The observations reported here demonstrate the existence of solids containing magnesiate ions and strongly suggest that stable solutions containing significant concentrations of such ions can readily be formed.

(19) NMR observations indicated no significant interaction between Et_2Mg and 15-crown-5 in tetrahydrofuran but partial formation of 1:1 and 2:1 (which could perhaps have been 3:1) complexes in diethyl ether.[2] Particularly since ^1H and ^{13}C NMR absorptions of the ethyl groups underwent little change on addition of the crown ether, we assumed that "ate" species are formed only in small amounts and that the changes in chemical shifts observed in diethyl ether resulted from coordination of oxygens of the crown ether to intact Et_2Mg. Such coordination presumably was not significant in tetrahydrofuran because oxygens of 15-crown-5 could not compete effectively with those of tetrahydrofuran. We have now observed, however, that the ^1H NMR spectra of some solutions formed by adding 15-crown-5 to a *benzene solution* of Np_2Mg show two sets of absorptions for the neopentyl groups consistent with the formation in the noncoordinating solvent of significant amounts of $NpMg^+$(crown) and of magnesiate anions and leaves less certain the identity of the species responsible for the NMR shifts observed for diethyl ether solutions.

Acknowledgment. We are grateful to the National Science Foundation for support of this research and for aiding in the purchase of the NMR spectrometers. We thank Professor Lloyd Jackman for numerous helpful discussions and Alan Freyer for obtaining the high-field NMR spectra.

Registry No. 1, 100-71-0; **2**, 536-75-4; $[EtMg^+(2,2,1\text{-cryptand})]_2Et_6Mg_2^{2-}$, 93842-25-2; $NpMg^+(2,1,1\text{-cryptand})Np_3Mg^-$, 93842-28-5; Et_2Mg, 557-18-6; Np_2Mg, 19978-31-5; Mg, 7439-95-4; 2,1,1-cryptand, 31250-06-3; 2,2,1-cryptand, 31364-42-8; 2,2,2-cryptand, 23978-09-8; pyridine, 110-86-1.

Supplementary Material Available: ORTEP drawings of the unit cell and tables of atomic coordinates, bond angles and bond lengths, anisotropic thermal parameters, root-mean-square amplitudes of thermal vibration, and observed and calculated structure factor amplitudes for both crystal structure (42 pages). Ordering information is given on any current masthead page.

Photoinduced Cyclizations of Mono- and Dianions of *N*-Acyl-*o*-chloroanilines and *N*-Acyl-*o*-chlorobenzylamines as General Methods for the Synthesis of Oxindoles and 1,4-Dihydro-3(2*H*)-isoquinolinones[1]

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Contribution from the Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061. *Received December 15, 1983*

Abstract: Formation of the monoanions of a series of *N*-acyl-*N*-alkyl-*o*-chloroanilines by means of LDA in THF followed by irradiation with near-UV light affords 1,3-dialkyloxindoles in good yields. Similar photoinduced cyclizations of dianions derived from *N*-acyl-*o*-chloroanilines leads to 3-alkyloxindoles. Photocyclizations of mono- and dianions prepared from α,β-unsaturated *o*-haloanilides proceed to form 3-alkylideneoxindoles. Carbanions derived from *N*-acyl-*o*-chlorobenzylamines also undergo photoassisted ring closure to afford 1,4-dihydro-3(2*H*)-isoquinolinones. The influence of near-UV light and the effect of inhibitors implicate a radical-chain mechanism as the major reaction pathway in this convenient new method for oxindole and isoquinolinone synthesis.

The importance of oxindoles and 1,4-dihydro-3(2*H*)-isoquinolinones as synthetic intermediates[2] and pharmaceutical agents[3] has lead to development of numerous methods for their preparation.[4] Among these, considerable attention has been given to reactions in which appropriate precursors having a side chain containing a reactive center positioned for construction of the heterocyclic ring are subjected to cyclization at the ortho position of an aromatic nucleus. For example, oxindoles are available by acid-catalyzed cyclization of α-hydroxyacetanilides,[5] cyclization of *N*-(*o*-bromophenyl)acetamides in the presence of NaH and CuBr,[6] the traditional Lewis acid catalyzed cyclization of α-haloacetanilides,[7] and by photocyclization of 2-(*N*-methylanilino)-acetoacetates followed by oxidative rearrangement.[8] 1,4-Dihydro-3(2*H*)-isoquinolinones have been synthesized by analogous intramolecular reactions, including acid-catalyzed cyclization of *N*-benzylamides derived from benzilic acid[9] and Friedel–Crafts cyclization of *N*-(α-chloroalkyl)phenylacetamides.[10] Recently,

(1) (a) Supported by National Science Foundation Grant CHE 80-22538. (b) From the Ph.D. dissertations of M. C. Sleevi, Virginia Polytechnic Institute and State University, June, 1979 and R. R. Goehring, Virginia Polytechnic Institute and State University, November, 1980. (c) For a preliminary report of this work, see: Wolfe, J. F.; Sleevi, M. C.; Goehring, R. R. *J. Am. Chem. Soc.* **1980**, *102*, 3646. (d) Dedicated to Prof. Milos Hudlicky in honor of his 65th birthday.

(2) (a) Sirowej, H.; Khan, S. A.; Plieninger, H. *Synthesis*, **1972**, 84. (b) Kubo, A.; Nakai, T. *Synthesis*, **1980**, 365. (c) Gassman, P. G.; Cue, B. W., Jr. Ger. Offen. 781 026, 1977; *Chem. Abstr.* **1979**, *90*, 54821. (d) Gassman, P. G.; Cue, B. W., Jr. U.S. Patent 800 129, 1977; *Chem. Abstr.* **1980**, *92*, 165 220. (e) Gassman, P. G.; Halweg, K. M. *J. Org. Chem.* **1979**, *44*, 628. (f) Pandey, G. D.; Tiwari, K. P. *Heterocycles* **1980**, *14*, 59.

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(4) For reviews, see: (a) Sumpter, W. C. *Chem. Rev.* **1945**, *37*, 443. (b) Elderfield, R. C. "Heterocyclic Compounds"; Wiley: New York, 1952; p 128. (c) Sundberg, R. I. "Chemistry of Indoles"; Academic Press: New York, 1970; p 357.

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(6) Kametani, T.; Ohsawa, T.; Ihara, M. *Heterocycles* **1980**, *14*, 277.

(7) See: Beckett, A. H.; Daisley, R. W.; Walker, J. *Tetrahedron* **1968**, *24*, 6093 and references cited therein.

(8) Schultz, A. G.; Hagmann, W. K. *J. Org. Chem.* **1978**, *43*, 3391, 4231.

(9) (a) Petyunin, P. A. *Zh. Obsch. Khim.* **1952**, *22*, 697. (b) Gardent, J.; Hamon, M. *Bull. Soc. Chim. Fr.* **1966**, *556*.

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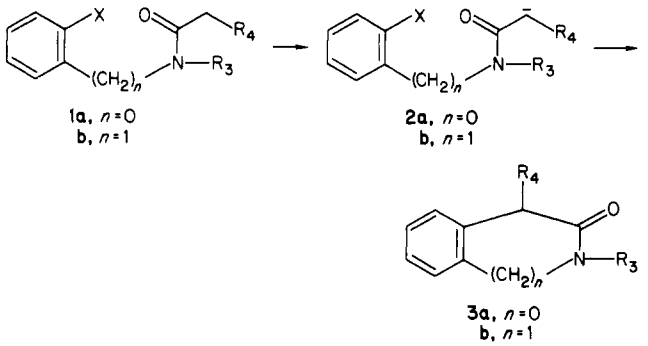
several ring closure reactions have been found to be suitable for the synthesis of both oxindoles and 1,4-dihydro-3(2*H*)-isoquinolinones. These include, intramolecular amido alkylations of *N*-phenyl- and *N*-benzylamides of bis(methoxycarbonylamino)acetic acid,[11] photolytic cyclizations of *N*-(α-chloroacyl)anilines and benzylamines,[12] cyclization of *N*-(*o*-bromophenyl)- and *N*-(*o*-bromobenzyl)acrylamides by means of Pd(II) reagents,[13] Friedel–Crafts cyclizations of *N*-phenyl- and *N*-benzyl-α-chloro-α-methylthioacetamides, and acid-catalyzed ring closure of the corresponding α-chloro-α-methylsulfinyl derivatives.[14]

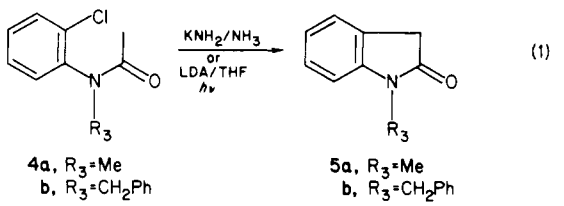
In spite of the apparent versatility represented by the methods described above, a majority of them fail to provide control over the direction of cyclization when the aromatic ring contains substituents *meta* to the reactive side chain.[5,7-12,14] The present study was based on the initial premise that a general, regiospecific synthesis of *N*-alkyloxindoles (**3a**) and *N*-alkyl-1,4-dihydro-3-



(2*H*)-isoquinolinones (**3b**) would result from cyclization of carbanions **2a–b** derived from *N*-acyl-*N*-alkyl-*o*-haloanilines (**1a**) and *N*-acyl-*N*-alkyl-*o*-halobenzylamines (**1b**). Although previous attempts to affect cyclization of carbanions **2a–b** through intramolecular aryne reactions had met with limited success,[15] it seemed possible that the difficulties associated with such reactions might be avoided by employing conditions whereby displacement of the normally recalcitrant halogen of carbanions **2a–b** could be accomplished by carrying out the cyclization step under conditions which would facilitate an electron-transfer mode of substitution analogous to the intermolecular $S_{RN}1$ mechanism for aromatic nucleophilic substitution.[16] We were encouraged by results in our laboratories[17] and elsewhere,[18] which demonstrated that carboxamide α-anions undergo intermolecular photostimulated $S_{RN}1$ reactions with carboaromatic and heteroaromatic halides. Moreover, Semmelhack and co-workers[19] had found that ketone enolates participated in photoinduced intramolecular $S_{RN}1$ reactions to form 6-, 7-, 8-, and 10-membered carbocyclic rings. Subsequently, we published a preliminary account of the photocyclization of several monoanions and dianions (R_3 = Li) of type **2a** to afford oxindoles in good yields.[1c] The present paper represents a description of the scope and limitations of this new method as it applies to the synthesis of both oxindoles and 1,4-dihydro-3(2*H*)-isoquinolinones.

