Cycloadditions of Isoquinolinium Salts: Evidence for a Two-Step Mechanism in a Stereocontrolled Synthesis of Substituted Tetralins[1]

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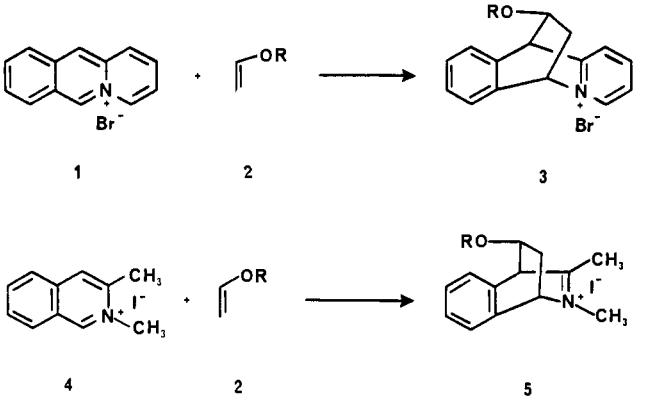
Abstract: A detailed investigation concerning the synthetic and mechanistic aspects of the inverse-electron demand Diels–Alder reaction of 2-(2,4-dinitrophenyl)isoquinolinium chloride (**7**) with vinyl ethers is described. The principle synthetic utility is the facile, stereoselective, and high-yield preparation of tetralins. The results presented in this paper are best explainable on the basis of a two-step mechanism. The isolation and characterization of "one-bond products" **38** derived from partitioning of the intermediate oxocarbonium ions **39** via solvent trapping and cycloaddition pathways is described. The effect of the substituents on the isoquinoline nucleus on the formation of one-bond products has also been investigated. When the 2,4-dinitrophenyl group on nitrogen is replaced by methyl, no one-bond product is formed, while replacement by carbethoxy results in the formation of mainly one-bond product **76**. The reaction of ethyl vinyl ether with 4-methoxy-2-(2,4-dinitrophenyl)isoquinolinium chloride **61** gave one-bond product **63**, a 1,3-adduct **65**, and 1,4-adduct **68**. Recycling experiments of the solvent-trapped one-bond products by regeneration of oxocarbonium ions followed by C–C bond formation have been carried out. For example, the one-bond product **40** gave a 6:1 mixture of adducts **16** and **52** on treatment with Dowex and methanol. The analyses of the results obtained by the recycling process coupled with other experimental observations helped us to deduce the following three processes, in order of decreasing rate: rate of ring closure, rate of solvent trapping, and rate of internal C–C bond rotation of the oxocarbonium ion intermediates, as operative in the cycloaddition reaction. Thus the faster rate of ring closure than the rate of internal C–C bond rotation observed in the intermediates successfully explains the observance of "cis" stereospecifity in a two-step reaction. Similarly, the exo vs. endo selectivity is also consistent with a stepwise mechanism.

The "inverse"-electron-demand Diels–Alder (IED) reaction was first envisaged by Bachmann and Deno[2] who suggested, in 1949, that the converse of the Alder rule[3] should hold, i.e., that electron-poor dienes should react preferentially with electron-rich dienophiles, thus exchanging the electronic roles of diene and dienophile in the classical Diels–Alder reaction. However, it was not until 1962 that Sauer and Wiest[4] first demonstrated the existence of an IED reaction through a kinetic study of the reaction of hexachlorocyclopentadiene with a series of dienophiles.

An early example of an IED reaction with a charged diene was reported by both Bradsher[5] and Fields[6] where acridizinium ion **1** reacted with electron-rich dienophiles such as vinyl ether **2** to form adduct **3**. Bradsher and Day[7] demonstrated that isoquinolinium salt **4**, a system analogous to acridizinium salt **1**, also undergoes IED reaction with vinyl ethers **2** to give the cycloadduct **5**. The reaction of **4** was extended to other electron-rich dienophiles, such as cyclopentadiene[8,9] and styrenes.[10] These reactions



were found to be regiospecific and highly stereoselective creating a tricyclic system containing as many as four chiral centers and an iminium ion. In nearly every case, the products were exclusively or predominantly the result of exo addition.[5i,k,8-12] The Bradsher group concluded that the reaction takes place in a concerted but nonsynchronous manner and that "charge-transfer complexes exist as intermediates or as stages along the reaction pathway."[5j]

In practice, a substituent at the 3-position of the isoquinolinium salt was required, because the parent isoquinolinium salt produced a product iminium ion which underwent reaction with a second mol of the dienophile, presumably, to give 2:1 adduct.[13] This limitation was overcome by Falck et al.[14] by using 2,4-dinitrophenyl salts of isoquinolines such as **6** and by trapping iminium ion containing cycloadducts **9** with methanol used as solvent to afford the adducts **10**. Without isolation of the intermediates such as

(1) Aspects of this research have been presented at the 10th International Congress of Heterocyclic Chemistry, Waterloo, Ontario, August 1985; the 11th European Colloquium on Heterocyclic Chemistry, Ferrara, Italy, October 1985; the 16th Northeast Regional meeting of ACS, Binghamton, NY, June 1986; and the 193rd National meeting of ACS, Denver, CO, April 1987.
(2) Bachmann, W. E.; Deno, N. C. *J. Am. Chem. Soc.* **1949**, *71*, 3062.
(3) Alder, K.; Stein, G. *Angew. Chem.* **1937**, *50*, 510.
(4) Sauer, J.; Wiest, H. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 269.
(5) (a) Bradsher, C. K.; Stone, J. A. *J. Org. Chem.* **1968**, *33*, 519. (b) Bradsher, C. K.; Stone, J. A. *Ibid.* **1969**, *34*, 1700. (c) Westerman, I. J.; Bradsher, C. K. *Ibid.* **1971**, *36*, 969. (d) Bradsher, C. K.; Harvan, D. J. *Ibid.* **1971**, *36*, 3778. (e) Burnham, W. S.; Bradsher, C. K. *Ibid.* **1972**, *37*, 355. (f) Parham, M. E.; Fraser, M. G.; Bradsher, C. K. *Ibid.* **1972**, *37*, 358. (g) Bradsher, C. K.; Day, F. H. *J. Heterocycl. Chem.* **1973**, *10*, 1031. (h) Bradsher, C. K. *Adv. Heterocycl. Chem.* **1974**, *16*, 289. (i) Bradsher, C. K.; Wallis, T. G.; Westerman, I. J.; Porter, N. A. *J. Am. Chem. Soc.* **1977**, *99*, 2588. (j) Bradsher, C. K.; Carlson, G. L. B.; Porter, N. A.; Westerman, I. J.; Wallis, T. G. *J. Org. Chem.* **1978**, *43*, 822. (k) Westerman, I. J.; Bradsher, C. K. *Ibid.* **1978**, *43*, 3002. (l) Westerman, I. J.; Bradsher, C. K. *Ibid.* **1979**, *44*, 727. (m) Bradsher, C. K.; Carlson, G. L. B.; Adams, M. G. *Ibid.* **1979**, *44*, 1199.
(6) (a) Fields, D. L.; Regan, T. H.; Dignan, J. C. *J. Org. Chem.* **1968**, *33*, 390. (b) Fields, D. L.; Regan, T. H. *Ibid.* **1970**, *35*, 1870. (c) Fields, D. L.; Regan, T. H. *Ibid.* **1971**, *36*, 2986, 2991. (d) Fields, D. L.; Regan, T. H. *Ibid.* **1971**, *36*, 2995. (e) Fields, D. L. *Ibid.* **1971**, *36*, 3002.
(7) Bradsher, C. K.; Day, F. H. *Tetrahedron Lett.* **1971**, 409.
(8) Bradsher, C. K.; Day, F. H.; McPhail, A. T.; Wong, P. S. *J. Chem. Soc., Chem. Commun.* **1973**, 156.
(9) Bradsher, C. K.; Day, F. H. *J. Heterocycl Chem.* **1974**, *11*, 23.
(10) Day, F. H.; Bradsher, C. K.; Chen, T. K. *J. Org. Chem.* **1975**, *40*, 1195.
(11) Bradsher, C. K.; Day, F. H.; McPhail, A. T.; Wong, P. S. *Tetrahedron Lett.* **1971**, 4205.
(12) Chen, T. K.; Bradsher, C. K. *J. Org. Chem.* **1979**, *44*, 4680.
(13) Reference 5h, page 303.

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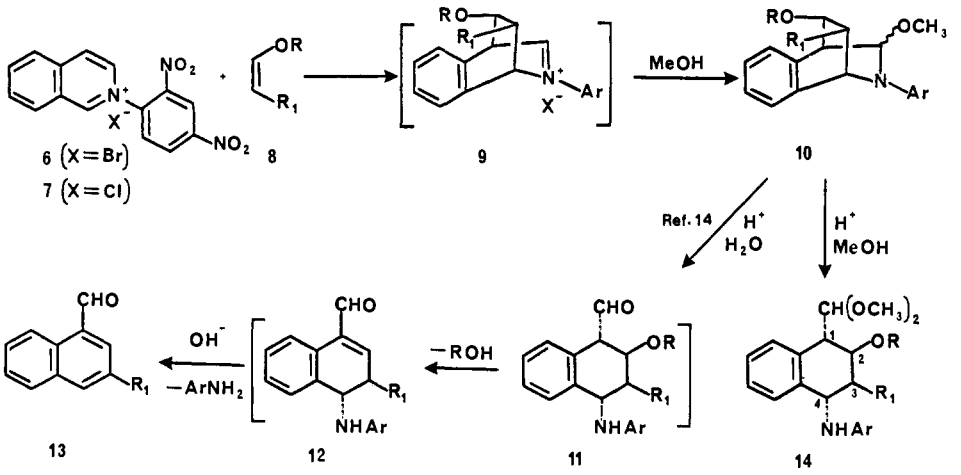
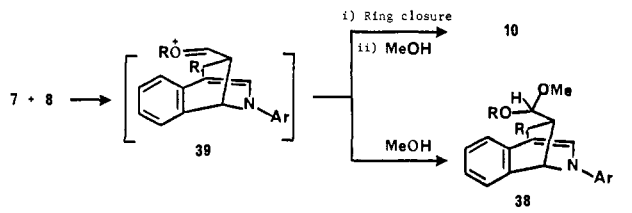
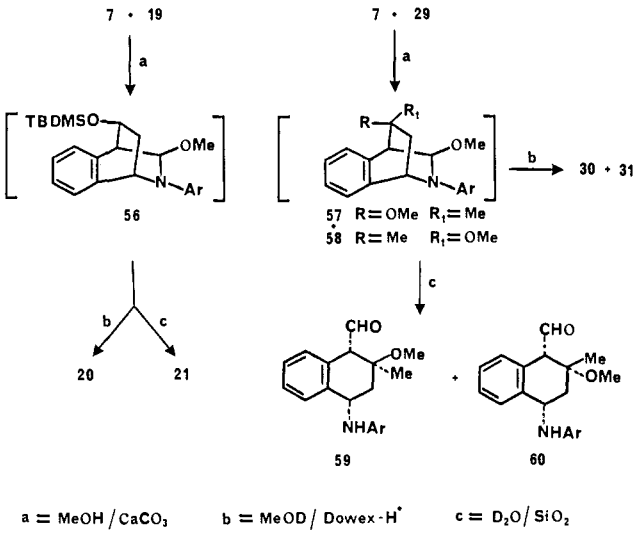
Scheme I



Scheme II



Scheme III



11 and **12**, the adducts **10** were converted to aromatic aldehydes **13** (Scheme I). There have been a few interesting applications of this cycloaddition reaction to synthetic problems.[14-19]

In this paper we describe our studies of the Bradsher reaction which have led to a useful, stereoselective synthesis of tetralins with up to four stereogenic centers. By our isolation of solvent-trapped intermediate oxocarbonium ions, we also demonstrate that the apparent cycloaddition is in fact a two-step process.

Results

The cycloadditions to the isoquinolinium salt **7** were carried out under nitrogen in anhydrous methanol containing $CaCO_3$ at temperatures ranging from 10 to 45 °C depending on the dienophile. In most of the cases where an attempt was made to isolate the tetralin aldehyde **11** via treatment of the initial cycloadduct **10** with Amberlyst-15/THF/H_2O, the desired **11** was usually contaminated by unsaturated aldehyde **12** and aromatic aldehyde **13**, obtained via single and double eliminations of leaving groups. In a few cases, we were able to obtain tetralin aldehydes (entries 6, 11, and 12 in Table I) by stirring the initial cycloadducts with wet silica gel. However, in general, when the initial tricyclic adduct **10** was treated, without any purification, with Dowex-50X8-H^+ in anhydrous methanol, it yielded dimethyl acetal **14** directly (Scheme I). The acetal **14** was extremely well behaved and survived basic and mild acidic conditions. The tetralins obtained in this study are illustrated in Table I. The stereochemistries of all the products described were assigned by using high-field NMR spectroscopy, decoupling experiments, and wherever necessary by nuclear Overhauser effect (nOe) experiments. Our detailed arguments are found in the Supplementary Material section.

In every cycloaddition when the reaction was worked up prior to acid treatment, there could be isolated a "one-bond product"[20] **38**. The oxocarbonium ion **39** appeared to be the common precursor for both cycloadduct **10** and one bond product **38** (Scheme II). The one-bond products are also included in Table I alongside their corresponding cycloadduct-derived tetralins. Since the tetralins and one-bond products arise from different workups, the yields reported are taken from duplicate experiments. In nearly every case, the one-bond products, upon treatment with Dowex-50X8-H^+ and methanol ("recycling" process), were transformed to tetralins. In Table II the products of the acid-catalyzed recycling experiments are recorded. The structures parallel those of the cyclic products of Table I, but there is some variation in stereochemistry and ether functionality which will be elucidated in the sequel.

