eastham, J. *J. Am. Chem. Soc.* **1964**, *86*, 2076–2077. (d) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: Elmsford, NY, 1974; p 3–18. (e) Coates, G. E.; Green, M. L. H.; Powell, P.; Wade, K. "Principles of Organometallic Chemistry"; Mathuen: London, 1968; Chapter 3.

(13) The ratio of the anti:syn forms of **6a** and **6b** was approximatly 87:13 and 84:16, respectively, in THF.

(14) (a) Kofron, W.; Yeh, M. J. *J. Org. Chem.* **1976**, *41*, 439–442. (b) Jung, M. E.; Blaier, P. A.; Lowe, J. A. *Tetrahedron Lett.* **1976**, 1439–1442. (c) Spender, T. A.; Loeng, W. *Ibid.* **1975**, 3889–3892. (d) Lyle, R. E.; Saavedra, J. E.; Lyle, G. G.; Fribush, H. M.; Marshall, J. L.; Lijinsky, W.; Singer, G. M. *Ibid.* **1976**, 4431–4434. (e) Lyle, R. E.; Fribush, H. M.; Lyle, G. G.; Saavedra, J. E. *J. Org. Chem.* **1978**, *43*, 1275–1276. (f) Ensley, H. E.; Lohr, R. *Tetrahedron Lett.* **1978**, 1415–1418. (g) Fraser, R. R.; Dhawan, K. L. *J. Chem. Soc., Chem. Commun.* **1976**, 674–675.

(15) (a) Jung, M. E.; Shaw, T. J.; Fraser, R. R.; Banville, J.; Taymaz, K. *Tetrahedron Lett.* **1979**, 4149–4152. (b) Bergbreiter, D. E.; Newcomb, M. *Ibid.* **1979**, 4145–4148. (c) Ludwig, J. W.; Newcomb, M.; Bergbreiter, D. E. *J. Org. Chem.* **1980**, *45*, 4666–4669.

(16) (a) Fraser, R. R.; Grindley, T. B.; Passannanti, S. *Can. J. Chem.* **1975**, *53*, 2473–2480. (b) Fraser, R. R.; Ng, L. K. *J. Am. Chem. Soc.* **1976**, *98*, 5895–5899.

(17) A refree has suggested that the actual base working in a system of RLi + HMPA at room temperature must be RCH_2NLiMe, formed by the reaction of RLi and HMPA, instead of RLi itself. This is entirely possible, but the reaction of **6b** with **1b** in HMPA at −78 °C gave the same result as that at room temperature (see entries 18 and 20 in Table I).