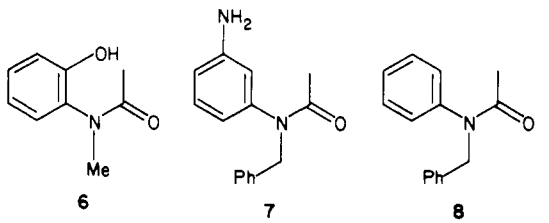
Results and Discussion

Oxindoles. Initial studies were carried out with anilides **4a–b** as potential precursors to oxindoles **5a–b** (eq 1). These exper-



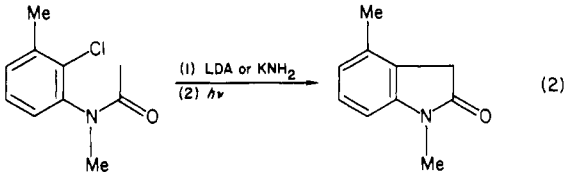
(1)

iments, as well as others leading to oxindoles, are summarized in Table I. Treatment of **4a** or **4b** with 3 equiv of KNH_2 in liquid NH_3 for 30–45 min without illumination afforded oxindoles **5a** and **5b** in yields of 51% and 43%, respectively (expt 2 and 6). Slightly higher yields were obtained when the reaction mixtures were irradiated with near-UV light (expt 1 and 5). Aryne-derived products **6** and **7** were obtained from **4a** and **4b**, respectively, in



both dark and illuminated reactions. Treatment of **4a** with 3 equiv of LDA in THF followed by 30 min of irradiation gave **5a** in 81% yield (expt 3), while the yield of **5a** was only 31% after 3 h in the dark. *N*-Benzylanilide **4b** behaved similarly, but somewhat more sluggishly, to give 32% of **5b**, 8% of reduction product **8** and 60% of recovered **4b** after 30 min of illumination with LDA (expt 7). Only starting material was obtained after 30 min in the dark (expt 8). On the basis of these experiments, subsequent preparations were conducted with LDA under illumination at ambient temperature. This approach worked smoothly to afford oxindoles **5a–e**.

Of particular note is the observation that *N*-chloro-3,*N*-dimethylacetanilide (**4c**), which cannot participate in an aryne



(2)

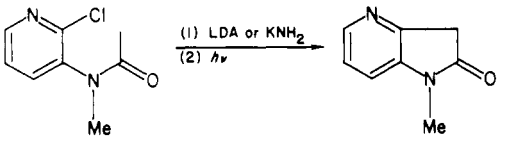
reaction, underwent photocyclization to give 1,4-dimethyloxindole (**5c**) in excellent yields with LDA or KNH_2 (expt 9 and 11). However, **4c** failed to cyclize with either base in the dark (expt 10 and 12). The rate of photoinduced cyclization of **4c** with KNH_2 in liquid NH_3 was decreased ca. 10-fold in the presence of 10 mol % of the radical scavenger, di-*tert*-butyl nitroxide (DTBN)[20] (expt 14).

1-Methyl-5-methoxyoxindole (**5d**) and 1-methyl-6-methoxyoxindole (**5e**) were easily prepared from the appropriate 4- and 5-methoxyanilides (expt 15 and 16). However, treatment of

(11) Ben-Ishai, D.; Peled, N.; Sataty, I. *Tetrahedron Lett.* **1980**, 569.
(12) (a) Hamada, T.; Okuno, Y.; Ohmori, M.; Nishi, T.; Yonemitsu, O. *Heterocycles* **1977**, *8*, 251. (b) Ikeda, M.; Hirao, K.; Okuno, Y.; Yonemitsu, O. *Tetrahedron Lett.* **1974**, 1181. (c) Ikeda, M.; Hirao, K.; Okuno, Y.; Numao, N.; Yonemitsu, O. *Tetrahedron* **1977**, *33*, 489.
(13) (a) Mori, M.; Chiba, K.; Ban, Y. *Tetrahedron Lett.* **1977**, 1807. (b) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1979**, 1133.
(14) Tamara, Y.; Uenishi, J.; Maeda, H.; Choi, H.; Ishibashi, H. *Synthesis* **1981**, 534.
(15) (a) For example, compounds **1a** (R_3 = H, R_4 = COMe; R_3 = Me; R_4 = Ph; and R_3 = Me, R_4 = H) underwent cyclization in the presence of excess KNH_2 in liquid NH_3 to give the expected oxindoles, while **1a** (R_3 = H, R_4 = Ph) failed to cyclize, and **1a** (R_3 = H, R_4 = H) gave only 2-methylbenzoxazole. See: Bunnett, J. F.; Kato, T.; Flynn, R. R.; Skorcz, J. A. *J. Org. Chem.* **1963**, *28*, 1 and references cited therein. (b) Treatment of several *N*-acyl-*o*-chlorobenzylamines of type **1b** under similar conditions gave <15% of the desired 1,4-dihydro-3(2*H*)-isoquinolinones. Fryer, R. I.; Early, J. V.; Zally, W. *J. Heterocycl. Chem.* **1967**, *4*, 149.
(16) For reviews on the $S_{RN}1$ reaction, see: (a) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413. (b) Wolfe, J. F.; Carver, D. R. *Org. Prep. and Proced. Int.* **1978**, *10*, 225. (c) Chanon, M.; Tobe, M. L. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 1. (d) Rossi, R. A.; de Rossi, R. H. In "Aromatic Substitution by the $S_{RN}1$ Mechanism"; American Chemical Society: Washington, DC, 1983; ACS Monogr. No. 1978.
(17) Wong, J.-W. Ph. D. dissertation, Virginia Polytechnic Institute and State University, June, 1981.
(18) Rossi, R. A.; Alonso, R. A. *J. Org. Chem.* **1980**, *45*, 1239.
(19) (a) Semmelhack, M. F.; Bargar, T. M. *J. Org. Chem.* **1977**, *42*, 1481. (b) Semmelhack, M. F.; Bargar, T. *J. Am. Chem. Soc.* **1980**, *102*, 7765.
(20) (a) Hoffman, A. K.; Feldman, A. M.; Geblum, E.; Hodgson, W. G. *J. Am. Chem. Soc.* **1964**, *86*, 639. (b) Nelson, S. F.; Bartlet, P. D. *Ibid.* **1966**, *88*, 143.

2,3-dichloro-, 2,4-dichloro-, and 2-chloro-5-(trifluoromethyl)-anilides **4f–h**, respectively, with LDA under illumination at −78 to +25 °C caused extensive decomposition of the substrates, and none of the expected oxindoles could be detected (expt 17–19).

Photocyclization of 2-chloro-3-(*N*-methylacetamido)pyridine (**4i**) by means of KNH_2 in liquid NH_3 or LDA in THF at −78

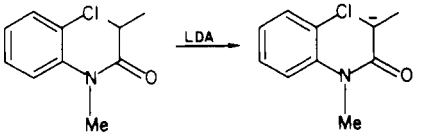


(3)

4j **5j**

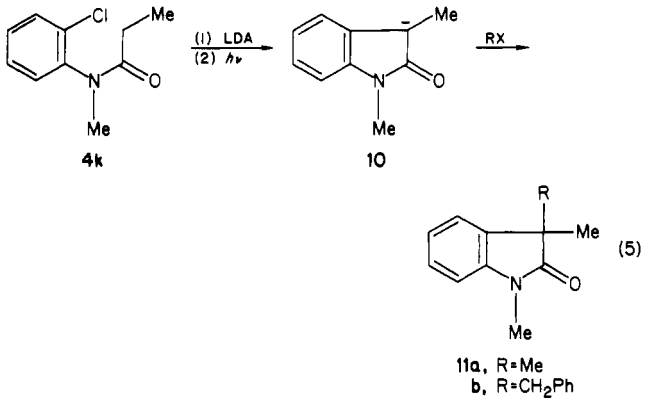
°C gave azaoxindole **5i** in good yield (expt 20 and 21). Temperatures above −30 °C led to decomposition of the intermediate carbanion. No reaction was observed in the dark or in the presence of DTBN.

Next, we turned our attention to the preparation of 1,3,3-trialkyloxindoles, with 1,3,3-trimethyloxindole (**11a**) as the initial target. Treatment of anilide **4j** with LDA produced tertiary carbanion **9** as evidenced by D_2O quenching. However, irradiation of **9** for 3 h gave mostly recovered **4j** along with several unidentified products. This obstacle was overcome easily as illustrated in eq 5 with *o*-chloroanilide **4k**, which has the *N*-alkyl group and



(4)

4j **9**



(5)

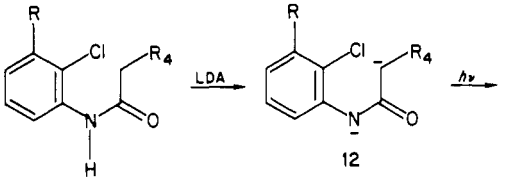
4k **10**

11a, R=Me
b, R=CH_2Ph

one of the incipient 3-substituents already in place. Conversion of **4k** into its secondary carbanion by means of LDA followed by photocyclization and quenching of the resulting oxindole carbanion **10** with methyl iodide or benzyl chloride afforded trisubstituted oxindoles **11a–b** in yields of 66% and 60%, respectively.

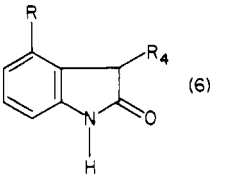
While the syntheses of *N*-alkyloxindoles described above are convenient and useful, any general method should also allow for the preparation of oxindoles without substituents on nitrogen. The applicability of the present methodology was demonstrated by converting anilides **4n–q** to anions **12** by means of LDA[21] followed by irradiation to give oxindoles **5n–q** (eq 6, Table I). As in reactions leading to *N*-alkyloxindoles, illumination was required for cyclization and DTBN had a strong inhibitory effect. Photocyclizations of dianions **12** generally proceeded approximately one-third as rapidly as monoanion cyclizations. Attempted photocyclization of the dianion of 2-chloro-3-acetamidopyridine (**4r**) gave recovered starting material (expt 30).