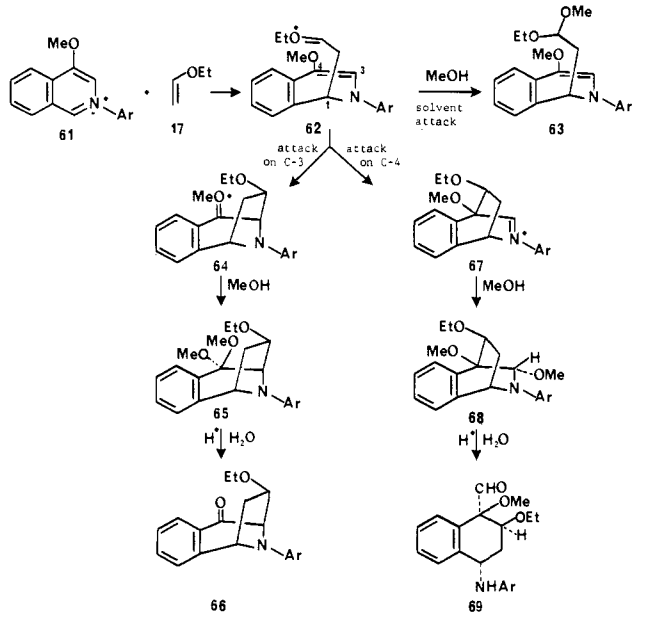
Discussion

An inspection of Table I reveals that our tetralin synthesis is very general and highly stereoselective, except for entry 10. Acyclic (entries 1, 3, 5, and 8), carbocyclic (entries 11 and 12), and heterocyclic (entry 7) vinyl ethers all participate in the cycloaddition and become incorporated into the tetralin framework. In order to rule out epimerization taking place during the ring-opening steps from initial tricyclic adduct to aldehyde or acetal product, the following experiments were carried out. First, the initial tricyclic adduct **56** of vinyl ether **19** was treated with silica gel containing D_2O, and **21** was produced with no deuterium incorporation (at C-1). Similar treatment of the cycloadduct mixture **57** and **58** of 2-methoxypropene (**29**) gave nearly 1:1

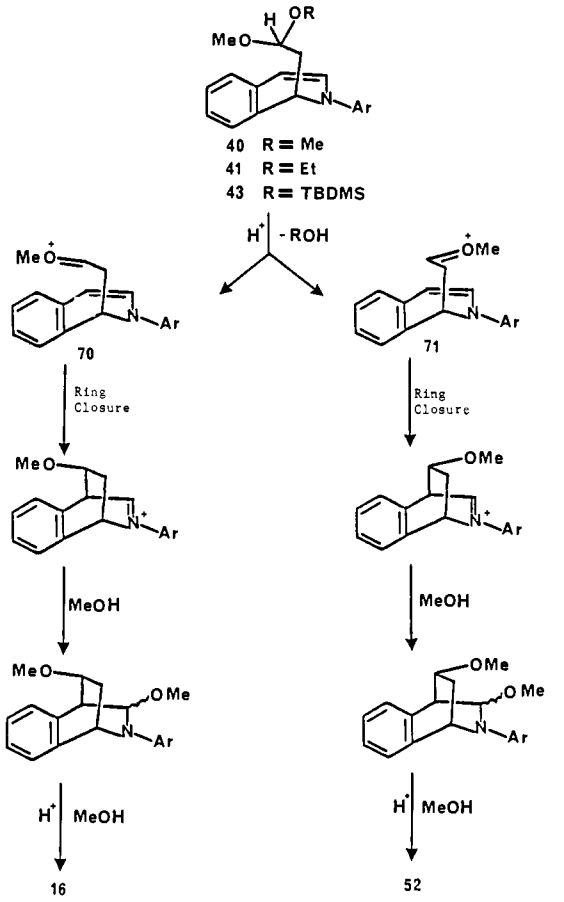
(14) Manna, S.; Falck, J. R.; Mioskowski, C. *J. Org. Chem.* **1982**, *47*, 5021.
(15) (a) Sammes, P. G.; Watt, R. A. *J. Chem. Soc., Chem. Commun.* **1976**, 367. (b) Gisby, G. P.; Sammes, P. G.; Watt, R. A. *J. Chem. Soc., Perkin Trans. 1* **1982**, 249.
(16) Falck, J. R.; Manna, S.; Mioskowski, C. *J. Am. Chem. Soc.* **1983**, *105*, 631.
(17) Franck, R. W.; Gupta, R. B. *J. Chem. Soc., Chem. Commun.* **1984**, 761.
(18) Franck, R. W.; Gupta, R. B. *Tetrahedron Lett.* **1985**, *26*, 293.
(19) Franck, R. W.; Gupta, R. B. *J. Org. Chem.* **1985**, *50*, 4632.

(20) In order to distinguish the solvent-trapped intermediates, which have only one new C–C bond formed, from the cycloadducts with two new C–C bonds, they are referred to as "one-bond products" in this paper.

Scheme IV



Scheme V



mixture of aldehydes **59** and **60** with no D incorporation. Furthermore, the treatment of **56** and the mixture of **57** and **58** with Dowex-H^+ and CH_3OD to produce 20 and 30 and 31, respectively, revealed no D uptake (Scheme III).

The regiochemistry of the cycloadducts is explicable by both a polar-concerted IED reaction or a two-step ionic process. The nucleophilic and electrophilic carbons of the reactants are properly matched for both mechanisms, and the previously reported[10,16] substituent effects on the reactivity of the system can be rationalized for either pathway. In our study of substituent effects with 4-methoxyisoquinoline salt **61** and enol ether **17**, we obtained three products: tetralin **69** derived from the expected sensitive cycloaddition product **68**, one-bond product **63** from the usual solvent trapping, and 1,3-product **66**, obtained via adducts **64** and **65**. The simplest interpretation of this outcome postulates a single intermediate ion **62** where the nucleophilic C3–C4 double bond is a part of both an enamine and an enol ether. The products arise out of a competition for the oxocarbonium ion among solvent and the two termini of the reactive double bond (Scheme IV). It is not necessary to include a separate concerted path for product **69**.

There is a dichotomy in the retention of stereochemistry of the dienophile (entry 9), as revealed in our tetralin products **27** and **28** accompanied by the solvent-intercepted intermediate **45** in the same reaction. Retention of configuration of dienophiles is used as evidence for a concerted cycloaddition pathway, while the interception of intermediates is assumed to be verification of a two-step process. Gompper's review[21] uses the interception of intermediates as the determining factor in distinguishing between concerted and stepwise cycloaddition.[22] During the study of cycloaddition to acridizinium and isoquinolinium ions, Bradsher had observed that some of his results, in particular a kinetic study, could be best explained on the basis of a two-step mechanism.[5b,c] However, the failure to detect the presence of intermediate oxocarbonium ions in these reactions seemed to be one of the prime reasons for his revision of an earlier proposal for a stepwise mechanism in favor of a nonsynchronous concerted mechanism.[5j]

Retention of Configuration of the Dienophile. A two-step process would be consistent with stereospecific retention if the ring-closure step were faster than the loss of configuration of the stereochemical probe in the intermediate. Our experimental results on the recycling of one-bond products do, in fact, demonstrate that the rate of ring closure is faster than the loss of configuration by C–C bond rotation in the oxocarbonium ion intermediates. For example, entries 1–5 (Table II) show that the compound **16** with exo stereochemistry and its endo isomer **52** are formed from five different one-bond products. However, the ratio of **16**:**52** in none of these cases is the same. Certainly, **16** and **52** are formed from the ring closure of oxocarbonium ion **70** and its rotamer **71**, respectively (Scheme V). If the rate of rotation for conversion between **70** and **71** were faster than their rate of ring closure, then identical ratios of **16**:**52**, independent of the method of generation of **70** and **71**, would be predicted. Thus, we conclude that rotation of oxocarbonium ion intermediates in our system is slow compared to cyclization. Similarly, the different ratios of **18**:**53** (Table II, entries 2, 3, and 4) and the results of recycling of one-bond products **46** and **47** which yielded **30** and **31** in different ratios (Table II, entries 7 and 8) are consistent with rotation being a slow step.

Rate of Ring Closure vs. Solvent Trapping. Our results also show that ring closure of our oxocarbonium ion intermediates is competitive with solvent trapping. The recycling of diethoxy one-bond product **42** in acidic methanol gives 94% of the products **18** and **53** with a C_2-ethoxyl group while only 6% of the products **16** and **52** contains a C_2-methoxyl group (Table II, entry 4). Thus, the majority of the ethoxycarbonium ions **72** and **73** undergoes ring closure, and only a small amount of **72** and **73** is trapped by the solvent to form **41**. Now, formation of methoxycarbonium ions **70** and **71** from the mixture of acetals **41** followed by ring closure can account for the minor products **16** and **52** containing C_2-methoxyl (Scheme VI). Had the rate of solvent trapping been faster than the ring closure, we would have observed more solvent equilibration of the acetal and, consequently, a larger proportion of the products containing C_2-methoxyl, but we did not.

The competition between ring closure and solvent trapping is influenced by the nucleophilicity of the enamine intermediate as shown by our experiments with *N*-carbethoxyisoquinolinium

(21) Gompper, R. *Angew. Chem., Int. Ed. Eng.* **1969**, *8*, 312.

(22) For other references which have used the isolation/lack of isolation of the intermediate derived product(s), in cationic polar cycloaddition, as the principal argument in deciding the mechanism of the reaction, see: Cheng, Y. S.; Ho, E.; Mariano, P. S.; Ammon, H. L. *J. Org. Chem.* **1985**, *50*, 5678. Seeliger, W.; Diepers, W. *Ann. Chem.* **1966**, *697*, 171.

Table I. Derived Tetralins and One-Bond Products from the Addition of Vinyl Ethers to 2-(2,4-Dinitrophenyl)isoquinolinium Chloride (**7**)

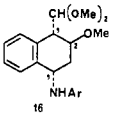
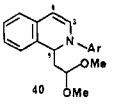
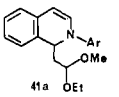
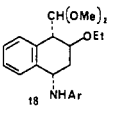
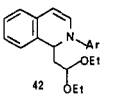
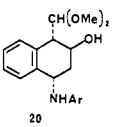
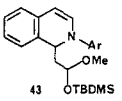
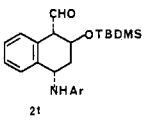
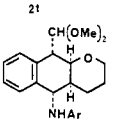
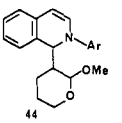
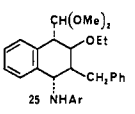
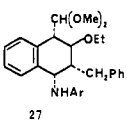
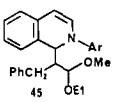
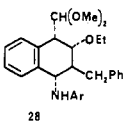
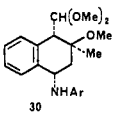
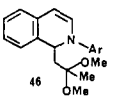
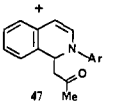
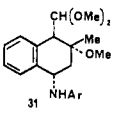
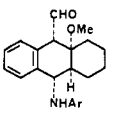
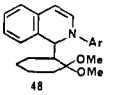
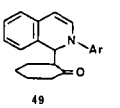
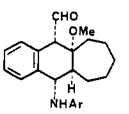
entry	vinyl ether	tetralin	yield	solvent	one-bond product	diasteromer ratio	yield
1	 15	 16	95	MeOH	 40		6
2	**15**			EtOH	 41a	78:22	4
3	 17	 18	90	MeOH	41b	17:83	8.5
4	**17**			EtOH	 42		6
5	 19	 20	90	MeOH	 43	80:20	6
6	**19**	 21	76				
7	 22	 23	88	MeOH	 44	90:7.5:2.5	9.5
8	 24	 25	89				
9	 26	 27	85	MeOH	 45	94:6	0.5
		 28	9				
10	 29	 30	45	MeOH	 46 +  47		12 9
		 31	43				
11	 32	 33	68	MeOH	 48		3
					 49		3
12	 34	 35	85				

Table I (Continued)

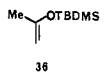
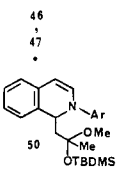
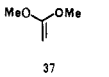
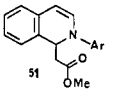
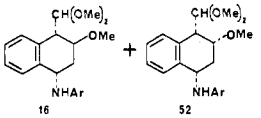
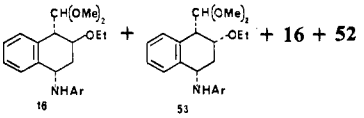
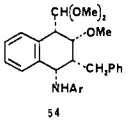
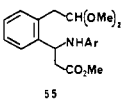
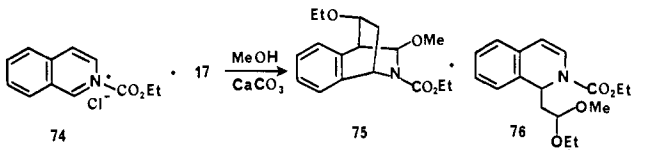
entry	vinyl ether	tetralin	yield	solvent	one-bond product	diasteromer ratio	yield
13	 36			MeOH	 46 + 47 + 50		30 + 26 + 14
14	 37			MeOH	 51		72

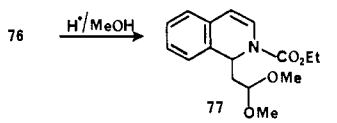
Table II. Products from the Recycling of One-Bond Products Using Dowex-H^+ and Methanol

entry	one-bond product	products from recycling	rel ratio of the products[a]
1	**40**	 16 + 52	86:14
2	**41a**	 16 + 53 + **16 + 52**	31:19:47:3
3	**41b**	**16 + 52 + 18 + 53**	15:10:65:10
4	**42**	**16 + 52 + 18 + 53**	5:1:80:14
5	**43**	**16 + 52**	40:60
6	**45**	 54 + **27** + unidentified products	55:35:10
7	**46**	**30 + 31**	65:35
8	**47**	**30 + 31**	43:57
9	**48**	**30 + 31**	43:57
10	**51**	 55	100

[a] Relative ratio of the products was determined by ^1H 400-MHz NMR spectrum obtained for the crude reaction products.

chloride (**74**). The addition of vinyl ether **17** to **74** furnished cycloadduct **75** in 14% yield and one-bond product **76** in 82% yield. Furthermore, the one-bond compound **76** on treatment with Dowex-H^+ and methanol for about 6 h formed **77** in 81% yield as a result of the solvent exchange of the acetal function.[23]

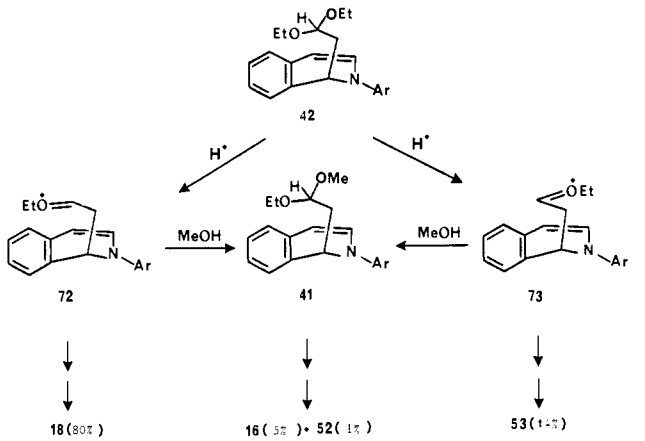




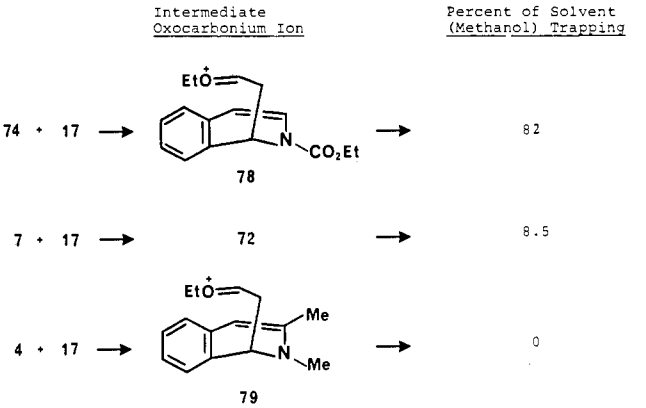
Since the intermediate enamine in **78** has somewhat reduced nucleophilicity compared to our standard system, the intermediate oxocarbonium ion **78** is now attacked preferentially by solvent. Enamine nucleophilicity can be invoked to explain the fact that no one-bond product can be detected in the cycloaddition of ethyl

(23) We have observed that the prolonged treatment of **76** with acidic methanol does lead to the products derived from the cycloadduct obtained as a result of second new C–C bond formation.