N-Methyl α,β-unsaturated anilides **13a–c** underwent intramolecular arylation exclusively at the α-position to afford 3-alkylideneoxindoles **14a–b** (eq 7, Table II). These reactions ex-



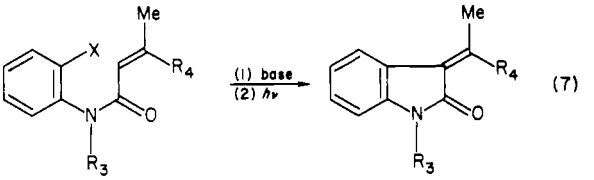
4n, R=Me
o–q, R=H

12



(6)

5n, R=Me
o–q, R=H



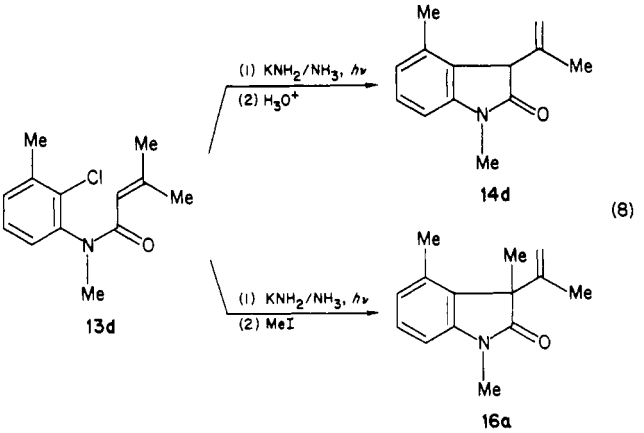
(7)

13a, R_3=Me; R_4=H; X=Cl
b, R_3=R_4=Me; X=Cl
c, R_3=R_4=Me; X=I

14a, R_3=Me; R_4=H
b, R_3=R_4=Me

hibited characteristics somewhat different from those involving saturated anilides **4**. Thus, **13a–b** underwent photocyclization with LDA in THF much more slowly than **4** (expt 31 and 35). For example, 15 h of irradiation was necessary to bring the yield of **14b** to 70% (expt 37). On the other hand, when KNH_2 in liquid NH_3 was employed, **13a–c** cyclized smoothly during 15 min of illumination to afford **14a–b** in excellent yields (expt 33, 44, and 45). Yields of **14a–b** were not significantly decreased in the dark, until 50 mol % of DTBN had been added to the reaction mixture (expt 34, 39, 41, 42, and 46). Interestingly, cyclization of **13b** in the dark was completely suppressed by 10 mol % of *p*-dinitrobenzene (expt 43 and 44); deconjugated anilide **18b** was recovered from the reaction mixture.

Treatment of 3-methylanilide **13d** with KNH_2 in liquid NH_3 for 3 h in the dark produced no cyclization products. Instead,



13d

14d

16a

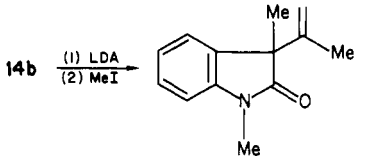
(8)

deconjugated anilide **18d** was obtained in 73% yield (expt 48). Irradiation of a similar reaction mixture afforded oxindole **14d** in 87% isolated yield (expt 49 and 50). Photocyclization of **13d** was not appreciably inhibited by 10 mol % of DTBN; however, 50 mol % of DTBN decreased the yield of **14d** by half (expt 49 and 51).

When **13d** was treated with KNH_2 in liquid NH_3 under photostimulation for 3 h and the resulting reaction mixture quenched with methyl iodide, tetrasubstituted oxindole **16a** was obtained in 73% yield (eq 8). Compounds related to **16a** also can be synthesized from 3-alkylideneoxindoles as exemplified by the

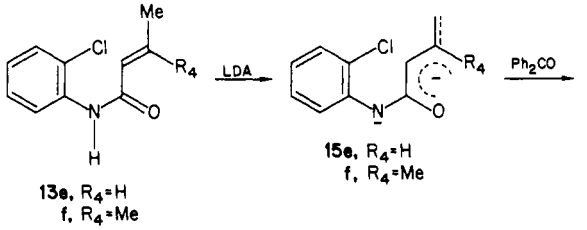
(21) Dianions of related anilides are not formed satisfactorily by means of KNH_2 in liquid NH_3. Gay, R. L.; Hauser, C. R. *J. Am. Chem. Soc.* **1967**, *89*, 1647.

preparation of **16b** in 97% yield from **14b** (eq 9).



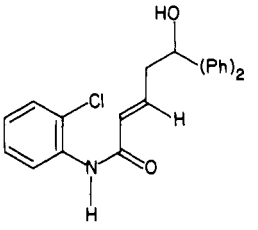
16b (9)

Conversion of α,β-unsaturated anilide **13e** to dianion **15e** by means of 3 equiv of LDA occurred in good yield as shown by trapping experiments with benzophenone to give carbinol **17** (eq 10). Irradiation of dianions **15e–f** for 3 h gave alkylideneoxindoles



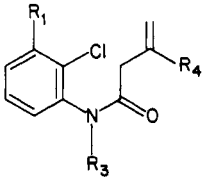
13e, R_4=H
f, R_4=Me

15e, R_4=H
f, R_4=Me



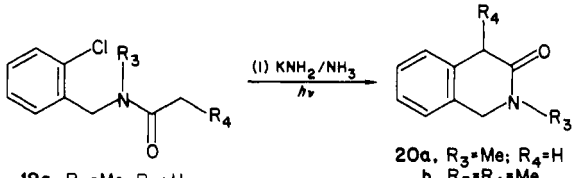
17 (10)

14e and **14f** in yields of 48% and 14%, respectively (expt 52 and 54). When 4 equiv of LDA was used to generate dianion **15f**, photocyclization afforded 89% of **14f** (expt 56). Dianions **15e–f** failed to cyclize without illumination. Thus, when the respective reaction mixtures were quenched after 3 h in the dark, deconjugated anilides **18e–f** were obtained.



18d, R_1=R_3=R_4=Me
e, R_1=R_3=R_4=H
f, R_1=R_3=H; R_4=Me

1,4-Dihydro-3(2*H*)-isoquinolinones. Photocyclization of the carbanions prepared from *N*-acyl-*N*-methyl-*o*-chlorobenzylamines **19a–c** by means of KNH_2 in liquid NH_3 gave 1,4-dihydro-3-

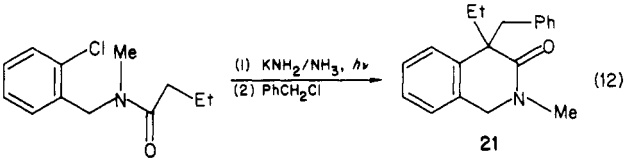


19a, R_3=Me; R_4=H
b, R_3=R_4=Me
c, R_3=Me; R_4=Et

20a, R_3=Me; R_4=H
b, R_3=R_4=Me
c, R_3=Me; R_4=Et (11)

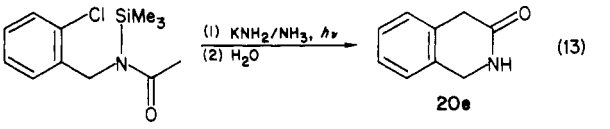
(2*H*)-isoquinolinones **20a–c** in yields of 54–62% (Table III, expt 59, 60, and 62). Cyclization of **19b** failed to proceed in the dark. Attempts to effect ring closure of **19a** using LDA in THF with irradiation periods up to 3 h returned starting material.[22]

The in situ cyclization–alkylation procedure used to prepare 1,3,3-trialkyloxindoles was shown to be applicable to the synthesis of similarly substituted isoquinolinones by the preparation of 2-methyl-4-ethyl-4-benzyl-3(2*H*)-isoquinolinone (**21**) from **19c** as shown in eq 12.



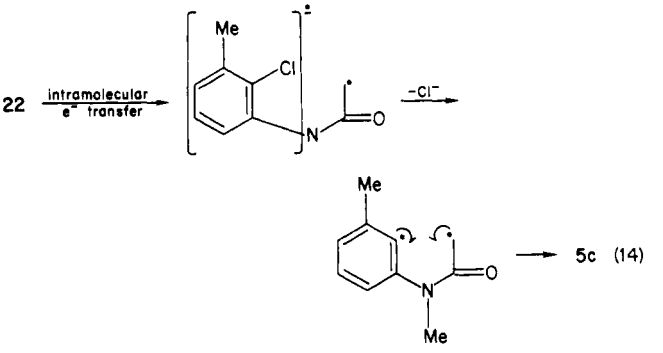
19c 21 (12)

Preparation of isoquinolinones without an N-substituent was first tested by attempting photocyclization of the dianion of *N*-acetyl-*o*-chlorobenzylamine (**19d**, R_3 = H; R_4 = H). Although the requisite dianion was easily generated by means of LDA,[23] irradiation for 1 h did not lead to cyclization. As expected,[21] KNH_2 in liquid NH_3 failed to produce sufficient equilibrium concentrations of the desired dianion. However, *N*-(trimethylsilyl)amide **19e** functioned moderately well as precursor to unsubstituted isoquinolinone **20e** as illustrated in eq 13 (expt 63).



19e 20e (13)

Mechanistic Considerations. Experiments 9–14 (Table I), conducted with 2-chloro-3-methyl-*N*-methylacetanilide (**4c**), provide evidence that the present photocyclizations proceed via the radical-chain sequence of Scheme I with substrates that cannot yield aryne intermediates. Initiation of the chain process is presumed to occur by photoassisted *intermolecular electron* transfer, perhaps with two carbanions **22** acting as a redox couple. The 10-fold decrease in reaction rate produced by 10 mol % of DTBN (expt 13 and 14) is consistent with the proposed chain reaction, but not with the conceivable nonchain process shown in eq 14. The latter pathway, which is initiated by *intramolecular*



electron transfer, also would be vulnerable to DTBN, but the extent of inhibition should be directly proportional to the molar quantity of DTBN. The lethargic rate of isoquinolinone formation in THF[22] may result from interception of an intermediate radical anion analogous to **25** by hydrogen atoms originating from the solvent. Although hydrogen atom abstraction also takes place during oxindole formation,[24] the relative rates of ring closure and hydrogen atom transfer favor production of the five-membered ring.

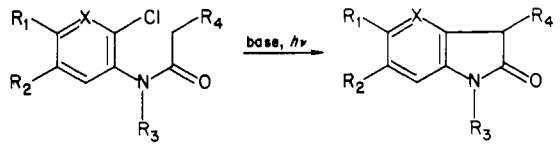
When KNH_2 in liquid NH_3 is used with certain saturated (**4a–b**) and unsaturated (**13a–c**) *o*-haloanilides that can yield aryne intermediates, cyclization occurs rapidly in the dark. At first

(22) This is in contrast to results reported by: Kessar, S. V.; Singh, P.; Chawla, R.; Kumar, P. *J. Chem. Soc., Chem. Comm.* **1981**, 1074. They cyclized similar systems using 4 equiv of LDA in THF by either irradiating for 1.5 h or stirring for 15 h at 25 °C in the dark.

(23) A D_2O quench of the dianion afforded **19d** containing 0.73 deuterium atom at the methyl group.

(24) Products resulting from dehalogenation were detected during photocyclizations (THF) of monoanions derived from **4a–e**, the dianion of **4n**, and the monoanion of **4b** in liquid NH_3 when ether or THF were employed as cosolvents. For similar results in intermolecular $S_{RN}1$ reactions, see: (a) Kim, J. K.; Bunnett, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 7463. (b) Tolbert, L. M.; Martone, D. P. *J. Org. Chem.* **1983**, *48*, 1185.

Table I. Cyclization of *N*-Acyl-*o*-chloroanilines **4** To Form Oxindoles **5**



4 **5**

expt	starting anilide	R_1	R_2	R_3	R_4	X	base (equiv)	irradiation time, h	oxindole	yield,[a] %
1	**4a**	H	H	Me	H	CH	KNH_2 (3)[b]	0.5	**5a**[c]	57
2	**4a**	H	H	Me	H	CH	KNH_2 (3)	0.5[d]	**5a**	51
3	**4a**	H	H	Me	H	CH	LDA (3)	0.5	**5a**	81
4	**4a**	H	H	Me	H	CH	LDA (3)	0.5[d]	**5a**	31
5	**4b**	H	H	CH_2Ph	H	CH	KNH_2 (3)[b]	0.5	**5b**[e-g]	57
6	**4b**	H	H	CH_2Ph	H	CH	KNH_2 (3)	0.5[d]	**5b**	43
7	**4b**	H	H	CH_2Ph	H	CH	LDA (3)	0.5	**5b**	32
8	**4b**	H	H	CH_2Ph	H	CH	LDA (3)	0.5[d]	**5b**	*h*
9	**4c**	H	H	Me	H	C-Me	LDA (3)	1.0	**5c**[g]	87
10	**4c**	H	H	Me	H	C-Me	LDA (3)	1.0[d]	**5c**	*h*
11	**4c**	H	H	Me	H	C-Me	KNH_2 (3)	0.5	**5c**	80
12	**4c**	H	H	Me	H	C-Me	KNH_2 (3)	0.5[d]	**5c**	*h*
13	**4c**	H	H	Me	H	C-Me	KNH_2 (3)	0.1	**5c**	46
14	**4c**	H	H	Me	H	C-Me	KNH_2 (3)	0.1[i]	**5c**	4
15	**4d**	OMe	H	Me	H	CH	LDA (3)	1.0	**5d**[j]	91
16	**4e**	H	OMe	Me	H	CH	LDA (3)	1.0	**5e**[k]	55
17	**4f**	H	H	Me	H	C-Cl	LDA (3)	1.0	**5f**	*l*
18	**4g**	Cl	H	Me	H	CH	LDA (3)	1.0	**5g**	*l*
19	**4h**	H	CF_3	Me	H	CH	LDA (3)	1.0[d]	**5h**	*l*
20	**4i**	H	H	Me	H	N	KNH_2 (3)	0.5	**5i**[g]	62
21	**4i**	H	H	Me	H	N	LDA (3)	4.0	**5i**	83
22	**4j**	H	H	Me	$(Me)_2$	CH	LDA (3)	1.0	**11a**	*h*
23	**4k**	H	H	Me	Me	CH	LDA (3)	4.0	**5k**[m]	45
24	**4l**	H	H	Me	*n*-Bu	CH	LDA (3)	3.0	**5l**[n]	73
25	**4m**	H	H	Me	Ph	CH	LDA (3)	3.0	**5m**[o]	64
26	**4n**	H	H	H	H	C-Me	LDA (4)	3.0	**5n**[p]	76
27	**4o**	H	H	H	H	CH	LDA (4)	3.0	**5o**[q]	74
28	**4p**	H	H	H	Me	CH	LDA (4)	3.0	**5p**[r]	73
29	**4q**	H	H	H	Ph	CH	LDA (4)	3.0	**5q**[s]	63
30	**4r**	H	H	H	H	N	LDA (4)	3.0	**5r**	*h*

[a] Isolated yield. [b] Ether on THF was used as cosolvent. [c] Mp 88–88.5 °C. Bunnett et al. (Bunnett, J. F.; Kato, T.; Flynn, R. R.; Skorez, J. A. *J. Org. Chem.* **1963**, *28*, 1) report 87–89 °C. [d] Reaction was connducted in the dark. [e] Mp 74–76 °C. [f] Satisfactory elemental analysis and ^1H NMR data were obtained for this compound. [g] Spectral and other details are given in the Experimental Section. [h] Only starting material was recovered. [i] 10 mol % of DTBN was added before illumination. [j] Mp 95–97 °C. Beckett et al. (Beckett, A. H.; Daisley, R. W.; Walker, J. *Tetrahedron* **1968**, *24*, 6093) report 98 °C. [k] Mp 108–110 °C; lit.[j] mp 108–110 °C. [l] Photolysis of reaction mixtures at −78 °C did not result in the desired oxindole. At higher temperature a tar was obtained. Reactions conducted in the dark at low temperature gave starting material. [m] Mp 54–55 °C. Wolfrom et al. (Wolfrom, M. L.; Georges, L. W.; Soltzberg, S. *J. Am. Chem. Soc.* **1934**, *56*, 1794) report 55 °C. [n] Bp 120–122 °C (0.6 mm). Daisley et al. (Daisley, R. W.; Walker, J. *J. Chem. Soc. C* **1971**, *1375*) report 128–130 °C (1.5 mm). [o] Mp 118–119 °C; lit.[c] mp 118–119 °C. [p] Mp 208–209.5 °C. Wright et al. (Wright, W. B., Jr.; Collins, K. H. *J. Am. Chem. Soc.* **1956**, *78*, 221) report 211–212 °C. [q] Mp 125–127 °C. Bayer (Bayer, A. *Ber.* **1978**, *11*, 583) reports 120 °C. [r] Mp 120–121 °C. Endler et al. (Endler, A. S.; Becker, E. I. "Organic Synthesis"; Wiley: New York, 1963; Collect Vol. IV, p 657) report 124 °C. [s] Mp 188–191 °C. Bruce et al. (Bruce, J. M.; Sutcliffe, F. K. *J. Chem. Soc.* **1957**, 4789) report 192 °C.

glance this could be taken as evidence for an aryne mechanism. However, expt 41–44 (Table II) involving unsaturated substrate **13b** indicate that this need not be the case. Thus, **13b** undergoes quantitative conversion to oxindole **14b** in the dark within 15 min (expt 41). The yield of **14b** is reduced to 54% in the presence of 50 mol % of DTBN (expt 42). However, when as little as 10 mol % of *p*-dinitrobenzene (DNB) is added to the reaction mixture, cyclization is completely inhibited (expt 43 and 44). The powerful inhibitory activity of DNB provides strong support for the radical chain mechanism of Scheme I. The greater effectiveness of DNB relative to DTBN may arise from the fact that the former reagent exhibits its inhibitory effect via a bimolecular electron transfer reaction in which a radical anion intermediate such as **26** in Scheme I donates an electron to DNB rather than to a substrate molecule, thereby preventing step 4 and breaking the propagating cycle. On the other hand, DTBN has only radicals such as **25** as targets for its inhibitory effect and is forced to compete with the intramolecular chain-carrying conversion of **25** to cyclic radical anion **26**.

Synthetic Implications. The present carbanion photocyclizations provide several important advantages over traditional synthesis of oxindoles and 1,4-dihydro-3(2*H*)isoquinolinones; these include the use of readily available starting materials, convenient experimental procedures, and predictable regiochemistry during ring closure. In order to utilize these reactions to the best advantage, the following reaction conditions should be considered: (1) 1-Alkyl-, 3-alkyl-, and 1,3-dialkyloxindoles are best prepared by photocyclizations using LDA in THF. (2) 1,3,3-Trialkyloxindoles are conveniently obtained through photocyclization of secondary carbanions, followed by in situ alkylation of the resulting oxindole monoanion. (3) The use of KNH_2 in liquid NH_3 is preferred over LDA in THF for cyclization of *N*-methyl α,β-unsaturated anilides; illumination may not be required unless the substrate contains a substituent at the 3-position. (4) Preparation of 3-alkylideneoxindoles without substituents on nitrogen requires photostimulation in the presence of LDA in THF. (5) *N*-Acyl-*N*-methyl-*o*-chlorobenzylamines give 1,4-dihydro-3(2*H*)-isoquinolinones more rapidly upon irradiation with KNH_2 in liquid NH_3 than with LDA in THF.

Experimental Section

General. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Boiling points are also uncorrected. Elemental analyses were performed by Analytical Services of VPI & SU under the direction of T E. Glass using a Perkin-Elmer 240 C, H and N analyzer, by Galbraith Laboratories, Knoxville, TN, and by Multichem Lab., Inc., Lowell, MA. Infrared spectra were obtained by using a

Table II. Cyclization of α,β-Unsaturated Anilides **13** To Form 3-Alkylideneoxindoles **14**

expt	starting anilide	base (equiv)	irradiation time, h	product	yield,[a] %
31	**13a**	LDA (3)	3.0	**14a**[b]	33 (5:1)[c]
32	**13a**	LDA (3)	3.0[d]	**14a**	43 (3:1)[c]
33	**13a**	KNH_2 (3)	3.0	**14a**	63 (3:1)[c]
34	**13a**	KNH_2 (3)	3.0[d]	**14a**	65 (5:1)[c]
35	**13b**	LDA (3)	3.0	**14b**[e]	50
36	**13b**	LDA (3)	3.0[d]	**14b**	15
37	**13b**	LDA (3)	15.0	**14b**	70
38	**13b**	KNH_2 (3)	3.0	**14b**	65
39	**13b**	KNH_2 (3)	3.0[d]	**14b**	65
40	**13b**	KNH_2 (3)	0.25	**14b**	100[f]
41	**13b**	KNH_2 (3)	0.25[d]	**14b**	100[f]
42	**13b**	KNH_2 (3)	0.25[d,g]	**14b**	54[h]
43	**13b**	KNH_2 (3)	0.25[d,i]	**18b**[b]	90
44	**13b**	KNH_2 (3)	0.25[d,j]	**18b**	100[f]
45	**13c**	KNH_2 (3)	0.25	**14b**	90
46	**13c**	KNH_2 (3)	0.17[d]	**14b**	92
47	**13c**	KNH_2 (3)	0.25[k]	**14b**	96
48	**13d**	KNH_2 (3)	3.0[d]	**18d**[b]	73
49	**13d**	KNH_2 (3)	3.0[k]	**14d**[b,l]	88
50	**13d**	KNH_2 (3)	0.25	**14d**	100[f]
51	**13d**	KNH_2 (3)	0.25[g]	**14d**	47[m]
52	**13e**	LDA (3)	3.0	**14e**	48 (5:1)[c,n]
53	**13e**	LDA (3)	3.0[d]	**18e**[b]	81
54	**13f**	LDA (3)	3.0[o]	**14f**	14[p]
55	**13f**	LDA (3)	3.0[d]	**18f**[b]	72
56	**13f**	LDA (4)	3.0	**14f**	89
57	**13f**	LDA (4)	3.0[d]	**18f**[b]	75
58	**13f**	LDA (4)	0.25	**14f**	11[q]