Scheme VI

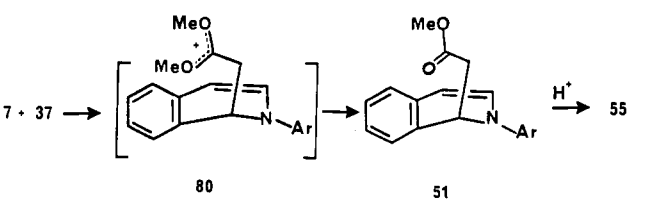


Scheme VII



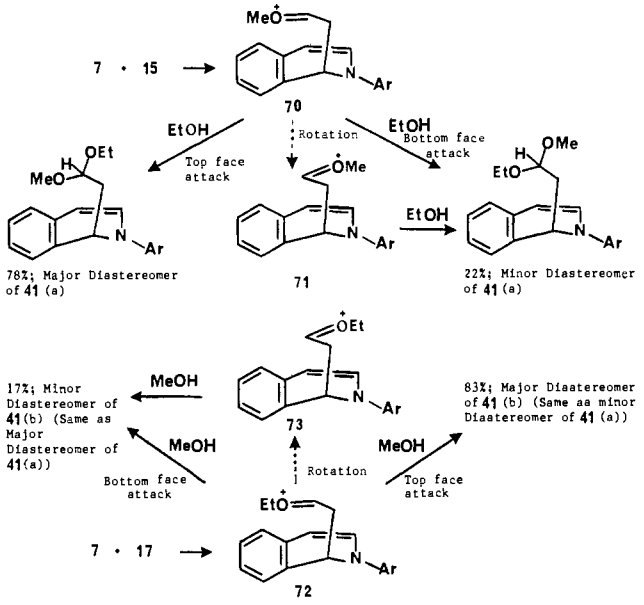
vinyl ether to *N*-methyl salt **4**. We could argue that the intermediate ion **79** now undergoes exclusive C–C bond formation because the *N*-methylenamine is so much more reactive than the enamines in our standard system (Scheme VII). Of course, one could also argue that a changeover to a concerted mechanism takes place in the *N*-methyl case.

A corollary electronic effect which changes the ratio of C–C bond formation to solvent trapping is revealed in entry **14** where a ketene acetal is the dienophile. Here the intermediate oxocarbonium ion **80** is stabilized by two oxygens and is not reactive



toward the enamine. Instead, the solvent can attack the dimethoxycarbonium ion at the methyl groups to afford ester **51**. Fields[6a] did obtain cycloadducts with ketene acetals and acri-

Scheme VIII



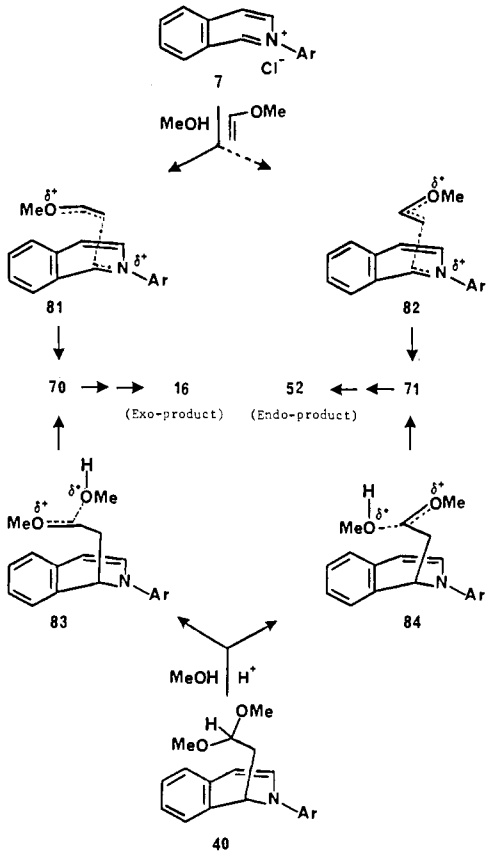
dizinium ions. Presumably, in his case the intermediate enamine is more basic, and there is no nucleophilic solvent to trap the oxonium ion, or the reaction of acridizinium ions could be concerted. Efforts to cyclize the ester **51** by intramolecular enamine acylation, precedented for more reactive enamines,[24] simply cleaves the enamine to form ring-opened aminoester **55**.

Solvent Trapping vs. Rotation of Oxonium Ions. In our discussion above, we have demonstrated that ring closure of the oxocarbonium ion, derived from salt **7**, by intramolecular enamine alkylation is faster than solvent trapping or rotation of the ion. To complete our analysis of this system, we show that rotation is in fact the slowest of the three processes. In entries 2 and 3 in Table I, we detect single isomers **16** and **18** from "cycloaddition" together with solvent-trapped products **41a** and **41b** as mixtures of diastereomers, respectively. We can discount an explanation for the mixtures where the initially formed oxocarbonium ions **70** and **72** are free to rotate through several conformations because we did not observe cycloadducts of the rotamers **71** and **73**. Thus the solvent trapping must occur on the diastereomeric faces of the single rotamers **70** and **72** which lead to the single cycloadducts observed. This argument is summarized in Scheme VIII.

Pertinent to our arguments is the work of Jencks[25] who has reported the value of 10^{11}/s for the rate constant for the addition of water to the oxocarbonium ions formed in the hydrolysis of simple aliphatic aldehydes. The rate constant for C–C bond rotation in oxocarboniums is 2×10^{11}/s (at room temperature, computed by conversion of the known energy barrier of 2 kcal/mol).[26] These data further support the plausibility of our arguments about the several competing pathways for oxocarbonium ion intermediates proposed in this paper.

Exo–Endo Stereochemistry. The changes in exo vs. endo addition must be consistent with our two-step mechanism. Our rationalization for exo addition is very similar to the electronic argument used by Bradsher,[5j] and the explanation for a changeover to endo addition requires taking into account steric factors. Thus, consider the case of addition of methyl vinyl ether **15** to the isoquinolinium salt **7**. The vinyl ether can align with **7** in two possible ways before actual bond formation begins to take place, viz, one in which the OMe group is proximal to the phenylene ring and in the other case the OMe group is proximal to the quaternary nitrogen atom. This highly organized orientation of the diene **7** and the dienophile **15** may be attributed to the weak

Scheme IX



electrostatic attractions, such as in π complexes, existing between them.[5j] The first step of the reaction can then lead to the formation of two oxocarbonium ion intermediates **70** and **71** (accepting that there is no free rotation around the C–C bond). The transition states (TSs) **81** and **82** leading to the two intermediates **70** and **71**, respectively, are shown in Scheme IX. The TS **81** in which the OMe group is distal to the nitrogen seems to be the favored one since it has the minimum coulombic repulsion between the developing positive charge on oxygen and receding positive charge on nitrogen, whereas in the other TS **82** the two positive charge centers lie closer together. Also, in TS **81** there is no steric repulsion between the OMe group and the Ar group. Thus the exo/endo ratio is now determined, since the rate of ring closure of **70** and **71** exceeds the rate of rotation. This electronic effect favoring exo **81** must be small since the introduction of substituents geminal and trans vicinal to the ether oxygen of the dienophile (entries 9–12) now produces mixtures or endo products. There must be a steric repulsion between the Ar group on the isoquinolinium N and the added substituents of these dienophiles in the developing exo transition state. Hence there is a changeover to the endo path which has fewer repulsions in these specific examples.

There are differences in exo–endo ratios of the tetralins formed by the acid-catalyzed recycling of one-bond products compared to the tetralins obtained directly. For example, while the cycloadduct of **7** and **15** gave only exo product **16**, the recycling of **40** formed both exo **16** and endo **52** products. The reason is simply that in the recycling experiment, intermediates **70** and **71** arise from transition states **83** and **84**, the relative energies of which are controlled by the subtle stereoelectronic effects of acetal cleavage. These differences are apparently not as large as those involving the charge separation effects that control the difference between TSs **81** and **82** (Scheme IX). Further, we note differences in ether functionalities of products in the recycling process as a function of the acetal rate of cleavage OTBDMS > OMe > OEt. For example, the recycling result of **43** (Table II, entry 5) reveals that OTBDMS group is exclusively cleaved in preference to OMe. On the other hand, entries 3 and 4 (Table II) indicate that cleavage

(24) Sobotka, W.; Beverung, W. N.; Munoz, G. G.; Sircar, J. C.; Meyer, A. I. *J. Org. Chem.* **1965**, *30*, 3667.
(25) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238.
(26) Karabatsos, G. J.; Fenoglio, D. J. *Top. Stereochem.* **1970**, *5*, 167.

of OMe is more facile than OEt.

A final argument against the oxocarbonium ion (e.g., **39**) as the common intermediate for cyclic and noncyclic products in the Bradsher reaction is to postulate that the one-bond product could also arise from a *stepwise reversal* of the initial cycloadduct iminium ion (e.g., **9**, Scheme I) which in turn is formed by a *concerted* mechanism. A control experiment which rules out the reversal of cycloadduct was carried out on **9** (R = TBDMS, R_1 = H), obtained by reaction of salt **7** and silyl vinyl ether **19** in acetonitrile. The iminium salt **9** (R = TBDMS, R_1 = H), without isolation, was treated with methanol and $CaCO_3$ followed by silica gel chromatography. One-bond product **43** was not detected by NMR or TLC, but the expected cycloadduct derived tetralin **21** was isolated.[27]

Conclusion

Independent of the mechanism of our version of the Bradsher cycloaddition, the tetralin synthesis described is very general and highly stereoselective. We believe it will have many applications in the synthesis of multifunctional polycyclics. We also conclude that the cycloadditions of vinyl ethers to 2,4-dinitrophenylisoquinolinium salt take place in a stepwise manner. The possibility that polar cycloadditions may proceed in two steps, despite orbital symmetry considerations favoring a synchronous mechanism, had already been suggested by Schmidt.[28] Recently, Hall[29] has presented evidence for the existence of a stepwise mechanism in some cases of inverse-electron demand Diels–Alder reactions of electrophilic α,β-unsaturated esters with vinyl ethers. The isolation and recycling of one-bond products in our system constitutes a unique experiment demonstrating the capture and regeneration of an intermediate in a reaction that has the "cis" specificity of the Diels–Alder reaction.

Experimental Section

Nuclear magnetic resonance spectra were obtained on a JEOL GX 400 MHz instrument by using $CDCl_3$ as solvent, and chemical shifts were recorded by using tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. The high resolution mass spectra were obtained by the Mass Spec Facility, The Pennsylvania State University, University Park, PA. Elemental analyses were performed by the Spang Microanalytical Laboratory, Eagle Harbor, MI. Melting points were determined on a Fisher-Johns melting point apparatus and were uncorrected.

Thin-layer chromatograms were done on precoated TLC sheets of silica gel 60 F_{254} (E. Merck) with use of (2,4-dinitrophenyl)hydrazine spray, potassium permanganate spray, and/or short- and longwave ultraviolet light to visualize the spots. Chromatotron (radial chromatography) plates were prepared by using Kieselgel 60 PF_{254} gipshaltig (E. Merck), and all separations using the chromatotron were done under nitrogen atmosphere.

Materials. Methyl vinyl ether was purchased from the Matheson Co. Inc., ethyl vinyl ether, dihydropyran, and 2-methoxypropene, were bought from Aldrich. *tert*-Butyldimethylsilyl vinyl ether,[30] *trans*-3-phenylprop-1-enyl ethyl ether,[31] 1-methoxycyclohexene,[32] and 1-methoxycycloheptene[32] were prepared according to literature methods. Dowex-50X8-400 and Amberlyst-15 were purchased from Aldrich, and Celite 545 was obtained from Fisher scientific. All the solvents used were dry and distilled.

General Procedures (for Tetralins). (a) Cycloaddition Reaction of Vinyl Ethers with Isoquinolinium Salt. To a solution of 2-(2,4-dinitrophenyl)isoquinolinium chloride (**7**) (332 mg, 1 mmol) in 5 mL of anhydrous methanol was added anhydrous powdered calcium carbonate (600 mg, 6 mmol) followed by vinyl ether (2 mmol) with stirring under N_2. The reaction mixture was allowed to stir at temperatures ranging from 10 to 45 °C, and the course of the reaction was monitored by TLC for the disappearance of the isoquinolinium salt (4 h–4 days). An additional amount of vinyl ether (2–4 mmol) was added during the course of the slow reactions. The reaction mixture was then filtered over Celite, the residue was washed with anhydrous dichloromethane, and the combined filtrate was evaporated to dryness to give the tricyclic adduct which was used in the next reaction without any further purification.

(b) Ring Opening of the Tricyclic Adduct to Bicyclic Products. (i) Using Dowex 50×8–400 and Methanol. A mixture of the tricyclic adduct so obtained, anhydrous methanol (10 mL), and Dowex-50×8–400 (250 mg) was stirred at room temperature under N_2 for 24 h. The mixture was then filtered to remove the resin, the residue was washed with dichloromethane, and the combined filtrate was added into cold water (150 mL). The aqueous mixture was then extracted with dichloromethane (3 × 30 mL), and the combined organic layers were washed with aqueous saturated sodium bicarbonate (20 mL), dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue thus obtained was purified by using a chromatotron to give the bicyclic adduct containing the acetal group.

(ii) Using Silica Gel. A mixture of tricyclic adduct, silica gel (4 g), tetrahydrofuran (25 mL), and water (4 mL) was stirred at room temperature for 4–16 h and monitored by TLC for the disappearance of the starting adduct. It was then filtered, the residue was washed with THF, and the combined filtrate was concentrated in vacuo. The crude product so obtained was purified by using chromatotron to give the bicyclic product with aldehyde group.

Compound 16: The reaction of salt **7** with methyl vinyl ether **15** following procedures a and b(i) gave **16** in 95% yield (chromatographic solvent, petroleum ether/CH_2Cl_2, 60:40); mp 174–176 °C; IR ($CHCl_3$) 1620, 1590, 1490, 1420, 1330, 1300, 1270, 1110, 1080 cm^{-1}; ^1H NMR δ 9.17 (d, 1 H, J = 2.93 Hz, Ar*H*), 8.93 (d, 1 H, J = 8.79 Hz, N*H*), 8.23 (dd, 1 H, J = 2.93, 9.52 Hz, Ar*H*), 7.37–7.20 (m, 4 H, Ar*H*), 7.12 (d, 1 H, J = 10.26 Hz, Ar*H*), 5.16 (ddd, 1 H, $J_{3e,4}$ = 5.13 Hz, $J_{3a,4}$ = 10.99 Hz, $J_{4,NH}$ = 8.79 Hz, C_4-*H*), 4.47 (d, 1 H, J = 5.13 Hz, C*H*$(OMe)_2$), 4.05 (m, 1 H, C_2-*H*), 3.49, 3.42, 3.34 (3s, 3 H each, 3 × OCH_3), 3.30 (br dd, 1 H, J = 5.13 Hz, C_1-*H*), 2.44 (ddd, 1 H, $J_{2,3e}$ = 5.13 Hz, $J_{3e,4}$ = 5.13 Hz, $J_{3e,3a}$ = 13.19 Hz, C_3-H_e), 2.29 (ddd, 1 H, $J_{2,3a}$ = 1.47 Hz, $J_{3a,4}$ = 10.99 Hz, $J_{3e,3a}$ = 13.19 Hz, C_3-H_a); high resolution mass spectrum calcd for $C_{20}H_{23}N_3O_7$ 417.1536, found 417.1552.

Compound 18: The reaction of **7** with ethyl vinyl ether **17** using procedures a and b(i) gave **18** in 90% yield (chromatographic solvent, petroleum ether/CH_2Cl_2, 60:40); mp 154–156 °C; IR ($CHCl_3$) 1620, 1590, 1490, 1420, 1330, 1300, 1280, 1110 cm^{-1}; ^1H NMR δ 9.17 (d, 1 H, J = 2.20 Hz, Ar*H*), 8.94 (d, 1 H, J = 8.06 Hz, N*H*), 8.23 (dd, 1 H, J = 2.20, 9.52 Hz, Ar*H*), 7.38–7.20 (m, 4 H, Ar*H*), 7.11 (d, 1 H, J = 9.53 Hz, Ar*H*), 5.17 (ddd, 1 H, $J_{3e,4}$ = 5.86 Hz, $J_{3a,4}$ = 9.25 Hz, $J_{4,NH}$ = 8.06 Hz, C_4-*H*), 4.47 (d, 1 H, J = 4.39 Hz, C*H*$(OMe)_2$), 4.15 (m, 1 H, C_2-*H*), 3.60 (m, 2 H, OCH_2CH_3), 3.49, 3.34 (2s, 3 H each, 2 × OCH_3), 3.28 (br dd, 1 H, J = 4.40 Hz, C_1-*H*), 2.38 (ddd, 1 H, $J_{2,3e}$ = 5.12 Hz, $J_{3e,4}$ = 5.86 Hz, $J_{3e,3a}$ = 13.92 Hz, C_3-H_e), 2.30 (ddd, 1 H, $J_{2,3a}$ = 2.93 Hz, $J_{3a,4}$ = 9.25 Hz, $J_{3e,3a}$ = 13.92 Hz, C_3-H_a), 1.21 (t, 3 H, J = 7.32 Hz, OCH_2CH_3); high resolution mass spectrum calcd for $C_{21}H_{25}N_3O_7$ 431.1692, found 431.1686.

Compound 20: *tert*-Butyldimethylsilyl vinyl ether **19** on cycloaddition with **7** following procedures a and b(i) gave **20** in 90% yield (chromatographic solvent, CH_2Cl_2/MeOH, 97:3); mp 143–145 °C: IR ($CHCl_3$) 3540, 1610, 1590, 1500, 1420, 1360, 1330, 1290, 1130, 1070, 970, 920, 890 cm^{-1}; ^1H NMR δ 9.16 (d, 1 H, J = 3.05 Hz, Ar*H*), 8.72 (d, 1 H, J = 7.93 Hz, N*H*), 8.29 (dd, 1 H, J = 2.44, 9.76 Hz, Ar*H*), 7.41–7.25 (m, 4 H, Ar*H*), 7.15 (d, 1 H, J = 7.16 Hz, Ar*H*), 5.15 (ddd, 1 H, $J_{3e,4}$ = 5.49 Hz, $J_{3a,4}$ = 4.27 Hz, $J_{4,NH}$ = 7.93 Hz, C_4-*H*), 4.74 (d, 1 H, J = 3.36 Hz, C*H*$(OMe)_2$), 4.16 (m, 1 H, C_2-*H*), 3.55, 3.37 (2s, 3 H each, 2 × OCH_3), 3.22 (dd, 1 H, J = 3.66, 5.49 Hz, C_1-*H*), 3.03 (d, 1 H, J = 2.44 Hz, O*H*), 2.41 (ddd, 1 H, $J_{2,3e}$ = 4.27 Hz, $J_{3e,4}$ = 5.49 Hz, $J_{3e,3a}$ = 12.82 Hz, C_3-H_e), 2.08 (ddd, 1 H, $J_{2,3a}$ = 10.38 Hz, $J_{3a,4}$ = 4.27 Hz, $J_{3e,3a}$ = 12.82 Hz, C_3-H_a); high resolution mass spectrum calcd for $C_{19}H_{21}N_3O_7$ 403.1379, found 403.1416.

Compound 21: Following procedures a and b(ii) the reaction of vinyl ether **19** with **7** gave **21** in 76% yield (chromatographic solvent, petroleum ether/CH_2Cl_2, 50:50); IR ($CHCl_3$) 1715, 1610, 1590, 1490, 1420, 1360, 1330, 1130, 830, cm^{-1}; ^1H NMR δ 9.71 (d, 1 H, J = 1.83 Hz, C*H*O), 9.16 (d, 1 H, J = 3.05 Hz, Ar*H*), 8.81 (d, 1 H, J = 8.54 Hz, N*H*), 8.28 (dd, 1 H, J = 2.44, 9.77 Hz, Ar*H*), 7.40–7.28 (m, 4 H, Ar*H*), 7.04 (d, 1 H, J = 9.77 Hz, Ar*H*), 5.28 (ddd, 1 H, $J_{3e,4a}$ = 5.12 Hz, $J_{3a,4a}$ = 10.26 Hz, $J_{4a,NH}$ = 8.54 Hz, C_4-*H*), 4.74 (m, 1 H, C_2-*H*), 3.69 (br dd, 1 H, C_1-*H*), 2.32 (ddd, 1 H, $J_{3e,3a}$ = 13.43 Hz, $J_{2e,3e}$ = 5.13 Hz, $J_{3e,4a}$ = 5.49 Hz, C_3-H_e), 1.95 (ddd, 1 H, $J_{2e,3a}$ = 1.83 Hz, $J_{3e,3a}$ = 13.43 Hz, $J_{3a,4a}$ = 10.26 Hz, C_3-H_a), 0.88 (s, 9 H, SiC$(CH_3)_3$), 0.13, 0.10, (2 s, 3 H each, Si$(CH_3)_2$).

Further elution gave a minor product (9%) which was characterized to be the unsaturated aldehyde (**12**, R_1 = H): ^1H NMR δ 9.79 (s, 1 H, C*H*O), 9.18 (d, 1 H, J = 2.93 Hz, Ar*H*), 8.77 (d, 1 H, J = 8.06 Hz,

(27) The yield of **21** was not high because the initial iminium ion **9** (R = TBDMS, R_1 = H) had reacted with a second mol of enol silyl ether as Bradsher[13] had observed in his work with reactive iminium ion in acetonitrile solvent.

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NH), 8.31 (dd, 1 H, J = 2.93, 9.52 Hz, ArH), 7.47–7.28 (m, 3 H, ArH), 7.06 (d, 1 H, J = 9.52 Hz, ArH), 7.02 (dd, 1 H, vinylic proton), 5.02 (m, 1 H, C_4-H), 3.01–2.96 (m, 2 H, C_3-H_2).

Compound 23: Following the general procedures a and b(i) cycloaddition with dihydropyran **22** yielded compound **23** in 88% yield (chromatographic solvent, CH_2Cl_2); mp 94–96 °C; IR ($CHCl_3$) 1610, 1590, 1500, 1430, 1330, 1310, 1270, 1130, 1110, 1070, 980, 920 cm^{-1}; ^1H NMR δ 9.19 (d, 1 H, J = 2.93 Hz, ArH), 8.99 (br d, 1 H, NH), 8.11 (br dd, 1 H, ArH), 7.31–7.13 (m, 4 H, ArH), 5.26 (dd, 1 H, $J_{4,NH}$ = 8.79 Hz, $J_{4,3a}$ = 10.26 Hz, C_4-H), 4.47 (d, 1 H, J = 3.66 Hz, CH(OMe)$_2$), 4.15 (dd, 1 H, $J_{1,2}$ = 1.47 Hz, $J_{2,3}$ = 2.20 Hz, C_2-H), 4.03, 3.66 (2 m, 1 H each, -O-CH_2), 3.52, 3.32 (2 s, 3 H each, 2 × OCH_3), 3.19 (dd, 1 H, J = 3.66, 1.47 Hz, C_1-H), 2.53 (m, 1 H, C_3-H), 1.84–1.50 (m, 4 H, pyrano ring protons); high resolution mass spectrum calcd for $C_{22}H_{25}N_3O_7$ 443.1692, found 443.1671.

***cis*-3-Phenylprop-1-enyl ethyl ether (24)**: A solution of *trans*-3-phenylprop-1-enyl ethyl ether (**26**) (650 mg, 4 mmol) in 0.5 mL of dimethyl sulfoxide was added with stirring to a flask containing potassium *tert*-butoxide (224 mg, 2 mmol) and dimethyl sulfoxide (1 mL) under N_2 at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for nearly 3 h. The reaction mixture was then diluted with ice-cold water (25 mL) and extracted with ether (3 × 25mL). The ethereal extract was then dried (anhydrous $MgSO_4$ and K_2CO_3) and concentrated under reduced pressure. The residue was subjected to preparative TLC separation (5% CH_2Cl_2 in petroleum ether) to give *cis*-3-phenylprop-1-enyl ethyl ether (**24**) (68 mg): ^1H NMR δ 7.23–7.07 (m, 5 H, ArH), 5.98 (d, 1 H, J = 6.71 Hz, *cis*-CH=CH-OEt), 4.48 (td, 1 H, J = 6.71, 7.33 Hz, *cis*-CH=CHCH$_2$Ph), 3.75 (q, 2 H, J = 7.32 Hz, -OCH_2CH$_3$), 3.35 (d, 2 H, J = 7.33 Hz, -CH_2Ph), 1.20 (t, 3 H, J = 7.32 Hz, -OC_2H_3).

trans-3-Phenylprop-1-enyl ethyl ether (**26**) (215 mg) was also recovered.

Compound 25: Following the general procedures a and b(i), the cycloadduct obtained with *cis*-3-phenylprop-1-enyl ethyl ether (**24**) in 89% yield was characterized to be **25** (chromatographic solvent, petroleum ether/CH_2Cl_2, 60:40); mp 140–142 °C; IR ($CHCl_3$) 1620, 1590, 1490, 1420, 1360, 1335, 1290, 1120, 1090, 920, 830 cm^{-1}; ^1H NMR δ 9.09 (d, 1 H, J = 3.05 Hz, ArH), 8.79 (br d, 1 H, NH), 8.09 (br dd, 1 H, ArH), 7.43–7.05 (m, 9 H, ArH), 6.72 (d, 1 H, J = 9.76 Hz, ArH), 4.88 (dd, 1 H, $J_{3,4}$ = 7.33 Hz, $J_{4,NH}$ = 9.16 Hz, C_4-H), 4.42 (d, 1 H, J = 4.27 Hz, CH(OMe)$_2$), 3.95 (dd, 1 H, $J_{1,2}$ = 4.27 Hz, $J_{2,3}$ = 3.05 Hz, C_2-H), 3.61–3.47 (m, 2 H, OCH_2CH$_3$), 3.45, 3.33 (2 s, 3 H each, CH(OCH_3)$_2$), 3.29 (dd, 1 H, J = 4.27, 4.27 Hz, C_1-H), 2.99 (m, 1 H, $^1/_2CH_2$Ph), 2.73 (m, 1 H, C_3-H), 2.56 (m, 1 H, $^1/_2CH_2$Ph), 1.22 (t, 3 H, J = 7.32 Hz, -O-CH_2CH_3); high resolution mass spectrum calcd for $C_{28}H_{31}N_3O_7$ 521.2162, found 521.2164.