[a] Isolated yield. [b] Spectral and other details are given in the Experimental Section. [c] Numbers in parentheses represent the ratio of trans:cis isomers. Structural assignments were based on those discussed by Autrey, R. L.; Tank, F. C. *Tetrahedron*, **1967**, *23*, 901. [d] Reaction was conducted in the dark. [e] Mp 82–83 °C. Daisley et al. (Daisley, R. W.; Walker, J. *J. Chem. Soc. C* **1971**, 1375) report 90–91 °C and Anthony (Anthony, W. C. *J. Org. Chem.* **1966**, *31*, 77) reports 72–74 °C. The ^1H NMR spectrum was consistent with the assigned structure. [f] GC yield. [g] 50 mol % of DTBN was present. [h] In addition, 43% of isomerized anilide, **18b**, was isolated. [i] 50 mol % of *p*-dinitrobenzene was present. [j] 10 mol % of *p*-dinitrobenzene was present. [k] 10 mol % of DTBN was present. [l] The 3-isopropenyloxindole was obtained instead of the expected 3-isopropylideneoxindole. [m] In addition, 52% of the isomerized anilide, **18d**, was obtained. [n] Mp 144 °C. Wenkert et al. (Wenkert, E.; Bernstein, B. S.; Udelhofen, J. H. *J. Am. Chem. Soc.* **1958**, *80*, 4899) report 142 °C. [o] The reaction was performed at room temperature. [p] Mp 188–190 °C. Anthony (Anthony, W. C. *J. Org. Chem.* **1966**, *31*, 77) reports 189–191 °C. [q] 26% starting material, **13f**, and 63% isomerized anilide, **18f**, were recovered.

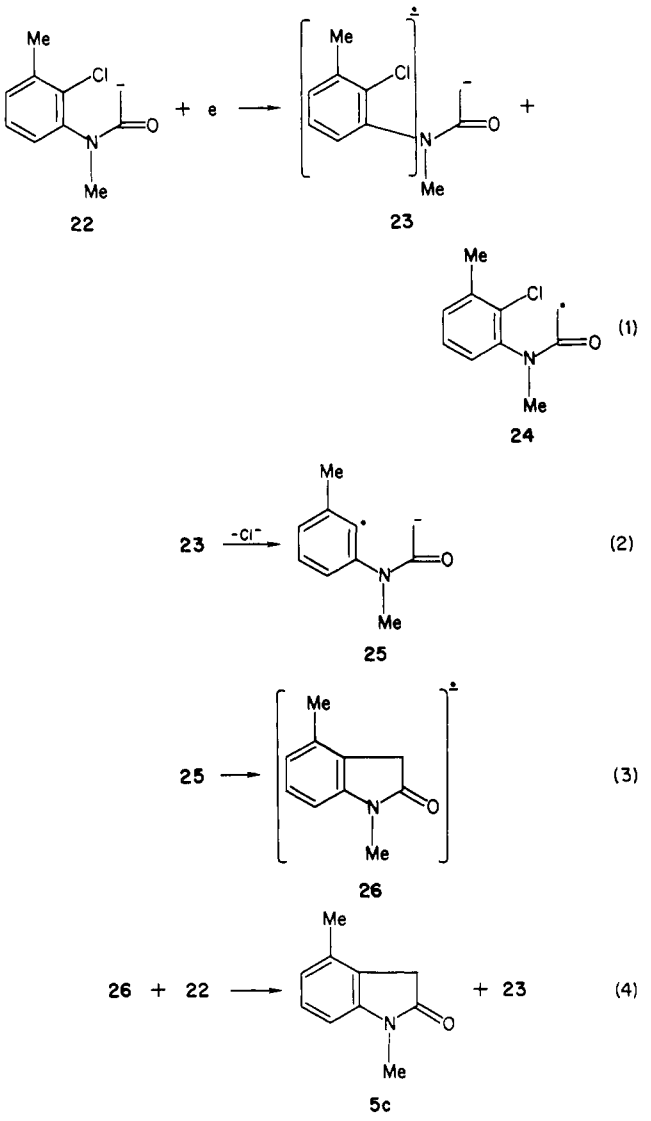
Table III. Cyclization of *N*-Acyl-*o*-chlorobenzylamines **19** To Form Isoquinolinones **20**

expt	starting anilide	irradiation, time, h	isoquinolinone	yield,[a] %
59	**19a**	1.0	**20a**[b]	62
60	**19b**	1.0	**20b**[c]	60
61	**19b**	1.0[d]	**20b**	*e*
62	**19c**	1.0	**20c**[c]	54
63	**19e**	1.0	**20e**[c]	43

[a] Isolated yield. [b] Mp 65–67 °C. Hoeft et al. (Hoeft, E.; Schultze, H. *J. Prakt. Chem.* **1966**, *32*, 12) report 67–69 °C. [c] Spectral and other details are given in the Experimental Section. [d] Reaction was conducted in the dark. [e] Starting material was recovered in 93% yield.

Perkin-Elmer 710 B infrared spectrophotometer. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Varian EM-390 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (Me_4Si) as internal standard. Thin-layer chromatography (TLC) was performed by using Eastman Chromatogram Sheets, Type 13181 (silica gel) with fluorescent indicator. Chromatography refers to ambient-pressure column chromatography using 60–200 mesh Davidson silica gel. Gas Chromatography (GC) was performed on a Varian Associates 90-P instrument equipped with a thermal conductivity detector, using 6 ft × $^1/_4$ in. columns containing the specified column packing and operating at the noted temperatures. Flow rates of helium were on the order of 40–50 mL/min. Anhydrous liquid ammonia (Matheson) was used directly from the tank since distillation from sodium was shown not to influence the outcome of the reactions. Tetrahydrofuran (THF) was distilled under nitrogen from lithium aluminum hydride or benzophenone potassium ketyl. Unless otherwise stated all chemicals were obtained from commercial sources and used as received. Solutions were dried by using anhydrous magnesium sulfate. Diisopropylamine was distilled under nitrogen from calcium hydride. Hexane solutions of *n*-butyllithium (purchased from Aldrich Chemical Co.) were periodically standardized against diphenylacetic acid by the procedure of Kofran and Baclawski.[25] Photostimulated reactions were carried out in an inert atmosphere using a Rayonet RPR-240 photoreactor equipped with four 12.5-W lamps emitting maximally at 350 nm. Di-*tert*-butyl nitroxide was prepared from 2-methyl-2-nitropropane.[26]

Scheme I



N-(2-Chloro-3-methylphenyl)acetamide (4n). The following procedure is typical of those used to prepare anilides **4a–r**. To a solution of 7.08 g (50 mmol) of 2-chloro-3-methylaniline in 50 mL of benzene cooled in an ice bath was added dropwise 7.66 g (75 mmol) of acetic anhydride in 50 mL of benzene. The reaction mixture was brought to reflux for 1 h and then cooled to room temperature. Water (200 mL) was added, the layers were separated, and the aqueous layer was extracted once with benzene. The combined benzene layers were washed with several portions of dilute HCl, saturated $NaHCO_3$, and finally water. The benzene layer was dried and filtered, and the solvent was removed in vacuo to give 8.02 g (87%) of **4n**. Recrystallization from methylene chloride/hexane gave pure **4n**: mp 131.5–132.5 °C (lit.[27] mp 133–134 °C); ^1H NMR ($CDCl_3$)

(25) Kofran, N. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.
(26) Kornblum, N.; Clutter, R. J.; Jones, W. J. *J. Am. Chem. Soc.* **1956**, *78*, 4003.

δ 2.21 (s, 3 H, 3 CH_3), 2.37 (s, 3 H, $COCH_3$), 6.83–7.27 (m, 2 H, aromatic), 7.67 (br s, 1 H, NH), 8.10 (d, 1 H, aromatic).

***N*-(2-Chloro-3-methylphenyl)-*N*-methylacetamide (4c).** *N*-(2-Chloro-3-methylphenyl)acetamide (**4n**) was methylated following the procedure of Pachter and Kloetzel.[28] After Kugelrohr distillation, **4c** was obtained as a colorless liquid which set to a white solid (95%). Recrystallization from petroleum ether at −40 °C gave white needles: mp 71–74 °C, bp 102–103 °C (0.30 mm); ^1H NMR ($CDCl_3$) δ 1.80 (s, 3 H, $COCH_3$), 2.45 (s, 3 H, 3 CH_3), 3.17 (s, 3 H, NCH_3), 7.03–7.40 (m, 3 H, aromatic); IR (5% solution in $CHCl_3$) 1657 cm^{-1} (C=O). Anal. Calcd for $C_{10}H_{12}ClNO$: C, 60.76; H, 6.12; N, 7.09. Found: C, 60.51; H, 6.13; N, 7.08.

General Procedure for the Cyclization of *N*-Acyl-*o*-chloroanilines 4 to Oxindoles 5. A. Using Potassium Amide in Liquid Ammonia. To a stirred solution of 6 mmol of KNH_2 prepared from 0.23 g of potassium metal in 100 mL of liquid NH_3 under a blanket of nitrogen in a vacuum-jacketed photoreaction vessel[16b] was added a solution of 2 mmol of starting anilide in 20 mL of ether. The resulting solution was irradiated for an appropriate time and then quenched by pouring onto 0.54 g (10 mmol) of solid NH_4Cl in a 1-L beaker. The ammonia was allowed to evaporate while being replaced by 100 mL of ether. After the ammonia had evaporated, 100 mL of water was added, the layers were separated, and the aqueous layer was extracted with several portions of ether. The combined ethereal extracts were dried and filtered, and the solvent was removed in vacuo to give crude products.