Compound 27: The cycloaddition reaction with *trans*-3-phenylprop-1-enyl ethyl ether (**26**) following procedures a and b(i) yielded a mixture of **27** and **28** (9:1) separated chromatographically by using a mixture of petroleum ether and CH_2Cl_2 (20–40%); major product **27** (yield 85%); mp 122–124 °C; IR ($CHCl_3$) 1610, 1590, 1490, 1430, 1360, 1330, 1310, 1280, 1140, 1130, 1110, 1080, 910 cm^{-1}; ^1H NMR δ 9.13 (d, 1 H, J = 2.93 Hz, ArH), 8.91 (d, 1 H, J = 9.52 Hz, NH), 8.09 (dd, 1 H, J = 2.93, 9.52 Hz, ArH), 7.39–7.01 (m, 9 H, ArH), 6.77 (d, 1 H, J = 9.53 Hz, ArH), 4.79 (dd, 1 H, $J_{4,NH}$ = 9.52 Hz, $J_{3,4}$ = 2.93 Hz, C_4-H), 4.54 (d, 1 H, J = 2.20 Hz, CH(OMe)$_2$), 3.97 (dd, 1 H, $J_{1,2}$ = 4.40 Hz, $J_{2,3}$ = 8.79 Hz, C_2-H), 3.86 (dq, 1 H, J = 7.33, 9.53 Hz, $^1/_2$OCH_2CH$_3$), 3.61 (dq, 1 H, J = 7.33, 9.53 Hz, $^1/_2$OCH_2CH$_3$), 3.56 (s, 3 H, OCH_3), 3.39 (dd, 1 H, J = 2.20, 4.40 Hz, C_1-H), 3.36 (s, 3 H, OCH_3), 3.32–3.10 (m, 1 H, $^1/_2CH_2$Ph), 2.55–2.46 (m, 2 H, C_3-H and $^1/_2CH_2$Ph), 1.24 (t, 3 H, J = 7.33 Hz, OCH$_2$CH$_3$); high resolution mass spectrum calcd for $C_{28}H_{31}N_3O_7$ 521.2162, found 521.2162.

Minor product 28: (yield 9%); IR ($CHCl_3$) 1625, 1590, 1495, 1420, 1335, 1280, 1110, 920, 830 cm^{-1}; ^1H NMR δ 9.02 (d, 1 H, J = 2.20 Hz, ArH), 8.89 (d, 1 H, J = 8.79 Hz, NH) 7.82 (dd, 1 H, J = 2.20, 9.53 Hz, ArH), 7.74 (d, 1 H, J = 8.06 Hz, ArH), 7.32–7.10 (m, 8 H, ArH), 4.84 (d, 1 H, J = 5.86 Hz, CH(OMe)$_2$), 4.63 (dd, 1 H, $J_{4,NH}$ = 8.79 Hz, $J_{3,4}$ = 3.36 Hz, C_4-H), 3.94 (dd, 1 H, $J_{1,2}$ = 3.67 Hz, $J_{2,3}$ = 5.13 Hz, C_2-H), 3.54, 3.51 (2 s, 3 H each, -CH(OCH_3)$_2$), 3.50–3.36 (m, 2 H, -OCH_2CH$_3$), 2.95 (dd, 1 H, J = 13.92, 3.66 Hz, $^1/_2CH_2$Ph), 2.63 (m, 1 H, C_3-H), 2.47 (dd, 1 H, J = 13.19, 10.26 Hz, $^1/_2CH_2$Ph), 1.08 (t, 3 H, J = 7.33, OCH$_2$CH$_3$); high resolution mass spectrum calcd for $C_{28}H_{31}N_3O_7$ 521.2162, found 521.2145.

Compound 30: The reaction of 2-methoxypropene (**29**) with **7** using methods a and b(i) gave a mixture of two compounds **30** and **31** which were separated chromatographically by using a 50:50 mixture of petroleum ether and CH_2Cl_2. The first to be eluted was **30** (45% yield): mp 193–95 °C; IR ($CHCl_3$) 1610, 1585, 1490, 1420, 1360, 1330, 1280, 1110, 1070, 920, 830 cm^{-1}; ^1H NMR δ 9.16 (d, 1 H, J = 2.93 Hz, ArH), 8.99 (d, 1 H, J = 8.06 Hz, NH), 8.18 (br d, J = 8.79 Hz, 1 H, ArH), 7.30–7.21 (m, 4 H, ArH), 7.17 (d, 1 H, J = 9.52 Hz, ArH), 5.16 (dt, J = 8.06, 8.06 Hz, C_4-H), 4.42 (d, 1 H, J = 1.46 Hz, CH(OMe)$_2$), 3.48, 3.40, 3.16 (3 s, 3 H each, 3 × OCH_3), 3.23 (br s, 1 H, C_1-H), 2.36 (br d, 2 H, J = 8.06 Hz, C_3-H_2), 1.42 (s, 3 H, CH_3); high resolution mass spectrum calcd for $C_{21}H_{25}N_3O_7$ 431.1692, found 431.1689.

Table III. ^1H NOEDS Percent Enhancement of Proton Signals on Irradiation of C_2-methyl Group of **30** and **31**

compd	proton		
	CH(OMe)$_2$	C_1-H	C_4-H
30	7	2.3	0
31	0	5.9	4.7

Table IV. ^1H NOEDS Percent Enhancement of Proton Signals on Irradiation of Methoxyl Group of **33** and **35**

compd	proton		
	CHO	NHAr	C_3-H
33	4.6	8	4.6
35	6.9	6.9	7.6

Compound 31: yield 43%; mp 178–180 °C; IR ($CHCl_3$) 1610, 1590, 1500, 1420, 1360, 1330, 1280, 1135, 1110, 1070, 965, 920, 830 cm^{-1}; ^1H NMR δ 9.16 (d, 1 H, J = 2.93 Hz, ArH), 9.03 (d, 1 H, J = 8.79 Hz, NH), 8.21 (br d, 1 H, J = 9.33, ArH), 7.30–7.20 (m, 5 H, ArH), 5.01 (dt, 1 H, J = 8.79, 8.79 Hz, C_4-H), 4.76 (br s, 1 H, CH(OMe)$_2$), 3.56, 3.42, 3.35 (3 s, 3 H each, 3 × OCH_3), 3.13 (br s, 1 H, C_1-H), 2.42–2.25 (m, 2 H, C_3-H_2), 1.22 (s, 3 H, CH_3); high resolution mass spectrum calcd for $C_{21}H_{25}N_3O_7$ 431.1692, found 431.1694.

Further confirmation of structures for compounds **30** and **31** was obtained by nuclear Overhauser effect experiments and the results are summarized in Table III.

Compound 59: The reaction of 2-methoxypropene **29** with **7** using procedure a, followed by hydrolysis with use of procedure b(ii) in D_2O, gave a major fraction containing **59** and **60** in almost equal amount together with small amounts of unsaturated aldehyde resulting from the loss of methanol from **59** and **60**: ^1H NMR δ 9.64 (d, 1 H, J = 3.66 Hz, CHO), 9.14 (d, 1 H, J = 2.93 Hz, ArH), 8.90 (d, 1 H, J = 8.79 Hz, NH), 8.27 (dd, 1 H, J = 2.93, 9.53 Hz, ArH), 7.41–7.06 (m, 5 H, ArH), 5.32 (ddd, 1 H, $J_{3e,4}$ = 5.86 Hz, $J_{3a,4}$ = 10.99 Hz, $J_{4,NH}$ = 8.79 Hz, C_4-H), 3.98 (br d, 1 H, C_1-H), 3.25 (s, 3 H, OCH_3), 2.51 (dd, 1 H, $J_{3e,4}$ = 5.86 Hz, $J_{3e,3a}$ = 13.92 Hz, C_3-H_e); 2.03 (dd, 1 H, $J_{3a,4}$ = 10.99 Hz, $J_{3a,3e}$ = 13.92 Hz, C_3-H_a), 1.41 (s, 3 H, CH_3).

Compound 60: ^1H NMR δ 9.76 (d, 1 H, J = 3.66 Hz, CHO), 9.15 (d, 1 H, J = 2.93 Hz, ArH), 9.06 (d, 1 H, J = 8.79 Hz, NH), 8.30 (dd, 1 H, J = 2.93, 9.52 Hz, ArH), 7.41–7.06 (m, 5 H, ArH), 5.08 (ddd, 1 H, $J_{3e,4}$ = 5.86 Hz, $J_{3a,4}$ = 6.60 Hz, $J_{4,NH}$ = 8.79 Hz, C_4-H), 3.64 (d, 1 H, J = 3.66 Hz, C_1-H), 3.20 (s, 3 H, OCH_3), 2.40 (dd, 1 H, $J_{3a,4}$ = 6.60 Hz, $J_{3e,3a}$ = 13.92 Hz, C_3-H_e), 2.26 (dd, 1 H, $J_{3e,4}$ = 5.86 Hz, $J_{3e,3a}$ = 13.92 Hz, C_3-H_a), 1.42 (s, 3 H, CH_3).

Compound 33: The reaction of 1-methoxycyclohexene **32** with **7** was carried out by using procedure a and b(ii) and purified by using CH_2Cl_2 as solvent to give **33** in 68% yield; mp 179–181 °C; IR ($CHCl_3$) 1710, 1615, 1590, 1495, 1420, 1360, 1335, 1300, 1295, 1140, 1120, 1070, 920, 830 cm^{-1}; ^1H NMR δ 9.76 (d, 1 H, J = 3.66 Hz, CHO), 9.19 (d, 1 H, J = 2.93 Hz, ArH), 9.12 (d, 1 H, J = 8.79 Hz, NH), 8.36 (dd, 1 H, J = 2.93, 9.52 Hz, ArH), 7.40–7.32 (m, 3 H, ArH), 7.12 (d, 1 H, J = 9.52 Hz, ArH), 7.05 (d, 1 H, J = 6.59 Hz, ArH), 4.79 (dd, 1 H, $J_{3,4}$ = 3.05 Hz, $J_{4,NH}$ = 8.79 Hz, C_4-H), 3.85 (d, 1 H, J = 3.66 Hz, C_1-H), 3.11 (s, 3 H, OCH_3), 2.37 (ddd, J = 3.05, 4.27, 10.38 Hz, C_3-H), 1.94–1.30 (m, 8 H). Anal. Calcd for $C_{22}H_{23}N_3O_6$: C, 62.11; H, 5.45; N, 9.88. Found: C, 61.96; H, 5.56; N, 9.75.

Compound 35: The reaction of 1-methoxycycloheptene **34** with **7** following procedures a and b(ii) gave **35** in 85% yield (chromatographic solvent, CH_2Cl_2); IR ($CHCl_3$) 1710, 1615, 1590, 1500, 1445, 1420, 1330, 1300, 1280, 1150, 1140, 1120, 1070, 920 cm^{-1}; ^1H NMR δ 9.77 (d, 1 H, J = 4.40 Hz, CHO), 9.17 (d, 1 H, J = 2.19 Hz, ArH), 9.08 (d, 1 H, J = 8.79 Hz, NH), 8.35 (dd, 1 H, J = 2.20, 9.53 Hz, ArH), 7.46–7.27 (m, 3 H, ArH), 7.11 (d, 1 H, J = 10.26 Hz, ArH), 7.07 (d, 1 H, J = 7.32 Hz, ArH), 4.81 (dd, 1 H, $J_{3,4}$ = 3.66 Hz, $J_{4,NH}$ = 8.80 Hz, C_4-H), 3.76 (d, 1 H, J = 3.36 Hz, C_1-H), 3.14 (s, 3 H, OCH_3), 2.59 (m, 1 H, C_3-H), 2.20–1.37 (m, 10 H).

The nuclear Overhauser effect experiments were carried out on compounds **33** and **35**, and the results (Table IV) were found to be consistent with the assigned structures.

General Procedure (for One-Bond Products). The cycloaddition reaction of various vinyl ethers to 2-(2,4-dinitrophenyl)isoquinolinium chloride (**7**) were carried out according to the general procedure a de-

scribed above. The reaction mixture at this stage was purified by using radial chromatography (chromatotron) (5–20% EtOAc in petroleum ether) to get the one-bond products. The spectral data of these compounds are as follows.

Compound 40: IR ($CHCl_3$) 1600, 1550, 1510, 1490, 1450, 1330, 1270, 1260, 1120, 1070, 910 cm^{-1}; ^1H NMR δ 8.71 (d, 1 H, J = 2.20 Hz, Ar*H*), 8.38 (dd, 1 H, J = 2.20, 9.53 Hz, Ar*H*), 7.64 (d, 1 H, J = 9.53 Hz, Ar*H*), 7.32–7.19 (m, 3 H, Ar*H*), 7.06 (d, 1 H, J = 7.33 Hz, Ar*H*), 6.21 (d, 1 H, $J_{3,4}$ = 7.33 Hz, C_4-vinylic *H*), 5.74 (dd, 1 H, $J_{1,3}$ = 1.46 Hz, $J_{3,4}$ = 7.33 Hz, C_3-vinylic *H*), 5.18 (ddd, 1 H, J = 1.46, 5.13, 8.80 Hz, C_1-*H*), 4.20 (dd, 1 H, J = 4.40, 7.33 Hz, C*H*$(OMe)_2$), 3.45, 3.26 (2 s, 3 H each, CH$(OMe)_2$), 2.23–2.08 (m, 2 H, CH_2CH$(OMe)_2$); high resolution mass spectrum calcd for $C_{19}H_{19}N_3O_6$ 385.1274, found 385.1272.

Major diastereomer of 41a/minor diastereomer of 41b: IR ($CHCl_3$, mixture of diastereomers) 1600, 1570, 1510, 1480, 1450, 1430, 1320, 1270, 1250, 1120, 1070, 940, 910 cm^{-1}; ^1H NMR δ 8.71 (d, 1 H, J = 2.93 Hz, Ar*H*), 8.38 (dd, 1 H, J = 2.87, 9.52 Hz, Ar*H*), 7.72 (d, 1 H, J = 9.53 Hz, Ar*H*), 7.06–7.32 (m, 4 H, Ar*H*), 6.21 (d, 1 H, $J_{3,4}$ = 7.33 Hz, C_4-vinylic *H*), 5.75 (dd, 1 H, $J_{1,3}$ = 1.46 Hz, $J_{3,4}$ = 7.33 Hz, C_3-vinylic *H*), 5.20 (ddd, 1 H, J = 1.46, 4.39, 8.06 Hz, C_1-*H*), 4.31 (dd, J = 3.67, 7.33 Hz, C*H*(OMe)OEt), 3.85–3.78 (m, 1 H, $^1/_2OCH_2CH_3$), 3.60–3.51 (m, 1 H, $^1/_2OCH_2CH_3$), 3.26 (s, 3 H, OCH_3), 2.24–2.10 (m, 2 H, CH_2CH(OMe)OEt), 1.35 (t, 3 H, J = 7.32 Hz, OCH_2CH_3); high resolution mass spectrum calcd for $C_{20}H_{21}N_3O_6$ 399.1430, found 399.1432.

Minor diastereomer of 41a/major diastereomer of 41b: ^1H NMR δ 8.70 (d, 1 H, J = 2.93 Hz, Ar*H*), 8.36 (d, 1 H, J = 2.20, 9.53 Hz, Ar*H*), 7.65 (d, 1 H, J = 9.53 Hz, Ar*H*), 7.32–7.19 (m, 3 H, Ar*H*), 7.07 (d, 1 H, J = 7.33 Hz, Ar*H*), 6.20 (d, 1 H, $J_{3,4}$ = 7.32 Hz, C_4-vinylic *H*), 5.73 (br dd, 1 H, $J_{3,4}$ = 7.32 Hz, C_3-vinylic-*H*), 5.19 (m, 1 H, C_1-*H*), 4.23 (dd, 1 H, J = 3.67, 8.06 Hz, C*H*(OMe)OEt), 3.53–3.49 (m, 1 H, $^1/_2OCH_2CH_3$), 3.46 (s, 3 H, OCH_3), 3.43–3.40 (m, 1 H, $^1/_2OCH_2CH_3$), 2.26–2.09 (m, 2 H, CH_2CH(OMe)OEt), 1.16 (t, 3 H, J = 7.33 Hz, OCH_2CH_3).

Compound 42: IR ($CHCl_3$) 1600, 1560, 1480, 1330, 1260, 1120, 1060, 930, 910 cm^{-1}; ^1H NMR δ 8.70 (d, 1 H, J = 2.94 Hz, Ar*H*), 8.34 (dd, 1 H, J = 2.93, 9.52 Hz, Ar*H*), 7.73 (d, 1 H, J = 9.52 Hz, Ar*H*), 7.30–7.18 (m, 3 H, Ar*H*), 7.06 (d, 1 H, J = 7.33 Hz, Ar*H*), 6.19 (d, 1 H, $J_{3,4}$ = 7.32 Hz, C_4-vinylic *H*), 5.73 (dd, 1 H, $J_{1,3}$ = 1.46 Hz, $J_{3,4}$ = 7.32 Hz, C_3-vinylic *H*), 5.19 (ddd, 1 H, J = 1.46, 4.40, 9.52 Hz, C_1-*H*), 4.35 (dd, 1 H, J = 4.39, 7.33 Hz, C*H*$(OEt)_2$), 3.86–3.78 (m, 1 H, $^1/_2OCH_2CH_3$), 3.57–3.48 (m, 2 H, OCH_2CH_3), 3.45–3.37 (m, 1 H, $^1/_2OCH_2CH_3$), 2.26–2.09 (m, 2 H, CH_2CH$(OEt)_2$), 1.34 (t, 3 H, J = 7.32 Hz, OCH_2CH_3), 1.15 (t, 3 H, J = 7.33 Hz, OCH_2CH_3); high resolution mass spectrum calcd for $C_{21}H_{23}N_3O_6$ 413.1587, found 413.1590.

Compound 43 (major diastereomer): IR ($CHCl_3$, mixture of diastereomers) 1600, 1560, 1490, 1450, 1320, 1270, 1120, 1070, 940, 910 cm^{-1}; ^1H NMR δ 8.69 (d, 1 H, J = 2.93 Hz, Ar*H*), 8.31 (dd, 1 H, J = 2.93, 9.52 Hz, Ar*H*), 7.83 (d, 1 H, J = 9.53 Hz, Ar*H*), 7.30–7.04 (m, 4 H, Ar*H*), 6.23 (d, 1 H, $J_{3,4}$ = 7.33 Hz, C_4-vinylic *H*), 5.76 (br dd, 1 H, $J_{3,4}$ = 7.33 Hz, 1 H, C_3-vinylic *H*), 5.27 (dd, 1 H, J = 6.60, 6.60 Hz, C_1-*H*), 4.66 (dd, 1 H, J = 5.13, 5.13 Hz, C*H*(OMe)OTBDMS), 3.23 (s, 3 H, OCH_3), 2.25 (ddd, 1 H, J = 5.13, 6.60, 14.65 Hz, $^1/_2CH_2$CH(OMe)-OTBDMS), 2.00 (ddd, J = 5.13, 6.60, 14.65, Hz, $^1/_2CH_2$CH(OMe)-OTBDMS), 0.97 (s, 9 H, $OSiC(CH_3)_3$), 0.14, 0.11 (2 s, 3 H each, $OSi(CH_3)_2$); high resolution mass spectrum calcd for $C_{24}H_{31}N_3O_6Si$ 485.1982, found 485.1944.

Minor diastereomer: ^1H NMR δ 8.71 (d, 1 H, J = 2.20 Hz, Ar*H*), 7.66 (d, 1 H, J = 9.53 Hz, Ar*H*), 7.30–7.04 (m, 4 H, Ar*H*), 6.19 (d, 1 H, $J_{3,4}$ = 7.33 Hz, C_4-vinylic *H*), 5.70 (dd, 1 H, $J_{1,3}$ = 1.23 Hz, $J_{3,4}$ = 7.33 Hz, C_3-vinylic *H*), 3.46 (s, 3 H, OCH_3), 2.28–1.98 (m, 2 H, CH_2CH(OMe)OTBDMS), 0.80 (s, 9 H, $OSiC(CH_3)_3$), −0.04, −0.15 (2 s, 3 H each, $OSi(CH_3)_2$).

Compound 44 (major diastereomer): ^1H NMR δ 8.72 (d, 1 H, J = 2.20 Hz, Ar*H*), 8.34 (dd, 1 H, J = 2.94, 9.53 Hz, Ar*H*), 7.67 (d, 1 H, J = 9.53 Hz, Ar*H*), 7.28–7.06 (m, 4 H, Ar*H*), 6.12 (dd, 1 H, J = 1.47, 7.33 Hz, C_3-*H*), 5.74 (dd, 1 H, J = 1.47, 3.66 Hz, C_4-*H*), 4.04 (d, 1 H, J = 6.60 Hz, -O-C*H*(OMe)), 3.89–3.85 (m, 1 H, $^1/_2$-O-CH_2-), 3.46–3.40 (m, 1 H, $^1/_2$-O-CH_2-), 3.04 (s, 3 H, OCH_3), 1.85–1.21 (m, 5 H, pyrano ring protons); high resolution mass spectrum calcd for $C_{21}H_{21}N_3O_6$ 411.1430, found 411.1431.

Compound 44 (first minor diastereomer): ^1H NMR δ 8.66 (d, 1 H, J = 2.20 Hz, Ar*H*), 8.36 (dd, 1 H, J = 2.20, 9.52 Hz, Ar*H*), 7.89 (d, 1 H, J = 9.53 Hz, Ar*H*), 7.33–7.17 (m, 3 H, Ar*H*), 7.02 (d, 1 H, 7.32 Hz, Ar*H*), 6.14 (d, 1 H, J = 7.33 Hz, C_4-*H*), 5.78 (dd, 1 H, J = 1.46, 7.33 Hz, C_3-*H*), 5.56 (dd, 1 H, J = 1.46, 5.13 Hz, C_1-*H*), 4.19 (d, 1 H, J = 6.59 Hz, -O-C*H*(OMe)), 3.92–3.87 (m, 1 H, $^1/_2$-O-CH_2-), 3.54 (s, 3 H, OCH_3), 3.44–3.38 (m, 1 H, $^1/_2$-O-CH_2-), 2.21–2.04 (m, 2 H), 1.66–1.46 (m, 2 H), 1.15–1.06 (m, 1 H); high resolution mass spectrum calcd for $C_{21}H_{21}N_3O_6$ 411.1430, found 411.1432.

Compound 44 (second minor diastereomer): ^1H NMR δ 8.64 (d, 1 H, J = 2.93 Hz, Ar*H*), 8.33 (dd, 1 H, J = 2.20, 9.53 Hz, Ar*H*), 7.59 (d, 1 H, J = 9.52 Hz, Ar*H*), 7.32–7.18 (m, 3 H, Ar*H*), 7.04 (d, 1 H, J = 7.33 Hz, Ar*H*), 6.30 (d, 1 H, J = 7.33 Hz, C_4-*H*), 5.80 (dd, 1 H, J = 1.47, 7.33 Hz, C_3-*H*), 5.11 (dd, 1 H, J = 1.47, 10.26 Hz, C_1-*H*), 4.13 (d, 1 H, J = 2.53 Hz, -C*H*(OMe)), 3.67–3.41 (m, 2 H, -O-CH_2-), 3.43 (s, 3 H, OCH_3), 2.35–2.28 (m, 1 H), 1.85–1.25 (m, 4 H); high resolution mass spectrum calcd for $C_{21}H_{21}N_3O_6$ 411.1430, found 411.1414.

Compound 45: IR ($CHCl_3$) 1600, 1580, 1520, 1480, 1340, 1320, 1120, 910 cm^{-1}; ^1H NMR δ 8.64 (d, 1 H, J = 2.93 Hz, Ar*H*), 8.29 (dd, 1 H, J = 2.93, 9.52 Hz, Ar*H*), 8.03 (d, 1 H, J = 9.52 Hz, Ar*H*), 7.32–7.08 (m, 8 H, Ar*H*), 6.85 (d, 1 H, J = 6.60 Hz, Ar*H*), 6.21 (d, 1 H, $J_{3,4}$ = 7.33 Hz, C_4-vinylic *H*), 5.92 (dd, 1 H, $J_{1,3}$ = 1.47 Hz, $J_{3,4}$ = 7.33 Hz, C_3-vinylic *H*), 5.41 (dd, 1 H, J = 1.47, 5.86 Hz, C_1-*H*), 4.09 (d, 1 H, J = 2.93 Hz, C*H*(OMe)OEt), 3.72–3.64 (m, 1 H, $^1/_2OCH_2CH_3$), 3.41–3.34 (m, 1 H, $^1/_2CH_2CH_3$), 3.10 (s, 3 H, O*Me*), 2.68–2.61 (m, 1 H, $^1/_2CH_2$Ph), 2.46–2.40 (m, 1 H, $^1/_2CH_2$Ph), 1.23 (t, 3 H, J = 7.33 Hz, OCH_2CH_3); high resolution mass spectrum calcd for $C_{27}H_{27}N_3O_6$ 489.1898, found 489.1862.

Compound 46: IR ($CHCl_3$) 1600, 1580, 1560, 1480, 1450, 1420, 1320, 1260, 1130, 1090, 1060, 1040, 970, 910 cm^{-1}; ^1H NMR δ 8.66 (d, 1 H, J = 2.19 Hz, Ar*H*), 8.36 (dd, 1 H, J = 2.19, 9.53 Hz, Ar*H*), 7.85 (d, 1 H, J = 9.53 Hz, Ar*H*), 7.29–7.16 (m, 4 H, Ar*H*), 6.27 (d, 1 H, $J_{3,4}$ = 7.33 Hz, C_4-vinylic *H*), 5.77 (d, 1 H, $J_{3,4}$ = 7.32 Hz, C_3-vinylic *H*), 5.28–5.25 (m, 1 H, C_1-*H*), 3.15, 3.11 (2s, 3 H each, CH$(OMe)_2$), 2.25–2.14 (m, 2 H, $CH_2C(OMe)_2$), 1.19 (s, 3 H, C*Me*$(OMe)_2$); high resolution mass spectrum, calcd for $C_{20}H_{21}N_3O_6$ 399.1430, found 399.1423.

Compound 47: IR ($CHCl_3$) 1710, 1600, 1570, 1510, 1480, 1400, 1330, 1270, 1130, 1100, 1070, 910 cm^{-1}; ^1H NMR δ 8.71 (d, 1 H, J = 2.93 Hz, Ar*H*), 8.35 (dd, 1 H, J = 2.93, 9.53 Hz, Ar*H*), 7.49 (d, 1 H, J = 9.52 Hz, Ar*H*), 7.51–7.13 (m, 4 H, Ar*H*), 6.16 (d, 1 H, $J_{3,4}$ = 7.33 Hz, C_4-vinylic *H*), 5.82 (dd, 1 H, $J_{1,3}$ = 1.46 Hz, $J_{3,4}$ = 7.33 Hz, C_3-vinylic *H*), 5.68–5.65 (m, 1 H, C_1-*H*), 3.06–3.04 (m, 2 H, CH_2COCH_3), 2.03 (s, 3 H, $COCH_3$); high resolution mass spectrum calcd for $C_{18}H_{15}N_3O_5$ 353.1012, found 353.1008.

Compounds 48 and 49: An inseparable 1:1 mixture of **48** and **49** was obtained; ^1H NMR δ 8.72 (d, 1 H, 2.93 Hz, Ar*H*), 8.69 (d, 1 H, J = 2.19 Hz, Ar*H*), 8.32 (dd, 1 H, J = 2.20, 9.53 Hz, Ar*H*), 8.29 (dd, 1 H, J = 2.93, 9.53 Ar*H*), 7.75 (d, 1 H, J = 9.52 Hz, Ar*H*), 7.60 (d, 1 H, J = 9.53 Hz, Ar*H*), 7.30–7.08 (m, 6 H, J = 9.52 Hz, Ar*H*), 7.03 (d, 1 H, J = 6.60 Hz, Ar*H*), 6.92 (d, 1 H, J = 7.33 Hz, Ar*H*), 6.60 (s, 1 H), 6.12 (d, 1 H, $J_{3,4}$ = 7.32 Hz, C_4-vinylic *H*), 5.89 (d, 1 H, $J_{3,4}$ = 8.06 Hz, C_4-vinylic *H*), 5.78–5.73 (m, 4 H, 2 × C_3-vinylic *H* and 2 × C_1-*H*), 3.75, 3.52 (2 s, 3 H each, CH$(OMe)_2$), 2.87–2.85 (m, 1 H), 2.28–1.24 (m, aliphatic ring protons).

Compound 50: IR ($CHCl_3$) 1600, 1590, 1560, 1510, 1490, 1450, 1330, 1260, 1140, 1100, 1070, 990, 910 cm^{-1}; ^1H NMR δ 8.69 (d, 1 H, J = 2.94 Hz, Ar*H*), 8.31 (dd, 1 H, J = 2.93, 9.52 Hz, Ar*H*), 7.93 (d, 1 H, J = 9.53 Hz, Ar*H*), 7.28–7.15 (m, 4 H, Ar*H*), 6.22 (d, 1 H, $J_{3,4}$ = 7.33 Hz, C_4-vinylic *H*), 5.71 (d, 1 H, $J_{3,4}$ = 7.33 Hz, C_3-vinylic *H*), 5.40–5.38 (m, 1 H, C_1-*H*), 2.91 (s, 3 H, O*Me*), 2.42 (dd, 1 H, J = 8.06, 14.66 Hz, $^1/_2CH_2$CMe(OTBDMS)OMe), 2.08 (dd, 1 H, J = 3.66, 14.66 Hz, $^1/_2CH_2$CMe(OTBDMS)OMe), 1.23 (s, 3 H, O*Me*), 0.94 (s, 9 H, $OSiC(CH_3)_3$), 0.20, 0.16 (2 s, 3 H each, $OSi(CH_3)_2$).