B. Using Lithium Diisopropylamide. A 125-mL three-neck round-bottomed flask was maintained under a positive pressure of argon. A solution of LDA in THF at −78 °C was prepared by adding sequentially to the flask 10 mL of THF, 2.10 mL (15 mmol) of diisopropylamine, 5 mL of THF, 15 mmol of *n*-BuLi (dropwise), and finally 5 mL of THF. After stirring for 5 min, a solution of the appropriate anilide (5 mmol) in 10 mL of THF was added dropwise. After the addition was complete, the solution of the anion was allowed to warm to room temperature and transferred by positive pressure via a cannula to the photoreaction vessel. The flask was rinsed with 70 mL of THF and these rinsings were also transferred, bringing the total volume of THF to 100 mL. The reaction mixture was then irradiated for the specified time period followed by quenching with saturated aqueous NH_4Cl (50 mL). The layers were separated, and the aqueous phase was extracted with several portions of ether. The extracts were dried and filtered, and the solvent was removed in vacuo to give the crude product. A similar procedure was used to cyclize dianions of anilides **4n–q** except that 20 mmol of LDA was employed.

***N*-Benzyloxindole (5b).** Following procedure A, a solution of 1.30 g (5 mmol) of *N*-benzyl-*o*-chloroacetanilide (**4b**) in 5 mL of benzene was added to a solution of 15 mmol of KNH_2 (from 0.59 g of potassium metal) in 300 mL of liquid NH_3. The resulting yellow solution was irradiated for 0.5 h and then quenched by pouring over solid NH_4Cl. The mixture was evaporated to dryness on a steam bath, cooled, and the residue taken up in 100 mL of water. The resulting suspension was extracted with ether (1 × 200 mL), the ethereal extract dried, and the solvent removed under reduced pressure to afford 1.08 g of a brown oil, which was redissolved in 100 mL of ether and extracted with 5% HCl (2 × 25 mL). The combined aqueous extracts were alkalized with dilute KOH and extracted with chloroform (3 × 50 mL). The combined chloroform extracts were dried, and the solvent was removed under reduced pressure. The residual yellow solid was recrystallized from hexane/$CHCl_3$ to yield 0.15 g (8%) of *N*-benzyl-*m*-aminoacetanilide (**7**) as a white solid: mp 108–109 °C; ^1H NMR ($CDCl_3$) δ 1.93 (2, 3 H, CH_3), 3.63 (s, 2 H, NH_2), 4.85 (s, 2 H CH_2), 6.33 (s, 1 H, H_2), 6.37 (d, J = 7 Hz, 1 H, H_4), 6.60 (d, J = 7 Hz, 1 H, H_6), 7.08 (t, J = 7 Hz, 1 H, H_5), 7.26 (s, 5 H, aromatic). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.02; H, 6.60; N, 11.58.

The ethereal layer from the acid extraction was washed with water and dried, and the solvent was removed under reduced pressure to yield a brown solid which was chromatographed on 20 g of silica gel. Elution with ether/hexane (3:2) afforded, after evaporation of the solvent, 0.64 g (57%) of *N*-benzyloxindole, as a yellow solid. Pure material was obtained by sublimation of the sample onto a cold trap from a flask immersed in a 130 °C bath at 0.025 mm: mp 76–77 °C; ^1H NMR ($CDCl_3$) δ 3.69 (s, 2 H, CH_2), 4.90 (s, 2 H, NCH_2), 7.42–6.58 (m, 9 H, aromatic); IR ($CDCl_3$) 1710 cm^{-1} (η=O). Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.28. Found: C, 80.69; H, 5.74; N, 6.26.

Similar experiments conducted with 10–20 mL of ether or THF as cosolvent gave increasing amounts of *N*-benzylacetanilide (**8**).

1,4-Dimethyloxindole (5c). From 0.99 g of **4c** after irradiation for 1 h according to general procedure B, 0.87 g of crude product was obtained as a brown crystalline solid. Flash chromatography[29] (100 g of silica gel, 1:3 ethyl acetate/petroleum ether) gave 0.70 g (87%) of **5c** as beige crystals: mp 119.5–121.5 °C; ^1H NMR ($CDCl_3$) δ 2.23 (s, 3 H, CH_3), 3.17 (s, 3 H, NCH_3), 3.23 (s, 2 H, CH_2), 6.55–7.30 (m, 3 H, aromatic); IR (5% solution in $CHCl_3$) 1705 cm^{-1} (C=O). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.57; H, 6.73; N, 8.89.

Procedure A gave **5c** in 80% yield. Formation of **5c** was not observed in the dark and starting material was recovered quantitatively.

***N*-Methyl-4-azoxindole (5i).** Cyclization of 0.50 g (27 mmol) of 2-chloro-3-(*N*-methylacetamido)pyridine (**4i**), according to general procedure B, gave the crude product as a brown solid, which was sublimed at 80 °C (0.05 mm) to afford 0.33 g (83%) of *N*-methyl-4-azoxindole (**5i**) as a white solid: mp 134–136 °C; ^1H NMR ($CDCl_3$) δ 3.21 (s, 3 H, CH_3), 3.60 (s, 2 H, CH_2), 6.91–7.22 (m, 2 H, aromatic), 8.15 (d, J = 5 Hz, H_5); IR ($CDCl_3$) 1710 cm^{-1} (C=O). Anal. Calcd for $C_8H_8N_2O_4$: C, 64.32; H, 5.44; N, 18.91. Found: C, 64.45; H, 5.26; N, 18.72.

Proceudre A or B without illumination, or with illumination in the presence of 10 mol % of DTBN, resulted in recovery of the starting anilide.

1,3,3-Trimethyloxindole (11a). According to general procedure B, the anion prepared from **4k** (0.40 g, 2 mmol) was irradiated for 3 h. Then the lights were turned off and a solution of 0.20 mL (2.5 mmol) of methyl iodide in 10 mL of THF was added. The resulting solution was stirred for 1 h then quenched with saturated NH_4Cl. The layers were separated and the aqueous phase extracted with several portions of ether. The combined organic extracts were washed with aqueous $Na_2S_2O_3$ to remove the pink color, dried, and filtered, and the solvent was removed in vacuo to give 0.30 g of crude product as a yellow oil. Kugelrohr distillation gave 0.23 g (66%) of **11a** as a very pale yellow oil: bp 60–70 °C (0.04 mm) [lit.[30] bp 110–112 °C (1 mm)]; ^1H NMR ($CDCl_3$) δ 1.35 (s, 6 H, CH_3), 3.20 (s, 3 H, NCH_3), 6.73–7.36 (m, 4 H, aromatic).

3-Benzyl-1,3-Dimethyloxindole (11b). In a manner analogous to the above procedure, a solution of 0.43 g (2.5 mmol) of benzyl bromide in 10 mL of THF was added instead of the solution of methyl iodide. After stirring for 1 h, quenching with saturated aqueous NH_4Cl, and a similar workup, 0.62 g of crude product was obtained as an orange oil. Column chromatography on 25 g of silica gel using hexane as the eluting solvent gave a small amount of unreached benzyl bromide. Elution with chloroform afforded 0.30 g (60%) of **11b** as an off-white solid. Recrystallization from hexane gave **11b** as white crystals: mp 89–94 °C; ^1H NMR ($CDCl_3$) δ 1.47 (s, 3 H, CH_3), 2.96 (s, 3 H, NCH_3), 3.03 (d, 2 H, CH_2), 6.50–7.57 (m, 9 H, aromatic); IR (2.5% solution in $CHCl_3$) 1710 cm^{-1} (C=O). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.27; H, 6.77; N, 5.58. Found: C, 81.10; H, 6.63; N, 5.65.

***N*-Methyl-2-chloro-3-methyl-3′,3′-dimethylacrylanilide (13d).** The following procedure is typical of the preparation of all unsaturated anilides. To a solution of 8.0 g (56 mmol) of 2-chloro-3-methylaniline in 50 mL of benzene was added 8.9 g (84 mmol) of anhydrous Na_2CO_3. A solution of 7.5 g (62 mmol) of 3,3-dimethylacryloyl chloride in 50 mL of benzene was added dropwise. A tan colored mixture resulted, which was stirred vigorously for 2 h. The mixture was partitioned with water. After separation of the benzene layer, the aqueous layer was extracted with several portions of ether. The organic layer was successively washed with 3 N HCl, saturated $NaHCO_3$ solution, and then water. The solution was dried and filtered, and the solvent was removed in vacuo to give 9.6 g (77%) of 2-chloro-3-methyl-3′,3′-dimethylacrylanilide. Recrystallization from hexane afforded white needle-like crystals: mp 71–73 °C; ^1H NMR ($CDCl_3$) δ 1.95 (s, 3 H, CCH_3), 2.20 (s, 3 H, CCH_3), 2.30 (s, 3 H, aromatic CH_3), 2.75 (m, 1 H, C=CH), 6.8–7.3 (m, 2 H, aromatic), 7.6 (br s, 1 H, NH), 8.3 (dd, 1 H, aromatic); IR ($CHCl_3$) 3360 (NH), 1660 cm^{-1} (C=O). Anal. Calcd for $C_{12}H_{14}NOCl$: C, 64.43; H, 6.31; N, 6.26. Found: C, 64.28; H, 6.33; N, 6.15.

Treatment of this anilide with 3 equiv of methyl iodide and potassium hydroxide in acetone[28] gave 94% of the N-methylated product **13d**, as a red oil, which was purified by Kugelrohr distillation to yield a yellow oil: bp 110 °C (0.5 mm); ^1H NMR ($CDCl_3$) δ 1.62 (s, 3 H, CCH_3), 2.10 (s, 3 H, CCH_3), 2.40 (s, 3 H, aromatic CH_3), 3.2 (s, 3 H, NCH_3), 5.31 (br s, 1 H, C=CH), 6.90–7.30 (m, 3 H, aromatic); IR (neat) 1620 cm^{-1} (C=O). Anal. Calcd for $C_{13}H_{16}NOCl$: C, 65.68; H, 6.78; N, 5.90. Found: C, 65.29; H, 6.80; N, 5.98.