Compound 51: IR ($CHCl_3$) 1725, 1600, 1570, 1510, 1480, 1450, 1430, 1330, 1270, 1150, 1140, 1100, 1070, 990, 970, 940, 910 cm^{-1}; ^1H NMR δ 8.71 (d 1 H, J = 2.19 Hz, Ar*H*), 8.38 (dd, 1 H, J = 2.93, 9.52 Hz, Ar*H*), 7.54 (d, 1 H, J = 9.52 Hz, Ar*H*), 7.32–7.18 (m, 3 H, Ar*H*), 7.13 (d, 1 H, J = 7.33 Hz, Ar*H*), 6.21 (d, 1 H, $J_{3,4}$ = 7.33 Hz, C_4-vinylic *H*), 5.82 (d, 1 H, $J_{3,4}$ = 7.32 Hz, C_3-vinylic *H*), 5.56–5.53 (m, 1 H, C_1-*H*), 3.63 (s, 3 H, $COOCH_3$), 2.94–2.83 (m, 2 H, CH_2COOCH_3); high resolution mass spectrum calcd for $C_{18}H_{15}N_3O_6$ 369.0961, found 369.0957.

The Recycling Experiment. General Procedure. A mixture of one-bond product (0.05 mmol), Dowex-50×8 (20 mg), and methanol (0.5 mL) was stirred at room temperature for 24 h under N_2. The resin was filtered off, and the filtrate was poured into water (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the organic layer was washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated under reduced pressure. The combined yield of the products obtained from the recycling experiment was nearly quantitative, and the relative ratio of the products in each experiment is included in Table II. The separation of the products was carried out by using chromatotron. The structures of the compounds **16**, **18**, **27**, **30**, and **31** were confirmed by direct comparison (TLC, ^1H 400-MHz NMR) with their respective authentic samples obtained from the cycloaddition reactions described above. The spectral data for the new compounds obtained in the recycling experiment are described below.

Compound 52: IR ($CHCl_3$) 1610, 1580, 1490, 1420, 1360, 1330, 1290, 1130, 1110, 1080, 940, 920 cm^{-1}; ^1H NMR δ 9.18 (d, 1 H, J = 3.06 Hz, Ar*H*), 9.16 (d, 1 H, J = 8.55 Hz, N*H*), 8.25 (dd, J = 2.44, 9.15 Hz, Ar*H*), 7.57 (d, 1 H, J = 7.94 Hz, Ar*H*), 7.32–7.21 (m, 3 H, Ar*H*), 7.16 (d, 1 H, J = 9.76 Hz, Ar*H*), 5.06 (ddd, 1 H, $J_{3e,4}$ = 6.71 Hz, $J_{3a,4}$ = 6.72 Hz, $J_{4,NH}$ = 8.55 Hz, C_4-*H*), 4.77 (d, 1 H, J = 4.88 Hz, C*H*$(OMe)_2$), 3.91 (dd, 1 H, $J_{1,2}$ = 4.27 Hz, $J_{2,3e}$ = 4.27 Hz, $J_{2,3a}$ = 7.93 Hz, C_2-*H*), 3.57, 3.47, 3.40 (3 s, 3 H each, 3 × OCH_3), 3.27 (dd, 1 H, J = 4.27, 4.88 Hz, C_1-*H*), 2.41 (ddd, 1 H, $J_{2,3e}$ = 3.66 Hz, $J_{3e,4}$ = 6.71 Hz, $J_{3e,3a}$ = 13.43 Hz, C_3-H_e), 2.36 (ddd, 1 H, $J_{3a,4}$ = 6.72 Hz, $J_{2,3a}$ = 7.94 Hz, $J_{3a,3e}$ = 13.43 Hz, C_3-H_a); high resolution mass spectrum calcd for $C_{20}H_{23}N_3O_7$ 417.1536, found 417.1540.

Compound 53: IR ($CHCl_3$) 1610, 1590, 1490, 1420, 1330, 1290, 1110, 950, 910 cm^{-1}; ^1H NMR δ 9.18 (d, 1 H, J = 2.44 Hz, Ar*H*), 9.06 (d, 1 H, J = 7.94 Hz, N*H*), 8.23 (dd, J = 2.44, 9.77 Hz, Ar*H*), 7.55 (d, 1 H, J = 7.93 Hz, Ar*H*), 7.32–7.20 (m, 3 H, Ar*H*), 7.14 (d, 1 H, J = 9.16 Hz, Ar*H*), 5.05 (ddd, 1 H, $J_{3e,4}$ = 7.32 Hz, $J_{3a,4}$ = 7.32 Hz, $J_{4,NH}$ = 8.55 Hz, C_4-*H*), 4.78 (d, 1 H, J = 4.27 Hz, C*H*$(OMe)_2$), 3.96 (ddd, 1 H, $J_{2,3e}$ = 3.66 Hz, $J_{1,2}$ = 4.88 Hz, $J_{2,3a}$ = 8.54 Hz, C_2-*H*), 3.61–3.53 (m, 2 H, OCH_2CH_3), 3.55, 3.46 (2 s, 3 H each, 2 × OCH_3), 3.29 (dd, 1 H, J = 4.27, 4.88 Hz, C_1-*H*), 2.41 (ddd, 1 H, $J_{2,3e}$ = 3.66 Hz, $J_{3e,4}$ = 7.32 Hz, $J_{3e,3a}$ = 13.43 Hz, C_3-H_e), 2.33 (ddd, 1 H, $J_{3a,4}$ = 7.32 Hz, $J_{2,3a}$ = 8.54 Hz, $J_{3a,3e}$ = 13.43 Hz, C_3-H_a), 1.20 (t, 3 H, J = 7.33 Hz, OCH_2CH_3); high resolution mass spectrum calcd for $C_{21}H_{25}N_3O_7$ 431.1692, found 431.1682.

Compound 54: IR ($CHCl_3$) 1610, 1580, 1490, 1410, 1330, 1290, 1260, 1120, 1110, 1090, 1070, 910 cm^{-1}; ^1H NMR δ 10.11 (d, 1 H, J = 10.26 Hz, N*H*), 9.15 (d, 1 H, J = 2.93 Hz, Ar*H*), 8.05 (dd, 1 H, J = 2.93, 9.53 Hz, Ar*H*), 7.90 (d, J = 8.06 Hz, Ar*H*), 7.29–7.01 (m, 8 H, Ar*H*), 6.73 (d, 1 H, J = 9.53 Hz, Ar*H*), 4.93 (dd, 1 H, $J_{3,4}$ = 5.13 Hz, $J_{4,NH}$ = 10.26 Hz, C_4-*H*), 4.83 (d, J = 7.33 Hz, C*H*$(OMe)_2$), 4.14 (dd, 1 H, $J_{1,2}$ = 2.93 Hz, $J_{2,3}$ = V small, C_2-*H*), 3.74 (s, 3 H, OCH_3), 3.48 (s, 6 H, 2 × 3 OCH_3), 3.19 (dd, 1 H, $J_{1,2}$ = 2.93 Hz, J = 7.33 Hz, C_1-*H*), 3.09–2.98 (m, 2 H, CH_2Ph), 2.60–2.54 (m, 1 H, C_3-*H*); high resolution mass spectrum calcd for $C_{27}H_{29}N_3O_7$ 507.2005, found 507.2008.

Compound 55: When **51** was stirred at room temperature for 3 days with Dowex and methanol, a 50% conversion of **51** to **55** took place. The remaining unreacted **51** (50%) was also isolated: IR ($CHCl_3$) 1730, 1610, 1590, 1490, 1430, 1330, 1310, 1280, 1160, 1120, 1070, 990, 970, 910 cm^{-1}; ^1H NMR δ 9.41 (d, 1 H, J = 6.60 Hz, N*H*), 9.13 (d, 1 H, J = 2.93 Hz, Ar*H*), 8.07 (dd, 1 H, J = 2.20, 9.53 Hz, Ar*H*), 7.28–7.16 (m, 4 H, Ar*H*), 6.98 (d, 1 H, J = 9.52 Hz, Ar*H*), 5.55 (ddd, 1 H, J = 4.40, 6.60, 8.14 Hz, ArC*H*NH), 4.61 (dd, 1 H, J = 3.67, 6.59 Hz, C*H*$(OMe)_2$), 3.71 (s, 3 H, $COOCH_3$), 3.45, 3.40 (2 s, 3 H each, CH$(OCH_3)_2$), 3.14 (dd, 1 H, J = 6.59, 13.92 Hz, $^1/_2CH_2CH(OMe)_2$), 2.98 (dd, 1 H, J = 4.40, 15.39 Hz, $^1/_2CH_2$COOMe), 2.97 (dd, 1 H, J = 4.40, 13.92 Hz, $^1/_2CH_2CH(OMe)_2$), 2.85 (dd, 1 H, J = 8.06, 15.39 Hz, $^1/_2CH_2$COOMe).

Reaction of 4-methoxyisoquinolinium salt 61 with 17: A mixture of 4-methoxyisoquinolinium salt **61** (18 mg, 0.05 mmol), anhydrous calcium carbonate (50 mg, 0.5 mmol), methanol (0.5 mL), and vinyl ether **17** (0.05 mL, 0.5 mmol) was stirred at room temperature under N_2 for 24 h. The reaction mixture was worked up as usual, and the crude reaction mixture was purified by using chromatotron (5–25% EtOAC in petroleum ether) when the following three fractions were obtained.

First fraction (5 mg): It consisted of **65** and **66**. **65**: ^1H NMR δ 8.67 (d, 1 H, J = 2.20 Hz, Ar*H*), 8.08 (dd, 1 H, J = 2.93, 9.53 Hz, Ar*H*), 7.62–7.23 (m, 4 H, Ar*H*), 6.86 (d, 1 H, J = 9.53 Hz, Ar*H*), 4.78–4.75 (m, 1 H, ArC*H*NAr), 4.60–4.55 (m, 1 H, C*H*OEt), 4.45 (d, 1 H, J = 6.59 Hz, CH(OEt)C*H*NAr), 3.61–3.39 (m, 2 H, OCH_2CH_3), 3.35 (s, 3 H, OCH_3), 2.80–2.73 (m, 1 H, $^1/_2CH_2$CHOEt), 2.61 (s, 3 H, OCH_3), 1.70 (dd, 1 H, J = 3.66, 13.46 Hz, $^1/_2CH_2$CHOEt), 1.14 (t, 3 H, J = 7.32 Hz, OCH_2CH_3).

66: The above fraction containing **65** and **66** was dissolved in acetone (0.5 mL), and 0.1 mL of water and Amberlyst-15 (10 mg) was added to it. After having been stirred at room temperature for 1 h, it was poured into water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was then dried ($MgSO_4$), and solvent was evaporated under reduced pressure. The residue so obtained was purified by using chromatotron to give **66** (4.5 mg, 24%): IR ($CHCl_3$) 1700, 1600, 1490, 1340, 1140, 1120, 1090, 970, 910 cm^{-1}; ^1H NMR δ 8.61 (d, 1 H, J = 2.94 Hz, Ar*H*), 8.12 (dd, 1 H, J = 2.93, 9.52 Hz, Ar*H*), 7.98 (d, 1 H, J = 7.33 Hz, Ar*H*), 7.56–7.36 (m, 2 H, Ar*H*), 7.24 (d, 1 H, J = 9.52 Hz, Ar*H*), 6.92 (d, 1 H, J = 8.79 Hz, Ar*H*), 4.82 (d, 1 H, J = 7.33 Hz, -CO-C*H*-CHOEt), 4.78 (d, 1 H, J = 6.59 Hz, ArC*H*NAr), 4.71 (ddd, 1 H, J = 2.93, 7.33, 8.79 Hz, C*H*OEt), 3.71–3.63 (m, 1 H, $^1/_2OCH_2CH_3$), 3.54–3.46 (m, 1 H, $^1/_2OCH_2CH_3$), 3.06 (ddd, 1 H, J = 6.60, 8.79, 13.18 Hz, $^1/_2CH_2$CHOEt), 1.90 (dd, 1 H, J = 2.93, 13.19 Hz, $^1/_2CH_2$CHOEt), 1.08 (t, 3 H, J = 7.33 Hz, OCH_2CH_3); high resolution mass spectrum calcd for $C_{19}H_{17}N_3O_6$ 383.1118, found 383.1117.

Second fraction (5 mg, 23%): It consisted of two diastereomers of **63** in the ratio 78:22; IR ($CHCl_3$) 1600, 1580, 1490, 1400, 1370, 1320, 1250, 1140, 1120, 1100, 1070, 910, 820 cm^{-1}.

Major diastereomer: ^1H NMR δ 8.66 (d, 1 H, J = 2.20 Hz, Ar*H*), 8.30 (dd, 1 H, J = 2.93, 9.52 Hz, Ar*H*), 7.69–7.09 (m, 5 H, Ar*H*), 5.19–5.15 (m, 1 H, C_1-*H*), 5.08 (s, 1 H, C_3-vinylic *H*), 5.33 (dd, 1 H, J = 5.13, 6.59 Hz, C*H*(OEt)OMe), 3.80–3.75 (m, 1 H, $^1/_2OCH_2CH_3$), 3.73 (s, 3 H, OCH_3), 3.58–3.46 (m, 1 H, $^1/_2OCH_2CH_3$), 3.30 (s, 3 H, OCH_3), 2.16–2.11 (m, 2 H, CH_2CH(OEt)OMe), 1.32 (t, 3 H, J = 7.33 Hz, OCH_2CH_3); high resolution mass spectrum calcd for $C_{21}H_{23}N_3O_7$ 429.1537, found 429.1547.

Minor diastereomer: ^1H NMR δ 8.60 (d, 1 H, J = 2.93 Hz, Ar*H*), 8.07 (d, 1 H, J = 2.94, 9.53 Hz, Ar*H*), 7.69–7.09 (m, 5 H, Ar*H*), 4.66 (s, 1 H, C_3-vinylic *H*), 3.82 (s, 3 H, OCH_3), 3.26 (s, 3 H, OCH_3), 1.05 (t, 3 H, J = 7.33 Hz, OCH_2CH_3).

Third fraction (7 mg): It contained a mixture of **68** and **69** identified by ^1H NMR. It was difficult to obtain **68** in pure form, and the mixture was completely converted to **69** by treating with aqueous acetone and Amberlyst-15 by using the procedure described above for the conversion of **65** to **66**.

68: ^1H NMR δ 8.68 (d, 1 H, J = 2.93 Hz, Ar*H*), 8.32 (dd, 1 H, J = 2.93, 9.53 Hz, Ar*H*), 7.69 (d, 1 H, J = 7.33 Hz, Ar*H*), 7.46–7.32 (m, 4 H, Ar*H*), 5.00 (s, 1 H, C*H*OMe), 4.92–4.91 (m, 1 H, ArC*H*N), 4.25 (dd, 1 H, J = 2.20, 8.06 Hz, C*H*OEt), 3.71 (s, 3 H, OCH_3), 3.62–3.42 (m, 2 H, OCH_2CH_3), 2.90 (s, 3 H, OCH_3), 2.65–2.60 (m, 1 H, $^1/_2CH_2$CHOEt), 1.67–1.56 (m, 1 H, $^1/_2CH_2$CHOEt), 1.11 (t, 3 H, J = 7.33 Hz, OCH_2CH_3).

69: 6 mg (29%); IR ($CHCl_3$) 1720, 1620, 1590, 1500, 1420, 1330, 1300, 1120, 1090, 960, 910 cm^{-1}; ^1H NMR δ 9.65 (s, 1 H, C*H*O), 9.21 (d, 1 H, J = 2.44 Hz, Ar*H*), 8.82 (d, 1 H, J = 8.54 Hz, N*H*), 8.33 (dd, 1 H, J = 2.45, 9.16 Hz, Ar*H*), 7.57 (dd, 1 H, J = 1.22, 7.94 Hz, Ar*H*), 7.47–7.26 (m, 3 H, Ar*H*), 7.03 (d, 1 H, J = 9.15 Hz, Ar*H*), 5.25 (ddd, 1 H, $J_{3e,4}$ = 4.89 Hz, $J_{3a,4}$ = 9.15 Hz, $J_{4,NH}$ = 8.54 Hz, C_4-*H*), 4.29 (dd, 1 H, $J_{2,3a}$ = 2.44 Hz, $J_{2,3e}$ = 6.71 Hz, C_2-*H*), 3.85–3.75 (m, 1 H, $^1/_2OCH_2CH_3$), 3.62–3.55 (m, 1 H, $^1/_2OCH_2CH_3$), 3.47 (s, 3 H, OCH_3), 2.69 (ddd, 1 H, $J_{3e,4}$ = 4.89 Hz, $J_{3e,2}$ = 6.71 Hz, $J_{3e,3a}$ = 14.04 Hz, C_3-H_e), 2.26 (ddd, 1 H, $J_{3a,2}$ = 2.44 Hz, $J_{3a,4}$ = 9.15 Hz, $J_{3a,3e}$ = 14.04 Hz, C_3-H_a), 1.29 (t, 3 H, J = 7.32 Hz, OCH_2CH_3); high resolution mass spectrum calcd for $C_{20}H_{21}N_3O_7$ 415.1380, found 415.1391.

Reaction of 74 with ethyl vinyl ether 17: To a mixture of isoquinoline (129 mg, 1 mmol), acetonitrile (3 mL), methanol (1 mL), and anhydrous calcium carbonate (600 mg, 6 mmol) at 0 °C was added ethyl chloroformate (130 mg, 1.2 mmol) dropwise with stirring under N_2. The reaction mixture was stirred at 0 °C for 10 min, and then vinyl ether **17** (288 mg, 4 mmol) was added dropwise. After having been stirred at 0 °C for 2 h, the reaction mixture was allowed to warm to room temperature, filter through Celite, and wash the residue with CH_2Cl_2, and the combined filtrate was concentrated under reduced pressure. The residue so obtained was purified by using chromatotron to give **76** (260 mg, 82%) and **75** (43 mg, 14%).

Compound 76: The ^1H NMR suggested that the product **76** consisted of two diastereomers in the ratio 80:20, and each diastereomer consisted of two rotamers in 2:1 ratio. Some of the proton resonances identified for each of the isomers are reported below. IR ($CHCl_3$) 1690, 1460, 1400, 1380, 1350, 1320, 1110, 1090, 990 cm^{-1}.

Major rotamer of major diastereomer: ^1H NMR δ 7.20–7.05 (m, 4 H, Ar*H*), 6.79 (d, 1 H, $J_{3,4}$ = 7.32 Hz, C_4-vinylic *H*), 5.86 (d, 1 H, $J_{3,4}$ = 8.06 Hz, C_3-vinylic *H*), 5.53–5.49 (m, 1 H, C_1-*H*), 4.43 (dd, 1 H, J = 4.40, 6.60 Hz, C*H* (OEt)OMe), 4.34–4.20 (m, 2 H, $NCO_2CH_2CH_3$), 3.69–3.60 (m, 1 H, $^1/_2CHOCH_2CH_3$), 3.47–3.40 (m, 1 H, $^1/_2CHOCH_2CH_3$), 3.26 (s, 3 H, OCH_3), 2.11–1.99 (m, 1 H, $^1/_2CH_2CH$(OEt)OMe), 1.90–1.79 (m, 1 H, $^1/_2CH_2CH$(OEt)OMe), 1.30 (t, 3 H, J = 7.32 Hz, $NCO_2CH_2CH_3$), 1.21 (t, 3 H, J = 7.32 Hz, $CHOCH_2CH_3$).

Minor rotamer of major diastereomer: ^1H NMR δ 6.92 (d, 1 H, $J_{3,4}$ = 7.33 Hz, C_4-vinylic *H*), 5.94 (d, 1 H, $J_{3,4}$ = 7.33 Hz, C_3-vinylic *H*), 5.40–5.36 (m, 1 H, C_1-*H*), 3.24 (s, 3 H, OCH_3), 1.35 (t, 3 H, J = 6.60 Hz, $NCO_2CH_2CH_3$), 1.23 (t, 3 H, J = 6.60 Hz, $CHOCH_2CH_3$).

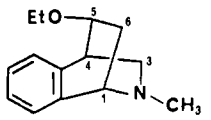
Major rotamer of minor diastereomer: ^1H NMR δ 5.84 (d, 1 H, C_3-vinylic *H*), 3.59–3.49 (m, 2 H, $CHOCH_2CH_3$), 3.31 (s, 3 H, OCH_3), 1.16 (t, 3 H, J = 6.60 Hz, $CHOCH_2CH_3$).

Minor rotamer of minor diastereomer: ^1H NMR δ 3.30 (s, 3 H, OCH_3); high resolution mass spectrum calcd for $C_{17}H_{23}NO_4$ 305.1627, found 305.1610.

Compound 75: The ^1H NMR spectrum indicated **75** to be a mixture of two rotamers in the ratio 4:3. Most of the peaks were very broad and were not resolved. The spectral data recorded for the inseparable mixture is as follows: IR ($CHCl_3$) 1690, 1460, 1400, 1380, 1350, 1320, 1290, 1280, 1120, 1090, 990 cm^{-1}; ^1H NMR δ 7.29–7.22 (m, 2 × 4 H, Ar*H*), 5.29–5.13 (br m, 2 × 1 H), 5.02–4.68 (br m, 2 × 1 H), 4.33–4.31 (m,

1 H), 4.21-4.19 (m, 1 H), 4.09 (br m, 3 H), 3.85-3.54 (m, 3 H), 3.50 (br s, 6 H, 2 × OCH_3), 3.47-3.21 (m, 4 H), 2.65-2.59 (m, 1 H), 2.44 (br m, 1 H), 1.46-1.43 (m, 1 H), 1.32-1.29 (m, 1 H), 1.28-1.18 (m, 6 H, 2 × $NCO_2CH_2CH_3$), 1.09, 1.02 (2 t, 3 H each, 2 × OCH_2CH_3); high resolution mass spectrum calcd for $C_{17}H_{23}NO_4$ 305.1630, found 305.1632.

In order to further confirm the structure assignment for compound **75**, it was treated with lithium aluminum hydride (LAH) as follows: A solution of **75** (36 mg, 0.118 mmol) in 1.5 mL of anhydrous ether was added dropwise to a stirred suspension of LAH (8 mg, 0.21 mmol) in 1 mL of anhydrous ether under N_2 at room temperature. The reaction mixture was then heated to reflux for 5 h. It was then cooled, and the excess LAH was carefully destroyed by adding ice-cold aqueous ethyl acetate. The reaction mixture was then extracted with ethyl acetate, and the organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. On purification using chromatotron, the residue gave **75a** (20 mg, 78%) consisting of only one isomer



75a

(TLC, ^1H 400-MHz NMR): IR ($CHCl_3$) 1600, 1450, 1370, 1350, 1340, 1240, 1090, 940, 910 cm^{-1}; ^1H NMR δ 7.36-7.18 (m, 4 H, Ar*H*), 3.94 (ddd, 1 H, J = 1.83, 3.05, 8.54 Hz, C_1-*H*), 3.90-3.88 (m, 1 H, C_5-*H*), 3.56 (dq, 1 H, J = 7.33, 9.16 Hz, $^1/_2OCH_2CH_3$), 3.44 (dd, 1 H, J = 1.83, 10.38 Hz, $^1/_2C_3$-H_2), 3.39 (dq, 1 H, J = 7.33, 9.16 Hz, $^1/_2OCH_2CH_3$), 3.35 (ddd, 1 H, J = 1.83, 1.83, 3.05 Hz, $^1/_2C_3$-H_2), 2.81 (ddd, 1 H, J = 3.66, 6.70, 14.65 Hz, $^1/_2C_6$-H_2), 2.19 (s, 3 H, NCH_3), 2.07 (dd, 1 H, J = 3.05, 10.38 Hz, C_4-*H*), 1.37 (ddd, 1 H, J = 2.46, 3.05, 14.65 Hz, $^1/_2C_6$-H_2), 1.07 (t, J = 7.33 Hz, OCH_2CH_3); high resolution mass spectrum calcd for $C_{14}H_{19}NO$ 217.1468, found 217.1468.

Reaction of 76 with Dowex and methanol: A mixture of **76** (80 mg, 0.26 mmol), Dowex-50×8 (50 mg), and methanol (1 mL) was stirred at room temperature for 5 h. The reaction was then worked up as described above for the recycling experiment. The crude product was purified by using chromatotron to give **77** (62 mg, 81%). The product **77** consisted of two rotamers in the ratio 2:1: IR ($CHCl_3$) 1695, 1630, 1570, 1450, 1400, 1375, 1350, 1330, 1290, 1120, 1100, 1075, 1055, 960, 910 cm^{-1}.

Major rotamer: ^1H NMR δ 7.21-7.06 (m, 4 H, Ar*H*), 6.79 (d, 1 H, J = 8.06 Hz, C_4-vinylic *H*), 5.86 (d, 1 H, J = 8.06 Hz, C_3-vinylic *H*), 5.52-5.48 (m, 1 H, C_1-*H*), 4.37 (dd, 1 H, J = 4.39, 4.40 Hz, *CH*-$(OMe)_2$), 4.25 (q, 2 H, J = 6.59 Hz, $NCO_2CH_2CH_3$), 3.31, 3.26 (2 s, 3 H each, $CH(OCH_3)_2$), 2.10-1.98 (m, 1 H, $^1/_2CH_2CH(OMe)_2$), 1.90-1.78 (m, 1 H, $^1/_2CH_2CH(OMe)_2$), 1.31 (t, 3 H, J = 6.59 Hz, $NCO_2CH_2CH_3$).

Minor rotamer: ^1H NMR δ 7.21-7.06 (m, 4 H, Ar*H*), 6.93 (d, 1 H, J = 8.06 Hz, C_4-vinylic *H*), 5.95 (d, 1 H, J = 8.06 Hz, C_3-vinylic *H*), 5.39-5.35 (m, 1 H, C_1-*H*), 4.29 (q, 2 H, J = 7.33 Hz, $NCO_2CH_2CH_3$), 3.30, 3.24 (2 s, 3 H each, $CH(OCH_3)_2$), 1.36 (t, 3 H, J = 7.33 Hz, $COOCH_2CH_3$).

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Supplementary Material Available: Structure assignments for tetralins and one-bond products and experimental data for compounds **26a**, **27a**, and **27b** (9 pages). Ordering information is given on any current masthead page.

Complex-Induced Proximity Effects: Remote Lithiations of Carboxamides

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Abstract: The reactions of *sec*-butyllithium with *N,N*-diisopropyl-2-methylpent-4-enamide (**8**), *N,N*-diisopropylcyclohex-3-enecarboxamide (**9**), *N,N*-diisopropyl-2-methyl-3-phenylpropanamide (**28**), *N,N*-diisopropyl-2-methyl-3-(phenylthio)propanamide (**29**), *N,N*-diisopropyl-3-(phenylthio)-2-((phenylthio)methyl)propanamide (**30**), *N,N*-diisopropyl-3-(phenylthio)-2-((phenylthio)methyl)butanamide (**31**), and *N,N*-diisopropyl-3-(phenylthio)-2-methylbutanamide (**39**) provide organolithium reagents that are the result of β-lithiations. The direction of these metalations to the β-protons in the presence of thermodynamically more acidic α-protons is notable, and the operation of a complex-induced proximity effect that dominates over resonance and inductive effects is suggested. The regio- and stereochemistry of the reactions of the β-lithiated amides and of the corresponding Grignard and aluminum derivatives with a number of electrophilic reagents is reported. High selectivity is observed in many cases, and rationales for the course of these reactions are provided. Lithiation of *N,N*-diisopropyl-2-methyl-4-(phenylthio)-butanamide (**47**) is shown to occur at the γ position, but the corresponding γ-vinyl- or γ-phenyl-substituted amides or an amide with δ-phenylthio substitution does not undergo analogous metalations.

Substitution of a carbon-hydrogen bond by a sequence that involves deprotonation and reaction of the resulting formal carbanion with an electrophile is a general synthetic strategy for making carbon-carbon and carbon-heteroatom bonds. In most cases the intermediate carbanion is generated by removal of a proton from a carbon which bears a functional group capable of stabilizing the adjacent negative charge by resonance and/or inductive effects. We have been exploring the possibility that association between a functional group and an organolithium base can provide a complex which kinetically leads to a transition structure in which the base removes a proton from a carbon which is not adjacent to the directing functionality.[1,2]

In this report we provide information about the direct β-lithiations of α-alkyl carboxamides which are β-substituted by a vinyl, phenyl, or phenylthio group, to give the organolithium reagents **2**. These cases are notable because the complex-induced proximity effect in these lithiations must dominate the more familiar res-

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