General Procedure for the Cyclization of Monoanions of *N*-Methyl α,β-Unsaturated Anilides 13a–d to *N*-Methyl-3-alkylideneoxindoles 14a–d. *N*-Methyl-3-ethylideneoxindole (14a). A. Using Potassium Amide in Liquid Ammonia. To a stirred solution of 12 mmol of KNH_2 amide (prepared from 0.47 g of potassium metal) in 200 mL of liquid

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NH_3, under a blanket of nitrogen in the vacuum-jacketed photoreaction vessel, was added a solution of 0.84 g (4 mmol) of *N*-methyl-*o*-chlorocrotonanilide in 20 mL of ether. The resulting solution was stirred for 10 min, then irradiated for 3 h and quenched with 1.08 g (20 mmol) of solid NH_4Cl. The ammonia was allowed to evaporate while being replaced by 200 mL of ether. The aqueous layer was then acidified to pH 1 and extracted with several portions of ether followed by chloroform. The combined extracts were dried and filtered, and the solvent was removed in vacuo to give 1.02 g of a brown semisolid. Flash chromatography (100 g of silica gel, gradient elution with 1:1 $CHCl_3$/hexane–$CHCl_3$) yielded 0.44 g (63%) of the two isomeric forms of **14a**. GC analysis (OV-211, 160–230 °C at 15 °C/min) of the mixture showed a 5:1 ratio of the trans:cis forms: *trans*-**14a**, mp 70–72 °C (lit.[31] mp 78–79 °C); ^1H NMR ($CDCl_3$) δ 2.2 (d, J = 9 Hz, 3 H CCH_3), 3.12 (s, 3 H, NCH_3), 6.53–7.60 (m, 4 H, aromatic); IR ($CHCl_3$) 1700 cm^{-1} (C=O). *cis*-**14a**,[31] ^1H NMR ($CDCl_3$) δ 2.45 (d, J = 9 Hz, 3 H, CCH_3), 3.15 (s, 3 H, NCH_3), 6.50–7.40 (m, 4 H, aromatic). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.02; H, 6.42; N, 7.99.

B. Using Lithium Diisopropylamide. A procedure similar to the general procedure for the preparation of oxindoles **5** was employed. However, irradiation was effected at 0 °C. The reaction mixture was then quenched with 50 mL of ice-cold 2 N HCl and extracted with several portions of ether and chloroform.

Inhibited Reaction of 13b with *p*-Dinitrobenzene. To a solution of KNH_2 prepared from 0.30 g (7.5 mg at) of potassium metal and 100 mL of liquid NH_3 was added 0.60 g (2.5 mmol) of anilide **13b** as a solution in 10 mL of ether along with 0.22 g (50 mol %) of *p*-dinitrobenzene (DNB). The greenish-black solution was stirred in the dark for 15 min and quenched with 0.68 g (12.5 mmol) of solid NH_4Cl. Usual workup afforded 0.62 g of a brown oil. Flash chromatography (100 g of silica gel, 3:1 $CHCl_3$/hexane) gave 0.05 g of DNB and 0.53 g of a yellow oil, which was distilled at 105 °C (0.20 mm) to give **18b** as a pale yellow oil (90%): NMR ($CDCl_3$) δ 1.72 (s, 3 H, CH_3), 2.76 (s, 2 H, CH_2), 3.2 (s, 3 H, NCH_3), 4.5 (br s, 1 H, C=CH_2), 4.77 (br s, 1 H, C=CH_2), 7.7–7.15 (m, 4 H, aromatic); IR 1640 cm^{-1} (C=O). Anal. Calcd for $C_{12}H_{14}NOCl$: C, 64.43; H, 6.31; N, 6.26. Found: C, 64.20; H, 6.19; N, 6.28. Similar results were obtained with 10 mol % of DNB.

1,4-Dimethyl-3-isopropenyloxindole (14d). Procedure A was used to prepare 15 mmol of KNH_2 in liquid NH_3, followed by addition of 1.19 g (5 mmol) of **13d** to give 1.10 g of a light brown oil. GC analysis revealed one component corresponding to **14d** (100%). Purification by flash chromatography (100 g silica gel, $CHCl_3$) gave 84% of **14d**, which contained some 1,4-dimethyl-3-isopropylindeneoxindole. Kugelrohr distillation gave a colorless liquid: bp 106 °C (0.15 mm); ^1H NMR ($CDCl_3$) δ 1.55 (s, 3 H, CCH_3), 2.20 (s, 3 H aromatic CH_3), 3.15 (s, 3 H, NCH_3), 4.00 (s, 1 H, CH), 4.98, 5.03 (2 s, 2 H, C=CH_2), 6.5–7.3 (m, 3 H, aromatic); IR (neat) 1660 cm^{-1} (η=O). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.26; H, 7.70; N, 6.98.

A similar reaction was performed in the dark to afford 1.13 g of a brown viscous oil. Kugelrohr distillation yielded 0.83 g (73%) of the deconjugated anilide **18d** as a yellow oil: bp 137 °C (1.5 mm); ^1H NMR ($CDCl_3$) δ 1.7 (s, 3 H, CCH_3), 2.8 (s, 2 H, CH_2), 3.2 (s, 3 H, NCH_3), 4.50 (br s, 1 H, C=CH_2), 4.75 (br s, 1 H, C=CH_2), 6.9–7.4 (m, 3 H, aromatic); IR (neat) 1620 cm^{-1} (C=O). Anal. Calcd for $C_{13}H_{15}NOCl$: C, 65.68; H, 6.78; N, 5.89. Found: C, 65.84; H, 6.78; N, 5.91.

1,3,4-Trimethyl-3-isopropenyloxindole (16a) from 13d. In a manner analogous to the above procedures using KNH_2 in liquid NH_3, the anion of **13d** (1.00 g, 4 mmol) was prepared and irradiated for 3 h. Then the lights were turned off and a solution of 0.4 mL (5 mmol) of methyl iodide in 10 mL of ether was added. The resulting solution was stirred for 1 h then quenched with solid NH_4Cl. After extraction, the ethereal layer was washed with saturated $Na_2S_2O_3$, dried, and filtered, and the solvent was removed in vacuo to give 0.91 g of a brown solid from which 0.72 g of a yellow solid was obtained on flash chromatography (100 g of silica gel, 4:1 $CHCl_3$/hexane). Crystallization from hexane/$CHCl_3$ gave 0.65 g (72%) of **16a** as a yellow solid: mp 82–83 °C ^1H NMR ($CDCl_3$) 1.40 (s, 3 H, CCH_3), 1.50 (s, 3 H, CCH_3), 2.20 (s, 3 H, aromatic CH_3), 3.2 (s, 3 H, NCH_3), 5.2 (br s, 2 H, C=CH_2), 6.6–7.3 (m, 3 H, aromatic); IR ($CHCl_3$) 1660 cm^{-1} (η=O). Anal. Calcd for $C_{14}H_{17}NO$: C, 77.74; H, 7.92; N, 6.48. Found: C, 77.92; H, 8.07; N, 6.39.

1,3-Dimethyl-3-isopropenyloxindole (16b) by Reaction of the Anion of 14b with Methyl Iodide. A 4 mmol solution of LDA in THF at −78 °C was prepared using general procedure B and then 0.375 g (2 mmol) of **14b** in 10 mL of THF was added dropwise. The solution was stirred for another 15 min and warmed to room temperature. A solution of 0.40 g (2.5 mmol) of methyl iodide in 10 mL of THF was added and the yellow solution stirred for 1 h. The reaction mixture was quenched with saturated NH_4Cl. The layers were separated, and the aqueous phase was extracted with several portions of ether. The combined organic extracts were washed with saturated $Na_2S_2O_3$. The solution was dried and filtered, and the solvent was removed in vacuo to give 0.42 g of crude **16b**, which was purified by Kugelrohr distillation, to give 0.37 g (97%) of **16b** as a pale yellow solid: bp 128 °C (0.02 mm), mp 53–55 °C; ^1H NMR ($CDCl_3$) δ 1.48 (s, 3 H, CH_3), 3.2 (s, 3 H, NCH_3) 5.05 (m, 2 H, C=CH_2), 6.75–7.9 (m, 4 H, aromatic); IR ($CHCl_3$) 1670 cm^{-1} (C=O). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.53; H, 7.63; N, 6.89.

Carbinol 17 by Reaction of Dianion 15e with Benzophenone. To a 15 mmol solution of LDA in THF prepared using procedure B a solution of **13e** (0.978 g, 5 mmol) in 10 mL of THF was added dropwise. After the addition was complete, the light yellow solution of dianion **15e** was warmed to room temperature. A solution of benzophenone (0.98 g, 5.3 mmol) in 10 mL of THF was added to the brown solution. The reaction mixture was stirred for 3 h and quenched with 50 mL of ice cold 2 N HCl. After usual workup, 1.98 g of a yellow-brown solid was obtained. The crude product was purified by flash chromatography (100 g silica gel, 1:1 $CHCl_3$/hexane) to afford 1.42 g (80%) of **17** as white needles: mp 142 °C; ^1H NMR ($CDCl_3$) δ 2.5 (s, 1 H, OH), 3.2 (d, J = 6 Hz, 2 H, CH_2), 6.0 (d, J = 15 Hz, 1 H, C=CH), 6.7–7.6 (m, 15 H, aromatic), 8.3 (dd, 1 H, aromatic); m/e (relative intensity) 377 (M^+, 0.5), 359 (97), 233 (7.17), 190 (66.5), 180 (77.4), 127 (40.4), 105 (100), 77 (49.6); IR ($CHCl_3$) 1660 cm^{-1} (C=O). Anal. Calcd for $C_{23}H_{20}ClNO_2$: C, 73.10, H, 5.30; N, 3.71. Found: C, 73.05; H, 5.38; N, 3.71.

Dark Reaction of Dianion 15e. Dianion **15e** was prepared from 0.98 g (5 mmol) of **13e** and 3 equiv of LDA in THF at −78 °C as described in the general procedure. The mixture was stirred in the dark for 3 h at 0 °C, quenched with 50 mL of ice-cold 1 N HCl, and worked up in the usual manner to give 0.96 g of a tan solid. Separation by flash chromatography (100 g of silica gel, 3:1 $CHCl_3$/hexane) yielded a white solid, which was recrystallized from hexane to give 0.79 g (81%) of **18e** as needle-like crystals: mp 72–74 °C; ^1H NMR ($CDCl_3$) δ 2.14 (d, J = 9 Hz, 2 H, CH_2), 5.2 (br s, 1 H, C=CH_2), 5.45 (br s, 1 H, C=CH_2), 5.77–6.32 (m, 1 H, vinyl H), 6.85–7.45 (m, 3 H, aromatic), 7.95 (br s, 1 H, NH), 8.4 (dd, J = 10 Hz, 1 H, aromatic); IR ($CHCl_3$) 1660 cm^{-1} (C=O). Anal. Calcd for $C_{10}H_{10}NOCl$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.21; H, 5.17; N, 7.14.

Dark Reaction of Dianion 15f. Dianion **15f** was prepared from 1.57 g (7.5 mmol) of **13f** and 3 equiv of LDA in THF at −78 °C as described in the general procedure. The reaction mixture was stirred for 3 h in the dark at 0 °C. The solution was then quenched with 50 mL of ice-cold 1 N HCl and worked up in the usual manner to afford 1.57 g of a tan solid, which on separation by flash chromatography (100 g of silica gel, 3:1 $CHCl_3$)/hexane), yielded 1.13 g (72%) of the deconjugated anilide **18f** as a white solid: mp 50–52 °C; ^1H NMR ($CDCl_3$) δ 1.85 (s, 3 H, CCH_3), 3.15 (s, 2 H, CH_2), 5.00 (br s, 1 H, C=CH_2), 5.52 (br s, 1 H, C=CH_2), 6.8–7.41 (m, 4 H, aromatic), 8.08 (br s, 1 H, NH), 8.35 (dd, 1 H, aromatic); IR ($CHCl_3$) 1660 cm^{-1} (C=O). Anal. Calcd for $C_{11}H_{12}NOCl$: C, 63.01; H, 5.77; N, 6.68. Found: C, 63.30; H, 5.83; N, 6.55.

General Procedure for the Preparation of *N*-(*o*-Chlorobenzyl)amides and *N*-(*o*-Chlorobenzyl)-*N*-methylamides 19a–c. *N*-Benzylamides were prepared from the appropriate benzylamine and either the acid chloride or acid anhydride in a manner analogous to the preparation of *N*-arylamides described earlier. Since, N-methylation using the procedure of Pachter and Kloetzel[28] did not give satisfactory yields, the following procedure was employed. A 250-mL three-necked flask equipped with a gas buret was charged with 2.64 g (55 mmol) of 50% NaH dispersion. After washing with hexane, 50 mL of THF was added, followed by a solution of 50 mmol of the appropriate *N*-(*o*-chlorobenzyl)amide in 50 mL of THF. The mixture was stirred at room temperature until H_2 evolution ceased (20–24 h). A solution of 8.52 g (60 mmol) of methyl iodide in 10 mL of THF was added and the resulting mixture stirred for 5 h, at which time more methyl iodide (0.85 g, 6 mmol) was added. After stirring for 20 h, the reaction was quenched by the addition of 100 mL of water. The reaction mixture was partitioned between ether and water, the layers separated, and the aqueous layer extracted several times with ether. The combined organic extracts were dried and filtered, and the solvent was removed in vacuo to furnish the crude product. Final purification of these products was achieved by distillation or column chromatography.

General Procedure for the Cyclization of the Monoanions of *N*-(*o*-Chlorobenzyl)-*N*-methylamides 19 to 1,4-Dihydro-3(2*H*)-isoquinolines 20. Isoquinolinones **20** were prepared by employing procedure A described above for the synthesis of *N*-methyloxindoles **5**.

2,4-Dimethyl-1,4-dihydro-3(2*H*)-isoquinolinone (20b). From 0.42 g of **19b**, 0.31 g of crude product was obained as an orange oil. Short

(31) Taconni, G.; Maggi, L. D.; Righetti, P.; Desimoni, G. *J. Chem. Soc., Perkin Trans. 2* **1976**, 150.

column chromatography (20 g of silica gel, 2:3 ethyl acetate/hexane) gave 0.21 g (60%) of **20b** as a pale yellow oil, pure by GC (2% Carbowax 20M at 200 °C): bp 155-160 °C (3 mm); ^{1}H NMR ($CDCl_3$) δ 1.47 (d, 3 H, CH_3), 3.08 (s, 3 H, NCH_3), 3.48 (q, 1 H, CH), 4.43 (dd, 2 H, $ArCH_2N$), 7.00-7.43 (m, 4 H, aromatic); IR (5% solution in $CHCl_3$) 1710 cm^{-1} (C=O); *m/e* (relative intensity) 175 (M^+, 42), 118 (100), 117 (65).

4-Ethyl-2-methyl-1,3-dihydro-3(2*H*)-isoquinolinone (20c). From 0.45 g of **19c**, 0.24 g of crude product was obtained as an orange oil. Short column chromatography (30 g of silica gel, 1:9 acetone/hexane) gave 0.20 g (54%) of **20c** as a yellow oil, pure by GC (2% Carbowax 20M at 200 °C): ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3 H, CH_3), 1.87 (m, 2 H, CH_2), 3.12 (s, 3 H, NCH_3), 3.48 (t, 1 H, CH), 4.50 (dd, 2 H, $ArCH_2N$), 7.07-7.53 (m, 4 H, aromatic); IR (5% solution in $CHCl_3$) 1710 cm^{-1} (C=O). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.19; H, 7.93; N, 7.40. Found: C, 75.91; H, 8.08; N, 7.16.

***N*-(*o*-Chlorobenzyl)-*N*-(trimethylsilyl)acetamide (19e) and Its Cyclization to 20d.** To a solution of 2.57 g (15 mmol) of *N*-(*o*-chlorobenzyl)acetamide in 30 mL of anhydrous THF, was added over 10 min with stirring, 9.5 mL of 1.6 M *n*-BuLi solution. The reaction was strictly maintained at -50 °C, during addition, while keeping a positive argon atmosphere. A solution of 1.65 g (15 mmol) of chlorotrimethylsilane in 5 mL of THF was added (20 min) at the same temperature. The reaction was further stirred for 0.5 h and was brought to room temperature. The resulting oil, after removing the THF, was distilled under reduced pressure to give 3.14 g (82%) of **19e**: bp 90-93 °C (3 mm); ^{1}H NMR ($CDCl_3$ containing no Me_4Si) δ 1.60 (s, 3 H, CH_3), 4.21 (s, 2 H, CH_2), 6.86-7.19 (m, 4 H aromatic); IR (neat) 1650 cm^{-1} (C=O).

From 2.0 g (5 mmol) of **19e**, following procedure A, was obtained 0.5 g (62%) of 1,4-dihydro-3(2*H*)-isoquinolinone (**20d**) as a dark brown solid, which was sublimed as yellow needles (43%): mp 149-151 °C (lit.[32] mp 149-150 °C). Spectral data were identical with those reported by Lyle.[32]

2-Methyl-4-ethyl-4-benzyl-3(2*H*)-isoquinolinone (21). After the anion of **20b** (prepared from 0.45 g of **19b**) was irradiated for 1 h, a solution of 0.28 g of (2.2 mmol) of benzyl chloride in 10 mL of ether was added and stirred for 1 h. Quenching with solid NH_4Cl and the usual workup gave 0.48 g of crude product as a yellow oil. Short column chromatography (20 g of silica gel, 1:4 ether/hexane) gave 0.18 g (32%) of **21** as a pale yellow solid. Recrystallization from hexane gave an analytical sample as the white cubes: mp 92-93 °C; ^{1}H NMR ($CDCl_3$) δ 0.65 (t, 3 H, CH_3), 2.30 (m, 2 H, CH_2), 2.90 (s, 3 H, NCH_3), 3.03 (dd, 2 H, $ArCH_2$), 3.47 (dd, 2 H $ArCH_2N$), 6.47-7.47 (m, 9 H, aromatic); IR (5% solution in $CHCl_3$) 1705 cm^{-1} (C=O). Anal. Calcd for $C_{19}H_{21}NO$: C, 81.72; H, 7.53; N, 5.02. Found: C, 81.69; H, 7.27; N, 5.02.

Supplementary Material Available: Tables of physical and spectral characteristics of starting materials **4**, **13**, and **20** and spectral data for certain products **5**, **14**, and **20** (10 pages). Ordering information is given on any current masthead page.

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Asymmetric Induction in the Claisen Rearrangement of *N*-Allylketene *N,O*-Acetals

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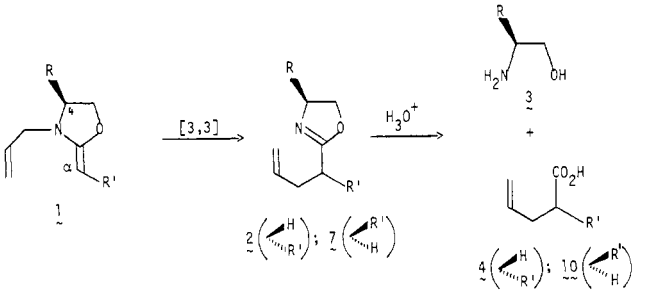
Abstract: Asymmetric C-C bond formation via the diastereoselective aza-Claisen rearrangement of *N*-allylketene *N,O*-acetal **1** is described. Diastereoselection noted for rearrangement **1** → **2** ranges from 84% to 96% and is a consequence of complete (*Z*)-*N,O*-acetal olefin selectivity in **1**, high C_α-*si*-face selectivity in the rearrangement of **1** to **2**, and the absence of C_α epimerization in oxazoline **2**. Experiments which establish the steric bulk of the C_4 appendage as a particularly important variable are also reported. Acid-catalyzed hydrolysis of rearranged oxazoline **2** completes an efficient, enantioselective synthesis of 2-substituted pent-4-enoic acid **4** and regenerates for recycling the chiral auxiliary reagent **3**, initially prepared from inexpensive α-amino acids.

The achievement of absolute stereochemical control continues to be a major goal in organic synthesis. While various methods of asymmetric induction have been recorded, remote and acyclic stereocontrol remain particularly challenging. In this regard, the regio- and stereochemically reliable Claisen rearrangement has been gainfully employed in a variety of self-immolative[1] enantioselective studies.[2] In contrast, the chiral auxiliary-mediated variant, in which auxiliary chirality is preserved, has been reported only once[3] prior to our work.[4] We were intrigued by the notion of auxiliary-reagent-mediated asymmetric Claisen rearrangements and have undertaken a study directed at the development of *N*-allylketene, *N,O*-acetal **1** as a useful chiral aza-Claisen substrate.

Substrate **1** is suitably disposed for an auxiliary-mediated Claisen rearrangement to oxazoline **2** (Scheme I). Subsequent acid-catalyzed hydrolysis of **2** would regenerate the chiral auxiliary amino alcohol **3** for recycling and provide optically active pent-4-enoic acid **4**, a versatile precursor in the enantioselective synthesis of biologically interesting compounds.[5] Inspection of the aza-

Scheme I



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